AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY

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American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision-making for specific clinical conditions. Most of the content herein is based on a systematic review of evidence published in peer-reviewed literature. In areas in which there was some uncertainty, professional judgment was applied.

These guidelines are a working document reflecting the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

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**A complete list of the Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines can be found in the Acknowledgement.*

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ABSTRACT

Objective: Development of these guidelines is mandated by the American Association of Clinical Endocrinologists (AACE) Board of Directors and the American College of Endocrinology (ACE) Board of Trustees and adheres to published AACE protocols for the standardized production of clinical practice guidelines (CPGs).

Methods: Recommendations are based on diligent review of clinical evidence with transparent incorporation of subjective factors.

Results: There are 9 broad clinical questions with 123 recommendation numbers that include 160 specific statements (85 [53.1%] strong [Grade A]; 48 [30.0%] intermediate [Grade B], and 11 [6.9%] weak [Grade C], with 16 [10.0%] based on expert opinion [Grade D]) that build a comprehensive medical care plan for obesity. There were 133 (83.1%) statements based on strong (best evidence level [BEL] 1 = 79 [49.4%]) or intermediate (BEL 2 = 54 [33.7%]) levels of scientific substantiation. There were 34 (23.6%) evidence-based recommendation grades (Grades A-C = 144) that were adjusted based on subjective factors. Among the 1,790 reference citations used in this CPG, 524 (29.3%) were based on strong (evidence level [EL] 1), 605 (33.8%) were based on intermediate (EL 2), and 308 (17.2%) were based on weak (EL 3) scientific studies, with 353 (19.7%) based on reviews and opinions (EL 4).

Conclusion: The final recommendations recognize that obesity is a complex, adiposity-based chronic disease, where management targets both weight-related complications and adiposity to improve overall health and quality of life. The detailed evidence-based recommendations allow for nuanced clinical decision-making that addresses real-world medical care of patients with obesity, including screening, diagnosis, evaluation, selection of therapy, treatment goals, and individualization of care. The goal is to facilitate high-quality care of patients with obesity and provide a rational, scientific approach to management that optimizes health outcomes and safety. **(Endocr Pract. 2016;22:Supp3;1-205)**

Abbreviations:
A1C = hemoglobin A1c; **AACE** = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **ACSM** = American College of Sports Medicine; **ADA** = American Diabetes Association; **ADAPT** = Arthritis, Diet, and Activity Promotion Trial; **ADHD** = attention-deficit hyperactivity disorder; **AHA** = American Heart Association; **AHEAD** = Action for Health in Diabetes; **AHI** = apnea-hypopnea index; ALT = alanine aminotransferase; **AMA** = American Medical Association; **ARB** = angiotensin receptor blocker; **ART** = assisted reproductive technology; **AUC** = area under the curve; **BDI** = Beck Depression Inventory; **BED** = binge eating disorder; **BEL** = best evidence level; **BLOOM** = Behavioral Modification and Lorcaserin for Overweight and Obesity Management; **BLOSSOM** = Behavioral Modification and Lorcaserin Second Study for Obesity Management; **BMI** = body mass index; **BP** = blood pressure; **C-SSRS** = Columbia Suicidality Severity Rating Scale; **CAD** = coronary artery disease; **CARDIA** = Coronary Artery Risk Development in Young Adults; **CBT** = cognitive behavioral therapy; **CCO** = Consensus Conference on Obesity; **CHF** = congestive heart failure; **CHO** = carbohydrate; **CI** = confidence interval; **COR-I** = Contrave Obesity Research I; **CPG** = clinical practice guideline; **CV** = cardiovascular; **CVD** = cardiovascular disease; **DASH** = Dietary Approaches to Stop Hypertension; **DBP** = diastolic blood pressure; **DEXA** = dual-energy X-ray absorptiometry; **DPP** = Diabetes Prevention Program; **DSE** = diabetes support and education; **EL** = evidence level; **ED** = erectile dysfunction; **ER** = extended release; **EWL** = excess weight loss; **FDA** = Food and Drug Administration; **FDG** = 18F-fluorodeoxyglucose; **GABA** = gamma-aminobutyric acid; **GERD** = gastroesophageal reflux disease; **GI** = gastrointestinal; **GLP-1** = glucagon-like peptide 1; **HADS** = Hospital Anxiety and Depression Scale; **HDL-c** = high-density lipoprotein cholesterol; **HR** = hazard ratio; HTN = hypertension; **HUNT** = Nord-Trøndelag Health Study; **ICSI** = intracytoplasmic sperm injection; **IFG** = impaired fasting glucose; **IGT** = impaired glucose tolerance; **ILI** = intensive lifestyle intervention; **IVF** = in vitro fertilization; **LAGB** = laparoscopic adjustable gastric banding; **LDL-c** = low-density lipoprotein cholesterol; **LES** = lower esophageal sphincter; **LSG** = laparoscopic sleeve gastrectomy; **LV** = left ventricle; **LVH** = left ventricular hypertrophy; **LVBG** = laparoscopic vertical banded gastroplasty; **MACE** = major adverse cardiovascular events; **MAOI** = monoamine oxidase inhibitor; **MI** = myocardial infarction; **MNRCT** = meta-analysis of non-randomized prospective or case-controlled trials; **MRI** = magnetic resonance imaging; **MUFA** = monounsaturated fatty acid; **NAFLD** = nonalcoholic fatty liver disease; **NASH** = nonalcoholic steatohepatitis; **NES** = night eating syndrome; **NHANES** = National Health and Nutrition Examination Surveys; **NHLBI** = National Heart, Lung, and Blood Institute; **NHS** = Nurses' Health Study; **NICE** = National Institute for Health and Care Excellence; **OA** = osteoarthritis; **OGTT** = oral glucose tolerance test; **OR** = odds ratio; **OSA** = obstructive sleep apnea; **PHQ-9** = Patient Health Questionnaire; **PCOS** = polycystic ovary syndrome; **PCP** = primary care physician; POMC = pro-opiomelanocortin; **POWER** = Practice-Based Opportunities for Weight Reduction; **PPI** = proton pump inhibitor; **PRIDE** = Program to Reduce Incontinence by Diet and Exercise;

PSA = prostate specific antigen; **QOL** = quality of life; **RA** = receptor agonist; **RCT** = randomized controlled trial; **ROC** = receiver operator characteristic; **RR** = relative risk; **RYGB** = Roux-en-Y gastric bypass; **SAD** = sagittal abdominal diameter; SBP = systolic blood pressure; **SCOUT** = Sibutramine Cardiovascular Outcome Trial; **SG** = sleeve gastrectomy; **SHBG** = sex hormone-binding globulin; **SIEDY** = Structured Interview on Erectile Dysfunction; **SNRI** = serotonin-norepinephrine reuptake inhibitors; **SOS** = Swedish Obese Subjects; **SS** = surveillance study; **SSRI** = selective serotonin reuptake inhibitors; **STORM** = Sibutramine Trial on Obesity Reduction and Maintenance; **TCA** = tricyclic antidepressant; **TONE** = Trial of Nonpharmacologic Intervention in the Elderly; **TOS** = The Obesity Society; **T2DM** = type 2 diabetes mellitus; **UKPDS** = United Kingdom Prospective Diabetes Study; **U.S.** = United States; **VAT** = visceral adipose tissue; **VLDL** = very low-density lipoprotein; **WC** = waist circumference; **WHO** = World Health Organization; **WHR** = waist-hip ratio; **WHtR** = waist-to-height ratio; **WMD** = weighted mean difference; **WOMAC** = Western Ontario and McMaster Universities osteoarthritis index; **XENDOS** = XEnical in the Prevention of Diabetes in Obese Subjects

"Corpulence is not only a disease itself, but the harbinger of others." Hippocrates

I. INTRODUCTION AND RATIONALE

Obesity rates have increased sharply over the past 30 years, creating a global public health crisis (1 [EL 3; SS]; 2 [EL 2; MNRCT]; 3 [EL 3; CSS]). Global estimates suggest that 500 million adults have obesity worldwide (2 [EL 2; MNRCT]) with prevalence rates increasing among children and adolescents (3 [EL 3; CSS]; 4 [EL 3; SS]; 5 [EL 3; SS]). Data from the National Health and Nutrition Examination Surveys show that roughly 2 of 3 United States (U.S.) adults have overweight or obesity, and 1 of 3 adults has obesity (1 [EL 3; SS]; 2 [EL 2; MNRCT]; 3 [EL 3; CSS]). The impact of obesity on morbidity, mortality, and health care costs is profound. Obesity and weight-related complications exert a huge burden on patient suffering and social costs (6 [EL 3; SS]; 7 [EL 3; SS]). Obesity is estimated to add $3,559 annually (adjusted to 2012 dollars) to per-patient medical expenditures as compared to patients who do not have obesity; this includes $1,372 each year for inpatient services, $1,057 for outpatient services, and $1,130 for prescription drugs (6 [EL 3; SS]).

In recent years, exciting advances have occurred in all 3 modalities used to treat obesity: lifestyle intervention, pharmacotherapy, and weight-loss procedures, including bariatric surgery (8 [EL 4; NE]). Clinical trials have established the efficacy of lifestyle and behavioral interventions in obesity; moreover, there are 5 weight-loss medications approved by the U.S. Food and Drug Administration (FDA) for chronic management of obesity (9 [EL 4; NE]; 10 [EL 4; NE]). Bariatric surgical practices have been developed and refined, together with improvements in pre- and postoperative care standards, resulting in better patient outcomes (11 [EL 4; NE]). The FDA has also recently approved devices involving electrical stimulation and gastric balloons for the treatment of obesity. In addition to enhanced treatment options, the scientific understanding of the pathophysiology of obesity has advanced, and it is now viewed as a complex chronic disease with interacting genetic, environmental, and behavioral determinants that result in serious complications (10 [EL 4; NE]). Adipose tissue itself is an endocrine organ which can become dysfunctional in obesity and contribute to systemic metabolic disease. Weight loss can be used to prevent and treat metabolic disease concomitant with an improvement in adipose tissue functionality. These new therapeutic tools and scientific advances necessitate development of rational medical care models and robust evidenced-based therapeutic approaches, with the intended goal of improving patient well-being and recognizing patients as individuals with unique phenotypes in unique settings.

In 2012, the American Association of Clinical Endocrinologists (AACE) published a position statement designating obesity as a disease and providing the rationale for this designation (12 [EL 4; NE]). Subsequently, AACE was joined by multiple professional organizations in submitting a resolution to the American Medical Association (AMA) to recognize obesity as a disease. In June 2013, following a vote by its House of Delegates, the AMA adopted a policy designating obesity as a chronic disease (13 [EL 4, NE]). These developments have the potential to accelerate scientific study of the multidimensional pathophysiology of obesity and present an impetus to our health care system to provide effective treatment and prevention.

In May of 2014, AACE and the American College of Endocrinology (ACE) sponsored their first Consensus Conference on Obesity (CCO) in Washington, DC, to establish an evidence base that could be used to develop a comprehensive plan to combat obesity (14 [EL 4; NE]). The conference convened a wide array of national stakeholders (the "pillars") with a vested interest in obesity. The concerted participation of these stakeholders was recognized as necessary to support an effective overall action plan, and they included health professional organizations, government regulatory agencies, employers, health care insurers, pharmaceutical industry representatives, research organizations, disease advocacy organizations, and health profession educators.

A key consensus concept that emerged from the CCO was that a more medically meaningful and actionable

definition of obesity was needed. It became clear that diagnosis based solely on body mass index (BMI) lacked the information needed for effective interaction and concerted policy regarding obesity among stakeholders (14 [EL 4; NE]) and was a barrier to the development of acceptable and rational approaches to medical care. It was agreed that the elements for an improved obesity diagnostic process should include BMI alongside an indication of the degree to which excess adiposity negatively affects an individual patient's health.

In response to this emergent concept from the CCO, the AACE proposed an "Advanced Framework for a New Diagnosis of Obesity." This document features an anthropometric component that is the measure of adiposity (i.e., BMI) and a clinical component that describes the presence and severity of weight-related complications (15 [EL 4; NE]). Given the multiple meanings and perspectives associated with the term "obesity" in our society, there was also discussion that the medical diagnostic term for obesity should be "adiposity-based chronic disease" (ABCD).

The paradigm for obesity care proposed by the National Heart, Lung, and Blood Institute (16 [EL 4; NE]), and FDA-sanctioned prescribing information for the use of obesity medications (17 [EL 4; NE]), largely bases indications for therapeutic modalities on patient BMI (a BMI-centric approach). As part of the AACE Clinical Practice Guidelines (CPG) for Developing a Diabetes Mellitus Comprehensive Care Plan (18 [EL 4; NE]), an algorithm for obesity management was proposed wherein the presence and severity of weight-related complications constitute the primary determinants for treatment modality selection and weight-loss therapy intensity (19 [EL 4; NE]). In this new complications-centric approach, the primary therapeutic endpoint is improvement in adiposity-related complications, not a preset decline in body weight (8 [EL 4; NE]). Thus, the main endpoint of therapy is to measurably improve patient health and quality of life. Other organizations such as the American Heart Association, the American College of Cardiology, The Obesity Society (20 [EL 4; NE]), the Obesity Medical Association (21 [EL 4; NE]), and the Endocrine Society (22 [EL 4; NE]) have also developed obesity care guidelines and algorithms incorporating aspects of a complications-centric approach.

This AACE/ACE evidence-based clinical practice guideline (CPG) is structured around a series of a priori, relevant, intuitive, and pragmatic questions that address key and germane aspects of obesity care: screening, diagnosis, clinical evaluation, treatment options, therapy selection, and treatment goals. In aggregate, these questions evaluate obesity as a chronic disease and consequently outline a comprehensive care plan to assist the clinician in caring for patients with obesity. This approach may differ from other CPGs. Specifically, in other CPGs: the scientific evidence is first examined and then questions are formulated only when strong scientific evidence exists (e.g., randomized controlled trials [RCTs]), and/or only certain aspects of management (e.g., pharmacotherapy) are chosen for a focused (but not comprehensive) CPG.

Neither of these approaches addresses the totality, multiplicity, or complexity of issues required to provide effective, comprehensive obesity management applicable to real-world patient care. Moreover, the nuances of obesity care in an obesogenic-built environment, which at times have an overwhelming socioeconomic contextualization, require diligent analysis of the full weight of extant evidence.

To this end, these CPGs address multiple aspects of patient care relevant to any individual patient encounter, assess the available evidence base, and provide specific recommendations. The strength of each recommendation is commensurate with the strength-of-evidence. In this way, these CPGs marshal the best existing evidence to address the key questions and decisions facing clinicians in the real-world practical care of patients with obesity. This methodology is transparent and outlined in multiple AACE/ACE processes for producing guideline protocols (23 [EL 4; NE]; 24 [EL 4; NE]; 25 [EL 4; NE]). Implementing these CPGs should facilitate high-quality care of patients with obesity and provide a rational, scientific approach to management that optimizes outcomes and safety. Thus, these CPGs will be useful for all health care professionals involved in the care of patients with, or at risk for, obesity and adiposity-related complications.

II. MANDATE

In 2015, the AACE Executive Committee and the AACE Board of Directors mandated the development of CPGs for obesity to provide a set of evidence-based recommendations for the comprehensive care of patients with overweight or obesity, including an end goal of optimizing patient outcomes. The selection of the chair, primary writers, and reviewers was made by the President of the AACE, in consultation with the AACE Executive Committee. The charge was to develop evidence-based CPGs in strict adherence with the process established in the 2004 AACE Protocol for Standardized Production of Clinical Practice Guidelines (23 [EL 4; NE]) and the 2010 and 2014 updates (24 [EL 4; NE]; 25 [EL 4; NE]). The development of these obesity CPGs complements other AACE/ACE activities in obesity medicine, namely the new complications-centric framework for the diagnosis and management of overweight and obesity (15 [EL 4; NE]), bariatric surgery CPGs (11 [EL 4; NE]), healthy eating CPGs (26 [EL 4; NE]), diabetes comprehensive care CPGs (18 [EL 4; NE]; 19 [EL 4; NE]), obesity and nutrition position statements (12 [EL 4; NE]), and other educational programs and white papers (14 [EL 4; NE]).

III. METHODS

This AACE/ACE CPG on Obesity is developed according to established AACE/ACE methodology for guidelines development (23 [EL 4; NE]; 24 [EL 4; NE]; 25 [EL 4; NE]) and is characterized by the following salient attributes:

1. Appointment of credentialed experts who have disclosed all multiplicities of interests, vetted by the AACE Publications Committee;
2. Incorporation of middle-range literature searching with: (*1*) an emphasis on strong evidence and the identification of all relevant RCTs and meta-analyses; (*2*) inclusion of relevant cohort studies, nested case-control studies, and case series; and (*3*) inclusion of more general reviews/opinions, mechanistic studies, and illustrative case reports when considered appropriate;
3. An orientation on questions that are directly relevant to patient care;
4. Use of a technical a priori methodology, which maps strength-of-evidence to recommendation grades and stipulates subjective factors established in the AACE/ACE Protocol for Standardized Production of Clinical Practice Guidelines (23 [EL 4; NE]; 24 [EL 4; NE]; 25 [EL 4; NE]); and
5. Employment of a multilevel review process and high level of diligence.

Task Force Assignments

The logistics and process for task force assignments adhered to the AACE Protocol for Standardized Production of Clinical Practice Guidelines (23 [EL 4; NE]; 24 [EL 4; NE]; 25 [EL 4; NE]). The selection of the chair, primary writing team, and reviewers was based on the expert credentials of these individuals in obesity medicine. All appointees are AACE members and are experts in obesity care. All multiplicities of interests for each individual participant are clearly disclosed and delineated in this document. No appointee is employed by industry, and there was no involvement of industry in the development of these CPGs.

Question/Problem Structure for Guidelines Development

The goal was to develop CPGs that are comprehensive and relevant to clinicians. Therefore, the questions for evidence-based review reflect the multiple aspects of management that must be addressed by clinicians as they evaluate, screen, and diagnose patients with obesity; establish a clinical database; make treatment decisions; and assess therapeutic outcomes. The primary writing team drafted questions for evidence-based review and, following multiple and interactive discussions, arrived at a consensus for the final question list addressed in these CPGs.

Evidence-Based Review

Once the questions were finalized, the next step was to conduct a systematic electronic search of the literature pertinent to each question. The task force chair assigned each question to a member of the task force writing team, and the team members executed a systematic electronic search of the published literature from relevant bibliographic databases for each clinical question. The objective was to identify all publications necessary to assign the true strength-of-evidence, given the totality of evidence available in the literature. The mandate was to include all studies that materially impact the strength of the evidence level. Thus, all RCTs and meta-analyses were to be identified (whether they provided positive or negative data with respect to each question) because these studies would predominate in scoring the strength-of-evidence. The writing team members also identified relevant nonrandomized interventions, cohort studies, and case-control trials, as well as cross-sectional studies, surveillance studies, epidemiologic data, case series, and pertinent studies of disease mechanisms. In the absence of RCTs, recommendations would necessarily rely on lower levels of evidence, which would in turn affect the strength of the ensuing recommendations.

For the systematic review of all clinical trials and meta-analyses, each task force member conducted a search of the Cochrane Library (which includes all references in the Cochrane Central Register of Controlled Trials) (27 [EL 4; NE]). A search was conducted without date limits for all trials, using "obesity" and/or "weight loss" as key search terms together with term(s) relevant to the question being addressed. In addition, all relevant trials and meta-analyses were identified in a search of the PubMed database. The task force members culled references for studies that were duplicates, not relevant, or devoid of original data or analyses that would not contribute to scientific substantiation or alter the evidence level and recommendation strength. In addition to these search strategies, the task force members used other databases, employed literature reviews, and included mechanistic data when this contributed to the discussion of the evidence.

References numerically cited in the text were then scored for strength-of-evidence using definitions provided in Table 1 (24 [EL 4; NE]). There are 4 intuitive levels of evidence based on study design and data quality: 1 = strong, 2 = intermediate, 3 = weak, and 4 = no clinical evidence. Where appropriate, comments were appended to the evidence level regarding judgments or factors that could influence the subsequent grading process (Table 2) (24 [EL 4; NE]). Reference citations in the document text include the reference number, the evidence level numerical descriptor (e.g., evidence level [EL] 1, 2, 3, or 4), and a semantic descriptor abbreviation.

Once the evidence base was systematically established and reviewed, task force members summarily described the evidence, including all references that could materially

Table 1
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step I: Evidence Rating (24 [EL 4; NE])

Numeric descriptor (evidence level)[a]	Semantic descriptor (reference methodology)
1	Meta-analysis of randomized controlled trials (MRCT)
1	Randomized controlled trial (RCT)
2	Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT)
2	Nonrandomized controlled trial (NRCT)
2	Prospective cohort study (PCS)
2	Retrospective case-control study (RCCS)
3	Cross-sectional study (CSS)
3	Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database) (SS)
3	Consecutive case series (CCS)
3	Single case reports (SCR)
4	No evidence (theory, opinion, consensus, review, or preclinical study) (NE)

[a] 1, strong evidence; 2, intermediate evidence; 3, weak evidence; and 4, no evidence.

affect the strength-of-evidence assessment and CPG recommendations. Task force members also formulated one or more recommendations based on the evidence in response to each question. Clinical questions are labeled "Q," and recommendations are labeled "R."

Formulation of Recommendations

The task force discussed and critiqued each of the evidence reviews and recommendations, which were then revised for consensus approval. The evidence ratings were used to grade the scientific strength of the recommendations. Recommendations (numerically labeled "R1, R2," etc.) are based on strength-of-evidence, indexed to the BEL, which corresponds to the strongest and most conclusive evidence (when taking the evidence level of all the references in each of the evidence reviews into consideration; Table 1). The BEL is accompanied by a recommendation Grade (A, B, C, or D) as shown in Figure 1 and Table 1. This recommendation grade maps to the BEL and can be adjusted upward or downward by 1 level as shown in Table 3 based on judgments and factors listed in Table 4. As prespecified in Table 4, comments may be appended to the recommendation grade and BEL regarding any relevant factors that may have influenced the grading process. Final recommendation grades may be interpreted as being based on strong (Grade A), intermediate (Grade B), weak (Grade C), or no (Grade D) scientific substantiation. The evidence base supporting each recommendation, with accompanying tables, figures, algorithm, and care model, will be provided in a future Appendix.

This transparent process leads to a final recommendation and grade that incorporates complex expert integration of scientific data (and, to a degree, factors reflecting real-world practice) to establish actionable, evidence-based guidelines for optimal clinical decision-making and patient care practices. Again, this document represents only

Table 2
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step II: Evidence Analysis and Subjective Factors (24 [EL 4; NE])

Study design	Data analysis	Interpretation of results
Premise correctness	Intent-to-treat	Generalizability
Allocation concealment (randomization)	Appropriate statistics	Logical
Selection bias		Incompleteness
Appropriate blinding		Validity
Using surrogate endpoints (especially in "first-in-its-class" intervention)		
Sample size (beta error)		
Null hypothesis versus Bayesian statistics		

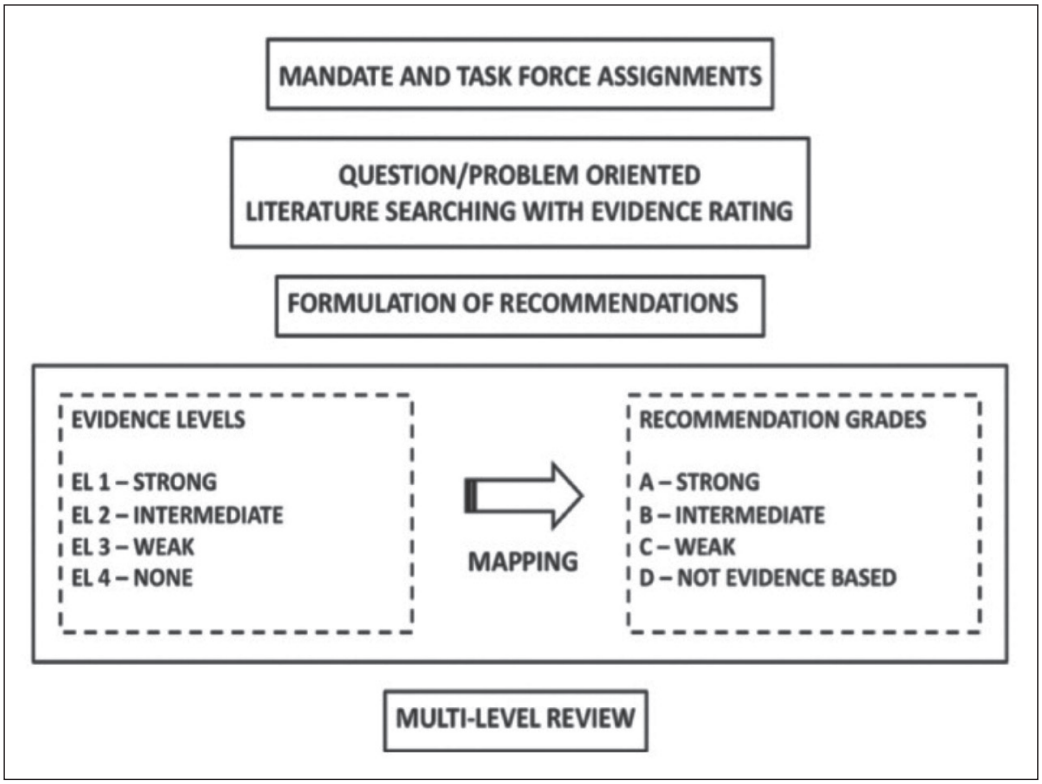

Fig. 1. 2010 American Association of Clinical Endocrinologists (AACE) Clinical Practice Guideline (CPG) methodology (24 [EL 4; NE]). Current AACE CPGs have a problem-oriented focus that results in a shortened production timeline, middle-range literature searching, emphasis on patient-oriented evidence that matters, greater transparency of intuitive evidence rating and qualifications, incorporation of subjective factors into evidence-recommendation mapping, cascades of alternative approaches, and an expedited multilevel review mechanism.

guidelines for clinical practice. Individual patient circumstances and presentations obviously differ, and ultimately, clinical management choices should be based on individual patients ' best interests, including patient input and reasonable clinical judgment by treating clinicians.

Prepublication Review and Critique

These CPGs were first drafted and agreed upon by the task force writing team and then critically reviewed by the AACE Obesity Scientific Committee, the special external reviewer, the AACE Publications Committee, the AACE Board of Directors, and the AACE Executive Committee. Where appropriate, revisions were incorporated at each step of this review process.

Summary

These CPGs include an Executive Summary consisting of 123 clinical practice recommendations with 160 specific statements, organized in response to 9 broad questions covering the spectrum of obesity management. The objectives of these CPGs are to provide an evidence-based resource addressing rational approaches to the care of patients with obesity and an educational resource for the development of a comprehensive care plan for clinical endocrinologists and other health care professionals who care for patients with obesity. To achieve these goals, these recommendations provide concise, accurate answers to each question, and a forthcoming detailed and extensively referenced Appendix organized to provide supporting evidence for each recommendation. This format does not attempt to present an encyclopedic citation of all pertinent primary references; however, sufficient key references are provided to designate the BEL for each recommendation. Although many studies rated at the highest evidence level are cited (i.e., RCTs and meta-analyses of these trials [EL 1]), in the interest of conciseness, derivative EL 4 review publications that include many primary evidence citations (EL 1, EL 2, and EL 3) are also included. In addition, rigorously reviewed guidelines by other organizations have been adopted for specific issues, such as physical activity guidelines by the American Academy of Sports Medicine (28 [EL 4; NE]), physical activity guidelines by the American Heart Association and the American College of Cardiology (29 [EL 4; NE]), healthy eating guidelines by the AACE and The Obesity Society (30 [EL 4; NE]), and perioperative bariatric surgery guidelines by the AACE, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery (11 [EL 4; NE]). Thus, these CPGs are

Table 3
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step III: Grading of Recommendations; How Different Evidence Levels Can Be Mapped to the Same Recommendation Grade[a] (24 [EL 4; NE])

Best evidence level	Subjective factor impact	Two-thirds consensus	Mapping	Recommendation grade
1	None	Yes	Direct	A
2	Positive	Yes	Adjust up	A
2	None	Yes	Direct	B
1	Negative	Yes	Adjust down	B
3	Positive	Yes	Adjust up	B
3	None	Yes	Direct	C
2	Negative	Yes	Adjust down	C
4	Positive	Yes	Adjust up	C
4	None	Yes	Direct	D
3	Negative	Yes	Adjust down	D
1, 2, 3, 4	NA	No	Adjust down	D

[a] Starting with the left column, best evidence levels (BELs), subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact ("none"), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up ("positive" impact) or down ("negative" impact). If a two-thirds consensus cannot be reached, then the recommendation Grade is D. NA/not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation Grade D).

not intended to serve as an obesity textbook, but rather to complement existing texts, other CPGs, and previously published AACE documents.

IV. EXECUTIVE SUMMARY

A. QUESTIONS

The evidence-based recommendations for the CPGs were organized in response to the following questions, which provided the structure for evidence review. Readers are referred to the future publication of the Appendix for detailed evidence reviews and references that support the recommendations and evidence level ratings for each reference as pertains to each question and associated recommendations. In the 123 numbered recommendations, there are 160 individual statements, of which 85 (53.1%) are Grade A, 48 (30.0%) are Grade B, 11 (6.9%) are Grade C, and 16 (10.0%) are Grade D. There are 133 (83.1%) statements that are Grade A or B indicating a strong or intermediate level of scientific substantiation. There are 34 (23.6%) evidence-based recommendation grades (Grades A-C = 144) that are adjusted based on subjective factors. Of these, 19 (55.9%) were due to clinical relevance and 15 (44.1%) were due to evidence gaps (Table 4).

Post-hoc Question: By inductive evaluation of all evidence-based recommendations, what are the core recommendations for medical care of patients with obesity?

Obesity and 3 Phases of Chronic Disease Prevention and Treatment

- ***Q1. Do the 3 phases of chronic disease prevention and treatment (i.e., primary, secondary, and tertiary) apply to the disease of obesity?***

The Anthropometric Component of the Diagnosis of Obesity

- ***Q2. How should the degree of adiposity be measured in the clinical setting?***
  - *Q2.1. What is the best way to optimally screen or aggressively case-find for overweight and obesity?*

- *Q2.2. What are the best anthropomorphic criteria for defining excess adiposity in the diagnosis of overweight and obesity in the clinical setting?*
- *Q2.3. Does waist circumference provide information in addition to BMI to indicate adiposity risk?*
- *Q2.4. Do BMI and waist circumference accurately capture adiposity risk at all levels of BMI, ethnicities, gender, and age?*

The Clinical Component of the Diagnosis of Obesity

- ***Q3. What are the weight-related complications that are either caused or exacerbated by excess adiposity?***
  - *Q3.1. Diabetes risk, metabolic syndrome, and prediabetes (IFG, IGT)*
  - *Q3.2. Type 2 diabetes*
  - *Q3.3. Dyslipidemia*
  - *Q3.4. Hypertension*
  - *Q3.5. Cardiovascular disease and cardiovascular disease mortality*
  - *Q3.6. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis*
  - *Q3.7. Polycystic ovary syndrome (PCOS)*
  - *Q3.8. Female infertility*
  - *Q3.9. Male hypogonadism*
  - *Q3.10. Obstructive sleep apnea*
  - *Q3.11. Asthma/reactive airway disease*
  - *Q3.12. Osteoarthritis*
  - *Q3.13. Urinary stress incontinence*
  - *Q3.14. Gastroesophageal reflux disease (GERD)*
  - *Q3.15. Depression*

- ***Q4. Does BMI or other measures of adiposity convey full information regarding the impact of excess body weight on the patient's health?***

Therapeutic Benefits of Weight Loss in Patients with Overweight or Obesity

- ***Q5. Do patients with excess adiposity and related complications benefit more from weight loss than patients without complications, and, if so, how much weight loss would be required?***
  - *Q5.1. Is weight loss effective to treat diabetes risk (i.e., prediabetes, metabolic syndrome) and prevent progression to type 2 diabetes? How much weight loss would be required?*
  - *Q5.2. Is weight loss effective to treat to type 2 diabetes? How much weight loss would be required?*
  - *Q5.3. Is weight loss effective to treat dyslipidemia? How much weight loss would be required?*
  - *Q5.4. Is weight loss effective to treat hypertension? How much weight loss would be required?*
  - *Q5.5. Is weight loss effective to treat or prevent cardiovascular disease? How much weight loss would be required?*
    - *Q.5.5.1. Does weight loss prevent cardiovascular disease events or* mortality?
    - Q.5.5.2. Does weight loss prevent cardiovascular disease events or mortality in diabetes?
    - *Q.5.5.3. Does weight loss improve congestive heart failure?*
  - *Q5.6. Is weight loss effective to treat nonalcoholic fatty liver disease and nonalcoholic steatohepatitis? How much weight loss would be required?*
  - *Q5.7. Is weight loss effective to treat PCOS? How much weight loss would be required?*
  - *Q5.8. Is weight loss effective to treat infertility in women? How much weight loss would be required?*
  - *Q5.9. Is weight loss effective to treat male hypogonadism? How much weight loss would be required?*
  - *Q5.10. Is weight loss effective to treat obstructive sleep apnea? How much weight loss would be required?*
  - *Q5.11. Is weight loss effective to treat asthma/reactive airway disease? How much weight loss would be required?*
  - *Q5.12. Is weight loss effective to treat osteoarthritis? How much weight loss would be required?*
  - *Q5.13. Is weight loss effective to treat urinary stress incontinence? How much weight loss would be required?*

Table 4
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step IV: Examples of Qualifiers (24 [EL 4; NE])

Cost-effectiveness
Risk-benefit analysis
Evidence gaps
Alternative physician preferences (dissenting opinions)
Alternative recommendations ("cascades")
Resource availability
Cultural factors
Relevance (patient-oriented evidence that matters)

- *Q5.14. Is weight loss effective to treat* gastroesophageal reflux disease (GERD)? How much weight loss would be required?
- *Q5.15. Is weight loss effective to improve symptoms of depression? How much weight loss would be required?*

Lifestyle/Behavioral Therapy for Overweight and Obesity

- ***Q6. Is lifestyle/behavioral therapy effective to treat overweight and obesity, and what components of lifestyle therapy are associated with efficacy?***
  - *Q6.1. Meal plan and macronutrient composition*
  - *Q6.2. Physical activity*
  - *Q6.3. Behavior interventions*

Pharmacotherapy for Overweight and Obesity

- ***Q7. Is pharmacotherapy effective to treat overweight and obesity?***
  - *Q7.1. Should pharmacotherapy be used as an adjunct to lifestyle therapy?*
  - *Q7.2. Does the addition of pharmacotherapy produce greater weight loss and weight-loss maintenance compared with lifestyle therapy alone?*
  - *Q7.3. Should pharmacotherapy only be used in the short term to help achieve weight loss or should it be used chronically in the treatment of obesity?*
  - *Q7.4. Are there differences in weight-loss drug efficacy and safety?*
  - *Q7.5. Should combinations of weight-loss medications be used in a manner that is not approved by the U.S. Food and Drug Administration?*

Individualization of Pharmacotherapy in the Treatment of Obesity

- ***Q8. Are there hierarchies of drug preferences in patients with the following disorders or characteristics?***
  - *Q8.1. Chronic kidney disease*
  - *Q8.2. Nephrolithiasis*
  - *Q8.3. Hepatic impairment*
  - *Q8.4. Hypertension*
  - *Q8.5. Cardiovascular disease and arrhythmia*
  - *Q8.6. Depression with or without selective serotonin reuptake inhibitors*
  - *Q8.7. Anxiety*
  - *Q8.8. Psychotic disorders with or without medications (lithium, atypical antipsychotics, monoamine oxidase inhibitors)*
  - *Q8.9. Eating disorders including binge eating disorder*
  - *Q8.10. Glaucoma*
  - *Q8.11. Seizure disorder*
  - *Q8.12. Pancreatitis*
  - *Q8.13. Opioid use*
  - *Q8.14. Women of reproductive potential*
  - *Q8.15. The elderly, age ≥65 years*
  - *Q8.16. Addiction/alcoholism*
  - *Q8.17. Post-bariatric surgery*

Bariatric Surgery

- ***Q9. Is bariatric surgery effective to treat obesity?***
  - *Q9.1. Is bariatric surgery effective to treat obesity and weight-related complications?*
  - *Q9.2. When should bariatric surgery be used to treat obesity and weight-related complications?*

B. RECOMMENDATIONS

Post-hoc Question: By inductive evaluation of all evidence-based recommendations, what are the core recommendations for medical care of patients with obesity?

- **R1.A.** The principal outcome and therapeutic target in the treatment of obesity should be to improve the health of the patient by preventing or treating weight-related complications using weight loss, not the loss of body weight per se **(Grade D)**.
- **R1.B.** The evaluation of patients for risk and existing burden of weight-related complications is a critical component of care and should be considered in clinical decisions and the therapeutic plan for weight-loss therapy **(Grade D)**.

Obesity and 3 Phases of Chronic Disease Prevention and Treatment

- ***Q1. Do the 3 phases of chronic disease prevention and treatment (i.e., primary, secondary, and tertiary) apply to the disease of obesity? (Table 5)***
  - **R2.** The modality and intensity of obesity interventions should be based on the primary, secondary, and tertiary phases of disease prevention; this 3-phase paradigm for chronic disease aligns with the pathophysiology and natural history of obesity and provides a rational framework for appropriate treatment at each phase of prevention **(Grade C; BEL 4, upgraded due to high relevance to natural history of the disease)**.

The Anthropometric Component of the Diagnosis of Obesity

- ***Q2. How should the degree of adiposity be measured in the clinical setting? (Fig. 2)***
  - *Q2.1. What is the best way to optimally screen or aggressively case-find for overweight and obesity?*
    - **R3.** All adults should be screened annually using a BMI measurement; in most populations a cutoff point of ≥25 kg/m^2 should be used to initiate further evaluation of overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.

Table 5. Definitions, Goals, and Methods for Phases of Prevention in Chronic Disease: General Practices in Chronic Disease and Specific Practices in Obesity

Phase of Intervention	Definition and Goals	Methods of Prevention
Primary Prevention	**GENERAL:** • Prevent a disease from occurring	**GENERAL:** • Eliminate risk factors, remove causes, or increase resistance to disease
	OBESITY: • Prevent the development of overweight and obesity	**OBESITY:** • Educate the public • Built environment • Promote healthy eating and regular physical activity
Secondary Prevention	**GENERAL:** • Halt the progression of disease from its early stage prior to complications to a more severe stage • Arrest the disease process to prevent complications or sequelae	**GENERAL:** • Use a screening test and follow-up diagnosis, followed by treatment
	OBESITY: • Prevent future weight gain and the development of weight-related complications in patients with overweight or obesity	**OBESITY:** • Screen using BMI • Diagnose using BMI and evaluation for complications • Treat with lifestyle/behavioral intervention ± weight-loss medications
Tertiary Prevention	**GENERAL:** • Use clinical activities that reduce complications and prevent further deterioration	**GENERAL:** • Use treatment strategies that limit adverse consequences of a disease on health
	OBESITY: • Treat with weight-loss therapy to eliminate or ameliorate weight-related complications and prevent disease progression	**OBESITY:** • Treat with lifestyle/behavioral intervention plus weight-loss medications • Consider bariatric surgery

Abbreviation: BMI = body mass index.

- *Q2.2. What are the best anthropomorphic criteria for defining excess adiposity in the diagnosis of overweight and obesity in the clinical setting? (Table 6)*
  - **R4.** BMI should be used to confirm an excessive degree of adiposity and to classify individuals as having overweight (BMI 25 to 29.9 kg/m^2) or obesity (BMI ≥30 kg/m^2), after taking into account age, gender, ethnicity, fluid status, and muscularity; therefore, clinical evaluation and judgment must be used when BMI is employed as the anthropometric indicator of excess adiposity, particularly in athletes and those with sarcopenia **(Grade A; BEL 2, upgraded due to high relevance)**.
  - **R5.** Other measurements of adiposity (e.g., bioelectric impedance, air/water displacement plethysmography, or dual-energy X-ray absorptiometry [DEXA]) may be considered at the clinician's discretion if BMI and physical examination results are equivocal or require further evaluation **(Grade C, BEL 2, downgraded due to evidence gaps)**. However, the clinical utility of these measures is limited by availability, cost, and lack of outcomes data for validated cutoff points **(Grade B; BEL 2)**.
- *Q2.3. Does waist circumference provide information in addition to BMI to indicate adiposity risk? (Table 7)*
  - **R6.** When evaluating patients for adiposity-related disease risk, waist circumference should be measured in all patients with BMI <35 kg/m^2 **(Grade A; BEL 2, upgraded due to high relevance)**. In many populations, a waist circumference cutoff point of ≥94 cm in men and ≥80 cm in women should be considered at risk and consistent with abdominal obesity; in the United States (U.S.) and Canada, cutoff points that can be used to indicate increased risk are ≥102 cm for men and ≥88 cm for women **(Grade A; BEL 2, upgraded due to high relevance)**.
- *Q2.4. Do BMI and waist circumference accurately capture adiposity risk at all levels of BMI, ethnicity, gender, and age?*
  - **R7.** A BMI cutoff point value of ≥23 kg/m^2 should be used in the screening and confirmation of excess adiposity in South Asian, Southeast Asian, and East Asian adults **(Grade B; BEL 2)**.
  - **R8.** Region- and ethnic-specific cutoff point values for waist circumference should be used as measures of abdominal adiposity and disease risk;

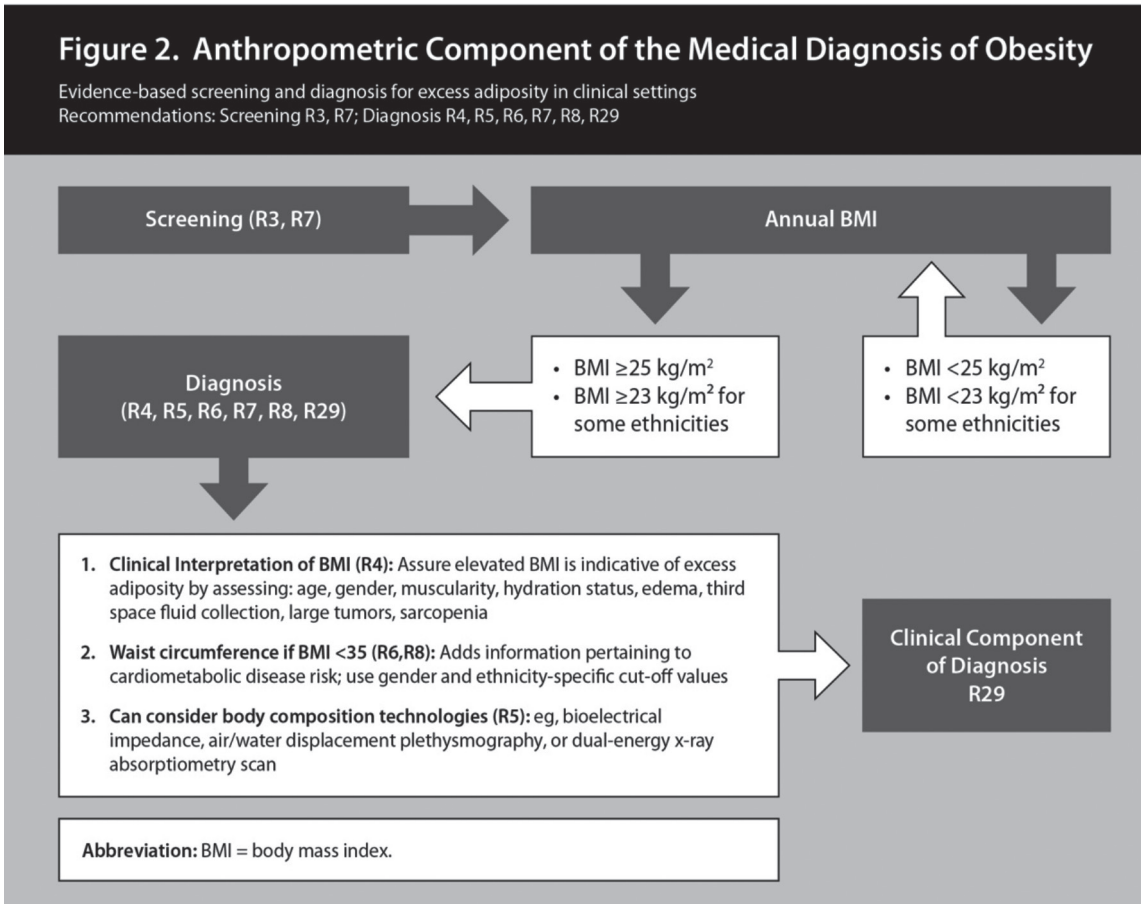

Fig. 2. The Clinical Component of the Diagnosis of Obesity.

in South Asian, Southeast Asian, and East Asian adults, men with values ≥85 cm and women ≥74 to 80 cm should be considered at risk and consistent with abdominal obesity **(Grade B; BEL 2)**.

The Clinical Component of the Diagnosis of Obesity

- ***Q3. What are the weight-related complications that are either caused or exacerbated by excess adiposity? (Fig. 3)***
  - *Q3.1. Diabetes risk, metabolic syndrome, and prediabetes (IFG, IGT)*
    - **R9.** Patients with overweight or obesity and patients experiencing progressive weight gain should be screened for prediabetes and type 2 diabetes mellitus (T2DM) and evaluated for metabolic syndrome by assessing waist circumference, fasting glucose, A1C, blood pressure, and lipid panel, including triglycerides and HDL-c **(Grade A; BEL 2, upgraded due to high clinical relevance)**.
    - **R10.** Due to variable risk for future diabetes, patients with overweight or obesity should be evaluated for risk of T2DM, which can be estimated or stratified using indices or staging systems that employ clinical data, glucose tolerance testing, and/or metabolic syndrome traits **(Grade B; BEL 2)**.
  - *Q3.2. Type 2 diabetes*
    - **R11.** Patients with T2DM should be evaluated for the presence of overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.
  - *Q3.3. Dyslipidemia*
    - **R12.** All patients with overweight or obesity and individuals experiencing progressive weight gain should be screened for dyslipidemia with a lipid panel that includes triglycerides, HDL-c, calculated LDL-c, total cholesterol, and non-HDL cholesterol; all patients with dyslipidemia should be evaluated for the presence of overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.
  - *Q3.4 Hypertension*
    - **R13.** Blood pressure should be measured in all patients with overweight or obesity as a screen for the presence of hypertension or prehypertension;

all patients with hypertension should be evaluated for the presence of overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.

- *Q3.5. Cardiovascular disease and cardiovascular disease mortality*
  - **R14.** Risk factors for cardiovascular disease should be assessed in patients with overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.
  - **R15.** Patients with overweight or obesity should be screened for active cardiovascular disease by history, physical examination, and with additional testing or expert referral based on cardiovascular disease risk status **(Grade A; BEL 2, upgraded due to high relevance)**.

- *Q3.6. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis*
  - **R16.** Screening for nonalcoholic fatty liver disease should be performed in all patients with overweight or obesity, T2DM, or metabolic syndrome with liver function testing, followed by ultrasound or other imaging modality if transaminases are elevated; all patients with nonalcoholic fatty liver disease should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

- *Q3.7. Polycystic ovary syndrome (PCOS)*
  - **R17.** Premenopausal female patients with overweight or obesity and/or metabolic syndrome should be screened for PCOS by history and physical examination; all patients with PCOS should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

- *Q3.8. Female infertility*
  - **R18.** Women with overweight or obesity should be counseled when appropriate that they are at increased risk for infertility and, if seeking assisted reproduction, should be informed of lower success rates of these procedures regarding conception and the ability to carry the pregnancy to live birth **(Grade B; BEL 2)**. All female patients with infertility should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

- *Q3.9. Male hypogonadism*
  - **R19.** All men who have an increased waist circumference or who have obesity should be assessed for hypogonadism by history and physical examination and be tested for testosterone deficiency if indicated; all male patients with hypogonadism should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

Table 6. Classification of Overweight and Obesity by BMI and Waist Circumference (31 [EL 4; NE])

Classification	BMI		Waist	
	BMI (kg/m^2)	Comorbidity Risk	Waist Circumference and Comorbidity Risk	
			Men ≤40 in (102 cm) Women ≤35 in (88 cm)	Men >40 in (102 cm) Women >35 in (88 cm)
Underweight	<18.5	Low but other problems		
Normal weight	18.5–24.9	Average		
Overweight	25–29.9	Increased	Increased	High
Obese class I	30–34.9	Moderate	High	Very high
Obese class II	35–39.9	Severe	Very high	Very high
Obese class III	≥40	Very severe	Extremely high	Extremely high

Abbreviations: BMI = body mass index; in = inches.

- **R20.** All male patients with T2DM should be evaluated to exclude testosterone deficiency **(Grade B; BEL 2)**.

- *Q3.10. Obstructive sleep apnea*
  - **R21.** All patients with overweight or obesity should be evaluated for obstructive sleep apnea during medical history and physical examination; this is based on the strong association between these disorders **(Grade B; BEL 2)**. Polysomnography and other sleep studies, at home or in a sleep lab, should be considered for patients at high risk for sleep apnea based on clinical presentation, severity of excess adiposity, and symptomatology **(Grade D)**. All patients with obstructive sleep apnea should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

- *Q.3.11. Asthma/reactive airway disease*
  - **R22.** All patients with overweight or obesity should be evaluated for asthma and reactive airway disease based on the strong association between these disorders **(Grade B; BEL 2)**. Medical history, symptomatology, physical examination, and spirometry and other pulmonary function tests should be considered for patients at high risk for asthma and reactive airway disease **(Grade D)**. All patients with asthma should be evaluated for the presence of overweight or obesity **(Grade D)**.

Table 7. Waist Circumference Thresholds for Abdominal Obesity (32 [EL4; NE])

POPULATION	ORGANIZATION	MEN	WOMEN
Europid	IDF	≥94 cm ≥37 inches	≥80 cm ≥31 inches
Caucasian	WHO	≥94 cm (⬆ risk) ≥37 inches ≥102 cm (⬆⬆ risk) ≥40 inches	≥80 cm (⬆ risk) ≥31 inches ≥88 cm (⬆⬆ risk) ≥35 inches
United States	AHA/NHLBI (ATPIII)	≥102 cm ≥40 inches	≥88 cm ≥35 inches
Canada	Health Canada	≥102 cm ≥40 inches	≥88 cm ≥35 inches
European	European Cardiovasc. Societies	≥102 cm ≥40 inches	≥88 cm ≥35 inches
Asian (including Japanese)	IDF	≥90 cm ≥35 inches	≥80 cm ≥31 inches
Asian	WHO	≥90 cm ≥35 inches	≥80 cm ≥31 inches
Japanese	Japanese Obesity Society	≥85 cm ≥33 inches	≥90 cm ≥35 inches
China	Cooperative Task Force	≥85 cm ≥33 inches	≥80 cm ≥31 inches
Middle East, Mediterranean	IDF	≥94 cm ≥37 inches	≥80 cm ≥31 inches
Sub-Saharan African	IDF	≥94 cm ≥37 inches	≥80 cm ≥31 inches
Ethnic Central and South American	IDF	≥90 cm ≥35 inches	≥80 cm ≥31 inches

Abbreviations: AHA = American Heart Association; ATPIII = Adult Treatment Panel III; IDF = International Diabetes Federation; WHO = World Health Organization.

Figure 3. Clinical Component of the Medical Diagnosis of Obesity

Candidates for weight-loss therapy can present with either excess adiposity (ie, the anthropometric component) or weight-related complications (ie, the clinical component)

Patients Present With Overweight or Obesity	Candidates for Weight-Loss Therapy	Patients Present With Weight-Related Disease or Complications	
Patients with BMI ≥25 kg/m^2 or ≥23 kg/m^2 in certain ethnicities and excess adiposity	Evaluate for weight-related complications: R9–R29 →	R9, R10	Prediabetes
		R9, R10	Metabolic syndrome
		R11	Type 2 diabetes
		R12	Dyslipidemia
		R13	Hypertension
		R14, R15	Cardiovascular disease
		R16	Nonalcoholic fatty liver disease
		R17	Polycystic ovary syndrome
		R18	Female infertility
	← Evaluate for overweight or obesity: R9–R29	R19, R20	Male hypogonadism
		R21	Obstructive sleep apnea
		R22	Asthma/reactive airway disease
		R23	Osteoarthritis
		R24	Urinary stress incontinence
		R25, R26	Gastroesophageal reflux disease
		R28	Depression

- *Q.3.12. Osteoarthritis*
  - **R23.** All patients with overweight or obesity should be screened by symptom assessment and physical examination for OA of the knee and other weight-bearing joints **(Grade B; BEL 2)**. All patients with OA should be evaluated for the presence of overweight or obesity **(Grade D)**.

- *Q.3.13. Urinary stress incontinence*
  - **R24.** All female patients with overweight or obesity should be screened for urinary incontinence by assessing symptomatology, based on the strong association between these disorders; all patients with urinary stress incontinence should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

- *Q.3.14. Gastroesophageal reflux disease (GERD)*
  - **R25.** Patients with overweight or obesity or who have increased waist circumferences should be evaluated for symptoms of GERD **(Grade B; BEL 2)**; all patients with GERD should be evaluated for the presence of overweight or obesity **(Grade C; BEL 3)**.
  - **R26.** Patients with obesity and GERD symptoms should be evaluated by endoscopy if medical treatment fails to control symptoms (Grade B; BEL 2).
  - **R27.** Endoscopy should be considered in patients with obesity and GERD symptoms prior to bariatric surgery **(Grade B; BEL 2)**.

- *Q.3.15. Depression*
  - **R28.** Patients with overweight or obesity should be screened for depression; all patients with depression should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

- ***Q4. Do BMI or other measures of adiposity convey full information regarding the impact of excess body weight* on the patient's health?**
  - **R29.** All patients with overweight or obesity should be clinically evaluated for weight-related complications because BMI alone is not sufficient to indicate the impact of excess adiposity on health status; therefore, the diagnostic evaluation of patients with obesity should include an anthropometric assessment of adiposity and a clinical assessment

of weight-related complications **(Grade A; BEL 2, upgraded due to high relevance)**. Patients with overweight or obesity should be reevaluated at intervals to monitor for any changes in adiposity and adiposity-related complications over time **(Grade A; BEL 2, upgraded due to high relevance)**.

Therapeutic Benefits of Weight Loss in Patients with Overweight or Obesity

- ***Q5. Do patients with excess adiposity and related complications benefit more from weight loss than patients without complications? Can weight loss be used to treat weight-related complications, and, if so, how much weight loss would be required? (Table 8)***

Note: Specific medications are mentioned or recommended below for use in different clinical settings based on available evidence for efficacy and safety. Medications may not be explicitly recommended if there are no data available for use in the specified clinical setting, even though weight loss associated with these medications may produce clinical benefits.

- *Q5.1. Is weight loss effective to treat diabetes risk (i.e., prediabetes, metabolic syndrome) and prevent progression to type 2 diabetes? How much weight loss would be required?*
  - **R30.** Patients with overweight or obesity and with either metabolic syndrome or prediabetes, or patients identified to be at high risk of T2DM based on validated risk-staging paradigms, should be treated with lifestyle therapy that includes a reduced-calorie healthy meal plan and a physical activity program incorporating both aerobic and resistance exercise to prevent progression to diabetes **(Grade A; BEL 1)**. The weight-loss goal should be 10% **(Grade B; BEL 2)**.
  - **R31.** Medication-assisted weight loss employing phentermine/topiramate ER, liraglutide 3 mg, or orlistat should be considered in patients at risk for future T2DM and should be used when needed to achieve 10% weight loss in conjunction with lifestyle therapy **(Grade A; BEL 1)**.
  - **R32.** Diabetes medications including metformin, acarbose, and thiazolidinediones can be considered in selected high-risk patients with prediabetes who are not successfully treated with lifestyle and weight-loss medications and who remain glucose intolerant **(Grade A; BEL 1)**.

- *Q5.2. Is weight loss effective to treat type 2 diabetes? How much weight loss would be required?*
  - **R33.** Patients with overweight or obesity and T2DM should be treated with lifestyle therapy to achieve 5 to 15% weight loss or more as needed to achieve targeted lowering of A1C **(Grade A; BEL 1)**. Weight-loss therapy should be considered regardless of the duration or severity of T2DM, both in newly diagnosed patients and in patients with longer-term disease on multiple diabetes medications **(Grade A; BEL 1)**.
  - **R34.** Weight-loss medications should be considered as an adjunct to lifestyle therapy in all patients with T2DM as needed for weight loss sufficient to improve glycemic control, lipids, and blood pressure **(Grade A; BEL 1)**.
  - **R35.** Patients with obesity (BMI ≥30 kg/m^2) and diabetes who have failed to achieve targeted clinical outcomes following treatment with lifestyle therapy and weight-loss medications may be considered for bariatric surgery, preferably Roux-en-Y gastric bypass, sleeve gastrectomy, or biliopancreatic diversion; also see recommendation 121 **(Grade B; BEL 1, downgraded due to evidence gaps)**.
  - **R36.** Diabetes medications that are associated with modest weight loss or are weight-neutral are preferable in patients with obesity and T2DM, although clinicians should not refrain from insulin or other medications when needed to achieve A1C targets **(Grade A; BEL 2, upgraded due to high relevance)**.

- *Q5.3. Is weight loss effective to treat dyslipidemia? How much weight loss would be required?*
  - **R37.** Patients with overweight or obesity and dyslipidemia (elevated triglycerides and reduced HDL-c) should be treated with lifestyle therapy to achieve 5 to 10% weight loss or more as needed to achieve therapeutic targets **(Grade A; BEL 1)**. The lifestyle intervention should include a physical activity program and a reduced-calorie healthy meal plan that minimizes sugars and refined carbohydrates, avoids trans fats, limits alcohol use, and emphasizes fiber **(Grade B; BEL 1, downgraded due to evidence gaps)**.
  - **R38.** Patients with overweight or obesity and dyslipidemia should be considered for treatment with a weight-loss medication combined with lifestyle therapy when necessary to achieve sufficient improvements in lipids (i.e., elevated triglycerides and reduced HDL-c) **(Grade A; BEL 1)**.

- *Q5.4. Is weight loss effective to treat hypertension? How much weight loss would be required?*
  - **R39.** Patients with overweight or obesity and elevated blood pressure or hypertension should be treated with lifestyle therapy to achieve 5 to 15% weight loss or more as necessary to achieve

Table 8: Treatment Goals Based on Diagnosis in the Medical Management of Patients With Obesity

	DIAGNOSIS		TREATMENT GOALS		
	Anthropometric Component	Clinical Component	Intervention/ Weight-Loss Goal	Clinical Goals	Qs & Rs
PRIMARY PREVENTION					
Primordial Prevention	BMI ≤25 (≤23 in certain ethnicities)	Obesogenic environment	• Public education • Built environment • Access to healthy foods	Decreased incidence of overweight/ obesity in populations	Q1,R2
Primary Prevention	BMI ≤25 (≤23 in certain ethnicities)	High-risk individuals or subgroups based on individual or cultural behaviors, ethnicity, family history, biomarkers, or genetics	• Annual BMI screening • Healthy meal plan • Increased physical activity	Decreased incidence of overweight/ obesity in high-risk individuals or identifiable subgroups	Q1,R2 Q2,R3
SECONDARY PREVENTION					
Overweight	BMI 25–29.9	No clinically significant or detectable weight-related complications	• Prevent progressive weight gain or • Weight loss	• Prevent progression to obesity • Prevent the development of weight-related complications	Q1,R2 Q4,R29
Obesity	BMI ≥30 (≥23 in certain ethnicities)	No clinically significant or detectable weight-related complications	• Weight loss or • Prevent progressive weight gain	Prevent the development of weight-related complications	Q1,R2 Q4,R29
TERTIARY PREVENTION					
Overweight or Obesity	BMI ≥25 (≥23 in certain ethnicities)	Metabolic syndrome	10%	Prevention of T2DM	Q3.1,R9,R10 Q5.1,R30,R31
		Prediabetes	10%	Prevention of T2DM	Q3.1,R9,R10 Q5.1,R30,R31
		T2DM	5% to ≥15%	• Reduction in A1C • Reduction in number and/or doses of glucose lowering medications	Q3.2,R11 Q5.2,R33,R34
		Dyslipidemia	5% to ≥15%	• Lower triglycerides • Higher HDL-c • Lower non-HDL-c	Q3.3,R12 Q5.3,R37,R38
		Hypertension	5% to ≥15%	• Lower systolic and diastolic BP • Reductions in number and/or doses of antihypertensive medications	Q3.4,R13 Q5.4,R39,R40
		Nonalcoholic fatty liver disease: Steatosis	5% or more	Reduction in intrahepatocellular lipid	Q3.6,R16 Q5.6,R45,R46
		Nonalcoholic fatty liver disease: Steatohepatitis	10% to 40%	Reduction in inflammation and fibrosis	Q3.6,R16 Q5.6,R45,R46
		Polycystic ovary syndrome	5% to 15% or more	• Ovulation • Regularization of menses • Reduced hirsuitism • Enhanced insulin sensitivity • Reduced serum androgen levels	Q3.7,R17 Q5.7,R48,R49
		Female infertility	10% or more	• Ovulation • Pregnancy	Q3.8,R18 Q5.8,R51
		Male hypogonadism	5% to 10% or more	Increase in serum testosterone	Q3.9,R19,R20 Q5.9,R52
		Obstructive sleep apnea	7% to 11% or more	• Improved symptomatology • Decreased apnea-hypopnea index	Q3.10,R21 Q5.10,R55
		Asthma/reactive airway disease	7% to 8% or more	• Improvement in forced expiratory volume at 1 second • Improved symptomatology	Q3.11,R22 Q5.11,R56
		Osteoarthritis	• ≥10% • 5% to 10% or more when coupled with exercise	• Improvement in symptomatology • Increased function	Q3.12,R23 Q5.12,R57, R58
		Urinary stress incontinence	5% to 10% or more	Reduced frequency of incontinence episodes	Q3.13,R24 Q5.13,R59
		Gastroesophageal reflux disease	10% or more	Reduced symptom frequency and severity	Q3.14,R25, Q15.5,R60
		Depression	Uncertain	• Reduction in depression symptomatology • Improvement in depression scores	Q3.15,R28 Q5.15,R63

Abbreviations: A1C = hemoglobin A1c; BMI = body mass index; BP = blood pressure; HDL-c = high-density lipoprotein cholesterol; T2DM = type 2 diabetes mellitus.

blood pressure reduction goals in a program that includes caloric restriction and regular physical activity **(Grade A; BEL 1)**.

- **R40.** Patients with overweight or obesity and elevated blood pressure or hypertension should be considered for treatment with a weight-loss medication combined with lifestyle therapy when necessary to achieve sufficient weight loss for blood pressure reduction **(Grade A; BEL 1)**.
- **R41.** Patients with hypertension considering bariatric surgery should be recommended for Roux-en-Y gastric bypass or sleeve gastrectomy, unless contraindicated, due to greater long-term weight reduction and better remission of hypertension than with laparoscopic adjustable gastric banding **(Grade B; BEL 1, downgraded due to evidence gaps)**.

- *Q5.5. Is weight loss effective to treat or prevent cardiovascular disease (CVD)? How much weight loss would be required?*
  - *Q5.5.1. Does weight loss prevent cardiovascular disease events or mortality?*
    - **R42.** Weight-loss therapy is not recommended based on available data for the expressed and sole purpose of preventing CVD events or to extend life, although evidence suggests that the degree of weight loss achieved by bariatric surgery can reduce mortality **(Grade B; BEL 2)**. Cardiovascular outcome trials assessing medication-assisted weight loss are currently ongoing or being planned.

  - *Q5.5.2. Does weight loss prevent cardiovascular disease events or mortality in diabetes?*
    - **R43.** Weight-loss therapy is not recommended based on available data for the expressed and sole purpose of preventing CVD events or to extend life in patients with diabetes **(Grade B; BEL 1, downgraded due to evidence gaps)**. Cardiovascular outcome trials assessing medication-assisted weight loss are currently ongoing or being planned.

  - *Q5.5.3. Does weight loss improve congestive heart failure and prevent cardiovascular disease events or mortality in patients with congestive heart failure?*
    - **R44.** Weight-loss therapy is not recommended based on available data for the expressed purpose of preventing CVD events or to extend life in patients with congestive heart failure, although evidence suggests that weight loss can improve myocardial function and congestive heart failure symptomatology in the short term **(Grade B; BEL 2)**.

- *Q5.6. Is weight loss effective to treat nonalcoholic fatty liver disease and nonalcoholic steatohepatitis? How much weight loss would be required?*
  - **R45.** Patients with overweight or obesity and nonalcoholic fatty liver disease should be primarily managed with lifestyle interventions, involving calorie restriction and moderate-to-vigorous physical activity, targeting 4 to10% weight loss (a range over which there is a dose-dependent beneficial effect on hepatic steatosis) **(Grade A; BEL 1)**.
  - **R46.** Weight loss as high as 10 to 40% may be required to decrease hepatic inflammation, hepatocellular injury, and fibrosis **(Grade A, BEL 1)**. In this regard, weight loss assisted by orlistat **(Grade B; BEL 2)**, liraglutide **(Grade A; BEL 1)**, and bariatric surgery **(Grade B; BEL 2)** may be effective.
  - **R47.** A Mediterranean dietary pattern or meal plan can have a beneficial effect on hepatic steatosis independent of weight loss **(Grade A; BEL 1)**.

- *Q5.7. Is weight loss effective to treat polycystic ovary syndrome (PCOS)? How much weight loss would be required?*
  - **R48.** Women with overweight or obesity and PCOS should be treated with lifestyle therapy with the goal of achieving 5 to 15% weight loss or more to improve hyperandrogenism, oligomenorrhea, anovulation, insulin resistance, and hyperlipidemia; clinical efficacy can vary among individual patients **(Grade A; BEL 1)**.
  - **R49.** Patients with overweight or obesity and PCOS should be considered for treatment with orlistat, metformin, or liraglutide, alone or in combination, because these medications can be effective in decreasing weight or improving PCOS manifestations, including insulin resistance, glucose tolerance, dyslipidemia, hyperandrogenemia, oligomenorrhea, and anovulation **(Grade A; BEL 1)**.
  - **R50.** Selected patients with obesity and PCOS should be considered for laparoscopic Roux-en-Y gastric bypass to improve symptomatology, including restoration of menses and ovulation **(Grade B; BEL 2)**.

- *Q5.8. Is weight loss effective to treat infertility in women with overweight and obesity? How much weight loss would be required?*
  - **R51.** Weight loss is effective to treat infertility in women with overweight and obesity and should be considered as part of the initial treatment to improve fertility; weight loss of ≥10% should be

targeted to augment the likelihood of conception and live birth **(Grade A; BEL 1)**.

- *Q5.9. Is weight loss effective to treat male hypogonadism? How much weight loss would be required?*
  - **R52.** Treatment of hypogonadism in men with increased waist circumference or obesity should include weight-loss therapy **(Grade B; BEL 2)**. Weight loss of more than 5 to 10% is needed for significant improvement in serum testosterone **(Grade D)**.
  - **R53.** Bariatric surgery should be considered as a treatment approach that improves hypogonadism in most patients with obesity, including patients with severe obesity (BMI >50 kg/m^2) and T2DM **(Grade A; BEL 1)**.
  - **R54.** Men with true hypogonadism and obesity who are not seeking fertility should be considered for testosterone therapy in addition to lifestyle intervention because testosterone in these patients results in weight loss, decreased waist circumference, and improvements in metabolic parameters (glucose, A1C, lipids, and blood pressure) **(Grade A; BEL 1)**.

- *Q5.10. Is weight loss effective to treat obstructive sleep apnea? How much weight loss would be required?*
  - **R55.** Patients with overweight or obesity and obstructive sleep apnea should be treated with weight-loss therapy including lifestyle interventions and additional modalities as needed, including phentermine/topiramate extended release (ER) or bariatric surgery; the weight-loss goal should be at least 7 to 11% or more **(Grade A; BEL 1)**.

- *Q5.11. Is weight loss effective to treat asthma/reactive airway disease? How much weight loss would be required?*
  - **R56.** Patients with overweight or obesity and asthma should be treated with weight loss using lifestyle interventions; additional treatment modalities may be considered as needed including bariatric surgery; the weight-loss goal should be at least 7 to 8% **(Grade A; BEL 1)**.

- *Q5.12. Is weight loss effective to treat osteoarthritis? How much weight loss would be required?*
  - **R57.** Patients with overweight or obesity and OA involving weight-bearing joints, particularly the knee, should be treated with weight-loss therapy for symptomatic and functional improvement and reduction in compressive forces during ambulation; the weight-loss goal should be ≥10% of body weight **(Grade A; BEL 1)**. A physical activity program should also be recommended in this setting because the combination of weight-loss therapy achieving 5 to 10% loss of body weight combined with physical activity can effectively improve symptoms and function **(Grade A; BEL 1)**.
  - **R58.** Patients with overweight or obesity and OA should undergo weight-loss therapy before and after total knee replacement **(Grade C; BEL 2, downgraded due to evidence gaps)**.

- *Q5.13. Is weight loss effective to treat urinary stress incontinence? How much weight loss would be required?*
  - **R59.** Women with overweight or obesity and stress urinary incontinence should be treated with weight-loss therapy; the weight-loss goal should be 5 to 10% of body weight or greater **(Grade A; BEL 1)**.

- *Q5.14. Is weight loss effective to treat gastroesophageal reflux disease (GERD)? How much weight loss would be required?*
  - **R60.** Patients with overweight or obesity and gastroesophageal reflux should be treated using weight loss; the weight-loss goal should be 10% of body weight or greater **(Grade A; BEL 1)**.
  - **R61.** Proton pump inhibitor (PPI) therapy should be administered as medical therapy in patients with overweight or obesity and persistent gastroesophageal reflux symptoms during weight-loss interventions **(Grade A; BEL 1)**.
  - **R62.** Roux-en-Y gastric bypass should be considered as the bariatric surgery procedure of choice for patients with obesity and moderate to severe gastroesophageal reflux symptoms, hiatal hernia, esophagitis, or Barrett's esophagus **(Grade B; BEL 2)**. Intragastric balloon for weight loss may increase gastroesophageal reflux symptoms and should not be used for weight loss in patients with established gastroesophageal reflux **(Grade A; BEL 1)**.

- *Q5.15. Is weight loss effective to improve symptoms of depression? How much weight loss would be required?*
  - **R63.** Patients with overweight or obesity and depression interested in losing weight should be offered a structured lifestyle intervention **(Grade A; BEL 1)**.

Lifestyle/Behavioral Therapy for Overweight and Obesity

- ***Q6. Is lifestyle/behavioral therapy effective to treat overweight and obesity, and what components of lifestyle therapy are associated with efficacy? (Fig. 4)***
  - **R64.** A structured lifestyle intervention program designed for weight loss (lifestyle therapy) and consisting of a healthy meal plan, physical activity, and behavioral interventions should be available to patients who are being treated for overweight or obesity **(Grade A; BEL 1)**.

- *Q6.1. Reduced-calorie meal plan and macronutrient composition. (Table 9)*
  - **R65.** Reducing total energy (caloric) intake should be the main component of any weight-loss intervention **(Grade A; BEL 1)**.
  - **R66.** Even though the macronutrient composition of meals has less impact on weight loss than adherence rates in most patients, in certain patient populations, modifying macronutrient composition may be considered to optimize adherence, eating patterns, weight loss, metabolic profiles, risk factor reduction, and/or clinical outcomes **(Grade A; BEL 1)**.

- *Q6.2. Physical activity*
  - **R67.** Aerobic physical activity training should be prescribed to patients with overweight or obesity as a component of lifestyle intervention; the initial prescription may require a progressive increase in the volume and intensity of exercise, and the ultimate goal should be ≥150 min/week of moderate exercise performed during 3 to 5 daily sessions per week **(Grade A; BEL 1)**.
  - **R68.** Resistance training should be prescribed to patients with overweight or obesity undergoing weight-loss therapy to help promote fat loss while preserving fat-free mass; the goal should be resistance training 2 to 3 times per week consisting of single-set exercises that use the major muscle groups **(Grade A; BEL 1)**.
  - **R69.** An increase in nonexercise and active leisure activity should be encouraged to reduce sedentary behavior in all patients with overweight or obesity (Grade A; BEL 1).
  - **R70.** The prescription for physical activity should be individualized to include activities and exercise regimens within the capabilities and preferences of the patient, taking into account health-related and physical limitations **(Grade C; BEL 4, upgraded due to high relevance)**.
  - **R71.** Involvement of an exercise physiologist or certified fitness professional in the care plan should be considered to individualize the physical activity prescription and improve outcomes **(Grade A; BEL 1)**.

- *Q6.3. Behavior interventions*
  - **R72.** Lifestyle therapy in patients with overweight or obesity should include behavioral interventions that enhance adherence to prescriptions for a reduced-calorie meal plan and increased physical activity (behavioral interventions can include: self-monitoring of weight, food intake, and physical activity; clear and reasonable goal-setting; education pertaining to obesity, nutrition, and physical activity; face-to-face and group meetings; stimulus control; systematic approaches for problem solving; stress reduction; cognitive restructuring [i.e., cognitive behavioral therapy], motivational interviewing; behavioral contracting; psychological counseling; and mobilization of social support structures) **(Grade A; BEL 1)**.
  - **R73.** The behavior intervention package is effectively executed by a multidisciplinary team that includes dietitians, nurses, educators, physical activity trainers or coaches, and clinical psychologists **(Grade C; BEL 4, upgraded due to high relevance)**. Psychologists and psychiatrists should participate in the treatment of eating disorders, depression, anxiety, psychoses, and other psychological problems that can impair the effectiveness of lifestyle intervention programs **(Grade B; BEL 2)**.
  - **R74.** Behavioral lifestyle intervention and support should be intensified if patients do not achieve a 2.5% weight loss in the first month of treatment, as early weight reduction is a key predictor of long-term weight-loss success **(Grade A; BEL 1)**. A stepped-care behavior approach should teach skills for problem solving and should evaluate outcomes **(Grade A; BEL 1)**.
  - **R75.** Behavioral lifestyle intervention should be tailored to a patient's ethnic, cultural, socioeconomic, and educational background **(Grade B; BEL 2)**.

Pharmacotherapy for Overweight and Obesity

- ***Q7. Is pharmacotherapy effective to treat overweight and obesity?***
  - *Q7.1. Should pharmacotherapy be used as an adjunct to lifestyle therapy or alone?*
    - **R76.** Pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone **(Grade A; BEL 1)**.

Figure 4. Lifestyle Therapy

Evidence-based lifestyle therapy for treatment of obesity should include 3 components
Recommendations: R64 through R75

Meal Plan (R64, R65, R66)	Physical Activity (R64, R67, R68, R69, R70, R71)	Behavior (R64, R72, R73, R74, R75)
• Reduced-calorie healthy meal plan • ~500–750 kcal daily deficit • Individualize based on personal and cultural preferences • Meal plans can include: Mediterranean, DASH, low-carb, low-fat, volumetric, high protein, vegetarian • Meal replacements • Very low-calorie diet is an option in selected patients and requires medical supervision Team member or expertise: dietitian, health educator	• Voluntary aerobic physical activity progressing to >150 minutes/week performed on 3–5 separate days per week • Resistance exercise: single-set repetitions involving major muscle groups, 2–3 times per week • Reduce sedentary behavior • Individualize program based on preferences and take into account physical limitations Team member or expertise: exercise trainer, physical activity coach, physical/occupational therapist	An interventional package that includes any number of the following: • Self-monitoring (food intake, exercise, weight) • Goal setting • Education (face-to-face meetings, group sessions, remote technologies) • Problem-solving strategies • Stimulus control • Behavioral contracting • Stress reduction • Psychological evaluation, counseling, and treatment when needed • Cognitive restructuring • Motivational interviewing • Mobilization of social support structures Team member or expertise: health educator, behaviorist, clinical psychologist, psychiatrist

- *Q7.2. Does the addition of pharmacotherapy produce greater weight loss and weight-loss maintenance compared with lifestyle therapy alone?*
  - **R77.** The addition of pharmacotherapy produces greater weight loss and weight-loss maintenance compared with lifestyle therapy alone **(Grade A; BEL 1)**.
  - **R78.** The concurrent initiation of lifestyle therapy and pharmacotherapy should be considered in patients with weight-related complications that can be ameliorated by weight loss **(Grade A; BEL 1)**.

- *Q7.3. Should pharmacotherapy only be used in the short term to help achieve weight loss or should it be used chronically in the treatment of obesity?*
  - **R79.** Pharmacotherapy should be offered to patients with obesity, when potential benefits outweigh the risks, for the chronic treatment of the disease **(Grade A; BEL 1)**. Short-term treatment (3 to 6 months) using weight-loss medications has not been demonstrated to produce longer-term health benefits and cannot be generally recommended based on scientific evidence **(Grade B; BEL 1, downgraded due to evidence gaps)**.

- *Q7.4. Are there differences in weight-loss drug efficacy and safety? (Table 10)*
  - **R80.** In selecting the optimal weight-loss medication for each patient, clinicians should consider differences in efficacy, side effects, cautions, and warnings that characterize medications approved for chronic management of obesity, and the presence of weight-related complications and medical history; these factors are the basis for individualized weight-loss pharmacotherapy; a generalizable hierarchical algorithm for medication preferences that would be applicable to all patients cannot currently be scientifically justified **(Grade A; BEL 1)**.

- **R81.** Clinicians and their patients with obesity should have available access to all approved medications to allow for the safe and effective individualization of appropriate pharmacotherapy (Grade D).

- *Q7.5. Should combinations of weight-loss medications be used in a manner that is not approved by the U.S. Food and Drug Administration?*
- **R82.** Combinations of FDA-approved weight-loss medications should only be used in a

Table 9. Association of Eating Patterns and Macronutrient Composition on Weight-Loss Efficacy

Eating Pattern or Macronutrient Change	Effect	Reference [EL]
Low glycemic index/load	• ⬆ Endothelial function • ⬇ Glycemic variability • Effects on energy expenditure • Decreased adipocyte diameter • No incremental effect on weight loss[1]	33 [EL 1; RCT], 34 [EL 1; RCT], 35 [EL 1; RCT, small N=13], 36 [EL 1; RCT]
Low carbohydrate	• Improved glycemic status and lipids • Improved other cardio-metabolic risk factors • Improved renal function • No incremental effect on weight loss (some studies show more short-term weight loss)[2]	37 [EL 4; NE], 38 [EL 1; RCT], 39 [EL 1; RCT], 40 [EL 1; RCT], 41 [EL 1; RCT], 42 [EL 1; RCT], 43 [EL 2; NRCT], 44 [EL 1; RCT], 45 [EL 1; RCT], 46 [EL 1; RCT], 47 [EL 1; RCT]
High protein	• Longer benefit on WC, %fat • Improved cardio-metabolic risk factors • Decreased adipocyte diameter • Animal (not plant) proteins associated with markers of inflammation • Less relative loss of muscle mass • No incremental effect on weight loss	33 [EL 1; RCT], 38 [EL 1; RCT], 45 [EL 1; RCT], 48 [EL 1; RCT], 49 [EL 1; RCT], 50 [EL 1; RCT], 51 [EL 1; RCT], 52 [EL 1; RCT], 53 [EL 1; RCT]
Moderate carbohydrate – moderate protein	• Improved body composition, lipid, ppINS • No incremental effect on weight loss	37 [EL 4; NE]. 54 [EL 1; RCT]
Low fat	• Beneficial effects on lipids • Benefits on lipids replacing with unsaturated fat • Improved renal function • No incremental effect on weight loss	37 [EL 4; NE], 41 [EL 1; RCT], 47 [EL 1; RCT], 55 [EL 1; RCT], 56 [EL 1; RCT]
High fat	• With lactation: when hypocaloric, great weight loss compared with hypocaloric low-carbohydrate diet	57 [EL 2; PCS]
Mediterranean-style	• Decreased risk certain cancers • EVOO supplementation – no effect on weight • Reduces cardio-metabolic risk factors and MetS • Reduces markers of inflammation • Improves hepatic steatosis and insulin sensitivity • Improves renal function • No incremental effect on weight loss	40 [EL 1; RCT], 58 [EL 1; RCT, post-hoc analysis], 59 [EL 2; PCS, post-hoc analysis], 60 [EL 1; RCT, secondary analysis], 61 [EL 2; PCS], 62 [EL 1; RCT], 63 [EL 1; RCT], 64 [EL 2; PCS], 65 [EL 2; PCS], 66 [EL 1; RCT]

Abbreviations: EL = evidence level; EVOO = extra-virgin olive oil; MetS = metabolic syndrome; ppINS = postprandial insulin response; WC = waist circumference.

[1] Incremental effect in comparison to a isocaloric control diet does not occur or is inconsistent.
[2] Short-term is <1 year.

manner approved by the FDA **(Grade A; BEL 1)** or when sufficient safety and efficacy data are available to assure informed judgment regarding a favorable benefit-to-risk ratio **(Grade D)**.

Individualization of Pharmacotherapy in the Treatment of Obesity

- ***Q8. Are there hierarchies of drug preferences in patients with the following disorders or characteristics? (Table 11)***

Note: Specific medications are mentioned or recommended below for use in different clinical settings based on efficacy, side effects, warnings and contraindications, organ clearance, mechanisms of action, and available data for use of the medication under these specific conditions. Medications may not be explicitly recommended if there are no data available for use in the specified clinical setting, even though weight loss associated with these medications may produce clinical benefits.

- *Q8.1. Chronic kidney disease*
  - **R83.** Weight-loss medications should not be used in the setting of end-stage renal failure, with the exception that orlistat and liraglutide 3 mg can be considered in selected patients with a high level of caution **(Grade B; BEL 2)**.
  - **R84.** The use of naltrexone ER/bupropion ER, lorcaserin, or phentermine/topiramate ER is not recommended in patients with severe renal impairment (<30 mL/min) **(Grade B; BEL 2)**.
  - **R85.** All weight-loss medications can be used with appropriate cautions in patients with mild (50 to 79 mL/min) and moderate (30 to 49 mL/min) renal impairment, except that in moderate renal impairment the dose of naltrexone ER/bupropion ER should not exceed 8 mg/90 mg twice per day, and the daily dose of phentermine/topiramate ER should not exceed 7.5 mg/46 mg **(Grade B; BEL 2)**.
  - **R86.** Orlistat should not be used in patients with, or at risk of, oxalate nephropathy **(Grade C; BEL 3)**. Liraglutide 3 mg should be discontinued if patients develop volume depletion, for example, due to nausea, vomiting, or diarrhea **(Grade B; BEL 2)**.

- *Q8.2. Nephrolithiasis*
  - **R87.** Naltrexone ER/bupropion ER, lorcaserin, and liraglutide 3 mg are preferred weight-loss medications in patients with a history, or at risk, of nephrolithiasis **(Grade D)**. Caution should be exercised in treating patients with phentermine/topiramate ER and orlistat who have a history of nephrolithiasis **(Grade A; BEL 1)**.

- *Q8.3. Hepatic impairment*
  - **R88.** All weight-loss medications should be used with caution in patients with hepatic impairment and should be avoided in severe hepatic impairment (i.e., Child-Pugh score >9) **(Grade C; BEL 3)**.
  - **R89.** Dose adjustments for some medications are warranted in patients with moderate hepatic impairment: specifically, the maximum recommended dose of naltrexone ER/bupropion ER is 1 tablet (8 mg/90 mg) in the morning; the maximum recommended dose of phentermine/topiramate ER is 7.5 mg/46 mg daily (Grade D).
  - **R90.** Clinicians should maintain a high index of suspicion for cholelithiasis in patients undergoing weight-loss therapy, regardless of the treatment modality; in high-risk patients, liraglutide 3 mg should be used with caution; effective preventive measures include a slower rate of weight loss, an increase in dietary fat, or administration of ursodeoxycholic acid **(Grade A; BEL 1)**.

- *Q8.4. Hypertension*
  - **R91.** In patients with existing hypertension, orlistat, lorcaserin, phentermine/topiramate ER, and liraglutide 3 mg are preferred weight-loss medications **(Grade B; BEL 1, downgraded due to evidence gaps)**. Heart rate should be carefully monitored in patients receiving liraglutide 3 mg and phentermine/topiramate ER **(Grade A; BEL 1)**. Naltrexone ER/bupropion ER should be avoided if other weight-loss medications can be used because weight loss assisted by naltrexone ER/bupropion ER cannot be expected to reduce blood pressure, and the drug is contraindicated in uncontrolled hypertension **(Grade B; BEL 1, downgraded due to evidence gaps)**.
  - **R92.** Renin-angiotensin system inhibition therapy (angiotensin receptor blocker or angiotensin converting enzyme inhibitor) should be used as the first-line drug for blood pressure control in patients with obesity **(Grade A; BEL 1)**.
  - **R93.** Combination antihypertension therapy with calcium channel blockers may be considered as second-tier treatment **(Grade A; BEL 1)**. Beta-blockers and thiazide diuretics may also be considered in some patients but can have adverse effects on metabolism; beta-blockers and alpha-blockers can promote weight gain **(Grade A; BEL 1)**.

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Table 10. Weight-Loss Medications: Key Clinical Trials, Baseline Characteristics, and Weight-Loss Efficacy (67 [EL 1; RCT]; 68 [EL 1; RCT]; 69 [EL 1; RCT]; 70 [EL 1; RCT]; 71 [EL 1; RCT]) *

Generic Name	Naltrexone ER/ Bupropion ER		Liraglutide 3 mg		Locaserin		Orlistat		Phentermine/ Topiramte ER		
Brand Name	**Contrave**		**Saxenda**		**Belviq**		**Xenical**		**Qsymia**		
Frequency	**Oral, BID**		**subQ, QD**		**Oral, BID**		**Oral, TID**		**Oral, QD**		
Total Daily Dose	**32 mg/360 mg**		**3 mg**		**20 mg**		**360 mg**		7.5 mg / 46 mg	15 mg / 92 mg	
	Drug	Control	Drug	Control	Drug	Control	Drug	Control	Drug	Drug	Control
Age (years)	44.4	43.7	45.2	45.0	43.8	43.7	43.2	41.6	51.1	51.0	51.2
Gender (% female)	85	85	78.7	78.1	80.5	78.0	79	78	70.0	70.0	70.0
Baseline Weight (kg)	99.7	99.5	106.2	106.2	100.3	100.5	100.5	101.8	102.6	103.0	103.3
Baseline Waist (cm)	108.8	110.0	115.0	114.5	108.9	110.2	n/a	n/a	112.6	113.2	113.4
Baseline BMI	36.1	36.2	38.3	38.3	36.0	35.9	36.0	36.1	36.2	36.6	36.7
Weight-Loss (%) Completers	-8.1	-1.8	-9.2	-3.5	-7.9	-4.0	-8.78	-4.26	-9.6	-12.4	-1.6
Weight Loss (%) ITT LOCF	-6.1	-1.3	-8.0	-2.6	-5.8	-2.8	-7.94	-4.14	-7.8	-9.8	-1.2
5% Weight Loss (in %) ITT LOCF	48	16	63.2	27.1	47.2	25.0	50.5	30.7	62	70	21
10% Weight Loss (in %) ITT LOCF	25	7	33.1	10.6	22.6	9.7	28.6	11.3	37	48	7

*There is a lack of clinical trials with head-to-head direct comparisons among the drugs approved for chronic weight management. For this table, data are delineated from a representative major randomized clinical trial for each drug. Each study was conducted over at least 1 year in duration, enrolled subjects with baseline weights of approximately 100 kg and average BMIs in the range of class II obesity (BMI 35-39.9 kg/m^2), and included data from subjects on the recommended doses for the medication. Each study also had to have data for weight loss % (completers), weight loss % (LOCF), 5% weight loss LOCF and 10% weight loss LOCF to be included in the chart.

Abbreviations: ITT = Intent-to-treat; LOCF = last observation carried forward.

Table 11. Preferred Weight-Loss Medications: Individualization of Therapy

KEY: ☐ PREFERRED DRUG ☐ USE WITH CAUTION ☐ AVOID

CLINICAL CHARACTERISTICS OR COEXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	Lorcaserin	Phentermine/ topiramate ER	Naltrexone ER/ bupropion ER	Liraglutide 3 mg
Diabetes Prevention (metabolic syndrome, prediabetes)			Insufficient data		Insufficient data	
Type 2 Diabetes Mellitus						
Hypertension				Monitor heart rate	Monitor BP and heart rate. Contraindicated in uncontrolled HTN	Monitor heart rate
Cardiovascular Disease	CAD			Monitor heart rate	Monitor heart rate, BP	Monitor heart rate
	Arrhythmia			Monitor heart rate, rhythm	Monitor heart rate, rhythm, BP	Monitor heart rate, rhythm
	CHF	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Chronic Kidney Disease	Mild (50-79 mL/min)					
	Moderate (30-49 mL/min)			Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg bid	
	Severe (<30 mL/min)	Watch for oxalate nephropathy	Urinary clearance of drug metabolites	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion
Nephrolithiasis		Calcium oxalate stones		Calcium phosphate stones		
Hepatic Impairment	Mild-Moderate (Child-Pugh 5–9)	Watch for cholelithiasis	Hepatic metabolism of drug	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg in AM	Watch for cholelithiasis
	Severe (Child-Pugh >9)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Depression			Insufficient safety data Avoid combinations of serotonergic drugs	Avoid maximum dose: 15 mg/92 mg per day	Insufficient safety data Avoid in adolescents and young adults	
Anxiety				Avoid max dose: 15 mg/92 mg per day		
Psychoses		Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Binge Eating Disorder			Insufficient data. Possible benefit based on reduction in food cravings	Insufficient data. Possible benefit based on studies with topiramate	Insufficient data. Possible benefit based on studies with bupropion Avoid in patients with purging or bulimia nervosa	Insufficient data
Glaucoma				Contraindicated, may trigger angle closure	May trigger angle closure	
Seizure Disorder				If discontinued, taper slowly	Bupropion lowers seizure threshold	
Pancreatitis		Monitor for symptoms				Monitor for symptoms Avoid if prior or current disease
Opioid Use					Will antagonize opioids and opiates	
Women of Reproductive Potential	Pregnancy	Use contraception and discontinue orlistat should pregnancy occur	Use contraception and discontinue lorcaserin should pregnancy occur	Use contraception and discontinue phentermine/topiramate should pregnancy occur (perform monthly pregnacy checks to identify early pregnancy; risk of cleft lip/palate)	Use contraception and discontinue naltrexone ER/bupropion ER should pregnancy occur	Use contraception and discontinue liraglutide should pregnancy occur
	Breast-feeding	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Age ≥65 years *		Limited data available	Insufficient data	Limited data available	Insufficient data	Limited data available
Alcoholism/ Addiction			Might have abuse potential due to euphoria at high doses	Insufficient data. Topiramate might exert therapeutic benefits	Avoid due to seizure risk and lower seizure threshold on bupropion	
Post-Bariatric Surgery		Insufficient data	Insufficient data	Limited data available	Insufficient data	Data available at 1.8 – 3.0 mg/day

* Use medications only with clear health-related goals in mind; assess patient for osteoporosis and sarcopenia.

Abbreviations: BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; HTN = hypertension.

- *Q8.5. Cardiovascular disease and cardiac arrhythmia*
  - **R94.** In patients with established atherosclerotic cardiovascular disease, orlistat and lorcaserin are preferred weight-loss medications **(Grade A; BEL 1)**. Liraglutide 3 mg, phentermine/topiramate ER, and naltrexone ER/bupropion ER are reasonable to use with caution, and to continue if weight-loss goals are met, with careful monitoring of heart rate and blood pressure **(Grade A; BEL 1)**. Cardiovascular outcome trials are planned or ongoing for all weight-loss medications except orlistat.
  - **R95.** Orlistat and lorcaserin are preferred weight-loss medications in patients with a history or risk of cardiac arrhythmia **(Grade B; BEL 1, downgraded due to evidence gaps)**. Naltrexone ER/bupropion ER, liraglutide 3 mg, and phentermine/topiramate ER are not contraindicated but should be used cautiously with careful monitoring of heart rate and rhythm **(Grade A; BEL 1)**.

- *Q8.6. Depression with or without selective serotonin reuptake inhibitor therapy*
  - **R96.** All patients undergoing weight-loss therapy should be monitored for mood disorders, depression, and suicidal ideation **(Grade A; BEL 2, upgraded due to high relevance)**.
  - **R97.** Orlistat, liraglutide 3 mg, and phentermine/topiramate ER at initiation (3.75 mg/23 mg) and low treatment (7.5 mg/46 mg) doses may be considered in patients with obesity and depression **(Grade A; BEL 1)**.
  - **R98.** Lorcaserin and naltrexone ER/bupropion ER should be used with caution in patients with obesity and depression or avoided if patients are taking medications for depression **(Grade A; BEL 1)**.

- *Q8.7. Anxiety*
  - **R99.** Maximal dose (15 mg/92 mg) phentermine/topiramate ER should be used with caution in patients with obesity and anxiety disorders **(Grade A; BEL 1)**.

- *Q8.8. Psychotic disorders with or without medications (lithium, atypical antipsychotics, monoamine oxidase inhibitors)*
  - **R100.** Patients with psychotic disorders being treated with antipsychotic medications should be treated with a structured lifestyle intervention to promote weight loss or prevent weight gain **(Grade A; BEL 1)**.
  - **R101.** Treatment with metformin may be beneficial in promoting modest weight loss and metabolic improvement in individuals with psychotic disorders who are taking antipsychotic medications **(Grade A; BEL 1)**.
  - **R102.** Caution must be exercised in using any weight-loss medication in patients with obesity and a psychotic disorder due to insufficient current evidence assessing safety and efficacy **(Grade D)**.

- *Q8.9. Eating disorders including binge eating disorder*
  - **R103.** Patients with overweight or obesity who are being considered for weight-loss therapy should be screened for binge eating disorder and night eating syndrome **(Grade B; BEL 3, upgraded due to high relevance)**.
  - **R104.** Patients with overweight or obesity who have binge eating disorder should be treated with a structured behavioral/lifestyle program in conjunction with cognitive behavioral therapy or other psychological interventions **(Grade A; BEL 1)**.
  - **R105.** In patients with overweight or obesity and binge eating disorder, treatment with orlistat or approved medications containing topiramate or bupropion may be considered in conjunction with structured lifestyle therapy, cognitive behavioral therapy, and/or other psychological interventions **(Grade A; BEL 1)**.
  - **R106.** Structured lifestyle therapy and/or selective serotonin reuptake inhibitor therapy may be considered in patients with obesity and night eating syndrome **(Grade B; BEL 1, downgraded due to evidence gaps)**.

- *Q8.10. Glaucoma*
  - **R107.** Liraglutide 3 mg, orlistat, and lorcaserin are preferred weight-loss medications in patients with a history, or at risk of, glaucoma **(Grade B; BEL 2)**. Phentermine/topiramate ER should be avoided and naltrexone ER/bupropion ER used with caution in patients with glaucoma **(Grade C; BEL 2, downgraded due to evidence gaps)**.

- *Q8.11. Seizure disorder*
  - **R108.** Phentermine/topiramate, lorcaserin, liraglutide, and orlistat are preferred weight-loss medications in patients with a history, or at risk, of seizure/epilepsy **(Grade B; BEL 1, downgraded due to evidence gaps)**. The use of naltrexone ER/bupropion ER should be avoided in these patients.

- *Q8.12. Pancreatitis*
  - **R109.** All patients with obesity should be monitored for typical symptoms of pancreatitis (e.g., abdominal pain or gastrointestinal [GI] distress) due to a proven association between these diseases **(Grade A; BEL 1)**.
  - **R110.** Patients receiving glyburide, orlistat, or incretin-based therapies (glucagon-like peptide-1 receptor agonists or dipeptidyl peptidase 4 inhibitors) should be monitored for the development of pancreatitis **(Grade C; BEL 3)**. Glyburide, orlistat, and incretin-based therapies should be withheld in cases of prior or current pancreatitis; otherwise there are insufficient data to recommend withholding glyburide for glycemic control, orlistat for weight loss, or incretin-based therapies for glycemic control or weight loss due to concerns regarding pancreatitis **(Grade D)**.

- *Q8.13. Opioid use*
  - **R111.** In patients requiring chronic administration of opioid or opiate medications, phentermine/topiramate ER, lorcaserin, liraglutide 3 mg, and orlistat are preferred weight-loss medications, while naltrexone ER/bupropion ER should not be used **(Grade B; BEL 1, downgraded due to evidence gaps)**.

- *Q8.14. Women of reproductive potential*
  - **R112.** Weight-loss medications must not be used in pregnancy **(Grade A; BEL 2, upgraded due to high relevance)**.
  - **R113.** All weight-loss medications should be used in conjunction with appropriate forms of contraception in women of reproductive potential **(Grade A; BEL 1)**.
  - **R114.** Weight-loss medications should not be used in women who are lactating and breast-feeding **(Grade D)**.

- *Q8.15. The elderly, ≥65 years*
  - **R115.** Elderly patients (≥65 years) should be selected for weight-loss therapy involving structured lifestyle interventions that include reduced-calorie meal plans and exercise, with clear health-related goals in mind that include prevention of T2DM in high-risk patients with prediabetes, blood pressure lowering, and improvements in OA, mobility, and physical function **(Grade A; BEL 1)**.
  - **R116.** Elderly patients with overweight or obesity being considered for weight-loss therapy should be evaluated for osteopenia and sarcopenia **(Grade B; BEL 2)**.
  - **R117.** Weight-loss medications should be used with extra caution in elderly patients with overweight or obesity (Grade A; BEL 1); additional studies are needed to assess efficacy and safety of weight-loss medications in the elderly.

- *Q8.16. Addiction/alcoholism*
  - **R118.** In patients with obesity and alcohol or other addictions, consider using orlistat or liraglutide 3 mg **(Grade A; BEL 1)**. Lorcaserin (abuse potential due to euphoria at suprapharmacologic doses) and naltrexone ER/bupropion ER (lowers seizure threshold) should be avoided in patients with alcohol abuse, and naltrexone ER/bupropion ER is contraindicated during alcohol withdrawal **(Grade A; BEL 1)**.

- *Q8.17. Post-bariatric surgery*
  - **R119.** Patients that have undergone bariatric surgery should continue to be treated with an intensive lifestyle intervention **(Grade A; BEL 1)**. Patients that have regained excess weight (≥25% of the lost weight), have not responded to intensive lifestyle intervention, and are not candidates for reoperation may be considered for treatment with liraglutide (1.8 to 3.0 mg) or phentermine/topiramate ER; the safety and efficacy of other weight-loss medications have not been assessed in these patients **(Grade D; BEL 3, downgraded due to evidence gaps)**.

Bariatric Surgery

- ***Q9. Is bariatric surgery effective to treat obesity?***

Note: A de novo evidence-based review of questions pertaining to bariatric surgery was not undertaken. The "Clinical Practice Guidelines for the Perioperative, Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient 2013-Update" from the AACE, The Obesity Society, and the American Society for Metabolic & Bariatric Surgery were reviewed and felt to be adequate in their current form. Key recommendations from these guidelines relevant to the questions generated for evidence-based review are copied below.

- *Q9.1. Is bariatric surgery effective to treat obesity and weight-related complications?*
  - **R120.** Patients with a BMI of ≥40 kg/m^2 without coexisting medical problems and for whom the procedure would not be associated with excessive risk should be eligible for bariatric surgery **(Grade A; BEL 1)**.

- *Q9.2. When should bariatric surgery be used to treat obesity and weight-related complications?*
  - **R121.** Patients with a BMI of ≥35 kg/m^2 and 1 or more severe obesity-related complications, including T2DM, hypertension, obstructive sleep apnea, obesity-hypoventilation syndrome, Pickwickian syndrome, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, pseudotumor cerebri, gastroesophageal reflux disease, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life may also be considered for a bariatric surgery procedure. Patients with BMI of 30 to 34.9 kg/m^2 with diabetes or metabolic syndrome may also be considered for a bariatric procedure, although current evidence is limited by the number of patients studied and lack of long-term data demonstrating net benefit.
    - BMI ≥35 kg/m^2 and therapeutic target of weight control and improved biochemical markers of CVD risk **(Grade A; BEL 1)**.
    - BMI ≥30 kg/m^2 and therapeutic target of weight control and improved biochemical markers of CVD risk **(Grade B; BEL 2)**.
    - BMI ≥30 kg/m^2 and therapeutic target of glycemic control in T2DM and improved biochemical markers of CVD risk **(Grade C; BEL 3)**.

  - **R122.** Independent of BMI criteria, there is insufficient evidence for recommending a bariatric surgical procedure specifically for glycemic control alone, lipid lowering alone, or CVD risk reduction alone **(Grade D)**.
  - **R123.** All patients should undergo pre-operative evaluation for weight-related complications and causes of obesity, with special attention directed to factors that could affect a recommendation for bariatric surgery or be ameliorated by weight loss resulting from the procedure **(Grade A; BEL 1)**.

General Guideline for Diagnosis and Medical Management of Patients with Overweight or Obesity

V. Appendix: Evidence Base

These evidence reviews provide a summary of the evidence in response to each question and provide the references upon which recommendations in the Executive Summary were based. In this CPG, there are 1,790 citations of which 525 (29.3%) are EL 1 (strong), 605 (33.8%) are EL 2 (intermediate), 308 (17.2%) are EL 3 (weak), and 352 (19.7%) are EL 4 (no clinical evidence). Most recommendations are based upon BEL 1 or 2: 133 (83.1%).

Post-hoc Question: By inductive evaluation of all evidence-based recommendations, what are the core recommendations for medical care of patients with obesity?

Executive Summary

- **R1.** Core recommendations in the medical care of patients with obesity are:
  - **R1.A.** The principal outcome and therapeutic target in the treatment of obesity should be to improve the health of the patient by preventing or treating weight-related complications using weight loss, not the loss of body weight per se **(Grade D)**.
  - **R1.B.** The evaluation of patients for risk and existing burden of weight-related complications is a critical component of care and should be considered in clinical decisions and the therapeutic plan for weight-loss therapy **(Grade D)**.

Evidence Base

These core principles were formulated by an inductive process based on consideration of all questions in these guidelines, all ensuing recommendations, and the evidence base supporting these recommendations. Thus, the core principles derive from the amalgamation of evidence, marshaled from multiple individual recommendations, and emerging from global examination of these recommendations relevant to an overall approach for patient care.

The core principles derive scientific validity to the degree that each individual evidence-based recommendation is consistent with the core principles and fidelity of these core principles to the aggregate of all recommendations. Because the recommendations regarding core principles were considered after evidence review for all individual questions and recommendations, they could be listed at the end in an Appendix. However, the core recommendations have been brought forward and listed first in an Executive Summary to allow for consideration of the individual recommendations in the context of these core recommendations.

These core recommendations are not compatible with a view of obesity management that is solely focused on weight loss, or with weight loss as the sole objective of therapeutic interventions. The recommendations instead reflect a medical approach to obesity as a disease, based on the evidence, where weight loss is used therapeutically to improve health by preventing or ameliorating weight-related complications. Weight loss is, therefore, a surrogate measure of effectiveness to the degree that weight loss improves health, analogous to cholesterol levels and the prevention of CVD events.

The current core recommendations would require that medications achieve weight loss that is sufficient to demonstrably improve health by preventing or treating

complications. Furthermore, it is clear from the evidence that the impact on health is highly variable among patients for any given degree of excess adiposity. For that reason, evaluation of patients with overweight or obesity for risk of weight-related complications, and the presence and severity of contemporaneous complications, is critical to assess the impact of adiposity on health and to use this information in decisions regarding therapy.

- ***Q1. Do the 3 phases of chronic disease prevention and treatment (i.e., primary, secondary, and tertiary) apply to the disease of obesity?***

Executive Summary

- **R2.** The modality and intensity of obesity interventions should be based on the primary, secondary, and tertiary phases of disease prevention; this 3-phase paradigm for chronic disease aligns with the pathophysiology and natural history of obesity and provides a rational framework for the appropriate treatment at each phase of prevention **(Grade C; BEL 4, upgraded due to high relevance to natural history of the disease)**.

Evidence Base

One of the concepts affirmed during multidisciplinary discussions at the 2014 AACE Consensus Conference on Obesity was that a comprehensive plan to combat obesity must include strategies at all 3 classic phases of chronic disease prevention and treatment: primary, secondary, and tertiary (14 [EL 4; NE]). The first elaboration of all 3 phases of prevention was by Leavell and Clark in 1965 (72 [EL 4; NE]), and these concepts have been subsequently developed by multiple authors (73 [EL 4; NE]; 74 [EL 4; NE]; 75 [EL 4; NE]; 76 [EL 4; NE]). Each phase of chronic disease prevention entails different therapeutic objectives and requires different treatment modalities. General definitions, goals, and methods of prevention for the 3 phases are delineated in Table 6.

The 3-category paradigm of primary, secondary, and tertiary prevention has been adopted in many fields of medicine and social sciences, including CVD (77 [EL 4; NE]; 78 [EL 4; NE]), obstetrics (79 [EL 4; NE]), infectious diseases (80 [EL 4; NE]), psychiatry (81 [EL 4; NE]), rheumatology (82 [EL 4; NE]), and thyroid disease (83 [EL 4; NE]), in addition to preventive medicine and public health where it is used to structure the scope of work for the U.S. Preventive Services Task Force (84 [EL 4; NE]). The phases of disease prevention have been used as a framework by the American Heart Association in developing its policy statements (85 [EL 4; NE]) and by the Academy of Nutrition and Dietetics in its position statement regarding interventions for the prevention and treatment of pediatric overweight and obesity (86 [EL 4; NE]).

Is the 3-phase paradigm appropriate and useful when applied to the prevention and treatment of obesity? Fletcher et al (76 [EL 4; NE]) proposed 3 criteria as to whether a medical condition should be included in the 3-phase preventive model. The first demands that the medical condition exact a substantial burden of human suffering. The evidence base presented within these guidelines provides ample testimony for the human and social costs of obesity. Second, there must be an effective screening test for the disease that maximizes sensitivity, specificity, safety, acceptability, and minimizes cost. The use of BMI and waist circumference (WC) as recommended within these guidelines readily meets these criteria. The final stipulation is that preventive interventions or treatments must exist at all 3 phases with acceptable effectiveness, safety, and cost. For example, once the condition is found at screening, early treatment for secondary prevention should be advantageous when compared with later treatment after the patient becomes symptomatic or develops complications. Also, there must exist tertiary interventions that can stabilize the disease and ameliorate complications. Again, the current guidelines find that these final criteria are met on the basis of evidence review.

The 3-phase paradigm for chronic disease aligns itself with the pathophysiology and natural history of obesity. Like other chronic diseases, susceptibility to obesity results from the inheritance of multiple genes with each allele conferring a small relative risk for the disease (87 [EL 3; SS]; 88 [EL 3; SS]). These multiple genes interact with each other and with the environment and behavior to produce individual variation in the risks of obesity (89 [EL 3; SS]). Primary prevention is warranted at this stage (90 [EL 2; MNRCT; heterogeneity of studies]), and interventions can prevent obesity from occurring even in individuals at higher risk as delineated in an evidence-based review in a National Institute for Health and Care Excellence (NICE) guideline (91 [EL 4; NE]). Interventions to prevent disease are sometimes categorized as primordial prevention, defined as eliminating risk factors in general populations such as through public education and modifications in the built environment, and primary prevention, defined as interventions that modify adverse levels of risk factors once present to prevent the disease, such as healthy lifestyle interventions in high-risk ethnic groups or in children with affected parents. If primary prevention measures are not undertaken or are unsuccessful, gene-environment interactions result in positive energy balance over time.

With routine screening using BMI, an early diagnosis of overweight or obesity can be made following a positive screen upon subsequent examination and interpretation of elevated BMI and WC results. In addition, as substantiated in the current guidelines, good clinical practice further mandates evaluation of the patient for weight-related complications. In patients with uncomplicated overweight or obesity (e.g., insulin sensitive patients who are metabolically healthy and who have no biomechanical complications), secondary prevention measures are warranted to

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Figure 5. Diagnosis and Medical Management of Obesity

DIAGNOSIS		COMPLICATION-SPECIFIC STAGING AND TREATMENT		
Anthropometric Component (BMI kg/m²)	**Clinical Component**	**Disease Stage**	**Chronic Disease Phase of Prevention**	**Suggested Therapy (based on clinical judgment)**
<25 <23 in certain ethnicities waist circumference below regional/ ethnic cutoffs		**Normal weight** (no obesity)	**Primary**	• **Healthy lifestyle:** healthy meal plan/ physical activity
25–29.9 23–24.9 in certain ethnicities	Evaluate for presence or absence of adiposity-related complications and severity of complications • Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease • Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Female infertility • Male hypogonadism • Obstructive sleep apnea • Asthma/reactive airway disease • Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Depression	**Overweight stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions
≥30 ≥25 in certain ethnicities		**Obesity stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider after lifestyle therapy fails to prevent progressive weight gain. (BMI ≥27)
≥25 ≥23 in certain ethnicties		**Obesity stage 1** (1 or more mild-moderate complications)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider after lifestyle therapy fails to achieve therapeutic target or initiate concurrent with lifestyle therapy. (BMI ≥27)
≥25 ≥23 in certain ethnicties		**Obesity stage 2** (at least 1 severe complication)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Add weight-loss medications:** Initiate concurrent with lifestyle therapy. (BMI ≥27) • **Consider bariatric surgery:** (BMI ≥35)

a. All patients with BMI ≥25 have either overweight stage 0, obesity stage 0, obesity stage 1, or obesity stage 2, depending on the initial clinical evaluation for presence and severity of complications. These patients should be followed over time and evaluated for changes in both anthropometric and clinical diagnostic components. The diagnoses of overweight/obesity stage 0, obesity stage 1, and obesity stage 2 are not static, and disease progression may warrant more aggressive weight-loss therapy in the future. BMI values ≥25 have been clinically confirmed to represent excess adiposity after evaluation for muscularity, edema, sarcopenia, etc.

b. Stages are determined using criteria specific to each obesity-related complication; stage 0 = no complication; stage 1 = mild-to-moderate; stage 2 = severe.

c. Treatment plans should be individualized; suggested interventions are appropriate for obtaining the sufficient degree of weight loss generally required to treat the obesity-related complication(s) at the specified stage of severity.

d. BMI ≥27 is consistent with the prescribing information mandated by the US Food and Drug Administration for weight-loss medications.

Abbreviation: BMI = body mass index.

Fig. 5. incorporates and summarizes many of the evidence-based recommendations provided in this document.

prevent further weight gain and the development of complications. This can be accomplished by lifestyle-behavioral therapy with consideration given to adjunctive treatment using weight-loss medications.

However, in chronic diseases like obesity, other subsets or overlapping subsets of genes and their interactions with the environment determine individual variation in the severity of the disease and the presence and severity of complications. This is evidenced by the demonstration of overlapping and nonoverlapping susceptibility genes associated with obesity and sleep apnea (92 [EL 3; SS]) and with obesity and diabetes (89 [EL 3; SS]; 93; [EL 3; SS]; 94 [EL 3; SS]). An analogy for obesity would be diabetes itself where separate genes determine the predilection for microvascular complications that can vary among individuals at any given level of hyperglycemia (95 [EL 3; SS]; 96 [EL 3; SS]). Once excess adiposity results in weight-related complications, it has become clear that overweight and obesity overtly produce adverse effects on the health of the patient, and tertiary interventions are warranted.

The degrees of weight loss sufficient to ameliorate various weight-related complications are established in these guidelines. Sufficiently aggressive treatment to achieve these weight-loss goals is warranted. Intensive lifestyle intervention assisted by weight-loss medications and consideration given to bariatric surgery will be beneficial in many patients. Thus, the 3-phase paradigm for chronic disease prevention is consistent with the pathogenesis and natural history of obesity and provides a rational framework for the appropriate modality used for prevention and the intensity of the intervention at each phase of prevention.

In the AACE Advanced Framework for a New Diagnosis of Obesity (15 [EL 4; NE]), a staging system was proposed for obesity consistent with the 3-phase paradigm for chronic diseases, which was designed to assist clinicians with therapeutic decisions (e.g., what are we treating and why are we treating it), as shown in Table 12. Stage 0 overweight or obesity is characterized by elevated BMI and the absence of weight-related complications following clinical evaluation to exclude a checklist of complications. This stage requires secondary disease prevention with the objective to prevent progressive weight gain and the development of weight-related complications. Appropriate therapy based on clinical judgment would include lifestyle therapy. Once a patient with overweight or obesity develops complications, this is an indication that excess adiposity is adversely affecting the health of the patient, and tertiary prevention is required to avert further disease deterioration and ameliorate complications via more aggressive weight-loss measures. Stage 1 obesity is characterized by mild to moderate complications (based on complication-specific criteria), which might require intensive lifestyle/behavioral therapy and the consideration of adding weight-loss medications. Stage 2 obesity is characterized by severe complications appropriately treated with concurrent initiation of intensive lifestyle/behavioral therapy plus a weight-loss medication, with consideration given to bariatric surgery.

There have been some differences in the definitions of primary, secondary, and tertiary prevention as clinical practice has evolved and as these concepts are applied to different disease entities (97 [EL 4; NE]). One point of discrepancy relates to whether a chronic pathophysiologic process is regarded as a risk factor or a disease. For example, if obesity is considered a risk factor for the actual disease of diabetes, then weight-loss therapy in patients with obesity would constitute primary prevention of diabetes. Alternatively, if obesity is considered a disease, then weight-loss therapy represents secondary prevention to prevent weight-related complications, and, in patients with obesity who have developed diabetes, weight loss is a tertiary intervention to prevent progressive obesity and to ameliorate diabetes as a weight-related complication.

In 2012, the AACE Position Statement on Obesity and Obesity Medicine designated obesity as a disease and delineated the rationale for this position based on accumulated scientific data (12 [EL 4; NE]). Briefly, it was concluded that obesity clearly met criteria for a disease because it is heavily influenced by genetic factors, has identifiable signs and symptoms, involves pathophysiologic processes in tissues (adipose, hypothalamus), and causes morbidity and mortality (12 [EL 4; NE]). Subsequently, the AACE was joined by multiple professional organizations in submitting a resolution to the AMA to recognize obesity as a disease. In June 2013, following a vote by its House of Delegates, the AMA adopted a policy designating obesity as a chronic disease (13 [EL 4; NE]). To be consistent with our scientific understanding of obesity, it is rational to approach obesity as a disease that can be prevented (primary), that can be treated to prevent worsening and the development of complications once it occurs (secondary), and that can be treated once complications have developed to prevent progressive disease and improve weight-related complications (tertiary).

- ***Q2. How should the degree of adiposity be measured in the clinical setting?***
  - *Q2.1. What is the best way to optimally screen or aggressively case-find for overweight and obesity?*

Executive Summary

- **R3.** All adults should be screened annually using a BMI measurement; in most populations a cut point of ≥25 kg/m^2 should be used to initiate further evaluation of overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.

- *Q2.2. What are the best anthropomorphic criteria for defining excess adiposity in the diagnosis of overweight and obesity in the clinical setting? (Table 6 in Executive Summary)*

Executive Summary

- **R4.** BMI should be used to confirm an excessive degree of adiposity and to classify individuals as having overweight (BMI 25 to 29.9 kg/m^2) or obesity (BMI ≥30 kg/m^2), after taking into account age, gender, ethnicity, fluid status, and muscularity; therefore, clinical evaluation and judgment must be used when BMI is employed as the anthropometric indicator of excess adiposity, particularly in athletes and those with sarcopenia **(Grade A; BEL 2, upgraded due to high relevance)**.
- **R5.** Other measurements of adiposity (e.g., bioelectric impedance, air/water displacement plethysmography, or DEXA) may be considered at the clinician's discretion if BMI and physical examination results are equivocal or require further evaluation **(Grade C, BEL 2, downgraded due to evidence gaps)**. However, the clinical utility of these measures is limited by availability, cost, and lack of outcomes data for validated cutoff points **(Grade B; BEL 2)**.

- *Q2.3. Does waist circumference provide information in addition to BMI to indicate adiposity risk?*

Executive Summary

- **R6.** When evaluating patients for adiposity-related disease risk, WC should be measured in all patients with BMI <35 kg/m^2 **(Grade A; BEL 2, upgraded due to high relevance)**. In many populations, a WC cutoff point of ≥94 cm in men and ≥80 cm in women should be considered at risk and consistent with abdominal obesity; in the U.S. and Canada, cutoff points that can be used to indicate increased risk are ≥102 cm for men and ≥88 cm for women **(Grade A; BEL 2, upgraded due to high relevance)**.

- *Q2.4. Do BMI and waist circumference accurately capture adiposity risk at all levels of BMI, ethnicity, gender, and age?*

Executive Summary

- **R7.** A BMI cutoff point value of ≥23 kg/m^2 should be used in the screening and confirmation of excess adiposity in South Asian, Southeast Asian, and East Asian adults **(Grade B; BEL 2)**.
- **R8.** Region- and ethnic-specific cutoff point values for WC should be used as measures of abdominal adiposity and disease risk; in South Asian, Southeast Asian, and East Asian adults, men with values ≥85 cm and women ≥74 to 80 cm should be considered at risk and consistent with abdominal obesity **(Grade B; BEL 2)**.

Evidence Base

Recommendation 3.

The BMI is an anthropometric measure that interrelates height and weight of individuals and is quantified as weight in kilograms divided by height in meters squared (kg/m^2). It is an indirect measure for estimation of total body fat mass. Using BMI as the primary screening tool for obesity and overweight is consistent with recommendations and guidelines developed by the U.S. Preventive

Table 12. Diagnostic Framework for Overweight/Obesity Consistent with the Phases of Chronic Disease Prevention (15 [EL 4; NE])

DIAGNOSIS	ANTHROPOMETRIC COMPONENT	CLINICAL COMPONENT*	PHASES OF PREVENTION/ TREATMENT
Normal	BMI <25 kg/m^2		PRIMARY
Overweight Stage 0	BMI 25–29.9 kg/m^2	No obesity-related complications	SECONDARY
Obesity Stage 0	BMI ≥30 kg/m^2	No obesity-related complications	
Obesity Stage 1	BMI ≥25 kg/m^2	Presence of 1 or more mild-to-moderate obesity-related complications	TERTIARY
Obesity Stage 2	BMI ≥25 kg/m^2	Presence of 1 or more severe obesity-related complications	

* Staging of complications as mild-moderate (Stage 1) or severe (Stage 2) is based on complications-specific criteria

Services Task Force (98 [EL 4; NE]), the American Heart Association (AHA) (20 [EL 4; NE]), the American College of Cardiology (ACC) (20 [EL 4; NE]), The Obesity Society (TOS) (20 [EL 4; NE]), the Canadian Task Force on Preventive Health Care (CTFPHC) (99 [EL 4; NE]), the American College of Obstetricians and Gynecologists (ACOG) (100 [EL 4; NE]), and NICE (101 [EL 4; NE]).

BMI is useful for the initial screening of the general population for classification of excess weight as it generally correlates with individual differences in adiposity and is associated with risk of comorbidities secondary to excess body fat (102 [EL 3; CSS]; 103 [EL 3; CSS]; 104 [EL 3; CSS]; 105 [EL 3; CSS]; 106 [EL 3; CSS]; 107 [EL 2; MNRCT]). There is a large body of evidence correlating higher BMI with cardiometabolic disease manifestations including diabetes (108 [EL 3; SS]; 109 [EL 2; PCS]; 110 [EL 2; PCS]; 111 [EL 2; MNRCT]; 112 [EL 2; PCS]; 113 [EL 2; MNRCT]), gestational diabetes (114 [EL 2; MNRCT]), and atherosclerotic CVD, including stroke, and recurrent coronary events in those with coronary artery disease (CAD) (115 [EL 2; PCS]; 116 [EL 2; RCCS]; 117 [EL 2; MNRCT]; 118 [EL 2; PCS]). Of note, a recent meta-analysis of prospective cohorts showed no sex differences when predicting risk of CAD with BMI increasing beyond 25 kg/m^2 (119 [EL 2; MNRCT]).

Mortality in prospective cohorts generally correlates with increasing BMI beyond 25 to 30 kg/m^2; however, the BMI value that marks the inflection point for increasing mortality risk varies among groups (120 [EL 2; MNRCT]; 121 [EL 2; PCS]; 122 [EL 2; MNRCT]; 123 [EL 2; PCS]; 124 [EL 2; MNRCT]). In the general population and in patients with T2DM, there is a J-shaped curve relating BMI with mortality with increments in mortality occurring once the BMI rises above 25 kg/m^2 (109 [EL 2; PCS]). In those individuals who have never smoked, there is conflicting evidence questioning the increased risk of BMI between 25 to 30 kg/m^2 in prospective cohorts while BMI values >30 kg/m^2 are associated with higher mortality (124 EL 2; MNRCT]; 125 [EL 2; MNRCT]; 126 [EL 2; MNRCT]; 127 [EL 2; MNRCT]; 128 [EL 2; PCS]).

Increasing BMI is also correlated with increased cancer incidence and cancer mortality. There is heterogeneity among the cancer types associated with increased BMI as a function of gender and in different populations (129 [EL 2; PCS]; 130 [EL 2; MNRCT]; 131 [EL 2; PCS]).

Recommendation 4.

BMI alone cannot identify excess adiposity and establish a diagnosis of overweight or obesity in all instances (132 [EL 2; PCS]; 133 [EL 3; CSS]; 134 [EL 3; CCS]). BMI has limited interindividual consistency for estimating body fat percentage and distribution (135 [EL 3; CSS]; 136 [EL 3; CSS]; 137 [EL 2; PCS]; 138 [EL 3; CSS]; 139 [EL 3; CSS]). In addition to fat mass, the weight measurement used in the calculation incorporates lean mass, bone mass, and fluid status; all of these body components contribute to weight independent of fat mass. To determine the degree to which the BMI value is indicative of excess adiposity, the clinician must consider muscularity, volume status (edema, dehydration), third-space fluid accumulation (e.g., ascites), sarcopenia, loss of muscle mass due to denervation or intrinsic myopathy, pregnancy, large tumors (e.g., uterine leiomyosarcomas), and lipodystrophy.

BMI may underestimate cardiometabolic risk in some patients (such as in the elderly), while overestimating risk in others (such as athletes), particularly when adjusted for clinical complications of adiposity (136 [EL 3; CSS]; 140 [EL 3; CSS]; 141 [EL 2; MNRCT]). Notably, BMI performs poorly in assessing the adiposity and associated health risks of athletes due to higher muscle mass, lower body fat, and lower cardiometabolic risk at higher BMI levels (142 [EL 3; CSS]; 143 [EL 3; CSS]). BMI also inadequately predicts cardiometabolic risk in those with sarcopenic obesity, which is correlated with higher mortality, while WC remains predictive (144 [EL 4; NE]; 145 [EL 2; PCS]; 146 [EL 2; MNRCT]; 147 [EL 2; PCS]; 148 [EL 2; MNRCT]; 149 [EL 2; PCS]; 150 [EL 2; PCS]; 151 [EL 2; PCS]). Mortality in the elderly has similarly been shown to be more strongly predicted by fat-free mass index than by BMI (152 [EL 2; PCS]).

There are a few circumstances where there may exist a paradoxical inverse relationship between BMI and mortality. The National Health Interview Survey demonstrated that BMI was inversely correlated with mortality in the elderly (≥65 years) (153 [EL 2; RCCS]), and there was a U-shaped mortality curve in a large U.S. prospective cohort of diabetes patients with the lowest mortality being among those with a BMI of 30 to 35 kg/m^2 (154 [EL 2; PCS]; 155 [EL 2; PCS]). A similar large United Kingdom (U.K.) cohort showed that mortality was lowest among those with diabetes and a BMI of 25 to 30 kg/m^2 (although higher CVD events were noted with BMI ≥25 kg/m^2) (156 [EL 2; PCS]), consistent with a meta-analysis highlighting the overestimation of risk using BMI in patients with T2DM (157 [EL 2; MNRCT]). Additionally, BMI was inversely associated with cerebrovascular accident in a cohort of patients with diabetes (158 [EL 2; PCS]). There is also an "obesity paradox" in chronic heart failure (159 [EL 2; MNRCT]). However, it is important to consider that other factors, including fitness and lean body mass, can account for the obesity mortality paradox at least in part (160 [EL 2; PCS]; 161 [EL 3; SS]).

Clinical judgment must be used to appropriately diagnose overweight and obesity following the use of BMI for screening, particularly in those with a low BMI but high clinical adiposity and those with high BMI but low clinical adiposity.

Recommendation 5.

Other measurements of adiposity may be considered at the clinician's discretion if BMI and physical examination results (including WC and/or waist-to-height ratio [WHtR]) are equivocal and require further evaluation (21 [EL 4; NE]). These include the use of bioelectric impedance, air/water displacement plethysmography, or DEXA scan. Bioelectric impedance is commonly used commercially and clinically but is dependent on the hydrational state of individuals. Bioelectric assessment of body composition did not improve prediction of CVD or mortality beyond BMI or WHtR in the EPIC-Norfolk cohort (162 [EL 2; PCS, N = 19]; 163 [EL 2; PCS]). Use of DEXA and air-displacement has increased, and they have been validated for reasonably accurate assessments of body fat percentage. The DEXA scan also allows for calculation of the fat mass index (total body fat mass [kg] divided by height [m^2]), which is a physiologic relevant measure of adiposity (164 [EL 3; CSS]; 165 [EL 3; CCS]; 166 [EL 3; CCS]; 167 [EL 2; PCS, N = 50 men]; 168 [EL 3; CSS, N = 62 men]; 169 [EL 3; CSS]; 170 [EL 3; CSS]; 171 [EL 3; CSS, N = 60]; 172 [EL 3; CSS]; 173 [EL 4; NE]). The clinical utility of these measures is limited by availability, cost, and lack of outcomes data, but they have been applied extensively in research settings. Body fat percentage cut points for obesity have been proposed by the World Health Organization (WHO) to be 25% for men and 35% for women (174 [EL 4; NE]).

Recommendation 6.

WC should be measured in all patients when screening for obesity and obesity-related comorbidities, especially when BMI is <35 kg/m^2, using currently recommended ethnic-specific cutoffs as advocated in the 2009 Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute (NHLBI); AHA; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (Table 3) (32 [EL 4; NE]). This is consistent with guidelines established by the NHLBI, National Institutes of Health (16 [EL 4; NE]), AHA/ACC/TOS (20 [EL 4; NE]), NLA (175 [EL 4; NE]), CTFPHC (99 [EL 4; NE]), and NICE (176 [EL 4; NE]). A 2007 consensus statement titled "Shaping America's Health: Association for Weight Management and Obesity Prevention" from TOS, the American Society for Nutrition, and the American Diabetes Association (ADA) (177 [EL 4; NE]) concluded that WC measurement would identify a "nontrivial" number of patients who are at increased cardiometabolic risk not otherwise identified by BMI but most likely would not affect management if NHLBI guidelines were followed based upon BMI and BMI categories (i.e., overweight and class I, II, and III obesity). In a recent scientific statement and systemic review from the AHA on "Identification of Obesity and Cardiovascular Risk in Ethnically and Racially Diverse Populations," annual WC measurements were recommended to gauge cardiovascular (CV) risk in diverse populations using WHO thresholds, due to the questionable utility of BMI (see Table 2 for disease risks relative to weight and WC) (178 [EL 4; NE]).

WC estimates visceral adipose tissue and is the most common and simplest anthropometric measurement of abdominal obesity. With progressive weight gain in insulin-resistant individuals, there is a relatively greater accumulation of fat in the visceral adipose tissue depot. This reflects a dysfunctional ability of adipose tissue in general to store fat (particularly subcutaneous fat) with a redistribution to intra-abdominal adipose tissue. This is accompanied by an influx of macrophages, inflammation, and dysregulation of secreted adipocytokines that adversely influences systemic metabolism. It is not surprising then that WC consistently and strongly predicts components of metabolic syndrome, T2DM, CVD risk factors, and CVD events in cross-sectional studies and prospective cohorts. The predictive value of WC is generally independent of, and stronger than, BMI and is evident at BMI <25 kg/m^2 (179 [EL 3; CSS]; 180 [EL 3; CSS]; 181 [EL 2; PCS]; 182 [EL 3; SS]; 183 [EL 3; CSS]; 184 [EL 3; CSS]; 185 [EL 3; CSS]; 186 [EL 3; CSS]; 187 [EL 3; CSS]; 188 [EL 3; CSS]; 189 [EL 2; PCS]; 190 [EL 2; MNRCT]; 191 [EL 3; CSS]; 192 [EL 2; RCCS]). Long-term follow-up of the Coronary Artery Risk Development in Young Adults (CARDIA) cohort using time-varying excess BMI ≥25 kg/m^2 and WC (≥94 cm for men and ≥80 cm for women) predicted risk of CVD better than either alone (193 [EL 2; PCS]). WC is correlated with mortality more positively and linearly than BMI and is a stronger independent predictor of mortality at all levels of BMI (194 [EL 3; SS]; 195 [EL 2; PCS]; 196 [EL 2; PCS]; 197 [EL 2; PCS]; 198 [EL 3; SS]; 199 [EL 2; PCS]; 200 [EL 2; MNRCT]; 201 [EL 2; MNRCT]). WC is also a better predictor of mortality in the elderly and in those with lower BMI, established CAD, or heart failure (202 [EL 2; MNRCT]; 203 [EL 2; MNRCT]; 204 [EL 2; PCS]; 205 [EL 2; PCS]; 206 [EL 3; CSS]; 207 [EL 2; PCS]; 208 [EL 2; PCS]).

Risks conferred by WC are continuous despite the use of categorical cutoff values. Thus, at any given BMI (above and below 35 kg/m^2), risks of diabetes and CVD increase progressively with additional increments in WC (200 [EL 2; MNRCT]). However, when the BMI exceeds 35 kg/m^2, most patients will exceed categorical WC cutoff values by virtue of a high body mass whether they are insulin resistant and have manifestations of cardiometabolic disease. Thus, above a BMI of 35 kg/m^2, WC cutoff values become less effective in differentiating cardiometabolic disease risk.

Not all studies definitively show WC or measures of abdominal adiposity to be superior to measurement of BMI alone in gauging cardiometabolic risk (209 [EL 2;

PCS]; 210 [EL 3; CSS]). BMI and WC similarly predicted CVD and fatal CVD in a middle-aged cohort from the Netherlands when comparing BMI values ≥30 kg/m^2 with those <25 kg/m^2 and WC values ≥88 cm versus <80 cm in women and ≥102 cm versus ≥94 cm in men (115 [EL 2; PCS]). As independent risk factors, WC was superior to BMI for predicting CVD events in women with a BMI of 25 to 29.9 kg/m^2; however, in all other subgroups of men and women, WC and BMI were equally strong risk predictors in a Framingham Study cohort (211 [EL 2; PCS]). In an analysis of 4 U.K. cohorts, WC was only independently associated with mortality when BMI was <22.5 kg/m^2 and for diabetes in women but not men (212 [EL 2; MNRCT]).

WHtR appeared to predict risk of cardiometabolic disease better than BMI and WC in 2 meta-analyses. Lee et al (213 [EL 2; MNRCT]) performed a meta-analysis of mostly cross-sectional studies showing WHtR had better discriminatory power for cardiometabolic risk variables than BMI based on receiver operator characteristic (ROC) curves, albeit with a small advantage over WC alone and of questionable clinical significance. The meta-analysis by Ashwell et al (214 [EL 2; MNRCT]) included some prospective studies, also using ROC, and again showed greater discriminatory power of WHtR over BMI and even WC for diabetes and CVD. A systematic review of WHtR suggested an approximate WHtR cutoff value of 0.5 across different sex and ethnicities (215 [EL 2; MNRCT]), and similar values of 0.47 in men and 0.51 in women were reportedly ideal for Chinese individuals with normal BMI and WC (216 [EL 3; CSS]). WHtR and waist-hip ratio (WHR) were also shown to be positively related to mortality, compared to a flat J-shape curve for WC and a U-shape curve for BMI, in a meta-regression analysis (217 [EL 2; MNRCT]). These results were similar to an analysis of WHR in National Health and Nutrition Examination Surveys (NHANES) (218 [EL 2; PCS]). However, a recent meta-analysis concluded that WHtR did not significantly predict diabetes better than WC and questioned its utility beyond simply measuring WC (219 [EL 2; MNRCT]).

Recommendations 7 and 8.

BMI cutoffs for identifying excess adiposity and risk of cardiometabolic disease are lower for some ethnicities and should be taken into account when screening (220 [EL 2; MNRCT]; 221 [EL 3; CSS]; 222 [EL 3; CSS]). Specifically, a lower BMI threshold for screening of obesity is recommended in South Asian, Southeast Asian, and East Asian adult populations. Based on the evidence that lower BMI values are correlated with risk of T2DM, the ADA recommends that screening for diabetes should be considered for all Asian American adults who present with BMI ≥23 kg/m^2 (223 [EL 4; NE]). This recommendation is consistent with guidance from a WHO Expert Consult group (224 [EL 4; NE]), the Japan Society for the Study of Obesity (225 [EL 4; NE]), and an extension of Asian-Pacific recommendations (226 [EL 2; MNRCT]). The body of evidence addressing this issue, including meta-analyses performed by the Working Group on Obesity in China, suggests that using a BMI cutoff of ≥23 kg/m^2 would be the optimal single criterion for screening all Asian ethnicities for obesity based upon correlations with cardiometabolic risk factors and increased risk of mortality (226 [EL 2; MNRCT]; 227 [EL 3; CSS]; 228 [EL 3; CSS]; 229 [EL 2; PCS]; 230 [EL 2; MNRCT]; 231 [EL 2; PCS]; 232 [EL 2; MNRCT]; 233 [EL 2; PCS]; 234 [EL 2; MNRCT]). Based on epidemiologic data, the WHO has proposed the following weight classifications in adult Asians: BMI <18.5 kg/m^2 indicates underweight, 18.5 to 22.9 kg/m^2 normal weight, 23 to 24.9 kg/m^2 overweight, 25 to 29.9 kg/m^2 obese class I, and ≥30 kg/m^2 obese class II (224 [EL 4; NE]).

WC cutoff points for predicting cardiometabolic disease exhibit ethnic variation, including a consistently lower threshold in South Asian, Southeast Asian, and East Asian adults. WC predicted increased risk with values starting at ≥84 cm for men and ≥74 cm for women in a large Hong Kong cohort, while a WC of 85 cm for men and 80 cm for women were recommended as cutoffs for central obesity in Chinese adults, according to the Cooperative Meta-Analysis Group of the Working Group on Obesity in China (226 [EL 2; MNRCT]; 235 [EL 3; CSS]). WC values also do not consistently correspond to BMI cutoff points as shown in white, black, and Hispanic adults from NHANES data (236 [EL 3; SS]). Further research is needed to identify specific cutoffs for individual metabolic and cardiovascular (CV) risk in a variety of ethnic populations (237 [EL 2; MNRCT]). Many cross-sectional studies have shown variation in cutoff values indicative of increased cardiometabolic risk among geographically defined ethnic groups.

- ***Q3. What are the weight-related complications that are either caused or exacerbated by excess adiposity? (Fig. 3 in Executive Summary)***
  - *Q3.1. Diabetes risk, metabolic syndrome, and prediabetes (IFG, IGT)*

Executive Summary

- **R9.** Patients with overweight or obesity and patients experiencing progressive weight gain should be screened for prediabetes and T2DM and evaluated for metabolic syndrome by assessing WC, fasting glucose, A1C, blood pressure, and lipid panel, including triglycerides and HDL-c **(Grade A; BEL 2, upgraded due to high clinical relevance)**.
- **R10.** Due to variable risk for future diabetes, patients with overweight or obesity should be evaluated for risk of T2DM, which can be estimated or stratified using indices or staging systems that employ clinical data, glucose tolerance

testing, and/or metabolic syndrome traits **(Grade B; BEL 2)**.

Evidence Base

There is a close association between obesity and cardiometabolic disease risk, which is the result of a pathophysiologic process involving insulin resistance, progressing to clinically identifiable prediabetic states, including metabolic syndrome and prediabetes, and culminating in T2DM and/or CVD (238 [EL 4; NE]; 239 [EL 4; NE]; 240 [EL 2; PCS]; 241 [EL 3; SS]; 242 [EL 4; NE]). Prevalence rates of T2DM have been increasing worldwide, resulting in a huge burden of patient suffering and social costs, which underscores the importance of finding effective strategies for prevention (243 [EL 3; SS]). To prevent T2DM, it will be necessary to intervene early in the cardiometabolic disease process, particularly in people with metabolic syndrome and prediabetes.

The most common diagnostic criteria for metabolic syndrome are those advocated by the Adult Treatment Panel III (ATP III) of the National Cholesterol Program and include abnormal values for WC, blood pressure (BP), triglycerides, HDL-c, and fasting glucose (32 [EL 4; NE]; 244 [EL 4; NE]). Prediabetes is present when either the fasting glucose and/or the 2-hour glucose following oral glucose challenge are above normal but below the threshold of diabetes, referred to as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), respectively (245 [EL 4; NE]). Because one trait used to identify metabolic syndrome is IFG, many patients meet criteria for both metabolic syndrome and prediabetes. Consensus statements by the ADA (246 [EL 4; NE]) and the AACE (247 [EL 4; NE]) recommend lifestyle intervention for patients with prediabetes, including use of diabetes medications (i.e., metformin) in patients at highest risk of T2DM.

Obesity can worsen insulin resistance and impel disease progression to metabolic syndrome and prediabetes and ultimately to diabetes and CVD (248 [EL 3; SS]; 249 [EL 2; MNRCT]; 250 [EL 4; NE]; 251 [EL 4; NE]). Ford et al (252 [EL 3; CSS]) found that the prevalence of metabolic syndrome increased by 28% in the National Health and Nutrition Examination Surveys from 1988-1994 to 1999-2000, and that this was attributable to 2 factors. One was the prevalence of obesity that increased from 22.5 to 30.5% over the same time (253 [EL 3; CSS]), and the other was an aging population with age-related increments in BP and glucose (254 [EL 3; CSS]).

Several meta-analyses have examined the relationship between BMI and metabolic syndrome or prediabetes, and, while BMI confers risk, most studies demonstrate that measures of central adiposity are superior to BMI. Van Dijk et al (255 [EL 2; MNRCT]) analyzed 20 studies that included 21,618 males and 24,139 females and found that both BMI and WC were correlated with all CVD risk factors. However, when comparing BMI with WC, the latter showed significantly better correlations to CVD risk factors, except for DBP in women and HDL-c and total cholesterol in men (255 [EL 2; MNRCT]). Savva et al (256 [EL 2; MNRCT]) conducted a meta-analysis of 24 cross-sectional studies and 10 prospective studies with 512,809 participants and found that WHtR had a stronger association with metabolic syndrome (relative risk [RR]: 0.92, 95% confidence interval [CI]: 0.89-0.96) and diabetes (RR: 0.71, 95% CI: 0.59-0.84) than BMI in cross-sectional studies. In addition, in prospective studies, WHtR appeared to be superior to BMI in detecting several outcomes, including incident CVD, CVD mortality, and all-cause mortality (256 [EL 2; MNRCT]). Kodama et al (219 [EL 2; MNRCT]) assessed 15 prospective cohort studies and determined that the pooled RR for diabetes was 1.62 (95% CI: 1.48, 1.78) for WHtR, 1.55 (95% CI: 1.43, 1.69) for BMI, 1.63 (95% CI: 1.49, 1.79) for WC, and 1.52 (95% CI: 1.40, 1.66) for WHR. Finally, Friedermann et al (257 [EL 2; MNRCT]) analyzed 63 studies of 49,220 children and reported a worsening of risk parameters for CVD in patients with overweight or obesity, including greater BP, blood lipids, fasting insulin, and left ventricular mass of 19.12 g (12.66 to 25.59 g, n = 223), compared to normal-weight children.

Despite strong associations, the precise mechanisms that link obesity with insulin resistance and cardiometabolic disease risk have not been clearly elucidated (258 [EL 4; NE]). Predisposition to insulin resistance and the progression of cardiometabolic risk factors to overt T2DM and CVD events involves the convergence of genetic factors, behavior, and the environmental milieu, including poor diet and sedentary lifestyle (258 [EL 4; NE]). While BMI is also an important factor, obesity is neither necessary nor sufficient as a predictor of diabetes because lean individuals can develop T2DM and most individuals with obesity do not develop diabetes (259 [EL 2; PCS, N = 22]).

In those individuals who develop diabetes, progressive weight gain and obesity are accompanied by preferential fat accretion in the intra-abdominal compartment, dysregulated secretion of adipocytokines (e.g., decreased adiponectin), an increase in systemic inflammation marked by elevated circulating IL-6, intracellular lipid accumulation in myocytes and hepatocytes, and oxidative stress responses (242 [EL 4; NE]; 250 [EL 4; NE]; 260 [EL 4; NE]; 261 [EL 4; NE]; 262 [EL 4; NE]; 263 [EL 4; NE]; 264 [EL 2; PCS]). These patients with dysfunctional adipose tissue will also develop clinical manifestations of metabolic syndrome, such as glucose intolerance, elevated BP, and dyslipidemia (238 [EL 4; NE]; 239 [EL 4; NE]; 242 [EL 4; NE]; 250 [EL 4; NE]; 260 [EL 4; NE]; 265 [EL 2; NRCT]). These clinical and molecular markers are indicative of underlying insulin resistance, which can afflict individuals who are lean or have obesity (259 [EL 2; PCS, N = 22]). Insulin sensitivity varies over 5-fold in individuals in a manner that is largely independent of BMI (266

[EL 2; PCS]; 267 [EL 4; NE]; 268 [EL 4; NE]; 269 [EL 2; PCS]). Those individuals on the insulin resistance side of the spectrum are at risk of developing metabolic syndrome and/or prediabetes (238 [EL 4; NE]; 239 [EL 4; NE]). Dysfunctional insulin-resistant adipocytes exhibit a diminished ability to store lipid and cause a redistribution of fat to the intra-abdominal compartment and the accumulation of lipid within muscle cells and hepatocytes, which further exacerbates insulin resistance at the level of these organs and contributes to abnormal glucose tolerance. Generalized obesity and weight gain can further drive lipid accumulation in muscle, liver, and the visceral compartment, and thus further impel progression of the cardiometabolic pathophysiologic process toward the end-stage manifestations of overt T2DM and CVD (250 [EL 4; NE]; 263 [EL 4; NE]; 270 [EL 2; PCS]).

Analyses of prospective diabetes risk in the Atherosclerosis Risk in Communities cohort indicated that weight gain in an insulin-sensitive background has no impact on risk for CVD, and cumulative rates of incident diabetes remain low (241 [EL 3; SS]; 271 [EL 3; SS]; 272 [EL 2; PCS]). By contrast, weight gain in individuals with a background of insulin resistance markedly increases diabetes risk. Thus, obesity and weight gain exacerbate cardiometabolic disease risk and promote progression to diabetes when occurring in insulin-resistant individuals. Ultimately, the chronic metabolic stress of insulin resistance must produce decompensation of insulin-secreting beta cells for progression to overt diabetes (258 [EL 4; NE]).

It is evident that not all those with obesity develop diabetes. In fact, a proportion of individuals with obesity do not exhibit metabolic syndrome traits and have been referred to as "metabolically healthy obese" (192 [EL 3; SS]; 240 [EL 2; PCS]; 241 [EL 2; PCS]; 273 [EL 3; SS]; 274 [EL 2; PCS]; 275 [EL 2; RCCS]; 276 [EL 2; PCS, selection bias]). Physiologic studies have demonstrated that subjects with obesity but without metabolic syndrome traits are relatively insulin sensitive (259 [EL 2; PCS, N = 22]; 266 [EL 3; SS]; 267 [EL 4; NE]; 268 [EL 2; PCS]; 269 [EL 4; NE]; 274 [EL 2; PCS]; 277 [EL 2; PCS]) and epidemiologic data indicate low risk of progression to diabetes and CVD (192 [EL 3; SS]; 241 [EL 3; SS]; 271 [EL 2; PCS]; 275 [EL 2; RCCS]; 276 [EL 2; PCS, selection bias]; 278 [EL 2; PCS]). This presents a challenge for health care professionals regarding the identification of patients at high risk of diabetes among the 70% of Americans with overweight or obesity. Diagnosing patients with metabolic syndrome (32 [EL 4; NE]; 244 [EL 4; NE]) and prediabetes (245 [EL 4; NE]) is helpful, because this effectively identifies individuals at high risk of diabetes and CVD (238 [EL 4; NE]; 239 [EL 4; NE]; 240 [EL 2; PCS]; 241 [EL 3; SS]; 248 [EL 3; SS]; 249 [EL 2; MNRCT]; 250 [EL 4; NE]; 251 [EL 4; NE]). Prediabetes can be diagnosed on the basis of IFG, IGT defined by the 2-hour level following an oral glucose tolerance test (i.e., post-OGTT), or by an elevation in hemoglobin A1C (245 [EL 4; NE]). Additionally, IFG is part of the metabolic syndrome, and many patients satisfy criteria for prediabetes and metabolic syndrome.

However, these entities alone will not identify significant proportions of at-risk patients (274 [EL 3; SS]; 278 [EL 2; PCS]). Various indices using information from history and physical examination (279 [EL 4; NE]; 280 [EL 2; PCS]; 281 [EL 3; SS]; 282 [EL 3; SS]; 283 [EL 3; SS]) such as the Framingham Risk Score (279 [EL 4; NE]) or commercial products that employ biomarkers (284 [EL 2; PCS]; 285 [EL 4; NE]; 286 [EL 4, NE]; 287 [EL 3; SS]) can also be used to stage risk in insulin-resistant patients, whether they meet diagnostic criteria for metabolic syndrome or prediabetes. Cardiometabolic disease staging has been validated to stratify diabetes risk over 40-fold based on the presence and absence of metabolic syndrome traits in the CARDIA and Atherosclerosis Risk in Communities cohort studies (241 [EL 3; SS]; 271 [EL 3; SS]). These risk-staging strategies can be used to identify patients at greatest risk for T2DM and CVD who may benefit from more aggressive preventive interventions.

- *Q3.2. Type 2 diabetes*

Executive Summary

- **R11.** Patients with T2DM should be evaluated for the presence of overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.

Evidence Base

There is a close association between obesity and T2DM, and there have been increments in prevalence of both diabetes and obesity worldwide. Currently, among U.S. adults, 34% have obesity (3 [EL 3; CSS]) and over 11% have diabetes (288 [EL 4; NE]), and the prevalence of diabetes is estimated to increase to 21% by 2050 (289 [EL 3; SS]). The close relation between obesity and T2DM is underscored by the term "diabesity," a term originated by Sims and coworkers in 1973 after they demonstrated that young, lean men developed elevations in blood glucose, insulin, and triglycerides, together with IGT, after 6 months of overfeeding resulting in a BMI increase to 28 kg/m^2 (290 [EL 4; NE]). Temporal relationships, racial aggregation, and geographic colocalization underscore the links between obesity and diabetes. In the U.S., 1980 was an inflection point characterized by a marked and progressive increase in obesity prevalence (291 [EL 3; SS]). This was followed 10 years later by a sharp increase in diabetes rates (292 [EL 3; SS]). Regarding racial or ethnic aggregation, rates of both obesity and diabetes are increased in African Americans and Hispanic Americans when compared with non-Hispanic whites (3 [EL 3; CSS]; 288 [EL 4; NE]). Finally, elevated rates of obesity and diabetes

overlap geographically in Appalachia and the Southern tier of states (292 [EL 3; SS]), and these areas have been termed the "Diabetes Belt" (293 [EL 3; SS]).

Two meta-analyses have assessed the association between obesity and diabetes. Vazquez et al (113 [EL 2; MNRCT]) examined 32 studies conducted in multiple countries between 1985 and 2004 (31 cohort studies and 1 nested case-control study) and found that the pooled RR for incident diabetes was 1.87 (95% CI, 1.67-2.10) for every standard deviation increase in BMI. Abdullah et al (111 [EL 2; MNRCT]) analyzed 18 prospective cohort studies and determined that the overall RR of diabetes for people with obesity compared to those with normal weight was 7.19 (95% CI: 5.74, 9.00) and for overweight was 2.99 (95% CI: 2.42, 3.72).

In addition to baseline BMI, other studies have shown that weight gain as an adult is a risk factor for diabetes (294 [EL 2; PCS]; 295 [EL 4; NE]; 296 [EL 2; MNRCT]). For example, in both the Nurses' Health Study and the Health Professionals Follow-up Study, individuals who gained 5.0 to 9.9 kg when compared to those who maintained their weight within 2 kg of their weight as a young adult had risks of diabetes, coronary heart disease, and hypertension that were increased by1.5-fold to 3-fold (295 [EL 4; NE]). These increases in risk were greater in adults with larger weight gains. Kodama et al (296 [EL 2; MNRCT]) conducted a meta-analysis of 15 prospective cohort studies that assessed the relationship between weight gain in adulthood and incident T2DM. The pooled RR for incident diabetes was 3.07 (95% CI: 2.49, 2.79) for a 5 kg/m^2 increment in BMI occurring early in adulthood and 2.12 (95% CI: 1.74, 2.58) for weight gain later in adulthood.

Obesity and weight gain have adverse consequences in patients who have diabetes. In addition to risk of other weight-related complications (e.g., sleep apnea), obesity and weight gain can worsen glucose control in diabetes. In one prospective study, deterioration in A1C levels occurred to a greater extent in 50 patients with obesity than in 50 patients who did not have obesity, and this was attributed to greater insulin resistance (297 [EL 1; RCT, nonblinded]). In a larger cohort study involving 705 patients with T2DM, progression of diabetes, defined as A1C >7% or need for additional diabetes medications, occurred more frequently in patients with obesity, and each 1-pound weight gain over the observation period was associated with a 2% increase in the rate of disease progression (298 [EL 2; PCS]). Obesity and increasing body weight were found to adversely affect psychological well-being in patients with diabetes, lead to feelings of inadequacy, and adversely affected treatment satisfaction (299 [EL 3; SS]; 300 [EL 1; RCT, nonblinded]). These psychological effects were associated with greater degrees of noncompliance with therapy. As will be noted below, obesity can also worsen dyslipidemia, hypertension, and CVD risk in patients with diabetes, as is the case in patients without diabetes.

The mechanisms that link obesity with diabetes are not fully known. T2DM represents end-stage disease arising from insulin resistance and the progression of cardiometabolic disease as discussed in Section Q3.1. Insulin resistance occurs early in life and may be exacerbated by the development of obesity, particularly abdominal obesity. This causes metabolic stress in β-cells, which hypersecrete insulin to maintain glucose homeostasis. T2DM results when insulin secretory capacity begins to fail, creating a state of relative insulin deficiency that can no longer compensate for insulin resistance. Obesity can worsen insulin resistance and exacerbate a metabolic milieu that can be directly toxic to beta cell function including inflammation, lipotoxicity, and glucose toxicity (258 [EL 4; NE]). In addition to obesity and insulin resistance, risk factors for developing T2DM include increasing age, lack of physical activity, a positive family history, and inheritance of multiple susceptibility genes, most of which appear to influence beta cell function (258 [EL 4; NE]).

Obesity has also become more common in children and adolescents with type 1 diabetes (T1DM) (301 [EL 2; PCS]). This can induce insulin resistance (302 [EL 2; PCS]) and worsen lipid parameters and BP (303 [EL 1; RCT]). A meta-analysis of 9 studies (8 cohort, 1 case-control) observed that childhood obesity increased risk of T1DM, and the pooled odds ratio was 2.03 (95% CI: 1.46, 2.80) (304 [EL 2; MNRCT]).

- *Q3.3. Dyslipidemia*

Executive Summary

- **R12.** All patients with overweight or obesity and individuals experiencing progressive weight gain should be screened for dyslipidemia with a lipid panel that includes triglycerides, HDL-c, calculated low-density lipoprotein cholesterol (LDL-c), total cholesterol, and non-HDL cholesterol; all patients with dyslipidemia should be evaluated for the presence of overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.

Evidence Base

In cohort and nested case-control studies, patients with obesity have been observed to exhibit increased plasma triglycerides, total cholesterol, and LDL-c, together with lower HDL-c levels (108 [EL 2; PCS]; 305 [EL 2; PCS]; 306 [EL 2; PCS]; 307 [EL 2; PCS]; 308 [EL 4; NE]; 309 [EL 3; SS]). In a study comparing younger and older men, these differences in lipids compared to age-matched controls were greater in younger men with obesity than the differences between older adults with obesity compared to their lean counterparts (305 [EL 2; PCS]). In fact, in a longitudinal study of young adults (CARDIA), dyslipidemia (low HDL-c and high triglycerides) was the first risk factor to appear over the subsequent 20 years (i.e., more than

obesity, hypercholesterolemia, hypertension, diabetes) and the only risk factor to occur first and be followed by clustering of the other risk factors more often than expected (310 [EL 2; PCS]). In other words, dyslipidemia was the first of the CV risk factors to appear in young adults gaining weight.

However, the relationship between BMI and circulating lipids is complex. For example, the Framingham Heart Study documented an increase in HDL-c and a decrease in triglycerides among 1,666 participants over 10 years, despite a modest increase in BMI, although those with the largest increase in BMI had the least favorable changes in lipids (311 [EL 2; PCS]). Some of the effects of obesity on lipids may result from high carbohydrate consumption that can drive hepatic very low-density lipoprotein (VLDL) production (312 [EL 1; RCT, nonblinded]). High alcohol intake can be associated with elevated triglycerides, particularly in patients with obesity (313 [EL 2; RCCS]).

Other effects are more directly attributable to insulin resistance (175 [EL 2; PCS]; [238, [EL 2; PCS]; 239 [EL 4; NE]; 265 [EL 4; NE]; 306 [EL 4; NE]; 308 [EL 4; NE]; 309 [EL 4; NE]; 314 [EL 2; NRCT]). The dyslipidemia associated with insulin resistance is characterized by elevated triglyceride levels, as a result of an excess of large, triglyceride-laden VLDL, and decreased concentrations of HDL-c (265 [EL 2; NRCT]). Levels of LDL-c may not be primarily affected; however, the cholesterol is packaged into smaller, denser low density lipoprotein (LDL) particles (265 [EL 2; NRCT]), which are more atherogenic (315 [EL 1; RCT]; 316 [EL 2; PCS]; 317 [EL 2; MNRCT]; 318 [EL 2; PCS]). This results in a higher LDL particle concentration for any given level of LDL-c. High triglycerides and low HDL-c constitute 2 of the 5 diagnostic criteria for metabolic syndrome, which is associated with increased risk of CVD (314 [EL 4; NE]). While there is accumulating evidence that elevated triglycerides constitute a direct or independent risk factor for CVD, it is uncertain whether the associations are due to indirect effects or links to other lipoprotein abnormalities and risk factors. For example, elevated concentrations of small, dense LDL particles are associated with high triglycerides and confer increased risk of CVD events independent of overall LDL-c levels (316 [EL 2; PCS]; 317 [EL 2; MNRCT]; 318 [EL 2; PCS]). After correction for other risk factors, the associations between high triglycerides and low HDL-c may (319 [EL 2; MNRCT]; 320 [EL 1; RCT]; 321 [EL 2; PCS]) or may not (322 [EL 2; PCS]) remain statistically significant.

High levels of LDL-c represent a major risk factor for CVD and can occur in patients with or without insulin resistance and obesity (323 [EL 4; NE]; 324 [EL 2; PCS]; 325 [EL 2; PCS]). Therefore, LDL-c should be measured and brought to recommended targets in all individuals, particularly in patients with obesity who are at additional risk for CVD (19 [EL 4; NE]; 326 [EL 4; NE]; 327 [EL 4; NE]). In patients with triglycerides ≥500 mg/dL, clearance mechanisms for triglyceride-enriched lipoproteins are saturated and chylomicronemia is likely or can be rapidly induced upon consumption of fatty meals or alcohol (327 [EL 4; NE]). These patients are at risk of pancreatitis when triglyceride levels approach 1,000 mg/dL (328 [EL 4; NE]).

- *Q3.4. Hypertension*

Executive Summary

- **R13.** BP should be measured in all patients with overweight or obesity as a screen for the presence of hypertension or prehypertension; all patients with hypertension should be evaluated for the presence of overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.

Evidence Base

Obesity and hypertension (HTN) frequently coexist, with an estimated 60 to 70% of HTN in adults attributable to excess weight, particularly when this involves increased visceral adiposity (329 [EL 4; NE]). Mechanisms of obesity-related HTN include sodium retention, increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone pathway, insulin resistance, and vascular endothelial dysfunction (329 [EL 4; NE]). Multiple cross-sectional and longitudinal studies have demonstrated an association between BMI or body weight and increased risk of HTN as a function of the degree of weight gain over time (329 [EL 4; NE]; 330 [EL 3; SS]; 331 [EL 2; PCS]; 332 [EL 3; SS]; 333 [EL 3; SS]).

Japanese men and women (68,205 adults) with normal BP aged 40 to 79 years were followed in a prospective, population-based cohort study to examine the association between BMI and risk of incident HTN defined as systolic BP (SBP) >140 mm Hg and DBP (DBP) >90 mm Hg, or HTN medication. HTN developed in 45% of subjects during the mean follow-up of 3.9 years. Compared to subjects with a BMI <19 kg/m^2, adjusted hazard ratios (95% CI) for HTN in adults with a baseline BMI of at least 25 kg/m^2 and age >40 or >60 years in men were 1.42 (1.17-1.73) and 1.34 (1.19-1.51) and for women 1.47 (1.33-1.62) and 1.29 (1.18-1.41), respectively (334 [EL 2; PCS]). A meta-analysis of 19 cross-sectional studies compared the performance of BMI against WC and WHR as indicators of HTN risk in ethnically diverse populations. The incremental increases in BP and the additional risk of HTN (SBP/DBP ≥140/90 mm Hg) were broadly similar for all 3 measures of adiposity (335 [EL 2; MNRCT]). Additional cross-sectional data from 16 cohorts compared BMI to WC and WHR in 9,095 men and 11,732 women of different ethnicities, aged 35 to 74 years (336 [EL 3; CSS]). Age-adjusted odds ratios for HTN in men for 1 standard deviation increase in BMI, WC, and WHR were 1.68, 1.66, and 1.45, respectively, and for women were 1.55, 1.51, and 1.28, respectively. HTN

in men had a stronger association with BMI than WHR ($P<0.001$) and in women stronger than WC ($P<0.05$) and WHR (<0.001).

Mean clinic BP and BP upon awakening were recorded for 2 weeks in 2,554 ambulatory patients with HTN (defined as clinic SBP/DBP >140/90 mm Hg and awakening BP >135/85 mm Hg). Compared with patients without obesity or T2DM, those with both obese and had significantly higher morning BP (138.8 ± 10.5 mm Hg vs. 133.1 ± 11.9 mm Hg, $P<0.0001$) and a higher incidence of morning HTN (73.0% vs. 49.9%, $P<0.0001$) (337 [EL 2; PCS]). A cross-sectional study of 300 people with overweight or obesity, who reported for a medical examination to a large semiurban area hospital, found HTN in 8.2% and 22.2% of those with overweight and obesity, respectively (338 [EL 3; CSS]). A retrospective review from a primary care medical records database of 9,086 adults (age ≥18 years) with HTN were grouped according to normal weight (<24.9 kg/m^2; n = 1,256), overweight (25.0 to 29.9 kg/m^2; n = 3,058), and obesity (≥30.0 kg/m^2; n = 4,772). Patients who had obesity were younger (<65 years) and more likely to have higher baseline BP ($P<0.05$), dyslipidemia ($P<0.05$), and T2DM ($P<0.001$) (339 [EL 2; RCCS]).

HTN is common in patients seeking bariatric surgery (340 [EL 2; PCS]; 341 [EL 2; PCS]; 342 [EL 2; NRCT]). HTN in pre-operative bariatric surgery patients included 43% of 1,106 patients (mean age 43 ± 11 years, 79% women) with a mean BMI of 45.1 kg/m^2 in a multicenter international study (340 [EL 2; PCS]), 68% of 2,458 subjects (18-78 years old, 79% women) with a median BMI of 45.9 kg/m^2 in The Longitudinal Assessment of Bariatric Surgery multicenter observational cohort study in the U.S. (341 [EL 2; PCS]), and 79% of 71 patients with nocturnal HTN evaluated by 24-hour ambulatory BP monitoring (342 [EL 2; NRCT]). Either prehypertension or HTN was found in 91% of 1,508 patients referred to a single institution for bariatric surgery (343 [EL 2; RCCS]).

- *Q3.5. Cardiovascular disease and cardiovascular disease mortality*

Executive Summary

- **R14.** Risk factors for cardiovascular disease should be assessed in patients with overweight or obesity **(Grade A; BEL 2, upgraded due to high relevance)**.
- **R15.** Patients with overweight or obesity should be screened for active cardiovascular disease by history, physical examination, and with additional testing or expert referral based on cardiovascular disease risk status **(Grade A; BEL 2, upgraded due to high relevance)**.

Evidence Base

The association between obesity and CVD has been extensively investigated. These studies have examined this relationship using the endpoints of CVD events, CVD mortality, and all-cause mortality, which are interrelated given that CVD is the most common cause of death in many societies. Mortality data for individuals with obesity has been controversial. Many epidemiologic cohort studies have used BMI as the surrogate for excess adiposity and reported a U-shaped or J-shaped relationship between mortality and BMI (122 [EL 4; NE]; 123 [EL 3; SS]; 124 [EL 3; CSS]; 126 [EL 2; PCS]; 208 [EL 2; MNRCT]; 344 [EL 2; MNRCT]; 345 [EL 2; MNRCT]; 346 [EL 3; CSS]; 347 [EL 2; PCS]). In all studies, there is a value at which increasing BMI begins to be associated with progressively increasing rates of mortality. Similarly, low values of BMI are also associated with increased mortality.

The controversy essentially involves BMI in the overweight range (25 to 29.9 kg/m^2). Various studies have reported that the overweight subgroup either is associated with decreased or unchanged mortality (126 [EL 3; SS]; 345 [EL 3; CSS]; 346 [EL 2; MNRCT]; 347 [EL 3; CSS]; 348 [EL 3; SS]) or with increased risk of mortality (122 [EL 2; PCS]; 123 [EL 2; MNRCT]; 124 [EL 2; MNRCT]; 208 [EL 2; PCS]) when compared to lean subgroups (18.5 to 24.9 kg/m^2). Therefore, the optimal BMI with respect to mortality has not been identified over a range that includes both normal and overweight. The optimal BMI, and the impact of overweight status on mortality, varies as a function of gender, ethnicity, age, and body fat distribution. Studies reporting that overweight status is associated with reduced mortality have been criticized along several lines including: (*1*) confounding effects of reverse causality where pre-existing diseases that increase mortality also cause weight loss (e.g., cigarette smoking, cancer) (349 [EL 2; MNRCT]); (*2*) underestimation of the effect of BMI by overcontrolling for weight-related risk factors and complications; and (*3*) bias resulting from wide ranges of BMI in comparator subgroups, particularly the reference group of lean subjects (18 to 24.9 kg/m^2), where higher mortality rates may apply to individuals with lower BMIs within the overall lean reference group (344 [EL 4; NE]). Finally, the use of BMI as a measure of obesity is problematic in this regard because it is not a direct measure of body fat, is particularly inaccurate as a measure of adiposity in elderly populations, and does not reflect relative fat accumulation in the intra-abdominal compartment (147 [EL 2; PCS]; 350 [EL 4; NE]).

Flegal and colleagues (345 [EL 3; SS]; 346 [EL 3; CSS]; 348 [EL 3; SS]) have published a key series of papers addressing the relationship between BMI and mortality involving the series of NHANES cross-sectional

population surveys. In NHANES I-III (years 1971-2000), the number of excess deaths and the relative risk of mortality attributable to overweight status was reduced in the overweight subgroup (BMI 25 to 29.9 kg/m^2) and unaltered in the obesity class I subgroup (30 to 34.9 kg/m^2) in comparison to the normal weight (18.5 to <25 kg/m^2) subgroup, while the number of excess deaths was elevated in obesity class II and III and underweight (<18.5 kg/m^2) categories (123 [EL 2; PCS]). This work was criticized for failing to control for reverse causality due to smoking and not taking into account differences in follow-up time.

However, subsequent analyses of these data did not alter the relative risks of mortality among the BMI subgroups after controlling for cigarette smoking, pre-existing illness, early deaths, and measurement of BMIs late in life (346 [EL 3; CSS]). By contrast, Adams et al (123 [EL 2; PCS]) studied 527,265 individuals (age range 50-71 years) enrolled in the NIH-AARP Diet and Health Study and found that mortality risk was significantly elevated in the overweight subgroup among never-smokers, in those without pre-existing conditions, or after exclusion of the first 5 years of follow-up when compared to normal weight (123 [EL 2; PCS]).

Flegal et al (126 [EL 2; MNRCT]) also conducted a meta-analysis involving 97 studies and 2.88 million participants that reported hazard ratios for mortality using standard BMI categories and reported hazard ratio (HR) of 0.94 (95% CI, 0.91-0.96) for overweight, 1.18 (CI, 1.12-1.25) for obesity (all grades combined), 0.95 (CI, 0.88-1.01) for grade I obesity, and 1.29 (CI, 1.18-1.41) for grades II and III obesity (126 [EL 2; MNRCT]).

The Prospective Studies Collaboration also conducted a meta-analysis assessing the association between BMI and mortality among 894,576 participants in 57 prospective studies and observed that mortality was lowest at BMI 22.5 to 25 kg/m^2 (124 EL 2; MNRCT]). Above this range, each 5 kg/m^2 increase in BMI was on average associated with approximately 30% higher overall mortality, including significant increments in mortality risk within the overweight subgroup. Below the range 22.5 to 25 kg/m^2, BMI was inversely associated with overall mortality, largely due to increased mortality from respiratory disease and lung cancer.

Berrington de Gonzalez et al (122 [EL 2; MNRCT]) conducted a pooled analysis of 19 prospective studies involving 1.46 million white adults with a mean follow-up of 10 years and found that a BMI of 20 to 24.9 kg/m^2 was associated with the lowest mortality rate while HRs were 1.47 (CI, 1.07-1.22) for BMI 15 to 18.4 kg/m^2, significantly elevated at 1.13 (CI, 1.09-1.17) for overweight BMI 25 to 29.9 kg/m^2, 1.44 (CI, 1.38-1.50) for class I obesity BMI 30 to 34.9 kg/m^2, 1.88 (CI, 1.77-2.00) for class II BMI 35 to 39.9 kg/m^2, and 2.51 (CI, 2.3-2.7) for class III BMI 40 to 49.9 kg/m^2. The rise in mortality rates with progressive overweight and obesity above a BMI of 25 kg/m^2 became more marked when cigarette smokers were excluded from the analysis.

The studies described above address obesity and mortality but not disease-specific mortality. In the NHANES analyses, overweight was associated with significantly decreased mortality from noncancer and non-CVD causes, which explains the small decrease in mortality in comparing overweight and normal weight subgroups (348 [EL 3; SS]). Furthermore, the decrease in mortality due to noncancer/non-CVD events in the overweight group was opposed by an increase in mortality from diabetes and kidney disease. Obesity (BMI ≥30 kg/m^2) was associated with significantly increased mortality from CVD, diabetes, and obesity-related cancers.

These data underscore the contention that, while overweight is not consistently associated with increased mortality, this does not indicate that overweight is not a serious health concern. Mortality is not necessarily indicative of health, disease burden, disability, or quality of life (QOL). In addition, all-cause mortality could represent the net balance of effects to increase and decrease mortality risk due to different diseases (348 [EL 3; SS]).

Unlike the discrepant results reported for all-cause mortality, overweight is more consistently associated with coronary heart disease or CVD mortality in comparison with normal weight subgroups (121 [EL 2; PCS]; 127 [EL 2; PCS]; 232 [EL 2; PCS]; 351 [EL 2; PCS]; 352 [EL 2; PCS]; 353 [EL 2; MNRCT]; 354 [EL 2; PCS]; 355 [EL 2; PCS]; 356 [EL 2; MNRCT]). While obesity is associated with increased CVD events and CVD mortality, the optimal BMI range and the BMI value at which risks begin to escalate remain uncertain. HRs for BMI values in the higher range of overweight (i.e., 27.5 to 29 kg/m^2) have been observed to range between 1.1 to 2.8 over 10 to 26 years of follow-up (121 [EL 2; PCS]; 351 [EL 2; PCS]; 352 [EL 2; PCS]; 353 [EL 2; PCS]; 354 [EL 2; PCS]). BMIs in the lower range of overweight (25 to 27 kg/m^2) can also be associated with increased CVD mortality (121 [EL 2; PCS]; 232 [EL 2; PCS]; 354 [EL 2; MNRCT]; 355 [EL 2; PCS]), while other reports find no difference in CVD mortality rates compared to normal weight (351 [EL 2; PCS]; 352 [EL 2; PCS]; 353 [EL 2; PCS]; 354 [EL 2; PCS]; 356 [EL 2; PCS]). Moreover, rather than a U-shaped or J-shaped curve, the relationship between BMI and CVD outcomes are generally more linear (344 [EL 4; NE]).

Two additional series of observations are relevant in considering the relationship between BMI and CVD outcomes. First, risks of CVD and CVD mortality are more highly attributable to manifestations of insulin resistance (WC, metabolic syndrome traits, fasting and 2-hour OGTT glucose values) than the independent effects of BMI per se (192 [EL 2; PCS]; 213 [EL 2; RCCS]; 241 [EL 2; PCS, selection bias]; 275 [EL 3; SS]; 276 [EL 2; MNRCT]). Physiologic studies have demonstrated that people with obesity but without metabolic syndrome traits are relatively

insulin sensitive (259 [EL 2; PCS, N = 22]; 266 [EL 3; SS]; 267 [EL 2; PCS]; 269 [EL 4; NE]; 274 [EL 2; PCS]; 277 [EL 2; PCS]), and epidemiologic data indicate low risk of progression to diabetes and CVD (192 [EL 2; PCS]; 241 [EL 2; RCCS]; 275 [EL 2; PCS, selection bias]; 276 [EL 3; SS]; 278 [EL 2; PCS]). Thus, overweight and obesity may not affect risk of CVD outcomes in a uniform manner but may exert greater unfavorable effects in those individuals who have greater underlying insulin resistance.

Second, the impact of overweight and obesity on CVD outcomes and mortality may be protective in the presence of certain concurrent diseases, referred to as the "obesity paradox." One example is congestive heart failure (CHF). An elevated BMI is associated with increased risk for developing CHF in part by predisposing to hypertension, diabetes, sleep apnea, and CVD (357 [EL 4; NE]; 358 [EL 3; SS]; 359 [EL 2; PCS]; 360 [EL 2; PCS]; 361 [EL 2; PCS]). The risk of CHF has been observed to increase by 5% in men and 7% in women for each unit increment of BMI (359 [EL 2; PCS]). However, once the patient presents with CHF, the presence of overweight and/or obesity may be protective regarding risks of future CVD mortality and hospitalizations (159 [EL 2; MNRCT]; 362 [EL 2; MNRCT]; 363 [EL 2; PCS]; 364 [EL 2; PCS]; 365 [EL 2; PCS]; 366 [EL 2; RCCS]; 367 [EL 2; PCS]; 368 [EL 2; PCS]; 369 [EL 2; RCCS]). Similarly, the obesity paradox may apply to other illnesses as illustrated by meta-analyses pertaining to acute coronary syndrome (370 [EL 2; MNRCT]) and existing CVD (371 [EL 2; MNRCT]).

Whether the obesity paradox applies to T2DM is controversial. Individual cohort studies and meta-analyses indicate that overweight and/or obesity can be associated with reduced mortality in patients with T2DM (157 [EL 2; MNRCT]; 372 [EL 1; RCT, post-hoc analysis]; 373 [EL 3; SS]; 374 [EL 2; MNRCT]; 375 [EL 2; RCCS]). However, many of these studies are characterized by few participants and inadequate control for cigarette smoking and other preexisting conditions (i.e., reverse causality). In fact, the obesity paradox for T2DM was eliminated after proper control or elimination of smokers and participants with a BMI <22 kg/m^2 in the comparator lean subgroup, suggesting that the paradox can be explained by a "sicker" underweight referent population (376 [EL 2; PCS]; 377 [EL 4; NE]; 378 [EL 4; NE]). Tobias et al (109 [EL 2; PCS]) studied 11,427 participants in the Nurses' Health Study and Health Professionals Follow-up Study who were free of CVD and cancer at the time of incident diabetes and who were then followed for a mean 15.8 years. A J-shaped curve was observed for all-cause mortality across BMI categories; compared to the referent subgroup with BMI 22.5 to 24.9 kg/m^2, the HR was 1.29 (CI, 1.05-1.59) for BMI 18.5 to 22.4 kg/m^2; 1.12 (CI, 0.98-1.29) for BMI 25 to 27.4 kg/m^2; 1.09 (CI, 0.94-1.26) for BMI 27.5 to 29.9 kg/m^2; 1.24 (CI, 1.08-1.42) for BMI 30 to 34.9 kg/m^2; and 1.33 (CI, 1.14-1.55) for BMI ≥35 kg/m^2. The relationship became linear when smokers were excluded from the analysis and L-shaped when only smokers were assessed. In those who had never smoked and after exclusion of early deaths, the HR rose progressively from 0.92 for BMI 18.5 to 22.4 kg/m^2, 1.00 referent BMI 22.5 to 24.9 kg/m^2, 1.14 for BMI 25 to 27.4 kg/m^2, 1.27 for BMI 27.5 to 29.9 kg/m^2, 1.34 for BMI 30 to 34.9 kg/m^2, and 1.58 for BMI ≥35 kg/m^2 (*P* for linear trend <0.001).

- *Q3.6. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis*

Executive Summary

- **R16.** Screening for nonalcoholic fatty liver disease should be performed in all patients with overweight or obesity, T2DM, or metabolic syndrome with liver function testing, followed by ultrasound or other imaging modality if transaminases are elevated; all patients with nonalcoholic fatty liver disease should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

Evidence Base

Nonalcoholic fatty liver disease (NAFLD) afflicts over 30% of adults in developed countries and is the most common cause of chronic liver disease (379 [EL 3; CSS]; 380 [EL 4; NE]). NAFLD represents an early stage along a spectrum that can progress through nonalcoholic steatohepatitis (NASH), hepatic cirrhosis, liver failure, and even hepatocellular carcinoma. NAFLD, or ectopic liver fat, represents one anatomic site of ectopic fat (abnormal fatty deposits not conventionally associated with storage, such as in subcutaneous and visceral adipose tissue) (381 [EL 4; NE]; 382 [EL 4; NE]), which also includes perinephric, pericardial, and intramuscular depots. Etiologic drivers and pathogenic mechanisms for the development of NAFLD include obesity and insulin resistance (383 [EL 2; PCS]), metabolic syndrome, and newer associated disorders, including disruption of intestinal microbiota (384 [EL 4; NE]) and decreased choline intake (385 [EL 3; CSS]). Of note, the data are not clear whether ingested fat content (e.g., saturated vs. polyunsaturated) plays a significant role in humans within the complex network of etiologic drivers (386 [EL 4; NE]), although Leslie et al (387 [EL 3; SS]) demonstrated that patients with NAFLD consume more prepared foods than fresh foods.

It has been difficult to determine the relative contributions of insulin resistance, obesity, or a combination along with other risk factors (dyslipidemia, inflammation, etc.) as part of metabolic syndrome in the initiation of NAFLD. In fact, Zeb et al (388 [EL 3; CSS]) found that the associated risk for NAFLD increases as the number of metabolic syndrome components increase, and Pagadala and McCullough (389 [EL 2; PCS]) observed that it was the distribution of adipose tissue, and not the BMI per se, that

was associated with NAFLD, especially in certain ethnicities such as Asians (390 [EL 4; NE]). Nevertheless, the association of NAFLD with obesity is profound, with over 60% of patients undergoing gastric bypass (bariatric) surgery having histologically confirmed NAFLD (391 [EL 2; RCCS]; 392 [EL 2; MNRCT]; 393 [EL 2; PCS, N = 48]).

While 70% of patients with obesity and PCOS have NAFLD, with hyperandrogenism being a specific risk factor (394 [EL 3; CSS, N = 51]), only 20% of patients with obesity and Cushing's have NAFLD (395 [EL 2; PCS, N = 50]) possibly due to suppression of inflammation by glucocorticoids (396 [EL 4; NE]). Moreover, Lee et al (397 [EL 3; CSS, N = 50]) found that obesity was an independent risk factor for NAFLD diagnosed by ultrasound, but hypertriglyceridemia, IFG, silent myocardial infarction (MI), and abnormal liver function tests were not. Specific factors mediating the presumed primary effects of adiposity on NAFLD include free fatty acids, inflammatory cytokines, and adipokines, particularly leptin, glypican-4, and adiponectin (398 [EL 4; NE]; 399 [EL 2; PCS]; 400 [EL 4; NE]; 401 [EL 3; CSS]) the last of which may act through glutathione peroxidase 1 gene expression (402 [EL 2; PCS]).

Based on the results of many small-scale clinical studies, Koliaki et al (403 [EL 4; NE]) concluded that, in the obese state, hepatic lipid overload is compensated for by upregulated hepatic oxidative capacity (increased mitochondrial β-oxidation, ketogenesis, anaplerosis) that may eventually lead to decompensation with evolving insulin resistance. A potential marker for impaired mitochondrial function as a harbinger of NAFLD in obesity is the cytokine nicotinamide phosphoribosyltransferase/visfatin—a cellular protector due to nicotinamide adenine dinucleotide biosynthetic function (404 [EL 2; PCS, N = 38]). Many other mitochondrial factors contribute to pathogenesis and serve as biomarkers, as reviewed by Paradies et al (405 [EL 4; NE]) and Gusdon et al (406 [EL 4; NE]). These studies implicate oxidative stress, inflammation, and mitochondrial dysfunction in the pathophysiology of NAFLD.

There are various hepatic and extrahepatic sequelae of NAFLD that can potentially exacerbate obesity-related complications, such as increased prevalence of gallstone disease (407 [EL 3; CSS]) or augmentation of inflammation and atherosclerosis, which contribute to CVD and chronic kidney disease (397 [EL 3; CSS, N = 50]). In NAFLD, the net increase in hepatic fat content associated with increased cholesterol synthesis and decreased cholesterol absorption may be independent of body weight and adiposity (408 [EL 2; PCS]). Once NAFLD is established, the presence of T2DM and the severity of hyperglycemia are associated with the development of fibrosis (409 [EL 3; CSS]). Moreover, insulin resistance can be promoted by NAFLD, thus fueling a vicious cycle leading to T2DM and increased morbidity (410 [EL 2; NRCT, N = 14]; 411 [EL 2; NRCT, N = 8]; 412 [EL 2; NRCT, N = 48]; 413 [EL 2; PCS, N = 10]).

The diagnosis of NAFLD is considered in patients with hepatic abnormalities (biochemical or with ultrasound) in the absence of significant alcohol consumption (>21 drinks per week for men, >14 drinks per week for women, for 2 years) and absence of other etiologies for hepatic steatosis or chronic liver disease, including exposure to hepatotoxic medications or agents, hepatitis C and chronic viral hepatitis, hemochromatosis and Wilson's disease, certain hereditary diseases affecting the liver, malnutrition or severe weight loss, refeeding syndrome, or autoimmune/immunological diseases (414 [EL 4; NE]). Optimal screening strategies for NAFLD have not been established. Liver biochemistries, including aspartate aminotransferase and alanine aminotransferase (ALT), may be within normal limits in patients with NAFLD and NASH, therefore lacking a desirable degree of sensitivity for screening (415 [EL 3; CSS]).

Liver ultrasound is a noninvasive procedure that has higher sensitivity for steatosis but is expensive and requires specific appointment scheduling (414 [EL 4; NE]). The American College of Gastroenterology recommends that routine "screening for NAFLD in adults attending primary care clinics or high-risk groups attending diabetes or obesity clinics is not advised at this time due to uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to the long-term benefits and cost-effectiveness of screening" (414 [EL 4; NE]). However, the presence of obesity, metabolic syndrome, and/or T2DM are powerful predictors of NAFLD (383 [EL 2; PCS]; 416 [EL 2; PCS]; 417 [EL 2; PCS, N = 46]; 418 [EL 3; CSS]; 419 [EL 2; MNRCT]) and warrant the measurement of hepatic transaminases followed by liver ultrasound when transaminases are elevated (397 [EL 4; NE]; 414 [EL 3; CSS, N = 50]). These measures identify patients with overweight or obesity with presumed NAFLD who could benefit from weight-loss therapy (see Q5.6).

Additional noninvasive strategies have been proposed to screen for patients with presumed NASH (420 [EL 2; MNRCT]; 421 [EL 4; NE]). Persistent elevation of liver biochemistries identifies those patients who would benefit from a liver biopsy for diagnostic and prognostic purposes (414 [EL 4; NE]). The NAFLD Fibrosis Score provides an area-under-the-curve value in ROC analyses of 0.85 for predicting bridging fibrosis or cirrhosis, and incorporates age, BMI, glycemia, platelet count, albumin, and AST/ALT ratio (420 [EL 2; MNRCT]; 422 [EL 3; SS]). The Enhanced Liver Fibrosis panel provides an ROC area-under-the-curve of 0.90 for detecting advanced fibrosis and incorporates levels of 3 matrix turnover proteins (hyaluronic acid, tissue inhibitor of metalloproteinase-1 [TIMP-1], and amino terminal propeptide of type III procollagen [PIIINP]) in plasma (421 [EL 4; NE]; 423 [EL 3; SS]). Additional biomarkers exist to gauge risks for progression and need for liver biopsy (397 [EL 3; CSS, N = 50]) including cytokeratin-18 (421 [EL 4; NE]; 424 [EL 2; MNRCT]);

the rs8192678 A allele of proliferator–activated receptor-γ coactivator (PGC)-1α in Taiwanese children with obesity (425 [EL 3; SS]) and other ethnicities (426 [EL 3; SS]); imaging technologies (427 [EL 3; SS]), including ultrasound or magnetic resonance imaging elastography (428 [EL 4; NE]; 429 [EL 4; NE]; 430 [EL 4; NE]); and other composite scoring systems (420 [EL 2; MNRCT]; 421 [EL 4; NE]; 431 [EL 3; SS]). An interesting recent finding by Wong et al (432 [EL 3; CSS]) using fat-water magnetic resonance imaging was that fatty pancreas was moderately associated with NAFLD and, furthermore, that fatty pancreas and NAFLD were associated with greater insulin resistance than NAFLD alone. It is likely that in the future predictive markers for NAFLD and sequelae will be based on a systems approach using proteomics and gene regulatory networks (433 [EL 4; NE]).

Liver biopsy is the "gold standard" for diagnosis and assessment of liver histopathology. Because this invasive procedure entails some risk of morbidity and mortality, it should be performed in those who would derive clinical benefits regarding prognostication and therapeutic decision-making. This includes, for example, patients with metabolic syndrome plus an at-risk NAFLD Fibrosis Score and when the etiology of the chronic liver disease is uncertain (414 [EL 4; NE]).

- *Q3.7. Polycystic ovary syndrome (PCOS)*

Executive Summary

- **R17.** Premenopausal female patients with overweight or obesity and/or metabolic syndrome should be screened for PCOS by history and physical examination; all patients with PCOS should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

Evidence Base

The prevalence of polycystic ovary syndrome (PCOS) in various populations around the world is 4 to 18% depending on diagnostic criteria (434 [EL 2; MNRCT]; 435 [EL 3; CSS]; 436 [EL 3; CSS]; 437 [EL 3; CSS]; 438 [EL 2; PCS]; 439 [EL 3; CSS]; 440 [EL 3; CSS]). Two commonly used diagnostic criteria include the National Institutes of Health (NIH) 1990 criteria, which requires hyperandrogenism (clinical or biochemical), oligomenorrhea/oligo-ovulation, and polycystic ovaries, and the Rotterdam 2003 criteria established by the European Society for Human Reproductive and Embryology/American Society for Reproductive Medicine, which defines PCOS as having 2 of the following 3 criteria: hyperandrogenism (clinical and/or biochemical), oligo/anovulation, and polycystic ovaries (by ultrasound) (441 [EL 4; NE]; 442 [EL 4; NE]). Meanwhile, the Androgen Excess and PCOS Society criteria stress the importance of androgen excess with oligo/anovulation or polycystic ovaries and the exclusion of other entities that may cause hyperandrogenism.

Theories of the pathogenesis of PCOS include: (*1*) the central hypothesis, which focuses on hypersecretion of luteinizing hormone (LH) leading to hypersecretion of androgens; (*2*) the peripheral hypothesis, which focuses on a defect or dysregulation of the ovaries and adrenals leading to hyperandrogenism and anovulation; and (*3*) a hypothesis that involves insulin resistance and hyperinsulinemia with inhibition of sex hormone-binding globulin (SHBG) and, thus, an increase of free androgen levels and direct stimulation of the ovaries (443 [EL 4; NE]).

Obesity is found in 30 to 75% of women with PCOS (444 [EL 4; NE]), with higher prevalence reported in the U.S. than in Europe (445 [EL 2; PCS]). A recent systemic review and meta-analysis found that in women with PCOS there is an increased prevalence of overweight (RR 1.95, 95% CI: 1.52-2.50), obesity (RR 2.77, 95% CI: 1.88-4.10), and central obesity (RR 1.73, 95% CI: 1.31-2.30) as compared to women without PCOS (434 [EL 2; MNRCT]). Thus, while PCOS can afflict normal weight women, there are higher rates of PCOS among women with obesity (434 [EL 2; MNRCT]; 444 [EL 4; NE]). Central adiposity is an independent risk factor associated with PCOS, and women with PCOS are more likely to have metabolic syndrome (446 [EL 4; NE]).

The relationship between obesity and PCOS has been under much investigation (435 [EL 3; CSS]; 441 [EL 4; NE]; 447 [EL 2; MNRCT]) with efforts to elucidate the role of obesity in the PCOS disease process (447 [EL 2; MNRCT]; 448 [EL 4; NE]; 449 [EL 2; PCS]; 450 [EL 2; PCS, N = 36]; 451 [EL 3; CSS]; 452 [EL 2; PCS]; 453 [EL 2; PCS, case-controlled]; 454 [EL 3; CSS]; 455 [EL 2; RCCS]; 456 [EL 3; SS, N = 20]; 457 [EL 2; PCS]; 458 [EL 2; RCCS]; 459 [EL 2; PCS, case-controlled]; 460 [EL 2; RCCS]). Here, we focus on several of the larger studies and conclusions from a recent meta-analysis (447 [EL 2; MNRCT]) that together determine the strength-of-evidence for this relationship. A large study in Germany of 411 women with PCOS (by NIH criteria) and 82 women without PCOS found that women with PCOS had increased BMI and insulin resistance associated with increased hyperandrogenism (i.e., Ferriman-Gallwey hirsutism score and Free Androgen Index) and decreased SHBG (454 [EL 3; CSS]). A case study in the United Kingdom of 263 women (n = 172 lean, 91 with overweight or obesity) with polycystic ovaries by ultrasound found that women with obesity and PCOS, as compared to women with PCOS but no obesity, demonstrated a higher degree of hirsutism and menstrual cycle disorders, higher free testosterone levels, and lower SHBG levels (449 [EL 2; PCS]). A study conducted in Korea of 194 women with PCOS (by Rotterdam criteria) investigated the incidence of glucose intolerance in East Asian women (weight categories:

lean BMI <23 kg/m^2, overweight BMI 23 to 25 kg/m^2, obesity BMI ≥25 kg/m^2) (461 [EL 2; PCS]). In this study, women with PCOS and glucose intolerance (assessed by OGTT) were heavier (average BMI 26.8 kg/m^2) as compared to women with PCOS and normal glucose tolerance (average BMI 22.3 kg/m^2), and glucose intolerance was observed to increase as a function of BMI ($P_{\text{for trend}}$<0.001) (460 [EL 2; RCCS]). In a prospective case-control study in Spain of 223 women (n = 85 lean, 47 with overweight, 65 with obesity) with PCOS (by Rotterdam criteria) and 25 women without PCOS, women with PCOS and obesity had significantly higher levels of total cholesterol, LDL-c, and triglycerides, and lower HDL-c, as compared to women with PCOS who were lean or overweight (453 [EL 2; PCS, case-controlled]). In a study conducted in Hong Kong, 295 premenopausal women with PCOS (by Rotterdam criteria) (n = 117 lean defined as BMI <23 kg/m^2, n = 178 with overweight or obesity defined as BMI ≥23 kg/m^2) were compared to 98 women without PCOS (462 [EL; 3; CSS]). Overall, nearly 25% of the women with PCOS met the definition for metabolic syndrome (defined by 2005 ATP III guidelines), whereas 3.1% of women without PCOS met the criteria; furthermore, metabolic syndrome was found to be more prevalent in PCOS patients with overweight or obesity (41.3%) as compared to lean women with PCOS (0.9%) (462 [EL 3; CSS]). A study in Germany of 184 women (n = 74 lean, 110 with overweight or obesity) with PCOS (by NIH criteria) and hirsutism (by modified Ferriman-Gallwey score) had significantly higher BMI, higher dehydroepiandrosterone sulfate, and Free Androgen Index, and significantly lower levels of SHBG (463 [EL 2; PCS]). Women with overweight or obesity (BMI ≥25 kg/m^2) were older, had higher fasting plasma glucose, fasting insulin, and 1-hour and 2-hour insulin and glucose levels, and increased homeostatic model for assessment of insulin resistance and Free Androgen Index, and lower insulin sensitivity index, SHBG, and HDL-c.

A recent meta-analysis assessed the effect of weight on PCOS characteristics and identified 30 studies from a comprehensive search of the literature (9,874 citations yielded in initial search, 1,485 studies identified for assessment of full text) (447 [EL 2; MNRCT]). The authors concluded that being a woman with PCOS and overweight or obesity incurred worse reproductive and metabolic features of PCOS. More specifically, women with obesity and PCOS fared worse than lean women with PCOS in all reproductive and metabolic measures, except for hirsutism (447 [EL 2; MNRCT]). Among women with PCOS, women with overweight did not differ from lean women with respect to levels of total testosterone, total cholesterol, LDL-c, or hirsutism. However, women with overweight exhibited values of SHBG, total testosterone, and fasting lipids that were statistically similar to those observed in women with obesity and PCOS (447 [EL 2; MNRCT]).

In summary, an association exists between PCOS and obesity. Further, women with PCOS who have obesity have a more severe metabolic and reproductive phenotype than women with PCOS who are lean. Women who have overweight with PCOS also appear to have a more severe phenotype than lean women with PCOS, but this effect is attenuated when compared to women with obesity and PCOS.

- *Q3.8. Female infertility*

Executive Summary

- **R18.** Women with overweight or obesity should be counseled when appropriate that they are at increased risk for infertility and, if seeking assisted reproduction, should be informed of lower success rates of these procedures regarding conception and the ability to carry the pregnancy to live birth **(Grade B; BEL 2)**. All female patients with infertility should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

Evidence Base

Infertility is defined as the inability to conceive after 12 months of unprotected intercourse. Several large retrospective studies have demonstrated that overweight and obesity in women increases infertility (464 [EL 2; PCS]; 465 [EL 2; PCS]; 466 [EL 2; PCS]; 467 [EL 2; PCS]; 468 [EL 2; RCCS]; 469 [EL 2; PCS]; 470 [EL 2; PCS]; 471 [EL 2; PCS]; 472 [EL 2; PCS, case-controlled]; 473 [EL 2; RCCS]). A recent prospective study followed 3,029 ovulatory subfertile women and found that the probability of spontaneous pregnancy decreased by ~5% for every 1.0 kg/m^2 increase in BMI >29 kg/m^2 (464 [EL 2; PCS]). Compared to women with BMI between 21 and 29 kg/m^2, the probability of spontaneous pregnancy was 26% lower in women with BMI ≥35 kg/m^2 and 43% lower in women with BMI ≥40kg/m^2 (464 [EL 2; PCS]).

In the Nurses' Health Study (NHS) (between 1989-1995), data reviewed from 20,417 women aged 25 to 46 years found that 25% of ovulatory infertility may be attributed to overweight and obesity (BMI ≥25 kg/m^2) (465 [EL 2; PCS]). In a recent retrospective study of the Collaborative Perinatal Project data, prepregnancy BMI was examined in a cohort of 7,327 women at 12 U.S. centers between 1959 and 1965 (466 [EL 2; PCS]). The authors found that the probability of fecundity (pregnancy during a given cycle) was reduced by 18% in women with obesity (BMI >30kg/m^2) (odds ratio [OR] 0.92, 95% CI: 0.84,1.01) and 8% in women with overweight (BMI 25 to 29.9kg/m^2) (OR 0.82, 95% CI: 0.72, 0.95) (466 [EL 2; PCS]). The impact of overweight and obesity was even more pronounced in previously nulliparous women where fecundity was decreased by 34% in women with obesity (OR 0.84, 95% CI: 0.77, 0.92) and 16% in women with

overweight (OR 0.66, 95% CI: 0.49, 0.89). Notably, this decreased fecundity was found even in women with overweight or obesity with normal menstrual cycles (466 [EL 2; PCS]).

Additionally, obesity during childhood may be an important predictor of infertility in women. Data reviewed from the NHS found that overweight or obesity during adolescence may be a predictor of ovulatory infertility in women with and without PCOS (467 [EL 2; PCS]). Finally, a recent systematic review and meta-analysis of women who conceived spontaneously found an increased risk of miscarriage in women with obesity compared to normal weight women (OR 1.31, 95% CI: 1.18, 1.46) (474 [EL 2; MNRCT]). Thus, an association exists between obesity and infertility (likely related to oligo/anovulation) as is suggested by these large retrospective studies.

Women with overweight or obesity who undergo fertility treatment are less likely to be successful in their attempts to conceive and carry a pregnancy to live birth as compared to women who are normal weight (475 [EL 2; RCCS]; 476 [EL 3; SS]). Data from the Society for Assisted Reproductive Technology Clinical Outcomes Reporting System (2007-2008) included outcomes of 152,500 cycles of assisted reproductive technology (ART) (475 [EL 2; RCCS]). A significant parallel was found between increasing BMI and cycle cancellation, and a rise in treatment failure with increasing BMI from overweight to BMI ≥50 kg/m^2. A retrospective study in the Netherlands examined the results of in vitro fertilization (IVF) in 8,457 women and found that women with a BMI ≥27 kg/m^2 had a significantly lower delivery rate (OR 0.67, 95% CI: 0.48, 0.94) compared to women with a BMI ≥20 to 26.9 kg/m^2 (477 [EL 2; PCS]). Another study included women undergoing IVF-intracytoplasmic sperm injection (ICSI), with 6,500 cycles included in the analysis. It found that implantation, pregnancy, and live birthrate decreased in women with obesity; specifically, with each unit of BMI increase there was a decrease in both pregnancy (OR 0.984, 95% CI: 0.972, 0.997) and birthrate (OR 0.981, 95% CI: 0.967, 0.995) (478 [EL 2; RCCS]). An Australian study of 3,586 women who received ART (including IVF, ICSI, and gamete intrafallopian transfer) found a significant linear reduction in fecundity in women with BMI ≥35 kg/m^2 compared to a BMI from 20 to 24.9 kg/m^2 (P<0.001), with a nearly 60% higher rate of fecundity in the latter (479 [EL 2; RCCS]).

Women with obesity may also require higher doses of medications for successful assisted pregnancy (480 [EL 2; RCCS]; 481 [EL 2; RCCS]; 482 [EL 2; RCCS]) and, if they do become pregnant, they may have lower birthrates (477 [EL 2; PCS]; 482 [EL 2; RCCS]). A study of 383 women who conceived with IVF or ICSI found that compared to women with a BMI <25 kg/m^2, women with a BMI ≥25 kg/m^2 had fewer oocytes collected (P = 0.03), had higher rates of abortion during the first 6 weeks (22% vs. 12%; P = 0.03), and lower live birthrates (63% vs. 75%; P = 0.04) (483 [EL 2; RCCS]).

In summary, although some trials did not find lower rates of implantation and pregnancy in women with overweight and obesity (480 [EL 2; RCCS]; 481 [EL 2; RCCS]; 484 [EL 2; RCCS]), the larger trials have shown an increase in cancellation rates and a decrease in fecundity and birthrate (477 [EL 2; PCS]; 479 [EL 2; RCCS]; 482 [EL 2; RCCS]). Furthermore, women with obesity undergoing ART may have higher rates of miscarriage (479 [EL 2; RCCS]; 480 [EL 2; RCCS]; 485 [EL 2; RCCS]; 486 [EL 2; RCCS]; 487 [EL 2; MNRCT]), although some studies did not find a difference in miscarriage rates (488 [EL 2; RCCS]; 489 [EL 2; RCCS]).

The mechanism by which obesity contributes to infertility may be multifactorial. Adipose tissue exerts an effect on gonadal function through adipokines (490 [EL 4; NE]). Notably, leptin, which is elevated in obesity, exerts effects on the hypothalamic-pituitary-gonadal axis (491 [EL 4; NE]), including the inhibition of ovarian follicle development (492 [EL 4; NE]), LH-stimulated estradiol production (492 [EL 4; NE]), and insulin-induced steroidogenesis in granulosa and theca cells (491 [EL 4; NE]). Adiponectin, which is decreased in obesity, is associated with hyperinsulinism (493 [EL 4; NE]), and hyperinsulinemia in turn results in decreased production of hepatic SHBG thus contributing to hyperandrogenism (490 [EL 4; NE]) and anovulation through granulosa cell apoptosis (494 [EL 4; NE]). These factors are not limited to women with PCOS (addressed in Section 3.7 of these guidelines).

- *Q3.9. Male hypogonadism*

Executive Summary

- **R19.** All men who have an increased WC or who have obesity should be assessed for hypogonadism by history and physical examination and be tested for testosterone deficiency if indicated; all male patients with hypogonadism should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.
- **R20.** All male patients with T2DM should be tested to exclude testosterone deficiency **(Grade B; BEL 2)**.

Evidence Base

Male hypogonadism is traditionally classified as primary or secondary. In primary hypogonadism, the testis is unable to secrete adequate amounts of testosterone even if maximally stimulated by gonadotropins (i.e., hypergonadotropic hypogonadism). In secondary disorders, the testis is potentially functional but inadequately stimulated by gonadotropins (i.e., hypogonadotropic hypogonadism). A recently introduced term of "compensated hypogonadism"

refers to reduced testosterone production, although maintained in the normal range due to gonadotropin levels higher than normal to "compensate" for subclinical testicular function (495 [EL 2; PCS]).

In epidemiologic studies, serum testosterone has a predictive value for the development of metabolic syndrome and T2DM (496, [EL 2; PCS]; 497 [EL 3; SS]). However, the exact mechanisms responsible for reduced testosterone levels in obesity remain unclear. Hyperinsulinemia is shown to suppress serum testosterone levels (498 [EL 2; PCS, N = 20]), and both insulin (499 [EL 2; PCS, N = 21]) and leptin (500 [EL 2; PCS, N = 38]) exert suppressive effects on gonadal steroidogenesis and may disrupt (LH) pulse amplitude. Aromatization of testosterone to estradiol in adipose tissue results in elevated serum estradiol and may contribute to inhibition of the hypothalamic–pituitary–gonadal axis and may diminish testosterone production (501 [EL 4; NE]). During 8 years of follow-up in the Rancho Bernardo Study, a significant inverse correlation was demonstrated between baseline total testosterone and fasting glucose, insulin levels, and glucose intolerance (502 [EL 2; PCS]). Pooled baseline data from 2 lipid treatment studies evaluated the relationship among obesity, metabolic syndrome, and total serum testosterone levels in 864 men (mean age 52 years) (503 [EL 2; MNRCT]). Serum testosterone levels decreased with increasing BMI ($P<0.0001$) in subjects with and without metabolic syndrome. Each component of metabolic syndrome (defined by the National Cholesterol Education Program ATP III criteria) in this study was examined (multiple linear regression) as to their individual contribution to low testosterone levels. Fasting blood glucose >110 mg/dL, T2DM, triglycerides >150 mg/dL, and BMI ≥30 kg/m^2 each had a relevant association with low serum testosterone.

The prevalence of male hypogonadism, defined as symptoms associated with low testosterone, in the general population has been reported to be 6% at baseline in the Massachusetts Male Aging Study (N = 1,691; aged 40-69 years) and 12% with a 7- to 10-year follow-up (504 [EL 2; PCS]); 5.6% in the Boston Area Community Health Survey in a multiethnic sample population over a broad age range (30-79 years; African American, Hispanic, and Caucasian men; N = 1,475) (505 [EL 3; SS]); and 2.1% in the European Male Aging Study prospective, cohort study (N = 3,369; mean age 60 ± 11 years) conducted in 8 European centers (506 [EL 2; PCS]). The Hypogonadism in Males study reported a 38.7% prevalence of laboratory-based hypogonadism using a single morning blood sample and diagnostic threshold for total testosterone <10.4 nmol/L (<300 ng/dL; normal reference range, 350 to 1,030 ng/dL by radioimmunoassay) among 2,162 men aged >45 years presenting for any reason to a U.S. primary care physician (507 [EL 3; CSS]).

Higher rates of clinical hypogonadism have been reported at 10 to 80% in selected patient groups (508 [EL 2; PCS]; 509 [EL 2; PCS, case-controlled]; 510 [EL 3; CSS]; 511 [EL 2; PCS, N = 33 men]; 512 [EL 2; PCS, only 21 of 75 patients studied in follow-up]; 513 [EL 2; MNRCT]; 514 [EL 3; CCS]; 515 [EL 2; MRCT, subanalysis of RCTs included]; 516 [EL 3; CSS]) including bariatric surgery (511 [EL 2; PCS, N = 33 men]), sexual or erectile dysfunction (ED) (504 [EL 2; PCS]; 505 [EL 3; SS]), and T2DM (509 [EL 2; MRCT, subanalysis of RCTs included]; 515 [EL 2; PCS, case-controlled]; 516 [EL 3; CSS]). In all these studies, the total testosterone level in men with obesity has been shown to be significantly and inversely related to one or more parameters of BMI, WC, and body fat mass. Age-adjusted risk for late onset hypogonadism, according to European Male Aging Study criteria, was evaluated in 3,293 ambulatory men with symptoms of sexual dysfunction at a single center (513 [EL 2; MNRCT]). Obesity (BMI >30 kg/m^2) and WC >102 cm were found to strongly predict CV risk (>20% at 10 years) in this cohort. In 33 men presenting for bariatric surgery with BMI 50.3 ± 6.1 kg/m^2, the prevalence of hypogonadism, as defined by total testosterone <300 ng/dL or free testosterone <65 pg/mL, was found to be 78.8% and 51.5%, respectively (511 [EL 2; PCS, N = 33 men]). Ippersiel et al (512 [EL 2; PCS, only 21 of 75 patients studied in follow-up]) reported symptoms of androgen deficiency in 93% of male subjects being evaluated for bariatric surgery, with low total serum testosterone reported in 39% of these men. In a consecutive series of 2,435 men (mean age 52 ± 13 years) with ED, 42% were at normal weight, while 42, 12, and 4% had a BMI of 25 to 29.9, 30 to 34.9, and ≥35 kg/m^2, respectively. Both SHBG and bound and unbound testosterone decreased as a function of obesity class, and lower testosterone levels were independently associated with greater BMI after multivariate analysis (514 [EL 3; CCS]). Obesity was also significantly associated with a higher organic contribution to ED as assessed by Structured Interview on Erectile Dysfunction (SIEDY scale 1) scores, compared to relational (SIEDY scale 2) and intrapsychic (SIEDY scale 3) determinants of ED.

In a systematic review and meta-analysis of prospective and cross-sectional studies, patients with T2DM had significantly lower testosterone levels compared to individuals without T2DM, and obesity increased these differences between individuals with and without T2DM, while aging decreased them (515 [EL 2; MRCT, subanalysis of RCTs included]). The prevalence of hypogonadism was found to be 15% in 100 consecutive Asian Indian men with T2DM aged 25 to 50 years, with a nonsignificant trend toward a higher prevalence in patients who had obesity in this small study group (509 [EL 2; PCS, case-controlled]). In other reports, the prevalence of testosterone deficiency in men with obesity and T2DM is reported to be as high as 50% (516 [EL 3; CSS]). From 2 independent observational registries, Saad et al (517 [EL 4; NE]) identified 411

men with obesity and hypogonadism and examined their cardiometabolic status as a function of obesity severity. In patients with class I obesity (BMI 30 to 34.9 kg/m^2, n = 214), 33.2% had prediabetes (defined by A1C 5.7 to 6.4%), 32.7% had T2DM, and 2.8% had a history of MI. In class II obesity (35 to 39.9 kg/m^2, n = 150), 19.3% had prediabetes, 51.3% had T2DM, and 11.5% had a history of MI. In patients with class III obesity (≥40 kg/m^2, n = 47), 6.3% had prediabetes, 55.3% had T2DM, and 23.4% had a history of MI (517 [EL 4; NE]). Thus, there are strong associations among obesity, hypogonadism, and cardiometabolic disease, and sufficient evidence exists to include measurement of serum testosterone in the diagnostic evaluation of metabolic syndrome and T2DM (518 [EL 3; SS]; 519 [EL 4; NE]). The 2010 Endocrine Society Clinical Practice Guidelines recommend that all men with T2DM be tested for hypogonadism (519 [EL 4; NE]).

• *Q3.10. Obstructive sleep apnea*

Executive Summary

- **R21.** All patients with overweight or obesity should be evaluated for obstructive sleep apnea during medical history and physical examination; this is based on the strong association of these disorders with each other **(Grade B; BEL 2)**. Polysomnography and other sleep studies, at home or in a sleep lab, should be considered for patients at high risk for sleep apnea based on clinical presentation, severity of excess adiposity, and symptomatology **(Grade D)**. All patients with obstructive sleep apnea should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

Evidence Base

Obstructive sleep apnea (OSA) results from sleep-related repetitive collapses of the upper airway producing decreased airflow and oxygenation. OSA continues to be underdiagnosed in the general population (520 [EL 3; SS]) and even more so in those with obesity. Even a 10% increase in body weight is associated with significant risk of developing OSA (521 [EL 2; PCS]). The prevalence of OSA is particularly high in patients with obesity and diabetes in whom prevalence rates as high as 86% have been reported (522 [EL 3; CSS]). OSA has been associated with CVDs, metabolic disorders, insulin resistance, and diabetes, and, therefore, its associated comorbidities result in a large population-level burden of morbidity (523 [EL 4; NE]). Symptoms include loud snoring, interruptions (apneic or hypopneic pauses) in breathing, and sleep-cycle fragmentation that in turn produce daytime fatigue, morning headache, lack of concentration, ED, and general decrease in QOL. Polysomnography is typically used to diagnose and gauge the severity of OSA. Neck circumferences >16 inches in women and >17 inches in men are associated with increased risk of OSA.

There are several key studies that demonstrate an association between excess weight and OSA with roughly 70% of patients with OSA also having obesity (524 [EL 4; NE]; 525 [EL 4; NE]; 526 [EL 4; NE]; 527 [EL 4; NE]; 528 [EL 2; PCS]; 529 [EL 2; PCS]; 530 [EL 2; PCS]; 531 [EL 4; NE]; 532 [EL 3; CCS]; 533 [EL 3; CSS]; 534 [EL 4; NE]; 535 [EL 4; NE]; 536 [EL 2; PCS post-hoc modeling]; 537 [EL 4; NE]; 538 [EL 4; NE]; 539 [EL 3; SS]; 540 [EL 2; PCS]; 541 [EL 3; CCS]; 542 [EL 2; PCS]). In fact, having a BMI >29 kg/m^2 increases the risk for OSA 10-fold (543 [EL 4; NE]). The context of this pathophysiologic association is significant because patients with OSA are also at higher risk, owing to independent associations, with CVD, T2DM, metabolic syndrome, reduced QOL, and mortality (522 [EL 3; CSS]; 526 [EL 4; NE]; 544 [EL 2; PCS]; 545 [EL 2; PCS]; 546 [EL 3; SS]; 547 [EL 3; SS]; 548 [EL 3; CSS]; 549 [EL 3; CSS]; 550 [EL 2; PCS]). This feed-forward pathway is made even more complicated by the vicious cycle of obesity leading to OSA and reciprocally OSA leading to obesity (524 [EL 4; NE]; 526 [EL 4; NE]; 543 [EL 4; NE]).

Pathologic mechanisms contributing to the influence of obesity on OSA include adipokine effects on the lung, mechanical effects on upper airway collapsibility and chest wall compliance, effects on respiratory drive, and hormonal derangements. Conversely, OSA is associated with decreased leptin and increased ghrelin, which increases hunger, leading to weight gain. Another mediator of obesity and brain function in the context of sleep disorders that may figure prominently is the central orexin system (551 [EL 4; NE]; 552 [EL 4; NE]; 553 [EL 4; NE]). These manifold relationships among signals and organ systems may explain the differential effects of weight gain (in patients with or without overweight or obesity) or weight loss (just in patients with overweight or obesity) on OSA (525 [EL 4; NE]; 526 [EL 4; NE]; 554 [EL 2; PCS]) and the critical importance of prevention of weight gain (555 [EL 4; NE]).

• *Q3.11. Asthma/reactive airway disease*

Executive Summary

- **R22.** All patients with overweight or obesity should be evaluated for asthma and reactive airway disease based on the strong association between these disorders **(Grade B; BEL 2)**. Based on medical history, symptomatology, and physical examination, spirometry and other pulmonary function tests should be considered for patients at high risk for asthma and reactive airway disease **(Grade D)**. All patients with asthma should be evaluated for the presence of overweight or obesity **(Grade D)**.

Evidence Base

Obesity is associated with increased asthma prevalence, severity, and recalcitrance to medical therapy (556 [EL 4; NE]; 557 [EL 3; SS]; 558 [EL 4; NE]; 559 [EL 3; SS]; 560 [EL 3; retrospective analysis of 4 PRCT]; 561 [EL 3; SS]; 562 [EL 3; retrospective analysis of 4 PRCT]; 563 [EL 3; retrospective analysis of cohorts]; 564 [EL 2; MNRCT]; 565 [EL 2; PCS]; 566 [EL 3; SS]; 567 [EL 3; SS]; 568 [EL 2; PCS]; 569 [EL 2; PCS]; 570 [EL 2; PCS]; 571 [EL 3; SS]). As adolescents transition into early adulthood, progressive obesity is associated with increased airway obstruction as manifested by significant decreases in forced expiratory volume in the first second and forced vital capacity (572 [EL 2; PCS, post-hoc analysis]). Classically, asthma is associated with chronic inflammation (via CD4 T helper 2 [T_H2] cells, cytokines [e.g., interleukin-5, -9], eosinophilia, and mast cells), mucous production, and abnormal bronchoconstriction and muscle reactivity (573 [EL 4; NE]). However, obesity may affect the pathophysiologic state via inflammatory and noninflammatory ways (mechanical, hormonal, beta 2-adrenergic receptor, vitamin D, leptin, protein kinase C-alpha, and other nonatopic mechanisms) (572 [EL 2; PCS, post-hoc analysis]; 573 [EL 4; NE]; 574 [EL 4; NE]).

- *Q3.12. Osteoarthritis*

Executive Summary

- **R23.** All patients with overweight or obesity should be screened by symptom assessment and physical examination for OA of the knee and other weight-bearing joints **(Grade B; BEL 2)**. All patients with OA should be evaluated for the presence of overweight or obesity **(Grade D)**.

Evidence Base

Osteoarthritis (OA) is a common disorder of the joints and is a leading cause of pain, disability, and loss of productivity. In 2006, OA was responsible for 97% of knee replacements and 83% of total hip replacements and was estimated to account for $10.5 billion in U.S. hospital charges (575 [EL 4; NE]). OA has been increasing in prevalence for 2 reasons. The first pertains to aging populations; OA is highly prevalent among the elderly and affects more that 37% of individuals over age 60 (576 [EL 3; SS]). Second, obesity is well-recognized as a risk factor for OA, particularly OA of the knee, and sharp increments in mean BMI in recent decades have contributed to higher OA prevalence (577 [EL 4; NE]; 578 [EL 4; NE]).

Excess body weight augments the load on the joints, such as the knee, which increases stress and hastens breakdown of cartilage (579 [EL 4; NE]). Forces transmitted across the knee joint approximate 2 to 3 times the body weight during walking due to kinetics of acceleration and muscle contractions and will increase commensurately with any weight gain (580 [EL 4; NE]). These stresses lead to erosion of smooth cartilage and degeneration in weight-bearing joints such as the knee, hip, and spine, resulting in pain, tenderness, and inflammation. Notably, obesity is also associated with increased OA in non-weight–bearing joints such as the hand (581 [EL 2; RCCS]; 582 [EL 2; PCS]), indicating that influence of obesity on OA may involve a complex interaction of genetic, metabolic, and inflammatory factors, in addition to biomechanical stress (583 [EL 4; NE]; 584 [EL 4; NE]).

Most research examining the relationship between obesity and OA has focused on the knee joint. Estimating prevalence across populations can be problematic due to variations in the definitions for obesity and knee OA among investigators. Even so, prospective studies consistently indicate that obesity increases relative risk of OA by 2- to 10-fold (585 [EL 2; PCS]; 586 [EL 2; PCS]; 587 [EL 3; SS]; 588 [EL 3; SS]; 589 [EL 2; PCS]; 590 [EL 2; PCS]; 591 [EL 3; CSS]; 592 [EL 2; PCS]), and cross-sectional and case-control studies have repeatedly demonstrated an association between obesity and OA in multiple populations (593 [EL 2; PCS, case-controlled]; 594 [EL 3; CSS]; 595 [EL 3; CSS]; 596 [EL 2; PCS]; 597 [EL 2; PCS]; 598 [EL 2; PCS]; 599 [EL 2; PCS]; 600 [EL 2; PCS, case-controlled]). The NHANES I demonstrated that women with obesity had nearly 4 times the risk of knee OA as compared to women who did not have obesity. In men with obesity, the risk was nearly 5 times greater than in their counterparts without obesity (587 [EL 3; SS]). The NHANES data further revealed that people in the highest quintile of body weight have up to 10 times the risk of knee OA as those in the lowest quintile (588 [EL 3; SS]). In the Framingham Study cohort, individuals with overweight who did not have knee OA at baseline were at greater risk of later developing the disease (585 [EL 2; PCS]; 590 [EL 2; PCS]). Other investigations, which performed repeated X-rays over time, also have found that being overweight significantly increased the risk of developing knee OA on the basis of both radiographic and symptomatic manifestations (589 [EL 2; PCS]). In a longitudinal study of men and women aged 40 to 64 years, Manninen et al (592 [EL 2; PCS]) reported that for every standard deviation increase in BMI (3.8 kg/m^2), there was a 40% increase in relative risk for developing OA of the knee. Blagojevic et al (601 [EL 2; MNRCT]) conducted a systematic review of 36 papers and reported all studies demonstrated that obesity and overweight were risk factors for knee OA and found that the random effects pooled OR for obesity compared to normal weight was 2.63 (95% CI: 2.28-3.05) (601 [EL 2; MNRCT]).

• *Q3.13. Urinary stress incontinence*

Executive Summary

- **R24.** All female patients with overweight or obesity should be screened for urinary incontinence by assessing symptomatology, based on the strong association between these disorders; all patients with urinary stress incontinence should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

Evidence Base

Obesity is recognized as a major risk factor for urinary incontinence in women. This relationship has been well-documented in multiple cross-sectional, case-control, and prospective cohort studies as delineated in systematic reviews by Hunskaar (602 [EL 2; MNRCT]) and Subak et al (603 [EL 2; MNRCT]). In the aggregate, there is a dose-response relationship with higher risk of urinary incontinence as BMI increases, with multivariate adjusted ORs for urinary incontinence ranging from 1.5 to 2 up to 4 to 5 in those with severe obesity. In the NHS II, 43% of 83,355 middle-aged women reported urinary incontinence, and the odds of severe urinary incontinence in individuals with BMI ≥30 kg/m^2 was 3.1 times greater (95% CI: 2.9, 3.3) than those with a BMI of 22 to 24 kg/m^2 (604 [EL 3; SS]). The EPINCONT study surveyed 34,755 Norwegian women and reported that there was a significant association between BMI and stress, urge, and mixed subtypes of urinary incontinence, although the relationship was strongest for stress and mixed types of incontinence (605 [EL 3; SS]). Similar findings were reported for data from Heart and Estrogen/Progestin Replacement Study (606 [EL 3; SS]) and the 1946 British Birth Cohort (607 [EL 3; SS]), with the associations with BMI being greater for stress or mixed urinary incontinence compared with urgency incontinence. Women with high BMI not only are more likely to develop incontinence, but they also tend to have more severe incontinence than women with lower BMI (605 [EL 3; SS]; 606 [EL 3; SS]).

The temporal association between BMI and urinary incontinence was demonstrated in the 1946 British Birth Cohort (608 [EL 2; PCS]), the Study of Women's Health Across the Nation (SWAN) (609 [EL 2; PCS]), the Leicestershire MRC Incontinence Study (610 [EL 3; SS]), and the NHS II (611 [EL 3; SS]). These studies show that earlier onset of obesity is associated with increased risk for urinary incontinence (608 [EL 2; PCS]), and that both higher BMI and greater weight gain as an adult are associated with increased risk of incident incontinence (609 [EL 2; PCS]; 610 [EL 3; SS]; 611 [EL 3; SS]). Regarding progressive weight gain, each 5-unit increase in BMI increases the risk of daily incontinence by approximately 60% (606 [EL 3; SS]; 612 [EL 3; SS]; 613 [EL 2; MNRCT]). The associations with BMI and weight gain are stronger for incident stress urinary incontinence and mixed incontinence, compared with incident urgency incontinence (609 [EL 3; SS]; 610 [EL 2; PCS]).

In addition to BMI, WC is an independent risk factor for urinary incontinence. In a study of 769 Korean women, it was found that in comparison with women in the lowest quartile of WC, ORs for stress incontinence increased significantly in a dose-dependent relationship (1.79, 3.50, and 6.07) for the next highest quartiles, respectively, after adjustments for BMI (614 [EL 3; CCS]). In the NHS, multivariate analyses that adjusted for BMI indicated that WC was independently associated with stress incontinence (615 [EL 3; SS]). Consistent with this observation, WC and WHR appeared to be associated only with stress incontinence and not with urgency incontinence in the SWAN (609 [EL 2; PCS]) and Heart and Estrogen/Progestin Replacement studies (606 [EL 3; SS]). However, data from the Boston Area Community Health Survey (616 [EL 3; CSS]) and the Korea National Health and Nutrition Examination Survey (617 [EL CSS]) indicated that measures of central adiposity are also correlated with urgency incontinence, and multiple investigators have established an association between metabolic syndrome and urge urinary incontinence (616 [EL 3; CSS]; 618 [EL 3; CSS]; 619 [EL 3; CSS]; 620 [EL 4; NE]).

Regarding mechanisms that link BMI and urinary incontinence, strong correlations have been observed between BMI, intra-abdominal pressure, and intravesical pressure predisposing to stress incontinence (621 [EL 2; RCCS]; 622 [EL 2; PCS, N = 12]; 623 [EL 3; CSS]). Furthermore, weight loss was associated with favorable changes in urodynamic indices including decreased initial intravesical pressure, decreased intravesical pressure at maximum capacity, and increased Valsalva leak point pressure (622 [EL 2; PCS, N = 12]; 623 [EL 3; CSS]; 624 [EL 1; RCT, N = 48]).

• *Q3.14. Gastroesophageal reflux disease (GERD)*

Executive Summary

- **R25.** Patients with overweight or obesity or who have increased WC should be evaluated for symptoms of GERD **(Grade B; BEL 2)**; all patients with GERD should be evaluated for the presence of overweight or obesity **(Grade C; BEL 3)**.
- **R26.** Patients with obesity and GERD symptoms should be evaluated by endoscopy if medical treatment fails to control symptoms **(Grade B; BEL 2)**.
- **R27.** Endoscopy should be considered in patients with obesity and GERD symptoms prior to bariatric surgery **(Grade B; BEL 2)**.

Evidence Base

Epidemiologic data have supported a strong association between excess adiposity and GERD. The prevalence of GERD in patients with overweight or obesity is significantly higher than in the general population and has been reported to be present in 15 to 65% of patients with obesity who seek weight-loss therapy, depending on the criteria for the diagnosis of GERD (625 EL 2; PCS]; 626 [EL 2; PCS]; 627 [EL 2; MNRCT]; 628 [EL 2; MNRCT]; 629 [EL 3; SS]; 630 [EL 2; PCS]; 631 [EL 2; PCS]; 632 [EL 2; PCS]; 633 [EL 2; PCS]; 634 [EL 2; RCCS]; 635 [EL 2; PCS]). There is evidence that obesity is associated with complications related to longstanding reflux such as erosive esophagitis and Barrett's esophagus. Central obesity, rather than BMI, appears to be more closely associated with these complications (636 [EL 4; NE]), but the underlying mechanisms for GERD in patients with obesity are not entirely clear and are likely multifactorial.

GERD has been associated with metabolic syndrome. GERD and metabolic syndrome were reported in 604 (16%) and 477 (12.6%) of 3,775 Japanese adults, respectively, who reported for their regular medical checkups (637 [EL 3; CCS]). GERD was diagnosed by endoscopy-proven reflux esophagitis, GERD symptoms (by standardized questionnaire scoring), or current medical therapy. Multiple logistic regression analysis showed that male gender, presence of hiatal hernia, metabolic syndrome, visceral adiposity, and gastric mucosal atrophy were significant predictors for the prevalence of GERD in this population. A cross-sectional study of 100 consecutive patients who had 24-hour pH-monitoring were assessed for the presence of metabolic syndrome (638 [EL 3; CSS]). Among these subjects, 54 were GERD-acid-positive and 46 were GERD-acid-free, and the gender distribution was comparable between groups. GERD-acid-positive patients were older (44.6 vs. 37.6 years, $P = 0.006$), had more overweight or obesity (83.3% vs. 60.9%, $P = 0.01$), and were more likely to have metabolic syndrome (50% vs. 20%; $P = 0.002$) with an OR of 4.11 (95% CI: 1.66-10.14). Multivariate regression analysis showed that metabolic syndrome and age >30 years, but not BMI, were independent factors associated with GERD. However, the only metabolic syndrome traits that were independently associated with GERD were increased WC and fasting blood glucose >100 mg/dL.

In patients with proven GERD or Barrett's esophagus randomly selected from a data registry and screened for metabolic syndrome (639 [EL 3; CSS]), obesity was present in 36% of patients with Barrett's esophagus (n = 118) and 38% of age- and gender-matched GERD controls (n = 113), with a similar pattern of trunk fat mass (13 kg and 14 kg, respectively) in both groups. Metabolic syndrome was more common in the Barrett's esophagus cohort using the National Cholesterol Education Program criteria (30% vs. 20%, $P<0.05$), but there was no significant difference when using the International Diabetes Federation criteria (42% vs. 37%, $P = 0.34$).

Among residents of Olmsted County, Minnesota, case patients (n = 103) with Barrett's esophagus were matched for age, gender, and duration of follow-up and compared to 2 control groups, 1 with and 1 without validated GERD symptoms (103 subjects in each group and none with known Barrett's esophagus) (640 [EL 2; PCS, case-controlled]). Using univariate and multivariate logistic regression for each control group, 64% of Barrett's cases, 47% of controls with GERD symptoms, and 50% of controls without GERD symptoms had metabolic syndrome. Metabolic syndrome was associated with a 2-fold increased risk of Barrett's esophagus compared to those with (OR, 2.00; $P = 0.02$) and without (OR, 1.90; $P = 0.04$) GERD symptoms and was independent of BMI, smoking, and alcohol intake.

In a study of men who presented for colorectal cancer screening and who were recruited for upper endoscopy, Barrett's esophagus was diagnosed in 70 of 822 (8.5%) subjects (641 [EL 3; CSS]). When mutually adjusting for covariates, Barrett's esophagus was associated with weekly GERD symptoms (OR, 2.33; CI, 1.34-4.05), age (OR per 10 years, 1.53; CI, 1.05-2.25), WHR (OR per 0.10, 1.44; CI, 0.898-2.32), and cigarette pack years. A model including these 4 factors was more likely to be associated with Barrett's esophagus in these men than a model based on GERD frequency and duration alone (0.72 vs. 0.61, $P<0.001$). A structured interview and anthropometric measures were conducted within a population-based, case-control study to match 247 controls with 237 cases of Barrett's esophagus (70% men, matched by age and gender) (642 [EL 2; PCS, case-controlled]). Using multivariable logistic regression analysis, all measures of abdominal obesity to include WC, WHR, and sagittal abdominal diameter (SAD) were strongly associated with risk of Barrett's esophagus in both the overall cohort (OR overall: WC 2.2, CI 1.4-3.5; WHR 1.8, CI 1.2-2.9, SAD 2.3, CI 1.4-3.7) and the men-only cohort (OR males only: WC 2.5, CI 1.4-4.3; WHR 2.4, CI 1.3-4.2; SAD 2.5, CI 1.4-4.3). In men, these associations were minimally attenuated by adjusting for symptoms of GERD, which suggests that non-GERD factors related to abdominal obesity may be important in the development of Barrett's esophagus. In women, there was modest association between measures of abdominal obesity and risk of Barrett's esophagus, but these were all abolished after adjusting for GERD symptoms.

To evaluate the possible association between BMI and esophageal adenocarcinoma, a nationwide population-based Swedish study of patients with newly diagnosed esophageal (n = 189) and gastroesophageal junction adenocarcinoma (n = 262) were matched to controls (n = 816) and included data on BMI 20 years before study inclusion (643 [EL 2; RCCS]). BMI appeared to have the largest

effect on gastroesophageal reflux frequency (i.e., >3 times per week). However, there was no increased risk of cancer among patients with BMI <25 kg/m^2 or ≥25 kg/m^2 20 years before inclusion, with or without adjustment for gastroesophageal reflux frequency, severity, or duration.

The relationship between obesity and GERD is not readily evident in all studies. A prospective cross-sectional study to assess the presence of GERD and GERD-related esophageal lesions (i.e., erosive esophagitis and Barrett's esophagus) was performed in 250 patients (mean age, 38.8 years; range, 18-64 years) with obesity (mean BMI, 45.3 kg/m^2; range, 35 to 76.2 kg/m^2) who were candidates for bariatric surgery (635 [EL 2; PCS]). All patients completed a validated GERD symptom questionnaire and had an upper endoscopy before surgery. GERD symptoms occurred in 38% of the patients (heartburn 29%, regurgitations 34%, or both 26%), 55% reported minor symptoms (defined as frequency <1/week and low intensity), and 16% were taking a PPI. The frequency and intensity of GERD symptoms were similar in patients with or without PPI use, and no relationship between WC and GERD symptoms was found. Endoscopy was normal in 49% of subjects and identified esophagitis in 5% (Los Angeles classification grade A, 92%; grade B, 0%; grade C, 8%), hiatal hernia in 13% (mean length, 4 cm), gastritis in 33% (*Helicobacter pylori* in 15%), and no evidence for Barrett's esophagus or esophageal adenocarcinoma. In addition, in patients with BMI <45 kg/m^2 or ≥45 kg/m^2, there was no difference observed in the prevalence of GERD symptoms or esophageal lesions.

In a cohort study of 25 patients (9 men and 16 women) referred for bariatric surgery, visceral adipose tissue (VAT) was quantitatively assessed by means of magnetic resonance imaging (MRI) (644 [EL 3; CSS, N = 16]). GERD symptoms were evaluated using a standardized questionnaire, and upper endoscopy and esophageal manometry assessed anatomic pathology and lower esophageal sphincter (LES) pressure, respectively. The cohort BMI ranged between 35.2 and 59.1 kg/m^2, and compared to women, men had significantly higher WHR (P<0.0001) and VAT (P = 0.0021). Of interest, LES pressure and GERD-related symptoms were not dependent on anthropometric measures or VAT, and VAT did not correlate with BMI, indicating increased adiposity in the subcutaneous tissue.

In addition, not all studies in patients with GERD show a clear association between acid reflux and an increased BMI or WC (645 [EL 2; RCCS]; 646 [EL 2; PCS]; 647 [EL 2; RCCS]). In a retrospective review of 122 consecutive multichannel intraluminal impedance-pH (MII-pH) studies, reflux was classified as acid reflux or nonacid reflux episodes among patients divided into normal weight, overweight, and obese weight groups (645 [EL 2; RCCS]). Patients showed a clear association between increased nonacid reflux and higher BMI, but there was no significant difference among the groups in the frequency of acid reflux. In 582 patients with obesity and GERD symptoms referred for manometry and ambulatory pH studies, the prevalence of obesity was greater in women (23% vs. 16%, P = 0.056), although more men had abdominal obesity (WC >99 cm, 41% vs. 28%, P = 0.001) (646 [EL 2; PCS]). Greater WC was associated with lower LES pressure, reduced abdominal LES length, peristaltic dysfunction, and increased exposure to esophageal acid (all P<0.001). However, multivariable analysis demonstrated that the effects of increasing WC on esophageal function did not explain increased acid reflux in the patients with obesity, suggesting independent effects of obesity and esophageal dysfunction on acid exposure.

Esophageal manometry and 24-hour pH results were extracted from a prospectively collected database in 245 patients (mean age, 52.2 ± 14 years; 54% men) and compared to subject anthropometric and endoscopy data (647 [EL 2; RCCS]). Supine acid exposure was significantly higher in patients with overweight and obesity than in normal-weight patients (both P = 0.02). In the normal-weight group (n = 87), the median acid exposure time was 1.1% (0 to 8.1%) supine, 7.7% (2.5 to 14.8%) upright, and 7.4% (2.7 to 11.7%) over 24 hours. In the overweight group (n = 104), the median acid exposure time was 4.9% (0.3 to 13.3%) supine, 11.1% (5.4 to 16.9%) upright, and 8.9% (4.7 to 15.8%) for 24 hours. In the obesity group (n = 54), the median acid exposure time was 4.1% (0.7 to 14.3%) supine, 10.5% (5 to 17.5%) upright, and 8.3% (5.3 to 14.7%) over 24 hours. Although an association between increasing BMI and acid exposure was observed, BMI was not independently predictive of acid reflux in this study. Multiple regression analysis showed that in the normal weight group, no contributing factor (i.e., hiatal hernia, LES pressure, intragastric pressure) was statistically significant in exposure to esophageal acid. In patients with overweight, presence of a hiatal hernia significantly predicted supine and total esophageal acid exposure (P = 0.005 and P = 0.01, respectively), as did decreasing LES pressure for the supine and the upright positions (P = 0.002 and P = 0.04, respectively). Increased intragastric pressure significantly contributed to total acid exposure in the obesity group (P = 0.05).

An important factor associated with GERD is the presence of a hiatal hernia (630 [EL 2; PCS]; 632 [EL 2; PCS]; 647 [EL 2; RCCS]; 648 [EL 2; RCCS]). GERD can occur with or without a hiatal hernia, and the latter is recognized as an obesity-related comorbidity. In 382 patients undergoing bariatric surgery, GERD was diagnosed preoperatively in 170 patients (44.5%), and hiatal hernia was detected intra-operatively in 142 patients (37.2%) (632 [EL 2; PCS]). In another cohort study of 378 patients, where a standard pre-operative workup was done before bariatric surgery, 60 patients were diagnosed with GERD (15.8%) and 42 with hiatal hernia (11.1%) prior to sleeve gastrectomy (630 [EL 2; PCS]). At surgery, 55 of these patients

(14.5%) were diagnosed with a hiatal hernia intra-operatively. To assess the prevalence of hiatal hernias radiographically, 181 patients (mean age, 44 years; mean BMI, 43 kg/m^2) had a pre-operative upper GI contrast study (648 [EL 2; RCCS]). The prevalence of GERD was 39.8% (reported as moderate to severe in 13.3%) and that of hiatal hernia was 37.0%, with moderate (2 to 5 cm) or large (>5 cm) hiatal hernia in 4.4% of patients. From 245 subjects studied prospectively with endoscopy, a hiatal hernia was significantly more often present in the overweight (n = 66, 63.5%) and obese groups (n = 30, 55.6%) compared with the normal weight subjects (n = 38, 43.7%; $P = 0.01$) and significantly contributed to acid reflux in the overweight, but not obesity, group (647 [EL 2; RCCS]).

Silent esophageal erosions are prevalent among patients with GERD, even though its natural history and clinical significance are unknown. A study of 4,565 participants (52% men; mean age, 46 ± 10 years) in a prospective health-screening cohort were identified as having GERD in the presence of weekly heartburn or acid regurgitation via a validated GERD questionnaire or by esophageal erosions identified by endoscopy (649 [EL 2; PCS]). Symptomatic GERD and endoscopic erosions were present in 14.9% (n = 678) and 7.3% (n = 335) of all participants, respectively, and categorized as symptomatic erosive GERD (n = 38, 5.6%), silent erosive GERD (n = 297, 43.8%), and nonerosive GERD (n = 343, 50.6%). Male gender and obesity were common predictors for both symptomatic and silent erosive GERD compared to controls. Higher symptom scores (OR, 3.7; CI, 1.8-7.8) and overlap of functional dyspepsia (OR, 35.4; CI, 14.9-84.3) were predictors of symptomatic versus silent erosive GERD. In a cross-sectional study of 260 Chinese patients referred for bariatric surgery, the prevalence of erosive esophagitis seen at endoscopy was 32.3% (650 [EL 3; CSS]). Multiple logistic regression showed that increased WC (OR, 1.03; CI, 1.01-1.04) and the presence of reflux symptoms (OR, 2.40; CI, 1.22-4.74) were independent risk factors associated with erosive esophagitis. Two post-hoc analyses included pooled data from RCTs to evaluate the effect of obesity on symptom resolution for nonerosive GERD (n = 704 from 2 RCTs) and healing rates for erosive esophagitis (n = 11,027 from 5 RCTs) in patients treated with PPI therapy (651 [EL 1; MRCT]). All subjects had endoscopy at baseline. There was no significant association between heartburn severity and BMI for the nonerosive GERD group. More severe erosive GERD (Los Angeles grade C or D) was present in patients who had overweight and obesity than in those at normal weight ($P<0.0001$).

A positive association between obesity and acid reflux has been documented in many studies (652 [EL 2; RCCS]; 653 [EL 2; PCS]; 654 [EL 2; PCS, N = 46]; 655 [EL 2; PCS]; 656 [EL 2; PCS, N = 24]), although not all (645 [EL 2; RCCS]; 646 [EL 2; PCS]; 647 [EL 2; RCCS]). A retrospective analysis of 460 patients suspected for GERD who underwent MII-pH were analyzed at least 10 days free from PPI therapy using a standardized symptom-based questionnaire (651 [EL 1; MRCT]). Positive predictors for pathology in MII-pH included GERD symptoms, a positive symptom index score, male gender, and obesity. Positive predictors of response to PPI therapy were typical GERD symptoms (heartburn and regurgitation), a positive symptom index score, and abnormal MII-pH measurements, in addition to atypical symptoms such as hoarseness and fullness. Persistent abnormal acid exposure, hypersensitive esophagus, and functional heartburn were evaluated in 151 patients with overweight or obesity and 95 normal-weight patients (mean age, 55 years; range, 18-75 years) with persistent GERD symptoms despite twice-daily PPI therapy (653 [EL 2; PCS]). All patients had normal endoscopy and underwent MII-pH monitoring, and reflux was classified as acid or nonacid episodes. A positive symptom index score was defined when >50% of symptoms were preceded by reflux episodes. Persistent abnormal acid exposure (% time pH <4) was found in 39 patients (BMI; increased in 31, normal in 8), hypersensitive esophagus in 77 patients (BMI; increased in 43, normal in 34), and functional heartburn in 118 patients (BMI; increased in 69, normal in 49). In all 3 groups, patients with increased BMI were more likely to have acid reflux than hypersensitive esophagus or functional heartburn ($P = 0.03$). The total number of reflux episodes and nonacid reflux episodes significantly increased as BMI increased, but there was no significant difference in acid reflux among groups.

In a prospective study of 46 individuals with overweight or obesity (mean age, 49 years; mean BMI, 30.6 kg/m^2; range, 25.1 to 45.6 kg/m^2) and asymptomatic for GERD, endoscopy revealed esophagitis in 13 of 28 subjects (Los Angeles grade A, n = 10; grade B, n = 3) (654 [EL 2; PCS, N = 46]). A significant positive correlation was seen between BMI and both total and supine acid reflux episodes (pH <4, via ambulatory impedance-pH monitoring) and time of acid reflux. In a group of patients seeking bariatric surgery, 124 patients were compared to 15 normal-weight volunteers, and all patients completed a standardized questionnaire for GERD symptoms severity, upper endoscopy, and MII-pH monitoring (655 [EL 2; PCS]). Participants were grouped according to symptoms and endoscopy findings (negative for both, positive for symptoms and negative for endoscopy, and positive for both). Subjects without GERD symptoms or endoscopy findings did not have a significant increase in reflux. Subjects with symptomatic GERD had significantly increased esophageal acid exposure and total number of refluxes, with a higher grade of reflux in patients with both GERD symptoms and endoscopy findings. Abdominal MRI, esophageal endoscopy, and manometry with MII-pH were performed in upright and supine subjects before and after a meal in 24 healthy volunteers with small (n = 24) and large (n = 27) WC (656 [EL 2; PCS, N = 24]). The cardiac mucosa was

significantly longer in the large WC group (2.5 vs. 1.75 mm, $P = 0.008$) and its length correlated with both intra-abdominal ($P = 0.045$) and total abdominal ($P = 0.034$) fat. The squamocolumnar junction was closer to the LES upper border (2.77 vs. 3.54 cm, $P = 0.02$), the LES was shorter (3.0 vs. 4.5 cm, $P = 0.43$), and gastric acidity extended more proximally within the LES in the large WC group.

Total and visceral obesity have recently been linked to GERD-related esophageal inflammation. To determine the correlation between GERD, esophageal inflammation, and obesity, 458 subjects receiving a comprehensive health examination also completed a standard GERD questionnaire, an upper endoscopy, and 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography scanning (657 [EL 2; PCS]). Erosive esophagitis was scored using the Los Angeles classification system and inflammatory activity was represented by standardized uptake values of FDG. Subjects with erosive esophagitis identified by endoscopy (n = 178, 38.9%) had significantly higher FDG uptake at the middle esophagus and esophagogastric junction ($P<0.001$ for both) and marginally higher uptake at the upper esophageal sphincter ($P = 0.062$), but no significant uptake in the stomach or duodenum. Heartburn was positively correlated with higher esophagus FDG values ($P = 0.003$), and the severity of erosive esophagitis seen at endoscopy also correlated with FDG uptake. Multivariate regression analyses showed that age ($P = 0.027$), alcohol intake ($P = 0.03$), subcutaneous adipose tissue ($P<0.001$), BMI ($P<0.001$), and WC ($P<0.001$) were all independently associated with higher esophageal FDG uptake.

- *Q3.15. Depression*

Executive Summary

- **R28.** Patients with overweight or obesity should be screened for depression; all patients with depression should be evaluated for the presence of overweight or obesity **(Grade B; BEL 2)**.

Evidence Base

Depressive disorders are characterized by "the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function." Symptoms include depressed mood, anhedonia, weight changes, sleep disturbances, fatigue, feelings of worthlessness and/or hopelessness, and potentially suicidal ideation (658 [EL 4; NE]). Multiple studies have demonstrated that an association exists between obesity and depression (658 [EL 4; NE]; 659 [EL 3; SS]; 660 [EL 3; SS]; 661 [EL 4; NE]; 662 [EL 4; NE]; 663 [EL 2; PCS]; 664 [EL 4; NE]; 665 [EL 3; SS]; 666 [EL 2; MNRCT]). Recently, data from the NHANES (2005-2010) found that 43% of adults with depression had obesity and that adults with depression were more likely to have obesity (662 [EL 4; NE]). Additionally, studies find that mood disorders, including major depression, are associated with weight gain, overweight, and obesity (661 [EL 4; NE]).

Studies have varied as to causality and temporal association. Thus, whether depression and other mental disorder lead to obesity (667 [EL 2; PCS]; 668 [EL 2; MNRCT]) or whether obesity results in the development of depression (669 [EL 2; PCS]) is yet to be fully elucidated, and both scenarios are likely operative. A recent meta-analysis of 15 studies (N = 58,745) found that obesity increased risk for depression and that depression increased the odds of developing obesity (666 [EL 2; MNRCT]). Another study (N = 487) found that weight loss was associated with a significant fall in Beck Depression Inventory (BDI) scores at 1 year and 4 years after the gastric banding procedure and that the greatest decrease in BDI scores was found in younger women with greater excess weight loss (670 [EL 3; SS]).

The association between obesity and depression may be mediated by a number of mechanisms. Obesity is associated with insulin resistance (671 [EL 2; PCS]; 672 [EL 4; NE]) and systemic inflammation (673 [EL 2; PCS]; 674 [EL 3; CCS]; 675 [EL 3; CSS]), as well as dysregulation of the hypothalamic-pituitary-adrenal axis (676 [EL 4; NE]; 677 [EL 4; NE]), and these factors have been implicated in the pathogenesis of depression. On the other hand, obesity can lead to social stigmatization, body dissatisfaction, diminished self-esteem, and stress in societies where thinness is equated with beauty (678 [EL 3; SS]; 679 [EL 4; NE]). Disordered eating patterns, disability, and pain associated with obesity can also increase risk of depression (680 [EL 3; SS]; 681 [EL 3; CSS]; 682 [EL 3; SS]).

- ***Q4. Do BMI or other measures of adiposity convey full information regarding the impact of excess body weight on the patient's health?***

Executive Summary

- **R29.** All patients with overweight or obesity should be clinically evaluated for weight-related complications because BMI alone is not sufficient to indicate the impact of excess adiposity on health status; therefore, the diagnostic evaluation of patients with obesity should include an anthropometric assessment of adiposity and a clinical assessment of weight-related complications **(Grade A; BEL 2, upgraded due to high relevance)**. Patients with overweight or obesity should be re-evaluated at intervals to monitor for any changes in adiposity and adiposity-related complications over time **(Grade A; BEL 2, upgraded due to high relevance)**.

Evidence Base

The following evidence addresses whether BMI alone is sufficient to indicate health status in evaluating patients with obesity, as a function of specific weight-related complications.

- **Diabetes risk, metabolic syndrome, and prediabetes (IFG, IGT).** A proportion of individuals with obesity are insulin sensitive, do not exhibit metabolic syndrome traits, and have been referred to as "metabolically healthy obese" (241 [EL 2; PCS, N = 22]; 259 [EL 3; SS]; 272 [EL 3; SS]; 274 [EL 2; PCS]). While obesity can exacerbate insulin resistance (683 [EL 4; NE]), insulin sensitivity largely varies independent of BMI (266 [EL 4; NE]; 268 [EL 2; PCS]), and the risk of diabetes is largely conferred by the presence of traits associated with insulin resistance (e.g., waist, triglycerides, HDL-c, BP, abnormal glucose tolerance) rather than BMI per se (192 [EL 3; SS]; 241 [EL 2; PCS]; 272 [EL 2; PCS]; 275 [EL 2; RCCS]; 276 [EL 2; PCS, selection bias]). Therefore, obesity as assessed by BMI is neither sufficient nor necessary as a pathogenic factor in the development of insulin resistance, metabolic syndrome, and prediabetes.
- **Type 2 diabetes.** The proportion of adults who were normal weight at the time of incident diabetes ranged from 9 to 21% (overall 12%) across a substantial number of large cohort studies (Atherosclerosis Risk in Communities [ARIC], CARDIA, Cardiovascular Health Study [CHS], Framingham Heart Study, and Multi-Ethnic Study of Atherosclerosis [MESA]) (374 [EL 2; MNRCT]). In the Behavior Risk Factor Surveillance System, the prevalence of diabetes is 4.1% in normal-weight individuals, 7.3% in overweight, 14.9% in class II obesity, and 25.6% in severe class III obesity; thus, the clear majority of individuals with obesity do not have diabetes (333 [EL 3; SS]). While BMI is a strong risk factor for T2DM, the data indicate that BMI is a poor indicator of the presence or absence of diabetes.
- **Dyslipidemia (including VLDL, LDL, and HDL).** Elevated BMI per se does not have a pronounced effect on concentrations of circulating LDL-c. High levels of LDL-c represent a major risk factor for CVD and can occur in patients with or without obesity (684 [EL 2; PCS]). However, in those patients with insulin resistance and metabolic syndrome, obesity can be associated with a dyslipidemia characterized by elevated triglyceride levels, as a result of an excess of large triglyceride-laden VLDL particles, as well as decreased concentrations of HDL-c (265 [EL 2; NRCT]). While levels of LDL-c may not be primarily affected, the cholesterol is packaged into smaller, denser LDL particles (315 [EL 1; RCT]), which are more atherogenic (316 [EL 2; PCS]; 317 [EL 2; MNRCT]; 318 [EL 2; PCS]). This dyslipidemia is a function of insulin resistance, which is not present in all individuals with obesity (274 [EL 2; PCS]; 275 [EL 3; SS]). High triglycerides and low HDL-c constitute 2 of the 5 diagnostic criteria for metabolic syndrome, which is associated with increased risk of CVD and T2DM (244 [EL 4; NE]).
- **Hypertension.** There is a strong association between elevated BMI and hypertension, with 23% of female and male patients with normal weight, 34 to 39% with overweight, 48 to 49% with class I obesity, 55 to 65% with class II obesity, and 63 to 64% with class III obesity having hypertension in the serial National Health and Nutrition Examination Survey III cross-sectional surveys from 1988 to 1994 (330 [EL 3; SS]). Thus, not all patients with obesity are hypertensive. Hypertension has other risk factors independent of obesity, including age, ethnicity/race, sedentary life style, cigarette smoking, high sodium intake, heavy alcohol use, stress, family history, and genetic factors (685 [EL 4; NE]). Elevated BP is a criterion for metabolic syndrome and is associated with increased WC and insulin resistance (244, [EL 2; PCS, N = 13]; 686 [EL 4; NE]).
- **CVD events and CVD mortality.** BMI is associated with increased risk of CVD events, principally through its association with other risk factors, such that independent risk conferred by BMI is usually minimized in multivariate analyses. For example, when adjusted for WC or the presence of metabolic syndrome, BMI is no longer a significant independent risk factor for CVD or becomes a much weaker predictor (192 [EL 3; SS]; 241 [EL 2; MNRCT]; 255 [EL 2; MNRCT]; 256 [EL 2; PCS]; 275 [EL 2; RCCS]; 276 [EL 2; PCS, selection bias]). BMI has minimal effect on other major CVD risk factors such as LDL-c, smoking, family history, and genetic factors (684 [EL 2; PCS]).
- **NAFLD and NASH.** NAFLD is recognized as the most common chronic liver disease in many countries, including the United States where it occurs in an estimated 23 to 30% of adults when diagnosed by ultrasound plus serum enzymes (687 [EL 4; NE]; 688 [EL 4; NE]). Seventy percent of patients with obesity have NAFLD, while 30% do not, and only 15 to 20% of patients with obesity have NASH (689 [EL 3; CCS, N = 23]). While the factors that predict which patients with NAFLD will progress to NASH and cirrhosis have not been elucidated, factors other than generalized obesity appear to predominate (690 [EL 2; RCCS]; 691 [EL 3; CCS, retrospective analysis]). In addition

to obesity, metabolic syndrome and insulin resistance have been implicated as major contributors to NAFLD and NASH. The risk of NAFLD increases as the number of metabolic syndrome traits increases (388 [EL 3; CSS]), and the distribution of adipose tissue and not BMI is a strong independent predictor of NAFLD (390 [EL 4; NE]), particularly in certain ethnicities, such as Asians (391 [EL 2; RCCS]).

- **Male hypogonadism.** The Hypogonadism in Males Study indicated that, for men with obesity the prevalence of hypogonadism (defined as total testosterone <300 ng/dL) was 52.4% (507 [EL 3; CSS]). Among all men >45 years of age, 38.7% had hypogonadism, including 32.3% of men with obesity, while only 17% of eugonadal men had obesity. T2DM, insulin resistance, and metabolic syndrome are also strong risk factors for hypogonadism (692 [EL 4; NE]). Metabolic syndrome is frequently associated with reduced testosterone and sex hormone–binding globulin levels (693 [EL 2; PCS, case-controlled, N = 52 cases, 20 controls]; 694 [EL 3; CSS]), and WC is an independent and stronger predictor of low testosterone than BMI (695 [EL 3; CSS]; 696 [EL 3; CSS]).
- **Female infertility and PCOS.** There is a U-shaped association between BMI and infertility, with increased risk at BMI <20 kg/m^2 and a progressive increase as the BMI rises above 24 kg/m^2, with 25% of infertility in women estimated to be attributable to obesity (465 [EL 2; PCS]). The prevalence rates of PCOS in women with underweight, normal-weight, overweight, and obesity were 8.2, 9.8, 9.9, and 9.0%, respectively, with rates rising to 12.4% when the BMI is >35 kg/m^2 (458 [EL 2; RCCS]). Thus, the majority of women with overweight and obesity do not experience infertility or PCOS, and these problems can also afflict normal-weight women (442 [EL 4; NE]). Central adiposity is an independent risk factor associated with decreased probability of conception independent of BMI in women with and without PCOS involving both natural and assisted reproductive technology (446 [EL 4; NE]; 697 [EL 2; PCS]; 698 [EL 2; PCS]).
- **Obstructive sleep apnea (OSA).** Obstructive sleep apnea affects ~70% of patients with obesity, and prevalence rates rise progressively as the BMI exceeds 29 kg/m^2 (523 [EL 4; NE]; 543 [EL 4; NE]). Clearly, not all patients with obesity have OSA (525 [EL 3; SS]; 546 [EL 4; NE]). Insulin resistance, abdominal obesity, enlarged neck circumference, and T2DM are also risk factors for OSA (522 [EL 3; CSS]; 545 [EL 2; PCS]; 546 [EL 3; SS]).
- **Osteoarthritis.** Increasing BMI is associated with progressive increments in the OR for OA of the knee up to an OR of 10 in patients with severe obesity when compared with normal weight individuals. However, OA can afflict individuals who are lean or who have obesity, and not all patients with overweight and obesity have OA (587 [EL 3; SS]; 588 [EL 3; SS]; 591 [EL 3; CSS]; 592 [EL 2; PCS]). Other independent risk factors for OA include age, work history, knee trauma, participation in certain sports, and elevated adipocytokines (583 [EL 3; SS]; 587 [EL 3; SS]; 588 [EL 3; CSS]; 591 [EL 2; PCS]; 592 [EL 4; NE]).
- **Urinary stress incontinence.** BMI increases risk for stress urinary incontinence (602 [EL 2; MNRCT]; 604 [EL 3; SS]) associated with increased intra-abdominal and intravesical pressure (623 [EL 3; CSS]), although the majority of women with obesity and overweight do not experience incontinence, and this disorder affects normal-weight individuals as well (602 [EL 3; SS]; 604 [EL 3; SS]; 699 [EL 2; MNRCT]). Other factors in addition to BMI constitute independent risk factors for urinary incontinence including age, WC, parity, previous hysterectomy, metabolic syndrome, and depression (699 [EL 3; SS]).
- **Gastroesophageal reflux disease.** Most (700 [EL 4; NE]; 701 [EL 3; SS]; 702 [EL 2; RCCS]) but not all (703 [EL 2; RCCS]) studies show a significant association between elevated BMI and presence of GERD. GERD is common in both individuals who are lean and those who have obesity, with the result that ORs attributable to obesity are somewhat modest in the range of 1.22 to 2.8 (701 [EL 3; SS]; 702 [EL 2; RCCS]). The pathophysiology involves abnormal functioning of the LES (704 [EL 4; NE]). Other risk factors include positive family history, cigarette smoking, hiatal hernia, delayed gastric emptying, *H. pylori* infection, and alcohol consumption (700 EL 4; NE]; 701 [EL 3; SS]; 702 [EL 2; RCCS]; 703 [EL 2; RCCS]; 704 [EL 4; NE]; 705 [EL 4; NE]).

- ***Q5. Do patients with excess adiposity and related complications benefit more from weight loss than patients without complications? Can weight loss be used to treat weight-related complications, and, if so, how much weight loss would be required? (Table 8 in Executive Summary)***

Note: Specific medications are mentioned or recommended below for use in different clinical settings based on available evidence for efficacy and safety. Medications may not be explicitly recommended if there are no data available for use in the specified clinical setting, even

though weight loss associated with these medications may produce clinical benefits.

- *Q5.1. Is weight loss effective to treat to diabetes risk (i.e., prediabetes, metabolic syndrome) and prevent progression to type 2 diabetes? How much weight loss would be required?*

Executive Summary

- **R30.** Patients with overweight or obesity and with either metabolic syndrome or prediabetes, or patients identified to be at high risk of T2DM based on validated risk-staging paradigms, should be treated with lifestyle therapy that includes a reduced-calorie healthy meal plan and a physical activity program incorporating both aerobic and resistance exercise to prevent progression to diabetes **(Grade A; BEL 1)**. The weight-loss goal should be 10% **(Grade B; BEL 2)**.
- **R31.** Medication-assisted weight loss employing phentermine/topiramate ER, liraglutide 3 mg, or orlistat should be considered in patients at risk for future T2DM and should be used when needed to achieve 10% weight loss in conjunction with lifestyle therapy **(Grade A; BEL 1)**.
- **R32.** Diabetes medications, including metformin, acarbose, and thiazolidinediones, can be considered in selected high-risk patients with prediabetes who are not successfully treated with lifestyle and weight-loss medications and who remain glucose intolerant **(Grade A; BEL 1)**.

Evidence Base

The goals of therapy in patients with insulin resistance and cardiometabolic disease risk are to prevent progression to T2DM and to improve CV risk by treating hypertension and dyslipidemia (18 [EL 4; NE]; 246 [EL 4; NE]; 247 [EL 4; NE]). Effective prevention of T2DM is critical for reducing patient suffering and the escalating social costs resulting from the rising prevalence rates of diabetes. In patients who have overweight or obesity, weight loss is highly effective in preventing or delaying progression to T2DM (706 [EL 1; RCT]; 707 [EL 1; RCT]; 708 [EL 1; RCT]; 709 [EL 1; RCT]; 710 [EL 1; RCT]; 711 [EL 1; RCT]), particularly in high-risk patients with prediabetes (706 [EL 1; RCT]; 707 [EL 1; RCT]; 708 [EL 1; RCT]) or metabolic syndrome (244 [EL 1; RCT]; 712 [EL 4; NE]; 713 [EL 4; NE]). Due to the high prevalence of overweight and obesity (~70% in the United States) and large individual variation in risk, risk stratification is required to target more aggressive weight-loss therapy to higher risk patients. Prediabetes and metabolic syndrome are 2 clinical constructs that effectively identify individuals at high risk of T2DM (18 [EL 4; NE]; 246 [EL 4; NE]; 247 [EL 4; NE]). Other risk-staging approaches (241 [EL 3; SS]; 271 [EL 3; SS]; 279 [EL 4; NE]; 280 [EL 2; PCS]; 281 [EL 3; SS]; 282 [EL 3; SS]; 283 [EL 3; SS]; 284 [EL 2; PCS]; 285 [EL 4; NE]; 286 [EL 4; NE]; 287 [EL 3; SS]), such as Cardiometabolic Disease Staging (241 [EL 3; SS]; 271 [EL 3; SS]), can be used to provide a more granular and quantitative stratification of diabetes and CVD risks.

Three major, randomized, clinical trials, the Diabetes Prevention Program (DPP) (708 [EL 1; RCT]; 714 [EL 2; PCS]; 715 [EL 1; RCT]), the Finnish Diabetes Prevention Study (707 [EL 1; RCT]; 716 [EL 1; RCT]; 717 [EL 1; RCT]), and the Da Qing Diabetes Prevention Study (706 [EL 1; RCT]; 718 [EL 1; RCT]) all demonstrated the impressive efficacy of weight loss accompanying lifestyle/behavioral therapy to prevent T2DM. At the same time, weight loss also ameliorated insulin sensitivity and reduced CVD risk factors, including improvements in BP, lipids, and markers of inflammation. In these studies, lifestyle modifications generally involved reductions in caloric intake (by 500 to 1,000 calories/day), behavioral interventions, and increases in physical activity. The DPP study randomized subjects with IGT to control, metformin, and lifestyle intervention subgroups over 4 years, and lifestyle modification was found to reduce progression to T2DM by 58% and metformin by 31%, compared with placebo (708 [EL 1; RCT]). Subjects achieved approximately 6% mean weight loss at 2 years and 4% weight loss at 4 years in the lifestyle intervention arm, and, in post-hoc analysis, a progressive 16% reduction in T2DM risk was seen with every kilogram of weight loss (708 [EL 1; RCT]; 714 [EL 2; PCS]). With observational follow-up after termination of the study, there was still a significant reduction in the cumulative incidence of T2DM in the lifestyle treatment group at 10 years, despite the fact that BMI levels had equalized among the 3 treatment arms (715 [EL 1; RCT]). In addition to the reductions in T2DM, there was evidence in the Da Qing study that CVD events and mortality were reduced after 23 years when comparing the combined subgroups treated with diet and physical activity with the controls (718 [EL 1; RCT]). A meta-analysis of 12 RCTs concluded that lifestyle was effective in preventing diabetes compared with controls, with RR of 0.60 (95% CI: 0.35, 1.05) after 1 year and 0.63 after 3 years (95% CI: 0.51, 0.79) with equal benefits noted in both men and women (719 [EL 1; MRCT]).

Weight loss through lifestyle changes alone can be difficult to maintain (720 [EL 1; MRCT]), and pharmacotherapy or surgery, employed as an adjunct to lifestyle therapy, can be considered. In RCTs comparing weight-loss medication plus lifestyle with lifestyle alone, orlistat (721 [EL 1; RCT]), phentermine/topiramate ER (712 [EL 1; RCT]; 722 [EL 1; RCT]), and liraglutide (3 mg/day) (68 [EL 1; RCT]) produced greater weight loss and more profound reductions in incident diabetes. Treatment with lifestyle therapy plus phentermine/topiramate ER achieved 12.1% weight loss after 2 years (compared to 2.5% weight

loss in lifestyle alone), as well as a 79% reduction in the annualized T2DM incidence rate in patients with metabolic syndrome or prediabetes at baseline (712 [EL 1; RCT]). Diabetes prevention trials employing lorcaserin or naltrexone ER/bupropion ER have not been published. Rates of incident diabetes were also reduced in patients treated with a variety of bariatric surgical procedures (723 [EL 2; RCCS]; 724 [EL 2; PCS]; 725 [EL 2; NRCT]; 726 [EL 3; CSS]; 727 [EL 2; NRCT]; 728 [EL 2; PCS, case-controlled]), which vary in their efficacy for weight loss.

The ability to prevent T2DM has been shown to be dependent on the magnitude of weight loss; however, is there a threshold for the degree of weight loss above which there is no additional benefit? In the DPP, maximal prevention of diabetes was observed at about 10% weight loss (714 [EL 2; PCS]). This is consistent with the study employing phentermine/topiramate ER where weight loss of 10% reduced incident diabetes by 79% and any further weight loss to ≥15% did not lead to additional prevention (712 [EL 1; RCT]). The bariatric surgery studies produced greater weight loss than observed following lifestyle and pharmacotherapy interventions, yet, in 2 studies, there was a maximum of 76 to 80% reduction in diabetes rates (725 [EL 2; NRCT]; 728 [EL 2; PCS, case-controlled]), similar to that observed in the phentermine/topiramate ER intervention, which had lesser weight loss.

These combined data suggest that 10% weight loss will reduce the risk of future T2DM by ~80%, and this represents a threshold above which further weight loss will not result in additional preventive benefits. Thus, residual risk for T2DM may exist that cannot be eliminated by weight loss. T2DM is a heterogeneous disease, and some individuals may have a heavy burden of genetic/environmental interactions that lead inexorably to T2DM regardless of weight loss. In any event, based on studies employing lifestyle (714 [EL 2; PCS]), weight-loss medications (712 [E; 1; RCT]), and bariatric surgery (725 [EL 2; NRCT]; 728 [EL 2; PCS, case-controlled]), an 80% reduction in progression to T2DM among high-risk individuals can be achieved if the intervention results in ≥10% weight loss.

Regular physical activity by itself (729 [EL 2; MNRCT]; 730 [EL 2; PCS]) or as part of a comprehensive lifestyle plan (706 [EL 1; RCT]; 707 [EL 1; RCT]; 708 [EL 1; RCT]; 714 [EL 2; PCS]; 716 [EL 1; RCT]) can also prevent progression to T2DM in high-risk individuals. Structured exercise improves fitness, muscle strength, and insulin sensitivity (731 [EL 1; RCT]; 732 [EL 2; PCS]; 733 [EL 1; RCT]). In the context of an overall lifestyle intervention, regular physical activity can contribute to weight loss and prevention of weight regain and improve CVD risk factors such as lipids and BP (706 [EL 1; RCT]; 707 [EL 1; RCT]; 708 [EL 1; RCT]). Studies have demonstrated beneficial effects of both aerobic and resistance exercise and additive benefits when both forms of exercise are combined (734 [EL 1; RCT]; 735 [EL 1; MRC, 8 controlled trials with unclear randomization]; 736 [EL 1; RCT]). For cardiometabolic conditioning, evidence-based guidelines proposed by the ADA, AHA, and the American College of Sports Medicine (ACSM) are well aligned (28 [EL 4; NE]; 29 [EL 4; NE]) in their recommendations for a combination of regular aerobic and resistance exercise. In patients who are unable to engage in optimal physical activity, studies have shown that a walking program is associated with reductions in diabetes incidence (737 [EL 3; SS]; 738 [EL 2; PCS]; 739 [EL 2; PCS]). Reductions in sedentary behavior may also be beneficial (740 [EL 2; PCS]).

Oral glucose-lowering agents have also been studied for their ability to prevent diabetes. RCTs have demonstrated efficacy for metformin (708 [EL 1; RCT]), acarbose (741 [EL 1; RCT]; 742 [EL 1; MRCT]), rosiglitazone (743 [EL 1; RCT]; 744 [EL 1; RCT]; 745 [EL 1; RCT]), and pioglitazone (746 [EL 1; RCT]). Hopper et al (747 [EL 1; RCT]) conducted a meta-analysis of 10 RCTs encompassing 20,872 subjects, including both weight-loss/lifestyle and pharmacologic interventions, and found that lifestyle approaches not involving diabetes drugs were superior to drug-based approaches in diabetes prevention (0.52, 95% CI: 0.46-0.58 vs. 0.70, 95% CI: 0.58-0.85, P<0.05). Metformin (first-line), acarbose, and thiazolidinediones have been recommended for consideration to prevent diabetes by the AACE (247 [EL 4; NE]) and the ADA (246 [EL 4; NE]) in patients with both prediabetes and metabolic syndrome traits.

- *Q5.2. Is weight loss effective to treat to type 2 diabetes? How much weight loss would be required?*

Executive Summary

- **R33.** Patients with overweight or obesity and T2DM should be treated with lifestyle therapy to achieve 5 to 15% weight loss or more as needed to achieve targeted lowering of A1C **(Grade A; BEL 1)**. Weight-loss therapy should be considered regardless of the duration or severity of T2DM, both in newly diagnosed patients and in patients with longer-term disease on multiple diabetes medications **(Grade A; BEL 1)**.
- **R34.** Weight-loss medications should be considered as an adjunct to lifestyle therapy in all patients with T2DM as needed for weight loss sufficient to improve glycemic control, lipids, and BP **(Grade A; BEL 1)**.
- **R35.** Patients with obesity (BMI ≥30 kg/m^2) and diabetes who have failed to achieve targeted clinical outcomes following treatment with lifestyle therapy and weight-loss medications may be considered for bariatric surgery, preferably Roux-en-Y gastric bypass, sleeve gastrectomy, or biliopancreatic diversion; also see recommendation

121 **(Grade B; BEL 1, downgraded due to evidence gaps)**.

- **R36.** Diabetes medications that are associated with modest weight loss or are weight-neutral are preferable in patients with obesity and T2DM, although clinicians should not refrain from insulin or other medications when needed to achieve A1C targets **(Grade A; BEL 2, upgraded due to high relevance)**.

Evidence Base

While the relationship between obesity and pathogenesis of T2DM is complex, weight loss represents highly effective therapy for glycemic control and improving CV risk factors in individuals with overweight/obesity and T2DM (748 [EL 4; NE]). The value of weight-loss therapy as a primary treatment approach in T2DM, whether at initial diagnosis or in conjunction with medical therapy at any time over the course of the disease, is emphasized in recent guidelines advocated by the AACE (15 [EL 4; NE]; 18 [EL 4; NE]), the Endocrine Society (22 [EL 4; NE]), and the American Society for Metabolic and Bariatric Surgery (11 [EL 4; NE]).

Lifestyle intervention is a critical component of weight-loss therapy in patients with obesity and T2DM. An analysis of response to nutritional intervention in the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that decrements in fasting glucose were correlated with degree of weight loss (749 [EL 1; RCT]), and, in another study, T2DM patients losing >6.9 kg (or at least 10% of baseline weight) over the course of 48 months experienced significant improvements in glucose, A1C, and lipid profiles (750 [EL 4; NE]). A systematic review and meta-analysis of 10 RCTs assessing lifestyle interventions in patients with T2DM found that the pooled effect of weight loss averaging 3.33 kg (95% CI: 5.06, 1.60) was a decline in A1C of 0.29% (95% CI: 0.61%, 0.03%) compared with standard care (751 [EL 1; MRCT]). Franz et al (752 [EL 1; MRCT]) conducted a meta-analysis of 11 RCTs employing lifestyle interventions with duration of at least 1 year encompassing 6,754 subjects. In the majority of studies considered, lifestyle intervention produced <5% weight loss, together with little or no beneficial effects on A1C, lipids, or BP. However, those treatment arms resulting in weight loss >5% experienced significant benefits regarding A1C, lipids, and BP. These later interventions employed more intense lifestyle programs, including energy restriction, regular physical activity, and frequent contact with health professionals.

An older meta-analysis assessed 22 RCTs of lifestyle interventions of variable intensity conducted before 2004 involving 4,659 participants with follow-up lasting 1 to 5 years (753 [EL 1; MRCT]). The pooled weight loss in comparison with usual care was 1.7 kg (95% CI: 0.3 to 3.2 kg); however, mean weight loss in the individual studies was variable, and changes in A1C corresponded to changes in weight.

More recently, the benefits of an intensive lifestyle and behavioral weight-loss intervention in T2DM was rigorously examined in the Look AHEAD (Action for Health in Diabetes) trial (754 [EL 1; RCT]; 755 [EL 1; RCT]). This study randomized T2DM patients to an intensive lifestyle intervention versus standard diabetes support and education. The intensive lifestyle intervention resulted in 4.7% weight loss after 4 years, accompanied by lower glycemia and A1C values with less need for diabetes medications, diabetes remission in ~10% of patients, lower DBP and SBPs, improved lipids (higher HDL, lower triglycerides), improvements in sleep apnea as reflected by lower apnea hypopnea index scores, increased mobility, slower progression of nephropathy, and improved QOL (754 [EL 1; RCT]; 755 [EL 1; RCT]; 756 [EL 1; RCT, post-hoc analysis]; 757 [EL 1; RCT]; 758 [EL 1; RCT, secondary observational analysis]; 759 [EL 1; RCT]; 760 [EL 1; RCT, hidden Markov models]; 761 [EL 1; RCT, post-hoc analysis]; 762 [EL 1; RCT, secondary analysis]). However, the principal outcome measure in Look AHEAD was CVD events, and the study was discontinued prematurely after an interim analysis showed no difference between treatment groups.

Increased physical activity is an important component of lifestyle therapy in diabetes. Structured physical activity can improve glycemic control in T2DM without a change in BMI (763 [EL 1; MRCT]) and can improve fitness, muscle strength, and insulin sensitivity in both T2DM and type 1 diabetes mellitus (T1DM) (763 [EL 1; MRCT]). In the context of an overall lifestyle intervention, regular exercise can contribute to weight loss and prevention of weight regain, lower A1C values, enhance mobility, and improve CV risk factors such as lipids and BP (760 [EL 4; NE]; 764 [EL 1; MRCT]; 765 [EL 1; RCT, hidden Markov models]). Studies have demonstrated beneficial effects of both aerobic and resistance exercise, and additive benefits when both forms of exercise are combined (760 [EL 1; RCT, hidden Markov models]; 766 [EL 4; NE]). Two meta-analyses of RCTs have concluded that structured physical activity programs featuring aerobic and/or resistance training can substantially lower A1C values in T2DM with minimal or no weight loss (767 [EL 1; RCT]; 768 [EL 1; MRCT]). Physical activity guidelines proposed by the ADA, the AHA, and the ACSM are well aligned and advocate aerobic and resistance exercise (28 [EL 1; MRCT]; 763 [EL 4; NE]). Physical activity will need to be specifically designed to accommodate patients with autonomic neuropathy, retinopathy, and diabetic foot disease (769 [EL 4; NE]; 770 [EL 4; NE]; 771 [EL 2; PCS]; 772 [EL 4; NE]).

The addition of weight-loss medications has been shown to achieve more weight loss than lifestyle interventions alone and to produce greater benefits regarding A1C lowering and improvements in cardiometabolic risk factors. All weight-loss medications approved for chronic

therapy of obesity have been studied in RCTs enrolling T2DM patients (71 [EL 1; RCT, post-hoc analysis]; 773 [EL 1; RCT, post-hoc analysis]; 774 [EL 1; RCT]; 775 [EL 1; RCT]; 776 [EL 2; RCT]; 777 [EL 1; RCT]; 778 [EL 1; RCT]; 779 [EL 1; RCT]). In these studies, all T2DM patients were treated with a lifestyle intervention and then randomized to placebo versus weight-loss medication. Weight loss in T2DM patients treated with orlistat (773 [EL 1; RCT, post-hoc analysis]; 774 [EL 1; RCT]; 775 [EL 1; RCT]), phentermine/topiramate ER (776 [EL 1; RCT]; 777 [EL 1; RCT]), lorcaserin (71 [EL 1; RCT]), naltrexone ER/bupropion ER (778 [EL 1; RCT]), and high-dose liraglutide (3 mg/day) (779 [EL 1; RCT]) consistently led to lower A1C, together with the reduced need for conventional diabetes medications in actively managed patients, when compared with patients treated with lifestyle modification alone.

Medication-assisted weight loss in many of these studies also resulted in reductions in BP, lower triglycerides, higher HDL-c, decreased levels of hepatic transaminases, and improvements in biomarkers of CV risk such as C-reactive protein, fibrinogen, and adiponectin. By way of example, treatment with phentermine/topiramate ER resulted in 9 to 10% weight loss in T2DM at 1 year, and reduced A1C by 0.4% in patients with mild diabetes (with a mean A1C value of 7.0% at baseline) and by 1.6% in patients with more severe, long-standing diabetes on multiple medications (with A1C value of 8.6% at baseline) (776 [EL 1; RCT]). Importantly, these improvements were significantly greater than the lifestyle intervention alone and occurred despite greater reductions in the need for conventional diabetes drugs. In a meta-analysis of 7 RCTs involving 1,249 patients with overweight/obesity and T2DM, Ruof et al (780 [EL 1; RCT]) found that those patients responding to orlistat (i.e., ≥5% weight loss) exhibited pooled mean weight loss of 8.6 kg and decrements of 1.16% in A1C, 5.3% in total cholesterol, and 5.2 mm Hg in SBP.

Weight loss achieved by lifestyle alone or with medications will lead to lowering of A1C at all phases of T2DM, both in recent-onset patients and in patients with chronic disease on multiple medications. This was observed with lifestyle therapy in the UKPDS study enrolling patients with newly diagnosed T2DM (749 [EL 1; RCT]) and in the Look AHEAD study in which 84% of patients were taking diabetes medications, nearly half on multiple medications and 15% on insulin, with an average duration of known diabetes of 6.8 years (781 [EL 1; MRCT]). In both the UKPDS and Look AHEAD studies, greater degrees of weight loss led to progressive lowering of A1C values (749 [EL 1; RCT]; 754 [EL 1; RCT]). In clinical trials of phentermine/topiramate ER, the medication plus lifestyle treatment arm in patients with T2DM experienced lower A1C and less need for diabetes medications than in the placebo plus lifestyle arm (776 [EL 1; RCT]; 777 [EL 1; RCT]). These benefits were observed both in the OB-202/DM-230 study featuring more recent-onset patients with disease duration of 5 years, more mild hyperglycemia with baseline A1C of 6.8%, and an average of 0.6 diabetes medications per patient, and in the CONQUER study in which the T2DM patients had diabetes for 8 to 9 years, higher baseline A1C of 8.7%, and 1.6 medications per patient (776 [EL 1; RCT]).

Bariatric surgery can be considered in T2DM when the BMI is ≥35 kg/m^2, particularly if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy (11 [EL 4; NE]). The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently trial was a randomized, controlled, single-center study comparing outcomes of intensive medical therapy alone versus intensive medical therapy plus Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) with 50 T2DM patients randomized to each arm (782 [EL 3; CSS, baseline characteristics of a planned RCT]; 783 [EL 1; RCT]). One-year and 3-year outcomes showed that a significantly higher percentage of bariatric surgery patients met the primary endpoint of A1C ≤6%, and this was associated with a decrease in the number of diabetes medications when compared to the patients treated by medical therapy alone.

When comparing medical versus surgical therapy, these data should be interpreted cautiously, because glycemic control in the medically treated patients was not optimal, and the study did not include a weight-loss arm using intensive lifestyle/behavior therapy plus weight-loss medications. The Swedish Obese Subjects (SOS) study was a nonrandomized, prospective, controlled of 4,047 subjects with obesity who who underwent bariatric surgery or received conventional treatment (784 [EL 1; RCT]; 785 [EL 2; PCS]). In a subgroup analysis of 343 patients with T2DM at baseline, bariatric surgery brought 72% into remission (i.e., blood glucose ≤110 mg/dL on no diabetes drugs) compared to 16% in remission in medically treated controls at 2 years, decreasing to remission of 30% in the bariatric group versus 7% in the medically treated controls at 15 years (784 [EL 1; RCT]). Additional trials and cohort studies have demonstrated clinical benefits of bariatric surgery procedures in T2DM (727 [EL 2; NRCT]; 786 [EL 1; RCT]; 787 [EL 4; NE]; 788 [EL 4; NE]; 789 [EL 1; RCT]; 790 [EL 1; RCT]; 791 [EL 1; RCT]).

Ribaric et al (792 [EL 1; RCT]) conducted a meta-analysis of 5 RCTs and 11 nonrandomized studies comparing bariatric surgery and conventional treatment in T2DM patients and determined that surgery led to lower BMI (-8.3 kg/m^2), A1C values (-1.1%), and fasting glucose levels (-24.9 mg/dL), and resulted in a 63.5% diabetes remission rate at 17 months compared with 15.6% remission in the conventional treatment group. Systematic reviews and meta-analyses by Gloy et al (793 [EL 1; MRCT]) and Buchwald et al (794 [EL 1; RCT]), involving nonrandomized

interventional trials, single-arm observational studies, and a few RCTs, concluded that bariatric surgery procedures led to T2DM remission rates of 60% and 78% accompanied by weight loss of 26.0 kg and 38.5 kg, respectively. Yu et al (794 [EL 1; RCT]) analyzed 2 RCTs and 24 cohort studies and determined that bariatric surgical procedures produced pooled mean decrements of 13.4 kg/m^2 in BMI, 1.8% in A1C, and 59.7 mg/dL in fasting glucose; the diabetes remission rate was 64.7% with the following order of effectiveness: biliopancreatic/duodenal switch, gastric bypass, gastric sleeve, gastric band. A meta-analysis of 27 studies of surgical outcomes following SG demonstrated a diabetes remission rate of 66% (795 [EL 1; RCT]). The relative effectiveness of individual procedures producing diabetes remission is controversial, with some meta-analyses favoring gastric bypass over gastric sleeve (794 [EL 1; RCT]; 796 [EL 2; MNRCT]; 797 [EL 2; MNRCT]) and others concluding that these procedures are equally effective, while the gastric band is consistently found to be less effective.

Many (794 [EL 1; RCT]; 796 [EL 2; MNRCT]; 797 [EL 2; MNRCT]) but not all (798 [EL 2; MNRCT]; 799 [EL 2; MNRCT]) studies indicate that greater degrees of weight loss following surgery are more likely to result in diabetes remission. In any event, remission is the proper terminology as opposed to cure since overt diabetes returns in over half of these patients in less than 10 years (784 [EL 1; RCT]). Bariatric surgery must be balanced against the inherent risks of surgical complications and mortality, and also against potential nutritional deficiencies, weight regain in some patients, and the need for lifelong lifestyle support and medical monitoring (11 [EL 4; NE]).

Iatrogenic weight gain in diabetes. While the clinical benefits of weight-loss therapy in T2DM have been documented, individuals with T2DM tend to have more difficulty achieving and maintaining weight loss than those without diabetes (797 [EL 2; MNRCT]; 800 [EL 2; MNRCT]). One reason that weight-loss attempts may sometimes be slightly less effective in diabetes is that several medications used to treat diabetes result in weight gain (18 [EL 4; NE]; 22 [EL 4; NE]; 801 [EL 2; NRCT]). The classes of drugs most likely to cause weight gain are insulin, insulin secretagogues (sulfonylureas and meglitinides), and thiazolidinediones. Other glucose-lowering medications are weight neutral (dipeptidyl peptidase 4 [DPP-4] inhibitors, alpha-glucosidase inhibitors, colesevelam, bromocriptine) or may lead to a modest degree of weight loss (metformin, pramlintide, glucagon-like peptide 1 [GLP-1] receptor agonists, sodium glucose co-transporter-2 inhibitors).

While clinicians should not refrain from prescribing insulin or other medications when needed to achieve A1C targets, the medication options that are weight neutral or associated with modest weight loss are preferable for patients with obesity and T2DM (18 [EL 4; NE]; 22 [EL 4; NE]).

- *Q5.3. Is weight loss effective to treat dyslipidemia? How much weight loss would be required?*

Executive Summary

- **R37.** Patients with overweight or obesity and dyslipidemia (elevated triglycerides and reduced HDL-c) should be treated with lifestyle therapy to achieve a 5 to 10% weight loss or more as needed to achieve therapeutic targets **(Grade A; BEL 1)**. The lifestyle intervention should include a physical activity program and a reduced-calorie healthy meal plan that minimizes sugars and refined carbohydrates, avoids trans fats, limits alcohol use, and emphasizes fiber **(Grade B; BEL 1, downgraded due to evidence gaps)**.
- **R38.** Patients with overweight or obesity and dyslipidemia should be considered for treatment with a weight-loss medication combined with lifestyle therapy when necessary to achieve sufficient improvements in lipids (i.e., elevated triglycerides and reduced HDL-c) **(Grade A; BEL 1)**.

Evidence Base

A dyslipidemia characterized by elevations in triglyceride levels (e.g., 150 to 400 mg/dL), reduced HDL-c, and increased concentrations of small, dense LDL particles is commonly observed in patients with obesity, particularly when obesity is accompanied by insulin resistance, metabolic syndrome, or prediabetes (244 [EL 4; NE]; 802 [EL 4; NE]). Hypertriglyceridemia is largely due to excess production of large triglyceride-enriched VLDL particles by the liver. The dyslipidemia of insulin resistance is responsive to lifestyle therapy, including alterations in macronutrient composition, weight loss in patients with overweight or obesity, physical activity, restriction of alcohol intake, and limited intake of sugars and refined carbohydrates. Since carbohydrates can drive hepatic VLDL production, the ingestion of carbohydrates, particularly sugars and refined carbohydrates, should be reduced and replaced with unsaturated fats and protein (29 [EL 4; NE]; 175 [EL 1; RCT, non-blinded]; 312 [EL 4; NE, analysis of diet composition]; 803 [EL 4; NE]; 804 [EL 4; NE]; 805 [EL 4; NE]; 806 [EL 2; MNRCT, randomization not a stipulated inclusion criterion]).

Healthy, reduced-calorie meal plans can be used to effectively treat dyslipidemia in patients with overweight or obesity, and the improvements in lipid profiles are proportional to the extent of weight loss. However, not all healthy meal patterns are appropriate for all patients with dyslipidemia. The dietary prescription will differ depending on the degree of elevation in fasting serum triglyceride

(327 [EL 4; NE]; 802 [EL 4; NE]), which is based upon differences in pathophysiology. When the triglyceride level is ≥500 mg/dL, additional mechanisms are likely operative that result in defective clearance mechanisms for triglyceride-enriched lipoproteins, which can become saturated upon consumption of fatty meals leading to chylomicronemia. These patients are at risk of pancreatitis when triglyceride levels approach 1,000 mg/dL (328 [EL 4; NE]) and should be placed on a low-fat diet, with less than 15 to 25% of total calories from fat, to reduce the release of new chylomicron particles from the gut into the circulation (327 [EL 4; NE]; 807 [EL 4; NE]). Therefore, the macronutrient composition of the diet should be modified based on the degree of hypertriglyceridemia and whether the primary abnormality being treated is elevated LDL-c (327 [EL 4; NE]; 328 [EL 4; NE]; 802 [EL 4; NE]; 807 [EL 4; NE]).

The relative dietary content of total fat and carbohydrate (CHO) can impact triglyceride and HDL-c levels. Three meta-analyses of controlled-feeding trials comparing low-fat (high-CHO) diets versus higher-fat (low-CHO) diets have conclusively demonstrated that high CHO consumption augments serum triglycerides and decreases HDL-c (806 [EL 2; MNRCT, randomization not a stipulated inclusion criterion]; 808 [EL 4; NE]; 809 [EL 2; MNRCT, randomization not a stipulated inclusion criterion]). Isocaloric replacement of each 1% of daily CHO calories with either saturated fat, polyunsaturated fat, or monounsaturated fat (MUFA) resulted in a 1 to 2% reduction in triglycerides (806 [EL 2; MNRCT, randomization not a stipulated inclusion criterion]). These findings have underscored recommendations to limit dietary CHO in patients with elevated triglycerides (327 [EL 4; NE]; 29 [EL 4; NE]; 802 [EL 4; NE]; 805 [EL 4; NE]).

Several dietary changes can prevent or mitigate the ability of CHO to increase triglycerides in the absence of weight loss. Dietary sugars and refined carbohydrates should be minimized, as the 1999-2006 cross-sectional study by the National Health and Nutrition Examination Survey (NHANES) showed that lower triglyceride levels were associated with a sugar consumption below 10% of total calories (810 [EL 3; CSS]), and a meta-analysis has substantiated that triglycerides will begin to rise when fructose consumption exceeds 50 to 100 kcal/day (811 [EL 1; MRCT]). Heavy alcohol intake should also be avoided (812 [EL 4; NE]). Randomized trials have also demonstrated that high fiber intake (813 [EL 4; NE]; 814 [EL 3; CSS]; 815 [EL 2; MNRCT]) can negate the increase in triglycerides in patients on higher CHO diets. Dietary trans fatty acids should be eliminated from the diet since their consumption can increase triglycerides and atherogenic lipoproteins (816 [EL 4; NE]) as well as increase the risk of CVD (817 [EL 4; NE]). Omega-3 polyunsaturated fatty acids (n-3 PUFAs), derived mainly from fatty fish and some plant products (e.g., flax seed), have a unique impact to decrease triglycerides. In large amounts (2 to 6 g/day), these fatty acids can lower triglycerides by 40% or more (818 [EL 4; NE, extensive literature review]; 819 [EL 4; NE]; 820 [EL 1; RCT]). These doses of n-3 PUFAs are difficult to achieve in the diet, and supplementation with purified capsules is usually necessary (327 [EL 4; NE]; 805 [EL 4; NE]).

Several healthy meal plans are associated with either no change or a decrease in triglycerides together with an increase in HDL-c despite featuring a low fat intake, including the DASH diet (821 [EL 1; RCT]; 822 [EL 1; RCT]), the OmniHeart Study diet that emphasizes protein and avoiding saturated fat (312 [EL 1; RCT, non-blinded]), and the Mediterranean diet (823 [EL 1; RCT]; 824 [EL 1; RCT]; 825 [EL 2; PCS]; 826 [EL 2; PCS]; 827 [EL 2; PCS]; 828 [EL 1; RCT]). For example, participants in the Framingham Heart Study Offspring Cohort who were scored in the highest quintile for the Mediterranean-style dietary pattern had the lowest triglyceride levels over 7 years of follow-up (825 [EL 2; PCS]).

Weight loss has a beneficial effect on lipids and lipoproteins (175 [EL 4; NE]; 805 [EL 4; NE]; 807 [EL 4; NE]; 829 [EL 3; CSS]; 830 [EL 4; NE]). Weight loss of 5 to 10% has been shown to amplify the benefits of changes in macronutrient composition resulting in a 20% decrease in triglycerides, a 15% reduction in LDL-c, and an 8 to 10% increase in HDL-c (831 [EL 1; MRCT]). However, greater degrees of weight loss can achieve progressive improvements in dyslipidemia (754 [EL 1; RCT]). The weight-loss goal should be commensurate with that needed to achieve the clinical target for reductions in triglycerides and the correction of dyslipidemia (832 [EL 2; MNRCT]). Meta-analyses have reported that for every kilogram of weight loss, triglyceride levels decrease by approximately 1.9% or 1.5 mg/dL (833 [EL 2; MNRCT]; 834 [EL 2; MNRCT]). Furthermore, there are beneficial effects of weight loss on LDL subclasses, characterized by reductions in small, dense LDL particle concentrations and an increase in the concentration of medium and large LDL particles, coupled to a mean increase in LDL particle size and reductions in total LDL particle concentration (835 [EL 1; RCT]; 836 [EL 2; PCS]; 837 [EL 1; RCT]; 838 [EL 1; RCT]; 839 [EL 1; RCT]; 840 [EL 2; PCS]).

The Preventing Obesity Using Novel Dietary Strategies (POUNDS LOST) trial evaluated 4 weight-loss diets that varied in macronutrient composition (841 [EL 1; RCT]). After 2 years, weight loss was similar among participants assigned to low and high protein (15% vs. 25% protein), low and high fat (20% vs. 40% fat), or low and high CHO (65% vs. 35% CHO) dietary treatments. Irrespective of macronutrient composition, all diets decreased triglyceride levels similarly (12 to 17%). These data suggest that during active weight loss, when patients are hypocaloric, there is less of an effect of macronutrient composition on lipids (i.e., fat vs. CHO intake) than what is observed during weight-maintenance or isocaloric diets. However, another

popular weight-loss alternative is a very low-CHO diet, defined as an intake of <30 to 35 g of CHO per day (842 [EL 4; NE]). A meta-analysis of RCTs that evaluated low-CHO versus low-fat (<30% of energy) diets found greater reductions in triglyceride levels on low-CHO diets (831 [EL 1; MRCT]). Consistent with these findings, Bonow and Eckel (842 [EL 4; NE]) concluded that low-CHO diets produced a more robust triglyceride-lowering effect than low-fat diets, despite a similar magnitude of weight loss after 1 year.

Three classic weight-loss RCTs employing lifestyle interventions are illustrative of effects on lipids. Dansinger et al (843 [EL 1; RCT]) compared 4 diets varying widely in macronutrient composition (Atkins, Zone, Weight Watchers, and Ornish) and found that weight loss was similar among the diet groups (~3 kg) at 1 year. After 2 months, the lower carbohydrate diets (Atkins, Zone) resulted in lower triglycerides and higher HDL-c but higher LDL-c compared with the high carbohydrate diet (Ornish); however, at 1 year, modest improvements in lipid parameters (e.g., total cholesterol/HDL-c ratio, LDL-c/HDL-c ratio) were similar among all subgroups.

The DPP randomized patients with impaired glucose tolerance to placebo, metformin, and lifestyle intervention treatment and determined that lifestyle intervention was most effective for weight loss (~4 kg) and diabetes prevention after 4 years (708 [EL 1; RCT]). While LDL-c was essentially unaffected, a reduction in triglycerides, an increase in HDL, and a decrease in the percentage of subjects exhibiting "pattern B" dyslipidemia (i.e., small, dense LDL particles) were only noted in the lifestyle intervention group (844 [EL 1; RCT]). In addition, weight loss associated with the lifestyle intervention reversed metabolic syndrome in 38% of those who met the criteria at baseline and prevented the development of metabolic syndrome by 28% in those who did not meet criteria at baseline (845 [EL 1; RCT]). In the Look AHEAD trial involving patients with T2DM, the intensive lifestyle intervention at 4 years resulted in more weight loss than standard diabetes support and education (6.2% vs. 0.9%) (755 [EL 1; RCT]), together with greater reductions in triglycerides (25.6 mg/dL vs. 19.7 mg/dL) and increases in HDL-c (3.7 mg/dL vs. 1.9 mg/dL), while LDL-c was largely unaffected (754 [EL 1; RCT]).

Both aerobic and resistance exercise can lower triglycerides and increase HDL-c whether or not these activities are accompanied by weight loss (846 [EL 2; PCS]; 847 [EL 3; CSS]; 848 [EL 1; RCT]; 849 [EL 1; RCT]; 850 [EL 1; RCT]; 851 [EL 4; NE]; 852 [EL 4; NE]; 853 [EL 1; RCT]). The effect of physical activity on triglyceride levels varies depending on level of intensity, caloric expenditure, and duration of activity, and is most consistently observed in individuals with fasting triglycerides levels that are ≥150 mg/dL (846 [EL 2; PCS]; 848 [EL 1; RCT]; 850 [EL 4; NE]; 851 [EL 1; RCT]). In a trial involving endurance exercise, an optimal fasting triglyceride level (e.g., <100 mg/dL) was associated with minimal (i.e., <5%) reductions in postexercise triglyceride levels, while reductions were much greater in individuals with high fasting triglyceride levels (≥150 mg/dL), low HDL-c, and abdominal obesity at baseline (846 [EL 2; PCS]). Higher baseline triglyceride levels (mean, 197 mg/dL) also translated into significant triglyceride reductions (26%) in a 6-month trial of subjects with overweight who walked 12 miles weekly at 40 to 55% of peak oxygen consumption (848 [EL 1; RCT]).

The ability of physical activity to reduce triglyceride levels can vary with the frequency and intensity of the physical activity (847 [EL 3; CSS]; 848 [EL 1; RCT]; 849 [EL 1; RCT]). The toning of large muscle groups (abdomen, back, legs, and arms) and exercise-induced improvements in insulin sensitivity augment the clearance of triglyceride-rich lipoproteins via induction of lipoprotein lipase, resulting in a lowering of triglyceride levels (837 [EL 4; NE]; 852 [EL 1; RCT]; 853 [EL 4; NE]; 854 [EL 1; RCT]; 855 [EL 1; RCT]). In addition, when used together with weight loss, physical activity has the particular ability to produce substantial and disproportionate increments in HDL-c relative to changes in other lipids (837 [EL 1; RCT]). Overall, exercise is most effective in lowering triglycerides (e.g., 15 to 30%) when baseline levels are elevated (i.e., >150 mg/dL), activity is moderate to intense, and total caloric intake is reduced (851 [EL 4; NE]).

Medication-assisted weight loss can also be used to effectively treat dyslipidemia. The RCTs involving orlistat (721 [EL 1; RCT]; 856 [EL 1; RCT]), lorcaserin (69 [EL 1; RCT]; 857 [EL 1; RCT]), phentermine/topiramate ER (71 [EL 1; RCT]; 858 [EL 1; RCT]), naltrexone ER/bupropion ER (67 [EL 1; RCT]; 779 [EL 1; RCT]; 859 [EL 1; RCT]), and liraglutide (68 [EL 1; RCT]; 780 [EL 1; RCT]) all demonstrate that the ensuing weight loss is accompanied by reductions in triglycerides and increases in HDL-c, and that these effects are more marked in individuals randomized to the weight-loss medication compared to those undergoing lifestyle changes plus placebo. With orlistat, there are also substantial reductions in LDL-c (9.4 to 11.4%), which exceed decreases observed in the patients treated with lifestyle changes alone (1.1 to 1.6%) (721 [EL 1; RCT]; 856 [EL 1; RCT]). In trials involving phentermine/topiramate ER and liraglutide 3 mg, modest reductions in LDL-c were observed that may (68 [EL 1; RCT]; 858 [EL 1; RCT]) or may not (71 [EL 1; RCT]; 780 [EL 1; RCT]) have exceeded those in the lifestyle changes plus placebo treatment arms. In one trial involving naltrexone ER/bupropion ER and a very intensive lifestyle intervention, increases in LDL-c were observed in both the medication (10%) and lifestyle (7.1%) treatment arms (859 [EL 1; RCT]); however, modest decreases in LDL-c were observed in all other trials of naltrexone ER/bupropion ER (67 [EL 1; RCT]; 779 [EL 1; RCT]). In lorcaserin clinical trials, LDL-c levels were minimally affected (69 [EL 1; RCT]; 857 [EL 1; RCT]).

Thus, regarding dyslipidemia, the main benefits of weight-loss medications are greater reductions in triglycerides and increases in HDL-c.

Bariatric surgery also improves dyslipidemia (860 [EL 4; NE]). Two meta-analyses have demonstrated that RYGB results in substantial decreases in LDL-c and triglycerides and increases in HDL-c, with improvement or normalization of hyperlipidemia in most patients (861 [EL 2; MNRCT]; 862 [EL 2; MNRCT]). In the Utah-Obesity study (863 [EL 1; NE]), LDL-c was decreased by 28 mg/dL, triglycerides were decreased by 65 mg/dL, and HDL-c was increased by 13 mg/dL at 6 years post RYGB, and these results are in agreement with findings published by other authors (341 [EL 2; PCS]; 864 [EL 2; PCS]; 865 [EL 4; NE]; 866 [EL 2; PCS]). Reductions in LDL-c were also accompanied by a decrease in the concentration of apoB-containing lipoproteins and reduced levels of oxidized LDL (866 [EL 2; PCS).

For decreasing LDL-c concentrations, the AHA recommends reducing saturated fat intake to <7% of calories and eliminating trans fats in conjunction with a healthy meal plan (29 [EL 4; NE]). The latest Dietary Guidelines for Americans have withdrawn the previously recommended limits on cholesterol (i.e., <300 mg/day) due to a lack of evidence that consumption of dietary cholesterol can affect serum cholesterol (867 [EL 4; NE]). Given the proven cardioprotective effects of statin therapy, high-risk patients with metabolic syndrome, prediabetes, hypertension, and/or dyslipidemia should be strongly considered for statin therapy in addition to lifestyle therapy, particularly when levels of LDL-c are ≥100 mg/dL (326 [EL 4; NE]; 327 [EL 4; NE]). The Jupiter study demonstrated reductions in CVD events in patients with elevated C-reactive protein, most of whom had metabolic syndrome, following a statin-induced lowering of LDL-c to below 70 mg/dL (868 [EL 1; RCT]).

- *Q5.4. Is weight loss effective to treat hypertension? How much weight loss would be required?*

Executive Summary

- **R39.** Patients with overweight or obesity and elevated blood pressure or hypertension should be treated with lifestyle therapy to achieve a 5 to 15% weight loss, or more as necessary, to achieve blood pressure reduction goals in a program that includes caloric restriction and regular physical activity **(Grade A; BEL 1)**.
- **R40.** Patients with overweight or obesity and elevated blood pressure or hypertension should be considered for treatment with a weight-loss medication, combined with lifestyle therapy when necessary, to achieve sufficient weight loss for blood pressure reduction **(Grade A; BEL 1)**.
- **R41.** Patients with hypertension considering bariatric surgery should be recommended for Roux-en-Y gastric bypass or sleeve gastrectomy, unless contraindicated, due to greater long-term weight reduction and significantly improved remission of hypertension than with laparoscopic adjustable gastric banding **(Grade B; BEL 1, downgraded due to evidence gaps)**.

Evidence Base

Dietary changes can be used to lower BP independent of weight loss. A randomized, parallel-design study compared the effects of a fiber-containing healthy diet and a fiber-supplemented diet on SBP over 3 months in patients with overweight or obesity (869 [EL 1; RCT]). SBP was lower in the fiber-containing healthy diet group compared to both the control and fiber-supplemented groups. In an RCT that assigned breakfast biscuits supplemented with 100 g soy fiber/day for 12 weeks, a significant improvement in body weight and BMI was observed, together with a reduction in diastolic blood pressure (DBP) of 4.8 mm Hg and a modest nonsignificant decrease in SBP (1.2 mm Hg) (870 [EL 1; RCT]). A 1,500 kcal/day diet supplemented with cheese containing probiotic *Lactobacillus plantarum* was assessed in 40 subjects during a 3-week, randomized, double-blind, placebo-controlled study with 25 subjects consuming probiotic cheese and 15 eating control cheese (50 grams of cheese each, providing 175 kcal) (871 [EL 1; RCT]). A positive association was observed between probiotic colonization and decreases in BMI and morning DBP, with a trend toward lower morning SBP after adjusting for BMI, age, and gender. Fruits, vegetables, and other whole foods contain numerous flavonoids and antioxidants which may reduce oxidative stress, improve endothelial function, and lower BP (872 [EL 1; RCT, N = 24]). People with hypertension enrolled in the DASH study consumed a diet rich in fruits and vegetables, low in sodium, and high in potassium, and had lower BP without weight loss (821 [EL 1; RCT]).

A systematic review and meta-analysis of cohort studies reported on the longitudinal effects of a DASH-like diet on the incidence of CVD (873 [EL 2; MNRCT]). Cohort studies were excluded from review if they included subjects with specified CVD risk factors (i.e., T2DM, metabolic syndrome, obesity, or hypertension). Only 6 studies met the criteria for review with a range of 21,000 to 88,500 subjects per study and 7 to 24 years of follow-up. The meta-analysis showed that a DASH-like diet significantly reduced the risk of CVD and stroke by 20% and 19%, respectively. A prospective cohort study evaluated the association between diet and mortality in 5,532 adults with hypertension in the third NHANES with an average follow-up of 8.2 years (874 [EL 2; PCS]). Hypertension was determined by self-reported diagnosis, antihypertensive medication use, or BP measurement, and food intake was assessed by a 24-hour dietary recall. Using a Cox proportional hazard model to account for multiple confounders,

consumption of a DASH-like diet (7.1% of subjects, n = 391) was associated with lower hazard ratios for all-cause mortality (HR 0.69, CI 0.52-0.92; $P = 0.01$) and stroke (HR 0.11, CI 0.03-0.47; $P = 0.003$). Mortality risk from CVD and cancer did not reach statistical significance. The mechanisms underlying BP reduction with increased intake of fruits and vegetables is unknown. In an attempt to separate the effects of minerals and fiber from other components of the DASH diet, 30 adults (15 with obesity and hypertension, and 15 lean with normal BP) received a baseline usual diet for 3 weeks and then were randomized to a DASH diet or a usual diet supplemented to match the DASH diet in potassium, magnesium, and fiber (875 [EL 1; RCT]). All 3 diets were administered for 3 weeks, were isocaloric, and were matched for nutrients (50% carbohydrate, 35% fat, and 15% protein, with 3,000 mg sodium and 700 mg calcium daily). In patients with obesity, SBP and DBP were lower on the DASH diet when compared to both the baseline usual diet (7.6 ± 1.4 / 5.3 ± 1.4 mm Hg, $P<0.001$ / $P<0.02$) and the supplemented usual diet (6.2 ± 1.4 / 3.7 ± 1.4 mm Hg, $P<0.005$ / $P<0.06$), whereas BP was not significantly different between any diet in lean adults with normal BP.

The Mediterranean diet food pattern has also been suggested to have beneficial effects on hypertension and CVD risk factors. A cross-sectional study of 3,204 asymptomatic patients evaluated the benefit of a Mediterranean diet on the prevalence of CVD risk factors using standard diagnostic criteria as assessed by their primary care physicians (876 [EL 3; CSS, baseline for RCT]). A dietitian interviewed each participant (using a dietary 14-point scoring system) for their degree of adherence to a Mediterranean diet plan. The consumption of a Mediterranean diet was found to be inversely associated with the clustering of obesity, hypertension, T2DM, and hypercholesterolemia.

Elevated BP is an established consequence of overweight and obesity. It is therefore not surprising that one of the associated benefits of weight reduction is the lowering of BP. A meta-analysis of 8 studies including over 2,100 participants who were randomized to either a weight-reducing diet or a control intervention demonstrated that weight loss was consistently associated with BP reductions (877 [EL 1; MRCT]). Weight-loss diets led to decrements in SBP/DBP of 4.5/3.2 mm Hg together with a 4.0 kg decrease in body weight compared with the control groups after a follow-up of 6 to 36 months. The results of this meta-analysis are consistent with earlier analyses suggesting that BP (SBP/DBP) decreased by 1.2/1.0 mm Hg for every kilogram of weight lost (878 [EL 4; NE]). Ultimately, a weight-reducing diet based on the DASH dietary pattern in combination with a lower sodium intake and moderate to no alcohol intake is one of the most comprehensive strategies for producing nonpharmacologic BP reduction.

An RCT to examine the effects of a reduced-calorie DASH diet on insulin sensitivity was performed in 144 adults with overweight or obesity and hypertension (879 [EL 1; RCT]). Subjects were randomly assigned to a DASH diet, a DASH diet with weight management (i.e., with aerobic exercise and caloric restriction) or a usual (control) diet. The DASH diet weight management group lost weight (8.7 kg, CI 2.0-9.7), whereas the DASH diet alone and usual diet groups maintained their weight. Greater reductions in BP (DBP and SBP) were observed in the DASH diet weight management subjects (16.1 and 9.9 mm Hg) compared to the DASH diet alone (11.2 and 7.5 mm Hg) and usual diet (3.4 and 3.8 mm Hg) groups ($P<0.001$). Also observed was a greater improvement in left ventricular mass ($P<0.05$) compared to participants consuming the DASH diet alone and usual diet. Thus, weight loss in patients on a reduced-calorie DASH diet may increase benefits over that in patients randomized to an isocaloric DASH diet.

In a prospective 1-year study, 222 of 376 patients with overweight (BMI 25 to 29.9 kg/m^2) and hypertension followed a low-calorie diet for the entire study period (880 [EL 2; PCS]). A mean body weight reduction of 8.1 kg was associated with reductions in SBP and DBP (4.2 and 3.3 mm Hg, respectively, $P<0.05$) and a significant decrease in aldosterone levels ($P<0.05$). Greater BP reduction was observed in patients who reached a normal BMI (SBP 5.0 mm Hg, DBP 4.5 mm Hg; n = 106) compared to those who did not (SBP 3.3 mm Hg, DBP 1.6 mm Hg; n = 116) ($P<0.01$), and half (52/106) of the patients who reached a normal BMI also normalized BP.

A systematic review and meta-analysis of RCTs addressed 1-year outcomes from weight-loss lifestyle interventions in patients with overweight/obesity and T2DM (752 [EL 1; MRCT]). Eleven trials with 6,754 subjects were included in the analysis, 8 of which compared 2 weight-loss interventions and the remaining 3 compared a weight-loss group with a usual diet (control) group (754 [EL 1; RCT]; 755 [EL 1; RCT]; 881 [EL 1; RCT]; 882 [EL 1; RCT]; 883 [EL 1; RCT]; 884 [EL 1; RCT]; 885 [EL 1; RCT]; 886 [EL 1; RCT]; 887 [EL 1; RCT]; 888 [EL 1; RCT]). Most of these lifestyle intervention studies resulted in <5% weight loss (mean 4.39 kg) at 1 year (752 [EL 1; MRCT]). Eight trials reported BP outcome, with no significant decrease in either mean SBP or DBP if weight loss was <5% from baseline (752 [EL 1; MRCT]).

However, the individual RCTs from this meta-analysis that employed meal replacements achieved greater declines in weight compared to the usual diet group (5.8 ± 6.8 kg vs. 1.7 ± 6.5 kg) and did achieve significant decreases in SBP (881 [EL 1; RCT]). Another study involving 99 adults (BMI 27 to 40 kg/m^2) randomized to a high-protein versus high-carbohydrate diet demonstrated similar decrements in weight and WC, and a trend toward lower SBP (5.03 vs. 0.76 mm Hg, $P = 0.05$), with the high-protein diet (884 [EL 1; RCT]). Two RCTs reported a weight loss of ≥5% over 1 year; these studies assessed the effectiveness of a Mediterranean

diet (887 [EL 1; RCT]) and intensive lifestyle intervention (ILI) in the Look AHEAD trial (754 [EL 1; RCT]; 888 [EL 1; RCT]). Both of these studies included regular physical activity and frequent health professional contact for participant behavioral support. Both the Mediterranean diet (n = 108, mean age 52 years, mean BMI 30 kg/m^2) and ILI (n = 5,145; 45-74 years; BMI >25 kg/m^2) reported a significant decline in SBP (5.1 mm Hg and 6.8 mm Hg, respectively; both P<0.001) and DBP (4.0 mm Hg and 3.0 mm Hg, respectively; both P<0.001) at 1 year.

Subjects on the Mediterranean diet had statistically significant reductions in SBP at 1 year compared to those on a low-fat diet (5.1 vs. 2.0 mm Hg), and more patients on the Mediterranean diet reached the BP goal (66% vs. 59%) (887 [EL 1; RCT]). However, the between-group differences in SBP were no longer statistically significant after 4 years, with 65% and 63% meeting the BP goal in the Mediterranean and low-fat diet groups, respectively. In this study, BP reductions were linked to the degree of weight loss, with a significantly lower BMI at 1 year in the Mediterranean group, but this difference was no longer statistically significant at years 3 and 4.

In the Look AHEAD trial, the magnitude of BP improvement was also directly associated with the degree of weight loss; the odds ratio for a 5 mm Hg decline in SBP was 1.24 for 2 to 5% weight loss, 1.56 for 5 to 10% weight loss, and even greater odds for >10% weight loss (887 [EL 1; RCT]). Progressive weight loss up to >15% of body weight also led to increasing reductions in DBP and SBP. In addition, during 4 years of ILI, subjects had significantly greater weight loss (6.15% vs. 0.88%, P<0.001), treadmill fitness (12.74% vs. 1.96%, P<0.001), SBP reductions (5.33 vs. 2.97 mm Hg, P<0.001), and DBP reductions (2.92 vs. 2.48 mm Hg, P = 0.01) than the usual care (control) group (888 [EL 1; RCT]). Thus, RCTs show that a weight loss of >5% is usually necessary for beneficial effects on BP for most patients. An ILI program that includes caloric restriction, regular physical activity, and frequent ongoing support from health professionals will be needed for a greater and sustained reduction in BP.

Physical activity is an important component of lifestyle interventions in patients with hypertension. The effects of resistance training on central BP was studied in 36 sedentary men with obesity who were randomized to either high-intensity resistance training 3 times per week or no training for 3 months (889 [EL 1; RCT]). Neither group had a significant decline in weight or WC, but the intervention group had significantly decreased central and brachial SBP and DBP. A 3-month randomized parallel-group study examined the effects of exercise on BP in 97 sedentary adult men and women (40-66 years, 10 with hypertension) with obesity (mean BMI 33 kg/m^2) (890 [EL 1; RCT]). Subjects were randomized to a control group (no exercise) or 1 of 3 exercise groups (aerobic treadmill walking, weight machine resistance, and combination of aerobic/resistance exercise) performed 30 minutes daily 5 days per week. There were no significant changes in BP among groups, although a secondary analysis in a subgroup of responders had improved SBP with the combination of aerobic/resistance exercise at 3 months compared to the baseline (6.3% lower, P = 0.005) (890 [EL 1; RCT]).

In examining data from over 5,000 individuals in a meta-analysis, endurance training reduced SBP/DBP in hypertensive individuals by 8.3/5.2 mm Hg, whereas lower reductions of 4.2/1.7 mm Hg were observed for prehypertensive individuals (891 [EL 1; MRCT]). Several studies suggest that the rate of developing hypertension in prehypertensive individuals is reduced by increased physical activity leading to greater fitness (892 [EL 4; NE]; 893 [EL 2; PCS, N = 4,884]; 894 [EL 2; MNRCT]). Many major health organizations, including the AHA, the Centers for Disease Control, and the ACSM, emphasize the importance of physical activity training including both aerobic and resistance exercise for lowering resting BP in hypertensive and prehypertensive individuals (20 [EL 4; NE]; 895 [EL 4; NE]; 896 [EL 4; NE]).

Medication-assisted weight loss is also associated with BP lowering. In these studies, subjects are placed on lifestyle interventions, randomized to medication versus placebo, and followed for 1 to 4 years. In 2 RCTs, orlistat at 1 year led to greater reductions in BP compared with placebo for both DBP (3.6 vs. 2.6 mm Hg and 4.5 vs. 2.7 mm Hg) and SBP (6 vs. 3 mm Hg and 7.3 vs. 5.2 mm Hg) in addition to greater degrees of weight loss (9.6% vs. 5.6% and 9.7% vs. 6.6%) (721 [EL 1; RCT]; 857 [EL 1; RCT]). Differences attesting to greater efficacy for orlistat versus placebo were still present after 4 years for BP reductions (DBP 2.6 vs. 1.9 mm Hg, SBP 4.9 vs. 3.4 mm Hg) and weight loss (5.2% vs. 2.7%) (721 [EL 1; RCT]). In the EQUIP and CONQUER trials, reductions in BP in patients randomized to phentermine/topiramate ER were greater than those observed in the placebo group for both diastolic (EQUIP, 1.5 vs. 0.4 mm Hg; CONQUER, 3.8 vs. 3.4 mm Hg) and SBP (EQUIP, 2.9 vs. 0.9 mm Hg; CONQUER, 5.6 vs. 2.4 mm Hg) at 1 year, and this was accompanied by ~9% placebo-subtracted weight loss in the phentermine/topiramate ER treatment group (71 [EL 1; RCT]; 858 [EL 1; RCT]).

Modest BP reductions were observed following treatment with lorcaserin versus placebo in the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) study (DBP 1.1 vs. 0.6 mm Hg; SBP 1.4 vs. 0.8 mm Hg) (857 [EL 1; RCT]). In contrast, similar decrements in BP were observed in the lorcaserin and placebo treatment groups in the Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) study (69 [EL 1; RCT]). Placebo-subtracted weight loss was 2.9% and 3.6% in the BLOSSOM and BLOOM studies, respectively. Liraglutide 3 mg resulted in 4.5% and 5.4% placebo-subtracted weight

loss in 2 clinical trials, and it lowered BP to a greater extent than placebo (DBP 2.9 vs. 1.1 mm Hg and 2.6 vs. 1.9 mm Hg; SBP 6.9 vs. 4 mm Hg and 4.5 vs. 1.5 mm Hg) (68 [EL 1; RCT]; 897 [EL 1; RCT]). Studies employing naltrexone ER/bupropion ER have failed to achieve greater BP reductions than placebo despite greater weight loss in patients taking the medication. In the Contrave Obesity Research I (COR-I) trial, placebo-subtracted weight loss at 1 year was 4.8%, while BP did not change in the naltrexone ER/bupropion ER arm, but was modestly reduced by 0.9 mm Hg diastolic and 1.9 mm Hg systolic in the placebo arm (67 [EL 1; RCT]). In the COR-BMOD trial, decreases in DBP and SBP were smaller in naltrexone ER/bupropion ER-treated patients than in the placebo group (DBP 1.4 vs. 2.8 mm Hg; SBP 1.3 vs. 3.9 mm Hg) despite a 4.2% placebo-subtracted weight loss (859 [EL 1; RCT]).

Bariatric surgery is effective in lowering BP in patients with obesity. In a controlled clinical trial comparing the effect of RYGB to intensive lifestyle therapy on obesity-related outcomes, the number of patients with nocturnal hypertension at 1 year decreased from 42 to 14 after RYGB ($P \leq 0.001$) and from 29 to 27 ($P = 0.79$) with lifestyle intervention (342 [EL 2; NRCT]). Patients undergoing laparoscopic adjustable gastric banding (LAGB) with a mean BMI of 45.7 kg/m^2 were compared to patients who refused surgery but agreed to be followed on a conventional diet (898 [EL 2; NRCT]). At 4 years, mean BMI had decreased to 37.7 kg/m^2 in the LAGB group and was unchanged in controls (45.2 to 46.5 kg/m^2). During this time, hypertension occurred in 11 control subjects (25.6%) and 1 LAGB patient (1.4%), and remitted in 1 control subject (2.3%) and 15 LAGB patients (20.5%, $P = 0.0001$). In a randomized, single-center trial, intensive medical therapy alone versus bariatric surgery was evaluated in 150 patients with obesity and T2DM over 1 year (783 [EL 1; RCT]). Weight loss was greater after RYGB (29.4 ± 9.0 kg) and SG (25.1 ± 8.5 kg) than in the medical-therapy group (5.4 ± 8.0 kg). The use of antihypertensive agents decreased significantly after both surgical procedures but increased in patients receiving only medical therapy.

In a meta-analysis of 57 studies (31 prospective and 26 retrospective) using various bariatric surgery procedures (vertical gastric banding, LAGB, SG, RYGB, and biliopancreatic diversion ± duodenal switch), 32 reported improvement of hypertension in 32,628 of 51,241 patients (odds ratio 13.24, $P<0.00001$), and 46 reported resolution of hypertension in 24,902 of 49,844 patients (odds ratio 1.70, $P = 0.01$) using a random-effects model due to heterogeneity between the studies (899 [EL 2; MNRCT]).

Bariatric surgery effectively produces weight loss and lowers BP at all levels of obesity. A systematic literature review identified 5 RCTs and 6 comparative observational studies (706 total patients) for a meta-analysis of surgical versus medical treatment outcomes over 1 to 3 years in patients with class 1 obesity (BMI 30 to 35 kg/m^2) and T2DM (900 [EL 2; MNRCT]). Bariatric surgery was associated with a greater reduction in BMI (mean difference 5.5 kg/m^2, $P<0.001$) and lower rate of hypertension (odds ratio 0.25, $P<0.001$). Another systematic review of bariatric surgery in patients with class II obesity or greater (BMI ≥35 kg/m^2) reported on long-term (>2 years) outcomes from 29 studies (n = 7,971 patients) employing RYGB (6 prospective and 5 retrospective cohorts), SG (2 retrospective cohorts), and LAGB (9 prospective and 5 retrospective cohorts) procedures (862 [EL 2; MNRCT]). Greater than 50% excess weight loss was seen in all RYGB and SG studies, but in only 31% of LAGB studies. The mean percent excess weight loss (%EWL) for RYGB was 66% (n = 3,544) compared to 45% (n = 4,109) for LAGB, and hypertension remission rates (BP <140/90 mm Hg without medication) were 38.2% for RYGB and 17.4% for LAGB. Insufficient comparative evidence existed in this study to assess outcomes for SG.

Improvements in BP and hypertension following bariatric surgery are also observed in patients who are "super-obese," which is often defined as having a BMI >50 kg/m^2. A 5-year prospective study of 55 adults following SG identified 27 patients as having super-obesity (901 [EL 2; PCS]). Reported mean %EWL for the cohort was 40% at year 5, and the combined improvement plus resolution rate for hypertension at the end of study was 61%. A 20-year outcome review of 2,615 patients receiving biliopancreatic diversion with duodenal switch (BPD-DS) at a single institution over an 18-year period (mean age 42; 69% women; mean BMI 52 kg/m^2) included patients with super-obesity (902 [EL 3; SS, N = 2,615]). A mean weight loss of 71% EWL was maintained for 5 to 20 years. Hypertension was present in 68% of all patients pre-operatively (n = 1,789) and was resolved in 64% of these patients and improved in 31% following BPD-DS surgery. Effects of RYGB on obesity-related complications after surgery were compared in 30 patients with super-obesity (BMI 64.1 kg/m^2) and 60 age- and gender-matched patients who did not have super-obesity (BMI 46.3 kg/m^2) (903 [EL 2; RCCS]). Baseline hypertension was more common in patients with super-obesity compared to those below the BMI threshold (77% vs. 53%, $P = 0.03$). At 5 years after surgery, the percent of total weight loss was comparable between subjects with and without super-obesity (27.4% VS. 29.7%), whereas %EWL was lower for patients who had super-obesity (44.9% vs. 66.5%); however, rates of remission (56.5% vs. 65.6%, $P = 0.58$) or improvement of HTN did not differ between the groups.

Lowered BP after bariatric surgery can be maintained long-term. In the Longitudinal Assessment of Bariatric Surgery multicenter observational cohort study, hypertension was present in 68% of 2,458 subjects with obesity (age 18-78 years, 79% women, median BMI 45.9 kg/m^2) (341 [EL 2; PCS]). Actual median and percent total body weight loss 3 years after surgery was 15.9% for LAGB and 31.5%

for RYGB, with most of the weight loss occurring in the first year after both procedures. Remission of hypertension occurred in 17.4% and 38.2% of patients after LAGB and RYGB, respectively. Long-term effects of weight loss after SG in 443 patients were observed at year 1 (241 of 443 patients, 54.4%), year 3 (128 of 259 patients, 49.4%), and year 5 (39 of 56 patients, 69.6%); the %EWL was 77%, 70%, and 56%, respectively, and the remission of hypertension was maintained in 46%, 48%, and 46%, respectively (904 [EL 2; PCS, retrospective analysis]).

When different bariatric surgical approaches are compared, patients experiencing greater weight loss generally have better outcomes regarding BP and hypertension. A retrospective, matched cohort analysis was performed to assess outcomes of 150 patients who underwent SG versus LAGB (905 [EL 3; SS, retrospective matched cohort]). Both cohorts were matched for age, gender, BMI, and preoperative comorbidities. The mean reduction in BMI was significantly higher for SG when compared to LAGB (11.9 kg/m^2 vs. 6.2 kg/m^2, P<0.01), as was the mean reduction in the number of medications used to control hypertension at 1 year (P<0.01). A prospective cohort study followed patients with hypertension undergoing SG or RYGB for 3 years (906 [EL 2; PCS]); 68% had remission of hypertension at 1 year, but 22% relapsed at year 3. The number of antihypertensive medications used before surgery was associated with a lower remission rate 1 year after surgery and a higher recurrence rate at 3 years. In both surgical subgroups, smaller weight loss during the first year was associated with a reduced likelihood of remission and increased recurrence of hypertension.

Another study randomized patients into SG or RYGB treatment arms and followed them for 3 months (907 [EL 1; RCT]). The mean values for age (36 and 31 years) and BMI (45.6 and 47.3 kg/m^2) were similar for the SG and RYGB groups. Both SG and RYGB were equally effective in promoting weight loss after 3 months, whereas SG was associated with better early remission rates for hypertension (P = 0.026). A longer 1-year retrospective review compared SG and RYGB from a prospectively collected database of 68 older adults (mean age 59 years; 24 SG and 44 RYGB) with a baseline mean BMI of 39.5 kg/m^2 (908 [EL 2; PCS, retrospective analysis]). One year after surgery, the mean BMIs in the SG and RYGB groups were 28.2 and 28.8 kg/m^2, respectively, and there was no significant difference between groups in mean %EWL or resolution of hypertension.

There are recent reports on the beneficial effects of bariatric surgery in older patients with obesity. A population-based observational study of 40 consecutive patients with a mean age of ≥64 years and class II or greater obesity underwent bariatric surgery at a single academic health center and were assessed for CVD risk at 1 year (909 [EL 2; PCS]). The %EWL was 57.5% and the prevalence of hypertension declined from 87.5% to 73.7% (P = 0.003) at 1 year. A retrospective review of medical record databases from a group of 2,375 patients who underwent bariatric surgery identified 98 patients >60 years old (910 [EL 3; SS]). This study group consisted of 80% women with a mean BMI of 47 kg/m^2, and hypertension was present in 90% of patients pre-operatively. The average %EWL at 1 year was 65.2% and was not statistically different between the younger and older patients. Among the patients with hypertension, 86% had reported resolution of hypertension and 14% reported improvement in BP.

In another study of older patients receiving bariatric surgery, 42 patients aged ≥60 years were matched with 84 patients aged <60 years (911 [EL 2; PCS, retrospective analysis]). No significant differences were observed between groups for mean operating time, length of hospital stay, morbidity rate, or mortality rate. The elderly group had significantly lower mean %EWL compared to controls at both 1 year (56% vs. 71%) and 2 years (52% vs. 74%), but rates of remission for hypertension at 2 years were comparable between the groups (81% vs. 77%).

- *Q5.5. Is weight loss effective to treat or prevent cardiovascular disease (CVD)? How much weight loss would be required?*
  - *Q5.5.1. Does weight loss prevent cardiovascular disease events or mortality?*

Executive Summary

- **R42.** Weight-loss therapy is not recommended based on available data for the expressed and sole purpose of preventing CVD events or to extend life, although evidence suggests that the degree of weight loss achieved by bariatric surgery can reduce mortality **(Grade B; BEL 2)**. Cardiovascular outcome trials assessing medication-assisted weight loss are currently ongoing or being planned.

- *Q5.5.2. Does weight loss prevent cardiovascular disease events or mortality in diabetes?*

Executive Summary

- **R43.** Weight-loss therapy is not recommended based on available data for the expressed and sole purpose of preventing CVD events or to extend life in patients with diabetes **(Grade B; BEL 1, downgraded due to evidence gaps)**. Cardiovascular outcome trials assessing medication-assisted weight loss are currently ongoing or being planned.

- *Q5.5.3. Does weight loss improve congestive heart failure and prevent cardiovascular disease events or mortality in patients with congestive heart failure?*

Executive Summary

- **R44**. Weight-loss therapy is not recommended based on available data for the expressed purpose of preventing CVD events or to extend life in patients with congestive heart failure, although evidence suggests that weight loss can improve myocardial function and congestive heart failure symptomatology in the short term **(Grade B; BEL 2)**.

Evidence Base

It is difficult to assess an independent effect of weight loss on CVD events and CVD mortality for several reasons: (*1*) the confounding effect of concurrent therapy specifically targeted to risk factors can affect mortality (e.g., statins, angiotensin converting enzyme inhibitors), (*2*) the need for long-term interventions and follow-up given the nature of the outcome (i.e., lifespan), (*3*) studies that largely do not differentiate between patients with obesity, with and without CVD risk factors, which could be the basis of heterogeneity in the response to weight loss regarding CVD outcomes, and (*4*) the apparent likelihood that interventions should be initiated before development of clinical CVD or a substantial subclinical atherosclerotic burden. Thus, there are few, if any, long-term RCTs assessing the effects of weight loss on mortality as a predetermined primary outcome measure. However, there are post-hoc analyses of data from prospective studies and retrospective cohort studies involving lifestyle interventions and bariatric surgery that suggest that weight loss can be associated with reduced mortality. Cardiovascular outcome trials assessing all 4 weight-loss medications approved by the FDA between 2012 and 2014 are ongoing or planned. Weight loss, whether resulting from lifestyle intervention, medication, or bariatric surgery, is associated with improvements in CVD risk factors as indicated by improvements in BP, lipids, glycemia, WC, and various biomarkers. However, the question remains whether these effects translate into reductions in CVD events and CVD mortality. The data that more consistently demonstrate reductions in mortality involve bariatric surgery, suggesting that weight loss >15% body weight is more likely to be associated with efficacy in this regard.

Williamson et al have prospectively studied the relationship between intentional weight loss and longevity, analyzing data from 43,457 women with overweight (912 [EL 2; PCS, retrospective analysis, N = 43,457]) and 49,337 men with overweight (913 [EL 2; PCS, retrospective analysis, N = 43,457]) who answered questionnaires describing weight-loss efforts in 1959-1960. In women with pre-existing weight-related complications, any weight loss was associated with a 20% reduction in all-cause mortality due to reduced mortality from cancers and diabetes. In women free of complications, ≥20% weight loss was associated with a 25% reduction in all-cause mortality while weight loss <20% was associated with a small to modest increase in mortality (912 [EL 2; PCS, retrospective analysis, N = 43,457]). Among men with health conditions, intentional weight loss had no effect on mortality; however, diabetes-associated mortality was reduced by 32% with <20% weight loss and by 36% in those losing ≥20% body weight (913 [EL 2; PCS, retrospective analysis, N = 43,457]). These same authors performed a prospective cohort study with a 12-year follow-up of 4,970 patients with overweight and diabetes enrolled in the American Cancer Society's Cancer Prevention Study 1. They found that intentional weight loss was associated with a 25% reduction in total mortality and a 28% reduction in CVD and diabetes mortality; these effects were largest among patients losing 9 to 13 kg (914 [EL 2; PCS]).

The Da Qing Diabetes Prevention Study randomized people with IGT to a control subgroup or to 1 of 3 lifestyle interventions (diet, physical activity, or diet + physical activity) (706 [EL 1; RCT]). After 23 years of follow-up, lifestyle intervention significantly reduced all-cause mortality from 38.4% in the controls to 28.1%; however, to achieve statistical significance, the 3 lifestyle treatment arms were combined in comparison with the controls (718 [EL 1; RCT]). Most RCTs assessing the effects of intentional weight loss achieved by lifestyle intervention do not demonstrate significant reductions in mortality when compared with the control group. One example is the Look AHEAD study in patients with T2DM randomized to intensive lifestyle therapy versus standard care, which prespecified mortality as an outcome. The Look AHEAD study was discontinued prematurely due to lack of effect of the ILI on mortality compared with standard care, despite the fact that the number of events was lower than planned (757 [EL 1; RCT]). However, a recent meta-analysis identified 15 RCTs (17,186 participants, BMI 30 to 46 kg/m^2, mean follow-up 27 months, and average weight loss 5.5 kg), and demonstrated a 15% reduction in all-cause mortality in those randomized to intentional weight loss compared with controls (915 [EL 1; MRCT]). Another meta-analysis of 12 studies and 14 cohorts involving 35,335 patients with CAD found that presumed intentional weight loss (4 cohorts) was associated with improved outcomes (RR, 0.67; 95% CI, 0.56-0.80; P<0.001), whereas observational weight loss unrelated to a weight-loss intervention (10 cohorts) was associated with worsened outcomes (RR, 1.62; 95% CI, 1.26-2.08; P<0.001; interaction P<0.001) (916 [EL 2; MNRCT]).

Other data addressing weight loss and mortality involves bariatric surgery. In comparison with usual care, various bariatric procedures were associated with a 29% lower all-cause mortality among 4,047 patients that were followed for an average of 10.9 years in the prospective SOS study (917 [EL 2; PCS]). The reduction in mortality was due to a decrease in deaths as a result of CVD as well as cancer. A retrospective cohort study in Utah of 7,925 patients receiving RYGB and a similar number of matched controls with 7.1 years of follow-up demonstrated a 40% reduction in all-cause mortality in the surgical group (918 [EL 3; SS, retrospective cohort, matched for age, sex, and BMI, N = 9,949]). A large retrospective cohort study involving 66,109 patients with obesity from Washington state (3,328 had bariatric surgery) observed a 33% lower all-cause mortality at 15 years of follow-up (919 [EL 2; PCS]).

However, a retrospective cohort study comparing outcomes in 847 U.S. veterans treated with bariatric surgery in 2000-2006 with 847 matched control patients did not find that bariatric surgery was associated with lower mortality (920 [EL 3; SS, retrospective cohort]). Due to recent improvements in bariatric outcomes and in order to incorporate a larger number of patients with a longer follow-up, these same authors studied 2,500 patients (74% men) who underwent bariatric surgery in Veterans Affairs bariatric centers from 2000-2011 and 7,462 carefully matched control patients. They found that mortality was significantly reduced at 1 to 5 years (HR = 0.45) and 5 to 14 years (HR = 0.47) following surgery (921 [EL 3; SS, retrospective cohort]).

Two meta-analyses of studies featuring bariatric surgery and nonsurgical controls demonstrated significant reductions in mortality in patients undergoing bariatric surgery. Kwok et al (922 [EL 2; MNRCT]) observed an OR of 0.48 for all-cause mortality and 0.54 for composite CVD events in the surgical patients, and Pontiroli et al (923 [EL 2; MNRCT]) observed an OR of 0.70 for all-cause mortality and 0.58 for CVD mortality. Pontiroli et al (923 [EL 2; MNRCT]) also compared gastric banding and gastric bypass and found that ORs were similar for all-cause mortality, but that the OR for CVD mortality favored gastric bypass (0.48 vs. 0.71).

In patients with T2DM, there is insufficient evidence to determine whether weight loss reduces mortality or CVD events. Nonrandomized cohort studies provide discrepant results (924 [EL 4; NE]) and are confounded by the inclusion of patients with unintentional weight loss and by variable specific therapy for comorbidities such as BP, lipids, and glycemia. As discussed, the Look AHEAD study was discontinued prematurely for lack of effect of ILI versus standard support and education on mortality and CVD outcomes, despite suboptimal event rates (757 [EL 1; RCT]). Harrington et al (925 [EL 2; MNRCT]) conducted a meta-analysis of 26 prospective studies involving people with and without diabetes and reported that intentional weight loss did not alter all-cause mortality (RR, 1.01; $P = 0.89$), while unintentional weight loss was associated with excess risk of 22% to 39%. However, intentional weight loss did produce a small benefit for individuals with obesity classified as unhealthy (with obesity-related risk factors), which included patients with diabetes (RR, 0.87; 95% CI, 0.77-0.99; $P = 0.028$). There was no evidence for weight loss conferring either benefit or risk among healthy people with obesity. Finally, a subanalysis of data in the SOS Study involving only patients with diabetes demonstrated that bariatric surgery reduced the incidence of myocardial infarctions compared with nonsurgical controls (HR, 0.56; CI, 0.34-0.93) (926 [EL 2; PCS]).

Regarding weight-loss therapy for CHF, there are insufficient clinical trial data available upon which to base a recommendation. Obesity increases the risk of CHF (357 [EL 2; PCS]; 358 [EL 3; SS]; 359 [EL 4; NE]) and is associated with structural and functional changes that impair myocardial function, including impaired left ventricle (LV) filling and increases in LV cavity size, LV end-systolic wall stress, and LV mass/height index (357 [EL 4; NE]; 927 [EL 2; PCS]). In addition, weight loss can improve myocardial function and symptomatology in the short term and enhance QOL (927 [EL 2; PCS]; 928 [EL 2; PCS, N = 9]; 929 [EL 2; PCS]; 930 [EL 2; PCS]; 931 [EL 4; NE]; 932 [EL 4; NE]; 933 [EL 2; PCS]; 934 [EL 2; PCS]; 935 [EL 3; SCR]; 936 [EL 1; RCT]; 937 [EL 1; RCT]). Unintentional weight loss and cardiac cachexia are associated with a poorer prognosis (931 [EL 4; NE]; 938 [EL 3; SS]). Clinical trials and RCTs are needed to assess longer-term outcomes, particularly given the "obesity paradox" in CHF that is evident in epidemiologic studies (369 [EL 2; RCCS]). Current guidelines for the management of heart failure provide conflicting directions for the prognosis and management of BMI. The ACC/AHA Guideline for the management of heart failure does not make any specific recommendation for management of BMI and acknowledges the lack of relevant data (939 [EL 4; NE]). The European Society of Cardiology in its 2001 guideline recommends weight loss for patients with overweight and obesity with heart failure, even though this recommendation is not supported by data from clinical trials (940 [EL 4; NE]), and its 2012 guideline recommends that obesity in CHF should be managed as recommended by "other guidelines" addressing obesity management in general, again without supportive data (941 [EL 4; NE]).

- *Q5.6. Is weight loss effective to treat nonalcoholic fatty liver disease and nonalcoholic steatohepatitis? How much weight loss would be required?*

Executive Summary

- **R45.** Patients with overweight or obesity and nonalcoholic fatty liver disease should be primarily

managed with lifestyle interventions, involving calorie restriction and moderate-to-vigorous physical activity, targeting 4 to 10% weight loss (a range over which there is a dose-dependent beneficial effect on hepatic steatosis) **(Grade A; BEL 1)**.

- **R46.** Weight loss as high as 10 to 40% may be required to decrease hepatic inflammation, hepatocellular injury, and fibrosis **(Grade A; BEL 1)**. In this regard, weight loss assisted by orlistat **(Grade B; BEL 2)**, liraglutide **(Grade A; BEL 1)**, and bariatric surgery **(Grade B; BEL 2)** may be effective.
- **R47.** A Mediterranean-type dietary pattern or meal plan can have a beneficial effect on hepatic steatosis independent of weight loss **(Grade A; BEL 1)**.

Evidence Base

The therapeutic imperative for patients with NAFLD is to slow down or abrogate disease progression from hepatic steatosis to NASH to cirrhosis to liver failure and adenocarcinoma. Evidence indicates that this can be accomplished in patients with hepatic steatosis and NASH using lifestyle intervention that achieves weight loss through caloric restriction and increased physical activity (942 [EL 3; SS]; 943 [EL 1; RCT, post-hoc analysis]; 944 [EL 1; RCT]; 945 [EL 1; RCT]; 946 [EL 2; PCS]; 947 [EL 1; RCT]; 948 [EL 2; PCS]; 949 [EL 2; NRCT]; 950 [EL 2; PCS]; 951 [EL 1; RCT]; 952 [EL 2; PCS]; 953 [EL 1; RCT]; 954 [EL 3; SS]; 955 [EL 1; RCT]; 956 [EL 1; RCT]). This therapeutic approach reverses 2 of the root causes of NAFLD, namely, insulin resistance and overweight or obesity.

Kani et al (951 [EL 1; RCT]) found that a soy-based dietary pattern was associated with improved liver function tests in subjects with NAFLD and mild obesity, but with only a 4% weight loss. Hickman et al (952 [EL 2; PCS]) found that a 4 to 5% weight loss with lifestyle intervention produced a sustained improvement in liver function tests in subjects with overweight and NAFLD. Elias et al (950 [EL 2; PCS]) found that a 5% weight loss (through a 500 to 1,000 kcal daily calorie reduction over a 6-month period) was associated with improvement in hepatic steatosis in patients with obesity and NAFLD by computed tomography. Aller et al (953 [EL 1; RCT]) also demonstrated that a 5% weight loss was associated with improved liver function tests, as well as improvements in various metabolic markers in subjects with obesity and NAFLD. The Look AHEAD trial demonstrated that, on average, an 8% loss of weight was associated with a significant reduction in hepatic steatosis (943 [EL 1; RCT, post-hoc analysis]). Goodpasteur et al (947 [EL 1; RCT]) found that implementing a lifestyle plan that incorporated calorie restriction (producing 8 to 10% weight loss in 12 months) and moderate-intensity physical activity (e.g., brisk walking, progressing up to 60 minutes/day for 5 days/week) was associated with improvements in liver function tests in patients with NAFLD. This is consistent with the findings of Kechagias et al (957 [EL 2; PCS]), in which a 10% weight gain over 4 weeks was sufficient to increase liver fat (as triglycerides). However, Yoshimura et al (955 [EL 1; RCT]) found that a 7% weight loss with calorie restriction was associated with improved liver function in NAFLD, but there was no additive effect of exercise training. In a randomized controlled study of people with NAFLD and a mean BMI in the range of 25 to 26 kg/m^2, improvements in hepatic steatosis as measured by magnetic resonance proton spectroscopy was achieved through community-based lifestyle modification programs (958 [EL 1; RCT]). Furthermore, while only 13% of patients losing <3% body weight in this study had remission of NAFLD, 40% with <3% weight loss and 97% with ≥8% weight loss had remission of NAFLD (958 [EL 1; RCT]).

In programs employing special diets, male Asians with overweight and NAFLD were placed on diets based on olive and canola oils, both high in MUFAs, and this resulted in a 5 to 6% weight loss and improved fatty liver grading by ultrasound and insulin sensitivity (959 [EL 1; RCT]). Lewis et al (960 [EL 2; PCS]) reported that a 6-week interventional cohort study in patients with severe obesity placed on a commercial Optifast very low-calorie diet produced a 14.7% reduction in mean liver volume and a 43% reduction in liver fat by MRI spectroscopy associated with a 7.5% weight loss. Notwithstanding the above beneficial effects of weight loss, Ryan et al (62 [EL 1; RCT]) found that consuming a Mediterranean diet (high in MUFAs) improved hepatic steatosis (assessed by magnetic resonance proton spectroscopy) and insulin sensitivity (using 3-h hyperinsulinemic–euglycemic clamps), but without any significant change in weight or WC.

Medications have also been shown to reduce hepatic steatosis. Pharmacotherapy with metformin in patients with overweight or obesity, insulin resistance, and NASH, in conjunction with lifestyle intervention targeting weight loss, can be considered when weight-loss efforts alone have failed; however, the evidence is not conclusive that metformin has a direct salutary effect on NAFLD per se (398 [EL 4; NE]). Many other nutritional and/or pharmacologic interventions to specifically manage NAFLD independent of weight loss in patients with obesity have been investigated alone and in combination, but further confirmatory studies are required (961 [EL 4; NE]; 962 [EL 1; RCT, N = 34]; 963 [EL 4; NE]; 964 [EL 1; RCT]; 965 [EL 1; RCT]; 966 [EL 1; RCT]).

There is also evidence that weight loss can produce histologic improvements in hepatic steatosis, inflammation, and fibrosis, whether associated with lifestyle intervention, orlistat, or bariatric surgery. In an RCT, 31 patients with obesity and biopsy-proven NASH were randomized to a diet plus exercise treatment resulting in a 9.3% weight loss

over 48 weeks (967 [EL 1; RCT]). While the diet plus exercise subgroup experienced significant improvements in the NASH histologic activity score, improvements in steatosis, lobular inflammation, and ballooning injury were only observed in those patients losing >7% body weight. In a study of orlistat-assisted weight loss, patients with NASH underwent a liver biopsy before and after treatment that involved a 6-month reduced-calorie diet plus orlistat, which resulted in a mean weight loss of 5.4%; out of 14 patients in this study. Weight loss led to a reduction in the histologic steatosis score in 10 patients, improvements in inflammation in 11 patients, and a reduction in the fibrosis score in 10 patients (968 [EL 2; PCS]).

Trials employing liraglutide (1.8 mg/day) in patients with T2DM demonstrated favorable effects on NAFLD. In an RCT involving patients with T2DM, obesity, and NAFLD, 39% of patients (9 of 23) who received liraglutide and underwent end-of-treatment liver biopsy had resolution of NAFLD, with 9% experiencing progression of fibrosis, compared with 9% (2 of 22) of patients in the placebo group showing histological resolution ($P = 0.019$) and 36% showing progressive fibrosis (969 [EL 1; RCT]). In other small RCTs and cohort studies, liraglutide therapy was associated with lowering of transaminases (970 [EL 1; RCT, small N = 14]; 971 [EL 2; PCS]; 972 [EL 2; PCS]; 973 [EL 1; MRCT]; 974 [EL 3; SS]), improvements in hepatic histology (971 [EL 2; PCS]), reductions in intrahepatocellular fat by MRI proton spectroscopy (973 [EL 1; MRCT]), and improvements in hepatic function (i.e., enhanced hepatic insulin sensitivity) (970 [EL 1; RCT, small N = 14]) in patients with NAFLD or NASH.

In 39 patients undergoing RYGB surgery, postoperative weight loss of 50 kg over 18 months led to marked improvements in histologic steatosis, hepatocellular ballooning, centrilobular fibrosis, lobular inflammation, and the fibrosis stage, while no significant change was noted in portal tract inflammation and fibrosis (975 [EL 3; SS]). Nineteen patients with biopsy-proven NASH at the time of RYGB surgery lost 40% of body weight after 21 months, and repeat biopsy demonstrated marked improvements in histologic steatosis, lobular inflammation, and portal and lobular fibrosis (976 [EL 2; PCS]). Importantly, histopathologic criteria for NASH were no longer present in 89% of patients.

Mummadi et al (977) conducted a meta-analysis of 15 interventional studies that included 766 paired liver biopsies. The reductions in BMI after bariatric surgery ranged from 19.11 to 41.76 kg/m^2, the pooled proportions of patients with improvement or resolution of steatosis, steatohepatitis, and fibrosis were 91.6%, 81.3%, and 65.5%, respectively, and a complete resolution of nonalcoholic steatohepatitis was observed in 69.5% of patients (977 [EL 2; MNRCT]).

- *Q5.7. Is weight loss effective to treat polycystic ovary syndrome (PCOS)? How much weight loss would be required?*

Executive Summary

- **R48.** Women with overweight or obesity and PCOS should be treated with lifestyle therapy with the goal of achieving 5 to 15% weight loss or more to improve hyperandrogenism, oligomenorrhea, anovulation, insulin resistance, and hyperlipidemia; clinical efficacy can vary among individual patients **(Grade A; BEL 1)**.
- **R49.** Patients with overweight or obesity and PCOS should be considered for treatment with orlistat, metformin, or liraglutide, alone or in combination, because these medications can be effective in decreasing weight and improving PCOS manifestations, including insulin resistance, glucose tolerance, dyslipidemia, hyperandrogenemia, oligomenorrhea, and anovulation **(Grade A; BEL 1)**.
- **R50.** Selected patients with obesity and PCOS should be considered for laparoscopic Roux-en-Y gastric bypass to improve symptomatology, including restoration of menses and ovulation **(Grade B; BEL 2)**.

Evidence Base

Studies have demonstrated that PCOS symptomatology is improved by weight loss achieved by a variety of lifestyle interventions including reduced-calorie diets (978 [EL 2; PCS, N = 20]; 979 [EL 1; RCT]; 980 [EL 1; RCT]; 981 [EL 2; PCS]; 982 [EL 1; RCT, small N = 11]; 983 [EL 2; PCS]; 984 [EL 2; PCS]; 985 [EL 2; PCS, BMI matched]; 986 [EL 2; PCS]; 987 [EL 2; PCS]; 988 [EL 2; PCS]; 989 [EL 2; PCS]; 990 [EL 2; PCS]), diets of various macronutrient composition with lifestyle interventions (991 [EL 1; RCT]; 992 [EL 2; PCS]; 993 [EL 1; RCT]; 994 [EL 2; PCS]; 995 [EL 2; PCS]), exercise and lifestyle programs (996 [EL 2; PCS]; 997 [EL 1; RCT]; 998 [EL 1; RCT, small N = 12]; 999 [EL 2; PCS]; 1000 [EL 1; RCT]; 1001 [EL 2; PCS]; 1002 [EL 2; PCS]; 1003 [EL 2; PCS]; 1004 [EL 1; RCT]), pharmacotherapy (1005 [EL 1; RCT]; 1006 [EL 1; RCT]; 1007 [EL 2; PCS]; 1008 [EL 2; PCS]), and bariatric surgery (1009 [EL 2; PCS]; 1010 [EL 3; SS]; 1011 [EL 3; CSS]; 1012 [EL 3; SS]). Thus, diet and lifestyle interventions should be an integral component in the treatment of patients with PCOS and overweight or obesity (441 [EL 4; NE]). In women with PCOS and obesity, the loss of intra-abdominal fat, but not subcutaneous fat, was associated with resumption of ovulation (1013 [EL 2; PCS]).

Multiple small, uncontrolled cohort studies have demonstrated beneficial effects of 5 to 15% weight loss attained with dietary intervention in PCOS (978 [EL 2; PCS, N = 20]; 979 [EL 1; RCT]; 980 [EL 1; RCT]; 981 [EL 2; PCS]; 982 [EL 1; RCT, small N = 11]; 983 [EL 2; PCS]; 984 [EL 2; PCS]; 985 [EL 2; PCS, BMI matched]; 986 [EL 2; PCS]; 987 [EL 2; PCS]; 988 [EL 2; PCS]; 989 [EL 2; PCS]; 990 [EL 2; PCS]). There have also been several RCTs examining the effect of weight loss with lifestyle interventions with or without exercise on PCOS symptomatology. The largest of these trials randomized 94 women with overweight or obesity (mean age 29.3 years, mean BMI 36.2 kg/m^2) to 3 intervention groups: (*1*) 20 weeks of diet only (n = 31), (*2*) diet and aerobic exercise (n = 31), and (*3*) diet and aerobic plus resistance exercise (n = 33); these groups attained weight loss of 8.9%, 10.6%, and 8.7%, respectively (P<0.001) (1014 [EL 1; RCT]). Fat mass decreased to a greater extent in the 2 exercise groups than in the diet only group (P≥0.03). All groups demonstrated improvements in hormonal abnormalities and CV risk factors associated with PCOS, including BP, testosterone, total cholesterol, LDL-c, triglyceride levels, fasting insulin, and fasting glucose; there were no statistically significant differences in the improvements in these parameters among the 3 intervention groups (1014 [EL 1; RCT]).

It is important to note that women with overweight and obesity and PCOS may have variable responses to weight loss. In a prospective, intervention trial of 65 women with PCOS (average age 22.5-23.7 years, mean BMI 33.3 to 36.2 kg/m^2), participants were placed on a 1,200 to 1,400 kcal/day diet for 6 months followed by a period of more moderate caloric restriction and physical activity (1015 [EL 2; RCT]). The women were monitored on average for 20.4 ± 12.5 months and the clinical responses could be categorized into 3 groups: (*1*) the persistent PCOS group, comprising 15.4% of the participant sample, who displayed no significant changes in hirsutism, androgen levels, or menstrual cycle regularity/restoration; (*2*) the partial responder group, comprising 47.7% of the sample, who had persistent hirsutism but restoration of menstrual cycles, though not always ovulatory; and (*3*) the complete responder group, comprising 36.9% of the sample, who demonstrated disappearance of the PCOS phenotype with resolution of hirsutism and restoration of normal menstrual function (1015 [EL 2; RCT]). The amount of weight loss was not statistically different between the 3 groups (12.7 kg, 15.3 kg, and 14.1 kg, respectively); thus, the study demonstrated that women with overweight/obesity and PCOS respond differently to weight loss, independent of the amount of weight they lose (1015 [EL 2; RCT]).

Pharmaceutical intervention trials have examined the efficacy of weight-loss medications and "insulin-sensitizing drugs" in PCOS. Regarding medicine-assisted weight loss, clinical trial data are available for orlistat (1006 [EL 1; RCT]; 1007 [EL 2; PCS]; 1008 [EL 2; PCS]; 1016 [EL 2; PCS]; 1017 [EL 1; RCT]; 1018 [EL 1; RCT]; 1019 [EL 1; RCT]), sibutramine (1020 [EL 1; RCT]; 1021 [EL 1; RCT]), rimonabant (1022 [EL 1; RCT]), and liraglutide (1023 [EL 2; PCS]; 1024 [EL 1; RCT]). One prospective, randomized, open-label trial of 21 women with PCOS (average age 27 years, average BMI 36.7 kg/m^2) compared the effect of 3 months of orlistat (120 mg 3 times per day) versus metformin (500 mg 3 times per day) on weight loss and clinical PCOS parameters (1006 [EL 1; RCT]). The study found that orlistat resulted in greater weight loss than metformin (4.69% vs. 1.02%, P = 0.006); however, orlistat and metformin treatments resulted in similar reductions in total testosterone (P = 0.039 and P = 0.048, respectively, compared to baseline). In addition, there were no significant effects on homeostatic model assessment of insulin resistance (HOMA-IR), SHBG, or lipid levels in either group (1006 [EL 1; RCT]). A larger prospective 6-month trial of orlistat (120 mg 3 times daily) followed by a low-calorie diet compared the response of 101 women with PCOS (average age 26.1 years, average BMI 34.5 kg/m^2) to BMI-matched women without PCOS (1016 [EL 2; PCS]). Weight loss was comparable in both groups, amounting to 12.9% in the group with PCOS and 14.9% in the group who did not have PCOS. Both groups experienced improvements in insulin sensitivity, glucose tolerance, WC, lipids, and androgen levels, although total testosterone, HDL-c, and LDL-c all improved to a greater extent in the PCOS patients having started at a higher baseline (1016 [EL 2; PCS]).

An open-label study in Iran randomized 80 women with PCOS (average age 27 years, average BMI 33.7 kg/m^2) to 3 months of treatment with either orlistat (120 mg 3 times daily, n = 40) or metformin (500 mg 3 times daily, n = 40) (1018 [EL 1; RCT]). Resulting body weight loss (4.48% in the orlistat group vs. 4.55% in the metformin group) and decrements in BMI and WC were similar in both treatment groups. Ovulation rate was 15% in the orlistat-treated group and 30% in the metformin-treated group, with no statistically significant difference between the groups (P = 0.108) (1018 [EL 1; RCT]).

Another open-label trial of 40 women with PCOS who were randomized to 3 months of 120 mg orlistat twice daily (n = 20; average age 28.8 years, average BMI 38.4 kg/m^2) or 1,000 mg metformin daily (n = 20; average age 30.6 years, average BMI 39.6 kg/m^2) found that both groups had a significant decrease in BMI, WC, and testosterone levels compared to baseline, with no statistically significant difference between the 2 groups (1019 [EL 1; RCT]). Ovulation rate was 25% in the orlistat group and 40% in the metformin group, and the difference was not statistically significant (P = 0.31) (1019 [EL 1; RCT]). Thus, orlistat and metformin both promoted weight loss and improved lipid and hormonal measures, induced ovulation, and restored menstrual cycles.

Both sibutramine and rimonabant have been withdrawn due to adverse events (CVD and psychological events, respectively) but serve as proof-of-principle that medication-assisted weight loss can exert a therapeutic effect in PCOS. Both drugs improved metabolic parameters, reduced androgen levels, and improved hirsutism in PCOS patients (1020 [EL 1; RCT]; 1021 [EL 1; RCT]; 1022 [EL 1; RCT]). In an RCT randomizing PCOS patients to a hypocaloric diet with and without sibutramine, only those patients who lost >10% of body weight experienced a reduction in the free androgen index (1021 [EL 1; RCT]). While liraglutide at 3 mg/day has been approved for weight loss, the efficacy of lower doses (0.6 to 2.4 mg/day) to induce weight loss has been examined in PCOS patients. An uncontrolled prospective study of 84 women with PCOS (mean age 35.5 years, mean BMI 35 kg/m^2) treated with 0.6 to 1.8 mg of liraglutide daily (titrated to 1.8 mg in 61.9% of the women in the sample) for an average of 27.8 weeks found that 81.7% of the women lost >5% of their body weight and 32.9% lost >10% of their body weight (1023 [EL 2; PCS]). This observational study did not report the effect of weight loss on hormonal levels and clinical manifestations of PCOS. Another study examined the effect of liraglutide on women with PCOS who had not lost weight with metformin therapy alone (1024 [EL 1; RCT]). This open-label study included 40 women who were then randomized to 1 of 3 arms: (*1*) 1,000 mg of metformin twice daily, (*2*) 1.2 mg of liraglutide twice daily, or (*3*) a combination of metformin and liraglutide at the same doses. Compared to the metformin and liraglutide alone groups, the group receiving the combination of these drugs lost the most weight (1.2 kg, 3.8 kg, and 6.5 kg, respectively; $P<0.001$) and had the largest corresponding decreases in BMI ($P<0.001$) and WC ($P = 0.029$) (1024 [EL 1; RCT]). Further trials are required to assess the safety of the long-term use of weight-loss medications in women with PCOS, many of whom may be seeking fertility treatment.

Multiple clinical trials and meta-analyses, including RCTs and comparator trials versus clomiphene and orlistat, have established the efficacy of metformin in the improvement of metabolic parameters, ovulation, and pregnancy rates in patients with PCOS (1025 [EL 1; MRCT]; 1026 [EL 1; MRCT]; 1027 [EL 1; MRCT]; 1028 [EL 2; MNRCT]; 1029 [EL 1; MRCT]). One meta-analysis assessing treatment with metformin demonstrated an improvement in both ovulation rates and pregnancy rates in women with PCOS versus placebo and in women taking metformin with clomiphene versus clomiphene alone (1025 [EL 1; MRCT]). Metformin therapy has been consistently shown to result in modest weight loss; it is not clear the degree to which weight loss versus other actions of the drug are responsible for the therapeutic effects. Similarly, thiazolidinediones, another class of insulin-sensitizing drugs associated with modest weight gain, can improve androgen and gonadotropin levels, insulin sensitivity, ovulation, and pregnancy rates (1030 [EL 1; MRCT]; 1031 [EL 1; MNRCT]). These data suggest that it is the insulin-sensitizing effect of weight loss that is largely responsible for the therapeutic efficacy of lifestyle interventions and weight-loss medications in PCOS.

Several small prospective trials have demonstrated that bariatric surgery is an effective intervention to produce significant weight loss and alleviate PCOS symptomatology. In a prospective, longitudinal, nonrandomized trial involving women who underwent surgery with either biliopancreatic diversion or by laparoscopic gastric bypass, 17 women were found to have PCOS (average age 29.8 years, average BMI 50.7 kg/m^2) and, of those, the authors obtained follow-up data on 12 women (1009 [EL 2; PCS]). The 12 women lost an average of 41 kg ($P<0.001$) after a 12 ± 5-month follow-up and all were found to have restored menstrual cycles, with 10 having ovulatory cycles. All 12 women had improvements in androgen levels, hirsutism, and measures of insulin resistance (as assessed by HOMA-IR). In another study, 24 women (mean age 34 years, mean BMI 50 kg/m^2) with PCOS underwent laparoscopic RYGB and were followed for an average of 27.5 ± 16 months; average %EWL was 56.7% and all of the women resumed menstruation. Hirsutism resolved in 52% of the women by 8 months and an additional 25% had moderate resolution of their hirsutism at 21 months (1010 [EL 3; SS]).

A retrospective review of 389 women with PCOS who underwent RYGB demonstrated improvements in LDL-c, triglycerides, A1C, and hepatic transaminases without differences in clinical response among Hispanic, non-Hispanic black, and white subgroups (1011 [EL 3; CSS]). In another cohort study in which 20 patients with PCOS underwent gastric bypass, menstruation was corrected in 82% and hirsutism had resolved in 29% of patients, and 77.8% of those with diabetes had complete remission (1012 [EL 3; SS]). All 6 patients who desired pregnancy following surgery conceived within 3 years of surgery. Larger, randomized trials are needed to assess response to bariatric procedures other than gastric bypass as well as to investigate long-term outcomes.

- *Q5.8. Is weight loss effective to treat infertility in women with overweight and obesity? How much weight loss would be required?*

Executive Summary

- **R51.** Weight loss is effective to treat infertility in women with overweight and obesity and should be considered as part of the initial treatment to improve fertility; weight loss of ≥10% should be targeted to augment likelihood of conception and live birth **(Grade A; BEL 1)**.

Evidence Base

Small cohort studies have shown that weight loss is effective in improving fertility in women with overweight and obesity (1001 [EL 3; SS, retrospective cohort]; 1002 [EL 2; PCS]; 1032 [EL 2; PCS]; 1033 [EL 2; PCS]) and that a 10% decrease in body weight may improve rates of fertility. Clark et al (1001 [EL 2; PCS]) placed 67 anovulatory women on a diet and physical activity lifestyle intervention, resulting in a mean reduction in weight of 10.2 kg; 60 of the 67 women became ovulatory, 52 achieved pregnancy, and 45 had a live birth. A lifestyle intervention program including 58 women with obesity and menstural irregularities resulted in a 10 kg weight loss over 32 weeks and resulted in return of regular menses in 80% of women and a pregnancy rate of 29% (1033 [EL 2; PCS]). A recent study of 52 women with overweight and obesity (average BMI 33 ± 6.7 kg/m^2, 56% with BMI ≥30 kg/m^2) investigated the effect of "meaningful weight loss" (defined as 10% of body weight) on fertility (1032 [EL 3; SS, retrospective cohort]). Each woman was seen by an endocrinologist and received counseling on diet and exercise, with or without weight-loss medication. The 32% of women who lost ≥10% of their body weight were more likely to conceive versus women with <10% weight loss (88% vs. 54%, respectively). Additionally, women with >10% weight loss were more likely to have live births (71% vs. 37%, respectively) and one-third conceived spontaneously. Notably, in this study, there were more women diagnosed with PCOS in the group with <10% weight loss (1032 [EL 3; SS, retrospective cohort]). Additional studies have confirmed that weight loss <10% is not effective in increasing pregnancy rates (1034 [EL 2; PCS]; 1035 [EL 1; RCT]). Thus, a 10% reduction in body weight appears to result in increased rates of pregnancy, albeit larger prospective trials are required to confirm these findings.

In an RCT, 49 women with obesity who were infertile for >3 years were randomized either to a 12-week intervention with a very-low energy diet (6 weeks) followed by a low-calorie diet or to a control group given weight-loss advice (1036 [EL 1; RCT]). The intervention group lost 6.9% of their initial body weight compared with 1.5% weight loss in the control group and achieved a significantly higher pregnancy rate (48% vs. 14%, $P = 0.007$), required fewer assistive reproductive technology cycles to conceive (2.4 cycles vs. 3.7 cycles, $P = 0.002$), and had higher rates of live birth (48% vs. 14%, $P = 0.02$) (1036 [EL 1; RCT]). In an RCT comparing lifestyle intervention and metformin in anovulatory women with obesity and PCOS, weight loss irrespective of the randomization group resulted in an OR of 9.0 for ovulation (1037 [EL 4; NE]). In another RCT, 38 women with obesity and infertility for >4 years were randomized to an intervention consisting of a low-calorie diet of meal replacements plus exercise versus a control group given recommendations for lifestyle change (1035 [EL 1; RCT]). The study found that the intervention group lost only 3.8 ± 3.0 kg, which was more than the control group (-0.5 ± 1.2 kg, $P<0.001$), but did not find a statistically significant difference in pregnancy rates at this level of weight loss (67% vs. 40%, $P = 0.119$) (1035 [EL 1; RCT]). Weight loss associated with bariatric surgery has also been observed to induce ovulation, improve sexual function, and increase the likelihood of pregnancy and live births (1038 [EL 3; SS]; 1039 [EL 2; PCS]; 1040 [EL 3; SS]; 1041 [EL 2; PCS]; 1042 [EL 3; CSS]; 1043 [EL 2; PCS]; 1044 [EL 2; PCS]; 1045 [EL 2; PCS]). Most of these are case-control studies, cohort studies, or case series involving small numbers of patients. The data are insufficient to identify the optimal time interval for delay of pregnancy following bariatric surgery; however, the general consensus is that pregnancy should be delayed 12 to 18 months, primarily to avoid nutritional deficiencies (1046 [EL 4; NE]; 1047 [EL 4; NE]).

In a systematic review of maternal and obstetric outcomes following obesity surgery, Maggard et al (1048 [EL 4; NE]) included 75 articles, 54 of which were case studies or case series, 8 were cohort studies, and 3 were matched cohort studies. The 3 matched cohort studies by Ducarme et al (1049 [EL 2; RCCS]), Patel et al (1050 [EL 3; SS]), and Wax et al (1051 [EL 3; SS]) showed fewer maternal complications for women who had undergone bariatric surgery compared with control patients with obesity. Guelinckx et al (1052 [EL 4; NE]) reviewed many of these same studies and concluded that enhanced fertility outcomes and improvements in maternal and fetal obstetric complications characterized women who had undergone obesity surgery compared with similar women with obesity.

Additional cohort studies (and case reports) have also examined whether weight-loss interventions improve outcomes of assisted reproductive technology (ART) treatments. Using lifestyle interventions that featured reduced-calorie diets (1001 [EL 2; PCS]; 1002 [EL 2; PCS]; 1035 [EL 1; RCT]; 1036 [EL 1; RCT]; 1053 [EL 3; SS]; 1054 [EL 3; SS, abstract]; 1055 [EL 4; abstract]) or very low-calorie diets (1036 [EL 1; RCT]; 1056 [EL 2; PCS, very small N = 10]), 4 of 8 studies assessing the effects of diet-induced weight loss showed statistically significant improvement in pregnancy rates or live births (1001 [EL 2; PCS]; 1002 [EL 2; PCS]; 1036 [EL 1; RCT]; 1053 [EL 3; SS]), 2 reported a nonsignificant trend toward increased pregnancy (1035 [EL 1; RCT]; 1054 [EL 3; SS, abstract]), and 1 showed a decrease in live birthrates (1055 [EL 4; abstract]). In a small prospective cohort of 10 women with obesity (4 of whom dropped out of the study) who were administered a very low-calorie diet, none of the women conceived (1056 [EL 2; PCS, very small N = 10]).

Bariatric surgery (1057 [EL 3; CCS]; 1058 [EL 3; SCR]) and nonsurgical procedures (1059 [EL 3; SS]) have also been shown to improve outcomes of ART treatments. However, the evidence regarding bariatric surgery involves

only 2 case reports (n = 5 and n = 1) and therefore further studies are needed. In 1 small study examining gastric balloons, 15 of 27 women became pregnant (1059 [EL 3; SS]). A systematic review of 11 studies supported the clinical recommendation of advising women with overweight and obesity to lose weight before ART treatments, although RCTs are needed for the development of more definitive recommendations (1060 [EL 4; NE]). Thus, on balance, while additional studies are needed, the data support the contention that weight loss before fertility treatment can result in higher rates of conception and, at times, natural conception.

The position of the Practice Committee of the American Society for Reproductive Medicine in 2015 was that "obese women wishing to conceive should consider a weight management program that focuses on preconception weight loss (to a BMI <35 kg/m^2), prevention of excess weight gain in pregnancy, and long-term weight reduction" (1047 [EL 4; NE]).

- *Q5.9. Is weight loss effective to treat male hypogonadism? How much weight loss would be required?*

Executive Summary

- **R52.** Treatment of hypogonadism in men with increased waist circumference or obesity should include weight-loss therapy **(Grade B; BEL 2)**. Weight loss of more than 5 to 10% is needed for significant improvement in serum testosterone **(Grade D)**.
- **R53.** Bariatric surgery should be considered as a treatment approach that improves hypogonadism in most patients with obesity, including patients with severe obesity (BMI >50 kg/m^2) and T2DM **(Grade A; BEL 1)**.
- **R54.** Men with hypogonadism and obesity who are not seeking fertility should be considered for testosterone therapy in addition to lifestyle intervention since testosterone in these patients results in weight loss, decreased waist circumference, and improvements in metabolic parameters (glucose, A1C, lipids, and blood pressure) **(Grade A; BEL 1)**.

Evidence Base

Multiple studies have demonstrated that weight loss accompanying bariatric surgery results in significant increases in serum testosterone in men (511 [EL 1; RCT]; 512 [EL 2; PCS, only 21 of 75 patients studied in follow-up]; 1061 [EL 2; PCS, N = 33 men]). Pellitero and colleagues (511 [EL 2; PCS, N = 33 men]) found that bariatric surgery was effective in reversing hypogonadism (defined as total testosterone <300 ng/dL) in patients (n = 33, age 40.5 ± 9.9 years) with marked obesity (mean BMI 50.3 ± 6.1 kg/m^2), with a decline in hypogonadism from 78.8% to 6% of patients after 18.8% weight loss in 1 year. Percent weight loss was also significantly associated with positive changes in SHBG ($P = 0.04$), inhibin-B ($P = 0.03$), and anti-Mullerian hormone ($P = 0.01$).

In a randomized study comparing RYGB (n = 17), SG (n = 11), and medical anti-diabetes therapy (n = 14), surgically induced weight loss improved hypogonadism in 42 men (aged 49 ± 8 years) with obesity (BMI 37 ± 3 kg/m2) and T2DM (A1C 9.2 ± 1.4%) to a greater extent than medical diabetes therapy (1061 [EL 1; RCT]). In this study, weight at 1 year decreased 26% with RYGB, 27% with SG, and 5% with anti-diabetes therapy. None of the men received testosterone therapy. Measurement of adiposity was determined by DEXA and leptin levels in 19 subjects. Total testosterone increased with RYGB (468 vs. 243 ng/dL, $P<0.001$) and SG (418 vs. 287 ng/dL, $P<0.01$), but not with anti-diabetes therapy (265 vs. 254 ng/dL). There was also an increase in free testosterone that was strongly correlated with the decrements in body weight ($P = 0.02$), A1C ($P = 0.04$), leptin ($P = 0.02$), and abdominal fat ($P = 0.009$). A systematic review and meta-analysis of studies from January 1969 to September 2012 identified 22 studies evaluating the effect of diet or bariatric surgery and 2 studies that compared diet and bariatric surgery (515 [EL 2; MRCT, subanalysis of RCTs included]). Both low-calorie diet and bariatric surgery were associated with significant ($P<0.0001$) increases in plasma SHBG and (bound and unbound) testosterone, while bariatric surgery was more effective. The increase in serum testosterone was greater in younger and heavier patients, and also in those without T2DM, although multiple regression analysis showed that the degree of weight loss was the best determinant of the increase in testosterone ($P = 0.029$).

Reductions in body weight and WC have been reported in men with obesity and hypogonadism treated with testosterone. A double-blind RCT involving 211 men with T2DM administered long-acting testosterone undecanoate reported statistically significant reductions in body weight, WC, and BMI in men without depression (1062 [EL 1; RCT]). A 14-item Hospital Anxiety and Depression Scale (HADS) identified baseline depression in 31% and anxiety in 18% of these men, without differences in baseline HADS for depression or anxiety between the testosterone and placebo groups. In the men without baseline depression (n = 151), body weight, BMI, WC, and total cholesterol were all significantly improved versus placebo. There was no improvement in body weight, BMI, or WC at 30 weeks in men with baseline depression (n = 48).

Another single-center RCT randomized 50 patients with metabolic syndrome (mean age 57 ± 8 years) to receive either placebo or 1,000 mg of long-acting testosterone undecanoate every 3 months (1063 [EL 1; RCT]). At 1 year, testosterone therapy markedly improved HOMA-IR ($P<0.001$), carotid intima-media thickness ($P<0.0001$), and high-sensitivity C-reactive protein ($P<0.001$) compared to

placebo. After 2 years, the prevalence of metabolic syndrome was reduced to 35% ($P<0.0001$) in testosterone-treated patients. The main determinants of change were declines in WC ($P<0.0001$), visceral fat mass ($P<0.0001$), and HOMA-IR. In middle-aged men (mean age 54.5 years) with obesity (mean BMI 42 kg/m^2) and hypogonadism, 54 weeks of testosterone therapy in addition to diet and exercise significantly improved cardiometabolic risk factors compared to diet and exercise alone, as indicated by primary cardiac endpoints (cardiac ejection fraction, diastolic function, endothelial function, carotid intima-media thickness, and epicardial fat thickness; $P<0.01$ for all parameters) and secondary metabolic endpoints including glycemic (HOMA, $P<0.01$; microalbuminuria, $P<0.01$), lipid (total cholesterol, $P<0.05$), and inflammatory (fibrinogen, $P<0.05$) parameters (1064 [EL 2; PCS]). These cardiometabolic factors reverted back to baseline within 6 months after testosterone cessation.

From 2 large independent registry studies of 261 (1065 [EL 2; PCS]) and 255 (1066 [EL 2; PCS]) men with obesity and hypogonadism, long-term testosterone therapy in 411 men (mean age 58.6 years, range 33-84 years) was shown to be effective for sustained weight loss, irrespective of their baseline weight. Injectable testosterone undecanoate resulted in significant decreases in weight, WC, and BMI over an 8-year period (6 years mean duration of follow-up) (518 [EL 3; SS]). Improvements in weight and BMI were significant and progressive year to year over the entire study period. There were also significant improvements in glycemia (fasting glucose and A1C), lipids (increased HDL-c and decreased total plus LDL cholesterol and triglycerides), and SBP/DBP ($P<0.001$ for all parameters) in each of the 3 BMI categories (class I, II, and III obesity). In addition, the progressive yearly decrements in weight and WC were seen in all men from these 2 registries aged ≤65 years (n = 450) and >65 years (n = 111), with total weight declines from baseline of 13.6 ± 7.6% and 13.3 ± 7.1% for the respective age groups (518 [EL 3; SS]). Treatment with parenteral testosterone undecanoate for up to 6 years also resulted in sustained improvements in body weight, WC, and glycemic control in 156 of these men with both obesity and T2DM (1067 [EL 2; PCS]). Serum A1C levels decreased from 8.1 ± 0.9% at baseline to 6.1 ± 0.7% ($P<0.0001$) following treatment, with significant declines for the first 5 years versus each previous year and approaching significance from years 5 to 6 ($P = 0.06$). In a systematic review and meta-analysis of RCTs in patients with T2DM, testosterone therapy was associated with significant reductions in fasting plasma glucose, A1C, fat mass, and triglycerides, although no significant change was seen in total and HDL cholesterol or BP (515 [EL 2; MRCT, subanalysis of RCTs included]).

In a cohort of 261 men (mean age 58 years) with late-onset hypogonadism treated every 3 months with long-acting testosterone undecanoate, the loss of 3% body weight at 1 year of treatment, a BMI >30 kg/m^2, and a WC >102 cm predicted sustained weight loss over the entire treatment period, regardless of age (1066 [EL 2; PCS]). The benefits of testosterone replacement in elderly men with hypogonadism (mean age 59 years) produced long-term benefits regarding weight loss and improvements in metabolic syndrome traits, including lipids, fasting glucose, A1C, HDL-c, hepatic transaminases, and blood pressure over 5 or more years in prospective observational cohort studies (1065 [EL 2; PCS]; 1068 [EL 2; PCS]; 1069 [EL 2; PCS]; 1070 [EL 2; PCS]). Zitzman and colleagues (1071 [EL 4; NE, abstract]; 1072 [EL 4; NE, abstract]) studied testosterone replacement in 381 men with hypogonadism over a period of up to 16 years. Serum testosterone increased from 5.3 ± 2.1 nmol/L to 15.6 ± 4.1 nmol/L, and body weight decreased from 106.8 ± 16.4 kg to 86.5 ± 12.7 kg by the end of the observation period. The weight loss was associated with a decline in BMI from 32.6 ± 5.5 kg/m^2 to 26.4 ± 3.3 kg/m^2 and significant improvements in glycemic control, lipids, BP, and heart rate. The prevalence of metabolic syndrome declined from 87% of subjects at baseline to 43% at 4 years ($P<0.001$). Long-term metabolic effects were associated with lower concentrations of SHBG, higher testosterone:estradiol ratios, and greater delta increases in serum testosterone.

Long-term testosterone therapy in men with obesity and hypogonadism appears to be safe and may have beneficial urologic outcomes. Significant increases were seen in prostate volume and prostate specific antigen (PSA), and significant decreases were observed in residual bladder volume and the International Prostate Symptoms Score (IPSS), in 162 men (mean age 59.7 ± 8.2 years) with obesity and hypogonadism treated for up to 5 years in a prospective registry study (1073 [EL 4; NE, abstract]). Three men developed prostate cancer after 18, 48, and 51 months of injectable testosterone undecanoate. Similar results for prostate volume, PSA, IPSS, and residual bladder volume were reported in another prospective registry study of 181 men treated for up to 5 years (1074 [EL 4; NE, abstract]). In a 5-year study of testosterone therapy in 20 men (mean age 57 years) with obesity, metabolic syndrome, and hypogonadism, there were no significant differences found in prostate size, PSA, maximal urinary flow, post-void residual volume, or hematocrit levels when compared to 20 matched controls without testosterone administration. Interestingly, the control group had a significantly higher incidence of prostatitis (30% vs. 10%, $P<0.01$) (1075 [EL 2; NRCT]).

To provide recommendations and standard operating procedures based on best evidence for diagnosis and treatment of hypogonadism in men, the endocrine subcommittee of the International Society of Sexual Medicine Standards Committee reviewed the medical literature and then had extensive internal discussions over 2 years, followed by public presentation and discussion with other

experts (1076 [EL 4; NE]). The committee concluded that although association does not mean causation, and follow-up of controlled trials was limited to 3 years, hypogonadism is associated with reduced longevity, risk of fatal CV events, obesity, sarcopenia, frailty, osteoporosis, and other chronic disease states. Their evidence-based recommendations included: (*1*) men with sexual dysfunction, visceral obesity, and metabolic diseases should be screened for hypogonadism and treated if diagnosed; (*2*) young men with hypogonadism should be treated; and (*3*) the risks and benefits of testosterone therapy should be carefully assessed in older men. They also concluded that there is no compelling evidence that testosterone therapy causes prostate cancer or its progression.

- *Q5.10. Is weight loss effective to treat obstructive sleep apnea? How much weight loss would be required?*

Executive Summary

- **R55.** Patients with overweight or obesity and obstructive sleep apnea should be treated with weight-loss therapy including lifestyle interventions and additional modalities as needed, including phentermine/topiramate ER or bariatric surgery; the weight-loss goal should be at least 7 to 11% or more **(Grade A; BEL 1)**.

Evidence Base

Obesity or overweight and obstructive sleep apnea (OSA) are related, and a bidirectional causality has been supported by many clinical studies. The unidirectional effects of weight loss in patients with overweight or obesity on improvement of OSA are provided by certain key clinical studies. The severity of sleep apnea is quantified by the apnea-hypopnea index (AHI), which reflects the average number of apneic/hypopneic episodes per hour during a polysomnography study. The AHI is correlated with the odds ratio for stroke and CVD events and, therefore, predicts adverse clinical outcomes (1077 [EL 2; MNRCT]). Tuomilehto et al (555 [EL 4; NE]) have reviewed strong evidence–level studies (RCTs and select nonrandomized trials) (760 [EL 1; RCT]; 1078 [EL 1; RCT]; 1079 [EL 2; PCS]; 1080 [EL 1; RCT, post-intervention follow-up data]; 1081 [EL 2; PCS]; 1082 [EL 2; PCS]; 1083 [EL 2; RCCS]; 1084 [EL 2; PCS, small N = 8]; 1085 [EL 1; RCT]; 1086 [EL 2; PCS]; 1087 [EL 2; PCS]; 1088 [EL 2; NRCT]; 1089 [EL 2; PCS]; 1090 [EL 2; PCS]; 1091 [EL 2; PCS]; 1092 [EL 2; PCS]; 1093 [EL 2; PCS]; 1094 [EL 2; PCS, only 4 patients in cohort]) and found that lifestyle change (including very low-calorie diet and/or cognitive-behavior intervention) resulting in 7 to 17% weight loss produced a 3 to 68% reduction in the AHI. The strongest of these studies demonstrated OSA improvement with at least 7 to 11% weight loss (759 [EL 1; RCT]; 1080 [EL 1; RCT, post-intervention follow-up data]). However, in the Sleep AHEAD study, significant reductions in the AHI were observed only in the subgroup losing 10% or more body weight (759 [EL 1; RCT]). The 10% weight-loss threshold for AHI reductions of >10 units was corroborated by a meta-analysis by Araghi et al (1095 [EL 2; MNRCT]). In addition, the higher the AHI at baseline, the greater the absolute decrease in AHI with weight loss (1095 [EL 2; MNRCT]).

Medication-assisted weight loss can also be effective in treating OSA. When compared to placebo plus lifestyle intervention, the addition of phentermine/topiramate ER led to greater weight loss and improvements in the AHI from a score of 44.2 at baseline (severe category) to 14.0 (mild category) (1096 [EL 1; RCT]). Liraglutide therapy in 158 patients with diabetes was associated with a 4.3% weight loss over 3 months, together with significant reductions in neck circumference and daytime sleepiness as measured by the Epworth Sleepiness Scale (1097 [EL 3; SS]). Bariatric surgery resulted in 27 to 47% weight loss and a 49 to 98% reduction in the AHI (555 [EL 4; NE]). In another study, LAGB resulted in 20.2% weight loss and a 54% improvement in sleepiness scores (1098 [EL 2; PCS]). However, Dixon et al (1099 [EL 1; RCT]) found that LAGB was not superior to conventional weight-loss programs in patients with OSA as measured by the AHI score. In a post-hoc analysis of an existing RCT on OSA, Sahlman et al (1100 [EL 1; RCT]) demonstrated improvements in several inflammatory mediators with weight loss (mean -10.7 kg weight and -5.1% total fat). The beneficial effects of lifestyle interventions and weight loss on OSA appear to be durable for at least 4 years, according to an analysis of Look AHEAD data performed by Kuna et al (1103 [EL 1; RCT]).

- *Q5.11. Is weight loss effective to treat asthma/reactive airway disease? How much weight loss would be required?*

Executive Summary

- **R56.** Patients with overweight or obesity and asthma should be treated with weight loss using lifestyle interventions; additional treatment modalities may be considered as needed including bariatric surgery; the weight-loss goal should be at least 7 to 8% **(Grade A; BEL 1)**.

Evidence Base

There are several clinical trials supporting the beneficial effects of weight loss on asthma in patients with obesity. Johnson et al (1102 [EL 2; PCS]) found that alternate-day calorie restriction (with an average of 8% weight loss) was associated with improvements in asthma symptoms, QOL, and peak expiratory flow, along with markers of oxidative stress and inflammation. Dandona et al (1103 [EL

2; PCS]) also found significant reductions in expression of key asthma-related genes (interleukin-4, disintegrin, and metalloproteinase 33), tumor necrosis factor (ligand) superfamily member 14, matrix metallopeptidase-9, C-C chemokine receptor type-2, and nitric acid metabolites with a weight loss of approximately 23% after RYGB. In another study, Leao da Silva et al (1104 [EL 2; PCS]) found that leptin levels were a marker for improvements in lung function in adolescents with obesity and asthma undergoing moderate-to-massive weight loss. Weight loss (average 7.5%) can also be associated with improvement in forced vital capacity in patients with obesity and severe asthma through mechanisms unrelated to inflammation (1105 [EL 1; RCT, relatively small sample size N = 22]).

- *Q5.12. Is weight loss effective to treat osteoarthritis? How much weight loss would be required?*

Executive Summary

- **R57.** Patients with overweight or obesity and OA involving weight-bearing joints, particularly the knee, should be treated with weight-loss therapy for symptomatic and functional improvement and reduction in compressive forces during ambulation; the weight-loss goal should be ≥10% of body weight **(Grade A; BEL 1)**. A physical activity program should also be recommended in this setting since the combination of weight-loss therapy achieving 5 to 10% loss of body weight combined with physical activity can effectively improve symptoms and joint function **(Grade A; BEL 1)**.
- **R58.** Patients with overweight or obesity and OA should undergo weight-loss therapy before and after total knee replacement **(Grade C; BEL 2, downgraded due to evidence gaps)**.

Evidence Base

Given the strong association between obesity and OA, investigators have examined whether weight loss is effective for primary prevention and for treatment to improve pain and functionality in patients with the disease. These studies have largely involved OA of the knee (585 [EL 2; PCS]; 1108 [EL 1; RCT]). One study that addressed primary prevention was the Framingham Knee Osteoarthritis Study, which was a nested, case-control study of women who developed symptomatic and radiographic knee OA during a 12-year longitudinal follow-up (1107 [EL 2; PCS]). The subgroups were compared for naturally occurring changes in body weight (i.e., no intervention); both high baseline weight and weight gain significantly increased the odds ratio for OA, and weight loss in women whose BMI was >25 kg/m^2 at baseline significantly diminished OA risk. Specifically, a weight loss of 5.1 kg was associated with a more than 50% reduction in the odds for developing OA.

Several RCTs have been conducted examining the effects of weight-loss interventions on knee OA. These RCTs often employ validated indices of OA severity as a primary outcome measure that includes findings and symptoms related to pain, stiffness, walking distance, stair climbing, and ability to squat (e.g., the Lequesne Index, the Knee Society Score, and the Western Ontario and McMaster Universities osteoarthritis index [WOMAC]). Toda et al (1108 [EL 2; PCS]) observed that diet-induced weight loss significantly improved the Lequesne score, and the improvement was best correlated with reductions in percentage of body fat. Christensen et al (1106 [EL 1; RCT]) found that a reduced-calorie diet produced an 11.1% weight loss and a significant improvement in the WOMAC index score compared with patients randomized to the control diet who experienced a 4.3% weight loss. The authors concluded that for every percent of body fat lost there was a 9.4% improvement in the WOMAC index, and that a weight reduction of 10% was needed to improve functionality. In another study by these authors, patients with obesity and OA were randomized to a very low-calorie diet of 415 kcal/day versus 810 kcal/day; these groups lost 13% and 12% of their body weight, respectively, and both groups noted similar marked improvements in knee and/or hip pain (1109 [EL 1; RCT]). Messier et al (1110 [EL 1; RCT]) randomized OA patients to diet plus exercise or exercise alone, which produced a mean weight loss of 8.5 kg and 1.8 kg, respectively, leading to significant improvements in self-reported disability, knee pain, physical performance measures, and knee strength without significant differences between the diet plus exercise and exercise only groups.

In the Arthritis, Diet, and Activity Promotion Trial (ADAPT), 316 patients with OA were randomized to healthy lifestyle control, diet only, exercise only, and diet plus exercise treatment groups. The diet plus exercise group (weight loss 5.7%) experienced greater benefits than the other treatment arms with significant improvements in physical function, walking distance, stair climb, and knee pain (1111 [EL 1; RCT, single-blinded]). The diet alone (4.9% weight loss) and exercise alone groups were no different from healthy lifestyle controls for most measures. In a subgroup of patients with extensive biomechanical testing, there were significant associations between the degree of weight loss and follow-up values of knee compressive force, resultant force, and abduction and medial rotation moment (1112 [EL 1; RCT, single-blinded]). The results indicated that for each unit of weight loss there was a 4-fold reduction in the load exerted on the knee during walking.

Finally, in the Intensive Diet and Exercise for Arthritis (IDEA) randomized clinical trial, 454 older adults with obesity with OA were randomized to diet and exercise, diet alone, or exercise alone treatment groups, which resulted in weight loss of 11.3%, 9.5%, and 1.9%, respectively (1113

[EL 1; RCT, single-blinded]). Knee compressive forces were lowered only in the diet alone and diet plus exercise groups, and the diet plus exercise group had the largest reduction in the WOMAC index pain score. Importantly, when weight-loss categories of >10%, 5 to 9.9%, and <5% were considered independent of treatment group, it was only those subjects losing >10% body weight who experienced significant improvements in knee compressive force, IL-6 level, pain, and function.

Several meta-analyses have been conducted assessing the efficacy of weight loss in the treatment of OA. Christensen et al (1114 [EL 1; MRCT]) conducted a meta-analysis of RCTs and concluded that a weight loss of >5% at a rate of 0.25% per week (i.e., over 20 weeks) could achieve improvements in the physical disability of OA. A systematic review of all related articles published in 2013 identified 36 prospective controlled studies enrolling participants with a diagnosis of knee or hip OA that were largely nonrandomized (1115 [EL 4; NE]). It was concluded that a high quality of evidence supports the use of diet-induced weight loss combined with exercise to improve the biomechanical outcome measures of OA. Evidence-based guidelines developed by the American College of Rheumatology (1116 [EL 4; NE]), the European League Against Rheumatism (1117 [EL 4; NE]), the American Academy of Orthopedic Surgeons (1118 [EL 4; NE]), the Osteoarthritis Research Society International (1119 [EL 4; NE]), and a systematic review of recommendations and guidelines (1120 [EL 4; NE]) all advocate aerobic and resistance exercise, as well as weight loss, in patients with overweight/obesity and OA.

There are limited data assessing the efficacy of medication-assisted weight loss in the treatment of OA (1121 [EL 4; NE]). In contrast, there are multiple studies examining the effects of bariatric surgery on OA. In 59 consecutive patients followed prospectively after bariatric surgery, there was a significant increase in medial joint space on knee X-rays and clear improvements in the Knee Society Score (KSS) (1122 [EL 2; PCS]). A meta-analysis of studies assessing the effects of bariatric surgery on OA included 13 studies and 3,837 patients, but only 2 studies had a control group; 11 were uncontrolled prospective studies (1123 [EL 4; NE]). All studies measuring intensity of knee pain, knee physical function, and knee stiffness showed a significant improvement after bariatric surgery with weight loss ranging from 14.5 to 35.2%. The quality of evidence was considered low for most of the included studies and moderate for 1 study. The conclusion was that bariatric surgery with subsequent marked weight loss is likely to improve knee pain, physical function, and stiffness in adult patients with obesity, but stressed the need for high-quality studies. A study by Peltonen et al (1124 [EL 3; SS, post-hoc comparison of random sample with previously published sample]) was the one deemed to be of moderate quality in this meta-analysis. It was a case-control study that included bariatric surgery cases enrolled in the SOS study. Weight loss associated with bariatric surgery was associated with a significant improvement in pain, including work-restricting pain, in knees and ankles of men and women with odds ratios of 1.4 to 4.8.

A second systematic review of the literature in patients with obesity undergoing bariatric surgery (1125 [EL 4; NE]) identified 6 studies for analysis; 5 were case series and 1 was the case controlled trial by Peltonen et al (1124). All studies demonstrated improvements in pain, functional scores, and/or joint space width, resulting in a conclusion by these authors that bariatric surgery can benefit patients with knee and hip OA, but that RCTs are also needed.

Obesity is associated with higher rates of treatment involving arthroplasty or knee and hip replacement (1126 [EL 3; SS]; 1127 [EL 3; SS]). Patients with obesity undergoing total knee replacement can experience significant improvements in pain and functionality as assessed using the KSS, the WOMAC index score, or other instruments (1128 [EL 3; SS]; 1129 [EL 3; SS]; 1130 [EL 2; RCCS]; 1131 [EL 3; SS]; 1132 [EL 4; NE]). The clinical and functional scores in patients with obesity are often lower both pre- and postoperatively, but the net improvement after knee replacement can be similar to that in controls without obesity. However, knee replacement surgery in patients with obesity is more often associated with complications such as deep prosthetic infections, impaired wound healing, superficial infections, and deep vein thrombosis (1127 [EL 3; SS]; 1128 [EL 3; SS]; 1129 [EL 3; SS]; 1130 [EL 2; RCCS]; 1131 [EL 3; SS]; 1132 [EL 4; NE]). Patients with severe obesity can experience inferior survival of the prosthesis after total knee replacement compared with patients without obesity (1133 [EL 2; PCS]; 1134 [EL 3; SS]; 1135 [EL 3; SS]), although this has not been consistently observed (1136 [EL 3; SS]; 1137 [EL 4; NE]). For these reasons, weight loss is recommended both before and after knee replacement surgery in patients with overweight and obesity. The evidence base addressing efficacy and safety of knee replacement consists of observational and retrospective analyses.

- *Q5.13. Is weight loss effective to treat urinary stress incontinence? How much weight loss would be required?*

Executive Summary

- **R59.** Women with overweight or obesity and stress urinary incontinence should be treated with weight-loss therapy; the weight-loss goal should be 5 to 10% of body weight or greater **(Grade A; BEL 1)**.

Evidence Base

Intervention studies have reported that weight loss is associated with improvement or resolution of urinary incontinence, with the probability of resolution correlated

to the degree of weight loss once >5% weight loss is achieved. Two prospective cohort studies demonstrated that lifestyle interventions improve the symptoms of stress incontinence in most individuals but that >5% weight loss is required for efficacy (1138 [EL 2; PCS]; 1139 [EL 2; PCS]). Four RCTs have assessed the efficacy of weight loss for the treatment of urinary stress incontinence. In 1 RCT, women with overweight and obesity who were randomized to a 3-month liquid diet lost 16 kg compared with no weight loss in the control group, and experienced a 60% reduction in weekly leakage episodes compared with a 15% reduction in the controls (624 [EL 1; RCT, N = 48]). The benefits were largely confined to those women losing >5% body weight.

In the DPP, the prevalence of urinary incontinence at end of study was 38% in the lifestyle group (greatest amount of weight loss), 48% in the metformin group (intermediate weight loss), and 46% in the placebo group (essentially no change in body weight) (1140 [EL 1; RCT, post-hoc analysis]). The difference between lifestyle and the metformin or placebo groups was greatest in women with stress incontinence as opposed to urge incontinence. In the Look AHEAD study, 27% of T2DM participants reported urinary incontinence (1141 [EL 1; RCT, postintervention follow-up data]). When comparing the ILI group (8 kg weight loss) versus the diabetes support and education control group (1 kg weight loss) at 1 year, fewer women in the intensive group reported urinary incontinence (25.3% vs. 28.6%, $P = 0.05$), and fewer participants without urinary incontinence at baseline experienced urinary incontinence in the intensive group (10.5% vs. 14.0%, $P = 0.02$). Each kilogram of weight loss was associated with a 3% reduction in the odds of developing urinary incontinence ($P = 0.01$), and a weight loss of 5 to 10% reduced these odds by 47% ($P = 0.002$) (1141 [EL 1; RCT, post-intervention follow-up data]).

Finally, the largest and most rigorous RCT was the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study, which enrolled 338 women with overweight or obesity reporting ≥10 episodes of incontinence weekly (1142 [EL 1; RCT]). These patients were randomized to an intensive weight-loss program (including diet, exercise, and behavior modification) or to a structured education control program. After 6 months, the intervention group achieved a mean weight loss of 8.0% compared to 2% in controls, as well as a 47% reduction in incontinence episodes compared to 28% in the control group ($P = 0.01$). This improvement was most marked in women with stress incontinence (57% vs. 33% in controls); the improvement in urge incontinence was not significant. At 12 months in the PRIDE study, the intervention group continued to report greater reductions in weekly stress urinary incontinence episodes (65% vs. 47%, $P<0.001$), and a greater proportion achieved ≥70% decrease in weekly total and stress urinary incontinence episodes (1143 [EL 1; RCT]). At 18 months, the percent weight loss in the intervention group had decreased from 8% at baseline to 5.5%, at which point a greater proportion of women in the weight-loss intervention group continued to have more than 70% improvement in urge incontinence episodes, but there were no significant differences between the groups for stress or total urinary incontinence (1143 [EL 1; RCT]).

Interventional cohort studies employing bariatric surgery have demonstrated improvements in urinary incontinence (622 [EL 2; PCS, N = 12]; 1039 [EL 2; PCS]; 1144 [EL 2; PCS]; 1145 [EL 3; SS]; 1146 [EL 2; PCS]; 1147 [EL 2; PCS]; 1148 [EL 2; PCS]). A systematic review identified 5 interventional cohort studies involving bariatric surgery, all of which reported improvements in stress incontinence symptoms in the clear majority of patients (602 [EL 2; MNRCT]). In 1 such study, gastric bypass surgery in 1,025 patients (78% women) produced a decrease in mean BMI from 51 to 33 kg/m^2 and a decrease in urinary incontinence from 23% of the patients affected at baseline to only 2% of patients 1 to 2 years postoperatively (1145 [EL 3; SS]).

- *Q5.14. Is weight loss effective to treat gastroesophageal reflux disease (GERD)? How much weight loss would be required?*

Executive Summary

- **R60.** All patients who have overweight or obesity and who have gastroesophageal reflux should be treated using weight loss; the weight-loss goal should be 10% of body weight or greater **(Grade A; BEL 1)**.
- **R61.** PPI therapy should be administered as medical therapy in patients who have overweight or obesity and who have persistent gastroesophageal reflux symptoms during dietary and weight-loss interventions **(Grade A; BEL 1)**.
- **R62.** Roux-en-Y gastric bypass should be considered as the bariatric surgery procedure of choice for patients who have obesity and moderate to severe gastroesophageal reflux symptoms, hiatal hernia, esophagitis, or Barrett's esophagus **(Grade B; BEL 2)**. Intragastric balloon for weight loss may increase gastroesophageal reflux symptoms and should not be used for weight loss in patients with established gastroesophageal reflux **(Grade A; BEL 1)**.

Evidence Base

The standard dietary treatment for GERD is to refrain from eating before going to sleep, avoid foods and beverages that trigger gastroesophageal reflux symptoms, and lose weight (1149 [EL 4; NE]). Other treatment measures have been used for persistent GERD symptoms, including elevation of the head of the bed during sleep and administration of medical therapy to suppress gastric acid. A randomized trial used breathing exercises as intervention

to induce a change from thoracic to abdominal breathing in an attempt to retrain the diaphragm and potentially strengthen the LES. Subjects had improvement in gastroesophageal reflux and esophageal pH with less PPI use and had an improved overall quality of life (1150 [EL 2; PCS]). In a 2006 systematic review of treatment modalities for GERD, only 16 of 100 clinical trials met inclusion criteria; trials had to contain a lifestyle intervention and outcomes of GERD measures (i.e., heartburn symptoms, ambulatory esophageal pH monitoring, and esophageal manometry) (1151 [EL 4; NE]). Evaluating the best available evidence at the time (cohort or case-controlled studies), head of bed elevation and left lateral decubitus position during sleep improved the overall time of esophageal pH <4, whereas weight loss improved both esophageal pH and GERD symptoms. In this review, there was no evidence found to support an improvement in gastroesophageal reflux after dietary interventions, alcohol cessation, or smoking cessation. Nadaleto and colleagues (1152 [EL 4; NE]) commented on 10 weight-loss trials for GERD treatment. Of these studies, 8 reported successful treatment of GERD (625 [EL 2; PCS]; 1153 [EL 1; RCT]; 1154 [EL 2; PCS]; 1155 [EL 1; RCT]; 1156 [EL 2; PCS]; 1157 [EL 1; RCT]; 1158 [EL 2; PCS]; 1159 [EL 1; RCT]) as determined by symptoms (625 [EL 2; PCS]; 1156 [EL 2; PCS]; 1157 [EL 1; RCT]; 1158 [EL 2; PCS]), esophageal pH monitoring (1154 [EL 1; RCT]; 1155 [EL 1; RCT]; 1159 [EL 1; RCT]), or both (1153 [EL 2; PCS]). Two trials were not successful (1160 [EL 2; PCS]; 1161 [EL 1; RCT, small N = 20]). It is important to note that most of these studies had small subject numbers, and many were of short duration, with only 4 studies >6 months (625 [EL 2; PCS]; 1155 [EL 1; RCT]; 1156 [EL 2; PCS]; 1161 [EL 1; RCT, small N = 20]) and 3 studies ≥12 months (1157 [EL 1; RCT]; 1158 [EL 2; PCS]; 1159 [EL 1; RCT]).

Patients identified with GERD by standardized questionnaire scoring and having symptoms for at least 6 months were recruited to assess the effect of weight loss in the presence of normal or mild (grade 1 Savary-Miller) esophagitis (1156 [EL 2; PCS]). None of the 34 patients were taking medical therapy for GERD and all were advised to lose weight, even though the mean BMI was 23.5 ± 2.3 kg/m^2. Eighty percent of patients lost a mean weight of 4 kg and experienced a 75% reduction of GERD symptoms, with a significant direct correlation between weight loss and GERD symptom scores.

Smith and colleagues (1157 [EL 1; RCT]) studied the effect of weight loss in 33 patients with cough diagnosed as secondary to airway reflux. There was a significant association between a high-calorie and high-fat diet and cough. Subjects had a mean BMI of 34 kg/m^2 (range 26.0 to 50.8 kg/m^2) and were randomized to either traditional dietary modification (i.e., avoidance of spicy foods, coffee, alcohol, and high-fat foods without regard to calories) or a weight-loss diet (600 calories below daily estimated energy requirements). Both groups lost significant weight, with BMI declines of 1.2 kg/m^2 for the traditional diet group and 1.3 kg/m^2 for the weight-loss diet group. Thus, weight loss, regardless of the diet, resulted in a significant reduction in gastroesophageal reflux–related cough symptoms.

The Nord-Trøndelag Health Study (HUNT study) was a prospective, population-based, cohort study of 29,610 adults who completed a questionnaire on heartburn and acid regurgitation over 2 periods (1995-1997 and 2006-2009) (1158 [EL 2; PCS]). Logistic regression analysis (stratified by anti-reflux medication and adjusted for age, gender, smoking, alcohol, education, and exercise) showed that weight loss was directly associated with a reduction of gastroesophageal reflux symptoms and increased treatment success with anti-reflux medication. Among people with a decrease in BMI >3.5 kg/m^2, the adjusted OR for resolution of any minor or severe gastroesophageal reflux symptoms was 1.98 (95% CI, 1.45-2.72) when using no anti-reflux medication or using it less than weekly, and 3.95 (CI, 2.03-7.65) when using anti-reflux medication at least weekly.

Singh and colleagues (625 [EL 2; PCS]) reported on a prospective cohort study of 332 subjects with obesity or overweight who were prospectively enrolled in a structured weight-loss program. Weight-loss strategies included dietary modifications, increased physical activity, and lifestyle behavioral changes. The baseline mean body weight (101 ± 18 kg), BMI (35 ± 5 kg/m^2), and waist circumference (103 ± 13 cm) were reassessed at 6 months, and 97% of subjects lost an average of 13 ± 7.7 kg. Overall, there was a significant decrease in the prevalence of GERD (15% vs. 37%, P<0.01), an 81% reduction in gastroesophageal reflux symptom scores, and a significant correlation between weight loss and reduced gastroesophageal reflux symptom scores. A total of 15% and 65% of subjects had partial and complete resolution of reflux symptoms, respectively.

In contrast to diet-induced weight loss, there is a dearth of data addressing the efficacy of weight loss assisted by medications approved for the chronic treatment of obesity. Some medications with a high rate of GI side effects (e.g., orlistat, liraglutide) can be associated with symptoms of dyspepsia, but it is unclear if these symptoms are caused by gastroesophageal reflux.

Esophageal pH monitoring was performed before and after a 4-month treatment with an energy-restricted diet, physical exercise, and intragastric balloon or sham placement in a randomized double-blind study of 17 young patients with marked obesity (166.5 kg, BMI 55 kg/m^2) (1154 [EL 1; RCT]). Five patients had pathologic gastroesophageal reflux at baseline, among which 3 reversed to normal and 2 remained abnormal, with 1 patient developing reflux de novo. Only marked weight loss appeared to have an effect on reflux in this short study. A double-blind

RCT studied 42 patients (BMI 43.4 kg/m^2) with GERD who received an intragastric balloon or sham treatment for 13 weeks, followed by intragastric balloon placement in all subjects for the remaining year (1159 [EL 1; RCT]). Baseline 24-hour pH monitoring identified reflux in 52% of subjects, pathologic total time of gastroesophageal reflux in 40%, and 19% with combined total, upright, and supine reflux. Esophageal acid exposure was related to BMI and visceral fat distribution. At 13 weeks, a reduction in acid reflux was observed by pH monitoring in sham-treated subjects who lost weight, whereas supine and total gastroesophageal reflux increased in the balloon-treated group. In addition, in initial sham-treated subjects, acid reflux worsened after balloon placement. Following balloon removal after 52 weeks, reflux improved. In another double-blind RCT of sham versus intragastric balloon placement, manometry and 24-hour pH measurements were performed in 32 patients at baseline and after 4 months, followed by 4 months of balloon treatment in all subjects (1155 [EL 1; RCT]). At baseline, LES dysfunction was identified in 22% of subjects, and increased upright and supine reflux was observed in 25% of patients. At 4 months, sham treatment resulted in 9.7% weight loss, improved LES function (increased LES length and higher LES pressure), and significantly decreased reflux. These values deteriorated in the subsequent 4 months after balloon placement, with a significant increase in gastroesophageal reflux (upright, supine, and total) and esophageal lesions, despite an overall 17.8% weight loss at 8 months. The initial balloon treatment group had a 9.9% weight loss at 4 months, similar to the sham-treated group, but with significantly increased (supine) reflux. During the second 4-month balloon period in this group, LES and reflux values returned toward baseline values, and the overall weight loss was 13.8% at 8 months.

PPI administration to decrease gastric acid production is the main pharmacologic treatment for gastroesophageal reflux symptoms. Several studies have assessed the efficacy of PPI therapy in patients with obesity and GERD. A study of patients with GERD who were all receiving the same PPI once or twice daily for at least 3 months were divided into 3 groups: patients who fully responded to once-daily PPI (group A); those who failed to respond to once-daily PPI therapy (group B); or those who received twice-daily PPI therapy (group C) (1162 [EL 3; SS]). A total of 245 patients were found to have significant cross-group differences (A vs. B vs. C) for hiatal hernia (33% vs. 51% vs. 52%), erosive esophagitis (19% vs. 51% vs. 30%), cough (24% vs. 44% vs. 43%), and *H. pylori* (25% vs. 33% vs. 48%). No differences were detected in BMI across patient groups, although group B had a greater proportion of subjects with obesity compared to groups A and C.

In another study of 1,888 patients with GERD and either normal or overweight status (mean BMI 26.4 ± 4.8 kg/m^2), the presence of male gender, lower baseline anxiety and depression scores, erosive GERD, and greater BMI were all associated with a positive response to PPIs after 8 weeks of therapy (1163 [EL 2; PCS]). Patients with concurrent irritable bowel symptoms had a significantly poorer response, whereas age, *H. pylori* status, and esophagitis grade had no influence on response to PPI treatment. Predominant reflux symptom and symptom subgroups were not predictive of PPI effectiveness in a prospective parallel randomized study of 105 patients with normal endoscopy and negative *H. pylori* status (1164 [EL 1; RCT]). Subjects were assessed by esophageal manometry and 24-hour pH monitoring before randomization to PPI or placebo. The positive response rate was 35.7% for the PPI group and 5.7% for the placebo group, and the only independent predictors of PPI response were BMI and LES pressure.

Obesity did not appear to alter the effectiveness of a single dose of PPI in the suppression of acid reflux as assessed by gastric pH monitoring in a double-blind RCT involving 18 patients with obesity and asymptomatic GERD (1165 [EL 1; RCT]). PPI administration resulted in higher gastric pH (percent time >pH 3 and 4) and a lower number of nocturnal acid breakthrough episodes than placebo.

Two post-hoc analyses were performed on pooled data from multicenter, double-blind, RCTs of PPI therapy in patients with nonerosive (n = 704) and erosive (n = 11,027) GERD to evaluate the effect of obesity on symptom resolution and healing of erosions (651 [EL 1; MRCT]). No significant association between baseline heartburn severity and BMI was observed in the group with nonerosive reflux. Significantly higher rates of erosive esophageal reflux were present in patients with overweight or obesity compared to those of normal weight. The percent of patients who achieved heartburn resolution and erosion healing with PPIs was similar across BMI categories. Heartburn resolution was significantly associated with PPI administration, increasing age, and male gender. Esophageal erosion healing was significantly associated with PPI therapy, increasing age, presence of a hiatal hernia, and lower erosion grade at baseline. Although PPI therapy is effective in treating GERD in patients with overweight or obesity, different PPIs can have variable effects on acid suppression (1165 [EL 1; RCT]; 1166 [EL 1; RCT, post-hoc analysis]), esophageal erosion healing (651 [EL 1; MRCT]; 1167 [EL 1; RCT, post-hoc analysis]), and heartburn symptom relief (651 [EL 1; MRCT]; 1167 [EL 1; RCT, post-hoc analysis]).

Two recent publications reviewed the literature on the efficacy of bariatric surgery for the treatment of GERD and reported that bariatric procedures have various outcomes on the symptomatic relief of GERD, with RYGB considered the most effective surgery for treatment of GERD (1152 [EL 4; NE]; 1168 [EL 4; NE]).

LAGB can result in normalization of esophageal pH and improve, and even resolve, GERD symptoms.

However, worsening or new GERD symptoms and esophagitis can occur during long-term follow-up. The effect of LAGB on GERD outcomes based on BMI status was reported by Woodman and colleagues (626 [EL 2; PCS]) after a 2-year follow-up of 395 patients (43% with GERD at baseline) in a prospective study. Complete resolution of GERD was reported in 80% of patients, and symptoms were reported as improved in 11%, unchanged in 7%, and worsened in 2% of patients. Baseline BMI was not significantly different among the GERD response categories (resolved, improved, and stable/worse), and there were no significant differences in the reduction of BMI or %EWL between responder groups. Patients randomly assigned to either LAGB or laparoscopic vertical banded gastroplasty (LVBG) were evaluated for GERD and esophageal function using a clinical GERD related QOL scale, esophageal manometry, 24-hour pH monitoring, and upper endoscopy (1169 [EL 1; RCT]). At 1 year, GERD had developed in 26% of LAGB patients and 22% of LVBG patients. In most of these patients, GERD resulted from pouch dilation or poor compliance, and 13 patients required reoperation (LAGB, 10; LVBG, 3). A total of 71 of these patients completed a 96-month follow-up, and 11.5% of LAGB patients and 9% of LVBG patients required PPI therapy.

In a review of 20 studies comprising a total of 3,307 patients with LAGB, the prevalence of GERD symptoms decreased from 32.9% (range, 16 to 57%) to 7.7% (range, 0 to 26.9%), and medication use declined from 27.5% to 9.5% after surgery (627 [EL 2; MNRCT]). In addition, LES pressures increased, LES relaxation decreased, pathologic gastroesophageal reflux decreased (from 55.8% to 29.4% of patients), and esophagitis declined (from 33.3% to 27% of patients). However, new GERD symptoms and new esophagitis developed in 15% (range, 6 to 20%) and 22.9% (range, 0 to 38%) of study patients, respectively.

A systematic review of laparoscopic sleeve gastrectomy (LSG) in 2011 identified 2 primary GERD outcome studies and 13 secondary GERD outcome studies. Only 11 of these studies reported on both pre- and postoperative GERD, of which 7 reported a decrease and 4 reported an increase in GERD after LSG (628 [EL 2; MNRCT]).

Howard and colleagues (1170 [EL 3; SS]) reported on a retrospective review of the effect of LSG in patients with GERD. Using a GERD standardized questionnaire score, 28 patients (166 kg and BMI 55.5 kg/m^2) were interviewed to evaluate their GERD symptoms, and all patients had both pre- and postoperative upper GI radiographic swallow studies. The mean %EWL was 40% (range, 17 to 83%) during a mean follow-up of 32 weeks (range, 8 to 92 weeks). After LSG, there was a 64% decline in GERD symptoms. However, 22% of patients reported new-onset GERD symptoms despite receiving daily antireflux therapy, and new-onset GERD was present on 18% of postoperative upper GI radiographs. In contrast, a 2-year prospective clinical study of 71 patients reported a low occurrence of new-onset reflux after LSG (1171 [EL 2; PCS]). Gastroesophageal function was evaluated using a validated symptom questionnaire, upper endoscopy, esophageal manometry, and 24-hour pH monitoring with patients divided into pathologic and normal pH groups. In the group with normal esophageal pH prior to LSG, de novo GERD occurred in only 5.4% of patients. In patients with pathologic reflux, the GERD symptom score significantly decreased from 53 to 13, as did total acid exposure (% pH <4) from 10.2% to 4.2%. No significant changes in LES pressure or esophageal peristalsis amplitude were found in either group.

Carabotti and colleagues (629 [EL 3; SS]) used a validated symptom questionnaire to separate upper GI symptoms in 97 patients after LSG into either GERD or dyspepsia, the latter subdivided into epigastric pain and postprandial distress. Before LSG, 53% of patients were asymptomatic, 27% had GERD, and 8% had dyspepsia. After a median of 13 months, 92% of patients reported upper GI symptoms, the most prevalent being postprandial distress (59%). The prevalence of GERD was not different before and after LSG. The only symptom strongly related to LSG was dysphagia (OR, 4.7; CI, 1.3-20.4; $P = 0.015$), which was present in 20% of the patients and more highly associated with postprandial distress than GERD. Both GERD and postprandial dyspepsia responded poorly to PPI therapy after LSG.

Hiatal hernia may affect GERD outcomes following LSG. In a study of 378 patients receiving pre-operative evaluation for LSG, symptomatic GERD was present in 15.8% and hiatal hernia in 11.1% of patients (630 [EL 2; PCS]). Intra-operatively, 14.5% of patients were diagnosed with hiatal hernia, for a total of 97 patients (26%) receiving LSG plus hiatal hernia repair. The mean follow-up was 18 months, and GERD remission occurred in 73.3% of patients after LSG. In the remaining patients, anti-reflux medications were diminished with complete control of symptoms in about one-third of these patients. Of note, de novo GERD symptoms developed in 23% of patients with LSG alone compared with no patients having LSG plus hiatal hernia repair. In this study, identification and repair of hiatal defects at the time of LSG had a significant impact on new-onset GERD after surgery. In a study evaluating GERD symptoms and erosive esophagitis in patients receiving LSG, the prevalence of hiatal hernias as evaluated by esophagogastroduodenoscopy (EGD) was reported to increase significantly after LSG (6.1% vs. 27.3%), and it occurred significantly more frequently in patients with erosive esophagitis after LSG (36.4% vs. 9.1%) (1172 [EL 2; PCS]). These 66 patients had significant decreases in mean values for BMI (36.3 vs. 25.8 kg/m^2), WC (109.5 vs. 85.7 cm), and metabolic syndrome (54.5% vs. 7.6%). However, significant increments in the prevalence of GERD symptoms (12.1% vs. 47%) and esophageal erosions (16.7% vs. 66.7%) were observed after LSG.

Contrary results on the beneficial effects of LSG on GERD symptoms have been reported elsewhere (1173 [EL 2; PCS]). GERD outcomes were studied in 78 patients following LSG with hiatal hernia repair compared to 102 patients without hiatal hernia undergoing only an LSG procedure. All patients received a GERD standardized symptom questionnaire, a double-contrast barium swallow radiograph, and an upper endoscopy before and at least 6 months after surgery. The prevalence, frequency, and intensity of GERD symptoms did not differ between the 2 groups at baseline. At follow-up, the LSG-only group had a significant decrease in the prevalence of typical GERD symptoms ($P = 0.003$), while the LSG plus hiatal hernia repair group reported a significantly higher heartburn frequency and intensity score ($P = 0.009$).

Some authors suggest that the differences observed in the literature for LSG outcomes in GERD may be related to surgical technique resulting in differences in the resulting gastric sleeve shape. Routine upper GI imaging was performed on postoperative day 1 or 2, and the radiographs were reviewed and classified as upper pouch, lower pouch, tubular, or dumbbell shape by 4 radiologists blinded to outcomes (interobserver agreement for the sleeve shape classification was 76.3%) (1174 [EL 2; PCS]). Sleeve shapes for the 110 patients studied (mean age 46 ± 12 years, mean BMI 45.1 ± 6 kg/m^2) were tubular (37%), dumbbell (32%), lower pouch (22%), and upper pouch (8%). The %EWL at 1, 3, and 6 months was 16.8%, 29.9%, and 39.1%, respectively, and was not affected by sleeve shape. After LSG, the mean reflux score was 5.7 ± 8, and the upper pouch shape was associated with greater severity of reflux symptoms.

Lazoura and colleagues (1175 [EL 2; PCS]) retrospectively studied upper GI gastrografin images obtained routinely on the third day after LSG to assess GERD symptoms and gastric sleeve shape. A total of 85 patients (82% women, mean age 40, mean BMI 42 kg/m^2) were evaluated for symptoms of GERD (heartburn, regurgitation, and vomiting) before LSG and postoperatively at 1, 6, and 12 months. Three radiologic patterns of the gastric sleeve shape were identified as tubular (66%), upper pouch (26%), and lower pouch (8%). Patients reported a nonsignificant tendency toward relief of heartburn for any sleeve pattern, and regurgitation and vomiting were significantly increased in patients with the tubular gastric shape.

Daes and colleagues (631 [EL 2; PCS]) suggest that narrowing of the distal sleeve, hiatal hernia, and dilation of the fundus predispose to GERD after LSG, and careful attention to surgical technique can result in significantly reduced GERD symptoms after LSG without predisposing patients to de novo GERD symptoms. In their study group of 234 patients having LSG, 49.2% (n = 66) of patients were diagnosed with GERD pre-operatively, and 25.3% (n = 34) were found to have hiatal hernia intra-operatively. Only 2 patients (1.5%) had GERD symptoms at the 1-year follow-up. These authors more recently reported on 382 patients that completed a standard evaluation before LSG and were followed prospectively at a single center (632 [EL 2; PCS]). GERD was diagnosed in 44.5% (n = 170) of patients pre-operatively, and hiatal hernia was detected in 37.2% (n = 142) of patients intra-operatively. After 22 months, only 2.6% (n = 10) of patients had GERD symptoms, and 94% of patients with GERD symptoms before LSG became asymptomatic.

RYGB has been shown to provide excellent long-term treatment for symptomatic GERD in patients with obesity. A study of 152 patients assessed changes in GERD symptoms, QOL, and patient satisfaction after RYGB surgery (1176 [EL 3; SS]). The mean BMI was 48 kg/m^2 and the mean %EWL was 68.8% at 12 months. After surgery, there were significant decreases in GERD-related symptoms, including heartburn (87% to 22%, $P<0.001$), water brash (18% to 7%, $P<0.05$), wheezing (40% to 5%, $P<0.001$), laryngitis (17% to 7%, $P<0.05$), and aspiration (14% to 2%, $P<0.01$). Medication use decreased significantly for both PPIs (44% to 9%, $P<0.001$) and histamine-H2-blockers (60% to 10%, $P<0.01$), physical function improved (87% vs. 71%; $P<0.05$), and overall patient satisfaction was 97% after RYGB.

In a study of 150 Chinese patients, GERD questionnaires and EGD were used to define the efficacy of RYGB for the treatment of GERD among 300 age- and gender-matched controls (1177 [EL 2; PCS]). Patients with obesity before surgery had a higher frequency of gastroesophageal reflux symptoms (16% vs. 8%, $P = 0.01$) and erosive esophagitis (34% vs. 17%, $P<0.01$) than controls. After RYGB, 26 patients completing reassessment at 1 year had significant reductions in weight, reflux symptoms (19% vs. 0%, $P = 0.05$), and erosive esophagitis (42% vs. 4%, $P<0.01$). In another study, 20 patients (16 women, mean age 38.9 ± 6.9 years, mean BMI 48.5 ± 6.2 kg/m^2) were assessed before and 6 months after RYGB for GERD symptoms using a standardized questionnaire, esophageal manometry, and ambulatory 24-hour pH monitoring (1178 [EL 2; PCS]). Mean weight loss was 42.5 ± 9.7 kg ($P<0.001$) and mean BMI was 33.2 ± 4.5 kg/m^2 at 6 months, with a significant improvement in reflux symptoms, percent time pH <4, LES pressure, and esophageal body amplitude.

A prospective study defined reflux symptoms as esophageal or extra-esophageal based on the Montreal Consensus in 86 patients (61 women; mean age 38 ± 12 years, mean BMI 45 kg/m^2, range 35 to 68 kg/m^2), and assessed patients before and 6 months after RYGB surgery (633 [EL 2; PCS]). Heartburn, regurgitation, and dysphagia were scored using a validated GERD symptoms questionnaire, and typical reflux syndrome was defined in the presence of either troublesome heartburn or regurgitation. Esophageal acid exposure and gastric pouch acidity were evaluated by endoscopy, esophageal manometry, and esophageal 24-hour pH monitoring. Extra-esophageal syndromes were present in 16 patients pre-operatively

and in 1 after RYGB. The prevalence of GERD was 64% before and 33% after RYGB. Typical reflux syndrome was present in 55% (n = 47) of patients pre-operatively and resolved in 79% (n = 39) of patients, with symptom complaint changing from heartburn before surgery (96%) to regurgitation (64%) after surgery, and 4 (10%) patients developed symptoms de novo. Inflammation of the esophageal mucosa improved in 27, was unchanged in 51, and worsened in 8 patients. Total acid exposure decreased, use of PPIs decreased, and GERD-related well-being improved 6 months after RYGB surgery. Whether regurgitation post-RYGB corresponds to reflux or poor eating habits deserves further investigation.

Resiliency of RYGB surgery in the treatment of GERD was assessed by data gathered prospectively using a standardized questionnaire inquiring about the presence and frequency of GERD symptoms in 606 patients (mean age 43 years, mean BMI 51 kg/m^2) (1179 [EL 2; PCS]). Of these, 239 patients (39%) reported GERD symptoms pre-operatively and 139 patients completed a long-term follow-up (mean 19 months). After RYGB, the %EWL was 18% at 3 months and progressed to 75% at 19 months. Frequency of GERD symptoms improved in 94% of patients, 2% reported no change, and 4% reported worse symptoms. There was no difference in GERD improvement or worsening at the long-term follow-up compared to symptoms at 3 months. Similarly, medication use decreased significantly at 3 months (30% to 3%) and was sustained long-term with only 5% of patients using anti-reflux medications at the end of the study.

Variable improvements in GERD have been reported following all bariatric procedures, but RYGB appears superior to both LAGB and LSG procedures. The Bariatric Outcomes Longitudinal Database is a prospective database of patients that underwent bariatric surgery by a surgeon in the American Society of Metabolic and Bariatric Surgery Center of Excellence program (1180 [EL 2; PCS]). GERD is graded on a 6-point scale, from 0 (no history of GERD) to 5 (prior surgery for GERD). Patients with GERD severe enough to require medications (grades 2, 3, and 4) are identified, and the resolution of GERD is noted based on a 6-month follow-up. Of a total of 116,136 patients, 36,938 patients had evidence of GERD pre-operatively. After excluding patients having concomitant hiatal hernia repair or fundoplication, a total of 22,870 patients remained with a 6-month follow-up (82% women, mean age 47.6 ± 11.1 years, mean BMI 46.3 ± 8.0 kg/m^2). The mean pre-operative GERD score improved for all patients after bariatric surgery: RYGB score from 2.80 to 1.33, LAGB score from 2.77 to 1.63, and LSG score from 2.82 to 1.85 (all comparisons P<0.0001). GERD score improvement was best in patients after RYGB (56.5%; 7,955/14,078), followed by LAGB (46%; 3,773/8,207), and then LSG surgery (41%, 240/585).

A retrospective review of the Bariatric Outcomes Longitudinal Database compared GERD symptoms in patients having either LSG or RYGB surgery (634 [EL 2; RCCS]). GERD symptoms preexisted in 44.5% of the LSG cohort (n = 4,832), and 84% continued to have symptoms postoperatively, with 8.6% developing GERD de novo. In comparison, GERD preexisted in 50.4% of the RYGB cohort (n = 33,867) and resolved in 63% of patients within 6 months (P<0.001). Among the LSG cohort, the presence of pre-operative GERD was associated with increased postoperative complications (15.1% vs. 10.6%), adverse GI events (6.9% vs. 3.6%), and increased need for revision surgery (0.6% vs. 0.3%). Of importance, the presence of GERD had no effect on weight loss after RYGB but was associated with decreased weight loss in the LSG group. In summary, LSG did not reliably relieve or improve GERD symptoms and induced GERD in some previously asymptomatic patients, and thus, LSG may be a relative contraindication for patients with GERD.

Reoperative (redo) fundoplication has been the mainstay of treatment for failed fundoplication procedures. However, RYGB has been shown to provide excellent control of GERD as a redo procedure for patients with persistent symptoms after either previous bariatric or other anti-reflux procedures. Eight women (mean age 49.5 years and BMI 36.3 kg/m^2) with prior LVBG (mean 132 months prior) with persistent symptoms of GERD were converted to RYGB, with acid reflux quantified using 48-hour (Bravo capsule) measurements (1181 [EL 2; PCS, only 8 patients]). The average time to follow-up after RYGB was 46.6 days and the resulting mean BMI was 32.7 kg/m^2. All patients had improved clinical symptoms (DeMeester scores), none returned to former PPI use, and the total time with pH <4 was reduced from 18.4% to 3.3%.

In another small group of patients having conversion from LSG to RYGB, a retrospective analysis was performed to assess outcomes for weight loss, T2DM resolution, and relief of gastroesophageal reflux symptoms (1182 [EL 3; SS]). The mean interval between the 2 procedures was almost 2 years for 18 patients who underwent operative conversion for reasons of insufficient weight loss (n = 9), severe reflux (n = 6), and persistence of T2DM (n = 3) with a median follow-up of 15.5 months. Weight loss was significantly improved (mean % excess BMI lost after RYGB was 65% vs. 47% before conversion) and all reflux symptoms were immediately relieved without any anti-reflux medication required at the end of follow-up.

A retrospective review of a prospective database identified 183 patients having either redo fundoplication (n = 119, 78 women, mean age 54.1 years) or RYGB (n = 64, 35 women, mean age 54.8 years) as the redo procedure for persistent symptomatic GERD (1183 [EL 2; PCS, retrospective review of database]). Data analyzed included demographics, esophageal manometry, 24-hour

pH monitoring, type of procedure, perioperative findings, complications, pre- and postoperative symptom (heartburn, regurgitation, dysphagia, and chest pain) scores (scale 0 to 3), and patient satisfaction score (scale 1 to 10, grade 2 and 3 scores considered to be significant). Patients who underwent RYGB had a significantly higher BMI and higher pre-operative severity of heartburn and regurgitation compared to the redo fundoplication group. Three-year follow-up data was available for 132 of the 183 patients (n = 89 fundoplication, n = 43 RYGB). Symptom severity significantly improved after both procedures, with the exception of more dysphagia in the RYGB group. Overall, there was no significant difference in patient satisfaction between the 2 groups, but satisfaction was greater with RYGB in a subset analysis of patients who had greater obesity or esophageal dysmotility.

Another retrospective review of 105 patients with prior anti-reflux operations assessed outcomes following RYGB as the redo surgery for intractable GERD (1184 [EL 3; SS]). During a mean follow-up time of 23.4 months, the median BMI decreased from 35 to 27.6 kg/m^2 (P<0.0001), the mean dysphagia score (ranging from 1 = no dysphagia to 5 = unable to swallow saliva) decreased from 2.9 to 1.5, and overall satisfaction was classified as excellent (using the GERD health-related quality of life [HRQL] instrument). The effect of surgery on the treatment of both short-segment and long-segment Barrett's esophagus was studied prospectively after 3 procedures: (*1*) calibrated fundoplication + posterior gastropexy (CFPG), (*2*) fundoplication + vagotomy + distal gastrectomy + Roux-en-Y gastrojejunostomy (FVDG-RYGB), and (*3*) laparoscopic RYGB in patients with obesity (1185 [EL 2; PCS]). Acid reflux was diminished after all 3 procedures. Persistence of GERD symptoms and erosive esophagitis was observed in 15% and 20% of patients, respectively, with short-segment Barrett's who had CFPG. Both GERD symptoms and erosive esophagitis improved in patients with long-segment Barrett's after FVDG-RYGB and RYGB procedures, the latter without any significant change in LES pressure. RYGB also resulted in a significant reduction in BMI (41.5 ± 4.3 kg/m^2 to 25.7 ± 1.3 kg/m^2) after 1 year. Thus, RYGB surgery has reported effectiveness for significantly improving reflux symptoms, erosive esophagitis, and Barrett's esophagus, in addition to weight loss, and is the procedure of choice for recalcitrant GERD in patients with obesity.

- *Q5.15. Is weight loss effective to improve symptoms of depression? How much weight loss would be required? (Table 8 in Executive Summary)*

Executive Summary

- **R63.** Patients with overweight or obesity and depression interested in losing weight should be offered a structured lifestyle intervention **(Grade A; BEL 1)**.

Evidence Base

There has been a long-standing debate regarding the relationship between weight loss and depression. Some studies suggest exacerbation of depression by obesity while others suggest attenuation of depressive symptomatology. Early studies conducted in the 1950s suggested that weight loss may be associated with increased depressive symptomatology (1186 [EL 2; PCS]; 1189 [EL 4; NE]), thus, a multitude of studies have been conducted over recent decades to assess the impact of weight loss on psychological outcomes, including depression in individuals with overweight and obesity seeking to lose weight (1188 [EL 4; NE]; 1191 [EL 4; NE]). Most of these studies have found that depressive symptoms improve with intentional weight loss (1190 [EL 1; MRCT]); however, challenges exist in interpreting the literature due to the variability in study design and the weight-loss intervention employed to test the hypothesis (1191 [EL 1; RCT]; 1192 [EL 1; RCT]; 1193 [EL 1; RCT]; 1194 [EL 1; RCT, N = 24]; 1195 [EL 1; RCT]; 1196 [EL 2; PCS]; 1197 [EL 1; RCT]; 1198 [EL 1; RCT]; 1199 [EL 2; PCS]; 1200 [EL 1; RCT]; 1201 [EL 1; RCT, N = 25]; 1202 [EL 1; RCT]; 1203 [EL 1; RCT]; 1204 [EL 1; RCT]; 1205 [EL 1; RCT]; 1206 [EL 1; RCT]; 1207 [EL 1; RCT]; 1208 [EL 1; RCT]; 1209 [EL 1; RCT]; 1210 [EL 1; RCT]; 1211 [EL 1; RCT]; 1212 [EL 1; RCT]; 1213 [EL 1; RCT]; 1214 [EL 2; PCS, post-hoc analysis]; 1215 [EL 1; RCT]; 1216 [EL 1; RCT]). These studies vary greatly with regard to: (*1*) the number of research subjects (ranging from 15 to 535, other than the Look AHEAD study that involved 5,145 patients) with overweight or obesity and T2DM; (*2*) BMI range (mean range 25.1 to 50.2 kg/m^2); (*3*) age range (31.2 to 58.9 years); (*4*) interventions used (lifestyle modification, dietary intervention, including meal replacement, exercise, pharmacotherapy, and bariatric surgery); and (*5*) methodology used to assess depressive symptomatology (the 2 measures most frequently used were the Beck Depression Inventory I and II [BDI and BDI-II] and the HADS). Most studies have demonstrated that lifestyle modification, dietary intervention, exercise, and bariatric surgery all improve depressive symptoms (670 [EL 1; RCT]; 1191 [EL 1; RCT]; 1193 [EL 1; RCT, N = 24]; 1194 [EL 1; RCT]; 1195 [EL 2; PCS]; 1199 [EL 1; RCT]; 1200 [EL 1; RCT]; 1203 [EL 1; RCT]; 1206 [EL 1; RCT]; 1207 [EL 1; RCT]; 1208 [EL 1; RCT]; 1209 [EL 1; RCT]; 1210 [EL 1; RCT]; 1212 [EL 2; PCS, post-hoc analysis]; 1214 [EL 3; SS]), with lifestyle modification being the most effective in reducing symptoms of depression in the nonsurgical trials (1191 [EL 1; RCT]; 1193 [EL 1; RCT]; 1194 [EL 1; RCT, N = 24]; 1195 [EL 1; RCT]; 1199 [EL 2; PCS]; 1200 [EL 1; RCT]; 1203 [EL 1; RCT]; 1206 [EL 1; RCT]; 1207 [EL 1; RCT]; 1208 [EL 1; RCT]; 1209 [EL 1; RCT]; 1212 [EL 1; RCT]).

One early intervention trial, the Women's Healthy Lifestyle Project, assessed change in depressive symptoms with weight-loss intervention in women with normal weight, overweight, and obesity (total N = 535, BMI 20 to 34 kg/m^2, age 44-50 years) (1191 [EL 1; RCT]). Women were randomized to a 20-week ILI with weekly meetings that included both education (decreasing fat intake and increasing physical activity) and behavior change strategies versus a control (no-treatment) group. Weight-loss goals were set based on each participant's initial BMI. BDI was used to assess symptoms of depression at baseline and 6 months. Weight loss in the intervention group averaged 11 ± 10 lbs (women with BMI <24 kg/m^2 lost an average of 8 ± 6 lbs; women with BMI >24 kg/m^2 lost an average of 13 ± 12 lbs), while the control group lost an average of 0.5 ± 7 lbs (1191 [EL 1; RCT]). BDI score decreased significantly from baseline to 6 months in the intervention group (BDI score: baseline 4.95 ± 4.72, 6-month follow-up 3.91 ± 4.48) but did not change in the control group (BDI score: baseline 4.30 ± 4.23, 6-month follow-up 4.46 ± 4.76), demonstrating that depression symptomatology was ameliorated by the weight-loss intervention (1191 [EL 1; RCT]).

The larger, more recent Look AHEAD study randomized 5,145 adults with overweight or obesity and T2DM to ILI or diabetes support and education (DSE) (mean baseline BMIs in the 2 subgroups were 36.3 kg/m^2 and 36.6 kg/m^2, and mean ages were 58.6 and 58.9 years, respectively); 5,129 of the participants completed the assessment of depression symptomatology with the BDI (1217 [EL 1; RCT, post-hoc analysis]). Significant depressive symptoms were defined by a BDI score ≥10. At 1 year, participants in the ILI group in comparison to those in the DSE group: (*1*) lost a significantly higher percent of their initial body weight (8.6 ± 6.9% vs. 0.7 ± 4.8%; *P*<0.001, effect size = 1.33); (*2*) experienced a greater reduction in their BDI score (BDI score –1.4 ± 4.7 vs. –0.4 ± 4.5; *P*<0.001, effect size = 0.23); and (*3*) had fewer symptoms of depression (6.3% vs. 9.6%; RR, 0.66; 95% CI, 0.5-0.8; *P*<0.001). Individuals in the ILI group with BDI ≥10 had the greatest decrease in BDI scores (–5.3) compared to those in the ILI group who had a baseline BDI <10 (–0.6) (1217 [EL 1; RCT, post-hoc analysis]). Thus, results from the Look AHEAD trial suggest that a weight loss of ~8% of body weight may confer a benefit with regard to attenuation of depressive symptomatology. A smaller study, the Patient-Reported Outcomes in the Practice-Based Opportunities for Weight Reduction (POWER) trial, included 451 individuals (average BMI 36.6 kg/m^2, average age 54 years) and also found that weight loss was associated with decreased depression symptomatology using a different measure, the Patient Health Questionnaire depression scale (PHQ-8) (1218 [EL 1; RCT]).

Results with regard to depressive symptomatology were more equivocal in the DPP trial that randomized 3,234 participants with impaired glucose tolerance and obesity (average BMI 34 kg/m^2, average age 50.6 years) to intensive lifestyle, metformin treatment, or placebo; 3,187 of the participants completed the BDI (1219 [EL 1; RCT, post-hoc analysis]). A BDI of ≥11 was considered to be mild depression (at baseline 10.3% of the participants met this definition) (1219 [EL 1; RCT, post-hoc analysis]). Participants taking antidepressant medications were included in the study (5.7% of the participants). Less than 1% of the participants at baseline who were taking antidepressant medication had a BDI score ≥11. At a mean follow-up of 3.2 years, the percent of participants in the study with BDI ≥11 decreased from 10.3% to 8.4%, and antidepressant medication use increased from 5.7% to 8.7%; however, the percent of individuals with either marker of depression did not change over the 3 years (1219 [EL 1; RCT, post-hoc analysis]). A recent noninterventional cohort study in older adults from the English Longitudinal Study of Ageing included 1,979 participants with overweight or obesity (mean BMI 29 kg/m^2; mean age 64 years) that were followed for 4 years and found that the proportions of participants developing depressed mood and low sense of well-being was greater in those who lost of ≥5% of body weight over this period compared with the weight stable or weight gain subgroups (1220 [EL 2; PCS]).

Several trials have demonstrated a decrease in depression symptoms following weight-loss intervention with bariatric surgery (670 [EL 2; PCS, post-hoc analysis]; 1214 [EL 2; PCS]; 1221 [EL 2; PCS]; 1222 [EL 3; SS]). The SOS registry includes 4,047 individuals with obesity (BMI ≥34 kg/m^2 in males and BMI ≥38 kg/m^2 in females, age range 37-60 years) who have either undergone surgical intervention (gastric bypass, vertical banded gastroplasty, fixed or variable banding; n = 655) or a conventional intervention (primary care follow-up with or without medications; n = 621). To assess effects after a 10-year follow-up, data analysis was conducted on 1,276 individuals in the cohort who had completed the HRQL, a battery of assessments, and the HADS to assess for depression and anxiety. The study found that, at the 10-year follow-up, depression had decreased more in the surgical group (–1.4, effect size 0.35; BMI change –6.7 kg/m^2) than in the conventional group (–0.5, effect size 0.14; BMI change 0.7 kg/m^2; *P*<0.005); however, it is important to note that the surgically treated group had higher depression at baseline compared to the conventionally treated group (HADS score 5.1 vs. 4.2) (1214 [EL 2; PCS, post-hoc analysis]). The authors note that this effect was more pronounced at the 1-year follow-up, with depression scores decreased by about one-half in the surgically treated group (1214 [EL 2; PCS, post-hoc analysis]). Additionally, using the HADS score to assess for depression at the 10-year follow-up, the percentage of patients with depression in the surgically treated group decreased from 24% to 15%, while remaining constant in

the conventionally treated group (16% to 14%) (1214 [EL 2; PCS, post-hoc analysis]).

An Australian study of 838 patients with obesity (average BMI 44 kg/m^2, range 35 to 86 kg/m^2; average age 44 years, range 16-76 years) who underwent LAGB demonstrated a BMI decrease to 32 kg/m^2 at 24 months and 36 months (1223 [EL 2; PCS]). At baseline, 25% of the patients (n = 211) were deemed to have depression and were on antidepressant medications. At a mean follow-up of 13 months, 57% of the patients were either taking a decreased dose of antidepressant medication or were no longer taking an antidepressant (1223 [EL 2; PCS]). Additionally, BDI-II was assessed in 342 of the patients at baseline and at a mean follow-up of 13 months (range 6 to 36 months); BDI scores decreased from 17.3 to 7.2 over the follow-up period (P<0.001) (1223 [EL 2; PCS]).

Another study assessed BDI in 487 patients (BMI 43.3 to 44.7 kg/m^2, age 38.2 to 43 years) before and 1 year after LAGB and found that weight loss was associated with a significant decrease in BDI score. The largest decreases in BDI scores were seen in younger women and individuals who lost more weight (670 [EL 3; SS]).

At the same time, it has been reported that bariatric surgery can result in increased rates of suicide, divorce, and alcoholism (1224 [EL 3; SS]; 1225 [EL 2; PCS]; 1226 [EL 4; NE]; 1227 [EL 4; NE]; 1228 [EL 4; NE]; 1229 [EL 4; NE]). Risk factors for suicide include lack of improvement in QOL after surgery, ongoing mobility restrictions, persisting sexual dysfunction, problematic spousal relationships, low self-esteem, and history of abuse as a child (1229 [EL 4; NE]). Thus, psychological evaluation is critical in screening patients pre-operatively (1224 [EL 3; SS]; 1225 [EL 2; PCS]; 1226 [EL 4; NE]; 1227 [EL 4; NE]; 1228 [EL 4; NE]; 1229 [EL 4; NE]), and pre- and postoperative psychological counseling should be made available to patients (1227 [EL 4; NE]; 1228 [EL 4; NE]).

It is not known whether a specific amount of weight loss is required to achieve an improvement in symptoms of depression or whether the intervention itself may prove to be helpful in mitigating or attenuating depressive symptoms in individuals with overweight or obesity. Thus, further studies are needed to elucidate whether a clear relationship exists between these factors.

As discussed, a decrease in depression symptomatology was demonstrated with a weight loss of ~8% of body weight in the Look AHEAD trial. Additionally, a study of 203 women with obesity (average BMI 38.3 kg/m^2, average age 50.1 years) with depressive symptomatology at baseline examined the effect of a concurrent weight loss and depression intervention. The study found that women with improvement in depression demonstrated 5 kg more weight loss compared to women without improvement in depression; however, this effect was only seen over the initial 6-month period of the intervention, whereas changes in depression and weight were not associated over 12 to 24 months (663 [EL 2; PCS]).

Some studies suggest that nondietary interventions may improve depressive symptoms even if no weight loss is observed (1190 [EL 1; MRCT]). A community-based obesity prevention program designed to achieve weight stability for African American women in North Carolina (Shape Program, Duke) included 185 women (average BMI 30.2 kg/m^2, average age 35.4 years) who were randomized to a control group or provided with a weight-loss intervention that included individualized goals, interactive voice response calls, coaching phone calls, skills training materials, and a membership to the YMCA (1230 [EL 1; RCT]). Despite the fact that weight was essentially stable in both subgroups, the intervention subgroup experienced a significant decrease in the rate of depression (as assessed by PHQ-8). The rate of depression in the intervention group decreased from 19% at baseline to 10% at the 18-month follow-up, while the rate of depression in the control group was 21% at baseline and 19% at 18 months (1225 [EL 2; PCS]). The authors propose that this decrease in rates of depression may have been due to the intervention itself (calls, follow-up, etc.) or was perhaps related to differences in accepted norms for weight in specific populations rather than "body satisfaction" (1230 [EL 1; RCT]).

In summary, most studies have demonstrated that lifestyle, dietary, physical activity, and bariatric surgery interventions improve symptoms of depression in individuals with overweight or obesity who are seeking to lose weight (670 [EL 1; RCT]; 1191 [EL 1; RCT]; 1193 [EL 1; RCT, N = 24]; 1194 [EL 1; RCT]; 1195 [EL 2; PCS]; 1199 [EL 1; RCT]; 1200 [EL 1; RCT]; 1203 [EL 1; RCT]; 1206 [EL 1; RCT]; 1207 [EL 1; RCT]; 1208 [EL 1; RCT]; 1209 [EL 1; RCT]; 1210 [EL 1; RCT]; 1212 [EL 2; PCS, post-hoc analysis]; 1214 [EL 3; SS]). The amount of weight loss required to improve depression symptomatology is not known. Study results vary from 1 large trial demonstrating that an ~8% decrease in body weight results in attenuation of depressive symptomatology to smaller studies suggesting that it may be the intervention itself (without any predicated weight loss) that confers benefit. Future studies may seek to quantify this relationship.

- *Q6. Is lifestyle/behavioral therapy effective to treat overweight and obesity, and what components of lifestyle therapy are associated with efficacy? (Figure 4 in Executive Summary)*

Executive Summary

- **R64.** A structured lifestyle intervention program designed for weight loss (lifestyle therapy) consisting of a healthy meal plan, physical activity, and behavioral interventions should be available to patients who are being treated for overweight or obesity **(Grade A; BEL 1)**.

- *Q6.1. Reduced-calorie meal plan and macronutrient composition (Table 9 in Executive Summary)*

Executive Summary

- **R65.** Reducing total energy (caloric) intake should be the main component of any weight-loss intervention **(Grade A; BEL 1)**.
- **R66.** Even though the macronutrient composition of meals has less impact on weight loss than adherence rates in most patients, in certain patient populations, modifying macronutrient compositions may be considered to optimize adherence, eating patterns, weight loss, metabolic profiles, risk factor reduction, and/or clinical outcomes **(Grade A; BEL 1)**.

Evidence Base

Dietary or eating patterns represent the totality of a human diet over the course of a specified time period. Eating patterns reflect macronutrient distribution and other nutrients but also eating-related behaviors, which is distinct from traditional itemizations of particular foods or nutrients consumed at a meal. When designed for reduced caloric intake, there are multiple eating patterns that are associated with weight-loss efficacy (Table 4). On balance, taking into consideration the strength of the evidence, there are insufficient clinical data to support the recommendation of a preferred distribution of one macronutrient over another for the specific purpose of weight loss. This conclusion also applies for children and adolescents based on the systematic review by Gow et al (1231 [EL 4; NE]) of 14 randomized or quasi-randomized, controlled trials.

However, there may be rationale for the selection of specific meal patterns with defined macronutrient composition in select patient groups (e.g., DASH diet for hypertension or Mediterranean-style diets for cardiovascular risk reduction). The DASH dietary pattern consists of a diet rich in fruits, vegetables, and low-fat dairy foods, while being low in fat content (saturated fat, total fat, and cholesterol), red meat, salt, sweets, and sugar-containing beverages. In RCTs, participants randomized to the DASH dietary pattern resulted in average reductions in SBP and DBP of 5.5 and 3.0 mm Hg, respectively, at 8 weeks (1232 [EL 1; RCT]), and further reductions were observed with progressive decrements in dietary sodium intake (1233 [EL 1; RCT]). Individuals who were hypertensive at baseline and/or self-identified as African American had greater BP responses to the dietary pattern. These improvements in BP occurred without change in weight.

The DASH dietary pattern can also be the basis of a calorie-restricted weight-reduction diet. In the nonrandomized phase 1 portion of the LIFE study, all participants were instructed to adopt the DASH dietary pattern with a 500 kcal restriction, along with increasing physical activity by more than 180 minutes per week over a 26-week period (1234 [EL 2; NRCT, post-hoc analysis of phase I: nonrandomized]). The mean weight loss in this trial was 6.3 kg, with 60% of the participants losing at least 4.5 kg. Similarly, the PREMIER clinical trial, which utilized the DASH dietary pattern as part of a behavioral lifestyle intervention, reported a weight loss of ~5 kg over a 6-month period (1235 [EL 1; RCT]).

One meal plan that can be effective in patients with cardiometabolic risk is represented by Mediterranean diets that are characterized by a reliance on olive oil, which contains the monounsaturated fat oleic acid as ~75% of fatty acids, as a fat source. Epidemiologic studies show that Mediterranean diets have been known to be associated with reduced CVD and mortality when compared with diets consumed in northern European countries. Mediterranean diets have been shown to have favorable clinical effects in patients with cardiometabolic risk and insulin resistance, including long-term outcome studies demonstrating prevention of T2DM and primary and secondary prevention of CVD (39 [EL 1; RCT]; 823 [EL 1; RCT]; 828 [EL 1; RCT]; 1236 [EL 1; RCT]; 1237 [EL 1; RCT]; 1238 [EL 1; RCT]; 1239 [EL 4; NE]; 1240 [EL 2; PCS]; 1241 [EL 2; MNRCT]; 1242 [EL 4; NE]; 1243 [EL 1; RCT]; 1244 [EL 1; RCT]).

The Lyon Diet Heart Study was a clinical trial that assessed the efficacy of Mediterranean diets for the secondary prevention of CVD events that demonstrated reduced rates of reinfarction and mortality in the Mediterranean diet group at the 4-year follow-up (823 [EL 1; RCT]; 1239 [EL 4; NE]). Mediterranean diets have also been shown to prevent metabolic syndrome and reduce rates of progression to T2DM (828 [EL 2; MNRCT]; 1241 [EL 4; NE]; 1242 [EL 1; RCT]; 1243 [EL 1; RCT]; 1244 [EL 1; RCT]). Additionally, there are cognitive-behavioral components of implementing dietary recommendations that influence the effects of macronutrient recommendations. For instance, structured, food-based, "whole-of-diet" counseling was more effective than a general approach to healthy eating for beneficial changes in dietary fat content (1245 [EL 1; RCT]).

In the POUNDS LOST trial, there were no differences in total, fat, or lean mass, body composition, abdominal or hepatic fat mass, or significant food cravings among low-carbohydrate, low-fat, and low-protein diet groups. All groups lost more fat than lean mass (58 [EL 1; RCT, post-hoc analysis]; 1246 [EL 1; RCT, post-hoc analysis]), although loss in fat-free mass was greater with high-fat, low-carbohydrate intakes (1247 [EL 1; RCT, post-hoc analysis]). In the landmark study by Shai et al (1238 [EL 1; RCT]), the Dietary Intervention-Randomized Controlled Trial [DIRECT], a low-fat diet was associated with less weight loss than a Mediterranean diet or low-carbohydrate diet, with greater lipid-lowering on the low-carbohydrate diet and better glycemic control with the Mediterranean diet. One emergent benefit of a healthy eating pattern,

such as the Mediterranean diet, is the decreased weight of food over time, primarily due to dietary increases in plant material and decreases in processed or fast foods and meats (1248 [EL 1; RCT, post-hoc analysis]; 1249 [EL 2; NRCT]).

In another systematic review of the evidence and representing an integration of the data, Abete et al (1250 [EL 4; NE]) concluded that improved weight loss is accomplished by changing typical diets composed of 15% protein, <30% fat, and 50 to 55% carbohydrate in favor of diets composed of 30% protein, greater consumption of monounsaturated and n-3 polyunsaturated fats, and 40% carbohydrates with greater amounts of fiber, isoflavones, and antioxidants. In a study by Lin et al (1251 [EL 1; RCT, post-intervention observational data]), although macronutrient modifications of a DASH-type eating pattern did not affect weight-loss efficacy, higher plant protein and lower saturated fat intake was associated with greater weight-loss maintenance. Based on findings of the International Study of Macro-/Micronutrients and Blood Pressure (INTERMAP), lower energy intake is associated with lower body mass index (BMI) in both genders (1252 [EL 3; CSS]). In addition, the INTERMAP univariate analysis supports increasing the intake of fresh fruit, pasta, and rice, and lowering the intake of meat (1252 [EL 3; CSS]).

For many commercial diets with variable macronutrient percentages, micronutrient deficiencies are more likely. An eating pattern with only moderately lower carbohydrate and higher protein was found to have the most favorable micronutrient content, compared with lower carbohydrate, low fat, and/or low protein eating patterns (33 [EL 1; RCT]). In another systematic review, Foreyt et al (37 [EL 4; NE]) affirmed the general concept that calorie intake and not the source of the calories is most important but also asserted that the story is more involved. Namely, that:

1. Higher protein intake, achieved through replacing carbohydrate and fat calories, can enhance satiety and therefore be useful in strategically addressing appetite triggers, without significant harm, especially renal;
2. Lower fat intake can reduce energy density and the potential for caloric overconsumption, with as yet unproven harm; and
3. Lower carbohydrate intake, especially with increased consumption of fiber and complex carbohydrates with lower calorie density, can reduce total daily caloric intake (37 [EL 4; NE]).

These statements are exemplified in a clinical study by Morenga et al (1253 [EL 1; RCT]) in which a relatively high-protein (30 g/day), high-fiber (>35 g/day) diet over 10 weeks produced significantly more weight loss than a conventional low-fat, high-carbohydrate diet. The statements are also supported by the finding by Dansinger et al (843 [EL 1; RCT]) that the efficacy of a particular commercial diet (Aktins, Ornish, Weight Watchers, and Zone) is determined by adherence, a behavioral metric, rather than macronutrient composition. Thus, these data strongly suggest that a reduced-calorie eating plan should be selected to reflect personal and cultural preferences in an effort to promote compliance.

The studies comparing diets of varying macronutrient composition extend over 1 to 2 years at most. The effects of different eating patterns on long-term clinical outcomes, such as weight-loss maintenance or progression to T2DM and CVD disease events, are very important but largely unknown.

Looking forward, there are indications that the salutary effects of certain macronutrient changes can affect hormonal profiles that have complex downstream metabolic effects (32 [EL 4; NE]; 1254 [EL 1; RCT]). Moreover, specific genotypes (1255 [EL 1; RCT]; 1256 [EL 2; PCS]; 1257 [EL 2; PCS]; 1258 [EL 2; PCS]; 1259 [EL 1; RCT]; 1260 [EL 1; RCT]; 1261 [EL 1; RCT]; 1262 [EL 1; RCT]) and molecular eating patterns (1263 [EL 4; NE]) cannot only modulate the weight-loss response to a specific eating pattern but also serve to guide personalized nutritional prescriptions. However, at least at the level of adipocyte gene expression, energy restriction still had more of an effect than macronutrient distribution (1264 [EL 1; RCT]).

In sum, the prime determinant of weight loss is energy balance and, from an eating pattern context, this is considered as total calorie intake. However, there are proven benefits of certain eating patterns with varying macronutrient distributions in select patient groups. There are also potential manipulations of macronutrient distributions that can address unhealthy eating behaviors. Last, all of the variables may in the future be modulated by molecular biology information to personalize nutritional approaches to weight loss.

- *Q6.2. Physical activity*

Executive Summary

- **R67.** Aerobic physical activity training should be prescribed to patients with overweight or obesity as a component of lifestyle intervention; the initial prescription may require a progressive increase in the volume and intensity of exercise, and the ultimate goal should be ≥150 min/week of moderate exercise performed during 3 to 5 daily sessions per week **(Grade A; BEL 1)**.
- **R68.** Resistance training should be prescribed to patients with overweight or obesity undergoing weight-loss therapy to help promote fat loss while preserving fat-free mass; the goal should be resistance training 2 to 3 times per week consisting of single-set exercises that use the major muscle groups **(Grade A; BEL 1)**.

- **R69.** An increase in nonexercise and active leisure activity should be encouraged to reduce sedentary behavior in all patients with overweight or obesity **(Grade A; BEL 1)**.
- **R70.** The prescription for physical activity should be individualized to include activities and exercise regimens within the capabilities and preferences of the patient, taking into account health-related and physical limitations **(Grade C; BEL 4, upgraded due to high relevance)**.
- **R71.** Involvement of an exercise physiologist or certified fitness professional in the care plan should be considered to individualize the physical activity prescription and improve outcomes **(Grade A; BEL 1)**.

Evidence Base

Recommendation 67.

Guidelines for treating or preventing obesity from the American College of Cardiology, the American Heart Association, The Obesity Society (20 [EL 4; NE]), and the ACSM (896 [EL 4; NE]) recommend physical activity or exercise prescription of at least moderate aerobic activity (such as brisk walking) ≥150 minutes per week (equal to ≥30 minutes daily 5 days per week) in addition to dietary and behavioral therapy for weight loss, with higher levels of physical activity to maintain weight loss or prevent weight gain.

Randomized trials (1265 [EL 1; RCU]; 1266 [EL 1; RCT]; 1267 [EL 1; RCT]; 1268 [EL 1; RCT]; 1269 [EL 1; RCT]) and meta-analyses (1270 [EL 4; NE]; 1271 [EL 1; MRCT]; 1272 [EL 1; MRCT]) have shown that exercise interventions can result in modest weight loss of about 1 to 3 kg utilizing aerobic training of ≥150 min/week at moderate intensity, and better outcomes with increasing amounts and intensity of exercise (1273 [EL 1; RCT]; 1274 [EL 1; RCT]; 1275 [EL 1; RCT]). A meta-analysis of pedometer interventions showed a modest weight loss of 1.3 kg with greater weight loss achieved in the longer duration studies (1276 [EL 2; MNRCT]). Another meta-analysis showed that aerobic training of moderate or high intensity has the highest potential to reduce visceral adipose tissue in males and females with overweight even in the absence of a hypocaloric diet (1277 [EL 2; MNRCT]).

When exercise is prescribed in addition to reduced-calorie dietary intervention there is an additional weight loss of about 1 to 3% of body weight, with greater loss associated with higher intensity and longer duration exercise programs (947 [EL 2; MNRCT]; 1277 [EL 1; MRCT]; 1278 [EL 2; MNRCT]; 1279 [EL 1; RCT]; 1280 [EL 1; RCT]; 1281 [EL 1; RCT]; 1282 [EL 1; RCT]), together with more fat mass loss and less fat-free mass loss (1283 [EL 2; MNRCT]; 1284 [EL 1; RCT]; 1285 [EL 1; RCT]; 1286 [EL 4; NE]; 1287 [EL 2; MNRCT]; 1288 [EL 2; MNRCT]). A systematic review looking at the effects of dietary energy restriction and exercise in middle-aged to older adults with overweight and obesity highlighted the importance of limiting the loss of fat-free mass in patients with sarcopenic obesity (1289 [EL 4; NE]). In postpartum women, structured exercise activities were shown to be associated with clinically relevant additional weight loss of >2.5 kg in a meta-analysis of RCTs (1290 [EL 1; MRCT]).

Clinical trials have shown that exercise can be employed to maintain weight loss, although more intensive programs are sometimes required for efficacy (1291 [EL 1; MRCT]; 1292 [EL 1; MRCT]; 1293 [EL 1; RCT]; 1294 [EL 1; RCT]; 1295 [EL 1; RCT]; 1296 [EL 1; RCT]). Other trials have shown a minimal benefit of exercise to maintain weight loss (1297 [EL 1; MRCT]; 1298 [EL 1; RCT]). A systematic review of RCTs showed that adding exercise to diet, or to diet and behavior therapy, was associated with improved weight loss for up to 36 months and improvements in cardiometabolic health (1299 [EL 1; MRCT]). A prospective study of 4,558 premenopausal women who had lost >5% body weight in the previous 2 years showed that more physical activity (≥30 min/day) and increased jogging or running were associated with less weight regain (−3.26 kg) (1300 [EL 2; PCS]). Greater amounts of exercise were associated with longer-term weight-loss maintenance in the DPP (1301 [EL 1; RCT, post-intervention survey]) and the Look AHEAD study (1302 [EL 1; RCT]), and with long-term weight loss in the National Weight Control Registry (1303 [EL 3; SS]; 1304 [EL 3; SS]).

Prospective cohort studies have also shown that those who engage in higher amounts and intensities of physical activity gain less weight than those who are more sedentary or exercise less (1192 [EL 1; RCT]; 1305 [EL 2; PCS]; 1306 [EL 2; PCS]). The HUNT study was an observational prospective cohort conducted over 33 years that concluded that physical activity above the current recommendations (150 min moderate intensity/week or 60 min vigorous activity/week) are needed to attenuate weight gain (1307 [EL 2; PCS]).

Exercise prescription has been successfully utilized as part of intensive behavioral intervention studies of weight loss for the prevention of diabetes in large trials including the DPP (708 [EL 1; RCT]), Finnish Diabetes Prevention Study (707 [EL 1; RCT]), Da Qing Diabetes Prevention Study (706 [EL 1; RCT]), and also in those with T2DM in the Look AHEAD trial (755 [EL 1; RCT]; 1302 [EL 1; RCT]). Two Cochrane reviews concluded that physical activity helps promote modest weight loss in those with prediabetes, and intense physical activity achieves more weight loss (3.6%) than diet alone in those diagnosed with diabetes (1308 [EL 1; MRCT]; 1309 [EL 1; MRCT]). For patients with T2DM and obesity, exercise training was shown to lower A1C even without BMI changes in 1 meta-analysis (763 [EL 1; MRCT]), while another meta-analysis showed greater A1C lowering with structured exercise versus exercise advice, and for exercise >150 minutes per

week versus <150 minutes per week (768 [EL 1; MRCT]). The ACSM and ADA joint position statement (1310 [EL 4; NE]) recommends "at least 150 min/week of moderate to vigorous aerobic exercise spread out during at least 3 days during the week, with no more than 2 consecutive days between bouts of aerobic activity.… undertake moderate to vigorous resistance training at least 2-3 days/week." These recommendations are reiterated and supported by both the 2015 ADA Foundations of Care (1311 [EL 4; NE]) and the updated AACE/ACE Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (18 [EL 4; NE]), with an emphasis on an individualized patient-centered approach.

Exercise is also an integral component of a comprehensive care plan for patients who have undergone bariatric surgery. Meta-analyses of observational studies of patients following bariatric surgery have shown a positive relationship between an increased amount of exercise and weight loss after surgery, with a 3.6 kg higher standardized mean weight loss and a 4% greater decline in BMI in active patients compared to those engaging in minimal exercise (1312 [EL 2; MNRCT]; 1313 [EL 2; MNRCT]). A trial utilizing pedometers postoperatively after Roux-en-Y gastric bypass showed that pedometer users trended toward increased weight loss at postoperative months 3 and 6 compared to controls (1314 [EL 4; NE, abstract]).

Recommendation 68.

RCTs and a related meta-analysis have compared the type, duration, and frequency of exercise for their effect on body composition and have demonstrated that weight training (resistance exercise) produced similar amounts of fat loss while preserving more fat-free mass when compared with aerobic training alone (1315 [EL 2; MNRCT]; 1316 [EL 1; MRCT]; 1317 [EL 1; RCT]; 1318 [EL 1; RCT, N = 40]; 1319 [EL 1; RCT]). Thus, resistance training can promote weight loss. There is also evidence for improved weight maintenance with resistance training (1320 [EL 1; RCT]; 1321 [EL 1; RCT]).

Resistance training added to aerobic exercise has been shown to enhance fat loss and body composition, and the combination is recommended in patients with obesity and diabetes for promoting loss of body fat and for improving cardiometabolic risk factors based on results from several interventional trials (736 [EL 1; RCT]; 767 [EL 1; RCT]; 1322 [EL 1; RCT]; 1323 [EL 1; RCT]). A meta-analysis also demonstrated the benefits of combined aerobic and resistance training in patients with obesity and known coronary artery disease (1324 [EL 1; MRCT]). One study randomizing participants to aerobic, resistance, or combination training for 8 months confirmed that the prescribed exercise was associated with modest weight loss, and showed that adding resistance training to aerobic training improved lean mass but doubled the time commitment for exercise (1325 [EL 1; RCT]). We endorse the resistance training prescription recommendations of the ACSM/ADA joint position statement (1310 [EL 4; NE]) for all patients with obesity. The general goal should be resistance training 2 to 3 times per week consisting of single-set exercises that use the major muscle groups with a load that permits 10 to 15 repetitions approaching fatigue and progressing over time to utilize heavier weight and more sets over time.

A meta-analysis of diabetes prevention trials was inconclusive regarding the role of resistance training due to lack of comprehensive and objective evaluation of the effects of muscular fitness (1326 [EL 2; MNRCT]), while another showed benefits of resistance training on all metabolic syndrome parameters (1327 [EL 1; MRCT]). Weight training was associated with a reduced gain in WC with age in the Health Professionals Follow-up prospective cohort of 10,500 men, and the authors concluded that further study into the optimal frequency and intensity of resistance exercise was warranted (1328 [EL 2; PCS]).

Circuit training, which consists of alternating sets of major muscle movement groups with little rest in between to introduce an aerobic component to the exercise session, holds promise, although more research is needed to evaluate its role in obesity. Post-exercise oxygen consumption is higher after circuit training, but total volume must be taken into account for overall caloric expenditure (1329 [EL 1; RCT, very small study of 7 subjects]; 1330 [EL 2; PCS, very small study of 8 subjects]).

Recommendation 69.

ACSM guidelines (896 [EL 4; NE]) discussed the concept of "non-exercise activity thermogenesis" developed by Levine et al (1331 [EL 4; NE]) as a better descriptor of "lifestyle forms of physical activity." They emphasized that "it is reasonable to conclude that increasing lifestyle physical activity should be a strategy included in weight management efforts," including physical activity that is not structured exercise, but energy expenditure beyond sleeping or eating. While it is obviously difficult to quantify and accurately study the effects of nonexercise physical activity, cross-sectional and observational studies reveal that physical inactivity is associated with obesity, especially abdominal obesity (1332 [EL 3; SS, large N: questionnaires to 15,239 subjects]; 1333 [EL 2; PCS, large study N = 50,277]; 1334 [EL 3; CSS, substudy]; 1335 [EL 3; CSS]; 1336 [EL 3; CSS]; 1337 [EL 3; CSS]; 1338 [EL 2; PCS]). A systematic review of sedentary behavior and health outcomes in longitudinal studies indicated a consistent relationship between self-reported sedentary behavior and weight gain from childhood to the adult years, though mixed associations are observed with weight gain during adulthood (1339 [EL 2; MNRCT]).

Leisure-time activity was shown to be an important determinant of long-term weight maintenance in the Sibutramine Trial on Obesity Reduction and Maintenance (STORM) trial, emphasizing the importance of nonexercise

physical activity in lifestyle interventions (1340 [EL 1; RCT]).

A systematic review of pedometer studies along with a meta-analysis of pedometer-based walking programs, both including randomized trials and observational studies, indicated that there is a modest but meaningful reduction in weight and BMI as a result of incorporating more nonexercise movement into daily life (1276 [EL 2; MNRCT]; 1341 [EL 2; MNRCT]). A Cochrane review of pedometer studies in the workplace also showed improvements in BMI and WC but limited the strength of conclusions due to low-quality data and insufficient evidence (1342 [EL 1; MRCT]). In a Canadian prospective cohort study by Katzmarzyk et al (740 [EL 2; PCS]), sitting time was independently associated with mortality, stressing the importance of avoiding sedentary behavior. The recommendation for reducing sedentary behavior is that sedentary periods last 90 minutes or less and are interrupted by periods of activity (740 [EL 2; PCS]).

Since the workforce is becoming increasingly sedentary, finding ways to increase nonexercise activity at work has been a focus of many studies. For example, a Cochrane review of workplace interventions analyzed the efficacy of initiatives to reduce sitting at work (e.g., sit-stand desks, policy changes, and counseling) compared to no intervention and concluded that the evidence was of low quality; however, the authors were hopeful that many ongoing trials would provide higher quality data (1343 [EL 2; MNRCT]).

For those patients who have T2DM, the ACSM and ADA recommend that "persons with T2DM are encouraged to increase their total daily unstructured physical activity" (1302 [EL 1; RCT]), and that all patients with obesity should be counseled and encouraged to increase nonexercise activity thermogenesis.

Recommendation 70.

Many patients with obesity cannot adhere to the optimal recommendations for exercise prescription due to physical limitations. It is important to individualize the prescription for physical activity to include activities and exercise regimens within the capabilities and preferences of the patient to allow for the optimal amount of conditioning. Lifestyle therapy should include increased physical activity even though the patient is unable to engage in optimal physical activity. For example, studies have consistently shown that a walking program is associated with reductions in the incidence of diabetes (737 [EL 3; SS]; 738 [EL 2; PCS]; 739 [EL 2; PCS]). Elderly patients or people with disabilities should try to approach the levels of activity in the guidelines to the greatest extent possible; however, even reduced activity regimens should be encouraged. In patients with physical limitations, the health care provider and the patient should together establish the exercise prescription with the goal of long-term compliance.

Recommendation 71.

Many of the large successful trials showing improved fat loss with physical activity (cited above) utilized the participation of exercise physiologists and other fitness professionals. One trial showed that the use of personal trainers improved adherence but not long-term weight loss; however, post-hoc analysis showed that levels of exercise needed for success were much higher than was recommended (1344 [EL 1; RCT]). Exercise trainers can be beneficial to patients with obesity and arthritis of the knee or hip in improving symptoms and functionality (1345 [EL 4; NE]). Sessions with a personal trainer have been shown to enhance the client's ability to progress through changes and intensification of the exercise program (1346 [EL 1; RCT, N = 20]; 1347 [EL 2; PCS]), and to augment adherence to exercise among women with obesity in a behavioral weight-loss program (1348 [EL 2; PCS]). Experienced and educated fitness professionals can assist in tailoring an exercise prescription to fit the needs, abilities, limitations, and desires of the patient, ultimately improving adherence and success.

- *Q6.3. Behavior interventions*

Executive Summary

- **R72.** Lifestyle therapy in patients with overweight or obesity should include behavioral interventions that enhance adherence to prescriptions for a reduced-calorie meal plan and increased physical activity (behavioral interventions can include: self-monitoring of weight, food intake, and physical activity; clear and reasonable goal-setting; education pertaining to obesity, nutrition, and physical activity; face-to-face and group meetings; stimulus control; systematic approaches for problem solving; stress reduction; cognitive restructuring [i.e., cognitive behavioral therapy]; motivational interviewing; behavioral contracting; psychological counseling; and mobilization of social support structures) **(Grade A; BEL 1)**.
- **R73.** The behavior intervention package is effectively executed by a multidisciplinary team that includes dietitians, nurses, educators, physical activity trainers or coaches, and clinical psychologists **(Grade C; BEL 4, upgraded due to high relevance)**. Psychologists and psychiatrists should participate in the treatment of eating disorders, depression, anxiety, psychoses, and other psychological problems that can impair the effectiveness of lifestyle intervention programs **(Grade B; BEL 2)**.
- **R74.** Behavioral lifestyle intervention and support should be intensified if patients do not achieve a 2.5% weight loss in the first month of

treatment, as early weight reduction is a key predictor of long-term weight-loss success **(Grade A; BEL 1)**. A stepped-care behavior approach should teach skills for problem-solving and should evaluate outcomes **(Grade A; BEL 1)**.

- **R75.** Behavioral lifestyle intervention should be tailored to a patient's ethnic, cultural, socioeconomic, and educational background **(Grade B; BEL 2)**.

Evidence Base

Recommendation 64 in these guidelines establishes that a reduction in caloric intake is the essential component of any lifestyle intervention in the treatment of obesity, and recommendations 66 through 70 attest to the important role of physical activity. In the current context, behavioral interventions represent a component of intensive lifestyle/behavior therapy that enhance adherence to diet and physical activity prescriptions. Behavioral treatment can include multiple interventions or strategies including: self-monitoring (keeping records of weight, food intake, and physical activity) (1349 [EL 2; PCS]; 1350 [EL 4; NE]; 1351 [EL 4; NE]; 1352 [EL 2; PCS]; 1353 [EL 1; RCT]); clear and reasonable goal setting; stimulus control (controlling cues associated with eating) (1354 [EL 2; NRCT]); meal portion control (1355 [EL 1; RCT]; 1356 [EL 1; RCT]); slower eating during meals; meal replacements or food provision (881 [EL 4; NE]; 1357 [EL 1; RCT]; 1358 [EL 1; RCT]; 1359 [EL 1; RCT]; 1360 [EL 1; RCT]; 1361 [EL 1; MRCT]); education pertaining to obesity, nutrition, and physical activity (1362 [EL 4; NE]); face-to-face meetings and group sessions; systematic approaches for problem solving; stress reduction; cognitive restructuring (i.e., cognitive behavioral therapy); motivational interviewing; behavioral contracting (1344 [EL 1; RCT]; 1363 [EL 1; RCT]); psychological counseling; a counseling approach that features the 5 A's (ask, advise, assess, assist, arrange); and mobilization of social support structures (1364 [EL 1; MNRCT]).

The delivery of many of these interventions can be accomplished by one-on-one meetings, group sessions, and/or Internet, telephone, or other "remote" technologies. Potential venues for the interventions include the clinic office, community facilities, and commercial entities. The behavior intervention package often requires a multidisciplinary team, including dietitians, educators, exercise trainers or coaches, and clinical psychologists. Psychologists and psychiatrists will need to participate in the treatment of eating disorders, depression, anxiety, psychoses, and other psychological problems that impair the effectiveness of lifestyle intervention programs unless addressed in a primary manner (1365 [EL 2; MNRCT, matched-study analysis, nonexhaustive literature search]). Effective behavioral intervention packages have been described and developed by multiple authors (1362 [EL 4; NE]; 1366 [EL 4; NE]; 1367 [EL 4; NE]; 1368 [EL 4; NE]; 1369 [EL 4; NE]).

It is difficult to evaluate the effectiveness of behavior programs per se since they are combined with various dietary and physical activity interventions in the treatment of obesity, and the behavioral component of therapy will vary in approach and in the extent to which any of the multiple strategies described above are incorporated. Nevertheless, RCTs have been conducted to assess the impact of behavioral therapy in weight-loss interventions and provide some insight regarding those practices that are associated with efficacy and the intensity required to enhance weight-loss outcomes. A systematic review and meta-analysis of RCTs evaluated combined behavioral weight management programs with diet-only and physical activity-only treatment arms in patients with overweight or obesity that were studied for ≥12 months (1279 [EL 2; MNRCT]). Eight studies representing 1,022 patients were reviewed. Six studies showed no significant difference in weight loss at 3 or 6 months between the combined behavioral weight management programs and diet-only, while combined behavior therapy produced significantly more weight loss at 12 months. In the 5 studies comparing combined behavioral weight management and physical activity only, significantly greater weight loss occurred in the combined behavioral therapy groups.

Perri and colleagues (1370 [EL 1; RCT]) demonstrated that increasing the intensity of behavior lifestyle instruction resulted in greater weight loss. A total of 612 adult patients with obesity were randomly assigned to low, moderate, or high doses of behavioral treatment, defined as 16, 32, or 48 sessions over 2 years, respectively. These patients were compared to controls who received nutrition education without instruction in behavior modification strategies. The 2-year mean reductions in body weight were 2.9%, 3.5%, 6.7%, and 6.8% for the controls and the low-, moderate-, and high-dose behavior therapy groups, respectively. The number of participants who achieved ≥5% weight loss at 2 years was also significantly higher in the moderate- and high-dose behavior therapy groups (both 58%), compared to the low-dose behavior therapy and control groups. Another study compared the effectiveness of 3 behavioral interventions that varied in intensity (173 consecutive patients seen in 3 outpatient centers) with an observational cohort study (1371 [EL 2; PCS]). The programs implemented either cognitive behavioral strategies combined with patient exercise and nutrition, a semistructured approach with basic counseling, or unstructured advice. At the end of the 17- to 20-month intervention period, the highly structured behavior group showed an average weight loss of 5.4 kg, which was significantly more than that observed in the semistructured and unstructured groups (2.8 kg and 1.2 kg, respectively).

In 2011, the Centers for Medicare and Medicaid Services (CMS) approved intensive behavioral weight-loss counseling by primary care physicians (PCPs) and other primary care providers for approximately 14 brief (10- to 15-minute) face-to-face sessions over 6 months. The effectiveness of this program was reviewed through a search of RCTs that assessed weight-loss therapy to include behavioral counseling, dietary advice, and exercise for at least 3 months (1372 [EL 1; RCT]). The RCTs reviewed had to include at least 15 participants with an attrition rate of <30% at 1 year. In 12 trials including 3,893 participants, none of the counseling delivered by PCPs followed the CMS guidelines. Mean weight loss at 6 months for intervention groups ranged from 0.3 kg to 6.6 kg compared to weight loss of 0.9 kg to 2.0 kg seen in controls. Interventions that prescribed calorie intake reductions of ≥500 kcal/day, increased walking activity of ≥150 minutes/week, and behavioral therapy support generally produced greater weight loss than interventions with fewer components of such care. The evidence review concluded that more intensive behavioral counseling can help provide effective weight loss, but that PCPs may not be routinely providing such care.

A second review of RCTs found that behavioral weight-loss interventions by PCPs result in only very small declines in body weight over 12 months in patients with overweight or obesity (1373 [EL 1; MRCT]). The 15 RCTs included 4,539 patients, and the inclusion criteria and type of interventions were heterogeneous. Pooled meta-analysis results found significant but small reductions in body weight of 1.4 kg and 1.23 kg at 12 and 24 months, respectively.

A third systematic review and meta-analysis set out to determine the effectiveness of multicomponent behavioral weight management programs implemented in routine everyday clinical practice including commercially available programs (1374 [EL 2; MNRCT]). Inclusion criteria for these studies required interventions to be widely available and presented by the therapists who would deliver the intervention in routine practice. Only 8 trials met the inclusion criteria. In the systematic review, pooled results from 5 studies of commercial weight management programs detected significant weight loss at 1 year. Two studies of a commercial program with meal replacements also observed significant weight loss. In contrast, pooled results from 5 interventions delivered by PCP teams resulted in no weight loss. In total, compared to other weight-loss programs, there was no evidence in this review that treatment interventions delivered within general primary care teams produced meaningful weight loss. This does not mean that weight-loss interventions are futile, but rather, may be misdirected.

A systematic review of psychological mediation of obesity-related lifestyle change interventions found that, despite limited data, higher patient autonomous motivation, self-efficacy, and self-regulation skills are good predictors of increasing activity and losing weight (1375 [EL 2; MNRCT]). Studies were included in this review if they reported intervention effects on behavioral mediators (i.e., self-regulatory control) and the relationship between these mediators and health outcomes in persons with overweight or obesity. Thirty-five studies were included, 42 putative mediators were assessed, 10 studies used formal mediation analyses, and 28 studies were RCTs. Mediators associated with a longer duration of weight control included higher levels of autonomous motivation, self-efficacy/barriers, self-regulation skills (i.e., self-monitoring), flexible eating restraint, and positive body image. Autonomous motivation, self-efficacy, and use of self-regulation skills were associated with increased activity, but no mediators were identified for dietary intake.

The DPP randomized 3,234 patients with impaired fasting glucose to placebo, metformin (850 mg twice daily), or behavior/lifestyle modification over 4 years with the goal of at least a 7% weight loss (708 [EL 1; RCT]). The design for the lifestyle intervention was based on a systematic review of weight-loss interventions in individuals primarily without diabetes, which resulted in weight loss of 5 to 8% of body weight at 12 months (1376 [EL 1; MRCT]), and the evidence that weight loss could prevent progression to T2DM in adults with prediabetes (1308 [EL 1; MRCT]). The ILI resulted in the greatest amount of weight loss and a 58% reduction in the progression to T2DM (708 [EL 1; RCT]). The incidence of T2DM was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. During the DPP trial, for every kilogram of weight loss there was a 16% reduction in T2DM risk (714 [EL 2; PCS]). The lifestyle intervention in the DPP included a 16-lesson lifestyle change curriculum that provided education on healthy eating, regular exercise, and behavior modification to assist participants in achieving the study weight-loss goals. The behavior lifestyle program was presented to patients by case managers on a one-to-one basis during the first 24 weeks and was flexible, culturally sensitive, and individualized. Subsequent individual sessions usually occurred monthly, and group sessions with case managers were provided to reinforce behavioral changes. O'Brien and colleagues (1377 [EL 1; RCT, post-hoc analysis]) stratified DPP patients by their educational attainment; 47% of participants had completed college. For patients in the behavior/lifestyle intervention, those who had completed college had a 68% decline in progression to T2DM, whereas those with less education had a 47% risk reduction. For patients taking metformin, there was a 49% versus 23% relative risk reduction in T2DM between college graduates and those with lesser education, respectively. These results raise the question of whether or not behavioral lifestyle intervention would be more effective if tailored to an individual's educational background.

In the DPP, substantial weight loss early in the course of the lifestyle intervention was associated with improved long-term efficacy. Forty-nine percent of participants in the DPP achieved the 7% weight loss study goal early on, at the end of the intense 16-session core intervention (1378 [EL 1; RCT, post-hoc analysis]). Patients who met the initial 6-month study goals were 1.5 to 3.0 times more likely to also meet these goals long term, indicating that weight loss in the first month of treatment proved to be a critical determinate of long-term weight loss. The 16-week DPP group-based intervention was adapted and randomly delivered to 32 adults with prediabetes and BMI >25 kg/m^2 (1379 [EL 1; RCT]). The percent weight loss at week 5 was significantly associated with greater weight loss at both 4 and 7 months. Only 12.5% of patients who failed to achieve a 2.5% weight loss during the first month were able to achieve ≥5% weight loss by month 7.

These results suggest that a stepped-care approach in the treatment of obesity could be beneficial, which would target more intensive interventions only to those individuals who did not lose sufficient weight early on following the initiation of a less intense program. A behavioral weight-loss program with or without stepped-care therapy was randomly assigned to 44 sedentary adults with obesity (1380 [EL 1; RCT]). Participants in the stepped-care behavior group received additional counseling, including problem-solving skills training, if they regained >1% body weight during the first 6 months of treatment. Patients were taught to use problem-solving skills to help resolve problems and evaluate outcomes. Patients in the stepped-care group lost significantly more weight and body fat, reported greater physical activity and dietary improvements, and had superior weight-loss maintenance at 12 months.

Other studies have found that early weight loss during a lifestyle intervention program predicted greater weight loss at the end of the study (1378 [EL 1; RCT, post-hoc analysis]; 1383 [EL 1; RCT]; 1384 [EL 1; RCT, single-blinded primary study, secondary subset analysis]; 1385 [EL 2; PCS]). Wadden et al (1381 [EL 1; RCT]) reported that among 76 women with obesity, attending a higher percentage of treatment sessions and losing more weight during the first month were both strongly associated with greater weight loss at the end of 1 year. Hadziabdic et al (1382 [EL 1; RCT, single-blinded primary study, secondary subset analysis]) enrolled 124 patients with obesity in a 12-month weight reduction program involving behavioral therapy that included an intensive 5-day educational intervention followed by 5 two-hour follow-up visits. One-third of patients lost >5% body weight after 12 months, and initial weight loss was a strong predictor of weight loss after 1 year.

Weight reduction early in a weight-loss program is a key predictor of long-term weight-loss success even in studies without behavior lifestyle intervention (1384 [EL 1; RCT]). A 2-year dietary intervention RCT evaluated 322 adults with obesity, with patients randomized to a low-fat, low-carbohydrate, or Mediterranean diet (1384 [EL 1; RCT]). Independent predictors of study drop-out were a higher baseline BMI and less weight loss at 6 months. In addition, a greater weight loss achieved at 6 months was the main predictor of long-term success of >5% weight loss.

Given the relationship reported between early weight loss and long-term weight loss success, it is important to recognize the optimal time and weight-loss threshold for identifying patients who are less likely to succeed. Once identified, nonresponders could be offered a more intensive, stepped-care intervention, based upon studies that show additional contact for behavioral counseling and support results in more successful weight loss.

The 2013 Guideline for the Management of Overweight and Obesity from the American Heart Association, the American College of Cardiology, and The Obesity Society reported that in adults with T2DM, a weight loss of 2 to 5% or 5 to 10% from behavioral lifestyle interventions results in lowering of A1C by 0.2 to 0.3% or 0.6 to 1.0%, respectively (20 [EL 4; NE]). A large retrospective cohort study found that patients with newly diagnosed T2DM who lost 10% of body weight after diagnosis were more likely to achieve A1C and BP targets, even with weight regain after 4 years, compared to individuals with stable weight or weight gain (1385 [EL 3; SS, retrospective cohort N = 2,574]).

A meta-analysis assessed RCTs studying the effectiveness of behavioral lifestyle interventions lasting ≥12 months on long-term weight loss in patients with T2DM (753 [EL 1; MRCT]). Twenty-two studies with 4,659 patients included follow-ups ranging from 1 to 5 years. Behavioral therapy addressed barriers to diet or physical activity and used strategies such as stimulus control and social support. There were considerable differences in the care provided to the comparison groups. In 9 studies the comparison group received usual care, but in 6 studies they received dietary, activity, and behavioral therapy intervention and differed from the intervention group only in other factors (i.e., type of diet, amount of calories, glucose monitoring, etc.). Pooled weight loss for any intervention compared to usual care was 1.7 kg or 3.1% of body weight. Comparison groups often achieved substantial weight loss of up to 10 kg, minimizing between-group differences. For instance, among patients with similar physical activity and behavioral intervention, those who had greater calorie restriction with a very low-calorie diet lost 3.0 kg or 1.6% body weight more than people who received a low-calorie diet. For those who received identical dietary and behavioral interventions, patients with more intense physical activity lost 3.9 kg or 3.6% of body weight more than those with less intense or less frequent activity.

A 2015 review and meta-analysis addressed behavioral lifestyle weight-loss interventions and metabolic outcomes in 'patients with T2DM who also had overweight or obesity (752 [EL 1; MRCT]). Studies included 11 RCTs of ≥12-months duration with a total of 6,754 patients and ≥70% completion rate. A total of 19 study groups were generated from 8 trials that compared 2 weight-loss interventions and 3 trials that compared weight-loss intervention with usual care/controls. Seventeen study groups that included 5 trials comparing differing amounts of macronutrients reported a weight loss of <5% and no significant beneficial effects on A1C, BP, or blood lipids. In studies that observed <5% weight loss, the average changes reported were a 2.0 to 4.9% weight loss (1.9 to 4.8 kg), a 0.2% decline in A1C, and 2.2 and 3.5 mm Hg decreases in SBP and DBP, respectively, all values being nonsignificant.

Only 2 of the 19 study groups reported a weight loss of ≥5%, namely, a Mediterranean-style diet in adults with newly diagnosed T2DM (887 [EL 1; RCT]) and an ILI in the Look AHEAD trial (754 [EL 1; RCT]; 888 [EL 1; RCT]). Participants in both of these studies had frequent contact with health professionals (primarily registered dietitians), and regular physical activity was recommended and monitored (≥150 and ≥175 min/week for the Mediterranean-diet study and Look AHEAD study, respectively). The Mediterranean-style diet was rich in vegetables, whole grains, and olive oil, and patients had their calorie intake restricted to 1,500 kcal/day for women and 1,800 kcal/day for men, whereas the Look AHEAD study used meal replacements or a structured food plan as well as one-on-one and group counseling sessions. Respectively, these 2 studies reported significant changes at 12-months that included weight loss of 7.2% and 8.6% (6.2 and 8.6 kg), A1C decline of 1.2% and 0.6%, SBP lowering of 2.3 and 9.9 mm Hg, and DBP lowering of 4.0 and 3.1 mm Hg. When the Look AHEAD data were averaged across 4 years, the ILI group, when compared to the standard DSE, had significantly greater weight loss (6.2% vs. 0.9%), better treadmill fitness (13% vs. 2%), lower A1C levels (0.4% vs. 0.1%), lower SBP (5.3 vs. 3.0 mm Hg) and DBP (2.9 vs. 2.5 mm Hg), and higher HDL-c (3.7 vs. 2.0 mg/dL) with decreased triglyceride levels (25.6 vs. 19.8 mg/dL) (755 [EL 1; RCT]). While both the ILI and DSE groups had medication intensification over the course of the Look AHEAD trial, more medications were used for glucose, lipid, and BP control in the DSE group with subsequent higher health-care costs. Thus, the majority of lifestyle weight-loss interventions in patients with T2DM reviewed by Franz et al (752 [EL 1; MRCT]) resulted in weight loss of <5% and did not significantly improve metabolic outcomes. A weight loss of >5% appears necessary for beneficial effects on A1C, lipids, and BP in patients with T2DM. Even greater improvements in the CVD risk factors were observed in patients who lost up to ≥15% of their body weight (754 [EL 1; RCT]). However, to achieve a level of >5% weight loss, patients with T2DM have been shown to require intense behavioral lifestyle interventions and frequent contact with trained health professionals.

A number of studies have looked at the feasibility of using interventional technology support for weight loss. A group-based behavioral intervention study randomly assigned 692 women to receive supplemental telephone counseling and tailored newsletters or a less-intensive control intervention for 2 years (1386 [EL 1; RCT]). The intervention began with small groups of women that met weekly for a 1-hour group session for 4 months, tapered to every other week for another 2 months, and then monthly for the remainder of the year. The behavior strategies and guidance discussed in group sessions were reinforced by brief telephone and/or email contact. At 1 and 2 years, respectively, the intervention group realized significantly more weight loss of 6% and 3.7% compared to 1.5% and 1.3% in the control group. In total, 44% and 15% of the intervention group participants lost ≥5% and ≥10% of body weight, respectively, at 2 years.

The Tobacco, Exercise and Diet Messages (TEXT ME) trial was a parallel-group, single blind, RCT of 710 patients with CVD who were randomized to receive 4 weekly text messages compared to usual care (1387 [EL 1; RCT]). Text messages provided advice, motivational reminders, and support for lifestyle behavior change, but the program was not interactive. Most patients reported the text-message program to be useful (91%), easy to understand (97%), and appropriate in frequency (86%). After 6 months, the intervention group had significant beneficial outcomes for BMI, physical activity, SBP, and LDL-c. A tailored, interactive text-message intervention RCT was conducted in 124 African-American adults with obesity (1388 [EL 1; RCT]). Patients were randomized to either standard care alone (i.e., one-on-one counseling sessions with a dietitian and physician) or standard care plus daily tailored text messages. Text messages were delivered in 3 phases for preparation, reinforcement, and maintenance of diet and exercise goals, reflection, and goal integration. Mean weight loss was 2.5 kg greater in the intervention group at 3 months and 3.4 kg greater at 6 months, but a high rate of attrition was a primary study limitation. A systematic review and meta-analyses of text-messaging intervention studies have reported strong evidence that the majority of published text-messaging interventions were effective when addressing T2DM self-management, weight loss, and physical activity (1389 [EL 4; NE]). At present, more research is needed to assess the preferred intervention characteristics, long-term outcomes, and cost-effectiveness of interactive technology-driven behavioral support in achieving weight loss.

A mobile phone-based Diabetes Prevention Program (mDPP) used a mobile application and pedometer to augment behavioral lifestyle intervention modified from the original DPP curriculum in adults with overweight who

were at risk for T2DM (1390 [EL 1; RCT]). The mDPP mobile app was used to supplement in-person educational sessions and included electronic diaries for self-monitoring of body weight, activity, and calorie intake. Interactive content included daily messages, video clips, and quizzes to reinforce positive behaviors. The control group received educational material about prediabetes, was given a display pedometer to count steps, and otherwise received standard medical care. The intervention group lost 6.8% (6.2 kg) of body weight at 5 months compared to a 0.3% (0.3 kg) weight gain in the control group. Compared to controls, the intervention group had significantly improved outcomes for steps per day, BP, hip circumference, and dietary intake of saturated fat and sugar-sweetened beverages. There was no significant effect on fasting glucose or lipid levels. A fully automated behavioral 6-month RCT used email, Internet, and mobile phone support among persons with prediabetes to improve physical activity and eating habits (1391 [EL 1; RCT]). Emails suggested stepped-care goals and were linked to individual Web-based support tools. A mobile phone app and automated phone calls provided further behavioral support. The participant retention rate was 71%, and patients were still interacting with the program at 6 months. The interactive group achieved significant beneficial changes in fasting glucose, A1C, BMI, WC, and lipids compared to controls.

A 2015 systematic review and meta-analysis of 12 studies assessed mobile phone app interventions with weight-related health outcomes (1392 [EL 2; MNRCT]). Compared to control groups, the use of a mobile phone app was associated with significant changes in BMI. The effect of a Web-based behavior change program on weight loss was also assessed in an RCT involving 65 adults with overweight or obesity that were at high risk of developing CVD (1393 [EL 1; RCT]). One group of patients was randomly assigned to a Web-based program, which supported healthy eating and physical activity to assist in weight management. The second group performed self-care. The respective retention rates for the intervention and control groups were 66% versus 94% at 6 months and 53% versus 88% at 12 months. Using intention-to-treat analysis with baseline observations carried forward revealed that the intervention group lost more weight compared to controls at 3 and 6 months, but not at 12 months. More patients in the intervention group lost ≥5% of body weight at 3 and 6 months, but not at 12 months. A limitation of this study was the high attrition rate in the intervention group.

A large, interactive Web-based program assessed eating behaviors in 22,800 patients using an 18-item Three-Factor Eating Questionnaire revised to measure uncontrolled eating, emotional eating, and cognitive restrained eating (1394 [EL 2; PCS]). The Web-based weight-loss program included information on healthy lifestyle, weekly chats with experts, social networking features, databases for recipe searches, and features to track an individual's weight, activity, and dietary intake. Subjects that completed the study decreased their uncontrolled eating score and increased their cognitive restrained eating. Men decreased their emotional eating, but no significant change was seen in women. The baseline cognitive restrained eating score was significantly and positively associated with weight loss in both men and women that completed the study.

The National Weight Control Registry, a U.S. database founded in 1993, has identified the lifestyle modifications practiced by free-living individuals who were able to successfully maintain weight loss. Thomas et al (1395 [EL 3; SS, registry analysis]) identified 2,886 participants with mean weight loss of 23.1 ± 0.4 kg at 10 years and found that ≥87% of these participants maintained a weight loss of ≥10%. The characteristics common to successful weight-loss maintainers included high levels of volitional physical activity (1396 [EL 3; SS, registry analysis]); reduced fat intake (1396 [EL 3; SS, registry analysis]); greater dietary restraint (1396 [EL 3; SS, registry analysis]); self-monitoring of weight, dietary intake, and physical activity (1396 [EL 3; SS, registry analysis]); consumption of low-/no-calorie sweetened beverages to limit total energy intake (1397 [EL 3; SS, registry analysis]); and limited television viewing time (≤10 hours per week) (1398 [EL 3; SS, registry analysis]).

Structured Lifestyle Intervention Programs. While the analysis of lifestyle/behavior therapy has been somewhat reductionist, in that diet, physical activity, and behavioral interventions were considered separately, it is clear that a surfeit of evidence has confirmed the efficacy of structured multidisciplinary programs that incorporate the combination of reduced-calorie meal plans, physical activity prescriptions, and a behavioral intervention package. The efficacy of structured multicomponent lifestyle therapy is amply demonstrated in RCTs that compare an intensive program of caloric reduction, physical activity, and behavior interventions with a standard or usual care control subgroup. Lifestyle therapy programs produced substantially greater weight loss in multiple such studies including the DPP (708 [EL 1; RCT]), the Look AHEAD study (888 [EL 1; RCT]), the ADAPT Study (1399 [EL 1; RCT]), the PREMIER Trial (1235 (EL 1; cRCT]), the Finnish Diabetes Prevention Study (707 [EL 1; RCT]), the Da Qing Diabetes Prevention Study (706 [EL 1; RCT]), the DIRECT study (1384 [EL 1; RCT]), the PRIDE study (623 [EL 3; CSS]), the POWER Study (1218 [EL 1; RCT]), and the Trial of Nonpharmacologic Intervention in the Elderly (TONE) Trial (1400 [EL 1; RCT]). While some patients do well with less intensive lifestyle interventions, the data strongly support the recommendation that structured lifestyle therapy programs should be available to patients who are being treated for the disease of obesity. The critical components of a reduced-calorie meal plan, physical activity, and behavioral interventions can be delivered in various

venues, including offices, clinics, community settings, work sites, and commercial entities, and can be delivered in face-to-face meetings and group sessions and/or using remote technologies (telephone, Internet, text messaging). RCTs have been conducted demonstrating the efficacy of several commercial programs (1401 [EL 2; MNRCT]; 1402 [EL 1; RCT]; 1403 [EL 1; RCT]; 1404 [EL 1; RCT]; 1405 [EL 1; RCT, extension study]). The studies referenced above demonstrate the efficacy of comprehensive structured programs that feature frequent contact between health care professionals and patients and that accommodate personal and cultural preferences of patients.

- ***Q7. Is pharmacotherapy effective to treat overweight and obesity?***
  - *Q7.1. Should pharmacotherapy be used as an adjunct to lifestyle therapy or alone?*

Executive Summary

- **R76.** Pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone **(Grade A; BEL 1)**.

Evidence Base

Comprehensive lifestyle modification is generally recommended for all individuals with overweight or obesity, either as the only initial approach to weight loss or in combination with weight-loss medications or bariatric surgery (1406 [EL 4; NE]). Lifestyle modification incorporates behavioral therapy, physical activity, and dietary modification. Most clinical trials assessing pharmacotherapy for obesity compare drug plus lifestyle modification to lifestyle modification plus placebo. The lifestyle interventions employed in these studies vary in intensity, frequency of contact, and in the extent of involvement of individual counseling, group counseling, printed materials, and/or recommendations for self-monitoring. For this reason, in comparing clinical trials, there is variable weight loss among participants randomized to the lifestyle plus placebo group. In essentially all studies of obesity medications, lifestyle modification is effective in achieving some weight loss; however, the addition of weight-loss medication consistently results in a greater degree of weight loss than lifestyle alone.

A few studies have compared the effects of pharmacotherapy without lifestyle modification to lifestyle alone or pharmacotherapy plus lifestyle. In a 20-week study of pharmacotherapy without lifestyle therapy, administration of benzphetamine and phenmetrazine resulted in significantly greater weight loss than placebo (1407 [EL 2; RCCS]). In studies that are more informative, lifestyle interventions in combination with either sibutramine, fenfluramine, or orlistat resulted in greater weight loss than in those patients randomized to drug alone or lifestyle alone (1353 [EL 1; RCT]; 1408 [EL 1; RCT]; 1409 [EL 1; RCT]; 1410 [EL 2; PCS]; 1411 [EL 1; RCT]). Thus, the drugs alone resulted in only modest weight loss with inferior outcomes compared to the use of weight-loss medications as an adjunct to lifestyle (1353 [EL 1; RCT]; 1408 [EL 1; RCT]; 1409 [EL 1; RCT]; 1410 [EL 2; PCS]; 1411 [EL 1; RCT]; 1412 [EL 2; PCS]). Weight regain may be greater after stopping pharmacotherapy when behavior modification is not included (1410 [EL 2; PCS]). There are no studies evaluating phentermine/topiramate ER, naltrexone ER/bupropion ER, lorcaserin, or liraglutide alone in the absence of lifestyle modification.

While a limited number of studies have examined the effects of drug therapy alone in the absence of lifestyle modification, the available data indicate that pharmacotherapy alone does not result in as much weight loss as achieved by pharmacotherapy plus lifestyle therapy. Weight regain may be less likely when behavioral therapy is provided as part of a weight management program. In addition, lifestyle modification therapy, via facilitation and education regarding increased physical activity and adherence to a healthy meal plan, may entrain the patient in lifestyle practices leading to better long-term outcomes (1406 [EL 4; NE]).

- *Q7.2. Does the addition of pharmacotherapy produce greater weight loss and weight-loss maintenance compared with lifestyle therapy alone?*

Executive Summary

- **R77.** The addition of pharmacotherapy produces greater weight loss and weight-loss maintenance compared with lifestyle therapy alone **(Grade A; BEL 1)**.
- **R78**. The concurrent initiation of lifestyle therapy and pharmacotherapy should be considered in patients with weight-related complications that can be ameliorated by weight loss **(Grade A; BEL 1)**.

Evidence Base

The study design of phase 3 clinical trials leading to FDA approval has consistently placed all volunteers on a lifestyle intervention with randomization to either weight-loss medication or placebo. Orlistat is an intestinal lipase inhibitor that causes weight loss by inducing fat malabsorption. Orlistat results in clinically significant weight loss that exceeds that observed in patients randomized to lifestyle alone and helps maintain weight loss and prevent weight regain. Mean weight loss with 120 mg orlistat 3 times/day has ranged from 4.6 to 10.2% of body weight versus 1.6 to 6.6% of body weight with placebo in studies ranging from 1 to 2 years (70 [EL 1; RCT]; 776 [EL 1; RCT]; 856 [EL 1; RCT]; 1413 [EL 2; MNRCT]; 1414 [EL

1; RCT]; 1415 [EL 1; RCT]; 1416 [EL 1; RCT]; 1417 [EL 1; MRCT]; 1418 [EL 1; RCT]; 1419 [EL 1; RCT]; 1420 [EL 1; RCT]). In a 4-year study, a mean weight loss of 3.0 kg with placebo versus 5.8 kg with the drug was reported by the end of the study (721 [EL 1; RCT]).

Phentermine, a norepinephrine releasing agent that suppresses appetite, is approved only for short-term use (i.e., <3 months). Phentermine combined with topiramate ER, a carbonic anhydrase inhibitor, is approved for chronic treatment of obesity. In combination with a lifestyle intervention, phentermine/topiramate ER has been shown to be effective in weight loss and weight-loss maintenance to a greater extent than in patients randomized to lifestyle alone in several large, randomized, placebo-controlled trials ranging up to 108 weeks (71 [EL 1; RCT]; 712 [EL 1; RCT]; 722 [EL 1; RCT]; 777 [EL 1; RCT]; 858 [EL 1; RCT]; 1421 [EL 1; RCT]). Phentermine/topiramate ER was studied in patients with overweight plus complications (BMI 27.0 to 29.9 kg/m^2) or obesity (BMI ≥30 kg/m^2) with and without complications, including patients with T2DM. The mean change in body weight ranged from −1.2 to −2.5%, −7.8 to −9.3%, and −10.5 to −12.1% for the placebo, 7.5/46 mg dose, and 15/92 mg dose, respectively.

Lorcaserin is a 5-hydroxytryptamine-2c (5-HT$_{2C}$) receptor agonist, which reduces appetite and food intake. Lorcaserin has been studied in patients with BMI ≥27 kg/m^2 and complications or BMI ≥30 kg/m^2 in conjunction with lifestyle modification at a dose of 10 mg twice daily in studies ranging from 1 to 2 years. It has been studied in patients with and without diabetes. Mean percent weight loss has ranged from 4.5 to 5.8% in patients randomized to lorcaserin versus 1.5 to 2.8% with placebo (69 [EL 1; RCT]; 778 [EL 1; RCT]; 857 [EL 1; RCT]). In a 2-year study, patients randomized to lorcaserin maintained lower body weights than with lifestyle alone, and patients that received lorcaserin who were rerandomized to placebo at the end of the first year regained weight up to the level achieved in the lifestyle intervention arm by the end of year 2 (857 [EL 1; RCT]).

Bupropion is a dopamine and norepinephrine reuptake inhibitor, and naltrexone is a μ-opioid receptor antagonist. The combination of naltrexone ER/bupropion ER has been approved for chronic weight management and works synergistically to suppress appetite via a central mechanism. Naltrexone ER/bupropion ER taken twice daily at a total daily dose of 32/360 mg was studied in 3 clinical trials of 56-week duration in patients with BMI ≥27 kg/m^2 and with HTN, dyslipidemia, and/or T2DM, or a BMI ≥30 kg/m^2. Mean weight loss ranged from 5.0 to 6.4% with naltrexone ER/bupropion ER versus 1.2 to 1.8% with placebo (67 [EL 1; RCT]; 779 [EL 1; RCT]; 1422 [EL 1; RCT]). In a fourth trial employing a high intensity lifestyle intervention, greater weight loss was achieved and maintained in patients randomized to naltrexone ER/bupropion ER than to placebo (9.3% vs. 5.0%) (859 [EL 1; RCT]). In all trials, weight loss was maintained in the treatment groups after the initial weight loss (67 [EL 1; RCT]; 779 [EL 1; RCT]; 859 [EL 1; RCT]; 1422 [EL 1; RCT]).

Liraglutide is a GLP-1 receptor agonist approved for treatment of T2DM at doses up to 1.8 mg/day and for weight loss at a higher dosage of 3.0 mg/day. When injected subcutaneously once daily, liraglutide 3 mg reduces appetite, increases satiety, and lowers energy intake via a central mechanism. In vitro studies suggest that GLP-1 directly stimulates pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript neurons and indirectly inhibits neurotransmission in neurons expressing neuropeptide Y and Agouti-related peptide via gamma-aminobutyric acid (GABA) in the arcuate nucleus of the hypothalamus. In 4 studies of 56-week duration involving patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with dyslipidemia, hypertension, or diabetes, weight loss ranged from 6.0 to 8.0% with 3 mg of liraglutide versus 0.2 to 2.6% with placebo (68 [EL 1; RCT]; 780 [EL 1; RCT]; 897 [EL 1; RCT]; 1423 [EL 1; RCT]; 1424 [EL 1; RCT]). One study included a run-in that featured 5% weight loss on a low-calorie diet, at which point patients were randomized to liraglutide 3 mg or placebo plus continuation of lifestyle. The initiation of liraglutide 3 mg led to an additional ~6% weight loss compared with those patients who continued the lifestyle intervention alone (1424 [EL 1; RCT]). In another study with a second-year extension, 85% of patients who lost ≥5% of body weight maintained this weight loss by the end of the second year (897 [EL 1; RCT]).

When combined with lifestyle intervention, all drugs currently approved by the FDA for chronic weight management produced greater weight loss and sustained the weight loss for a greater length of time than did lifestyle intervention alone (1425 [EL 4; NE]). The degree of weight loss achieved with the addition of these medications has consistently been associated with greater health benefits.

- *Q7.3. Should pharmacotherapy only be used in the short term to help achieve weight loss or should it be used chronically in the treatment of obesity?*

Executive Summary

- **R79.** Pharmacotherapy should be offered to patients with obesity, when potential benefits outweigh the risks, for the chronic treatment of their disease **(Grade A; BEL 1)**. Short-term treatment (3 to 6 months) using weight-loss medications has not been demonstrated to produce longer-term health benefits and cannot be generally recommended based on scientific evidence **(Grade B; BEL 1, downgraded due to evidence gaps)**.

Evidence Base

Obesity is a disease with complications that include T2DM, CVD, metabolic syndrome, some types of cancer, OSA, OA, disability, GERD, urinary incontinence, NAFLD, depression, and decreased lung function (1426 [EL 4; NE]). These complications can be prevented or ameliorated by weight-loss therapy (1425 [EL 4; NE]). Medication-assisted weight loss can effectively improve BP, dyslipidemia, glycemia, markers of inflammation, and insulin resistance (67 [EL 1; RCT]; 68 [EL 1; RCT]; 69 [EL 1; RCT]; 71 [EL 1; RCT]; 712 [EL 1; RCT]; 721 [EL 1; RCT]; 722 [EL 1; RCT]; 777 [EL 1; RCT]; 778 [EL 1; RCT]; 779 [EL 1; RCT]; 780 [EL 1; RCT]; 856 [EL 1; RCT]; 857 [EL 1; RCT]; 858 [EL 1; RCT]; 859 [EL 1; RCT]; 897 [EL 1; RCT]; 1417 [EL 1; MRCT]; 1421 [EL 1; RCT]; 1422 [EL 1; RCT]; 1423 [EL 1; RCT]; 1424 [EL 1; RCT]; 1427 [EL 1; RCT]).

Short-term pharmacotherapy has been shown to be effective for weight loss (1428 [EL 4; NE]). When sympathomimetic drugs became available over 4 decades ago, obesity was not recognized as a chronic disease, and it was accepted that short-term pharmacotherapy may be appropriate. Most drugs were only studied in the short term and were FDA-approved for such use, which was generally a period of 12 weeks or less. Short-term trials of phentermine, diethylpropion, phendimetrazine, and benzphetamine demonstrated greater weight loss versus placebo (1429 [EL 1; MRCT]; 1430 [EL 1; RCT]; 1431 [EL 1; RCT, small group sizes: 12 to 13 for each of 3 groups]; 1432 [EL 1; RCT]). In a 36-week study, intermittent therapy with phentermine showed equal efficacy to continuous therapy (1433 [EL 2; NRCT, allocation concealment]). In a 16-week study, intermittent therapy with diethylpropion showed equal efficacy to continuous therapy as long as the active drug was initiated first (1434 [EL 2; NRCT, allocation concealment]). Short-term treatment with orlistat was also proven effective over 12 weeks, alone and in combination with sibutramine (1435 [EL 1; RCT]). It was generally accepted that short-term use of weight-loss medications (3 to 6 months) could be used to assist patients during the early phase of weight loss upon initiation of lifestyle therapy and a reduced-calorie meal plan. The medications used in this manner predictably resulted in greater weight loss than that achieved by lifestyle alone. However, patients would begin to regain weight upon discontinuance of the medication, and there are no data showing that short-term therapy produces long-term health benefits in terms of reversal of weight-related complications. As our scientific understanding of obesity has advanced, it has become clear that obesity is a chronic disease (12 [EL 4; NE]) that generally requires long-term therapy. For this reason, short-term use of weight-loss medications cannot be generally recommended based on available scientific evidence.

Weight loss as a result of clinical interventions, even with pharmacologic assistance, typically plateaus at around 6 to 9 months. Multiple pathophysiologic mechanisms act to restore weight to its elevated baseline during and after weight-loss interventions in patients with overweight or obesity. This is due to metabolic adaptations that counteract weight loss, including decreases in spontaneous physical activity (1436 [EL 1; RCT]), reduced physical activity (1436 [EL 1; RCT]), decreased resting energy expenditure (1437 [EL 2; PCS, weight-matched subjects]), efficiency of muscle metabolism (1438 [EL 1; RCT, only 10 subjects]), and changes in leptin, ghrelin, and other gut hormones that augment appetite and encourage weight regain (1439 [EL 2; PCS]). These mechanisms that drive weight regain are part of the pathophysiology of obesity as a disease and must be counterbalanced by efforts to maintain weight loss over an extended time.

In pharmacotherapy trials following the weight-loss plateau, weight is typically regained after the medication is stopped (780 [EL 1; RCT]; 857 [EL 1; RCT]; 1409 [EL 1; RCT]; 1418 [EL 1; RCT]). Increasing the duration of treatment does not typically lead to greater weight loss; however, the effect of the medication transitions from promotion of weight loss to assisting in weight maintenance. Current medications approved for long-term use all show efficacy in weight-loss maintenance (67 [EL 1; RCT]; 68 [EL 1; RCT]; 69 [EL 1; RCT]; 71 [EL 1; RCT]; 712 [EL 1; RCT]; 721 [EL 1; RCT]; 722 [EL 1; RCT]; 777 [EL 1; RCT]; 778 [EL 1; RCT]; 779 [EL 1; RCT]; 780 [EL 1; RCT]; 856 [EL 1; RCT]; 857 [EL 1; RCT]; 858 [EL 1; RCT]; 859 [EL 1; RCT]; 897 [EL 1; RCT]; 1417 [EL 1; MRCT]; 1421 [EL 1; RCT]; 1422 [EL 1; RCT]; 1423 [EL 1; RCT]; 1424 [EL 1; RCT]; 1427 [EL 1; RCT]).

Thus, available data support the need for long-term use of weight-loss medications in appropriate patients, consistent with the pathophysiology of obesity. Currently available medications have been prospectively studied with good success in randomized controlled trials for 1 to 4 years. However, the optimal duration of therapy is unknown. Additional studies are needed to establish the optimal long-term use of weight-loss medications including the assessment of intermittent therapy.

- *Q7.4. Are there differences in weight-loss drug efficacy and safety? (Table 10 in Executive Summary)*

Executive Summary

- **R80.** In selecting the optimal weight-loss medication for each patient, clinicians should consider differences in efficacy, side effects, cautions, and warnings that characterize medications approved for chronic management of obesity, as well as the presence of weight-related complications and medical history; these factors are the basis for individualized weight-loss pharmacotherapy; a generalizable hierarchical algorithm for medication preferences that would be applicable to all

patients cannot currently be scientifically justified **(Grade A; BEL 1)**.

- **R81.** Clinicians and their patients with obesity should have available access to all approved medications to allow for the safe and effective individualization of appropriate pharmacotherapy **(Grade D)**.

Evidence Base

Weight-loss medications are prescribed as an adjunct to lifestyle therapy and help to achieve a greater degree of weight loss than that produced by dietary changes and physical activity alone. The National Institutes of Health obesity treatment algorithm (16 [EL 4; NE]) embodies FDA-sanctioned indications for all weight-loss medications, which can be used in patients with overweight having a BMI of 27 to 29.9 kg/m^2 plus one or more complications (e.g., hypertension, hyperlipidemia, T2DM) or with obesity (BMI ≥30 kg/m^2) regardless of whether complications are present. These criteria constitute the indications for drug use in the prescribing information for weight-loss medications.

The efficacy of all weight-loss medications has been assessed in RCTs randomizing patients with overweight or obesity to drug plus lifestyle intervention versus placebo plus lifestyle intervention. In most instances, the lifestyle intervention consisted of a caloric deficit of ~500 kcal/day in addition to increased physical activity. The primary outcome measures for the RCTs denote the amount of weight loss and reflect the FDA Obesity Drug Guidance for efficacy (17 [EL 4; NE]). For approval, RCTs must demonstrate that mean placebo-subtracted weight loss is ≥5% in patients taking the drug, and/or the proportion of drug-treated patients who lose ≥5% of baseline weight is ≥35% and approximately double the proportion that lose ≥5% in the placebo group. The RCT program for any given medication should include ≥4,500 participants, and efficacy and safety should be assessed over a study period of at least 1 year. Secondary endpoints of interest include BP and pulse, lipids, fasting glucose and insulin, WC, QOL, and A1C in patients with diabetes. All approved weight-loss medications have been evaluated under this level of scrutiny.

RCTs leading to the approval of currently available weight-loss medications have demonstrated differences in efficacy regarding mean percent weight loss and the proportion of patients who obtained 5% and 10% weight-loss thresholds (10 [EL 4; NE]; 1440 [EL 4; NE]). However, it is difficult to directly compare these parameters because there are no head-to-head trials of any significant size for the 5 medications approved for chronic management of obesity: orlistat, phentermine/topiramate ER, lorcaserin, naltrexone ER/bupropion ER, and liraglutide 3 mg. Note, the one exception is an RCT that included orlistat and liraglutide 3 mg treatment arms and demonstrated greater weight loss after 1 year in the liraglutide 3 mg treatment arm (7.8%) than in the patients randomized to orlistat (3.9%) (897 [EL 1; RCT]). Furthermore, weight-loss medications were generally tested in different study populations and employed lifestyle interventions that varied in intensity.

Until more reliable data are available from head-to-head trials, differences in efficacy can best be compared by examining placebo-subtracted weight loss across the various trials. Figure 1 shows weight loss achieved in both drug and placebo treatment arms for the key phase 3 RCTs leading to the approval of each of the weight-loss medications and features data obtained using the recommended treatment dose for each medication, not necessarily the maximal dose. The medication showing the greatest placebo-subtracted weight loss is phentermine/topiramate ER at 8%. Intermediate values were obtained for naltrexone ER/bupropion ER and liraglutide 3 mg at ~6%, followed by orlistat and lorcaserin at 4 to 4.5%. Table 10 shows the baseline characteristics of the patients in the drug and control groups in each of these RCTs, as well as the proportion of participants who achieved categorical weight loss of 5% and 10% for each drug. In conjunction with the lifestyle intervention (which varied in intensity between the different RCTs), all medications resulted in 1-year completers achieving a mean weight loss of 7.9 to 9.6% from baseline.

Despite these apparent differences in efficacy, the amount of weight loss achieved by these medications was sufficient to improve the health of patients with obesity as reflected in greater improvements in WC, BP, lipids, fasting glucose and insulin, and QOL in most trials. It should be considered that even a modest sustained weight loss of 5% is likely to result in clinically meaningful reductions in triglycerides, blood glucose, A1C, and the risk for developing T2DM (20 [EL 4; NE]; 754 [EL 1; RCT]). Furthermore, the 5 approved weight-loss medications each represent a unique class of drug with different mechanisms of action, unlike other disease states where there may be several drugs with very similar mechanisms of action. Each drug also has its own side-effect profile with the potential for both mild and serious adverse reactions. For this reason, benefits and risks must be considered, and the clinician must individualize therapy based on each patient's unique characteristics. As a consequence, a generalizable hierarchical algorithm for weight-loss medication preferences that would be applicable to all patients cannot be scientifically justified. Differences in efficacy, side effects, warnings and cautions, the presence of weight-related complications, and other clinical factors must be considered in selecting the optimal weight-loss medication for each individual patient.

Orlistat is a reversible inhibitor of GI lipases and specifically reduces the absorption of dietary fat due to the inhibition of triglyceride hydrolysis (1441 [EL 1; RCT]). Orlistat (120 mg) 3 times a day before meals is the standard prescription dose. Orlistat has also been approved in a reduced dosage form (60 mg) for over-the-counter sales. Orlistat exerts its therapeutic activities in the lumen of the

stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. Because of the inhibition of these enzymes, dietary fat remains undigested as triglycerides and cannot be converted to absorbable free fatty acids and monoglycerides. This leads to decreased calorie absorption.

Orlistat is primarily associated with GI side effects. Because it is active in the lumen of the GI tract and reduces the absorption of triglycerides, many adverse events are related to lipid malabsorption (1442 [EL 4; NE]). The most common issues after 1 year were oily spotting (26.6% vs. 1.3% in placebo), flatus with discharge, and fecal urgency. Orlistat, like all weight-loss medications, is contraindicated in pregnancy and hypersensitivity to the drug. Additional contraindications include malabsorption syndromes and cholestasis. Warnings include increased urinary oxalate with risk of oxalate stone formation and nephropathy, rare cases of hepatic failure, cholelithiasis, and interference with absorption of fat-soluble vitamins, cyclosporine, thyroid hormone, and anti-epileptic drugs (1442 [EL 4; NE]).

A randomized, double-blind, placebo-controlled, multicenter registration study was conducted comparing orlistat (120 mg) 3 times per day with a placebo plus lifestyle intervention control (70 [EL 1; RCT]). Patients in the orlistat (120 mg) group lost significantly more weight than those in the placebo group, 8.78% versus 4.26%, respectively, in year 1 among completers ($P = 0.001$). More participants treated with orlistat (120 mg) lost 5% or more of their initial weight in year 1 compared to those in the placebo group, 50.5% versus 30.7%, respectively ($P<0.001$).

The combination of phentermine, an anorexigenic agent, and topiramate, a drug used for treatment of epilepsy and migraine prophylaxis, is approved for chronic weight management. While the mechanism of action of sympathomimetics such as phentermine has not been fully elucidated, weight loss is believed to be due to increased release of biogenic amines (mainly norepinephrine, but also possibly dopamine) from storage sites in nerve terminals (1443 [EL 4; NE]). Topiramate administration is associated with both appetite suppression and satiety enhancement although, again, the underlying mechanisms are unknown. These effects may be due to a combination of pharmacologic effects, including the augmentation of the activity of the neurotransmitter gamma-aminobutyrate, modulation of voltage-gated ion channels, inhibition of AMPA/kainate excitatory glutamate receptors, or inhibition of carbonic anhydrase. The most common side effects occurring with a greater frequency than in placebo groups are attributable to either phentermine, such as insomnia and dry mouth, or are due to the carbonic anhydrase activity of topiramate, such as paresthesia and dysgeusia (1444 [EL 4; NE]). Contraindications include glaucoma, hyperthyroidism, and monoamine oxidase inhibitor (MAOI) administration. Warnings include metabolic acidosis, cognitive impairment, elevated heart rate, nephrolithiasis, hypokalemia, and mood disorders. While phentermine/topiramate ER is contraindicated in pregnancy like all weight-loss medications, extra precaution should be taken because topiramate used to treat epilepsy has been associated with an increased risk of fetal cleft lip and palate among mothers taking the drug during the first month of pregnancy (1444 [EL 4; NE]). Women of reproductive potential should take a pregnancy test initially and every month while on the medication (can be performed using home pregnancy testing) and should use effective birth control. Co-administration of the maximal dose of phentermine/topiramate ER (15 mg/92 mg) with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the estradiol level by 16% and increased the progestin component by 22% (1444 [EL 4; NE]), which could be associated with irregular menstruation or spotting.

A double-blind RCT compared the phentermine/topiramate ER standard dose of 7.5 mg/46 mg with placebo plus lifestyle (71 [EL 1; RCT]) and demonstrated that mean weight loss in the drug and placebo treatment arms were 9.6% and 1.6% ($P<0.0001$), respectively, in the completer population. Weight loss of ≥5% was achieved in 62% of patients assigned to phentermine/topiramate ER and in 21% of patients in the placebo group.

Lorcaserin selectively acts as an agonist of the 5-HT_{2c} receptor to suppress appetite (1445 [EL 4; NE]). Preclinical studies indicate that 5-HT_{2c} receptors are located on the pro-opiomelanocortin (POMC) neurons in the arcuate nucleus and stimulate the release of alpha-melanocortin-stimulating hormone (alpha-MSH), which in turn acts on melanocortin-4 receptors in the paraventricular nucleus in the anorexigenic pathway. As a serotonergic agonist, lorcaserin has the potential to interact with other medications affecting serotonin to cause serotonin syndrome or neuroleptic malignant syndrome-like reactions (1445 [EL 4; NE]). Because of this, use of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, bupropion, triptans, MAOIs, lithium, dextromethorphan, and dopamine agonists should be avoided in patients taking lorcaserin. Patients with depression and taking SSRIs and SNRIs were excluded from RCTs involving lorcaserin; therefore, safety data for lorcaserin administration is lacking in these patients.

Side effects associated with lorcaserin include headache, dizziness, fatigue, nausea, and dry mouth. Warnings include cognitive impairment, euphoria, priapism, bradycardia, leucopenia, and elevated prolactin. Valvular heart disease has been reported in patients that take medications with 5-HT_{2b} agonist activity such as fenfluramine. In a pooled analysis of 3 RCTs involving 7,794 patients receiving echocardiograms, lorcaserin was not significantly associated with the development of valvulopathy (RR 1.16; CI, 0.81, 1.67) (1445 [EL 4; NE]). Nevertheless, it is advised to stop the medication should valvulopathy

develop and to avoid its use in patients with existing valvulopathy.

In an RCT randomizing participants to lorcaserin (10 mg) twice daily or placebo plus lifestyle intervention (69 [EL 1; RCT]), completer analysis showed greater weight reduction with lorcaserin (7.9%) than in the placebo group (2.8%) (P<0.001). Among patients receiving lorcaserin (10 mg) twice daily, 47.2% lost ≥5% of baseline body weight, whereas only 25.0% of patients receiving placebo achieved the same level of weight loss (P<0.001).

Naltrexone ER/bupropion ER is a combination of 2 medications that were previously approved for other indications (1446 [EL 4; NE]). Bupropion is a weak inhibitor of neuronal reuptake of dopamine and norepinephrine, which has been used to treat depression and seasonal affective disorder and to aid in smoking cessation. Naltrexone is a μ-opioid antagonist used in the treatment of addiction. These 2 drugs exert complementary actions in the central nervous system to reduce food intake via activation of the anorexigenic pathway, dampening of reward pathways, and reducing compulsive feeding behavior and the pleasure of feeding. In the hypothalamus, bupropion stimulates POMC expressing neurons to increase alpha-MSH production, which results in reduced food intake (1447 [EL 1; RCT, human proof-of-concept trial; note there are also preclinical studies in this paper]). Naltrexone further augments alpha-MSH release by blocking opioid-receptor mediated POMC auto-inhibition. Preclinical data also suggest that both drugs reduce food intake by regulating reward pathways in the mesolimbic dopamine circuit.

The most common side effect in patients taking naltrexone ER/bupropion ER is nausea (32.5% vs. 6.7% with placebo), which generally occurs early and then diminishes with an infrequent need to discontinue the medication (1448 [EL 4; NE]). Other side effects associated with the medication are headache, vomiting, dizziness, insomnia, and dry mouth. Ideally, naltrexone ER/bupropion ER should not be taken with high-fat meals since this can result in significant increments in bupropion and naltrexone systemic exposure (1448 [EL 4; NE]). In patients taking naltrexone ER/bupropion ER, mean BP rises by 1 mm Hg during the first 8 weeks and then returns to baseline; however, the BP does not decrease below baseline when changes in BP commensurate with the weight loss achieved are considered. In addition, naltrexone ER/bupropion ER increases heart rate by 1.7 beats per minute. For these reasons, patients with uncontrolled HTN should avoid taking naltrexone ER/bupropion ER. Because naltrexone is an opioid receptor antagonist, naltrexone ER/bupropion ER should not be taken by patients who are regularly taking opioids or who are experiencing opiate withdrawal. Since bupropion is an antidepressant medication, it has a boxed warning of increased risk of suicidal thoughts and behaviors, especially in children, adolescents, and young adults. Bupropion can also lower the seizure threshold; therefore, it should not be used in people with a seizure disorder. Warnings include suicidal behavior and ideation, neuropsychiatric symptoms, seizures, increased BP and heart rate, and hepatotoxicity (1448 [EL 4; NE]). Contraindications include uncontrolled hypertension, seizure disorder, bulimia or anorexia nervosa due to seizure risk, chronic use of opioid drugs, abrupt discontinuation of alcohol, and MAOI use.

In a 56-week RCT randomized participants to naltrexone ER/bupropion ER (32 mg/360 mg daily) or placebo plus lifestyle (67 [EL 1; RCT]), weight loss in the completer population was greater in patients receiving the drug (8.0%) than in the placebo group (1.9%) (P<0.001). Regarding categorical weight loss, the proportion of patients achieving ≥5% weight loss was 48% in the naltrexone ER/bupropion ER group and 16% in the placebo group (P<0.001).

Liraglutide is an acylated human GLP-1 receptor agonist that is injected subcutaneously once per day. Doses up to 1.8 mg/day are approved for treatment of T2DM. However, the dose-response for weight loss is greater than that for glycemic control, and 3 mg of liraglutide per day is approved for a weight-loss indication. GLP-1 receptors are expressed in the brain, and liraglutide acts centrally to increase postprandial satiety and fullness ratings and to reduce hunger and prospective food consumption (1423 [EL 1; RCT]). Endogenous GLP-1 has a half-life of 1.5 to 2 minutes due to degradation by the dipeptidyl peptidase-4 enzyme, but liraglutide is stable against degradation by peptidases and has a half-life of 13 hours. The most common side effects associated with liraglutide 3 mg are nausea, diarrhea, vomiting, and constipation (1449 [EL 4; NE]). After initiation of the drug, nausea generally occurs early during the titration period and then diminishes. Liraglutide 3 mg administration is associated with a mean 2 to 3 beat/min increase in heart rate. Warnings include injection site reactions, pancreatitis, acute cholelithiasis and cholecystitis, tachycardia, acute kidney injury and chronic kidney disease, and suicidal behavior and ideation. Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice, and, while such a relationship has not been demonstrated in humans, the drug is contraindicated in patients with personal or family history of medullary thyroid carcinoma or with multiple endocrine neoplasia type 2 (1449 [EL 4; NE]). Acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide, although it is does not appear that pancreatitis events are more common as a result of liraglutide administration per se (1450 [EL 2; RCCS]). If patients exhibit symptoms of pancreatitis, liraglutide should be discontinued.

Liraglutide 3 mg was studied in a 56-week double-blind, placebo-controlled RCT (68 [EL 1; RCT]) that demonstrated greater weight loss in patients randomized

to liraglutide (9.2%) than in the placebo plus lifestyle group (3.5%) in a completers-only analysis ($P<0.001$). The proportion of patients achieving ≥5% weight loss was 63.2% in the liraglutide group and 27.1% in the placebo group.

Given the differences among weight-loss medications, clinicians and their patients with obesity should have available all medications to allow for safe and effective selection of the most appropriate medication in individual patients.

- *Q7.5. Should combinations of weight-loss medications be used in a manner that is not approved by the U.S. Food and Drug Administration?*

Executive Summary

- **R82.** Combinations of FDA-approved weight-loss medications should only be used in a manner approved by the FDA **(Grade A; BEL 1)** or when sufficient safety and efficacy data are available to assure informed judgment regarding a favorable benefit-to-risk ratio **(Grade D)**.

Evidence Base

Combination therapy for obesity is logical in that appetite regulation involves multiple pathways and targeting more than 1 pathway concurrently may have additive or synergistic effects. In addition, using 2 drugs at lower doses may help avoid unwanted side effects so that each medication is better tolerated (1451 [EL 4; NE]; 1452 [EL 4; NE]. Combination therapies are generally more successful in clinical trials than monotherapies (1453 [EL 4; NE]). Medications have been used off label to treat obesity, sometimes in combination with approved weight-loss medications, and 2 FDA-approved medications have sometimes been used in nonapproved combinations (1454 [EL 4; NE]; 1455 [EL 3; SS]. In a survey of 473 obesity medicine physicians, off-label prescription of combinations of approved and non-FDA approved weight-loss medications was highly prevalent (1455 [EL 3; SS]).

While combination therapy has rationale, there is little data attesting to safety and efficacy for the combined use of weight-loss medications in the absence of the FDA approval process. The combination of phentermine and fenfluramine was the first widely used combination drug therapy for obesity. Even though each drug individually was approved for the treatment of obesity, the combination was not approved and did not undergo the FDA approval process assessing efficacy and safety. This combination resulted in synergistic weight loss (1456 [EL 1; RCT]; 1457 [EL 1; RCT]), but use was halted due to adverse events such as cardiac valvulopathy. Fenfluramine was subsequently withdrawn from the market. It has been suggested that phentermine increased exposure to fenfluramine or increased exposure to serotonin, which may have further increased the risk for valvulopathy (1458 [EL 4; NE]). This illustrates the potential danger of using nonapproved combinations before safety can be established in carefully conducted RCTs. The combination of lorcaserin and phentermine is frequently prescribed (1455 [EL 3; SS]), but there is currently only a single published trial demonstrating the short-term safety and efficacy of this combination (i.e., 12 weeks) (1459 [EL 4; NE, abstract]). That study is the only published trial of drugs currently approved by the FDA for weight loss used in a non-FDA approved combination. Orlistat has also been used off label in combination with other drugs. However, even orlistat, which acts to inhibit lipase in the intestinal lumen, can interfere with the absorption of many drugs, and its combination with other obesity drugs has not been carefully studied (1460 [EL 4; NE]).

There are currently no long-term studies of approved weight-loss drugs in non-FDA approved combinations. Combination drug therapy for obesity is promising and deserves further study. However, until more data is available attesting to efficacy and safety, the use of nonapproved combinations of weight-loss drugs is not recommended.

- ***Q8. Are there hierarchies of drug preferences in patients with the following disorders or characteristics? (Table 11 in Executive Summary)***

Note: Specific medications are mentioned or recommended below for use in different clinical settings based on efficacy, side effects, warnings and contraindications, organ clearance, mechanisms of action, and available data for use of the medication under these specific conditions. Medications may not be explicitly recommended if there are no data available for use in the specified clinical setting, even though weight loss associated with these medications may produce clinical benefits.

Q8.1. Chronic kidney disease

Executive Summary

- **R83.** Weight-loss medications should not be used in the setting of end-stage renal failure, with the exception that orlistat and liraglutide 3 mg can be considered in selected patients with a high level of caution **(Grade B; BEL 2)**.
- **R84.** The use of naltrexone ER/bupropion ER, lorcaserin, or phentermine/topiramate ER is not recommended in patients with severe renal impairment (<30 mL/min) **(Grade B; BEL 2)**.
- **R85.** All weight-loss medications can be used with appropriate cautions in patients with mild (50 to 79 mL/min) and moderate (30 to 49 mL/min) renal impairment, except that in moderate renal impairment the dose of naltrexone ER/bupropion ER should not exceed 8 mg/90 mg twice per day, and

the daily dose of phentermine/topiramate ER should not exceed 7.5 mg/46 mg **(Grade B; BEL 2)**.

- **R86.** Orlistat should not be used in patients with, or at risk of, oxalate nephropathy **(Grade C; BEL 3)**. Liraglutide 3 mg should be discontinued if patients develop volume depletion, for example, due to nausea, vomiting, or diarrhea **(Grade B; BEL 2)**.

Evidence Base

Clinicians need to consider renal function in their selection of weight-loss medications for individual patients. The naltrexone ER/bupropion ER combination has not had a dedicated study of its use in renal impairment. Individually, both naltrexone and bupropion and their respective metabolites are largely excreted in the urine, and the limited data available indicate that clearances are impaired in chronic kidney disease. While naltrexone has been used to treat uremic pruritus, its peak plasma concentration was elevated at least 6-fold in patients with end-stage renal disease (1461 [EL 2; PCS, N = 8: HPLC methods paper]). A bupropion trial comparing normal participants to subjects with moderate to severe renal impairment (glomerular filtration rate 30.9 ± 10.8 mL/min) demonstrated a 2-fold greater exposure in the bupropion subgroup (1462 [EL 2; PCS, N = 27]). Consequently, the recommendation in moderate to severe renal impairment is to limit the maximum dose to 1 tablet twice per day (1448 [EL 4; NE]). Naltrexone ER/bupropion ER is not recommended in the setting of severe renal failure.

Liraglutide has been shown to be well tolerated in patients with mild renal insufficiency (1463 [EL 1; MRCT]). Dose adjustments have not been shown to be necessary with varying degrees of renal impairment from mild to severe (1464 [EL 2; PCS]). In patients treated with GLP-1 agonists such as liraglutide, there have been reports of acute kidney injury and worsening chronic kidney disease sometimes requiring dialysis (1464 [EL 4; NE]; 1465 [EL 2; PCS]; 1466 [EL 3; SCR]). These events have occurred both in patients without known renal disease as well as those with known disease. Most reported cases occurred in patients who had volume depletion due to nausea, vomiting, or diarrhea. Therefore, renal function should be monitored, and caution should be used when initiating or escalating doses of liraglutide in patients with renal impairment (1449 [EL 4; NE]). Liraglutide has been studied in an RCT involving patients with T2DM and end-stage renal disease (1467 [EL 1; RCT]). Plasma liraglutide levels were elevated in end-stage renal disease and were associated with increased GI side effects; therefore, reduced treatment doses and a more prolonged titration period were recommended.

Lorcaserin is metabolized in the liver resulting in 2 main metabolites: lorcaserin sulfamate metabolite (M1) and N-carbamoyl-glucuronide metabolite (M5). In mild, moderate, and severe renal impairment, the terminal half-life of M1 is prolonged by 26%, 96%, and 508%, and the half-life of M5 is prolonged by 0%, 26%, and 22%, respectively. Since the metabolites M1 and M5 accumulate in patients with severely impaired renal function, lorcaserin is not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min) or patients with end-stage renal disease (1445 [EL 4; NE]).

Orlistat may cause some patients to develop increased levels of urinary oxalate (1442 [EL 4; NE]). Cases of oxalate nephrolithiasis and oxalate nephropathy with renal failure following the administration of orlistat have been reported. Orlistat administration has been associated with acute renal injury (1468 [EL 3; SS]) and a chronic decline in renal function (1469 [EL 3; SCR]). Renal function should be monitored in patients at risk for renal impairment. Orlistat should be used with caution in those with a history of hyperoxaluria or calcium oxalate nephrolithiasis (1442 [EL 4; NE]).

Phentermine/topiramate ER has been studied at the maximal treatment dose of 15 mg/92 mg in participants with varying degrees of renal failure (1444 [EL 4; NE]). Both phentermine and topiramate are largely excreted intact in the urine. In participants with mild (50 to 79 mL/min), moderate (30 to 49 mL/min), and severe (<30 mL/min) renal impairment, the phentermine area under the curve ($AUC_{0\text{-}inf}$) was 22%, 45%, and 91% higher compared with healthy volunteers, respectively, and the topiramate $AUC_{0\text{-}inf}$ was 25%, 85%, and 126% higher in these same patients. In studies of topiramate as a single agent, serum topiramate levels were elevated in patients with renal impairment, and a half-dose was recommended in moderate and severe renal impairment (1470 [EL 2; PCS, age/sex/weight-matched]). The prescribing information indicates that in moderate (30 to 49 mL/min) or severe (<30 mL/min) renal impairment the dose of phentermine/topiramate ER should not exceed 7.5 mg/46 mg daily. The medication has not been studied in end-stage renal disease (1444 [EL 4; NE]).

- *Q8.2. Nephrolithiasis*

Executive Summary

- **R87.** Naltrexone ER/bupropion ER, lorcaserin, and liraglutide (3.0 mg) are the preferred weight-loss medications in patients at risk or with a history of nephrolithiasis **(Grade D)**. Caution should be exercised in treating patients with phentermine/topiramate ER and orlistat who have a history of nephrolithiasis **(Grade A; BEL 1)**.

Evidence Base

Nephrolithiasis is not a known adverse effect of treatment with naltrexone, bupropion, lorcaserin, or liraglutide, and there are no metabolic effects directly linked to their mechanisms of action to increase the risk of nephrolithiasis

(1445 [EL 4; NE]; 1448 [EL 4; NE]; 1449 [EL 4; NE]). Phentermine/topiramate ER has been associated with an increased risk of nephrolithiasis (1444 [EL 4; NE]), which is likely due to the topiramate component that reduces urinary citrate excretion via inhibition of carbonic anhydrase, thus increasing urine pH (1471 [EL 3; CSS]; 1472 [EL 2; MNRCT]) and the risk of calcium phosphate stone formation (1471 [EL 3; CSS]). It is recommended to avoid concomitant use of other drugs that inhibit carbonic anhydrase and to use caution while on a ketogenic diet because of a theoretically increased risk of kidney stone formation. A retrospective cohort of children on a ketogenic diet, however, did not reveal an increased risk of nephrolithiasis when using carbonic anhydrase inhibitors, including topiramate, beyond a ketogenic diet alone (1473 [EL 3; SS, retrospective cohort]). Nephrolithiasis risk was increased during trials of phentermine/topiramate using the maximal treatment dose of 15/92 mg but not the lower doses (71 [EL 1; RCT]). Oxalate nephrolithiasis and nephropathy have also been reported with orlistat treatment, which was likely due to its potential for increased urinary oxalate excretion as a consequence of fat malabsorption secondary to its lipase inhibition. Caution is advised when prescribing orlistat to patients with a history of hyperoxaluria or calcium oxalate stones (1442 [EL 4; NE]; 1474 [EL 4; NE]).

- *Q8.3. Hepatic impairment*

Executive Summary

- **R88.** All weight-loss medications should be used with caution in patients with hepatic impairment and should be avoided in patients with severe hepatic impairment (Child-Pugh score >9) **(Grade C; BEL 3)**.
- **R89.** Dose adjustments for some medications are warranted for patients with moderate hepatic impairment. For these patients, the maximum recommended dose of naltrexone ER/bupropion ER is 1 tablet (8 mg/90 mg) in the morning, and the maximum recommended dose of phentermine/topiramate ER is 7.5 mg/46 mg daily (Grade D).
- **R90.** Clinicians should maintain a high index of suspicion for cholelithiasis in patients undergoing weight-loss therapy regardless of the treatment modality. Liraglutide 3 mg should be used with caution in high-risk patients. Effective preventive measures include a reduced rate of weight loss, an increase in dietary fat, and administration of ursodeoxycholic acid **(Grade A; BEL 1)**.

Evidence Base

No cases of transaminases greater than 3 times the upper limit of normal (ULN) with bilirubin greater than 2 times the ULN were reported in bupropion ER/naltrexone ER clinical trials (1448 [EL 4; NE]). Hepatitis and clinically significant liver dysfunction have been observed in patients taking naltrexone as a single agent for treatment of addiction. However, often other potential causative or contributory etiologies, including pre-existing alcoholic liver disease, hepatitis B and/or C infection, and concomitant usage of other potentially hepatotoxic drugs, were identified in patients with elevated transaminases. A clinical study of patients with alcoholism showed that naltrexone exposure did not significantly increase transaminases (1475 [EL 4; NE]).

The bupropion ER/naltrexone ER combination has not been evaluated in patients with hepatic impairment. Naltrexone, bupropion, and their respective metabolites are largely excreted in the urine. However, based on currently available information, systemic exposure is 2- to 3-fold higher for bupropion and its metabolites and up to 10-fold higher for naltrexone and its metabolites in subjects with moderate to severe hepatic impairment (1448 [EL 4; NE]). Therefore, the maximum recommended daily dose of the bupropion/naltrexone combination is 1 tablet in the morning for patients with hepatic impairment.

Liraglutide is metabolized as a large protein without a specific organ as a major route of elimination. Single-dose pharmacokinetics for liraglutide were evaluated in subjects with varying degrees of hepatic impairment, including subjects with mild (Child-Pugh score 5 to 6) to severe (Child-Pugh score >9) hepatic impairment (1449 [EL 4; NE]). Liraglutide AUC was 11%, 14%, and 42% lower in subjects with mild, moderate, and severe hepatic impairment, respectively, than in healthy subjects. Liraglutide at the 1.8-mg dose was associated with improved ALT in the setting of T2DM and elevated liver enzymes (973 [EL 1; MRCT]). Experience in patients with mild, moderate, or severe hepatic impairment is limited. Therefore, liraglutide labels suggest exercising caution in these settings but do not make recommendations for dose adjustments.

Lorcaserin is largely metabolized by the liver, and inactive metabolites are excreted in the urine. Lorcaserin has been evaluated in clinical trials of patients with normal and impaired hepatic function (1445 [EL 4; NE]). The half-life of lorcaserin is prolonged by 59% (to 19 hours) in patients with moderate hepatic impairment (Child-Pugh score 7 to 9). Serum lorcaserin AUC is approximately 22% and 30% higher after ingestion in patients with mild and moderate hepatic impairment, respectively. No adverse hepatic-related events have been reported in large clinical trials (69 [EL 1; RCT]; 1476 [EL 1; RCT]. Lorcaserin does not require a dose adjustment for patients with mild (Child-Pugh score 5 to 6) to moderate (Child-Pugh score 7 to 9) hepatic impairment (1445 [EL 4; NE]). However, lorcaserin has not been studied in patients with severe hepatic impairment, and use in this setting requires a high level of caution.

Absorption of orlistat from the GI tract is minimal, and the drug was approved without the requirement of a long-term study on safety (1442 [EL 4; NE]). Although rare, a few cases of post-marketing hepatic injury (1477 [EL 3; SCR]), including hepatocellular necrosis and acute hepatic failure, have been reported, with some resulting in liver transplantation or death (1478 [EL 3; SCR]). The prescribing information for orlistat recommends that patients report symptoms of hepatic dysfunction (anorexia, pruritus, jaundice, dark urine, light-colored stools, or right upper quadrant pain) and discontinue use of the medication immediately (1442 [EL 4; NE]).

Both phentermine and topiramate are largely excreted intact in the urine. The phentermine/topiramate ER combination was studied in a single-dose, open-label study that compared normal volunteers to patients with mild (Child-Pugh score 5 to 6) and moderate (Child-Pugh score 7 to 9) hepatic impairment (1444 [EL 4; NE]). Phentermine AUC was 37% and 60% higher, respectively, in patients with mild and moderate hepatic impairment than in healthy volunteers. The pharmacokinetics of topiramate were not affected by mild to moderate hepatic impairment in this study. No dose adjustments are needed for patients with mild hepatic impairment. In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), dosing should not exceed 7.5 mg/46 mg once daily (1444 [EL 4; NE]). Phentermine/topiramate ER has not been studied in patients with severe hepatic impairment (Child-Pugh score 10 to 15), and prescribing for this population is not recommended.

Cholelithiasis. The incidence of cholesterol gallstone formation and symptomatic cholelithiasis is greater in people with obesity (particularly those with more marked elevations in body mass index [BMI]), and the risk of cholelithiasis is further augmented by weight loss (1479 [EL 4; NE]; 1480 [EL 4; NE]; 1481 [EL 4; NE]). Thus, acute weight loss could lead to an obstructive pattern of liver function test abnormalities by inducing cholelithiasis. The incidence of new gallstone formation is 10 to 12% after 8 to 16 weeks of a low-calorie diet and >30% in the first 1.5 years after gastric bypass surgery (1479 [EL 4; NE]). The minority (approximately one-third) of these stones are symptomatic. In a clinical trial, incidence of cholelithiasis was 2.9% (47/1,649) for patients randomized to orlistat and 1.8% (30/1,655) for patients randomized to placebo (721 [EL 1; RCT]). In clinical trials of liraglutide 3 mg, the incidence of cholelithiasis was greater in patients taking the drug than in those taking placebo (68 [EL 1; RCT]; 780 [EL 1; RCT]). Overall, cholelithiasis was reported in 1.5% of patients treated with liraglutide 3 mg versus 0.5% given placebo, and the incidence remained higher even after controlling for the amount of weight lost (1449 [EL 4; NE]).

Risk factors for gallstones during weight loss include weight loss >25% of starting body weight, rate of weight loss >1.5 kg per week, a very low-calorie diet containing little or no fat, periods of absolute fasting, and elevated triglyceride levels (1479 [EL 4; NE]; 1480 [EL 4; NE]; 1481 [EL 4; NE]). For these reasons, clinicians should recommend a moderate rate of weight loss and inclusion of dietary fat for high-risk patients undergoing weight-loss therapy. In addition, multiple RCTs and meta-analyses have confirmed that cholelithiasis may be prevented by administering ursodeoxycholic acid (500 to 600 mg/day) during the first 4 to 6 months of weight loss (1482 [EL 1; MRCT]; 1483 [EL 1; MRCT]; 1484 [EL 1; RCT]; 1485 [EL 1; RCT]; 1486 [EL 1; RCT]) or following weight-loss diets high in fat content (1482 [EL 1; MRCT]).

- *Q8.4. Hypertension*

Executive Summary

- **R91.** Orlistat, lorcaserin, phentermine/topiramate ER, and liraglutide 3 mg are preferred weight-loss medications for patients with existing hypertension **(Grade B; BEL 1, downgraded due to evidence gaps)**. Heart rate should be monitored carefully in patients receiving liraglutide 3 mg and phentermine/topiramate ER **(Grade A; BEL 1)**. Naltrexone ER/bupropion ER should be avoided if other weight-loss medications can be used because weight loss assisted by naltrexone ER/bupropion ER cannot be expected to lower blood pressure and the drug is contraindicated in patients with uncontrolled hypertension **(Grade B; BEL 1, downgraded due to evidence gaps)**.
- **R92.** Renin-angiotensin system inhibition therapy (angiotensin receptor blocker or angiotensin-converting enzyme inhibitor) should be used as the first-line drug for blood pressure control in patients with obesity **(Grade A; BEL 1)**.
- **R93.** Combining antihypertension therapy with calcium channel blockers may be considered as second-tier treatment **(Grade A; BEL 1)**. Beta-blockers and thiazide diuretics may also be considered in some patients but can have adverse effects on metabolism, and beta-blockers and alpha-blockers can promote weight gain **(Grade A; BEL 1)**.

Evidence Base

Patients with obesity are prone to BP elevation and HTN (1487 [EL 3; CSS, N = 15,971 women and 13,846 men]; 1488 [EL 3; CSS, N = 6,931 in 1998 and 6,861 2008-2011]). BMI increases and decreases are associated with significant increases and decreases, respectively, in SBP and DBP, with the strongest effect shown in patients age ≥50 years (1487 [EL 3; CSS, N = 15,971 women and 13,846 men]). Pathophysiologic mechanisms of HTN may differ between individuals with and without obesity, which

may result in different responses to treatment. Patients with obesity often require more drugs to control BP and have a greater risk of treatment-resistant HTN than do lean individuals (339 [EL 2; RCCS]; 1489 [EL 1; RCT, subgroup analysis]; 1490 [EL 4; NE]). A retrospective review from a primary care medical records database of 9,086 adults (age >18 years) with HTN and dyslipidemia categorized patients as normal weight (BMI <24.9 kg/m^2; n = 1,256), overweight (BMI 25.0 to 29.9 kg/m^2; n = 3,058), and obese (BMI >30.0 kg/m^2; n = 4,772), and found that patients with obesity were more likely to be prescribed antihypertensive agents yet less likely to attain BP goals (339 [EL 2; RCCS]). When considering management of patients with overweight or obesity and HTN, it is important to consider approaches to weight-loss therapy that effectively reduce BP and to select antihypertension medications, when needed, that do not antagonize weight-loss therapy and adversely affect metabolic and CVD risk factors.

Weight loss has been well-documented to reduce both SBP and DBP, whether achieved by lifestyle intervention, weight-loss medications, or bariatric surgery. The effect of lifestyle therapy was well-documented in the Look AHEAD study of patients with T2DM, which demonstrated that greater amount of weight loss, up to and including the highest category of weight loss (≥15%), progressively decreased SBP and DBP (754 [EL 1; RCT]). However, weight loss assisted by medications may not be uniformly beneficial for BP control. Sibutramine effectively reduced body weight but was associated with increases in BP above baseline (1491 [EL 1; MRCT]). The Sibutramine Cardiovascular Outcome Trial (SCOUT) trial later assessed the safety of sibutramine in patients with CVD and/or T2DM (a patient group for whom the drug was contraindicated), and showed that sibutramine administration was associated with an increased incidence of nonfatal myocardial infarction (MI) and strokes (1492 [EL 1; RCT]). For this reason, sibutramine was withdrawn from patient use in the U.S. and many other countries in 2010.

Weight loss assisted by orlistat reduces BP and pulse (721 [EL 1; MRCT]; 856 [EL 1; RCT]; 1414 [EL 1; RCT]; 1416 [EL 1; RCT]; 1442 [EL 1; RCT]; 1493 [EL 1; RCT]; 1494 [EL 1; RCT]; 1495 [EL 1; RCT]; 1496 [EL 4; NE]). A Cochrane Database Systematic Review of clinical trials demonstrated weighted mean differences (WMDs) between orlistat and placebo of –2.5 mm Hg (95% CI, –4.0 to –0.9 mm Hg) for reductions in SBP and –1.9 mm Hg (95% CI, –3.0 to –0.9 mm Hg) for DBP (1491 [EL 1; MRCT]). Similarly, RCTs showed that lorcaserin was associated with reductions in BP and pulse (69 [EL 1; RCT]; 857 [EL 1; RCT]; 1445 [EL 4; NE]), although the overall reductions in BP were modest, amounting to –1.8 mm Hg for SBP (versus –0.7 mm Hg with placebo) and –1.6 mm Hg for DBP (versus 0.6 mm Hg with placebo) (1445 [EL 4; NE]).

Both phentermine/topiramate ER and liraglutide 3 mg yield weight loss associated with clinically significant reductions in BP, albeit with small increases in resting heart rate. In phase 3 clinical trials, treatment with phentermine/topiramate ER was associated with substantial reductions in BP and antihypertensive medications relative to placebo (71 [EL 4; NE]; 722 [EL 1; RCT]; 858 [EL 1; RCT]; 1444 [EL 1; RCT]). In the EQUIP trial (858 [EL 1; RCT]), the maximal dose of phentermine/topiramate ER (15 mg/92 mg) produced placebo-subtracted differences of –3.8 mm Hg in SBP and –1.9 mm Hg in DBP. In the CONQUER trial (71 [EL 1; RCT]), which included patients with HTN taking ≤2 HTN medications, the treatment dose 7.5 mg/46 mg produced placebo-subtracted reductions in BP of –2.3 mm Hg for SBP and –0.7 mm Hg for DBP, and the maximal dose (15 mg/92 mg) yielded placebo-subtracted differences of –3.2 mm Hg for SBP and –1.1 mm Hg for DBP. Phentermine/topiramate ER administration was also associated with increases in resting heart rate of 1 to 2 beats/min (1444 [EL 4; NE]). BP-lowering effects of phentermine/topiramate ER may be partially explained by the carbonic anhydrase activity of topiramate, which results in BP reductions when used as a single agent (1497 [EL 1; RCT]; 1498 [EL 1; RCT]).

Clinical trials of liraglutide 3 mg for treatment of obesity have also shown clinically significant reductions in BP (68 [EL 1; RCT]; 780 [EL 1; RCT]; 897 [EL 1; RCT]; 1424 [EL 1; RCT]; 1449 [EL 4; NE]). In a study of patients with overweight or obesity and comorbidities (68 [EL 1; RCT]), liraglutide 3 mg produced placebo-subtracted reductions of –2.8 mm Hg and -0.9 mm Hg in SBP and DBP, respectively. In patients with T2DM, liraglutide 3 mg produced placebo-subtracted reductions of –2.6 mm Hg in SBP and –0.4 mm Hg in DBP (780 [EL 1; RCT]). Administration of liraglutide 3 mg was associated with increases in resting heart rate of 2 to 4 beats/min (68 [EL 1; RCT]; 780 [EL 1; RCT]; 897 [EL 1; RCT]; 1424 [EL 1; RCT]; 1449 [EL 4; NE]), which may represent a class effect of GLP-1 receptor agonists as demonstrated in a recent meta-analysis (1499 [EL 1; MRCT]).

RCTs evaluating efficacy and safety of naltrexone ER/bupropion ER demonstrated little or no decrease in DBP and SBP in patients randomized to the drug, and any decreases in BP were less than those observed with placebo despite greater weight loss with naltrexone ER/bupropion ER treatment (67 [EL 4; NE]; 779 [EL 1; RCT]; 859 [EL 1; RCT]; 1422 [EL 1; RCT]; 1448 [EL 1; RCT]). In the Contrave Obesity Research I (COR-I) RCT, the reduction in SBP was –0.1 mm Hg in patients randomized to naltrexone ER/buproprion ER and –1.9 mm Hg in those randomized to placebo, and DBP did not change from baseline with the drug but decreased by –0.9 mm Hg with placebo (67 [EL 1; RCT]). Overall, in the placebo-controlled RCTs, administration of naltrexone ER/bupropion ER was associated with ~1 mm Hg increase from baseline in both SBP

and DBP at weeks 4 and 8, while the BP was similar to baseline at week 12 and slightly less than baseline at week 56 (1448 [EL 4; NE]). At the same time, patients randomized to placebo experienced decreases in mean BP of ~2 to 3 mm Hg below baseline throughout the studies (1448 [EL 4; NE]). Thus, the largest mean differences between the groups were observed during the first 12 weeks. Naltrexone ER/bupropion ER administration was associated with an increase in resting pulse of ~1 beat/min (67 [EL 4; NE]; 779 [EL 1; RCT]; 859 [EL 1; RCT]; 1422 [EL 1; RCT]; 1448 [EL 1; RCT]). The prescribing information for naltrexone ER/bupropion ER states that the drug is contraindicated in patients with uncontrolled HTN and warns all patients to monitor BP and pulse (1448 [EL 4; NE]).

Preferred antihypertensive drugs in patients with overweight or obesity would lower BP while maintaining body weight and avoiding adverse effects on metabolism (e.g., glycemia, insulin sensitivity, and lipids). The total body of evidence suggests that the aldosterone axis plays a particularly prominent role in the pathophysiology of HTN with obesity and that antagonism of the mineralocorticoid receptor is equally or more effective than other antihypertensive drugs, notwithstanding differences in ethnicity, as the initial agent for lowering BP in patients with obesity and HTN (1500 [EL 4; NE]; 1501 [EL 1; RCT, post-hoc analysis]; 1502 [EL 1; RCT]).

Insulin sensitivity does not change with the use of angiotensin receptor blockers (ARBs) for treatment of HTN in patients with obesity. A randomized crossover design study of ARB versus placebo showed that ARB significantly lowered BP but did not change insulin sensitivity assessed by intravenous glucose tolerance testing (1503 [EL 1; RCT]). In a similar study, the relative effects of different antihypertension therapies on glucose metabolism were evaluated in 412 subjects with obesity (1504 [EL 1; RCT]). Baseline characteristics of patients included mean age 56 years, BMI 35 ± 7 kg/m^2, and mean SBP/DBP of 159/94 mm Hg. BP reductions were significant and similar in groups of patients administered hydrochlorothiazide combined with either a calcium channel blocker (amlodipine) or an ARB (valsartan). However, the combination of amlodipine and hydrochlorothiazide was associated with greater postprandial glucose excursions than the valsartan combination.

Combination beta-blocker/hydrochlorothiazide therapy has also been shown to limit the beneficial metabolic effects of drug-induced weight loss. A placebo-controlled randomized study in 171 patients with HTN and obesity evaluated how the interactions between sibutramine and different antihypertensive drugs affect insulin sensitivity (1505 [EL 1; RCT]). Relative to placebo, sibutramine treatment resulted in significantly greater decreases in body weight, BMI, and waist circumference (WC) but a greater increase in DBP. Sibutramine-induced weight loss, reduction of visceral obesity, and improvements in glucose tolerance and hypertriglyceridemia were attenuated more in the metoprolol/hydrochlorothiazide group than in the combination calcium channel blocker/ARB therapy group. Beta-blockers and alpha-blockers prescribed as antihypertensive agents may cause weight gain. Diet-induced thermogenesis, fat oxidation rate, and weekly activity were 50% (P<0.01), 32% (P = 0.04), and 30% (P<0.01) lower, respectively, in patients taking beta-blockers than in control patients (1506 [EL 3; CSS, 2 studies]). The adjusted mean body weight was significantly higher in patients taking beta-blockers who attended a diabetes clinic (9.2 ± 1.2 kg, P = 0.0002) or HTN clinic (17.2 ± 3.2 kg, P = 0.004) than in patients who attended these clinics and were not treated with beta-blockers. Weight-neutral agents used to control BP include ARBs, angiotensin-converting enzyme inhibitors, and calcium channel blockers, although more robust studies are needed to investigate the effect of antihypertension drugs on weight change (1507 [EL 1; MRCT]).

In a study of HTN and left ventricular hypertrophy (LVH), 875 patients were randomized to receive losartan ARB therapy, and BMI classification was followed for 4.8 years (1508 [EL 1; RCT, post-hoc analysis]). LVH was present in 54% of patients with class 1 obesity (BMI 30-34.9 kg/m^2) and 79% of patients with more severe obesity (≥35 kg/m^2) versus 31% of normal-weight individuals (P<0.01 for both comparisons). Regression analyses showed that higher BMI predicted poorer outcomes, with less reduction in LVH and greater reduction in left ventricle ejection fraction (both P<0.05) independent of BP reduction, T2DM status, and weight change. During follow-up, 91 patients had an MI, stroke, or cardiovascular (CV)-related death. In this study, an increase in baseline BMI of 1 kg/m^2 predicted a 5% higher incidence of CV events and 10% higher incidence of CV mortality (both P<0.05). A meta-analysis of 28 RCTs comprising 2,403 patients with HTN (mean age range, 44-67 years) showed that LVH regression with antihypertensive medications was greater in the overweight and obesity groups than in subjects of normal weight (1509 [EL 1; MRCT]). Improved LVH occurred even with less reduction of SBP (analyzed using WMDs) in obese (WMD 16.9 mm Hg) and overweight (WMD 20.3 mm Hg) groups relative to the normal-weight (WMD 24.9 mm Hg) group (P<0.001 from baseline for all groups). Renin-angiotensin system inhibitor therapy was the most effective treatment for reducing LVH in patients with overweight and obesity (P<0.001), followed by beta-blockers, calcium channel blockers, and diuretics.

- *Q8.5. Cardiovascular disease and cardiac arrhythmia*

Executive Summary

- **R94**. In patients with established atherosclerotic CV disease, orlistat and lorcaserin are the preferred weight-loss medications **(Grade A; BEL**

1). Liraglutide 3 mg, phentermine/topiramate ER, and naltrexone ER/bupropion ER are reasonable to use with caution and continue if weight-loss goals are met, with careful monitoring of heart rate and BP **(Grade A; BEL 1)**. Cardiovascular outcome trials are planned or ongoing for all weight-loss medications except orlistat.

- **R95.** Orlistat and lorcaserin are preferred weight-loss medications for patients with a history or risk of cardiac arrhythmia **(Grade B; BEL 1, downgraded due to evidence gaps)**. Naltrexone ER/bupropion ER, liraglutide 3 mg, and phentermine/topiramate ER are not contraindicated but should be used cautiously with careful monitoring of heart rate and rhythm **(Grade A; BEL 1)**.

Evidence Base

Naltrexone ER/bupropion ER, lorcaserin, phentermine/topiramate ER, orlistat, and liraglutide 3 mg have no known association with an increased risk for CV events. Sibutramine, a norepinephrine and serotonin reuptake inhibitor, was removed from the market after a large trial of subjects with obesity and established atherosclerotic CVD and/or diabetes (SCOUT) demonstrated that sibutramine was associated with a slightly increased incidence of nonfatal MI and stroke (1492 [EL 1; RCT]). However, a subanalysis of these data demonstrated that CV risk was actually lower if moderate weight loss (3 to 10 kg) was achieved (1510 [EL 1; RCT]). Nevertheless, the results of the SCOUT trial in obese patients with known pre-existing CV risk introduces concern regarding weight-loss medication that adversely affects CV risk factors, and weight-loss benefits may not offset the increases in CVD risk caused by the addition of such agents. CV outcome trials are planned or ongoing for all weight-loss medications (with the exception of orlistat).

All FDA-approved agents for long-term treatment of obesity have been shown in clinical trials to improve certain modifiable CV risk factors, including WC, lipids, and glycemic measures. The remaining relevant considerations include effects on heart rate and BP. The Endocrine Society Clinical Practice Guideline on Pharmacologic Management of Obesity suggests using lorcaserin or orlistat and avoiding sympathomimetic agents for patients with established CVD (22 [EL 4; NE]). In support of this recommendation, orlistat's mechanism of action has no known interaction that increases risk and has been consistently shown to improve CV risk factors in clinical trials (721 [EL 1; MRCT]; 856 [EL 1; RCT]; 1414 [EL 1; RCT]; 1416 [EL 1; RCT]; 1442 [EL 1; RCT]; 1493 [EL 1; RCT]; 1494 [EL 1; RCT]; 1495 [EL 1; RCT]; 1496 [EL 4; NE]). In addition, small decreases in pulse and BP were observed in clinical trials of lorcaserin (69 [EL 1; RCT]; 857 [EL 1; RCT]; 1445 [EL 4; NE]).

Bupropion is a dopamine and norepinephrine reuptake inhibitor and a component of the naltrexone ER/bupropion ER combination therapy. Bupropion alone was associated with slight increases in BP and heart rate in a small, short-term study of subjects with pre-existing left ventricular impairment, ventricular arrhythmias, and/or conduction disease, but did not yield any adverse effects beyond a slight elevation in supine BP (1511 [EL 2; NRCT, allocation concealment]). In a RCT of bupropion in patients with untreated stage 1 HTN (SBP 140-159 mm Hg and/or DBP 90-99 mm Hg), doses of 300 and 400 mg/day decreased BP less so than with placebo, and the 400 mg/day group had a small increase in mean heart rate relative to placebo (1512 [EL 1; RCT]). Smokers with known CVD who were prescribed bupropion 150 mg twice daily for 7 weeks and followed for 52 weeks did not show detrimental changes in heart rate or BP and did not have an increased incidence of serious adverse CV events (1513 [EL 1; RCT]). Two RCTs showed that bupropion 150 mg twice daily for 8 to 9 weeks did not result in any significant differences in BP, heart rate, or adverse CV events at 1-year follow-up versus placebo in smokers admitted for acute coronary syndrome (1514 [EL 1; RCT]; 1515 [EL 1; RCT]). In a recent meta-analysis evaluating smoking cessation therapies, bupropion appeared to have a cardioprotective effect against major adverse CV events relative to nicotine replacement, varenicline, and/or placebo, even in subjects at high CV risk (1516 [EL 1; MRCT]).

The naltrexone ER/bupropion ER combination for weight loss is contraindicated in patients with uncontrolled HTN and contains a warning to monitor BP and pulse in all patients (1448 [EL 4; NE]). This is because phase 3 clinical trials demonstrated that patients randomized to naltrexone ER/bupropion ER had little or no decrease in diastolic and SBP, and any decreases in BP were less than those observed with placebo despite greater weight loss with naltrexone ER/bupropion ER treatment (67 [EL 1; MRCT]; 1422 [EL 4; NE]; 1448 [EL 1; RCT]; 1516 [EL 1; RCT]). In addition, naltrexone ER/bupropion ER was associated with an increase in resting pulse of ~1 beat/min (67 [EL 1; RCT]; 779 [EL 1; RCT]; 859 [EL 1; RCT]; 1422 [EL 1; RCT]). In post-hoc subanalyses, the differences in BP-lowering effects between medication and placebo groups was not significant for patients with baseline SBP ≥130 mm Hg, and greater weight loss was associated with greater reductions in BP in both subgroups (859 [EL 1; RCT]). The Light Study was a CV outcomes trial assessing patients randomized to placebo or naltrexone ER/bupropion ER but was halted early due to procedural irregularities necessitating the initiation of a new outcomes study.

Phentermine/topiramate ER also has a warning to monitor for potential increases in heart rate and use with caution in patients with stable arrhythmia because the clinical significance of the heart rate elevation is unknown

(1444 [EL 4; NE]). Phentermine is a sympathomimetic amine, which increases central norepinephrine release to decrease appetite (1517 [EL 4; NE, preclinical]). Sympathomimetic agents such as phentermine could theoretically increase CV risk due to the effects of amplified adrenergic tone on heart rate and BP, although short-term trials of phentermine alone for weight loss have not substantiated these concerns (1430 [EL 1; RCT]; 1518 [EL 1; RCT]; 1519 [EL 1; RCT]). An observational study of patients ranging from normotensive to hypertensive (34%) demonstrated no significant increase in heart rate or reductions in DBP and SBP following 92 weeks of phentermine treatment (1520 [EL 3; SS]).

Topiramate is suspected to have arrhythmogenic potential based in vitro analyses (1521 [EL 4; NE, preclinical]) but has not been associated with an increased incidence of sudden death in patients with epilepsy (1522 [EL 4; NE]). Trials evaluating the efficacy and safety of topiramate monotherapy for obesity and diabetes showed improvements in CV risk factors and no increase in risk for CV events (1497 [EL 1; RCT]; 1498 [EL 1; RCT]; 1523 [EL 1; RCT]; 1524 [EL 1; RCT]; 1525 [EL 1; RCT]; 1526 [EL 1; RCT]). In phase 3 clinical trials, treatment with phentermine/topiramate ER was associated with increases in resting heart rate of 1 to 2 beats/min, but the combination also led to substantial reductions in BP with an accompanying decrease in antihypertensive medications relative to placebo (71 [EL 1; RCT]; 722 [EL 1; RCT]; 858 [EL 1; RCT]). In the EQUIP (858 [EL 1; RCT]) and CONQUER (71 [EL 1; RCT]) trials, the increase in pulse relative to the placebo group was observed in patients randomized to the maximal dose of phentermine/topiramate ER (15 mg/92 mg), but not in the subgroups receiving the initiation dose (3.75 mg/23 mg) or treatment dose (7.5 mg/46 mg). Subgroup analysis of the CONQUER RCT showed that reductions in triglycerides, non-HDL-c, and BP were correlated with the degree of weight loss in patients with dyslipidemia and HTN, respectively (1527 [EL 1; RCT]). Evaluation of CV safety during the clinical trials revealed low rates of major adverse cardiac events (MACE) in both placebo and treatment groups, and using broader MACE criteria (cardiovascular/neurovascular events) showed a significantly lower risk of events in the phentermine/topiramate ER treatment groups (1528 [EL 4; NE]). Larger trials evaluating CV outcomes are currently planned (1529 [EL 4; NE]).

Meta-analyses of GLP-1 receptor agonist trials used to treat T2DM do not suggest increased incidence of MACE (1530 [EL 1; MRCT]; 1531 [EL 1; MRCT]; 1532 [EL 1; MRCT]). However, a meta-analysis of albiglutide trials showed that more patients had atrial fibrillation or atrial flutter in the albiglutide (1.4%) group than in comparator groups (0.6%) (1533 [EL 1; MRCT]). Clinical trials of liraglutide 3 mg for treatment of obesity have shown that reductions in both diastolic (0.9-3.7 mm Hg) and systolic (2.8-5.6 mm Hg) BP correlated with the amount of weight loss and led to an increase in resting heart rate of 2 to 4 beats/min (68 [EL 1; RCT]; 780 [EL 1; RCT]; 897 [EL 1; RCT]; 1424 [EL 1; RCT]; 1449 [EL 4; NE]). The increase in heart rate likely represents a class effect of GLP-1 receptor agonists, as acknowledged in a recent meta-analysis (1499 [EL 1; MRCT]). Another recent meta-analysis showed that GLP-1 receptor agonists generally have favorable effects on lipids in the treatment of T2DM (1534 [EL 1; MRCT]), and clinical trials involving liraglutide 3 mg have also shown improvement in lipid profiles (68 [EL 1; RCT]; 780 [EL 1; RCT]; 897 [EL 1; RCT]; 1424 [EL 1; RCT]; 1449 [EL 4; NE]).

Although the SCALE Diabetes RCT had a low rate of cardiac arrhythmias, they occurred more frequently in the liraglutide 3 mg treatment arm than in the placebo arm (5 events versus 2 events per 100 patient-years, respectively) (780 [EL 1; RCT]). Most of the arrhythmias were classified as sinus tachycardia, with 1 event each of atrial fibrillation and atrial flutter in the liraglutide 3 mg group and a low number of adjudication-confirmed MACE occurring at a similar rate in treatment and placebo groups (780 [EL 1; RCT]). In another trial, 1 patient developed atrial fibrillation while taking liraglutide 3 mg (897 [EL 1; RCT]). A patient-level pooled analysis of phase 2/3 liraglutide clinical trials showed that the incidence ratio of adjudicated MACE associated with liraglutide was 0.73 (95% CI 0.38-1.41) versus all comparator drugs and placebo (1535 [EL 1; MRCT]). While the effects of GLP-1 agonists on CVD risk factors and myocardial function are encouraging (1536 [EL 4; NE]; 1537 [EL 4; NE]), a long-term trial assessing CV outcomes with liraglutide is required and currently underway in patients with T2DM (1538 [EL 1; RCT]).

- *Q8.6. Depression with or without selective serotonin reuptake inhibitor therapy*

Executive Summary

- **R96.** All patients undergoing weight-loss therapy should be monitored for mood disorders, depression, and suicide ideation **(Grade A; BEL 2, upgraded due to high relevance)**.
- **R97.** Orlistat, liraglutide 3 mg, and phentermine/topiramate ER at initiation (3.75 mg/23 mg) and low treatment (7.5 mg/46 mg) doses may be considered in patients with obesity and depression **(Grade A; BEL 1)**.
- **R98.** Lorcaserin and naltrexone ER/bupropion ER should be used with caution in patients with obesity and depression or avoided if patients are taking medications for depression **(Grade A; BEL 1)**.

Evidence Base

Obesity is associated with increased rates of depression and mood disorders (658 [EL 4; NE]; 659 [EL 3; SS]; 660 [EL 3; SS]; 661 [EL 4; NE]; 662 [EL 4; NE]; 663 [EL 2; PCS]; 664 [EL 4; NE]; 665 [EL 3; SS]; 666 [EL 2; MNRCT]). Therefore, the effects of weight-loss medications on mood and depression must be carefully considered and have been assessed as safety issues in clinical trials of each FDA-approved medication.

Orlistat and liraglutide 3 mg appear to have the safest profile for use in patients with depression. A 2-year trial showed that rates of depression with orlistat treatment were 3.4% and 2.5% in the orlistat (n = 613) and placebo (n = 524) groups, respectively (1442 [EL 4; NE]). The intra-intestinal action of orlistat, combined with its minimal systemic absorption, indicate that the presence of pharmacologic effects that alter psychological processes are highly unlikely. The rates of suicidal ideation were 0.2% in the liraglutide 3 mg group (n = 3,384) and 0% in the placebo group (n = 1,941) (1449 [EL 4; NE]). One patient in the liraglutide 3 mg group attempted suicide (1449 [EL 4; NE]). In the 2-year SCALE Maintenance study, depression was reported in 3.8% of patients randomized to liraglutide 3 mg and 3.4% of patients taking placebo, and the Patient Health Questionnaire (PHQ-9) scores for depression remained low and unaltered in both groups during the study (1424 [EL 1; RCT]). The prescribing information recommends monitoring for and discontinuing medication if suicidal ideation occurs and avoiding the medication in patients with a history of suicide ideation or attempt (1449 [EL 4; NE]).

In safety trials of lorcaserin 10 mg twice per day, overall rates of depression were 2.6% in the lorcaserin group and 2.4% in the placebo group in studies lasting up to 1 year, and the study drug was discontinued in 1.3% of the lorcaserin group and 0.6% of the placebo group due to depression, mood, or suicidal ideation (1448 [EL 4; NE]). In the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) study, 3,182 adults with overweight and obesity were randomized to receive lorcaserin 10 mg twice daily (n = 1,538) or placebo (n = 1,499) (857 [EL 1; RCT]). Depression and depressive symptomatology were assessed at interval time points throughout the study using the Beck Depression Inventory II (BDI-II), and patients who had a history of depression or major psychiatric disorders within the last 2 years were excluded from study participation. Incidence of depression/depressive symptoms during the first year was 2.5% and 2.2% in the lorcaserin and placebo group, respectively, and 3.0% and 2.0% in the lorcaserin and placebo groups, respectively, during the second year. Suicidal thoughts were reported in 1.3% of participants in both the lorcaserin and the placebo groups, and BDI-II scores decreased over the duration of the study in both groups.

The Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) trial included 4,008 adults with overweight or obesity randomized to receive lorcaserin 10 mg twice per day (n = 1,602), lorcaserin 10 mg daily (n = 801), or placebo (n = 1,601) (69 [EL 1; RCT]). Depression and depressive symptomatology were assessed at interval time points throughout the study utilizing the BDI-II. In the lorcaserin 10 mg twice per day, lorcaserin 10 mg daily, and placebo groups, incidence of depression was 1.9%, 1.1%, and 1.8%, respectively; incidence of depressed mood was 0.6%, 0.9%, and 0.9%, respectively; and incidence of suicidal ideation was 0.9%, 0.6%, and 0.7%, respectively (69 [EL 1; RCT]). All groups had lower BDI-II scores at 52 weeks (–0.8%, –0.8%, and –0.7%, respectively) (69 [EL 1; RCT]). In the BLOOM-DM (diabetes mellitus) study of patients with obesity and T2DM, the prevalence of depression was 2.3%, 5.3%, and 2.0% in the lorcaserin 10 mg twice daily (n = 256), lorcaserin 10 mg daily (n = 95), and the placebo groups (n = 252), respectively (778 [EL 1; RCT]). The emergence of depression or increased severity of depression symptoms, such as changes in mood or behavior, should be monitored with lorcaserin, and the medication should be discontinued if suicidal thoughts or ideation occur (1448 [EL 4; NE]).

Two other considerations are important in this regard for lorcaserin. Lorcaserin is "believed to selectively activate the 5-HT_{2C} receptor on orexigenic proopiomelanocortin neurons in the hypothalamus," based on receptor binding affinity values (i.e., K_i) that are approximately 10-fold less than those observed for the 5-HT_{2B} and 5-HT_{2A} serotonin receptor subtypes (1445 [EL 4; NE]). Because lorcaserin is a serotonergic drug, minimizing exposure to other serotonin-active medications is important to prevent serotonin syndrome, which is caused by excessive agonism of serotonin receptors in the central and peripheral nervous systems. Symptoms range from mild to lethal and often, but not always, include a triad of autonomic hyperactivity (tachycardia, HTN, diarrhea, diaphoresis, and hyperthermia), neuromuscular abnormalities (hyperreflexia and clonus), and changes in mental status (1539 [EL 4; NE]). In the safety trials of lorcaserin, 2 patients (one of which was taking dextromethorphan) developed symptoms of serotonin excess, including tremor, confusion, chills, disorientation, and hyperhidrosis. The safety of lorcaserin with concurrent use of SSRIs, SNRIs, bupropion, tricyclic antidepressants (TCAs), or MAOIs has not been established because all of these medications were excluded from clinical trials of lorcaserin. Therefore, "extreme caution and careful observation" is recommended with concurrent use of lorcaserin and any of the above listed psychotropic agents (1445 [EL 4; NE]).

The second consideration is that euphoria and dissociative events can be induced at suprapharmacologic doses (e.g., 40 and 60 mg/day), and for this reason, lorcaserin has

the potential for drug dependence. In clinical trials assessing pharmacologic doses of lorcaserin (20 mg/day) in patients with overweight or obesity, euphoria was observed in 0.17% of patients taking lorcaserin and 0.03% taking placebo (1445 [EL 4; NE]). This euphoria may be due to cross-reactivity with 5-HT_{2A} receptors (1540 [EL 4; NE]).

Antiepileptic medications, such as topiramate, increase suicidal thoughts and behaviors in patients with or without a history of depression (1541 [EL 2; MNRCT, meta-analysis of observational data, N = 5,130,795]). Composite data from 4 trials investigating phentermine/topiramate ER showed depression in 2.2% of the placebo group (n = 1,561), 3.3% of the phentermine/topiramate ER 3.75 mg/23 mg group (n = 240), 2.8% of the phentermine/topiramate ER 7.5 mg/46 mg group (n = 498), and 4.3% of the phentermine/topiramate ER 15 mg/92 mg group (n = 1,580) at 1 year (1444 [EL 4; NE]). In most cases, the depression occurred during the first 12 weeks of treatment, and the incidence was about twice as high in individuals with previous history of depression (1444 [EL 4; NE]). Depression as an adverse event led to the discontinuation of the study drug in 0.2% of the placebo group, 0% of the phentermine/topiramate 3.75 mg/23 mg group, 0.8% of the 7.5 mg/46 mg group, and 1.3% of the 15 mg/92 mg group (1444 [EL 4; NE]). The EQUIP trial of phentermine/topiramate ER utilized the PHQ-9 to monitor depressive symptoms and depression and the Columbia Suicidality Severity Rating Scale (C-SSRS) to assess suicidality. Notably, this trial included patients with a history of depression with or without treatment with antidepressant medications and excluded patients with substantial depressive symptoms (PHQ-9 score ≥10). Depression was present in 1.2% of the placebo group (n = 513), 3.3% of the phentermine/topiramate ER 3.75 mg/23 mg group (n = 240) ($P = 0.077$ compared with placebo), and 4.7% of the 15 mg/92 mg group (n = 511) ($P = 0.0007$ compared with placebo). Thus, depression was higher in the group taking phentermine/topiramate ER 15 mg/92 mg. PHQ-9 scores improved similarly in all groups over the course of the study, and suicidality did not increase according to the C-SSRS (857 [EL 1; RCT]).

In the CONQUER trial, 2,487 patients with overweight or obesity and 2 or more comorbidities were randomized to a placebo group (n = 993), phentermine/topiramate ER 7.5 mg/46 mg group (n = 498), or phentermine/topiramate ER 15 mg/92 mg group (n = 994) for 56 weeks. Patients with depression or a history of depression, including those taking antidepressant medications (with the exception of TCAs and MAOIs), were included in the study, and baseline rates of depression/depressive symptoms were 16 to 18% in the study groups. Prevalence of depression was 4% in the placebo group, 4% in the phentermine/topiramate ER 7.5 mg/46 mg group, and 7% in the phentermine/topiramate ER 15 mg/92 mg group. Discontinuation of phentermine/topiramate in the 15 mg/92 mg group due to depression was statistically more frequent than in the placebo group ($P = 0.0009$) (71 [EL 1; RCT]). The SEQUEL trial was a 1-year extension of the CONQUER trial for a total of 108 weeks of treatment with phentermine/topiramate ER. The incidence of depression-related adverse events during treatment was 7.9% in the placebo group, 3.9% in the 7.5 mg/46 mg group, and 8.1% in the 15 mg/92 mg group. Suicidality was similar among the randomization groups (722 [EL 1; RCT]). Due to its phentermine component, phentermine/topiramate ER should not be taken within 14 days of taking an MAOI due to an increased risk of hypertensive crisis (1444 [EL 4; NE]).

The COR-I study investigating naltrexone ER/bupropion ER included 1,742 patients with overweight or obesity (BMI 27-45 kg/m^2) with hyperlipidemia or hypertension and excluded patients with serious psychiatric illness (67 [EL 1; RCT]). In this study, depression as assessed by the Inventory of Depressive Symptomatology Self-Report (IDS-SR) was 1.1% in the placebo group (n = 569), 1.6% in the naltrexone ER/bupropion ER 16 mg/360 mg group (n = 569), and 0.5% in the naltrexone ER/bupropion ER 32 mg/360 mg group (n = 573). The study found that use of naltrexone ER/bupropion ER was not associated with increased frequency of depression, suicidality, or mood disorders (67 [EL 1; RCT]). The COR-II study, which included 1,496 patients with obesity (BMI 30-45 kg/m2) and hyperlipidemia or hypertension, also found no increase in incidence of depression or suicidality with naltrexone ER/bupropion ER. Specifically, depression occurred in 1.6% of the placebo group (n = 492) and 1.3% of the naltrexone ER/bupropion ER 32 mg/360 mg group (n = 992) (1422 [EL 1; RCT]). These studies did not assess use of naltrexone ER/bupropion ER in patients with severe psychiatric illness, as patients with history of major depression may have worsening symptoms and increased suicidal ideation and behavior (67 [EL 1; RCT]; 1422 [EL 1; RCT]; 1448 [EL 4; NE]).

Overall, no suicides or suicide attempts were reported in placebo-controlled trials of up to 56 weeks duration, and rates of suicidal ideation were 0.2% in the placebo group (n = 1,515) and 0.03% in the naltrexone ER/bupropion ER group (n = 3,239) (1448 [EL 4; NE]). Patient-reported rates of depression were 6.3% with naltrexone ER/bupropion ER and 5.9% with placebo (1448 [EL 4; NE]).

The prescribing information for naltrexone ER/bupropion ER states that patients should be monitored for depression or suicidal thoughts while taking the drug, and the drug should be discontinued if these symptoms arise (1448 [EL 4; NE]). Generally, antidepressants have the potential to initiate or worsen depression in any individual with or without a previous diagnosis and can precipitate manic or hypomanic episodes. Because patients with serious psychiatric illness were excluded from phase 3 clinical trials, more safety data is needed in patients with depression and other psychiatric illnesses.

Additionally, interactions between bupropion and other psychotropic medications may be problematic in patients requiring these therapies. While bupropion alone is used to treat depression and facilitate smoking cessation, the naltrexone ER/bupropion ER combination is not approved for these indications. Studies using bupropion for smoking cessation have reported mood changes, including depression and mania. Additionally, naltrexone ER/bupropion ER should not be used in younger patients because buproprion may increase suicidal thoughts in children, teenagers, and young adults. Lastly, naltrexone ER/bupropion ER should not be used within 14 days of taking an MAOI due to increased risk for hypertensive crisis (1448 [EL 4; NE]).

In summary, obesity and depression can occur together, and depression as well as concurrent use of antidepressants and other psychotropic medications should be considered when prescribing weight-loss medications. Orlistat and liraglutide 3 mg appear to have the least effect on mood and depression, although 1 attempted suicide was reported in the liraglutide 3 mg group. Studies of lorcaserin, phentermine/topiramate ER, and naltrexone ER/bupropion ER have included assessment of depression, depressive symptoms, and suicidality. Clinical trials assessing efficacy and safety of phentermine/topiramate ER included patients with depression and those taking SSRIs, and found that the highest dose of phentermine/topiramate ER (15 mg/92 mg) was associated with an increased incidence of depression, although the overall incidences were low. Lorcaserin was not tested in any patients taking antidepressant medications (SSRI, SNRI, bupropion, TCA, or MAOI); thus, drug safety and risk of serotonin syndrome with concurrent use of these medications is unknown. Patients with serious psychiatric illness were excluded from clinical trials investigating naltrexone ER/bupropion ER. Therefore, extra caution is warranted when using lorcaserin and naltrexone ER/bupropion ER in patients with obesity and depression until more safety data are available. Furthermore, patients taking MAOIs cannot be treated with phentermine/topiramate ER or naltrexone ER/bupropion ER due to the risk of hypertensive crisis.

- *Q8.7. Anxiety*

Executive Summary

- **R99.** Maximal dose (15 mg/92 mg) phentermine/topiramate ER should be used with caution in patients with obesity and anxiety disorders **(Grade A; BEL 1)**.

Evidence Base

Anxiety disorders are the most common class of mental health disorders in the United States with a 28.8% lifetime incidence (1542 [EL 4; NE]). Anxiety disorders often feature persistent symptoms of "excessive fear and anxiety" (658 [EL 4; NE]), and an association has been shown between obesity and anxiety. A recent meta-analysis examined data from 16 studies (2 prospective and 14 cross-sectional studies) (1543 [EL 2; MNRCT]). The 2 prospective studies showed mixed results (1544 [EL 2; PCS, N = 74,332]; 1545 [EL 2; PCS]), with the larger 10-year study of 33,777 individuals showing that obesity was associated with an increased risk of anxiety in men but not women (1544 [EL 2; PCS, N = 74,332]) and the other small study of 544 mothers interviewed 3 times over 30 years showing that obesity was positively associated with risk for anxiety in women (1545 [EL 2; PCS]). The pooled odds ratio from the 14 cross-sectional studies was 1.4 (CI: 1.2-1.6), with a positive association between obesity and anxiety in both men and women (1543 [EL 2; MNRCT]).

Prevalence of anxiety has been assessed in safety trials of the FDA-approved weight-loss medications. Studies of orlistat treatment showed that prevalence of anxiety was 4.7% and 2.9% in the orlistat (n = 1,913) and placebo (n = 1,466) groups, respectively, at 1 year and 2.8% and 2.1% in the orlistat (n = 613) and placebo (n = 524) groups, respectively, at 2 years (1442 [EL 4; NE]). Safety trials of lorcaserin showed that anxiety was reported in 3.5% and 3.2% in the lorcaserin (n = 256) and placebo (n = 252) groups, respectively (1445 [EL 4; NE]). In the lorcaserin BLOSSOM study, 1 subject had a severe anxiety attack (69 [EL 1; RCT]). A 1-year trial showed that incidence of anxiety increased with higher doses of phentermine/topiramate ER, as anxiety was reported in 2.9% of the placebo group, 4.6% of the 3.75 mg/23 mg treatment group, 4.8% of the 7.5 mg/46 mg group, and 7.9% of the 15 mg/92 mg group (1444 [EL 4; NE]). In most cases, the anxiety occurred during the first 12 weeks of treatment with phentermine/topiramate ER. The 2-year SEQUEL study also showed a dose-dependent increase in the incidence of anxiety with phentermine/topiramate ER treatment, with 3.1% in the placebo group (n = 227), 6.5% in the 7.5 mg/46 mg group (n = 153), and 9.5% in the 15 mg/92 mg group (n = 295) reporting anxiety; furthermore, 3 subjects developed severe anxiety and one discontinued the medication in the high-dose group (722 [EL 1; RCT]). The EQUIP trial also showed a dose-dependent increase in anxiety with a statistically significant difference between the high-dose (15 mg/92 mg) and placebo groups; specifically, anxiety was reported in 1.2% of the placebo group (n = 513), 2.9% of the 3.75 mg/23 mg group (n = 241) ($P = 0.128$ vs. placebo), and 3.7% of the 15 mg/92 mg group (n = 511) ($P = 0.0084$ vs. placebo) (858 [EL 1; RCT]).

In a 1-year clinical trial of bupropion ER/naltrexone ER, the incidence of anxiety was 6.1% in the treatment group and 4.4% in the placebo group (1448 [EL 4; NE]). In the COR-I study, incidence of anxiety, as assessed by the IDS-SR, was not different between treatment and placebo groups and was 2.1% with bupropion ER/naltrexone ER 16 mg/360 mg (n = 569), 1.9% with bupropion ER/naltrexone

ER 32 mg/360 mg (n = 573), and 2.1% with placebo (n = 569) (67 [EL 1; RCT]).

Incidence of anxiety was 2.0% in the liraglutide 3 mg group (n = 3,384) and 1.6% in the placebo group (n = 1,941) (1449 [EL 4; NE]). In the safety and tolerability trial of liraglutide 3 mg, anxiety was reported in 2.2% of patients receiving liraglutide 2.4 or 3.0 mg/day (n = 93) and 1.0% of patients receiving placebo (n = 98), with 2 subjects in the placebo group withdrawing due to anxiety (897 [EL 1; RCT]). Additionally, 1 case of acute stress disorder and 2 cases of nervousness were reported (897 [EL 1; RCT]).

Because the prevalence of anxiety disorders is high in the general population, the potential for anxiety should be considered when prescribing weight-loss medications. Because a dose-dependent increase in anxiety has been demonstrated with phentermine/topiramate ER, caution should be used when prescribing phentermine/topiramate ER to an individual with anxiety disorder and the highest dose should be avoided especially if other options are available.

- *Q8.8. Psychotic disorders with or without medications (e.g., lithium, atypical antipsychotics, and monoamine oxidase inhibitors (MAOIs)*

Executive Summary

- **R100.** Patients with psychotic disorders treated with antipsychotic medications should be treated with a structured lifestyle intervention to promote weight loss or prevent weight gain **(Grade A; BEL 1)**.
- **R101.** Treatment with metformin may be beneficial for promoting modest weight loss and metabolic improvement in individuals with psychotic disorders who are taking antipsychotic medications **(Grade A; BEL 1)**.
- **R102.** Caution must be exercised when using any weight-loss medication for patients with obesity and a psychotic disorder due to insufficient evidence assessing safety and efficacy (Grade D).

Evidence Base

An association exists between obesity and serious mental health problems, including psychotic disorders such as schizophrenia (1546 [EL 4; NE]; 1547 [EL 2; MNRCT]). By definition, individuals with schizophrenia spectrum and other psychotic disorders experience at least one or more of the following: delusions, hallucinations, disorganized thinking, disorganized motor behavior, or negative symptoms (i.e., diminished emotional expression or avolition) (658 [EL 4; NE]). Prevalence of obesity in patients with serious mental health disorders, including schizophrenia, bipolar disorder, and depression, is higher than that observed in the general population (1548 [EL 4; NE]; 1549 [EL 3; SS]), with a prevalence as high as 79% (27% overweight and 52% obese) (1550 [EL 3; SS]). Other studies estimate 76% (29% overweight and 47% obese) of patients with psychosis (1551 [EL 3; CSS]) and 46% (29% overweight and 17% obese) of patients with schizophrenia (1552 [EL 3; SS]). The relationship between serious mental health disorders and obesity may be due to interactions between genetic, environmental, and disease-specific factors, as well as treatment with antipsychotic medications (1546 [EL 4; NE]; 1553 [EL 4; NE]; 1554 [EL 1; MRCT]; 1555 [EL 2; MNRCT]), such as clozapine, olanzapine, and risperidone, that are associated with obesity, metabolic syndrome, and diabetes (1556 [EL 3; SS, N = 42,437]; 1557 [EL 4; NE]). Because obesity increases risk for weight-related complications in these patients (1548 [EL 4; NE]), developing interventions to prevent and treat obesity is especially important for this high-risk population. In some cases, switching antipsychotic medications may alleviate some of the weight gain (1558 [EL 1; MRCT]); however, focused efforts on the prevention and treatment of obesity are necessary for many patients.

Multiple RCTs that compare lifestyle interventions with control conditions for patients with psychoses have demonstrated that lifestyle interventions improve weight loss (1559 [EL 1; RCT]; 1560 [EL 1; RCT]; 1561 [EL 1; RCT]; 1562 [EL 1; RCT]; 1563 [EL 1; RCT]; 1564 [EL 1; RCT]), reduce weight gain (1560 [EL 1; RCT]; 1565 [EL 1; RCT, pilot study, N = 18]; 1566 [EL 2; PCS]; 1567 [EL 1; RCT]), improve cardiometabolic disease risk factors (1559 [EL 1; RCT]; 1560 [EL 1; RCT]; 1562 [EL 1; RCT]; 1564 [EL 1; RCT]), and ameliorate depressive symptoms (1561 [EL 1; RCT]; 1568 [EL 1; RCT]; 1569 [EL 1; RCT]). The types of lifestyle interventions vary widely and include healthy eating approaches, physical activity, behavioral interventions, and/or reduced-calorie diets. Daumit et al (1559 [EL 1; RCT]) randomized 291 outpatients with a psychotic disorder to an 18-month lifestyle intervention or a control group receiving standard care. Lifestyle modification resulted in a between-group difference in weight of –3.7 kg ($P = 0.002$), and 37.8% of the patients with lifestyle modification lost ≥5% body weight compared to 22.7% of the control group ($P = 0.009$) (1559 [EL 1; RCT]). A lifestyle intervention that encouraged healthy eating and physical activity reduced the prevalence of metabolic syndrome and improved related risk factors in the absence of weight loss (1562 [EL 1; RCT]). Wu et al (1564 [EL 1; RCT]) found that a lifestyle intervention produced a modest weight loss of 0.5 kg and improved insulin sensitivity index, whereas the control group gained 1.2 kg. Alvarez-Jimenez et al (1560 [EL 1; RCT]) compared a behavioral intervention with nonstructured routine care and found that the behavioral intervention resulted in less weight gain (mean difference –2.8 kg) over a 3-month time period in 61 patients with a psychotic disorder treated with antipsychotic drugs. A meta-analysis that included 25 RCTs demonstrated that

lifestyle interventions promoted weight loss (effect size –0.84, P = 0.0002), prevented weight gain (effect size –0.46, P = 0.02), and improved cardiometabolic disease risk factors in patients with psychotic disorders (1570 [EL 1; MRCT]).

Pharmaceutical studies of FDA-approved long-term weight-loss medications have excluded patients with psychotic disorders (1442 [EL 4; NE]; 1444 [EL 4; NE]; 1445 [EL 4; NE]; 1448 [EL 4; NE]; 1449 [EL 4; NE]). However, trials have assessed orlistat and, as proof-of-principle, other pharmacologic agents not approved by the FDA for weight loss in this patient population. These trials assessed the ability of these medications to counteract weight gain and the detrimental metabolic effects of antipsychotics for schizophrenia and other serious mental health disorders. A recent meta-analysis found that 19 agents have been investigated (1571 [EL 1; MRCT]), with metformin studied the most extensively in several RCTs (1564 [EL 1; RCT]; 1572 [EL 1; RCT]; 1573 [EL 1; RCT]; 1574 [EL 1; RCT]; 1575 [EL 1; RCT]; 1576 [EL 1; RCT]; 1577 [EL 1; RCT]; 1578 [EL 1; RCT]; 1579 [EL 1; RCT]; 1580 [EL 1; RCT]). Several trials of topiramate varying in size and methodology (1581 [EL 1; RCT]; 1582 [EL 1; RCT]; 1583 [EL 1; RCT]; 1584 [EL 1; RCT]), a pilot study of naltrexone (1585 [EL 1; RCT]; 1586 [EL 1; RCT]), and a trial assessing orlistat (1587 [EL 1; RCT]) have also been performed.

The largest RCT of metformin treatment randomized 148 individuals with overweight or obesity (average BMI 34.6 kg/m^2, average age 43.2 years) with diagnosed schizophrenia or schizoaffective disorder treated with various antipsychotic medications to receive 16 weeks of metformin (titrated to 1,000 mg twice per day) or placebo (1575 [EL 1; RCT]). Both groups received weekly diet and exercise counseling. After 4 months of treatment, a statistically significant difference was observed between the metformin and placebo groups in terms of weight loss (metformin group: –3.0 kg, 95% CI = –4.0 to –2.0; placebo group: –1.0 kg, 95% CI = –2.0 to 0; between-group: –2.0 kg, 95% CI = –3.4 to –0.6; P = 0.0065), change in BMI (between-group: –0.7 kg/m^2, 95% CI = –1.1 to –0.2; P = 0.0063), change in triglyceride (between-group: –20.2 mg/dL, 95% CI = –39.2 to –1.3; P = 0.037), and change in hemoglobin A1C (between-group: –0.07%, 95% CI = –0.14 to –0.004; P = 0.039) (1575 [EL 1; RCT]). The authors concluded that 16 weeks of metformin induced modest weight loss in patients with schizophrenia or schizoaffective disorder, and the significant time-by-treatment interaction suggested longer duration of treatment may provide further benefit. Another RCT conducted in China included 128 patients with schizophrenia who had gained >10% of their body weight from treatment with antipsychotic medication during their first psychotic episode (1564 [EL 1; RCT]). Patients were assigned to one of the following 4 groups for 12 weeks: (*1*) metformin 750 mg/day plus lifestyle, (*2*) metformin 750 mg/day, (*3*) placebo plus lifestyle, or (*4*) placebo. Weight, BMI, and insulin resistance decreased in the metformin, metformin plus lifestyle, and placebo plus lifestyle groups but increased in the placebo group (metformin plus lifestyle weight change: –4.7 kg, BMI change: –1.8 kg/m^2; metformin weight change: –3.2 kg, BMI change: –1.2 kg/m^2; placebo plus lifestyle weight change: –1.4 kg, BMI –0.5 kg/m^2; placebo weight change: +3.1 kg, BMI change: +1.2 kg/m^2) (1564 [EL 1; RCT]). Specifically, metformin plus lifestyle was most effective for weight loss, and metformin alone was more effective than placebo plus lifestyle- and placebo alone treatments (1564 [EL 1; RCT]).

Smaller RCTs have examined whether metformin is effective for individuals treated for longer periods with olanzapine, a second-generation antipsychotic that antagonizes dopamine (D1-4) and serotonin (5-HT$_{2A}$ and 5-HT$_{2C}$) receptors and is known to cause weight gain. One study randomized 40 patients taking olanzapine to receive 14 weeks of treatment with metformin 850 to 1,700 mg/day (n = 20, BMI 23 kg/m^2) or placebo (n = 20, BMI 23 kg/m^2) and showed that metformin did not prevent weight gain (1572 [EL 1; RCT]). Another study randomized 80 patients who were taking olanzapine (5-20 mg/day for ≥4 months) to receive 12 weeks of metformin 850 to 2,550 mg/day (n = 40) or placebo (n = 40) (1573 [EL 1; RCT]). The metformin group lost a mean of 1.4 kg (P = 0.01); whereas, the placebo group remained relatively weight stable with a 0.18-kg loss (P = 0.7).

Finally, studies have examined the ability of metformin to prevent weight gain in patients with schizophrenia by starting metformin simultaneously with olanzapine. One study randomized 40 normal-weight patients (average BMI 21-22 kg/m^2, average age 25 years) with schizophrenia to receive either 12 weeks with olanzapine plus metformin 750 mg/day (n = 20) or olanzapine plus placebo (n = 20) (1574 [EL 1; RCT]) and showed that the olanzapine plus placebo group gained more weight than the olanzapine plus metformin group (+6.9 kg versus +1.9 kg, respectively; t = –2.86, P<0.02). Several studies, including RCTs, suggest that metformin may be modestly beneficial for preventing weight gain or promoting weight loss in patients with schizophrenia taking antipsychotic medications.

Studies have also investigated the efficacy of topiramate for weight loss or prevention of weight gain in patients with schizophrenia treated with antipsychotics (1581 [EL 1; RCT]; 1582 [EL 1; RCT]; 1583 [EL 1; RCT]; 1584 [EL 1; RCT]). In an RCT, 72 patients were randomized to receive 12 weeks of treatment with olanzapine plus topiramate 100 mg/day or olanzapine plus placebo daily (1581 [EL 1; RCT]). The group that received olanzapine plus topiramate lost a mean of 1.27 kg (P = 0.003), while the olanzapine plus placebo group gained a mean of 6.05 kg (P<0.001) (between group t-test t = 1.9, P = 0.05) (1581 [EL 1; RCT]). Additionally, the group that received

olanzapine plus topiramate demonstrated improvements in fasting plasma glucose, total cholesterol, triglyceride, and SBP and DBP, while these parameters increased in the olanzapine plus placebo group (1581 [EL 1; RCT]). In another trial, 66 hospitalized patients with schizophrenia (average BMI 27-29 kg/m^2, average age 34-37 years) were randomized to receive placebo, topiramate 100 mg/day, or topiramate 200 mg/day for 12 weeks (1582 [EL 1; RCT]). Weight loss was significantly greater in the topiramate 200 mg/day subgroup than in the topiramate 100 mg/day and placebo groups (F-distribution = 7.32, degrees of freedom [df] = 2, P = 0.002), with mean weight changes of –0.3 kg in the placebo group, -1.68 kg in the topiramate 100 mg/day group, and -5.35 kg in the topiramate 200 mg/day at 12 weeks (1582 [EL 1; RCT]). An open-label trial comparing olanzapine plus topiramate versus olanzapine alone for a cohort of patients with schizophrenia found less weight gain in the olanzapine plus topiramate group than the olanzapine alone group (2.66 kg versus 4.02 kg, P = 0.038) (1584 [EL 1; RCT]). Thus, topiramate may be beneficial for promoting weight loss or preventing weight gain in patients with schizophrenia treated with antipsychotics, but additional larger RCTs are needed to confirm these findings.

The utility of naltrexone has also been investigated for promoting weight loss in patients with schizophrenia. A pilot study randomized 24 women with schizophrenia or schizoaffective disorder (average BMI 40-42 kg/m^2, average age 41-50 years) to 8 weeks of treatment with naltrexone 25 mg/day (n = 11) or placebo (n = 12) (1585 [EL 1; RCT]; 1586 [EL 1; RCT]). Women in the naltrexone group lost 3.40 kg (95% CI: 5.16-1.65), whereas the placebo group gained 1.37 kg (95% CI: 0.30-3.03) (F-distribution = 14.79, P = 0.001). This pilot suggests a potential benefit of treatment with naltrexone for patients with schizophrenia, but larger and longer-term studies are needed. An ongoing trial is investigating the effect of naltrexone over 52 weeks of treatment in patients with schizophrenia (http://clinicaltrials.gov).

In a study investigating the efficacy of orlistat for weight loss in patients with schizophrenia (average BMI 32-33 kg/m^2, age 37-38 years) treated with antipsychotics (clozapine and olanzapine), 71 patients were randomized to receive orlistat or placebo for 16 weeks (1587 [EL 1; RCT]). Although men appeared to benefit from treatment with orlistat (–2.36 kg versus 0.62 kg, P = 0.011) women did not (1.94 kg versus 0.22 kg). The addition of orlistat to clozapine also reduces the frequency of constipation associated with taking clozapine (1588 [EL 1; RCT]). More studies are required to assess the efficacy of orlistat for weight loss in patients with schizophrenia that are taking antipsychotic medications. Lorcaserin was effective for managing olanzapine-induced weight gain in 1 of 2 patients with schizophrenia (1589 [EL 3; SCR]).

In summary, with the exception of orlistat, medications approved by the FDA for chronic treatment of obesity have not been studied in patients with schizophrenia and other psychotic disorders. As this patient population is at particularly high risk for obesity and metabolic perturbations, investigating and implementing strategies to minimize weight gain and promote weight loss in patients with serious mental health disorders is essential. These studies also emphasize that naltrexone ER/bupropion ER (1448 [EL 4; NE]), phentermine, and phentermine/topiramate ER (1444 [EL 4; NE]) should not be used within 14 days of an MAOI and that caution must be exercised when combining lorcaserin with other serotonergic drugs (1445 [EL 4; NE]). Additionally, metformin may be beneficial for promoting modest weight loss in individuals with schizophrenia who are taking antipsychotic medications. Preliminary evidence indicates that single-agent topiramate and naltrexone may be beneficial for these patients, although further studies are needed to substantiate these preliminary results.

- *Q8.9. Eating disorders including binge eating disorder*

Executive Summary

- **R103.** Patients with overweight or obesity being considered for weight-loss therapy should be screened for binge eating disorder and night eating syndrome **(Grade B; BEL 3, upgraded due to high relevance)**.
- **R104.** Patients with overweight or obesity who have a binge eating disorder should be treated with a structured behavioral/lifestyle program in conjunction with cognitive behavioral therapy or other psychologic interventions **(Grade A; BEL 1)**.
- **R105.** In patients with overweight or obesity and binge eating disorder, treatment with orlistat or approved medications containing topiramate or bupropion may be considered in conjunction with structured lifestyle therapy, cognitive behavioral therapy, and/or other psychologic interventions **(Grade A; BEL 1)**.
- **R106.** Structured lifestyle therapy and/or selective serotonin reuptake inhibitor therapy may be considered in patients with obesity and night eating syndrome **(Grade B; BEL 1, downgraded due to evidence gaps)**.

Evidence Base

Eating disorders "are characterized by persistent disturbance of eating food and eating-related behavior that results in the altered consumption or absorption of food and significantly impairs physical health or psychological functioning" (658 [EL 4; NE]). Binge eating disorder

(BED) and night eating syndrome (NES) are eating disorders commonly associated with obesity (1590 [EL 4; NE]).

BED is the most common eating disorder in the United States with prevalences of 2.8% overall (1591 [EL 4; NE]) and 2 to 47% in patients with obesity (1590 [EL 4; NE]). BED is defined as recurrent episodes of binge eating (at least 3 times per week) associated with at least three of the following features: eating more rapidly than usual, feeling uncomfortably full, eating a large amount of food when not hungry, eating alone because of embarrassment associated with one's eating, feeling disgusted with oneself or guilty after a binge eating episode, and having distress regarding binge eating (658 [EL 4; NE]). The association between BED and obesity has been well-documented (1590 [EL 4; NE]; 1592 [EL 3; SS]; 1593 [EL 4; NE]), and primary treatment of BED is often associated with weight loss in patients with obesity.

Cognitive behavioral therapy (CBT) for BED may be associated with modest weight loss (1594 [EL 1; RCT]). A systematic review of RCTs indicated that combination therapies involving CBT and psychotropic medications for BED improve binge eating and promote weight loss (1595 [EL 1; MRCT]). However, a meta-analysis reviewed 26 phase 2/3 short-term trials (6-24 weeks in duration) assessing emerging pharmacotherapy for BED and generally concluded that the addition of medications specific for BED to psychological interventions modestly increased weight loss over psychological intervention alone (1596 [EL 4; NE]).

A matched-study meta-analysis demonstrated that patients with obesity and BED treated with lifestyle therapy tend to have less favorable weight-loss outcomes than patients with obesity alone (1365 [EL 2; MNRCT, matched-study analysis, non-exhaustive literature search]). In this meta-analysis, the pooled results indicated that patients with obesity and BED lost an average of 1.3 kg with lifestyle interventions, whereas patients with obesity and no BED lost 10.5 kg; however, both groups experienced similar reduction in depressive symptoms.

Several RCTs have concluded that lifestyle/behavioral therapy is more effective for weight loss than CBT, although the amount of weight loss tends to be modest (1594 [EL 1; RCT]; 1597 [EL 1; RCT]). In 2 trials of intensive lifestyle interventions (1598 [EL 1; RCT]; 1599 [EL 3; CSS]), including the Look AHEAD study (1598 [EL 1; RCT]), patients with BED achieved clinically significant weight loss equal to patients without BED. This was also the conclusion of an interventional cohort study that showed BED did not affect the amount of weight loss achieved by women participating in any of the 3 lifestyle interventions (1600 [EL 1; RCT]). In a RCT involving adolescents, lifestyle therapy and CBT were equally effective for producing weight loss (weight losses of 7% and 6.9%, respectively, at month 6 and 8.8% and 8.3%, respectively, at month 12) (1601 [EL 1; RCT]). Therefore, the data indicate that intensive structured lifestyle interventions effectively facilitate weight loss in patients with BED and obesity.

The role of weight-loss medication has not been rigorously studied in patients with obesity and BED. Several studies have been conducted with orlistat. Two RCTs that compared orlistat and diet to diet alone (1602 [EL 1; RCT]) and orlistat and CBT delivered using guided self-help to CBT alone (1603 [EL 1; RCT]) found that the groups randomized to orlistat experienced significantly greater weight loss than the respective control groups in each study (7.4% versus 2.3% and 3.3% versus 1.6% in the diet and CBT trials, respectively) (1602 [EL 1; RCT]; 1603 [EL 1; RCT]). However, one 12-week RCT found that taking orlistat with behavioral weight-loss therapy did not result in more weight loss than behavioral weight-loss therapy alone (1604 [EL 1; RCT]). A RCT randomized 44 patients with obesity and subclinical binge eating to treatment with liraglutide or control and showed that the liraglutide group had greater reductions in weight, WC, SBP, and fasting glucose, as well as a significant improvement in binge eating (1605 [EL 1; RCT]). Liraglutide also led to higher serum ghrelin levels, which may have diminished the weight-loss efficacy of the drug.

In the mesocorticolimbic reward system, opioids modulate the reward sensation from consumption of palatable foods while dopamine regulates food-seeking behavior (1606 [EL 4; NE]). In an RCT, naltrexone did not affect intensity of food cravings, but did eliminate the positive association between craving intensity and reward-driven eating (1607 [EL 1; RCT]) and decrease reward activation responses to foods on functional MRI studies (1608 [EL 1; RCT, N = 20]). Naltrexone reduced the subjective pleasure derived from eating certain foods (1607 [EL 1; RCT]; 1608 [EL 1; RCT, N = 20]) but did not affect body weight in placebo-controlled RCTs when given as a single agent (1447 [EL 4; NE]; 1606 [EL 1; RCT, human proof-of-concept trial; note there are also preclinical studies in this paper]).

Bupropion is a dopamine/norepinephrine reuptake inhibitor that reduces short-term food intake in rodents and is associated with modest weight reduction in humans when given as a single agent (1447 [EL 4; NE]; 1606 [EL 1; RCT, human proof-of-concept trial; note there are also preclinical studies in this paper]). A placebo-controlled, double-blind RCT of women with BED found that bupropion (300 mg/day) increased weight loss relative to placebo (1609 [EL 1; RCT]). Weight loss associated with the combination naltrexone ER/bupropion ER was associated with improved control over eating and reduced food cravings as assessed by the Control of Eating Questionnaire relative to placebo in all clinical trials (67 [EL 1; RCT]; 779 [EL 1; RCT]; 859 [EL 1; RCT]; 1422 [EL 1; RCT]). These mechanisms of action and findings regarding the improved control of eating are promising; however, future trials should address clinical outcomes and therapeutic

efficacy of naltrexone ER/bupropion ER in patients with obesity and BED.

Three RCTs assessing topiramate therapy (starting dose 25 mg titrated up to 600 mg/day and study durations 14-21 weeks) in patients with BED found significantly greater weight loss with topiramate than with placebo (range –4.5 to –6.8 kg with topiramate and –0.2 to –1.2 kg with placebo) (1610 [EL 1; RCT]; 1611 [EL 1; RCT]; 1612 [EL 1; RCT]). Of these 3 RCTs, the greatest magnitude of weight loss was observed in the study that combined CBT with topiramate (1610 [EL 1; RCT]). Additionally, one 16-week RCT (n = 60) comparing zonisamide (100 mg/day titrated up to 600 mg/day) with placebo found greater weight loss with the drug (-4.8 kg) than with placebo (–1.0 kg) ($P<0.001$) (1613 [EL 1; RCT]).

NES is defined by "recurrent episodes of night eating," including "excessive food consumption after the evening meal" with individuals awake and aware that they are eating (658 [EL 4; NE]).The prevalence of NES is approximately 1.5% in the general population and is higher in individuals with obesity, ranging from 8 to 43% (1590 [EL 4; NE]). Patients with obesity and NES treated with lifestyle therapy tend to lose less weight than their counterparts without NES (1614 [EL 2; PCS]; 1615 [EL 3; CCS]), although this was not the case in 1 study (1616 [EL 2; PCS, case-controlled]).

Studies have examined the effectiveness of SSRIs for the treatment of NES. An 8-week study found that individuals with overweight or obesity (n=14) with NES treated with sertraline (50-200 mg/day, n = 14) lost more weight than the placebo group (n = 14) (–2.9 kg vs. –0.3 kg) (1617 [EL 1; RCT]). One study investigating escitalopram showed no difference in weight change between the drug and placebo groups (1618 [EL 1; RCT]). More studies are needed to assess efficacy of weight-loss medications in patients with obesity and NES.

Lisdexamfetamine dimesylate, used to treat attention-deficit hyperactivity disorder (ADHD), has been approved for the treatment of BED with a recommended maintenance dose of 50 to 70 mg/day. Lisdexamfetamine reduced the number of binge days per week by an average of ~1.5 days, and, although not approved for weight loss, was associated with modest weight loss of 1 to 2 kg (1619 [EL 1; RCT]). No safety or efficacy data are available for the combination of lisdexamfetamine with weight-loss medications. A 10-week RCT showed that atomoxetine, an adrenergic transmitter uptake inhibitor also used for ADHD treatment, yielded more weight loss than did placebo (2.7 kg vs. 0.0 kg) (1620 [EL 1; RCT]).

Other psychotropic drugs have been tested in patients with obesity and BED. Two meta-analyses (1595 [EL 1; MRCT]; 1597 [EL 1; RCT]) concluded that SSRIs have limited efficacy for the treatment of BED and yield mixed results with respect to weight loss. One short 6-week RCT that predominantly included women found that fluoxetine produced greater weight loss than did placebo (3.9 kg vs. 0.7 kg) (1621 [EL 1; RCT]), but other RCTs did not show a statistically significant difference in weight loss when fluoxetine was added to behavioral weight loss (1622 [EL 1; RCT]) or CBT (1623 [EL 1; RCT]; 1624 [EL 1; RCT, post-intervention follow-up]; 1625 [EL 1; RCT]). Additionally, small, short-term (6-12 weeks) RCTs showed a greater decrease in BMI with sertraline (1626 [EL 1; RCT]), citalopram (1627 [EL 1; RCT]), and escitalopram (1628 [EL 1; RCT]) than with respective placebos. Duloxetine, an SNRI, and imipramine, a tricyclic antidepressant, also resulted in more weight loss relative to their respective placebos (1629 [EL 1; RCT]; 1630 [EL 1; RCT]). However, current data do not support use of ADHD drugs, SSRIs, or SNRIs in patients with obesity and BED for the purpose of weight loss.

Q8.10. Glaucoma

Executive Summary

- **R107.** Liraglutide 3 mg, orlistat, and lorcaserin should be the preferred weight loss medications for patients with a history of or at risk for glaucoma **(Grade B; BEL 2)**. In patients with glaucoma, phentermine/topiramate ER should be avoided and naltrexone ER/bupropion ER should be used with caution **(Grade C; BEL 2, downgraded due to evidence gaps)**.

Evidence Base

Liraglutide 3.0 mg, orlistat, and lorcaserin have no known association with risk for glaucoma (1442 [EL 4; NE]; 1445 [EL 4; NE]; 1449 [EL 4; NE]). Although no case reports of lorcaserin-associated glaucoma have been published, bilateral angle-closure glaucoma was reported in a patient taking dexfenfluramine, another serotonin receptor agonist (1631 [EL 3; SCR]).

Phentermine/topiramate ER is contraindicated in patients with a history of glaucoma (1444 [EL 4; NE]). Topiramate has been implicated in multiple case reports of acute-onset glaucoma (1632 [EL 3; SS]). Recently, acute bilateral angle closure was detected in a 39-year-old female who had started phentermine/topiramate ER 1 week earlier and resolved upon cessation of the drug (1633 [EL 3; SCR]). A case-control study of subjects seeing an ophthalmologist in Canada showed an increased relative risk of glaucoma (RR = 1.54) among new users of topiramate, whereas current users had no increase in risk (1634 [EL 2; RCCS]). Similarly, a retrospective population-based cohort study in Taiwan revealed that patients prescribed topiramate had greater than sevenfold higher risk for glaucoma during the first month than their matched controls, but the difference in risk was not significant after the first month (1635 [EL 3; SS]). The data were also consistent with a recent systematic review that analyzed the ophthalmologic

effects of topiramate, including cases of angle-closure glaucoma (1636 [EL 2; MNRCT]). Phentermine monotherapy is also contraindicated in patients with a history of glaucoma (1637 [EL 4; NE]), and a case report was documented of a young adult female with acute myopia and angle closure that developed 3 weeks after starting phentermine and resolved after discontinuation (1638 [EL 3; SCR]).

Caution is advised regarding the use of naltrexone ER/bupropion ER due to the possible increase in risk for acute glaucoma with bupropion (1448 [EL 4; NE]). Epidemiologic studies have shown that antidepressants such as bupropion may increase the risk for angle-closure glaucoma. A recent case control study in the United States showed that patients prescribed topiramate had a fivefold increase in risk of glaucoma, and those prescribed bupropion had a twofold increase in risk (1639 [EL 2; RCCS]). However, a short-term randomized crossover study of patients showed that 300 mg bupropion daily did not increase ocular pressure in a cohort of healthy volunteers, and bupropion administration was associated with a lower risk of open-angle glaucoma over the long term in a large managed-care population (1640 [EL 1; RCT]; 1641 [EL 3; SS]). The prescribing information for naltrexone ER/bupropion ER carries a warning that states, "the pupillary dilation that occurs following use of many antidepressant drugs, including bupropion, … may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy." (1448 [EL 4; NE]).

- *Q8.11. Seizure disorder*

Executive Summary

- **R108.** Phentermine/topiramate, lorcaserin, liraglutide, and orlistat are the preferred weight-loss medications for patients with a history of or at risk for seizure/epilepsy **(Grade B; BEL 1, downgraded due to evidence gaps)**. The use of naltrexone ER/bupropion ER should be avoided in these patients.

Evidence Base

Phentermine/topiramate ER, lorcaserin, liraglutide 3.0 mg, and orlistat have no known mechanistic or clinical data that supports an increased risk of seizure (1442 [EL 4; NE]; 1444 [EL 4; NE]; 1445 [EL 4; NE]; 1449 [EL 4; NE]). Naltrexone ER/bupropion ER is contraindicated in patients with a seizure disorder, history of seizures, and high risk of seizures, including patients with bulimia or anorexia nervosa, alcohol withdrawal or abrupt discontinuation of alcohol, and use of benzodiazepines, barbiturates, and antiepileptic drugs (1448 [EL 4; NE]). Caution should be used when prescribing naltrexone ER/bupropion ER with concomitant use of other drugs or metabolic conditions that may lower the seizure threshold. Co-administration with a high-fat meal should also be avoided because this approach can augment the circulating AUC following oral drug ingestion (1448 [EL 4; NE]).

Bupropion is a norepinephrine and dopamine reuptake inhibitor (1642 [EL 4; NE]) and is implicated in lowering the seizure threshold (1643 [EL 4; NE]). Many previous studies have shown that in patients without a personal or family history of seizure, bupropion is associated with a slightly increased incidence of seizure relative to placebo or a matched comparator (1644 [EL 4; NE]; 1645 [EL 2; PCS]; 1646 [EL 2; PCS]). A Cochrane review that included a meta-analysis of bupropion treatment for smoking cessation across 82 trials estimated an incidence of 6 seizures in the bupropion arms versus none in the placebo arms, although this incidence of approximately 1:1500 was lower than the expected incidence of 1:1000 (1647 [EL 1; MRCT]). A recent analysis of the naltrexone ER/bupropion ER trials showed that epileptic seizures were the most common serious adverse event, with an incidence of 0.4% (1648 [EL 4; NE]).

- *Q8.12. Pancreatitis*

Executive Summary

- **R109.** All patients with obesity should be monitored for typical symptoms of pancreatitis (e.g., abdominal pain or GI distress) due to a proven association between the two conditions **(Grade A; BEL 1)**.
- **R110.** Patients receiving glyburide, orlistat, or incretin-based therapies (glucagon-like peptide-1 receptor agonists or dipeptidyl peptidase 4 inhibitors) should be monitored for pancreatitis (Grade C; BEL 3). Glyburide, orlistat, and incretin-based therapies should be withheld in cases of prior or current pancreatitis; otherwise, data are insufficient to recommend withholding glyburide for glycemic control, orlistat for weight loss, or incretin-based therapies for glycemic control or weight loss due to concerns regarding pancreatitis (Grade D).

Evidence Base

Obesity and some obesity-related therapies have been associated with pancreatitis as summarized below:

- Obesity is associated with increased prevalence of gallstone disease and risk for gallstone pancreatitis (1649 [EL 2; PCS]; 1650 [EL 2; PCS]; 1651 [EL 4; NE]).
- The prevalence of hypertriglyceridemia and risk for pancreatitis is higher in patients with obesity (1652 [EL 3; CSS]; 254 [EL 3; CSS]).

- Association of BMI >30 kg/m^2 and abdominal adiposity regardless of BMI is associated with pancreatitis due to increased inflammation, with direct and indirect effects of cytokines and adipokines, dysregulation of autophagy, and increased intrapancreatic fat (1649 [EL 2; PCS]; 1652 [EL 3; CSS]; 1653 [EL 2; MNRCT]; 1654 [EL 2; PCS]; 1655 [EL 2; PCS]; 1656 [EL 4; NE]). The strength of evidence showing the association between obesity and pancreatitis is well established.
- Case reports have shown occurrence of pancreatitis with the use of certain medications for weight loss or hyperglycemia management, such as glyburide (1657 [EL 2; RCCS]) and orlistat (1658 [EL 3; SCR]; 1659 [EL 3; SCR]).
- The association between incretin-based therapies (dipeptidyl peptidase-4 [DPP-4] inhibitors and GLP-1 receptor agonists [RAs]) used in obesity care and pancreatitis is controversial in the medical literature. The association between incretin-based therapies and pancreatitis is supported by analyses of the French pharmacovigilance database (2008-2013) (1660 [EL 3; SS]), a population-based case-controlled study in the U.S. (1661 [EL 2; RCCS]), a pathologic study that suggests the potential for pancreatitis (1662 [EL 2; RCCS]), as well as animal and observational clinical studies with T2DM that, collectively, are methodologically flawed. Any potential risks are far outweighed by the clinical benefits of these drugs, as reviewed in multiple publications (1652 [EL 3; CSS]; 1663 [EL 4; NE]; 1664 [EL 3; SS]). Furthermore, an analysis of the Association of British Clinical Diabetologists database (1665 [EL 1; MRCT, this represents the highest level substudy in report]; 1666 [EL 3; SS]; 1667 [EL 4; NE]) failed to demonstrate that the incidence of pancreatitis was greater in patients taking liraglutide or exenatide than the historical incidence in patients with T2DM not on GLP-1 RA therapy. Moreover, meta-analyses by Monami et al (1668 [EL 1; MRCT]) and Shyangdan et al (1669 [EL 1; MRCT]) demonstrated a lack of association between GLP-1 RAs and pancreatitis, and Monami et al (1670 [EL 1; MRCT]) showed a lack of association between DPP-4 inhibitors and pancreatitis. More recently, a population-based, case-controlled study in Denmark failed to demonstrate an association between incretin-based therapy and pancreatitis after adjusting for gallstones, alcoholism, obesity, or other pancreatitis-associated comorbidities or medications (1450 [EL 2; RCCS]). Overall, there is insufficient evidence to conclude that incretin-based therapies cause or are significantly associated with pancreatitis. Therefore, the appropriate use of these drugs should not be withheld based on concern for pancreatitis (except per clinical judgment in cases of prior or current pancreatitis). However, investigators agree that more research is required, particularly in patients with obesity taking medications prescribed specifically for weight loss. Until a conclusive recommendation can be reached, exercising caution and monitoring for development of pancreatitis when administering these drugs is prudent in patients with obesity.
- Although the anti-epileptic agent valproate has been rarely associated with pancreatitis, this association has not been shown with topiramate (1671 [EL 4; NE]).

In addition to increasing the risk for pancreatitis, the obese state, particularly in conjunction with alcohol or gallstones, is associated with increased severity and complications following acute pancreatitis, particularly when alcohol or gallstones are also present. This association may be due to increased inflammation, impaired immunity, altered hepatic detoxification of humoral mediators, concurrent insulin resistance, impaired pancreatic exocrine/endocrine function, hyperglycemia, peripancreatic fat with necrosis and nidus for infection, respiratory insufficiency due to obesity-related lung disease (including restrictive and ventilation-perfusion mismatch with hypoxia), and decreased microcirculation (1653 [EL 2; MNRCT]; 1672 [EL 3; SS]; 1673 [EL 4; NE]; 1674 [EL 3; CSS]; 1675 [EL 2; PCS]; 1676 [EL 2; MNRCT]; 1677 [EL 2; PCS, post-hoc analysis]). However, a prospective study by Sawalhi et al (1678 [EL 2; PCS]) showed that although obesity was associated with greater severity of acute pancreatitis, metabolic syndrome was not.

- *Q8.13. Opioid use*

Executive Summary

- **R111.** Phentermine/topiramate ER, lorcaserin, liraglutide 3 mg, and orlistat are preferred weight-loss medications for patients requiring chronic administration of opioid or opiate medications, and naltrexone ER/bupropion ER should not be used **(Grade B; BEL 1, downgraded based on evidence gaps)**.

Evidence Base

Phentermine/topiramate ER, lorcaserin, liraglutide 3.0 mg, and orlistat have no known drug interactions with opioid medications (1442 [EL 4; NE]; 1444 [EL 4; NE]; 1445 [EL 4; NE]; 1449 [EL 4; NE]). Naltrexone ER/bupropion ER combines bupropion, a norepinephrine and dopamine reuptake inhibitor, with naltrexone, an opioid receptor antagonist with high binding affinity for the mu-opioid

receptor and less affinity for the kappa-opioid receptor (1448 [EL 4; NE]). While the mechanisms responsible for reduced food intake are not defined in humans, preclinical data suggest that bupropion stimulates POMC-producing neurons in the hypothalamus to produce more alpha-melanocortin-stimulating hormone (the anorexigenic factor), while naltrexone binds to mu-opioid receptors on POMC neurons to block an auto-inhibitory effect of beta-endorphin that is also secreted by POMC cells (1447 [EL 4; NE]; 1679 [EL 4; NE]; 1680 [EL 4; NE, preclinical]; 1681 [EL 4; NE, preclinical]; 1682 [EL 1; RCT, human proof-of-concept trial; note there are also preclinical studies in this paper]). These drugs may also combine to reduce food intake by affecting mesolimbic system reward pathways (1606 [EL 4; NE]).

As an opioid receptor antagonist, naltrexone is contraindicated in patients requiring chronic administration of opioid or opiate agonist drugs or during acute opiate withdrawal (1448 [EL 4; NE]). Naltrexone blocks the effects of opioid drugs used for cough suppression, treatment of diarrhea, and analgesia (1448 [EL 4; NE]; 1683 [EL 4; NE]). Therefore, naltrexone ER/bupropion ER should be avoided or discontinued in patients requiring chronic opioids and temporarily discontinued for those requiring short-term opiate treatment. Caution should be exercised because long-term use of naltrexone increases the concentration of opioid receptors in the brain and produces a temporary exaggeration of responses to the subsequent administration of opioid agonists (1684 [EL 4; NE, preclinical]). Thus, lower doses of opioids may be necessary after cessation of naltrexone ER/bupropion ER in the latter setting. An opioid-free interval of 7 to 10 days is recommended after cessation of opioid drugs and before beginning naltrexone ER/bupropion ER to avoid precipitation of withdrawal symptoms. In addition, the administration of large doses of opioids to overcome naltrexone-induced opioid receptor blockade could predispose an individual to opioid overdose. Naltrexone ER/bupropion ER should also be avoided in patients taking naltrexone for treatment of opioid addiction or alcohol dependence (1685 [EL 1; MRCT]).

- *Q8.14. Women of reproductive potential*

Executive Summary

- **R112.** Weight-loss medications must not be used in pregnancy **(Grade A; BEL 2, upgraded due to high relevance)**.
- **R113.** All weight-loss medications should be used in conjunction with appropriate forms of contraception in women of reproductive potential **(Grade A; BEL 1)**.
- **R114.** Weight-loss medications should not be used in women who are lactating and breastfeeding **(Grade D)**.

Evidence Base

Currently available medications approved for chronic management of obesity have been studied in large RCTs that generally include a larger proportion of females to males, and females of reproductive potential have been well represented. For example, women with mean ages of approximately 40 to 44 years accounted for 79 to 87% of participants enrolled in orlistat trials, including the Orlistat Dose-Ranging Study, the Euro Multicenter Orlistat Study, an 18-month RCT, and a 2-year RCT (856 [EL 1; RCT]; 1414 [EL 1; RCT]; 1415 [EL 1; RCT]; 1418 [EL 1; RCT]; 1686 [EL 1; RCT]). The XEnical in the Prevention of Diabetes in Obese Subjects (XENDOS) trial to prevent T2DM included 55% women with mean age 43 years (721 [EL 1; RCT]). Phase 3 trials of phentermine/topiramate ER included EQUIP with women (mean age 43 years) accounting for 83% of the 1,200 participants (858 [EL 1; RCT]), and CONQUER with women (mean age 51 years) accounting for 70% of nearly 2,500 participants (71 [EL 1; RCT]). As for the lorcaserin trials, 83% of 3,000 patients in the BLOOM study were women with mean age 44 years (857 [EL 1; RCT]), and 81% of over 4,000 people were female (mean age 44 years) in the BLOSSOM trial (69 [EL 1; RCT]). For naltrexone ER/bupropion ER, 85 to 90% of over 4,000 participants randomized in the COR I, COR II, and COR BMOD trials were female with a mean age ~44 years (67 [EL 1; RCT]; 859 [EL 1; RCT]; 1422 [EL 1; RCT]). Liraglutide 3 mg trials also featured a high proportion of females, including 75% of 564 participants (mean age 46 years) in a 20-week dose-ranging study (1687 [EL 1; RCT]), 76% of 268 patients in a 2-year efficacy and safety trial (897 [EL 1; RCT]), and 84% of over 400 patients (mean age 46 years) in the SCALE Maintenance trial (1424 [EL 1; RCT]). Women of reproductive potential were required to use contraception but were not excluded from any of these trials. Thus, data are sufficient to assess the efficacy and safety of all weight-loss medications in women of reproductive potential.

All weight-loss medications are contraindicated during pregnancy (category X) in FDA-sanctioned prescribing information, and appropriate forms of contraception are required for women of reproductive potential. Obesity medications should be stopped immediately if conception occurs. Orlistat is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. While no embryotoxicity or teratogenicity was evident in preclinical studies, the prescribing information for orlistat states that if pregnancy occurs, the patient should be apprised of the potential hazard of maternal weight loss to the fetus (1442 [EL 4; NE]). Data from the Swedish Medical Birth Register indicated that no apparent increase in risk of major malformation to the fetus occurs after maternal use of orlistat (1688 [EL 3; SS]), and, because it is unknown if orlistat is

present in human milk, caution should be exercised with breastfeeding.

Prescribing information for phentermine/topiramate ER includes a warning of "fetal toxicity" and precautions for females of reproductive potential, citing studies that indicate exposure to topiramate during the first trimester of pregnancy may increase the risk of oral clefts (1444 [EL 4; NE]). This association was first noted in registries of patients taking high doses of topiramate for epilepsy (1689 [EL 2; MNRCT]; 1690 [EL 3; SS]; 1691 [EL 3; SS]). Therefore, the prescribing information advocates a negative pregnancy test before treatment and monthly tests thereafter (which can be accomplished by the patient performing home pregnancy tests), along with effective contraception (1444 [EL 4; NE]). The drug should also be avoided in women who are breastfeeding. A meta-analysis of 6 studies including 3,420 patients and 1.2 million controls determined that the odds ratio for oral cleft is 6.26 (CI: 3.13-12.51) with first trimester exposure in women taking topiramate for epilepsy, migraine, appetite suppression, insomnia, and psychiatric disorders (1689 [EL 2; MNRCT]).

Lorcaserin is contraindicated during pregnancy due to the lack of benefit of weight loss during pregnancy and the potential for fetal harm (1445 [EL 4; NE]). Animal studies did not show teratogenicity or embryolethality with exposure to high doses of lorcaserin. Although it is not known whether lorcaserin is excreted in human milk, discontinuation of the drug during breastfeeding is recommended (1445 [EL 4; NE]).

Naltrexone ER/bupropion ER is also contraindicated during pregnancy due to the lack of benefit of weight loss in pregnancy and the potential for fetal harm (1448 [EL 4; NE]). Twenty-one inadvertent pregnancies occurred during clinical trials, with 11 yielding healthy full-term infants and 4 spontaneous abortions. One study suggested a small increase in risk of congenital heart malformations (1692 [EL 3; SS]); however, the International Bupropion Pregnancy Registry, a retrospective cohort study using the United Healthcare database, and other studies did not show an increased risk of fetal malformations (1693 [EL 2; RCCS]; 1694 [EL 2; PCS]; 1695 [EL 2; MNRCT]). Because the drug's constituents are excreted in human milk, naltrexone ER/buproprion ER is not recommended while breastfeeding.

Liraglutide 3 mg is contraindicated during pregnancy because weight loss offers no potential benefit and may result in fetal harm (1449 [EL 4; NE]). With the exception of one case report of a normal pregnancy in a patient taking 1.8 mg/day (1696 [EL 3; SCR]), no published studies have documented liraglutide use during pregnancy, although results of animal studies raise concerns about teratogenicity. Although whether liraglutide is excreted in human milk is unknown, one study showed that the drug was excreted at 50% of maternal plasma concentration in lactating rats (1449 [EL 4; NE]).

Both orlistat (1697 [EL 1; RCT]) and liraglutide 1.8 mg (1023 [EL 1; RCT]; 1024 [EL 1; RCT]; 1698 [EL 2; PCS]; 1699 [EL 2; PCS]) have been effective for modifying eating behaviors, weight loss, improving metabolic parameters, and regulating ovulation in women with polycystic ovary syndrome.

- *Q8.15. The elderly (age ≥65 years)*

Executive Summary

- **R115.** Elderly patients (age ≥65 years) should be selected for weight-loss therapy involving structured lifestyle interventions that include reduced-calorie meal plans and exercise, with clear health-related goals that include prevention of T2DM in high-risk patients with prediabetes, blood pressure reduction, and improvements in OA, mobility, and physical function **(Grade A; BEL 1)**.
- **R116.** Elderly patients with overweight or obesity being considered for weight loss therapy should be evaluated for osteopenia and sarcopenia **(Grade B; BEL 2)**.
- **R117.** Weight-loss medications should be used with extra caution in elderly patients with overweight or obesity **(Grade A; BEL 1).** Additional studies are needed to assess efficacy and safety of weight-loss medications in the elderly.

Evidence Base

Caution must be exercised with management of obesity in the elderly, generally defined as age ≥65 years. First, some epidemiological reports discuss an "obesity paradox" in the elderly based on the conclusion that elderly with overweight or obesity have lower mortality rates than lean individuals (1700 [EL 4; NE]), as has been reported for patients with congestive heart failure (369 [EL 2; RCCS]). The appearance of reduced mortality in elderly individuals with overweight or obesity is controversial and is counterbalanced by arguments of reverse causality due to preexisting conditions (e.g., smoking) that result in a "sicker" underweight reference population (378 [EL 4; NE]) or other confounders. The debate regarding epidemiologic relationships between age, obesity, and mortality has been extensive (1701 [EL 2; MNRCT]; 1702 [EL 4; NE]; 1703 [EL 4; NE]). In any event, the obesity paradox raises the question as to whether the benefits of intentional weight loss are diminished in the elderly. In this regard, differentiating between effects of unintentional and intentional weight loss is important.

Second is the problem of sarcopenic obesity (144 [EL 4; NE]). Muscle mass and quality decline with age, and excess fat mass increases the burden on weak muscles and

has a negative impact on muscle function. Baumgartner et al (1704 [EL 3; SS]) defined obesity as relative skeletal muscle index (muscle mass adjusted by height squared) less than 2 standard deviations below the gender-specific mean of a young reference group and percent body fat greater than the median value for gender-specific group (27% body fat in men and 38% body fat in women, corresponding to a BMI of approximately 27 kg/m^2). The prevalence of sarcopenic obesity increases with age, from 13.5% in men and 5.3% in women in the sixth decade to 17.5% and 8.4% in men and women, respectively, older than 80 years (1705 [EL 4; NE]). Patients with sarcopenic obesity experience reduced grip strength, greater functional impairment, limited mobility, increased disability, and greater fall risk (1705 [EL 4; NE]). Skeletal muscle is infiltrated with larger amounts of intramuscular fat and marbling, which is associated with poor strength and performance (1706 [EL 2; PCS]), as well as insulin resistance (1707 [EL 3; CSS]).

Weight loss is associated with reductions in both fat and lean mass. The loss of lean mass can exacerbate weakness and muscle dysfunction (1289 [EL 4; NE]; 1708 [EL 4; NE]), while resistance exercise can improve these parameters (1709 [EL 4; NE]). Adding endurance or resistance exercise to a weight-loss program preserves lean mass during weight loss (1288 [EL 2; MNRCT]; 1710 [EL 2; NRCT, allocation concealment]; 1711 [EL 1; RCT]) and becomes a valuable addition to lifestyle therapy in elderly patients with obesity (1289 [EL 4; NE]; 1709 [EL 4; NE]). For these reasons, elderly patients being considered for weight loss should be screened for sarcopenic obesity by examining muscle strength and performing a review of systems assessing functionality. Muscle strength can be easily measured by handgrip dynamometry, which is cheaper than and as clinically relevant as measuring muscle mass by DEXA, computed tomography scan, or bioelectrical impedance analysis. The prevalence of sarcopenia is 4 to 12% when defined by assessment of muscle mass and 4 to 9% when assessed by BMI and handgrip (1712 [EL 3; CSS]; 1713 [EL 4; NE]).

Third, elderly individuals are more likely to have osteopenia and increased risk for fracture, which can be exacerbated by weight loss. Obesity helps maintain bone mineral density and reduces incidence of osteoporosis and hip fracture (1714 [EL 2; PCS, post-hoc cross-sectional study of the cohort]; 1715 [EL 3; SS]; 1716 [EL 3; CSS]; 1717 [EL 2; PCS]; 1718 [EL 2; PCS]). However, weight loss results in a diminution in bone mass (1719 [EL 2; PCS]; 1720 [EL 2; PCS]), which can place individuals at increased risk for fracture (1721 [EL 2; PCS]; 1722 [EL 2; PCS]). For this reason, much caution should be exercised when considering weight-loss therapy for patients with obesity and osteopenia. Finally, elderly patients are more likely to have nutritional deficiencies, polypharmacy, abnormalities in renal and hepatic function, subclinical CVD, and impaired cognition, which can increase the risks associated with various weight-loss interventions.

An often-quoted large observational study found that weight loss was associated with increased mortality in the elderly, but the study did not differentiate between intentional and unintentional weight loss (1723 [EL 2; PCS]). Similarly, other studies report that weight loss is associated with increased, rather than decreased, mortality in the elderly (1724 [EL 4; NE]; 1725 [EL 4; NE]; 1726 [EL 4; NE]; 1727 [EL 2; PCS]; 1728 [EL 2; PCS]). However, these studies are not randomized, use self-reported weight for the most part, do not distinguish weight loss between subjects with obesity and those without, and do not assess whether weight loss is intentional or nonintentional. When some of these variables are taken into account, other cohort studies demonstrate that intentional weight loss in the elderly either has no effect on (1729 [EL 2; PCS]; 1730 [EL 2; PCS]; 1731 [EL 2; PCS]) or decreases mortality (912 [EL 2; PCS]; 913 [EL 2; PCS, retrospective analysis, N = 43,457]; 914 [EL 2; PCS, retrospective analysis, N = 43,457]).

Several RCTs have addressed effects of intentional weight loss on mortality in the elderly. Villareal et al (1317 [EL 1; RCT]) studied 107 frail elderly subjects with obesity for 1 year and randomized patients to a control group, a diet group with a 500 to 750 kcal-deficit diet and 1 g protein/kg/day, an exercise group, and a combined diet-plus-exercise group. The diet group and the exercise group reversed their state of frailty more than the control group, but the combination of diet and exercise was most effective for achieving the best physical performance, functional status, aerobic endurance capacity, and quality of life (QOL). The loss of body weight and fat mass was similar in the diet and the diet-plus-exercise groups. Adverse effects included a small reduction in lean body mass and bone mineral density in the diet group (–5% and –2.6%, respectively) and in the diet-plus-exercise group (–3% and –1.1%, respectively) (1317 [EL 1; RCT]). In the Arthritis, Diet and Activity Promotion Trial (ADAPT), 318 patients age >60 years (mean age 69 years, BMI 34 kg/m^2) with knee OA were randomized to a healthy lifestyle, reduced-calorie diet, exercise, or diet-plus-exercise group (1111 [EL 1; RCT, single-blinded]; 1399 [EL 1; RCT]). Weight loss was significantly greater in the diet and the diet-plus-exercise group, and these groups experienced significant improvements in measures of physical function and pain scores (1111 [EL 1; RCT, single-blinded]). Moreover, the mortality rate for those randomized to the 18-month diet and diet-plus-exercise interventions (n = 159, mean weight loss 4.8 kg, 15 deaths) was 50% lower than for those randomized to the subgroups that did not lose weight (i.e., control and exercise-only groups) (1399 [EL 1; RCT]). The TONE Trial studied 585 older adults with overweight or obesity undergoing treatment for hypertension (mean age 66 years, BMI 31 kg/m^2) (1732 [EL 1; RCT]). These

patients were randomized to 1 of the following 4 treatment arms in a 2 × 2 factorial design and followed for 12 years: with or without dietary weight loss and with or without sodium restriction. The incidence of mortality did not differ significantly between the dietary weight-loss groups (n = 291; mean weight loss 4.4 kg) and those not randomly assigned to weight-loss groups (n = 294; mean weight loss 0.8 kg). The adjusted HR was 0.82 (95% CI: 0.55, 1.22).

Kritchevsky et al (916 [EL 1; MRCT]) conducted a meta-analysis of 15 RCTs with mortality data that randomized patients to weight loss or no weight loss groups and reported a follow-up of at least 18 months. The all-cause mortality risk was 15% lower in the weight-loss groups (RR 0.85; 95% CI, 0.73-1.00), and results were similar in the trials that recruited older subjects with a mean age of ≥55 years at baseline (RR 0.84; 95% CI, 0.71-0.99) (916 [EL 1; MRCT]).

In lifestyle interventions, the health benefits of weight-loss therapy are similar in healthy individuals and younger adults. However, while reduced-calorie diets are critical in lifestyle therapy directed at weight loss, the addition of aerobic and resistance exercise is particularly beneficial in the elderly due to improvements in physical function and amelioration of frailty (1733 [EL 1; RCT]; 1734 [EL 1; RCT]). The DPP enrolled prediabetic men and women with obesity over an age range of 25 to 84 years (1735 [EL 1; RCT, post-hoc analysis]). Patients were randomized to intensive lifestyle intervention, metformin, or placebo for 4 years. Among those receiving the intensive lifestyle intervention, participants between 60 and 85 years of age lost a greater percentage of body weight than their younger counterparts and experienced the greatest reduction in incidence of diabetes, with 3.3 cases per 100 person-years versus 6.3 cases per 100 person-years in the age 25 to 44 years subgroup. In contrast, elderly subjects randomized to metformin exhibited a trend toward increased incidence of diabetes (9.3 cases per 100 person-years) relative to the younger cohort (6.6 cases per 100 person-years) (1735 [EL 1; RCT, post-hoc analysis]). Therefore, a lifestyle intervention resulting in weight loss was highly effective for preventing progression to diabetes in elderly patients with obesity and impaired glucose tolerance.

At least 4 studies (1736 [EL 2; PCS]; 1737 [EL 1; RCT]; 1738 [EL 2; PCS]; 1739 [EL 2; PCS]) demonstrated that intentional weight loss was associated with improvements in metabolic control, as shown by better glucose tolerance, increased insulin sensitivity, and improvements in CVD risk factors. Elderly individuals with HTN experience reductions in BP and antihypertensive medications following weight loss. In the TONE study, elderly participants randomized to a reduced-calorie diet that lost ≥3.4 kg lowered BP and reduced their use of antihypertensive drugs (1400 [EL 1; RCT]; 1740 [EL 1; RCT]). In a sample of elderly subjects with obesity, pulmonary function improved after weight loss of up to 10 kg, but not after exercise alone (1741 [EL 1; RCT]).

The beneficial effects of weight loss in patients with OA are particularly applicable to elderly patients. Lifestyle interventions that include a combination of reduced-calorie diet and exercise have been shown to improve pain, physical disability, mobility, performance, and self-efficacy in elderly patients with radiographic evidence of OA (1107 [EL 1; RCT, single-blinded]; 1110 [EL 2; PCS]; 1111 [EL 1; RCT]; 1742 [EL 1; RCT]; 1743 [EL 1; RCT]). Systematic reviews of weight-loss interventions in people age >60 years revealed significantly improved glucose tolerance and physical functioning and reduced incidence of diabetes, as well as significant benefits for those with OA, diabetes, and CVD risk (144 [EL 4; NE]; 1701 [EL 4; NE]; 1703 [EL 2; MNRCT]; 1744 [EL 1; MRCT]; 1745 [EL 4; NE]). Negative outcomes included slightly decreased bone mineral density and lean body mass. These studies tended to focus on metabolic and CVD risk, and studies are needed to address potential benefits of weight loss on mobility, bladder function, sexual health, mood, and QOL, all of which are particularly meaningful for elderly patients with obesity (1746 [EL 4; NE]).

Limited data are available that address efficacy and safety of weight-loss medications in the elderly. Of the 5 obesity medications approved for chronic therapy, the clinical trials program for phentermine/topiramate ER had the largest number of patients age ≥65 years. In these trials, 254 (7%) patients were ≥65 years of age, and efficacy or safety were similar between elderly and younger participants (1444 [EL 4; NE]). In the 2 main RCTs, the mean age of participants was 43 years with a range of 18 to 71 years in the EQUIP study (858 [EL 1; RCT]) and 51 years with a range of 19 to 71 years in the CONQUER study (71 [EL 1; RCT]). RCTs evaluating liraglutide 3 mg had the next highest number of elderly participants and included 232 (6.9%) patients ≥65 years of age and 17 (0.5%) patients ≥75 years (1449 [EL 4; NE]). No differences in efficacy, safety, and pharmacokinetics were noted between elderly and younger adult subgroups. The SCALE Obesity trial enrolled subjects with mean age 45 years with a range of 18 to 78 years (68 [EL 1; RCT]), whereas patients in the SCALE Diabetes had a mean age of 55 years with a range of 18 to 82 years (780 [EL 1; RCT]), and those in the SCALE Maintenance trial had a mean age of 46 years with a range of 18 to 73 years (1424 [EL 1; RCT]). In 9 elderly patients (mean age 68) with overweight or obesity and T2DM, liraglutide 3 mg reduced body weight (–2 kg), fat mass, and android fat, and increased the skeletal muscle index measure of lean mass (1747 [EL 2; PCS]).

The RCT development programs for lorcaserin, naltrexone ER/bupropion ER, and orlistat enrolled fewer patients ≥65 years and did not contain sufficient numbers to assess differences in efficacy and safety between older

and younger patients. For orlistat, 7 RCTs, each lasting 1 to 2 years, included over 2,800 patients with an age range of 17 to 78 years (1442 [EL 4; NE]), and the 4-year XENDOS study included 3,304 patients with an age range of 30 to 58 years (721 [EL 1; RCT]). Analysis of a subpopulation of older subjects in 1 RCT showed that orlistat therapy was similarly effective in older (≥65 years) and younger adults in a primary care setting (70 [EL 1; RCT]; 1748 [EL 4; NE, abstract]). The lorcaserin trials enrolled 135 (2.5%) patients ≥65 years of age. The pharmacokinetics (AUC and C_{max}) of lorcaserin were not statistically different when comparing 12 healthy elderly (≥65 years) and younger adults (1445 [EL 4; NE]). Naltrexone ER/bupropion ER trials included 62 (2%) subjects ≥65 years of age and none ≥75 years (1448 [EL 4; NE]). Age did not affect the pharmacokinetics of bupropion in the elderly (1448 [EL 4; NE]).

Information on the efficacy and safety of bariatric surgery in the elderly is limited. Several small case studies have evaluated outcomes of bariatric surgery in patients ≥60 years of age (1749 [EL 3; SS]; 1750 [EL 3; SS]; 1751 [EL 3; SS]; 1752 [EL 3; SS, prospectively collected database]; 1753 [EL 3; SS]; 1754 [EL 3; SS]; 1755 [EL 3; SS]). Collectively, these few studies suggest that relative to younger patients undergoing the same procedures, elderly achieve less weight loss, have higher incidence of perioperative morbidity, and show reduced improvement in weight-related complications (1745 [EL 4; NE]). However, bariatric surgery results in substantial weight loss with low incidence of mortality in the elderly and has beneficial effects on health and various weight-related complications. Although the laparoscopic adjustable gastric band procedure may be preferred due to fewer operative complications, efficacy and safety have not been compared among the multiple bariatric procedures.

- *Q8.16. Addiction/alcoholism*

Executive Summary

- **R118.** In patients with obesity and alcohol or other addictions, orlistat or liraglutide 3 mg should be considered **(Grade A; BEL 1)**. Lorcaserin (abuse potential due to euphoria at suprapharmacologic doses) and naltrexone ER/bupropion ER (lowers seizure threshold) should be avoided in patients with alcohol abuse, and naltrexone ER/bupropion ER is contraindicated during alcohol withdrawal **(Grade A; BEL 1)**.

Evidence Base

Patients with disorders of addiction and/or alcoholism along with overweight or obesity present unique challenges in management focused on reducing caloric intake. Using functional magnetic resonance imaging, behavioral impulse control is related to an anatomic connection between, among others, the ventromedial prefrontal cortex (reward signals) and dorsolateral prefrontal cortex (control centers) in the brain (1756 [EL 2; PCS]). Reward behaviors related to food addiction are mediated by the ventral tegmental area-nucleus accumbens (mesolimbic) dopaminergic system (1757 [EL 4; NE]). These neuronal reward circuits appear to adapt to periods of self-imposed food restriction or drug-induced anorexia when food is abundant in the environment. This creates or exacerbates states of disordered eating, such as BED, which in turn can impair weight-loss outcomes (1758 [EL 4; NE]). Ghrelin has also been investigated in the context of addiction and brain reward systems, although specific, approved, anti-obesity pharmaceutical agents targeting ghrelin are not commercially available (1759 [EL 4; NE]).

Among the current compendium of FDA-approved pharmaceuticals for long-term management of obesity, naltrexone (decreases reward and craving) and topiramate (antiepileptic, mood-stabilizing, decreases alcohol consumption) are also used for alcohol abuse disorders (1760 [EL 3; SS, large retrospective cohort N = 375,777]; 1761 [EL 1; MRCT, relatively small number of studies N = 7]). Naltrexone is a mu-opioid receptor antagonist used for opiate addiction that is associated with weight loss and offers some appeal for use in patients with food addictions (1762 [EL 4; NE]; 1763 [EL 3; SS]). Wang et al (1764 [EL 1; RCT]) found that combined naltrexone and bupropion therapy decreased hypothalamic activation in response to food cues while also increasing activation of other brain areas involved in inhibitory control, awareness, and memory. In a RCT, Cambridge et al (1765 [EL 2; NRCT]) found that a novel mu-opioid receptor antagonist reduced motivational responding in patients with BED.

Patients with alcoholism/addiction or bulimia may be susceptible to seizures. Bupropion was originally FDA-approved as an atypical antidepressant in 1985 but was withdrawn in 1986 after an increased incidence of seizures was noted in bulimic patients (1766 [EL 1; RCT]; 1767 [EL 3; SS]). The drug was reintroduced in 1989 when the incidence of seizures was shown to be dose-related and similar to that of other antidepressants. The cumulative 2-year risk of seizures in patients receiving the maximum recommended dose of ≤450 mg/day was 0.48%, and predisposing factors were noted in many of the reported cases (1768 [EL 4; NE]). Weight-loss medications containing bupropion, even those with combined naltrexone-bupropion, should not be used in patients with a seizure disorder because bupropion can lower seizure thresholds or in patients with bulimia or undergoing alcohol withdrawal. Moreover, bupropion with or without naltrexone, should be used with caution in patients with excessive use of alcohol and at risk for seizures. The prescribing information for naltrexone ER/bupropion ER states that the drug is contraindicated in patients undergoing abrupt discontinuation of alcohol and should be used with caution in patients who abuse alcohol.

Topiramate is effective for treating alcoholism (1761 [EL 1; MRCT, relatively small number of studies N = 7]; 1769 [EL 1; RCT]), addiction to cigarette smoking (1770 [EL 1; RCT]), methamphetamine (1771 [EL 1; RCT, secondary analysis]; 1772 [EL 1; RCT]), and cocaine (1773 [EL 1; RCT]), and comorbid cocaine addiction and alcohol dependence (1774 [EL 1; RCT]). The anti-addiction properties of topiramate may relate to its enhancement of GABAergic transmission and inhibition of glutamatergic transmission, both of which seem to decrease dopaminergic activity in mesocorticolimbic brain areas that are related to alcohol addiction (1775 [EL 4; NE]). Topiramate may also reduce alcohol craving through an inhibitory effect on the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate types of glutamate receptors. These same processes may underlie the ability of topiramate to counteract food addiction (1776 [EL 4; NE]). In a systematic review of 26 phase 2 and 3 controlled trials, topiramate was uniquely found to reduce BED and weight (1596 [EL 4; NE]). An extended-release preparation of topiramate is a component of the phentermine/topiramate ER combination, and may be advantageous for treating patients with obesity and alcoholism. However, no safety or efficacy data are available on the use of phentermine/topiramate ER in this clinical setting.

Greene et al (1777 [EL 4; NE]) cautioned against using weight-loss medications with addictive potential. Some argue that agents with lower addictive potential, such as pancreatic lipase inhibitors (e.g., orlistat) or serotonergic agents (e.g., lorcaserin), should be considered over those with greater addictive potential, such as noradrenergic agents (e.g., phentermine) or sympathomimetics (e.g., D-amphetamine), especially in patients susceptible to addictive drugs. Even so, it is important to consider that lorcaserin at supratherapeutic doses can induce euphoria and dissociative thought processes and has potential for abuse (1445 [EL 4; NE]). Despite theoretical rationale, O'Neill et al (1778 [EL 1; RCT]) were unable to demonstrate that a selective dopamine D3 receptor antagonist modulates brain activation to food images in BED, although learning of cue-reward associations has not been tested.

- *Q8.17. Post-bariatric surgery*

Executive Summary

- **R119.** Patients who have undergone bariatric surgery should continue to be treated with an intensive lifestyle intervention **(Grade A; BEL 1).** Patients who have regained excess weight (≥25% of weight lost), failed to respond to intensive lifestyle intervention, and are not candidates for reoperation may be considered for treatment with liraglutide 1.8 to 3.0 mg or phentermine/topiramate ER. The safety and efficacy of other weight-loss medications have not been assessed in these patients **(Grade D; BEL 3; downgraded due to evidence gaps)**.

Evidence Base

Bariatric surgery is intended to manage excess weight that is severe and/or associated with severe weight-related complications in patients who do not respond sufficiently to pharmacotherapy and/or lifestyle therapy. However, some post-bariatric surgery patients regain excess weight, despite attempts at optimizing lifestyle, and are not candidates for reoperation. Excess weight regain is defined as ≥25% of the lost weight, and occurs in approximately 37% of patients post-surgery (1779 [EL 2; PCS]). This regain is largely due to the appearance of maladaptive eating behaviors, including subjective and objective binge eating as well as picking and nibbling (1780 [EL 3; CSS]). Weight regain can increase risk for reappearance of prior weight-related complications such as T2DM, which developed in 24% of patients 3 years after Roux-en-Y gastric bypass in 1 study (1781 [EL 3; SS]). In these patients, intensifying nutritional and behavioral counseling is warranted (1782 [EL 4; NE]). Initiating or resuming weight-loss medications can be considered in recalcitrant patients, although guidelines to define surgical failure are insufficient (1783 [EL 4; NE]).

In a retrospective review, liraglutide (1.2-3.0 mg/day for 8-28 weeks) effectively managed weight regain (defined as >15% of the lowest weight achieved) in 15 bariatric surgery patients (1784 [EL 3; SS]). In patients with T2DM, other glucose-lowering medications that are weight neutral or promote modest weight loss (e.g., metformin or the sodium-glucose co-transporter 2 class of agents) may be considered for treatment of hyperglycemia if no contraindications or anticipated intolerances are present. Food cravings are increased in some patients after bariatric surgery (1785 [EL 3; CSS]) and may also represent a therapeutic target using dietary manipulations (e.g., low-fat or low-carbohydrate) or weight-loss medications that target appetite and reward centers (e.g., topiramate or naltrexone). Though not yet commercially available, leptin therapy for weight regain following weight loss (1786 [EL 2; PCS, small cohort N = 10]; 1787 [EL 2; PCS, small cohort N = 6]; 1788 [EL 2; PCS, small cohort N = 10] may prove efficacious in the post-bariatric surgery patient. More data are required for developing optimal evidence-based approaches for management of excessive weight regain in post-bariatric surgery patients and the use of weight-loss medications in this context.

- ***Q9. Is bariatric surgery effective to treat obesity?***

Note: A de novo evidence-based review of questions pertaining to bariatric surgery was not undertaken. The "Clinical Practice Guidelines for the Perioperative,

Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient 2013-Update" from AACE, The Obesity Society, and the American Society for Metabolic & Bariatric Surgery were reviewed and concluded to be adequate in their current form. Key recommendations from these guidelines relevant to the questions generated for evidence-based review are copied below.

- *Q9.1. Is bariatric surgery effective to treat obesity and weight-related complications?*

Executive Summary

- **R120.** Patients with a BMI of ≥40 kg/m^2 without coexisting medical problems and for whom the procedure would not be associated with excessive risk should be eligible for bariatric surgery **(Grade A; BEL 1)**.

- *Q9.2. When should bariatric surgery be used to treat obesity and weight-related complications?*

Executive Summary

- **R121.** Patients with a BMI of ≥35 kg/m^2 and 1 or more severe obesity-related complications, including T2DM, hypertension, obstructive sleep apnea, obesity hypoventilation syndrome, Pickwickian syndrome, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, pseudotumor cerebri, gastroesophageal reflux disease, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired QOL may also be considered for a bariatric surgery procedure. Patients with BMI of 30 to 34.9 kg/m^2 with diabetes or metabolic syndrome may also be considered for a bariatric procedure, although current evidence is limited by the number of patients studied and lack of long-term data demonstrating net benefit.
  - BMI ≥35 kg/m^2 and therapeutic target of weight control and improved biochemical markers of CVD risk **(Grade A; BEL 1)**.
  - BMI ≥30 kg/m^2 and therapeutic target of weight control and improved biochemical markers of CVD risk **(Grade B; BEL 2)**.
  - BMI ≥30 kg/m^2 and therapeutic target of glycemic control in T2DM and improved biochemical markers of CVD risk **(Grade C; BEL 3)**.
- **R122.** Independent of BMI criteria, there is insufficient evidence to recommend a bariatric surgical procedure specifically for glycemic control, lipid lowering, or CVD risk reduction alone **(Grade D)**.
- **R123.** All patients should undergo pre-operative evaluation for weight-related complications and causes of obesity, with special attention directed to factors that may affect a recommendation for bariatric surgery or be ameliorated by weight loss resulting from the procedure **(Grade A; BEL 1)**.

Evidence Base

Bariatric surgery is a proven intervention to induce weight loss for severe obesity, defined as a BMI ≥40 kg/m^2 with or without obesity-related complications, or a BMI ≥35 kg/m^2 (or BMI ≥30 kg/m^2 for laparoscopic adjustable gastric banding) with at least 1 obesity-related complication (11 [EL 4; NE]). The reader is referred to the AACE, the Obesity Society, and the American Society of Metabolic and Bariatric Surgery Clinical Practice Guidelines for the nonsurgical management of patients undergoing bariatric surgery for a comprehensive review of the evidence base that supports the best evidence levels and recommendation grades in the executive summary. These guidelines have been reviewed and are adopted in the current guidelines for the timing, indications, and selection of bariatric surgery procedures for weight loss.

VI. ACKNOWLEDGMENTS

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VIII. REFERENCES

1. **Flegal KM, Carroll MD, Kit BK, Ogden CL.** Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA*. 2012;307(5):491-497. [EL 3; SS]
2. **Finucane MM, Stevens GA, Cowan MJ, et al.** National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet*. 2011;377(9765):557-567. [EL 2; MNRCT]
3. **Ogden CL, Carroll MD, Kit BK, Flegal KM.** Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014;311(8):806-814. [EL 3; CSS]
4. **Ogden CL, Carroll MD, Kit BK, Flegal KM.** Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA*. 2012;307(5):483-490. [EL 3; SS]
5. **Skinner AC, Skelton JA.** Prevalence and trends in obesity and severe obesity among children in the United States, 1999-2012. *JAMA Pediatr.* 2014;168(6):561-566. [EL 3; SS]
6. **Cawley J, Meyerhoefer C.** The medical care costs of obesity: an instrumental variables approach. *J Health Econ*. 2012;31(1):219-230. [EL 3; SS]
7. **Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK.** Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. *Obesity (Silver Spring)*. 2008;16(10):2323-2330. [EL 3; SS]
8. **Garvey WT.** New tools for weight-loss therapy enable a more robust medical model for obesity treatment: rationale for a complications-centric approach. *Endocr Pract*. 2013;19(5):864-874. [EL 4; NE]
9. **Apovian CM, Garvey WT, Ryan DH.** Challenging obesity: Patient, provider, and expert perspectives on the roles of available and emerging nonsurgical therapies. *Obesity*. 2015;23(Suppl 2):S1-S26. [EL 4; NE]
10. **Cefalu WT, Bray GA, Home PD, et al.** Advances in the science, treatment, and prevention of the disease of obesity: reflections from a Diabetes Care editors' expert forum. *Diabetes Care*. 2015;38(8):1567-1582. [EL 4; NE]
11. **Mechanick JI, Youdim A, Jones DB, et al.** Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Endocr Pract*. 2013;19(2):337-372. [EL 4; NE]
12. **Mechanick JI, Garber AJ, Handelsman Y, Garvey WT.** American Association of Clinical Endocrinologists' position statement on obesity and obesity medicine. *Endocr Pract*. 2012;18(5):642-648. [EL 4; NE]
13. **American Medical Association.** *H440.842 Recognition of Obesity as a Disease*. 2013. Available at: https://www.ama-assn.org/ssl3/ecomm/PolicyFinderForm.pl?site=www.ama-assn.org&uri=/resources/html/PolicyFinder/policyfiles/HnE/H-440.842.HTM. [EL 4; NE]
14. **Garvey WT, Garber AJ, Mechanick JI, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology consensus conference on obesity: building an evidence base for comprehensive action. *Endocr Pract*. 2014;20(9):956-976. [EL 4; NE]
15. **Garvey WT, Garber AJ, Mechanick JI, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocr Pract*. 2014;20(9):977-989. [EL 4; NE]
16. **Pi-Sunyer FX, Becker DM, Bouchard C and NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.** *The Practical Guide: Identification, Evaluation and Treatment of Overweight and Obesity in Adults*. *National Institutes of Health publication number 00-4084*. U.S. Department of Health and Human Services; 2000. Available at: http://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf. Accessed January 16, 2016. [EL 4; NE]

17. **Colman E.** Food and Drug Administration's Obesity Drug Guidance Document: a short history. *Circulation*. 2012;125(17):2156-2164. [EL 4; NE]
18. **Handelsman Y, Bloomgarden ZT, Grunberger G, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract*. 2015; 21(Suppl 1):S1-S87. [EL 4; NE]
19. **Garber AJ, Abrahamson MJ, Barzilay JI, et al.** AACE/ACE comprehensive diabetes management algorithm 2015. *Endocr Pract*. 2015;21(4):438-447. [EL 4; NE]
20. **Jensen MD, Ryan DH, Apovian CM, et al.** 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63(25 Pt B):2985-3023. [EL 4; NE]
21. **Seger JC, Horn DB, Westman EC, et al.** Obesity Algorithm, presented by the American Society of Bariatric Physicians. Available at: www.obesityalgorithm.org. Obesity Medicine Association. 2015. Accessed October 25, 2015. [EL 4; NE]
22. **Apovian CM, Aronne LJ, Bessesen DH, et al.** Endocrine Society. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362. [EL 4; NE]
23. **Mechanick JI, Bergman DA, Braithwaite SS, Palumbo PJ.** American Association of Clinical Endocrinologists Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines. American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines. *Endocr Pract*. 2004;10(4):353-361. [EL 4; NE]
24. **Mechanick JI, Camacho PM, Cobin RH, et al.** American Association of Clinical Endocrinologists Protocol for Standardized Production of Clinical Practice Guidelines--2010 update. *Endocr Pract*. 2010;16(2):270-283. [EL 4; NE]
25. **Mechanick JI, Camacho PM, Garber AJ, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology Protocol for Standardized Production of Clinical Practice Guidelines, Algorithms, and Checklists - 2014 Update and the AACe G4G Program. *Endocr Pract*. 2014;20(7):692-702. [EL 4; NE]
26. **Gonzalez-Campoy JM, St Jeor ST, Castorino K, et al.** Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society: executive summary. *Endocr Pract*. 2013;19(5):875-887. [EL 4; NE]
27. Available at: http://www.cochranelibrary.com. [EL 4; NE]
28. **Colberg SR, Albright AL, Blissmer BJ, et al.** Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. Exercise and type 2 diabetes. *Med Sci Sports Exerc*. 2010;42(12):2282-2303. [EL 4; NE]
29. **Eckel RH, Jakicic JM, Ard JD, et al.** 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S76-S99. [EL 4; NE]
30. **Gonzalez-Campoy JM, St Jeor ST, Castorino K, et al.** Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society. *Endocr Pract*. 2013;19(Suppl 3):S1-S82. [EL 4; NE]
31. **World Health Organization (WHO).** *Report of a WHO Consultation on Obesity. Obesity: Preventing and Managing the Global Epidemic*. Geneva: World Health Organization; 1997. Available at: http://whqlibdoc.who.int/hq/1998/WHO_NUT_NCD_98.1_(p1-158).pdf. [EL 4; NE]
32. **Alberti KG, Eckel RH, Grundy SM, et al.** Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645. [EL 4; NE]
33. **Gardner CD, Kim S, Bersamin A, et al.** Micronutrient quality of weight-loss diets that focus on macronutrients: results from the A TO Z study. *Am J Clin Nutr*. 2010;92(2):304-312. [EL 1; RCT]
34. **Buscemi S, Cosentino L, Rosafio G, et al.** Effects of hypocaloric diets with different glycemic indexes on endothelial function and glycemic variability in overweight and in obese adult patients at increased cardiovascular risk. *Clin Nutr*. 2013;32(3):346-352. [EL 1; RCT]
35. **Rizkalla SW, Prifti E, Cotillard A, et al.** Differential effects of macronutrient content in 2 energy-restricted diets on cardiovascular risk factors and adipose tissue cell size in moderately obese individuals: a randomized controlled trial. *Am J Clin Nutr*. 2012;95(1):49-63. [EL 1; RCT, small N = 13]
36. **Ebbeling CB, Swain JF, Feldman HA, et al.** Effects of dietary composition on energy expenditure during weight-loss maintenance. *JAMA*. 2012;307(24):2627-2634. [EL 1; RCT]
37. **Foreyt JP, Salas-Salvado J, Caballero B, et al.** Weight-reducing diets: are there any differences? *Nutr Rev*. 2009(67 Suppl 1):S99-S101. [EL 4; NE]
38. **Frisch S, Zittermann A, Berthold HK, et al.** A randomized controlled trial on the efficacy of carbohydrate-reduced or fat-reduced diets in patients attending a telemedically guided weight loss program. *Cardiovasc Diabetol*. 2009;8:36. [EL 1; RCT]
39. **Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S.** A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. *Diabetes Obes Metab*. 2010;12(3):204-209. [EL 1; RCT]
40. **Tirosh A, Golan R, Harman-Boehm I, et al.** Renal function following three distinct weight loss dietary strategies during 2 years of a randomized controlled trial. *Diabetes Care*. 2013;36(8):2225-2232. [EL 1; RCT]
41. **Gadgil MD, Appel LJ, Yeung E, Anderson CA, Sacks FM, Miller ER 3rd.** The effects of carbohydrate, unsaturated fat, and protein intake on measures of insulin sensitivity: results from the OmniHeart trial. *Diabetes Care*. 2013;36(5):1132-1137. [EL 1; RCT]
42. **Kerksick CM, Wismann-Bunn J, Fogt D, et al.** Changes in weight loss, body composition and cardiovascular

disease risk after altering macronutrient distributions during a regular exercise program in obese women. *Nutr J*. 2010;9:59-77. [EL 1; RCT]

43. **Kerksick C, Thomas A, Campbell B, et al.** Effects of a popular exercise and weight loss program on weight loss, body composition, energy expenditure and health in obese women. *Nutr Metab*. 2009;6:23. [EL 1; RCT]
44. **McLaughlin T, Carter S, Lamendola C, et al.** Effects of moderate variations in macronutrient composition on weight loss and reduction in cardiovascular disease risk in obese, insulin-resistant adults. *Am J Clin Nutr.* 2006; 84(4):813-821. [EL 1; RCT]
45. **Muzio F, Mondazzi L, Harris WS, Sommariva D, Branchi A.** Effects of moderate variations in the macronutrient content of the diet on cardiovascular disease risk factors in obese patients with the metabolic syndrome. *Am J Clin Nutr.* 2007;86(4):946-951. [EL 1; RCT]
46. **Summer SS, Brehm BJ, Benoit SC, D'Alessio DA.** Adiponectin changes in relation to the macronutrient composition of a weight-loss diet. *Obesity (Silver Spring)*. 2011;19(11):2198-2204. [EL 1; RCT]
47. **Bradley U, Spence M, Courtney CH, et al.** Low-fat versus low-carbohydrate weight reduction diets: effects on weight loss, insulin resistance, and cardiovascular risk: a randomized control trial. *Diabetes*. 2009;58(12):2741-2748. [EL 1; RCT]
48. **Brooking LA, Williams SM, Mann JI.** Effects of macronutrient composition of the diet on body fat in indigenous people at high risk of type 2 diabetes. *Diabetes Res Clin Pract*. 2012;96(1):40-46. [EL 1; RCT]
49. **Delbridge EA, Prendergast LA, Pritchard JE, Proietto J.** One-year weight maintenance after significant weight loss in healthy overweight and obese subjects: does diet composition matter? *Am J Clin Nutr.* 2009;90(5):1203-1214. [EL 1; RCT]
50. **Lim SS, Noakes M, Keogh JB, Clifton PM.** Long-term effects of a low carbohydrate, low fat or high unsaturated fat diet compared to a no-intervention control. *Nutr Metab Cardiovasc Dis*. 2010;20(8):599-607. [EL 1; RCT]
51. **Lopez-Legarrea P, de la Iglesia R, Abete I, Navas-Carretero S, Martinez JA, Zulet MA.** The protein type within a hypocaloric diet affects obesity-related inflammation: the RESMENA project. *Nutrition*. 2014; 30(4):424-429. [EL 1; RCT]
52. **Cheng HL, Griffin H, Claes BE, et al.** Influence of dietary macronutrient composition on eating behaviour and self-perception in young women undergoing weight management. *Eat Weight Disord*. 2014;19(2):241-247. [EL 1; RCT]
53. **Tang M, Armstrong CL, Leidy HJ, Campbell WW.** Normal vs. high-protein weight loss diets in men: effects on body composition and indices of metabolic syndrome. *Obesity (Silver Spring)*. 2013;21(3):E204-E210. [EL 1; RCT]
54. **Lasker DA, Evans EM, Layman DK.** Moderate carbohydrate, moderate protein weight loss diet reduces cardiovascular disease risk compared to high carbohydrate, low protein diet in obese adults: a randomized clinical trial. *Nutr Metab (Lond)*. 2008;5:30. [EL 1; RCT]
55. **Tapsell L, Batterham M, Huang XF, et al.** Short term effects of energy restriction and dietary fat sub-type on weight loss and disease risk factors. *Nutr Metab Cardiovasc Dis*. 2010;20(5):317-325. [EL 1; RCT]
56. **Tapsell LC, Batterham MJ, Teuss G, et al.** Long-term effects of increased dietary polyunsaturated fat from walnuts on metabolic parameters in type II diabetes. *Eur J Clin Nutr.* 2009;63(8):1008-1015. [EL 1; RCT]
57. **Mohammad MA, Sunehag AL, Haymond MW.** Effect of dietary macronutrient composition under moderate hypocaloric intake on maternal adaptation during lactation. *Am J Clin Nutr.* 2009;89(6):1821-1827. [EL 2; PCS]
58. **de Souza RJ, Bray GA, Carey VJ, et al.** Effects of 4 weight-loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: results from the POUNDS LOST trial. *Am J Clin Nutr.* 2012;95(3):614-625. [EL 1; RCT, post-hoc analysis]
59. **Buckland G, González CA, Agudo A, et al.** Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. *Am J Epidemiol*. 2009;170(12):1518-1529. [EL 2; PCS, post-hoc analysis]
60. **Babio N, Toledo E, Estruch R, et al.** Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. *CMAJ*. 2014;186(17):E649-E657. [EL 1; RCT, secondary analysis]
61. **Richard C, Couture P, Desroches S, Lamarche B.** Effect of the Mediterranean diet with and without weight loss on markers of inflammation in men with metabolic syndrome. *Obesity (Silver Spring)*. 2013;21(1):51-57. [EL 2; PCS]
62. **Ryan MC, Itsiopoulos C, Thodis T, et al.** The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. *J Hepatol*. 2013;59(1):138-143. [EL 1; RCT]
63. **Stendell-Hollis NR, Thompson PA, West JL, Wertheim BC, Thomson CA.** A comparison of Mediterranean-style and MyPyramid diets on weight loss and inflammatory biomarkers in postpartum breastfeeding women. *J Womens Health (Larchmt)*. 2013;22(1):48-57. [EL 1; RCT]
64. **Di Daniele N, Petramala L, Di Renzo L, et al.** Body composition changes and cardiometabolic benefits of a balanced Italian Mediterranean Diet in obese patients with metabolic syndrome. *Acta Diabetol*. 2013;50(3):409-416. [EL 2; PCS]
65. **Richard C, Couture P, Desroches S, et al.** Effect of the Mediterranean diet with and without weight loss on surrogate markers of cholesterol homeostasis in men with the metabolic syndrome. *Br J Nutr.* 2012;107(5):705-711. [EL 2; PCS]
66. **Shai I, Spence JD, Schwarzfuchs D, et al.** Dietary intervention to reverse carotid atherosclerosis. *Circulation*. 2010;121(10):1200-1208. [EL 1; RCT]
67. **Greenway FL, Fujioka K, Plodkowski RA, et al.** COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595-605. [EL 1; RCT]
68. **Pi-Sunyer X, Astrup A, Fujioka K, et al.** SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373(1):11-22. [EL 1; RCT]
69. **Fidler MC, Sanchez M, Raether B, et al.** A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab*. 2011;96(10):3067-3077. [EL 1; RCT]
70. **Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR.** Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med*. 2000;9(2):160-167. [EL 1; RCT]
71. **Gadde KM, Allison DB, Ryan DH, et al.** Effects of low-dose, controlled-release, phentermine plus topiramate

combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9774): 1341-1352. [EL 1; RCT]

72. **Leavell HR, Clark EG.** *Preventive Medicine for the Doctor in His Community: An Epidemiologic Approach*. 3rd ed. New York, NY: McGraw-Hill; 1965. [EL 4; NE]
73. **Fletcher RH, Fletcher SW, Wagner EH.** *Clinical Epidemiology: The Essentials*. 3th ed. Baltimore, MD: Lippincott Williams & Wilkins; 1996. [EL 4; NE]
74. **Jekel JF, Katz DL, Elmore JG, Wild DMG.** *Epidemiology, Biostatistics, Preventive Medicine, and Public Health*. 3rd ed. Philadelphia, PA: W.B. Saunders Company; 2007. [EL 4; NE]
75. **Maciosek MV, Coffield AB, Edwards NM, Flottemesch TJ, Goodman MJ, Solberg LI**. Priorities among effective clinical preventive services: results of a systematic review and analysis. *Am J Prev Med*. 2006; 31(1):52-61. [EL 4; NE]
76. **Fletcher RH, Fletcher SW, Fletcher GS.** Chapter 10: Prevention. In: *Clinical Epidemiology: The Essentials*. 5th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2014. [EL 4; NE]
77. **Mensah GA, Dietz WH, Harris VB, et al.** Prevention and control of coronary heart disease and stroke—nomenclature for prevention approaches in public health: a statement for public health practice from the Centers for Disease Control and Prevention. *Am J Prev Med*. 2005; 29(5 Suppl 1):152-157. [EL 4; NE]
78. **Rassi A, Dias JC, Marin-Neto JA, Rassi A.** Challenges and opportunities for primary, secondary, and tertiary prevention of Chagas' disease. *Heart*. 2009;95(7):524-534. [EL 4; NE]
79. **Dekker G, Sibai B.** Primary, secondary, and tertiary prevention of pre-eclampsia. *Lancet*. 2001;357(9251): 209-215. [EL 4; NE]
80. **Kiss S, Damico FM, Young LH.** Ocular manifestations and treatment of syphilis. *Semin Ophthalmol*. 2005;20(3): 161-167. [EL 4; NE]
81. **Lee C, McGlashan TH, Woods SW.** Prevention of schizophrenia: can it be achieved? *CNS Drugs*. 2005; 19(3):193-206. [EL 4; NE]
82. **Felson DT, Zhang Y.** An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum*. 1998;41(8):1343-1355. [EL 4; NE]
83. **Wiersinga WM, Bartalena L.** Epidemiology and prevention of Graves' ophthalmopathy. *Thyroid*. 2002; 12(10):855-860. [EL 4; NE]
84. **U.S. Preventive Services Task Force.** Procedure manual - Section 1.3 Scope of work. Available at: http://www.uspreventiveservicestaskforce.org/. U.S. Preventive Services Task Force. 2014. [EL 4; NE]
85. **Weintraub WS, Daniels SR, Burke LE, et al.** Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation*. 2011;124(8):967-990. [EL 4; NE]
86. **Hoelscher DM, Kirk S, Ritchie L, Cunningham-Sabo L. Academy Positions Committee.** Position of the Academy of Nutrition and Dietetics: interventions for the prevention and treatment of pediatric overweight and obesity. *J Acad Nutr Diet*. 2013;113(10):1375-1394. [EL 4; NE]
87. **Speliotes EK, Willer CJ, Berndt SI, et al.** Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42(11): 937-948. [EL 3; SS]
88. **Locke AE, Kahali B, Berndt SI, et al.** Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;518(7538):197-206. [EL 3; SS]
89. **Willer CJ, Speliotes EK, Loos RJ, et al.** Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet*. 2009; 41(1):25-34. [EL 3; SS]
90. **DeMattia L, Lemont L, Meurer L.** Do interventions to limit sedentary behaviours change behaviour and reduce childhood obesity? A critical review of the literature. *Obes Rev*. 2007;8(1):69-81. [EL 2; MNRCT; heterogeneity of studies]
91. **National Institute for Health and Care Excellence (NICE) Guideline.** Maintaining a healthy weight and preventing excess weight gain among adults and children. *National Institute of Health and Care Excellence*. Available at: http://www.nice.org.uk/guidance/ng7. 2015. [EL 4; NE]
92. **Palmer LJ, Buxbaum SG, Larkin E, et al.** A whole-genome scan for obstructive sleep apnea and obesity. *Am J Hum Genet*. 2003;72(2):340-350. [EL 3; SS]
93. **Timpson NJ, Lindgren CM, Weedon MN, et al.** Adiposity-related heterogeneity in patterns of type 2 diabetes susceptibility observed in genome-wide association data. *Diabetes*. 2009;58(2):505-510. [EL 3; SS]
94. **Frayling TM, Timpson NJ, Weedon MN, et al.** A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*. 2007;316(5826):889-894. [EL 3; SS]
95. **Bowden DW, Sale M, Howard TD, et al.** Linkage of genetic markers on human chromosomes 20 and 12 to NIDDM in Caucasian sib pairs with a history of diabetic nephropathy. *Diabetes*. 1997;46(5):882-886. [EL 3; SS]
96. **Vardarli I, Baier LJ, Hanson RL, et al.** Gene for susceptibility to diabetic nephropathy in type 2 diabetes maps to 18q22.3-23. *Kidney Int*. 2002;62(6):2176-2183. [EL 3; SS]
97. **Starfield B, Hyde J, Gervas J, Heath I.** The concept of prevention: a good idea gone astray? *J Epidemiol Community Health*. 2008;62(7):580-583. [EL 4; NE]
98. **Moyer VA, LeFevre ML, Siu AL, et al.** U.S. Preventive Services Task Force. Screening for and management of obesity in adults: U.S. Preventative Services Task Force recommendation statement. *Ann Intern Med*. 2012; 157(5):373-378. [EL 4; NE]
99. **Lau DC. Obesity Canada Clinical Practice Guidelines Steering Committee and Expert Panel.** Synopsis of the 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. *CMAJ*. 2007;176(8):1103-1106. [EL 4; NE]
100. **American College of Obstetricians and Gynecologists.** The role of the obstetrician-gynecologist in the assessment and management of obesity. 2005. [EL 4; NE]
101. **National Institute for Health and Care Excellence**. Identification, assessment and management of overweight and obesity in children, young people and adults. (Clinical Guideline 189). Available at: http://www.nice.org.uk/guidance/cg189. NICE: National Institute for Health and Care Excellence. 2014. Accessed January 16, 2016. [EL 4; NE]
102. **Heymsfield SB, Peterson CM, Thomas DM, et al.** Scaling of adult body weight to height across sex and race/ethnic groups: relevance to BMI. *Am J Clin Nutr.* 2014;100(6):1455-1461. [EL 3; CSS]

103. **Gray DS, Fujioka K.** Use of relative weight and Body Mass Index for the determination of adiposity. *J Clin Epidemiol*. 1991;44(6):545-550. [EL 3; CSS]
104. **Strain GW, Zumoff B.** The relationship of weight-height indices of obesity to body fat content. *J Am Coll Nutr*. 1992;11(6):715-718. [EL 3; CSS]
105. **Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y.** Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am J Clin Nutr*. 2000;72(3):694-701. [EL 3; CSS]
106. **Flegal KM, Shepherd JA, Looker AC, et al.** Comparisons of percentage body fat, body mass index, waist circumference, and waist-stature ratio in adults. *Am J Clin Nutr*. 2009;89(2):500-508. [EL 3; CSS]
107. **Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH.** The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009;9:88. [EL 2; MNRCT]
108. **Bays HE, Chapman RH, Grandy S, SHIELD Investigators' Group.** The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. *Int J Clin Pract*. 2007;61(5):737-747. [EL 3; SS]
109. **Tobias DK, Pan A, Jackson CL, et al.** Body-mass index and mortality among adults with incident type 2 diabetes. *N Engl J Med*. 2014;370(3):233-244. [EL 2; PCS]
110. **Twig G, Afek A, Derazne E, et al.** Diabetes risk among overweight and obese metabolically healthy young adults. *Diabetes Care*. 2014;37(11):2989-2995. [EL 2; PCS]
111. **Abdullah A, Peeters A, de Courten M, Stoelwinder J.** The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. *Diabetes Res Clin Pract*. 2010;89(3):309-319. [EL 2; MNRCT]
112. **Schienkiewitz A, Schulze MB, Hoffmann K, Kroke A, Boeing H.** Body mass index history and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Am J Clin Nutr*. 2006;84(2):427-433. [EL 2; PCS]
113. **Vazquez G, Duval S, Jacobs DR, Silventoinen K.** Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev*. 2007;29:115-128. [EL 2; MNRCT]
114. **Torloni MR, Betrán AP, Horta BL, et al.** Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. *Obes Rev*. 2009;10(2):194-203. [EL 2; MNRCT]
115. **van Dis I, Kromhout D, Geleijnse JM, Boer JM, Verschuren WM.** Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20,000 Dutch men and women aged 20-65 years. *Eur J Cardiovasc Prev Rehabil*. 2009; 16(6):729-734. [EL 2; PCS]
116. **Wormser D, Kaptoge S, Di Angelantonio E, et al.** Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet*. 2011;377(9771):1085-1095. [EL 2; RCCS]
117. **Strazzullo P, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, Scalfi L.** Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. *Stroke*. 2010;41(5):e418-26. [EL 2; MNRCT]
118. **Rea TD, Heckbert SR, Kaplan RC, et al.** Body mass index and the risk of recurrent coronary events following acute myocardial infarction. *Am J Cardiol*. 2001;88(5): 467-472. [EL 2; PCS]
119. **Mongraw-Chaffin ML, Peters SA, Huxley RR, Woodward M.** The sex-specific association between BMI and coronary heart disease: a systematic review and meta-analysis of 95 cohorts with 1.2 million participants. *Lancet Diabetes Endocrinol*. 2015;3(6):437-449. [EL 2; MNRCT]
120. **Katzmarzyk PT, Craig CL, Bouchard C.** Adiposity, adipose tissue distribution and mortality rates in the Canada Fitness Survey follow-up study. *Int J Obes Relat Metab Disord*. 2002;26(8):1054-1059. [EL 2; MNRCT]
121. **Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW.** Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med*. 1999;341(15):1097-1105. [EL 2; PCS]
122. **Berrington de Gonzalez A, Hartge P, Cerhan JR, et al.** Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363(23):2211-2219. [EL 2; MNRCT]
123. **Adams KF, Schatzkin A, Harris TB, et al.** Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med*. 2006;355(8):763-778. [EL 2; PCS]
124. **Whitlock G, Lewington S, Sherliker P, et al.** Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009; 373(9669):1083-1096. [EL 2; MNRCT]
125. **Lenz M, Richter T, Mühlhauser I.** The morbidity and mortality associated with overweight and obesity in adulthood: a systematic review. *Dtsch Arztebl Int*. 2009; 106(40):641-648. [EL 2; MNRCT]
126. **Flegal KM, Kit BK, Orpana H, Graubard BI.** Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013; 309(1):71-82. [EL 2; MNRCT]
127. **McGee DL. Diverse Populations Collaboration.** Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol*. 2005;15(2):87-97. [EL 2; MNRCT]
128. **Jiang J, Ahn J, Huang WY, Hayes RB.** Association of obesity with cardiovascular disease mortality in the PLCO trial. *Prev Med*. 2013;57(1):60-64. [EL 2; PCS]
129. **Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L.** Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet*. 2014;384(9945):755-765. [EL 2; PCS]
130. **Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M.** Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578. [EL 2; MNRCT]
131. **Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ.** Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17):1625-1638. [EL 2; PCS]
132. **Prentice AM, Jebb SA.** Beyond body mass index. *Obes Rev*. 2001;2(3):141-147. [EL 2; PCS]
133. **Romero-Corral A, Somers VK, Sierra-Johnson J, et al.** Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes*. 2008;32(6):959-966. [EL 3; CSS]

134. **Bedogni G, Pietrobelli A, Heymsfield SB, et al.** Is body mass index a measure of adiposity in elderly women? *Obes Res*. 2001;9(1):17-20. [EL 3; CCS]
135. **De Lorenzo A, Bianchi A, Maroni P, et al.** Adiposity rather than BMI determines metabolic risk. *Int J Cardiol*. 2013;166(1):111-117. [EL 3; CSS]
136. **Gómez-Ambrosi J, Silva C, Galofré JC, et al.** Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. *Int J Obes*. 2012;36(2):286-294. [EL 3; CSS]
137. **Lear SA, Humphries KH, Kohli S, Birmingham CL.** The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. *Obesity (Silver Spring)*. 2007;15(11):2817-2824. [EL 2; PCS]
138. **Frankenfield DC, Rowe WA, Cooney RN, Smith JS, Becker D.** Limits of body mass index to detect obesity and predict body composition. *Nutrition*. 2001;17(1):26-30. [EL 3; CSS]
139. **Gallagher D, Visser M, Sepúlveda D, Pierson RN, Harris T, Heymsfield SB.** How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol*. 1996;143(3):228-239. [EL 3; CSS]
140. **Gómez-Ambrosi J, Silva C, Galofré JC, et al.** Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. *Obesity (Silver Spring)*. 2011;19(7):1439-1444. [EL 3; CSS]
141. **Okorodudu DO, Jumean MF, Montori VM, et al.** Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. *Int J Obes*. 2010;34(5):791-799. [EL 2; MNRCT]
142. **Ode JJ, Pivarnik JM, Reeves MJ, Knous JL.** Body mass index as a predictor of percent fat in college athletes and nonathletes. *Med Sci Sports Exerc*. 2007;39(3):403-409. [EL 3; CSS]
143. **Santos DA, Dawson JA, Matias CN, et al.** Reference values for body composition and anthropometric measurements in athletes. *PLoS One*. 2014;9(5):e97846. [EL 3; CSS]
144. **Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V.** Sarcopenic obesity: a new category of obesity in the elderly. *Nutr Metab Cardiovasc Dis*. 2008;18(5):388-395. [EL 4; NE]
145. **Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG.** Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. *J Am Geriatr Soc*. 2014;62(2):253-260. [EL 2; PCS]
146. **Winter JE, MacInnis RJ, Wattanapenpaiboon N, Nowson CA.** BMI and all-cause mortality in older adults: a meta-analysis. *Am J Clin Nutr*. 2014;99(4):875-890. [EL 2; MNRCT]
147. **Janssen I, Katzmarzyk PT, Ross R.** Body mass index is inversely related to mortality in older people after adjustment for waist circumference. *J Am Geriatr Soc*. 2005;53(12):2112-2118. [EL 2; PCS]
148. **Chang SH, Beason TS, Hunleth JM, Colditz GA.** A systematic review of body fat distribution and mortality in older people. *Maturitas*. 2012;72(3):175-191. [EL 2; MNRCT]
149. **Rolland Y, Gallini A, Cristini C, et al.** Body-composition predictors of mortality in women aged ≥ 75 y: data from a large population-based cohort study with a 17-y follow-up. *Am J Clin Nutr*. 2014;100(5):1352-1360. [EL 2; PCS]
150. **Lisko I, Tiainen K, Stenholm S, Luukkaala T, Hervonen A, Jylhä M.** Body mass index, waist circumference, and waist-to-hip ratio as predictors of mortality in nonagenarians: the Vitality 90+ Study. *J Gerontol A Biol Sci Med Sci*. 2011;66(11):1244-1250. [EL 2; PCS]
151. **Wannamethee SG, Shaper AG, Lennon L, Whincup PH.** Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr*. 2007;86(5):1339-1346. [EL 2; PCS]
152. **Murphy RA, Reinders I, Garcia ME, et al.** Adipose tissue, muscle, and function: potential mediators of associations between body weight and mortality in older adults with type 2 diabetes. *Diabetes Care*. 2014;37(12): 3213-3219. [EL 2; PCS]
153. **Graf CE, Karsegard VL, Spoerri A, et al.** Body composition and all-cause mortality in subjects older than 65 y. *Am J Clin Nutr*. 2015;101(4):760-767. [EL 2; RCCS]
154. **Jackson CL, Yeh HC, Szklo M, et al.** Body-mass index and all-cause mortality in US adults with and without diabetes. *J Gen Intern Med*. 2014;29(1):25-33. [EL 2; PCS]
155. **Zhao W, Katzmarzyk PT, Horswell R, et al.** Body mass index and the risk of all-cause mortality among patients with type 2 diabetes mellitus. *Circulation*. 2014;130(24): 2143-2151. [EL 2; PCS]
156. **Costanzo P, Cleland JG, Pellicori P, et al.** The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. *Ann Intern Med*. 2015;162(9):610-618. [EL 2; PCS]
157. **Liu XM, Liu YJ, Zhan J, He QQ.** Overweight, obesity and risk of all-cause and cardiovascular mortality in patients with type 2 diabetes mellitus: a dose-response meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2015;30(1):35-45. [EL 2; MNRCT]
158. **Li W, Katzmarzyk PT, Horswell R, et al.** Body mass index and stroke risk among patients with type 2 diabetes mellitus. *Stroke*. 2015;46(1):164-169. [EL 2; PCS]
159. **Sharma A, Lavie CJ, Borer JS, et al.** Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. *Am J Cardiol*. 2015;115(10): 1428-1434. [EL 2; MNRCT]
160. **Kokkinos P, Faselis C, Myers J, et al.** Cardiorespiratory fitness and the paradoxical BMI-mortality risk association in male veterans. *Mayo Clin Proc*. 2014;89(6):754-762. [EL 2; PCS]
161. **Allison DB, Zhu SK, Plankey M, Faith MS, Heo M.** Differential associations of body mass index and adiposity with all-cause mortality among men in the first and second National Health and Nutrition Examination Surveys (NHANES I and NHANES II) follow-up studies. *Int J Obes Relat Metab Disord*. 2002;26(3):410-416. [EL 3; SS]
162. **Pietiläinen KH, Kaye S, Karmi A, Suojanen L, Rissanen A, Virtanen KA.** Agreement of bioelectrical impedance with dual-energy X-ray absorptiometry and MRI to estimate changes in body fat, skeletal muscle and visceral fat during a 12-month weight loss intervention. *Br J Nutr*. 2013;109(10):1910-1916. [EL 2; PCS, N = 19]
163. **Myint PK, Kwok CS, Luben RN, Wareham NJ, Khaw KT.** Body fat percentage, body mass index and waist-to-hip ratio as predictors of mortality and cardiovascular disease. *Heart*. 2014;100(20):1613-1619. [EL 2; PCS]
164. **Miyatake N, Takenami S, Kawasaki Y, Fujii M.** Comparison of air displacement plethysmograph and bioelectrical impedance for assessing body composition changes during weight loss in Japanese women. *Diabetes Obes Metab*. 2005;7(3):268-272. [EL 3; CSS]

165. **McCrory MA, Gomez TD, Bernauer EM, Molé PA.** Evaluation of a new air displacement plethysmograph for measuring human body composition. *Med Sci Sports Exerc*. 1995;27(12):1686-1691. [EL 3; CCS]
166. **Vescovi JD, Zimmerman SL, Miller WC, Hildebrandt L, Hammer RL, Fernhall B.** Evaluation of the BOD POD for estimating percentage body fat in a heterogeneous group of adult humans. *Eur J Appl Physiol*. 2001;85(3-4): 326-332. [EL 3; CCS]
167. **Sasai H, Nakata Y, Nemoto M, et al.** Air displacement plethysmography for estimating body composition changes with weight loss in middle-aged Japanese men. *Obes Facts*. 2010;3(6):357-362. [EL 2; PCS, N = 50 men]
168. **Sardinha LB, Lohman TG, Teixeira PJ, Guedes DP, Going SB.** Comparison of air displacement plethysmography with dual-energy X-ray absorptiometry and 3 field methods for estimating body composition in middle-aged men. *Am J Clin Nutr.* 1998;68(4):786-793. [EL 3; CSS, N = 62 men]
169. **Hames KC, Anthony SJ, Thornton JC, Gallagher D, Goodpaster BH.** Body composition analysis by air displacement plethysmography in normal weight to extremely obese adults. *Obesity (Silver Spring)*. 2014; 22(4):1078-1084. [EL 3; CSS]
170. **Lowry DW, Tomiyama AJ.** Air displacement plethysmography versus dual-energy x-ray absorptiometry in underweight, normal-weight, and overweight/obese individuals. *PLoS One*. 2015;10(1):e0115086. [EL 3; CSS]
171. **Salamone LM, Fuerst T, Visser M, et al.** Measurement of fat mass using DEXA: a validation study in elderly adults. *J Appl Physiol (1985)*. 2000;89(1):345-352. [EL 3; CSS, N = 60]
172. **Micklesfield LK, Goedecke JH, Punyanitya M, Wilson KE, Kelly TL.** Dual-energy X-ray performs as well as clinical computed tomography for the measurement of visceral fat. *Obesity (Silver Spring)*. 2012;20(5):1109-1114. [EL 3; CSS]
173. **Kendler DL, Borges JL, Fielding RA, et al.** The official positions of the International Society for Clinical Densitometry: indications of use and reporting of DXA for body composition. *J Clin Densitom*. 2013;16(4):496-507. [EL 4; NE]
174. **World Health Organization Expert Committee.** Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser.* 1995;854:1-452. [EL 4; NE]
175. **Bays HE, Toth PP, Kris-Etherton PM, et al.** Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. *J Clin Lipidol*. 2013;7(4): 304-383. [EL 4; NE]
176. **Stegenga H, Haines A, Jones K, Wilding J.** Guideline Development Group. Identification, assessment, and management of overweight and obesity: summary of updated NICE guidance. *BMJ*. 2014;349:g6608. [EL 4; NE]
177. **Klein S, Allison DB, Heymsfield SB, et al.** Waist circumference and cardiometabolic risk: a consensus statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *Obesity (Silver Spring)*. 2007;15(5):1061-1067. [EL 4; NE]
178. **Rao G, Powell-Wiley TM, Ancheta I, et al.** Identification of obesity and cardiovascular risk in ethnically and racially diverse populations: a scientific statement from the American Heart Association. *Circulation*. 2015;132(5):457-472. [EL 4; NE]
179. **Carroll JF, Chiapa AL, Rodriquez M, et al.** Visceral fat, waist circumference, and BMI: impact of race/ethnicity. *Obesity (Silver Spring)*. 2008;16(3):600-607. [EL 3; CSS]
180. **Janssen I, Katzmarzyk PT, Ross R.** Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr.* 2004;79(3):379-384. [EL 3; CSS]
181. **Shah RV, Murthy VL, Abbasi SA, et al.** Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA Study. *JACC Cardiovasc Imaging*. 2014;7(12):1221-1235. [EL 2; PCS]
182. **Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB.** Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. *Am J Clin Nutr.* 2002;76(4):743-749. [EL 3; SS]
183. **Knowles KM, Paiva LL, Sanchez SE, et al.** Waist circumference, body mass index, and other measures of adiposity in predicting cardiovascular disease risk factors among Peruvian adults. *Int J Hypertens*. 2011;2011: 931402. [EL 3; CSS]
184. **Janiszewski PM, Janssen I, Ross R.** Does waist circumference predict diabetes and cardiovascular disease beyond commonly evaluated cardiometabolic risk factors? *Diabetes Care*. 2007;30(12):3105-3109. [EL 3; CSS]
185. **Zhu S, Heymsfield SB, Toyoshima H, Wang Z, Pietrobelli A, Heshka S.** Race-ethnicity-specific waist circumference cutoffs for identifying cardiovascular disease risk factors. *Am J Clin Nutr.* 2005;81(2):409-415. [EL 3; CSS]
186. **Dobbelsteyn CJ, Joffres MR, MacLean DR, Flowerdew G.** A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The Canadian Heart Health Surveys. *Int J Obes Relat Metab Disord*. 2001;25(5):652-661. [EL 3; CSS]
187. **Ardern CI, Katzmarzyk PT, Janssen I, Ross R.** Discrimination of health risk by combined body mass index and waist circumference. *Obes Res*. 2003;11(1):135-142. [EL 3; CSS]
188. **Janssen I, Katzmarzyk PT, Ross R.** Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. *Arch Intern Med*. 2002;162(18):2074-2079. [EL 3; CSS]
189. **Rexrode KM, Buring JE, Manson JE.** Abdominal and total adiposity and risk of coronary heart disease in men. *Int J Obes Relat Metab Disord*. 2001;25(7):1047-1056. [EL 2; PCS]
190. **de Koning L, Merchant AT, Pogue J, Anand SS.** Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *Eur Heart J*. 2007;28(7):850-856. [EL 2; MNRCT]
191. **Balkau B, Deanfield JE, Després JP, et al.** International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation*. 2007;116(17):1942-1951. [EL 3; CSS]
192. **Yusuf S, Hawken S, Ounpuu S, et al.** Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet*. 2005;366(9497): 1640-1649. [EL 2; RCCS]
193. **Reis JP, Allen N, Gunderson EP, et al.** Excess body mass index- and waist circumference-years and incident cardiovascular disease: the CARDIA study. *Obesity*. 2015;23(4):879-885. [EL 2; PCS]

194. **Koster A, Leitzmann MF, Schatzkin A, et al.** Waist circumference and mortality. *Am J Epidemiol*. 2008; 167(12):1465-1475. [EL 3; SS]
195. **Bigaard J, Tjønneland A, Thomsen BL, Overvad K, Heitmann BL, Sørensen TI.** Waist circumference, BMI, smoking, and mortality in middle-aged men and women. *Obes Res*. 2003;11(7):895-903. [EL 2; PCS]
196. **Dhaliwal SS, Welborn TA, Goh LG, Howat PA.** Obesity as assessed by body adiposity index and multivariable cardiovascular disease risk. *PLoS One*. 2014;9(4):e94560. [EL 2; PCS]
197. **Staiano AE, Reeder BA, Elliott S, et al.** Body mass index versus waist circumference as predictors of mortality in Canadian adults. *Int J Obes*. 2012;36(11):1450-1454. [EL 2; PCS]
198. **Jacobs EJ, Newton CC, Wang Y, et al.** Waist circumference and all-cause mortality in a large US cohort. *Arch Intern Med*. 2010;170(15):1293-1301. [EL 3; SS]
199. **Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB.** Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. *Circulation*. 2008;117(13):1658-1667. [EL 2; PCS]
200. **Cerhan JR, Moore SC, Jacobs EJ, et al.** A pooled analysis of waist circumference and mortality in 650,000 adults. *Mayo Clin Proc*. 2014;89(3):335-345. [EL 2; MNRCT]
201. **Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD.** Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. *Obes Rev*. 2011; 12(9):680-687. [EL 2; MNRCT]
202. **de Hollander EL, Bemelmans WJ, Boshuizen HC, et al.** The association between waist circumference and risk of mortality considering body mass index in 65- to 74-year-olds: a meta-analysis of 29 cohorts involving more than 58 000 elderly persons. *Int J Epidemiol*. 2012; 41(3):805-817. [EL 2; MNRCT]
203. **Coutinho T, Goel K, Corrêa de Sá D, et al.** Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: role of "normal weight central obesity". *J Am Coll Cardiol*. 2013;61(5):553-560. [EL 2; MNRCT]
204. **Sobiczewski W, Wirtwein M, Jarosz D, Gruchala M.** Superiority of waist circumference and body mass index in cardiovascular risk assessment in hypertensive patients with coronary heart disease. *Blood Press*. 2015;24(2):90-95. [EL 2; PCS]
205. **Visscher TL, Seidell JC, Molarius A, van der Kuip D, Hofman A, Witteman JC.** A comparison of body mass index, waist-hip ratio and waist circumference as predictors of all-cause mortality among the elderly: the Rotterdam study. *Int J Obes Relat Metab Disord*. 2001; 25(11):1730-1735. [EL 2; PCS]
206. **Testa G, Cacciatore F, Galizia G, et al.** Waist circumference but not body mass index predicts long-term mortality in elderly subjects with chronic heart failure. *J Am Geriatr Soc*. 2010;58(8):1433-1440. [EL 3; CSS]
207. **Lim RB, Chen C, Naidoo N, et al.** Anthropometrics indices of obesity, and all-cause and cardiovascular disease-related mortality, in an Asian cohort with type 2 diabetes mellitus. *Diabetes Metab*. 2015;41(4):291-300. [EL 2; PCS]
208. **Pischon T, Boeing H, Hoffmann K, et al.** General and abdominal adiposity and risk of death in Europe. *N Engl J Med*. 2008;359(20):2105-2120. [EL 2; PCS]
209. **Bray GA, Jablonski KA, Fujimoto WY, et al.** Relation of central adiposity and body mass index to the development of diabetes in the Diabetes Prevention Program. *Am J Clin Nutr*. 2008;87(5):1212-1218. [EL 2; PCS]
210. **Abbasi F, Malhotra D, Mathur A, Reaven GM, Molina CR.** Body mass index and waist circumference associate to a comparable degree with insulin resistance and related metabolic abnormalities in South Asian women and men. *Diab Vasc Dis Res*. 2012;9(4):296-300. [EL 3; CSS]
211. **Freiberg MS, Pencina MJ, D'Agostino RB, Lanier K, Wilson PW, Vasan RS.** BMI vs. waist circumference for identifying vascular risk. *Obesity (Silver Spring)*. 2008; 16(2):463-469. [EL 2; PCS]
212. **Taylor AE, Ebrahim S, Ben-Shlomo Y, et al.** Comparison of the associations of body mass index and measures of central adiposity and fat mass with coronary heart disease, diabetes, and all-cause mortality: a study using data from 4 UK cohorts. *Am J Clin Nutr*. 2010; 91(3):547-556. [EL 2; MNRCT]
213. **Lee CM, Huxley RR, Wildman RP, Woodward M.** Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin Epidemiol*. 2008;61(7):646-653. [EL 2; MNRCT]
214. **Ashwell M, Gunn P, Gibson S.** Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev*. 2012;13(3):275-286. [EL 2; MNRCT]
215. **Browning LM, Hsieh SD, Ashwell M.** A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. *Nutr Res Rev*. 2010;23(2):247-269. [EL 2; MNRCT]
216. **Zhu Q, Shen F, Ye T, Zhou Q, Deng H, Gu X.** Waist-to-height ratio is an appropriate index for identifying cardiometabolic risk in Chinese individuals with normal body mass index and waist circumference. *J Diabetes*. 2014;6(6):527-534. [EL 3; CSS]
217. **Carmienke S, Freitag MH, Pischon T, et al.** General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis. *Eur J Clin Nutr*. 2013;67(6):573-585. [EL 2; MNRCT]
218. **Reis JP, Macera CA, Araneta MR, Lindsay SP, Marshall SJ, Wingard DL.** Comparison of overall obesity and body fat distribution in predicting risk of mortality. *Obesity*. 2009;17(6):1232-1239. [EL 2; PCS]
219. **Kodama S, Horikawa C, Fujihara K, et al.** Comparisons of the strength of associations with future type 2 diabetes risk among anthropometric obesity indicators, including waist-to-height ratio: a meta-analysis. *Am J Epidemiol*. 2012;176(11):959-969. [EL 2; MNRCT]
220. **Deurenberg P, Yap M, van Staveren WA.** Body mass index and percent body fat: a meta analysis among different ethnic groups. *Int J Obes Relat Metab Disord*. 1998;22(12):1164-1171. [EL 2; MNRCT]
221. **Fernández JR, Heo M, Heymsfield SB, et al.** Is percentage body fat differentially related to body mass index in Hispanic Americans, African Americans, and European Americans? *Am J Clin Nutr*. 2003;77(1):71-75. [EL 3; CSS]
222. **Katzmarzyk PT, Bray GA, Greenway FL, et al.** Ethnic-specific BMI and waist circumference thresholds. *Obesity (Silver Spring)*. 2011;19(6):1272-1278. [EL 3; CSS]

223. **Hsu WC, Araneta MR, Kanaya AM, Chiang JL, Fujimoto W.** BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. *Diabetes Care*. 2015;38(1):150-158. [EL 4; NE]
224. **World Health Organization Western Pacific Region, International Association for the Study of Obesity and International Association for the Study of Obesity**. *The Asia-Pacific perspective: Redefining obesity and its treatment*. *Australia: Health communications*. 2000. Available at: http:// http://www.wpro.who.int/nutrition/documents/docs/Redefiningobesity.pdf. [EL 4; NE]
225. **Pan WH, Yeh WT.** How to define obesity? Evidence-based multiple action points for public awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pac J Clin Nutr.* 2008;17(3):370-374. [EL 4; NE]
226. **Zhou BF. Cooperative Meta-Analysis Group of the Working Group on Obesity in China.** Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults--study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci*. 2002;15(1):83-96. [EL 2; MNRCT]
227. **Razak F, Anand SS, Shannon H, et al.** Defining obesity cut points in a multiethnic population. *Circulation*. 2007;115(16):2111-2118. [EL 3; CSS]
228. **Ntuk UE, Gill JM, Mackay DF, Sattar N, Pell JP.** Ethnic-specific obesity cutoffs for diabetes risk: cross-sectional study of 490,288 UK biobank participants. *Diabetes Care*. 2014;37(9):2500-2507. [EL 3; CSS]
229. **He W, Li Q, Yang M, et al.** Lower BMI cutoffs to define overweight and obesity in China. *Obesity (Silver Spring)*. 2015;23(3):684-691. [EL 2; PCS]
230. **Zhou BF.** Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases--report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. *Biomed Environ Sci*. 2002;15(3):245-252. [EL 2; MNRCT]
231. **Gu D, He J, Duan X, et al.** Body weight and mortality among men and women in China. *JAMA*. 2006;295(7):776-783. [EL 2; PCS]
232. **Chen Y, Copeland WK, Vedanthan R, et al.** Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. *BMJ*. 2013;347:f5446. [EL 2; MNRCT]
233. **Lin WY, Tsai SL, Albu JB, et al.** Body mass index and all-cause mortality in a large Chinese cohort. *CMAJ*. 2011;183(6):E329-36. [EL 2; PCS]
234. **Zheng W, McLerran DF, Rolland B, et al.** Association between body-mass index and risk of death in more than 1 million Asians. *N Engl J Med*. 2011;364(8):719-729. [EL 2; MNRCT]
235. **Ko GT, Tang JS.** Waist circumference and BMI cut-off based on 10-year cardiovascular risk: evidence for "central pre-obesity". *Obesity (Silver Spring)*. 2007; 15(11):2832-2839. [EL 3; CSS]
236. **Okosun IS, Tedders SH, Choi S, Dever GE.** Abdominal adiposity values associated with established body mass indexes in white, black and hispanic Americans. A study from the Third National Health and Nutrition Examination Survey. *Int J Obes Relat Metab Disord*. 2000;24(10):1279-1285. [EL 3; SS]
237. **Wang Z, Ma J, Si D.** Optimal cut-off values and population means of waist circumference in different populations. *Nutr Res Rev*. 2010;23(2):191-199. [EL 2; MNRCT]
238. **Reaven GM.** Insulin resistance: the link between obesity and cardiovascular disease. *Med Clin North Am*. 2011;95(5):875-892. [EL 4; NE]
239. **Eckel RH, Grundy SM, Zimmet PZ.** The metabolic syndrome. *Lancet*. 2005;365(9468):1415-1428. [EL 4; NE]
240. **Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM, San Antonio Heart Study.** The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. *Diabetes Care*. 2003;26(11):3153-3159. [EL 2; PCS]
241. **Guo F, Moellering DR, Garvey WT.** The progression of cardiometabolic disease: validation of a new cardiometabolic disease staging system applicable to obesity. *Obesity (Silver Spring)*. 2014;22(1):110-118. [EL 3; SS]
242. **Nigro J, Osman N, Dart AM, Little PJ.** Insulin resistance and atherosclerosis. *Endocr Rev*. 2006;27(3):242-259. [EL 4; NE]
243. **Zhuo X, Zhang P, Barker L, Albright A, Thompson TJ, Gregg E.** The lifetime cost of diabetes and its implications for diabetes prevention. *Diabetes Care*. 2014;37(9):2557-2564. [EL 3; SS]
244. **Grundy SM, Cleeman JI, Daniels SR, et al. American Heart Association, National Heart, Lung, and Blood Institute.** Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112(17):2735-2752. [EL 4; NE]
245. **American Diabetes Association.** Classification and diagnosis of diabetes. *Diabetes Care*. 2015;38:S8-S16. [EL 4; NE]
246. **Nathan DM, Davidson MB, DeFronzo RA, et al. American Diabetes Association.** Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*. 2007;30(3):753-759. [EL 4; NE]
247. **Garber AJ, Handelsman Y, Einhorn D, et al.** Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocr Pract*. 2008;14(7):933-946. [EL 4; NE]
248. **Alexander CM, Landsman PB, Teutsch SM, Haffner SM. Third National Health and Nutrition Examination Survey (NHANES III), National Cholesterol Education Program (NCEP).** NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003;52(5):1210-1214. [EL 3; SS]
249. **Gami AS, Witt BJ, Howard DE, et al.** Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49(4):403-414. [EL 2; MNRCT]
250. **Després JP, Lemieux I.** Abdominal obesity and metabolic syndrome. *Nature*. 2006;444(7121):881-887. [EL 4; NE]
251. **Misra A, Khurana L.** Obesity and the metabolic syndrome in developing countries. *J Clin Endocrinol Metab*. 2008;93(11 Suppl 1):S9-S30. [EL 4; NE]
252. **Ford ES, Giles WH, Mokdad AH.** Increasing prevalence of the metabolic syndrome among u.s. Adults. *Diabetes Care*. 2004;27(10):2444-2449. [EL 3; CSS]
253. **Flegal KM, Carroll MD, Ogden CL, Johnson CL.** Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002;288(14):1723-1727. [EL 3; CSS]
254. **Alexander CM, Landsman PB, Grundy SM.** The influence of age and body mass index on the metabolic

syndrome and its components. *Diabetes Obes Metab*. 2008;10(3):246-250. [EL 3; CSS]
255. **van Dijk SB, Takken T, Prinsen EC, Wittink H.** Different anthropometric adiposity measures and their association with cardiovascular disease risk factors: a meta-analysis. *Neth Heart J*. 2012;20(5):208-218. [EL 2; MNRCT]
256. **Savva SC, Lamnisos D, Kafatos AG.** Predicting cardiometabolic risk: waist-to-height ratio or BMI. A meta-analysis. *Diabetes Metab Syndr Obes*. 2013;6:403-419. [EL 2; MNRCT]
257. **Friedemann C, Heneghan C, Mahtani K, Thompson M, Perera R, Ward AM.** Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. *BMJ*. 2012; 345:e4759. [EL 2; MNRCT]
258. **Eckel RH, Kahn SE, Ferrannini E, et al.** Obesity and type 2 diabetes: what can be unified and what needs to be individualized? *J Clin Endocrinol Metab*. 2011;96(6): 1654-1663. [EL 4; NE]
259. **Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ.** Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes*. 1996;45(5):633-638. [EL 2; PCS, N = 22]
260. **Van Gaal LF, Mertens IL, De Block CE.** Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444(7121):875-880. [EL 4; NE]
261. **Olefsky JM, Glass CK.** Macrophages, inflammation, and insulin resistance. *Annu Rev Physiol*. 2010;72:219-246. [EL 4; NE]
262. **Lara-Castro C, Fu Y, Chung BH, Garvey WT.** Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. *Curr Opin Lipidol*. 2007;18(3):263-270. [EL 4; NE]
263. **Lara-Castro C, Garvey WT.** Intracellular lipid accumulation in liver and muscle and the insulin resistance syndrome. *Endocrinol Metab Clin North Am*. 2008;37(4):841-856. [EL 4; NE]
264. **Lutsey PL, Pereira MA, Bertoni AG, Kandula NR, Jacobs DR.** Interactions between race/ethnicity and anthropometry in risk of incident diabetes: the multiethnic study of atherosclerosis. *Am J Epidemiol*. 2010; 172(2):197-204. [EL 2; PCS]
265. **Garvey WT, Kwon S, Zheng D, et al.** Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. *Diabetes*. 2003;52(2):453-462. [EL 2; NRCT]
266. **Hollenbeck C, Reaven GM.** Variations in insulin-stimulated glucose uptake in healthy individuals with normal glucose tolerance. *J Clin Endocrinol Metab*. 1987;64(6):1169-1173. [EL 2; PCS]
267. **Bogardus C, Lillioja S.** Pima Indians as a model to study the genetics of NIDDM. *J Cell Biochem*. 1992;48(4):337-343. [EL 4; NE]
268. **Lara-Castro C, Garvey WT.** Diet, insulin resistance, and obesity: zoning in on data for Atkins dieters living in South Beach. *J Clin Endocrinol Metab*. 2004;89(9):4197-4205. [EL 4; NE]
269. **Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G.** Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). *J Clin Invest*. 1997;100(5):1166-1173. [EL 2; PCS]
270. **Neeland IJ, Turer AT, Ayers CR, et al.** Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. *JAMA*. 2012;308(11):1150-1159. [EL 2; PCS]
271. **Guo F, Garvey WT.** Development of a weighted cardiometabolic disease staging (CMDS) system for the prediction of future diabetes. *J Clin Endocrinol Metab*. 2015;100(10):3871-3877. [EL 3; SS]
272. **Guo F, Garvey WT.** Cardiometabolic disease risk in metabolically healthy and unhealthy obesity: stability of metabolic health status in adults. *Obesity (Silver Spring)*. 2015. [EL 2; PCS]
273. **Stefan N, Kantartzis K, Machann J, et al.** Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med*. 2008;168(15):1609-1616. [EL 2; PCS]
274. **Wildman RP, Muntner P, Reynolds K, et al.** The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med*. 2008;168(15):1617-1624. [EL 3; SS]
275. **Meigs JB, Wilson PW, Fox CS, et al.** Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*. 2006; 91(8):2906-2912. [EL 2; PCS]
276. **Kip KE, Marroquin OC, Kelley DE, et al.** Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Circulation*. 2004;109(6):706-713. [EL 2; PCS, selection bias]
277. **Liao Y, Kwon S, Shaughnessy S, et al.** Critical evaluation of adult treatment panel III criteria in identifying insulin resistance with dyslipidemia. *Diabetes Care*. 2004;27(4): 978-983. [EL 2; PCS]
278. **Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB.** Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005;112(20):3066-3072. [EL 2; PCS]
279. **Kannel WB, McGee D, Gordon T.** A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol*. 1976;38(1):46-51. [EL 4; NE]
280. **Pryor DB, Shaw L, McCants CB, et al.** Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Ann Intern Med*. 1993; 118(2):81-90. [EL 2; PCS]
281. **Ridker PM, Buring JE, Rifai N, Cook NR.** Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007;297(6):611-619. [EL 3; SS]
282. **Lindström J, Tuomilehto J.** The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Care*. 2003;26(3):725-731. [EL 3; SS]
283. **Bang H, Edwards AM, Bomback AS, et al.** Development and validation of a patient self-assessment score for diabetes risk. *Ann Intern Med*. 2009;151(11):775-783. [EL 3; SS]
284. **Hodge AM, Jenkins AJ, English DR, O'Dea K, Giles GG.** NMR-determined lipoprotein subclass profile predicts type 2 diabetes. *Diabetes Res Clin Pract*. 2009; 83(1):132-139. [EL 2; PCS]
285. **Frazier-Wood AC, Garvey WT, Dall T, Honigberg R, Pourfarzib R.** Opportunities for using lipoprotein subclass profile by nuclear magnetic resonance spectroscopy in assessing insulin resistance and diabetes prediction.

Metab Syndr Relat Disord. 2012;10(4):244-251. [EL 4; NE]

286. **Kolberg JA, Gerwien RW, Watkins SM, Wuestehube LJ, Urdea M.** Biomarkers in Type 2 diabetes: improving risk stratification with the PreDx (R) Diabetes Risk Score. *Expert Rev Mol Diagn*. 2011;11(8):775-792. [EL 4; NE]
287. **Shafizadeh TB, Moler EJ, Kolberg JA, et al.** Comparison of accuracy of diabetes risk score and components of the metabolic syndrome in assessing risk of incident type 2 diabetes in Inter99 cohort. *PLoS One*. 2011;6(7):e22863. [EL 3; SS]
288. **Centers for Disease Control and Prevention, US Department of Health and Human Services.** Diabetes Report Card 2014. 2015. Available at: http://www.cdc.gov/diabetes/library/reports/congress.html. [EL 4; NE]
289. **Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF.** Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr.* 2010;8:29. [EL 3; SS]
290. **Sims EA, Danforth E, Horton ES, Bray GA, Glennon JA, Salans LB.** Endocrine and metabolic effects of experimental obesity in man. *Recent Prog Horm Res*. 1973;29:457-496. [EL 4; NE]
291. **Fryar CD, Carroll MD, Ogden CL and Division of Health and Nutrition Examination Surveys.** *Health E-Stats: Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1960–1962 Through 2009–2010*. National Center for Health Statistics; 2012. Available at: http://www.cdc.gov/nchs/data/hestat/obesity_adult_09_10/obesity_adult_09_10.pdf. Accessed January 20, 2016. [EL 3; SS]
292. **Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services.** Estimated county-level prevalence of diabetes and obesity - United States, 2007. *MMWR Morb Mortal Wkly Rep*. 2009;58(45):1259-1263. [EL 3; SS]
293. **Barker LE, Kirtland KA, Gregg EW, Geiss LS, Thompson TJ.** Geographic distribution of diagnosed diabetes in the U.S.: a diabetes belt. *Am J Prev Med*. 2011; 40(4):434-439. [EL 3; SS]
294. **Wannamethee SG, Shaper AG.** Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. *Diabetes Care*. 1999;22(8):1266-1272. [EL 2; PCS]
295. **Willett WC, Dietz WH, Colditz GA.** Guidelines for healthy weight. *N Engl J Med*. 1999;341(6):427-434. [EL 4; NE]
296. **Kodama S, Horikawa C, Fujihara K, et al.** Quantitative relationship between body weight gain in adulthood and incident type 2 diabetes: a meta-analysis. *Obes Rev*. 2014; 15(3):202-214. [EL 2; MNRCT]
297. **Yki-Järvinen H, Ryysy L, Kauppila M, et al.** Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab*. 1997;82(12):4037-4043. [EL 1; RCT, non-blinded]
298. **Pani LN, Nathan DM, Grant RW.** Clinical predictors of disease progression and medication initiation in untreated patients with type 2 diabetes and A1C less than 7%. *Diabetes Care*. 2008;31(3):386-390. [EL 2; PCS]
299. **Mosnier-Pudar H, Hochberg G, Eschwege E, et al.** How patients' attitudes and opinions influence self-care behaviours in type 2 diabetes. Insights from the French DIABASIS Survey. *Diabetes Metab*. 2010;36(6 Pt 1): 476-483. [EL 3; SS]
300. **Brod M, Cobden D, Lammert M, Bushnell D, Raskin P.** Examining correlates of treatment satisfaction for injectable insulin in type 2 diabetes: lessons learned from a clinical trial comparing biphasic and basal analogues. *Health Qual Life Outcomes*. 2007;5:8. [EL 1; RCT, non-blinded]
301. **Conway B, Miller RG, Costacou T, et al.** Temporal patterns in overweight and obesity in Type 1 diabetes. *Diabet Med*. 2010;27(4):398-404. [EL 2; PCS]
302. **Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ.** Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes*. 2000;49(4):626-632. [EL 2; PCS]
303. **Purnell JQ, Hokanson JE, Marcovina SM, Steffes MW, Cleary PA, Brunzell JD.** Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. Diabetes Control and Complications Trial. *JAMA*. 1998; 280(2):140-146. [EL 1; RCT]
304. **Verbeeten KC, Elks CE, Daneman D, Ong KK.** Association between childhood obesity and subsequent Type 1 diabetes: a systematic review and meta-analysis. *Diabet Med*. 2011;28(1):10-18. [EL 2; MNRCT]
305. **Karaouzene N, Merzouk H, Aribi M, et al.** Effects of the association of aging and obesity on lipids, lipoproteins and oxidative stress biomarkers: a comparison of older with young men. *Nutr Metab Cardiovasc Dis*. 2011; 21(10):792-799. [EL 2; PCS]
306. **Hu D, Hannah J, Gray RS, et al.** Effects of obesity and body fat distribution on lipids and lipoproteins in nondiabetic American Indians: The Strong Heart Study. *Obes Res*. 2000;8(6):411-421. [EL 2; PCS]
307. **Lamon-Fava S, Wilson PW, Schaefer EJ.** Impact of body mass index on coronary heart disease risk factors in men and women. The Framingham Offspring Study. *Arterioscler Thromb Vasc Biol*. 1996;16(12):1509-1515. [EL 2; PCS]
308. **Larsson B, Svärdsudd K, Welin L, Wilhelmsen L, Björntorp P, Tibblin G.** Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br Med J (Clin Res Ed)*. 1984;288(6428): 1401-1404. [EL 2; PCS]
309. **Després JP, Lemieux I, Bergeron J, et al.** Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol*. 2008;28(6):1039-1049. [EL 4; NE]
310. **Paynter NP, Kiefe CI, Lewis CE, Loria CM, Goff DC, Lloyd-Jones DM.** Accumulation of metabolic cardiovascular risk factors in black and white young adults over 20 years. *J Am Heart Assoc*. 2015;4(4):10.1161/JAHA.114.001548. [EL 2; PCS]
311. **Ingelsson E, Massaro JM, Sutherland P, et al.** Contemporary trends in dyslipidemia in the Framingham Heart Study. *Arch Intern Med*. 2009;169(3):279-286. [EL 2; PCS]
312. **Appel LJ, Sacks FM, Carey VJ, et al.** Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA*. 2005;294(19):2455-2464. [EL 1; RCT, non-blinded]
313. **Bessembinders K, Wielders J, van de Wiel A.** Severe hypertriglyceridemia influenced by alcohol (SHIBA). *Alcohol Alcohol*. 2011;46(2):113-116. [EL 2; RCCS]
314. **Grundy SM, Brewer HB,Jr, Cleeman JI, Smith SC Jr, Lenfant C. American Heart Association, National Heart, Lung, and Blood Institute.** Definition of

metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004; 109(3):433-438. [EL 4; NE]

315. **Zambon A, Hokanson JE, Brown BG, Brunzell JD.** Evidence for a new pathophysiological mechanism for coronary artery disease regression: hepatic lipase-mediated changes in LDL density. *Circulation*. 1999; 99(15):1959-1964. [EL 1; RCT]
316. **St-Pierre AC, Cantin B, Dagenais GR, et al.** Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol*. 2005;25(3):553-559. [EL 2; PCS]
317. **Ip S, Lichtenstein AH, Chung M, Lau J, Balk EM.** Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. *Ann Intern Med*. 2009;150(7):474-484. [EL 2; MNRCT]
318. **Mora S, Szklo M, Otvos JD, et al.** LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;192(1):211-217. [EL 2; PCS]
319. **Hokanson JE, Austin MA.** Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3(2):213-219. [EL 2; MNRCT]
320. **Manninen V, Tenkanen L, Koskinen P, et al.** Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*. 1992;85(1):37-45. [EL 1; RCT]
321. **Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR.** High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med*. 1977;62(5):707-714. [EL 2; PCS]
322. **Pocock SJ, Shaper AG, Phillips AN.** Concentrations of high density lipoprotein cholesterol, triglycerides, and total cholesterol in ischaemic heart disease. *BMJ*. 1989;298(6679):998-1002. [EL 2; PCS]
323. **Gordon T, Kannel WB.** Multiple risk functions for predicting coronary heart disease: the concept, accuracy, and application. *Am Heart J*. 1982;103(6):1031-1039. [EL 4; NE]
324. **Kannel WB, McGee DL.** Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care*. 1979;2(2):120-126. [EL 2; PCS]
325. **Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR.** Diabetes, blood lipids, and the role of obesity in coronary heart disease risk for women. The Framingham study. *Ann Intern Med*. 1977;87(4):393-397. [EL 2; PCS]
326. **Jellinger PS, Smith DA, Mehta AE, et al.** American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract*. 2012;18 Suppl 1:1-78. [EL 4; NE]
327. **Jacobson TA, Ito MK, Maki KC, et al.** National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. *J Clin Lipidol*. 2014;8(5):473-488. [EL 4; NE]
328. **Ewald N, Hardt PD, Kloer HU.** Severe hypertriglyceridemia and pancreatitis: presentation and management. *Curr Opin Lipidol*. 2009;20(6):497-504. [EL 4; NE]
329. **Kotchen TA.** Obesity-related hypertension: epidemiology, pathophysiology, and clinical management. *Am J Hypertens*. 2010;23(11):1170-1178. [EL 4; NE]
330. **Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH.** The disease burden associated with overweight and obesity. *JAMA*. 1999;282(16):1523-1529. [EL 3; SS]
331. **Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB.** Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med*. 2002;162(16):1867-1872. [EL 2; PCS]
332. **Doll S, Paccaud F, Bovet P, Burnier M, Wietlisbach V.** Body mass index, abdominal adiposity and blood pressure: consistency of their association across developing and developed countries. *Int J Obes Relat Metab Disord*. 2002;26(1):48-57. [EL 3; SS]
333. **Mokdad AH, Ford ES, Bowman BA, et al.** Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289(1):76-79. [EL 3; SS]
334. **Tsujimoto T, Sairenchi T, Iso H, et al.** Impact of obesity on incident hypertension independent of weight gain among nonhypertensive Japanese: the Ibaraki Prefectural Health Study (IPHS). *J Hypertens*. 2012;30(6):1122-1128. [EL 2; PCS]
335. **Obesity in Asia Collaboration.** Is central obesity a better discriminator of the risk of hypertension than body mass index in ethnically diverse populations? *J Hypertens*. 2008;26(2):169-177. [EL 2; MNRCT]
336. **Nyamdorj R, Qiao Q, Lam TH, et al. Decoda Study Group.** BMI compared with central obesity indicators in relation to diabetes and hypertension in Asians. *Obesity*. 2008;16(7):1622-1635. [EL 3; CSS]
337. **Toyama M, Watanabe S, Miyauchi T, et al.** Diabetes and obesity are significant risk factors for morning hypertension: from Ibaraki Hypertension Assessment Trial (I-HAT). *Life Sci*. 2014;104(1-2):32-37. [EL 2; PCS]
338. **Mandal A.** Study of prevalence of type 2 diabetes mellitus and hypertension in overweight and obese people. *J Family Med Prim Care*. 2014;3(1):25-28. [EL 3; CSS]
339. **Chopra I, Kamal KM, Candrilli SD, Kanyongo G.** Association between obesity and therapeutic goal attainment in patients with concomitant hypertension and dyslipidemia. *Postgrad Med*. 2014;126(1):66-77. [EL 2; RCCS]
340. **Dreyer N, Dixon JB, Okerson T, Finkelstein EA, Globe D.** Prevalence of comorbidities and baseline characteristics of LAP-BAND AP(R) subjects in the Helping Evaluate Reduction in Obesity (HERO) study. *PLoS One*. 2013;8(11):e78971. [EL 2; PCS]
341. **Courcoulas AP, Christian NJ, Belle SH, et al.** Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. *JAMA*. 2013;310(22):2416-2425. [EL 2; PCS]
342. **Nordstrand N, Hertel JK, Hofsø D, et al.** A controlled clinical trial of the effect of gastric bypass surgery and intensive lifestyle intervention on nocturnal hypertension and the circadian blood pressure rhythm in patients with morbid obesity. *Surgery*. 2012;151(5):674-680. [EL 2; NRCT]
343. **Mostaedi R, Lackey DE, Adams SH, Dada SA, Hoda ZA, Ali MR.** Prevalence of undiagnosed and inadequately treated type 2 diabetes mellitus, hypertension, and dyslipidemia in morbidly obese patients who present for bariatric surgery. *Obes Surg*. 2014;24(6):927-935. [EL 2; RCCS]
344. **Lewis CE, McTigue KM, Burke LE, et al.** Mortality, health outcomes, and body mass index in the overweight range: a science advisory from the American Heart Association. *Circulation*. 2009;119(25):3263-3271. [EL 4; NE]

345. **Flegal KM, Graubard BI, Williamson DF, Gail MH.** Excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2005;293(15):1861-1867. [EL 3; SS]
346. **Flegal KM, Graubard BI, Williamson DF, Gail MH.** Impact of smoking and preexisting illness on estimates of the fractions of deaths associated with underweight, overweight, and obesity in the US population. *Am J Epidemiol*. 2007;166(8):975-982. [EL 3; CSS]
347. **Orpana HM, Berthelot JM, Kaplan MS, Feeny DH, McFarland B, Ross NA.** BMI and mortality: results from a national longitudinal study of Canadian adults. *Obesity (Silver Spring)*. 2010;18(1):214-218. [EL 3; CSS]
348. **Flegal KM, Graubard BI, Williamson DF, Gail MH.** Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2007;298(17):2028-2037. [EL 3; SS]
349. **Lawlor DA, Hart CL, Hole DJ, Davey Smith G.** Reverse causality and confounding and the associations of overweight and obesity with mortality. *Obesity (Silver Spring)*. 2006;14(12):2294-2304. [EL 2; MNRCT]
350. Poirier P. Adiposity and cardiovascular disease: are we using the right definition of obesity? *Eur Heart J*. 2007; 28(17):2047-2048. [EL 4; NE]
351. **Rosengren A, Wedel H, Wilhelmsen L.** Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. *Eur Heart J*. 1999;20(4):269-277. [EL 2; PCS]
352. **Manson JE, Willett WC, Stampfer MJ, et al.** Body weight and mortality among women. *N Engl J Med*. 1995; 333(11):677-685. [EL 2; PCS]
353. **Song YM, Sung J.** Body mass index and mortality: a twelve-year prospective study in Korea. *Epidemiology*. 2001;12(2):173-179. [EL 2; PCS]
354. **Shaper AG, Wannamethee SG, Walker M.** Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. *BMJ*. 1997;314(7090):1311-1317. [EL 2; PCS]
355. **Lee IM, Manson JE, Hennekens CH, Paffenbarger RS.** Body weight and mortality. A 27-year follow-up of middle-aged men. *JAMA*. 1993;270(23):2823-2828. [EL 2; PCS]
356. **Baik I, Ascherio A, Rimm EB, et al.** Adiposity and mortality in men. *Am J Epidemiol*. 2000;152(3):264-271. [EL 2; PCS]
357. **Poirier P, Giles TD, Bray GA, et al.** Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2006;113(6):898-918. [EL 4; NE]
358. **He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK.** Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med*. 2001;161(7):996-1002. [EL 3; SS]
359. **Kenchaiah S, Evans JC, Levy D, et al.** Obesity and the risk of heart failure. *N Engl J Med*. 2002;347(5):305-313. [EL 2; PCS]
360. **Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM.** Risk factors for heart failure in the elderly: a prospective community-based study. *Am J Med*. 1999;106(6):605-612. [EL 2; PCS]
361. **Wilhelmsen L, Rosengren A, Eriksson H, Lappas G.** Heart failure in the general population of men--morbidity, risk factors and prognosis. *J Intern Med*. 2001;249(3): 253-261. [EL 2; PCS]
362. **Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA.** Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J*. 2008;156(1):13-22. [EL 2; MNRCT]
363. **Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH.** The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol*. 2001;38(3):789-795. [EL 2; PCS]
364. **Lissin LW, Gauri AJ, Froelicher VF, Ghayoumi A, Myers J, Giacommini J.** The prognostic value of body mass index and standard exercise testing in male veterans with congestive heart failure. *J Card Fail*. 2002;8(4):206-215. [EL 2; PCS]
365. **Davos CH, Doehner W, Rauchhaus M, et al.** Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. *J Card Fail*. 2003;9(1):29-35. [EL 2; PCS]
366. **Lavie CJ, Osman AF, Milani RV, Mehra MR.** Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *Am J Cardiol*. 2003;91(7): 891-894. [EL 2; RCCS]
367. **Mosterd A, Cost B, Hoes AW, et al.** The prognosis of heart failure in the general population: The Rotterdam Study. *Eur Heart J*. 2001;22(15):1318-1327. [EL 2; PCS]
368. **Khalid U, Ather S, Bavishi C, et al.** Pre-morbid body mass index and mortality after incident heart failure: the ARIC Study. *J Am Coll Cardiol*. 2014;64(25):2743-2749. [EL 2; PCS]
369. **Curtis JP, Selter JG, Wang Y, et al.** The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med*. 2005;165(1):55-61. [EL 2; RCCS]
370. **Niedziela J, Hudzik B, Niedziela N, et al.** The obesity paradox in acute coronary syndrome: a meta-analysis. *Eur J Epidemiol*. 2014;29(11):801-812. [EL 2; MNRCT]
371. **Wang ZJ, Zhou YJ, Galper BZ, Gao F, Yeh RW, Mauri L.** Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: a systematic review and meta-analysis. *Heart*. 2015;101(20):1631-1638. [EL 2; MNRCT]
372. **Doehner W, Erdmann E, Cairns R, et al.** Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: an analysis of the PROactive study population. *Int J Cardiol*. 2012;162(1):20-26. [EL 1; RCT, post-hoc analysis]
373. **McEwen LN, Karter AJ, Waitzfelder BE, et al.** Predictors of mortality over 8 years in type 2 diabetic patients: Translating Research Into Action for Diabetes (TRIAD). *Diabetes Care*. 2012;35(6):1301-1309. [EL 3; SS]
374. **Carnethon MR, De Chavez PJ, Biggs ML, et al.** Association of weight status with mortality in adults with incident diabetes. *JAMA*. 2012;308(6):581-590. [EL 2; MNRCT]
375. **Logue J, Walker JJ, Leese G, et al.** Association between BMI measured within a year after diagnosis of type 2 diabetes and mortality. *Diabetes Care*. 2013;36(4):887-893. [EL 2; RCCS]
376. **Shah RV, Abbasi SA, Yamal JM, et al.** Impaired fasting glucose and body mass index as determinants of mortality in ALLHAT: is the obesity paradox real? *J Clin Hypertens (Greenwich)*. 2014;16(6):451-458. [EL 2; PCS]
377. **Preston SH, Stokes A.** Obesity paradox: conditioning on disease enhances biases in estimating the mortality risks of obesity. *Epidemiology*. 2014;25(3):454-461. [EL 4; NE]

378. **Lajous M, Banack HR, Kaufman JS, Hernan MA.** Should patients with chronic disease be told to gain weight? The obesity paradox and selection bias. *Am J Med*. 2015;128(4):334-336. [EL 4; NE]
379. **Browning JD, Szczepaniak LS, Dobbins R, et al.** Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology*. 2004; 40(6):1387-1395. [EL 3; CSS]
380. **Bellentani S, Scaglioni F, Marino M, Bedogni G.** Epidemiology of non-alcoholic fatty liver disease. *Dig Dis*. 2010;28(1):155-161. [EL 4; NE]
381. **Walker GE, Marzullo P, Ricotti R, Bona G, Prodam F.** The pathophysiology of abdominal adipose tissue depots in health and disease. *Horm Mol Biol Clin Investig*. 2014; 19(1):57-74. [EL 4; NE]
382. **Britton KA, Fox CS.** Ectopic fat depots and cardiovascular disease. *Circulation*. 2011;124(24):e837-41. [EL 4; NE]
383. **Marchesini G, Avagnina S, Barantani EG, et al.** Aminotransferase and gamma-glutamyltranspeptidase levels in obesity are associated with insulin resistance and the metabolic syndrome. *J Endocrinol Invest*. 2005; 28(4):333-339. [EL 2; PCS]
384. **Knaapen M, Kootte RS, Zoetendal EG, et al.** Obesity, non-alcoholic fatty liver disease, and atherothrombosis: a role for the intestinal microbiota? *Clin Microbiol Infect*. 2013;19(4):331-337. [EL 4; NE]
385. **Guerrerio AL, Colvin RM, Schwartz AK, et al.** Choline intake in a large cohort of patients with nonalcoholic fatty liver disease. *Am J Clin Nutr*. 2012;95(4):892-900. [EL 3; CSS]
386. **Green CJ, Hodson L.** The influence of dietary fat on liver fat accumulation. *Nutrients*. 2014;6(11):5018-5033. [EL 4; NE]
387. **Leslie T, Pawloski L, Kallman-Price J, et al.** Survey of health status, nutrition and geography of food selection of chronic liver disease patients. *Ann Hepatol*. 2014;13(5): 533-540. [EL 3; SS]
388. **Zeb I, Katz R, Nasir K, Ding J, Rezaeian P, Budoff MJ.** Relation of nonalcoholic fatty liver disease to the metabolic syndrome: the Multi-Ethnic Study of Atherosclerosis. *J Cardiovasc Comput Tomogr*. 2013; 7(5):311-318. [EL 3; CSS]
389. **Boza C, Riquelme A, Ibañez L, et al.** Predictors of nonalcoholic steatohepatitis (NASH) in obese patients undergoing gastric bypass. *Obes Surg*. 2005;15(8):1148-1153. [EL 2; PCS]
390. **Pagadala MR, McCullough AJ.** Non-alcoholic fatty liver disease and obesity: not all about body mass index. *Am J Gastroenterol*. 2012;107(12):1859-1861. [EL 4; NE]
391. **Kwon YM, Oh SW, Hwang SS, Lee C, Kwon H, Chung GE.** Association of nonalcoholic fatty liver disease with components of metabolic syndrome according to body mass index in Korean adults. *Am J Gastroenterol*. 2012;107(12):1852-1858. [EL 2; RCCS]
392. **Machado M, Marques-Vidal P, Cortez-Pinto H.** Hepatic histology in obese patients undergoing bariatric surgery. *J Hepatol*. 2006;45(4):600-606. [EL 2; MNRCT]
393. **Beymer C, Kowdley KV, Larson A, Edmonson P, Dellinger EP, Flum DR.** Prevalence and predictors of asymptomatic liver disease in patients undergoing gastric bypass surgery. *Arch Surg*. 2003;138(11):1240-1244. [EL 2; PCS, N = 48]
394. **Jones H, Sprung VS, Pugh CJ, et al.** Polycystic ovary syndrome with hyperandrogenism is characterized by an increased risk of hepatic steatosis compared to nonhyperandrogenic PCOS phenotypes and healthy controls, independent of obesity and insulin resistance. *J Clin Endocrinol Metab*. 2012;97(10):3709-3716. [EL 3; CSS, N = 51]
395. **Rockall AG, Sohaib SA, Evans D, et al.** Hepatic steatosis in Cushing's syndrome: a radiological assessment using computed tomography. *Eur J Endocrinol*. 2003;149(6): 543-548. [EL 2; PCS, N = 50]
396. **Tarantino G, Finelli C.** Pathogenesis of hepatic steatosis: the link between hypercortisolism and non-alcoholic fatty liver disease. *World J Gastroenterol*. 2013;19(40):6735-6743. [EL 4; NE]
397. **Lee S, Jin Kim Y, Yong Jeon T, et al.** Obesity is the only independent factor associated with ultrasound-diagnosed non-alcoholic fatty liver disease: a cross-sectional case-control study. *Scand J Gastroenterol*. 2006;41(5):566-572. [EL 3; CSS, N = 50]
398. **Dietrich P, Hellerbrand C.** Non-alcoholic fatty liver disease, obesity and the metabolic syndrome. *Best Pract Res Clin Gastroenterol*. 2014;28(4):637-653. [EL 4; NE]
399. **Stefan N, Machicao F, Staiger H, et al.** Polymorphisms in the gene encoding adiponectin receptor 1 are associated with insulin resistance and high liver fat. *Diabetologia*. 2005;48(11):2282-2291. [EL 2; PCS]
400. **Parola M, Marra F.** Adipokines and redox signaling: impact on fatty liver disease. *Antioxid Redox Signal*. 2011;15(2):461-483. [EL 4; NE]
401. **Yoo HJ, Hwang SY, Cho GJ, et al.** Association of glypican-4 with body fat distribution, insulin resistance, and nonalcoholic fatty liver disease. *J Clin Endocrinol Metab*. 2013;98(7):2897-2901. [EL 3; CSS]
402. **Carazo A, Leon J, Casado J, et al.** Hepatic expression of adiponectin receptors increases with non-alcoholic fatty liver disease progression in morbid obesity in correlation with glutathione peroxidase 1. *Obes Surg*. 2011;21(4): 492-500. [EL 2; PCS]
403. **Koliaki C, Roden M.** Hepatic energy metabolism in human diabetes mellitus, obesity and non-alcoholic fatty liver disease. *Mol Cell Endocrinol*. 2013;379(1-2):35-42. [EL 4; NE]
404. **Ruiz JR, Lasa A, Simon E, Larrarte E, Labayen I.** Lower plasma NAMPT/visfatin levels are associated with impaired hepatic mitochondrial function in non-diabetic obese women: a potential link between obesity and non-alcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis*. 2012;22(2):e1-e2. [EL 2; PCS, N = 38]
405. **Paradies G, Paradies V, Ruggiero FM, Petrosillo G.** Oxidative stress, cardiolipin and mitochondrial dysfunction in nonalcoholic fatty liver disease. *World J Gastroenterol*. 2014;20(39):14205-14218. [EL 4; NE]
406. **Gusdon AM, Song KX, Qu S.** Nonalcoholic fatty liver disease: pathogenesis and therapeutics from a mitochondria-centric perspective. *Oxid Med Cell Longev*. 2014;2014:637027. [EL 4; NE]
407. **Fracanzani AL, Valenti L, Russello M, et al.** Gallstone disease is associated with more severe liver damage in patients with non-alcoholic fatty liver disease. *PLoS One*. 2012;7(7):e41183. [EL 3; CSS]
408. **Simonen P, Kotronen A, Hallikainen M, et al.** Cholesterol synthesis is increased and absorption decreased in non-alcoholic fatty liver disease independent of obesity. *J Hepatol*. 2011;54(1):153-159. [EL 2; PCS]
409. **Nakahara T, Hyogo H, Yoneda M, et al.** Type 2 diabetes mellitus is associated with the fibrosis severity in

patients with nonalcoholic fatty liver disease in a large retrospective cohort of Japanese patients. *J Gastroenterol*. 2014;49(11):1477-1484. [EL 3; CSS]

410. **Tamura Y, Tanaka Y, Sato F, et al.** Effects of diet and exercise on muscle and liver intracellular lipid contents and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2005;90(6):3191-3196. [EL 2; NRCT, N = 14]
411. **Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI.** Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes*. 2005;54(3):603-608. [EL 2; NRCT, N = 8]
412. **Larson-Meyer DE, Heilbronn LK, Redman LM, et al.** Effect of calorie restriction with or without exercise on insulin sensitivity, beta-cell function, fat cell size, and ectopic lipid in overweight subjects. *Diabetes Care*. 2006;29(6):1337-1344. [EL 2; NRCT, N = 48]
413. **Thomas EL, Brynes AE, Hamilton G, et al.** Effect of nutritional counselling on hepatic, muscle and adipose tissue fat content and distribution in non-alcoholic fatty liver disease. *World J Gastroenterol*. 2006;12(36):5813-5819. [EL 2; PCS, N = 10]
414. **Chalasani N, Younossi Z, Lavine JE, et al.** The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Am J Gastroenterol*. 2012;107(6):811-826. [EL 4; NE]
415. **Kunde SS, Lazenby AJ, Clements RH, Abrams GA.** Spectrum of NAFLD and diagnostic implications of the proposed new normal range for serum ALT in obese women. *Hepatology*. 2005;42(3):650-656. [EL 3; CSS]
416. **Marchesini G, Bugianesi E, Forlani G, et al.** Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology*. 2003;37(4):917-923. [EL 2; PCS]
417. **Ryan MC, Wilson AM, Slavin J, Best JD, Jenkins AJ, Desmond PV.** Associations between liver histology and severity of the metabolic syndrome in subjects with nonalcoholic fatty liver disease. *Diabetes Care*. 2005; 28(5):1222-1224. [EL 2; PCS, N = 46]
418. **Leite NC, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR.** Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. *Liver Int*. 2009;29(1):113-119. [EL 3; CSS]
419. **Vernon G, Baranova A, Younossi ZM.** Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther.* 2011; 34(3):274-285. [EL 2; MNRCT]
420. **Musso G, Gambino R, Cassader M, Pagano G.** Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 2011;43(8):617-649. [EL 2; MNRCT]
421. **Wieckowska A, McCullough AJ, Feldstein AE.** Noninvasive diagnosis and monitoring of nonalcoholic steatohepatitis: present and future. *Hepatology*. 2007; 46(2):582-589. [EL 4; NE]
422. **Angulo P, Hui JM, Marchesini G, et al.** The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology*. 2007;45(4): 846-854. [EL 3; SS]
423. **Lichtinghagen R, Pietsch D, Bantel H, Manns MP, Brand K, Bahr MJ.** The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values. *J Hepatol*. 2013;59(2):236-242. [EL 3; SS]
424. **Yang ZH, Yang SX, Qin CZ, Chen YX.** Clinical values of elevated serum cytokeratin-18 levels in hepatitis: a meta-analysis. *Hepat Mon*. 2015;15(5):e25328. [EL 2; MNRCT]
425. **Lin YC, Chang PF, Chang MH, Ni YH.** A common variant in the peroxisome proliferator-activated receptor-gamma coactivator-1alpha gene is associated with non-alcoholic fatty liver disease in obese children. *Am J Clin Nutr*. 2013;97(2):326-331. [EL 3; SS]
426. **Lin YC, Chang PF, Chang MH, Ni YH.** Genetic variants in GCKR and PNPLA3 confer susceptibility to nonalcoholic fatty liver disease in obese individuals. *Am J Clin Nutr*. 2014;99(4):869-874. [EL 3; SS]
427. **Yoo HJ, Park MS, Lee CH, et al.** Cutoff points of abdominal obesity indices in screening for non-alcoholic fatty liver disease in Asians. *Liver Int*. 2010;30(8):1189-1196. [EL 3; CSS]
428. **Venkatesh SK, Yin M, Ehman RL.** Magnetic resonance elastography of liver: technique, analysis, and clinical applications. *J Magn Reson Imaging*. 2013;37(3):544-555. [EL 4; NE]
429. **Ferraioli G, Filice C, Castera L, et al.** WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 3: liver. *Ultrasound Med Biol*. 2015;41(5):1161-1179. [EL 4; NE]
430. **Barr RG, Ferraioli G, Palmeri ML, et al.** Elastography assessment of liver fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. *Radiology*. 2015;276(3):845-861. [EL 4; NE]
431. **Pérez-Gutiérrez OZ, Hernández-Rocha C, Candia-Balboa RA, et al.** Validation study of systems for non-invasive diagnosis of fibrosis in nonalcoholic fatty liver disease in Latin population. *Ann Hepatol*. 2013; 12(3):416-424. [EL 3; SS]
432. **Wong VW, Wong GL, Yeung DK, et al.** Fatty pancreas, insulin resistance, and beta-cell function: a population study using fat-water magnetic resonance imaging. *Am J Gastroenterol*. 2014;109(4):589-597. [EL 3; CSS]
433. **Moore JB.** Non-alcoholic fatty liver disease: the hepatic consequence of obesity and the metabolic syndrome. *Proc Nutr Soc*. 2010;69(2):211-220. [EL 4; NE]
434. **Lim SS, Davies MJ, Norman RJ, Moran LJ.** Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18(6):618-637. [EL 2; MNRCT]
435. **Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO.** The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*. 2004;89(6):2745-2749. [EL 3; CSS]
436. **Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R.** Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab*. 1998;83(9):3078-3082. [EL 3; CSS]
437. **Diamanti-Kandarakis E, Kouli CR, Bergiele AT, et al.** A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. *J Clin Endocrinol Metab*. 1999;84(11):4006-4011. [EL 3; CSS]
438. **Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF.** A prospective study of the prevalence of the polycystic ovary syndrome in unselected

Caucasian women from Spain. *J Clin Endocrinol Metab*. 2000;85(7):2434-2438. [EL 2; PCS]

439. **March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ.** The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod*. 2010;25(2): 544-551. [EL 3; CSS]
440. **Tehrani FR, Simbar M, Tohidi M, Hosseinpanah F, Azizi F.** The prevalence of polycystic ovary syndrome in a community sample of Iranian population: Iranian PCOS prevalence study. *Reprod Biol Endocrinol*. 2011;9:39. [EL 3; CSS]
441. **Legro RS, Arslanian SA, Ehrmann DA, et al.** Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98(12):4565-4592. [EL 4; NE]
442. **Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group.** Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*. 2004; 19(1):41-47. [EL 4; NE]
443. **Salehi M, Bravo-Vera R, Sheikh A, Gouller A, Poretsky L.** Pathogenesis of polycystic ovary syndrome: what is the role of obesity? *Metabolism*. 2004;53(3):358-376. [EL 4; NE]
444. **Ehrmann DA.** Polycystic ovary syndrome. *N Engl J Med*. 2005;352(12):1223-1236. [EL 4; NE]
445. **Carmina E, Legro RS, Stamets K, Lowell J, Lobo RA.** Difference in body weight between American and Italian women with polycystic ovary syndrome: influence of the diet. *Hum Reprod*. 2003;18(11):2289-2293. [EL 2; PCS]
446. **Pasquali R.** Obesity, fat distribution and infertility. *Maturitas*. 2006;54(4):363-371. [EL 4; NE]
447. **Lim SS, Norman RJ, Davies MJ, Moran LJ.** The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. *Obes Rev*. 2013;14(2):95-109. [EL 2; MNRCT]
448. **Barber TM, McCarthy MI, Wass JA, Franks S.** Obesity and polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2006;65(2):137-145. [EL 4; NE]
449. **Kiddy DS, Sharp PS, White DM, et al.** Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. *Clin Endocrinol*. 1990; 32(2):213-220. [EL 2; PCS]
450. **Buyalos RP, Pekonen F, Halme JK, Judd HL, Rutanen EM.** The relationship between circulating androgens, obesity, and hyperinsulinemia on serum insulin-like growth factor binding protein-1 in the polycystic ovarian syndrome. *Am J Obstet Gynecol*. 1995;172(3):932-939. [EL 2; PCS, N = 36]
451. **Cupisti S, Dittrich R, Binder H, et al.** Influence of body mass index on measured and calculated androgen parameters in adult women with Hirsutism and PCOS. *Exp Clin Endocrinol Diabetes*. 2007;115(6):380-386. [EL 3; CSS]
452. **Economou F, Xyrafis X, Livadas S, et al.** In overweight/obese but not in normal-weight women, polycystic ovary syndrome is associated with elevated liver enzymes compared to controls. *Hormones (Athens)*. 2009;8(3): 199-206. [EL 2; PCS]
453. **Castelo-Branco C, Steinvarcel F, Osorio A, Ros C, Balasch J.** Atherogenic metabolic profile in PCOS patients: role of obesity and hyperandrogenism. *Gynecol Endocrinol*. 2010;26(10):736-742. [EL 2; PCS, case-controlled]
454. **Hahn S, Tan S, Sack S, et al.** Prevalence of the metabolic syndrome in German women with polycystic ovary syndrome. *Exp Clin Endocrinol Diabetes*. 2007;115(2): 130-135. [EL 3; CSS]
455. **Barcellos CR, Rocha MP, Hayashida SA, Mion Junior D, Lage SG, Marcondes JA.** Impact of body mass index on blood pressure levels in patients with polycystic ovary syndrome. *Arq Bras Endocrinol Metabol*. 2007;51(7): 1104-1109. [EL 2; RCCS]
456. **Marsden PJ, Murdoch AP, Taylor R.** Tissue insulin sensitivity and body weight in polycystic ovary syndrome. *Clin Endocrinol*. 2001;55(2):191-199. [EL 3; SS, N = 20]
457. **Conway GS, Agrawal R, Betteridge DJ, Jacobs HS.** Risk factors for coronary artery disease in lean and obese women with the polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 1992;37(2):119-125. [EL 2; PCS]
458. **Yildiz BO, Knochenhauer ES, Azziz R.** Impact of obesity on the risk for polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;93(1):162-168. [EL 2; RCCS]
459. **Sharifi F, Hajihosseini R, Mazloomi S, Amirmogaddami H, Nazem H.** Decreased adiponectin levels in polycystic ovary syndrome, independent of body mass index. *Metab Syndr Relat Disord*. 2010;8(1):47-52. [EL 2; PCS, case-controlled]
460. **Liou TH, Yang JH, Hsieh CH, Lee CY, Hsu CS, Hsu MI.** Clinical and biochemical presentations of polycystic ovary syndrome among obese and nonobese women. *Fertil Steril*. 2009;92(6):1960-1965. [EL 2; RCCS]
461. **Lee H, Oh JY, Sung YA, Chung H, Cho WY.** The prevalence and risk factors for glucose intolerance in young Korean women with polycystic ovary syndrome. *Endocrine*. 2009;36(2):326-332. [EL 2; PCS]
462. **Cheung LP, Ma RC, Lam PM, et al.** Cardiovascular risks and metabolic syndrome in Hong Kong Chinese women with polycystic ovary syndrome. *Hum Reprod*. 2008;23(6):1431-1438. [EL 3; CSS]
463. **Cupisti S, Kajaia N, Dittrich R, Duezenli H, W Beckmann M, Mueller A.** Body mass index and ovarian function are associated with endocrine and metabolic abnormalities in women with hyperandrogenic syndrome. *Eur J Endocrinol*. 2008;158(5):711-719. [EL 2; PCS]
464. **van der Steeg JW, Steures P, Eijkemans MJ, et al.** Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Hum Reprod*. 2008;23(2): 324-328. [EL 2; PCS]
465. **Rich-Edwards JW, Spiegelman D, Garland M, et al.** Physical activity, body mass index, and ovulatory disorder infertility. *Epidemiology*. 2002;13(2):184-190. [EL 2; PCS]
466. **Gesink Law DC, Maclehose RF, Longnecker MP.** Obesity and time to pregnancy. *Hum Reprod*. 2007;22(2): 414-420. [EL 2; PCS]
467. **Rich-Edwards JW, Goldman MB, Willett WC, et al.** Adolescent body mass index and infertility caused by ovulatory disorder. *Am J Obstet Gynecol*. 1994;171(1): 171-177. [EL 2; PCS]
468. **Green BB, Weiss NS, Daling JR.** Risk of ovulatory infertility in relation to body weight. *Fertil Steril*. 1988; 50(5):721-726. [EL 2; RCCS]
469. **Wise LA, Rothman KJ, Mikkelsen EM, Sørensen HT, Riis A, Hatch EE.** An internet-based prospective study of body size and time-to-pregnancy. *Hum Reprod*. 2010; 25(1):253-264. [EL 2; PCS]
470. **Hassan MA, Killick SR.** Negative lifestyle is associated with a significant reduction in fecundity. *Fertil Steril*. 2004;81(2):384-392. [EL 2; PCS]

471. **Bolúmar F, Olsen J, Rebagliato M, Sáez-Lloret I, Bisanti L.** Body mass index and delayed conception: a European multicenter study on infertility and subfecundity. *Am J Epidemiol*. 2000;151(11):1072-1079. [EL 2; PCS]
472. **Grodstein F, Goldman MB, Cramer DW.** Body mass index and ovulatory infertility. *Epidemiology*. 1994;5(2): 247-250. [EL 2; PCS, case-controlled]
473. **Jensen TK, Scheike T, Keiding N, Schaumburg I, Grandjean P.** Fecundability in relation to body mass and menstrual cycle patterns. *Epidemiology*. 1999;10(4):422-428. [EL 2; RCCS]
474. **Boots C, Stephenson MD.** Does obesity increase the risk of miscarriage in spontaneous conception: a systematic review. *Semin Reprod Med*. 2011;29(6):507-513. [EL 2; MNRCT]
475. **Luke B, Brown MB, Missmer SA, et al.** The effect of increasing obesity on the response to and outcome of assisted reproductive technology: a national study. *Fertil Steril*. 2011;96(4):820-825. [EL 2; RCCS]
476. **Luke B, Brown MB, Stern JE, et al.** Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. *Hum Reprod*. 2011;26(1): 245-252. [EL 3; SS]
477. **Lintsen AM, Pasker-de Jong PC, de Boer EJ, et al.** Effects of subfertility cause, smoking and body weight on the success rate of IVF. *Hum Reprod*. 2005;20(7):1867-1875. [EL 2; PCS]
478. **Bellver J, Ayllón Y, Ferrando M, et al.** Female obesity impairs in vitro fertilization outcome without affecting embryo quality. *Fertil Steril*. 2010;93(2):447-454. [EL 2; RCCS]
479. **Wang JX, Davies M, Norman RJ.** Body mass and probability of pregnancy during assisted reproduction treatment: retrospective study. *BMJ*. 2000;321(7272): 1320-1321. [EL 2; RCCS]
480. **Wittemer C, Ohl J, Bailly M, Bettahar-Lebugle K, Nisand I.** Does body mass index of infertile women have an impact on IVF procedure and outcome? *J Assist Reprod Genet*. 2000;17(10):547-552. [EL 2; RCCS]
481. **Dechaud H, Anahory T, Reyftmann L, Loup V, Hamamah S, Hedon B.** Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer. *Eur J Obstet Gynecol Reprod Biol*. 2006;127(1):88-93. [EL 2; RCCS]
482. **Fedorcsák P, Dale PO, Storeng R, et al.** Impact of overweight and underweight on assisted reproduction treatment. *Hum Reprod*. 2004;19(11):2523-2528. [EL 2; RCCS]
483. **Fedorcsák P, Storeng R, Dale PO, Tanbo T, Abyholm T.** Obesity is a risk factor for early pregnancy loss after IVF or ICSI. *Acta Obstet Gynecol Scand*. 2000;79(1):43-48. [EL 2; RCCS]
484. **Wattanakumtornkul S, Damario MA, Stevens Hall SA, Thornhill AR, Tummon IS.** Body mass index and uterine receptivity in the oocyte donation model. *Fertil Steril*. 2003;80(2):336-340. [EL 2; RCCS]
485. **Winter E, Wang J, Davies MJ, Norman R.** Early pregnancy loss following assisted reproductive technology treatment. *Hum Reprod*. 2002;17(12):3220-3223. [EL 2; RCCS]
486. **Loveland JB, McClamrock HD, Malinow AM, Sharara FI.** Increased body mass index has a deleterious effect on in vitro fertilization outcome. *J Assist Reprod Genet*. 2001;18(7):382-386. [EL 2; RCCS]
487. **Metwally M, Ong KJ, Ledger WL, Li TC.** Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril*. 2008;90(3):714-726. [EL 2; MNRCT]
488. **Lashen H, Ledger W, Bernal AL, Barlow D.** Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization. *Hum Reprod*. 1999;14(3):712-715. [EL 2; RCCS]
489. **Roth D, Grazi RV, Lobel SM.** Extremes of body mass index do not affect first-trimester pregnancy outcome in patients with infertility. *Am J Obstet Gynecol*. 2003; 188(5):1169-1170. [EL 2; RCCS]
490. **Metwally M, Li TC, Ledger WL.** The impact of obesity on female reproductive function. *Obes Rev*. 2007;8(6): 515-523. [EL 4; NE]
491. **Spicer LJ.** Leptin: a possible metabolic signal affecting reproduction. *Domest Anim Endocrinol*. 2001;21(4):251-270. [EL 4; NE]
492. **Moschos S, Chan JL, Mantzoros CS.** Leptin and reproduction: a review. *Fertil Steril*. 2002;77(3):433-444. [EL 4; NE]
493. **Gil-Campos M, Canete RR, Gil A.** Adiponectin, the missing link in insulin resistance and obesity. *Clin Nutr*. 2004;23(5):963-974. [EL 4; NE]
494. **Billig H, Chun SY, Eisenhauer K, Hsueh AJ.** Gonadal cell apoptosis: hormone-regulated cell demise. *Hum Reprod Update*. 1996;2(2):103-117. [EL 4; NE]
495. **Tajar A, Forti G, O'Neill TW, et al.** Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *J Clin Endocrinol Metab*. 2010;95(4):1810-1818. [EL 2; PCS]
496. **Camacho EM, Huhtaniemi IT, O'Neill TW, et al.** Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *Eur J Endocrinol*. 2013;168(3):445-455. [EL 2; PCS]
497. **Selvin E, Feinleib M, Zhang L, et al.** Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care*. 2007;30(2):234-238. [EL 3; SS]
498. **Pasquali R, Macor C, Vicennati V, et al.** Effects of acute hyperinsulinemia on testosterone serum concentrations in adult obese and normal-weight men. *Metabolism*. 1997; 46(5):526-529. [EL 2; PCS, N = 20]
499. **Pitteloud N, Hardin M, Dwyer AA, et al.** Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *J Clin Endocrinol Metab*. 2005;90(5):2636-2641. [EL 2; PCS, N = 21]
500. **Isidori AM, Caprio M, Strollo F, et al.** Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. *J Clin Endocrinol Metab*. 1999;84(10):3673-3680. [EL 2; PCS, N = 38]
501. **Mah PM, Wittert GA.** Obesity and testicular function. *Mol Cell Endocrinol*. 2010;316(2):180-186. [EL 4; NE]
502. **Oh JY, Barrett-Connor E, Wedick NM, Wingard DL, Rancho Bernardo Study.** Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. *Diabetes Care*. 2002; 25(1):55-60. [EL 2; PCS]
503. **Kaplan SA, Meehan AG, Shah A.** The age related decrease in testosterone is significantly exacerbated in obese men with the metabolic syndrome. What are the

implications for the relatively high incidence of erectile dysfunction observed in these men? *J Urol*. 2006;176(4 Pt 1):1524-1527. [EL 2; MNRCT]

504. **Araujo AB, O'Donnell AB, Brambilla DJ, et al.** Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab*. 2004;89(12): 5920-5926. [EL 2; PCS]
505. **Araujo AB, Esche GR, Kupelian V, et al.** Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab*. 2007;92(11):4241-4247. [EL 3; SS]
506. **Wu FC, Tajar A, Beynon JM, et al.** Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med*. 2010;363(2):123-135. [EL 2; PCS]
507. **Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C.** Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract*. 2006;60(7):762-769. [EL 3; CSS]
508. **Haring R, Ittermann T, Völzke H, et al.** Prevalence, incidence and risk factors of testosterone deficiency in a population-based cohort of men: results from the study of health in Pomerania. *Aging Male*. 2010;13(4):247-257. [EL 2; PCS]
509. **Ganesh HK, Vijaya Sarathi HA, George J, et al.** Prevalence of hypogonadism in patients with type 2 diabetes mellitus in an Asian Indian study group. *Endocr Pract*. 2009;15(6):513-520. [EL 2; PCS, case-controlled]
510. **Kaplan SA, Lee JY, O'Neill EA, Meehan AG, Kusek JW.** Prevalence of low testosterone and its relationship to body mass index in older men with lower urinary tract symptoms associated with benign prostatic hyperplasia. *Aging Male*. 2013;16(4):169-172. [EL 3; CSS]
511. **Pellitero S, Olaizola I, Alastrue A, et al.** Hypogonadotropic hypogonadism in morbidly obese males is reversed after bariatric surgery. *Obes Surg*. 2012; 22(12):1835-1842. [EL 2; PCS, N = 33 men]
512. **Ippersiel V, Lepot A, Gruson D, et al.** Hypogonadotropic hypogonadism among a population of obese men: prevalence, risk factors and reversibility after weight loss induced by bariatric surgery. *e-SPEN Journal*. 2013;8(2): e37-e43. [EL 2; PCS, only 21 of 75 patients studied in follow-up]
513. **Corona G, Rastrelli G, Maggi M.** Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes. *Best Pract Res Clin Endocrinol Metab*. 2013;27(4):557-579. [EL 2; MNRCT]
514. **Corona G, Mannucci E, Fisher AD, et al.** Low levels of androgens in men with erectile dysfunction and obesity. *J Sex Med*. 2008;5(10):2454-2463. [EL 3; CCS]
515. **Corona G, Monami M, Rastrelli G, et al.** Type 2 diabetes mellitus and testosterone: a meta-analysis study. *Int J Androl*. 2011;34(6 Pt 1):528-540. [EL 2; MRCT, subanalysis of RCTs included]
516. **Dhindsa S, Miller MG, McWhirter CL, et al.** Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care*. 2010;33(6):1186-1192. [EL 3; CSS]
517. **Kelly DM, Jones TH.** Testosterone: a metabolic hormone in health and disease. *J Endocrinol*. 2013;217(3): R25-R45. [EL 4; NE]
518. **Saad F, Yassin A, Doros G, Haider A.** Effects of long-term treatment with testosterone on weight and waist size in 411 hypogonadal men with obesity classes I-III: observational data from two registry studies. *Int J Obes (Lond)*. 2015;40(1):162-170. [EL 3; SS]
519. **Bhasin S, Cunningham GR, Hayes FJ, et al. Task Force, Endocrine Society.** Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95(6):2536-2559. [EL 4; NE]
520. **Young T, Evans L, Finn L, Palta M.** Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep*. 1997;20(9):705-706. [EL 3; SS]
521. **Peppard PE, Young T, Palta M, Dempsey J, Skatrud J.** Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000;284(23):3015-3021. [EL 2; PCS]
522. **Foster GD, Sanders MH, Millman R, et al.** Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care*. 2009;32(6):1017-1019. [EL 3; CSS]
523. **Young T, Peppard PE, Gottlieb DJ.** Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165(9):1217-1239. [EL 4; NE]
524. **Wolk R, Shamsuzzaman AS, Somers VK.** Obesity, sleep apnea, and hypertension. *Hypertension*. 2003;42(6): 1067-1074. [EL 4; NE]
525. **Young T, Skatrud J, Peppard PE.** Risk factors for obstructive sleep apnea in adults. *JAMA*. 2004;291(16): 2013-2016. [EL 4; NE]
526. **Young T, Peppard PE, Taheri S.** Excess weight and sleep-disordered breathing. *J Appl Physiol (1985)*. 2005;99(4): 1592-1599. [EL 4; NE]
527. **Taheri S.** The link between short sleep duration and obesity: we should recommend more sleep to prevent obesity. *Arch Dis Child*. 2006;91(11):881-884. [EL 4; NE]
528. **Watanabe M, Kikuchi H, Tanaka K, Takahashi M.** Association of short sleep duration with weight gain and obesity at 1-year follow-up: a large-scale prospective study. *Sleep*. 2010;33(2):161-167. [EL 2; PCS]
529. **Xiao Q, Arem H, Moore SC, Hollenbeck AR, Matthews CE.** A large prospective investigation of sleep duration, weight change, and obesity in the NIH-AARP Diet and Health Study cohort. *Am J Epidemiol*. 2013;178(11): 1600-1610. [EL 2; PCS]
530. **Holliday EG, Magee CA, Kritharides L, Banks E, Attia J.** Short sleep duration is associated with risk of future diabetes but not cardiovascular disease: a prospective study and meta-analysis. *PLoS One*. 2013;8(11):e82305. [EL 2; PCS]
531. **McNeil J, Doucet É, Chaput JP.** Inadequate sleep as a contributor to obesity and type 2 diabetes. *Can J Diabetes*. 2013;37(2):103-108. [EL 4; NE]
532. **Sabanayagam C, Shankar A.** Sleep duration and cardiovascular disease: results from the National Health Interview Survey. *Sleep*. 2010;33(8):1037-1042. [EL 3; CCS]
533. **Grandner MA, Chakravorty S, Perlis ML, Oliver L, Gurubhagavatula I.** Habitual sleep duration associated with self-reported and objectively determined cardiometabolic risk factors. *Sleep Med*. 2014;15(1):42-50. [EL 3; CSS]
534. **Grandner MA, Hale L, Moore M, Patel NP.** Mortality associated with short sleep duration: The evidence, the possible mechanisms, and the future. *Sleep Med Rev*. 2010;14(3):191-203. [EL 4; NE]
535. **Grandner MA, Patel NP.** From sleep duration to mortality: implications of meta-analysis and future directions. *J Sleep Res*. 2009;18(2):145-147. [EL 4; NE]

536. **Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM.** Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177(9):1006-1014. [EL 2; PCS, post-hoc modeling]
537. **Silber MH, Ancoli-Israel S, Bonnet MH, et al.** The visual scoring of sleep in adults. *J Clin Sleep Med*. 2007; 3(2):121-131. [EL 4; NE]
538. **Knutson KL, Turek FW.** The U-shaped association between sleep and health: the 2 peaks do not mean the same thing. *Sleep*. 2006;29(7):878-879. [EL 4; NE]
539. **Engeda J, Mezuk B, Ratliff S, Ning Y.** Association between duration and quality of sleep and the risk of pre-diabetes: evidence from NHANES. *Diabet Med*. 2013; 30(6):676-680. [EL 3; SS]
540. **Taheri S, Lin L, Austin D, Young T, Mignot E.** Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med*. 2004;1(3):e62. [EL 2; PCS]
541. **Chaput JP, Després JP, Bouchard C, Tremblay A.** Short sleep duration is associated with reduced leptin levels and increased adiposity: results from the Quebec family study. *Obesity (Silver Spring)*. 2007;15(1):253-261. [EL 3; CCS]
542. **Patel SR, Malhotra A, White DP, Gottlieb DJ, Hu FB.** Association between reduced sleep and weight gain in women. *Am J Epidemiol*. 2006;164(10):947-954. [EL 2; PCS]
543. **Pillar G, Shehadeh N.** Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care*. 2008;31 Suppl 2: S303-S309. [EL 4; NE]
544. **Peppard PE, Young T, Palta M, Skatrud J.** Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342(19): 1378-1384. [EL 2; PCS]
545. **Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP.** Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J*. 2004;25(9):735-741. [EL 2; PCS]
546. **Hiestand DM, Britz P, Goldman M, Phillips B.** Prevalence of symptoms and risk of sleep apnea in the US population: results from the national sleep foundation sleep in America 2005 poll. *Chest*. 2006;130(3):780-786. [EL 3; SS]
547. **Partinen M, Guilleminault C.** Daytime sleepiness and vascular morbidity at seven-year follow-up in obstructive sleep apnea patients. *Chest*. 1990;97(1):27-32. [EL 3; SS]
548. **Tuomilehto H, Peltonen M, Partinen M, et al.** Sleep-disordered breathing is related to an increased risk for type 2 diabetes in middle-aged men, but not in women--the FIN-D2D survey. *Diabetes Obes Metab*. 2008;10(6):468-475. [EL 3; CSS]
549. **Finn L, Young T, Palta M, Fryback DG.** Sleep-disordered breathing and self-reported general health status in the Wisconsin Sleep Cohort Study. *Sleep*. 1998;21(7):701-706. [EL 3; CSS]
550. **Punjabi NM, Caffo BS, Goodwin JL, et al.** Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med*. 2009;6(8):e1000132. [EL 2; PCS]
551. **de Lecea L, Kilduff TS, Peyron C, et al.** The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci U S A*. 1998;95(1):322-327. [EL 4; NE]
552. **Sakurai T, Amemiya A, Ishii M, et al.** Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*. 1998;92(4):573-585. [EL 4; NE]
553. **Nixon JP, Mavanji V, Butterick TA, Billington CJ, Kotz CM, Teske JA.** Sleep disorders, obesity, and aging: the role of orexin. *Ageing Res Rev*. 2015;20:63-73. [EL 4; NE]
554. **Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T.** Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. *Arch Intern Med*. 2005;165(20):2408-2413. [EL 2; PCS]
555. **Tuomilehto H, Seppä J, Uusitupa M.** Obesity and obstructive sleep apnea--clinical significance of weight loss. *Sleep Med Rev*. 2013;17(5):321-329. [EL 4; NE]
556. **Ford ES.** The epidemiology of obesity and asthma. *J Allergy Clin Immunol*. 2005;115(5):897-909. [EL 4; NE]
557. **Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F.** Body mass index and asthma severity in the National Asthma Survey. *Thorax*. 2008;63(1):14-20. [EL 3; SS]
558. **Popkin BM.** Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. *Am J Clin Nutr*. 2006;84(2):289-298. [EL 4; NE]
559. **Akerman MJ, Calacanis CM, Madsen MK.** Relationship between asthma severity and obesity. *J Asthma*. 2004; 41(5):521-526. [EL 3; SS]
560. **Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM.** Influence of body mass index on the response to asthma controller agents. *Eur Respir J*. 2006;27(3):495-503. [EL 3; retrospective analysis of 4 PRCT]
561. **Sutherland ER, Lehman EB, Teodorescu M, Wechsler ME. National Heart, Lung, and Blood Institute's Asthma Clinical Research Network.** Body mass index and phenotype in subjects with mild-to-moderate persistent asthma. *J Allergy Clin Immunol*. 2009;123(6): 1328-1334. [EL 3; SS]
562. **Camargo CA, Boulet LP, Sutherland ER, et al.** Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. *J Asthma*. 2010;47(1):76-82. [EL 3; retrospective analysis of 4 PRCT]
563. **Telenga ED, Tideman SW, Kerstjens HA, et al.** Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. *Allergy*. 2012;67(8):1060-1068. [EL 3; retrospective analysis of cohorts]
564. **Beuther DA, Sutherland ER.** Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med*. 2007; 175(7):661-666. [EL 2; MNRCT]
565. **Camargo CA, Weiss ST, Zhang S, Willett WC, Speizer FE.** Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med*. 1999;159(21):2582-2588. [EL 2; PCS]
566. **Chen Y, Dales R, Tang M, Krewski D.** Obesity may increase the incidence of asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. *Am J Epidemiol*. 2002;155(3):191-197. [EL 3; SS]
567. **Gunnbjörnsdóttir MI, Omenaas E, Gíslason T, et al.** Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms. *Eur Respir J*. 2004;24(1):116-121. [EL 3; SS]
568. **Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M.** Incidence and prevalence of asthma among adult Finnish men and women of the Finnish Twin Cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. *Chest*. 1999;115(4):928-936. [EL 2; PCS]

569. **Nystad W, Meyer HE, Nafstad P, Tverdal A, Engeland A.** Body mass index in relation to adult asthma among 135,000 Norwegian men and women. *Am J Epidemiol*. 2004;160(10):969-976. [EL 2; PCS]
570. **Romieu I, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F.** Body mass index, change in body silhouette, and risk of asthma in the E3N cohort study. *Am J Epidemiol*. 2003;158(2):165-174. [EL 2; PCS]
571. **Uddenfeldt M, Janson C, Lampa E, et al.** High BMI is related to higher incidence of asthma, while a fish and fruit diet is related to a lower- Results from a long-term follow-up study of three age groups in Sweden. *Respir Med*. 2010;104(7):972-980. [EL 3; SS]
572. **Strunk RC, Colvin R, Bacharier LB, et al.** Airway obstruction worsens in young adults with asthma who become obese. *J Allergy Clin Immunol Pract*. 2015;3(5):765-771. [EL 2; PCS, post-hoc analysis]
573. **Leiria LO, Martins MA, Saad MJ.** Obesity and asthma: beyond T(H)2 inflammation. *Metabolism*. 2015;64(2):172-181. [EL 4; NE]
574. **Danielewicz H.** What the genetic background of individuals with asthma and obesity can reveal: is beta2-adrenergic receptor gene polymorphism important? *Pediatr Allergy Immunol Pulmonol*. 2014;27(3):104-110. [EL 4; NE]
575. **Sowers MR, Karvonen-Gutierrez CA.** The evolving role of obesity in knee osteoarthritis. *Curr Opin Rheumatol*. 2010;22(5):533-537. [EL 4; NE]
576. **Dillon CF, Rasch EK, Gu Q, Hirsch R.** Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. *J Rheumatol*. 2006;33(11):2271-2279. [EL 3; SS]
577. **Felson DT.** Weight and osteoarthritis. *J Rheumatol Suppl*. 1995;43:7-9. [EL 4; NE]
578. **Powell A, Teichtahl AJ, Wluka AE, Cicuttini FM.** Obesity: a preventable risk factor for large joint osteoarthritis which may act through biomechanical factors. *Br J Sports Med*. 2005;39(1):4-5. [EL 4; NE]
579. **Creamer P, Hochberg MC.** Osteoarthritis. *Lancet*. 1997;350(9076):503-508. [EL 4; NE]
580. **D'Lima DD, Fregly BJ, Patil S, Steklov N, Colwell CW.** Knee joint forces: prediction, measurement, and significance. *Proc Inst Mech Eng H*. 2012;226(2):95-102. [EL 4; NE]
581. **Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM.** Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. *Epidemiology*. 1999;10(2):161-166. [EL 2; RCCS]
582. **Carman WJ, Sowers M, Hawthorne VM, Weissfeld LA.** Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. *Am J Epidemiol*. 1994;139(2):119-129. [EL 2; PCS]
583. **Lago F, Dieguez C, Gómez-Reino J, Gualillo O.** The emerging role of adipokines as mediators of inflammation and immune responses. *Cytokine Growth Factor Rev*. 2007;18(3-4):313-325. [EL 4; NE]
584. **Griffin TM, Guilak F.** Why is obesity associated with osteoarthritis? Insights from mouse models of obesity. *Biorheology*. 2008;45(3-4):387-398. [EL 4; NE]
585. **Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF.** Obesity and knee osteoarthritis. The Framingham Study. *Ann Intern Med*. 1988;109(1):18-24. [EL 2; PCS]
586. **Fletcher E, Lewis-Fanning E.** Chronic rheumatic diseases-part IV: a statistical study of 1,000 cases of chronic rheumatism. *Postgrad Med J*. 1945;21(235):176-185. [EL 2; PCS]
587. **Anderson JJ, Felson DT.** Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. *Am J Epidemiol*. 1988;128(1):179-189. [EL 3; SS]
588. **Davis MA, Ettinger WH, Neuhaus JM.** Obesity and osteoarthritis of the knee: evidence from the National Health and Nutrition Examination Survey (NHANES I). *Semin Arthritis Rheum*. 1990;20(3 Suppl 1):34-41. [EL 3; SS]
589. **Schouten JS, van den Ouweland FA, Valkenburg HA.** A 12 year follow up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. *Ann Rheum Dis*. 1992;51(8):932-937. [EL 2; PCS]
590. **Felson DT, Zhang Y, Hannan MT, et al.** Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. *Arthritis Rheum*. 1997;40(4):728-733. [EL 2; PCS]
591. **Hochberg MC, Lethbridge-Cejku M, Scott WW,Jr, Reichle R, Plato CC, Tobin JD.** The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: data from the Baltimore Longitudinal Study of Aging. *J Rheumatol*. 1995;22(3): 488-493. [EL 3; CSS]
592. **Manninen P, Riihimäki H, Heliövaara M, Mäkelä P.** Overweight, gender and knee osteoarthritis. *Int J Obes Relat Metab Disord*. 1996;20(6):595-597. [EL 2; PCS]
593. **Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C.** Knee osteoarthritis and obesity. *Int J Obes Relat Metab Disord*. 2001;25(5):622-627. [EL 2; PCS, case-controlled]
594. **Hart DJ, Spector TD.** The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. *J Rheumatol*. 1993;20(2):331-335. [EL 3; CSS]
595. **Lachance L, Sowers M, Jamadar D, Jannausch M, Hochberg M, Crutchfield M.** The experience of pain and emergent osteoarthritis of the knee. *Osteoarthr Cartil*. 2001;9(6):527-532. [EL 3; CSS]
596. **Cicuttini FM, Baker JR, Spector TD.** The association of obesity with osteoarthritis of the hand and knee in women: a twin study. *J Rheumatol*. 1996;23(7):1221-1226. [EL 2; PCS]
597. **Toivanen AT, Heliövaara M, Impivaara O, et al.** Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis--a population-based study with a follow-up of 22 years. *Rheumatology*. 2010;49(2):308-314. [EL 2; PCS]
598. **Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK.** Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC Musculoskelet Disord*. 2008;9:132. [EL 2; PCS]
599. **Lohmander LS, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Engström G.** Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. *Ann Rheum Dis*. 2009;68(4):490-496. [EL 2; PCS]
600. **Holliday KL, McWilliams DF, Maciewicz RA, Muir KR, Zhang W, Doherty M.** Lifetime body mass index, other anthropometric measures of obesity and risk of knee or hip osteoarthritis in the GOAL case-control study. *Osteoarthr Cartil*. 2011;19(1):37-43. [EL 2; PCS, case-controlled]

601. **Blagojevic M, Jinks C, Jeffery A, Jordan KP.** Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthr Cartil*. 2010;18(1):24-33. [EL 2; MNRCT]
602. **Hunskaar S.** A systematic review of overweight and obesity as risk factors and targets for clinical intervention for urinary incontinence in women. *Neurourol Urodyn*. 2008;27(8):749-757. [EL 2; MNRCT]
603. **Subak LL, Richter HE, Hunskaar S.** Obesity and urinary incontinence: epidemiology and clinical research update. *J Urol*. 2009;182(6 Suppl):S2-S7. [EL 2; MNRCT]
604. **Danforth KN, Townsend MK, Lifford K, Curhan GC, Resnick NM, Grodstein F.** Risk factors for urinary incontinence among middle-aged women. *Am J Obstet Gynecol*. 2006;194(2):339-345. [EL 3; SS]
605. **Hannestad YS, Rortveit G, Sandvik H, Hunskaar S. Norwegian EPINCONT study.** A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of incontinence in the county of Nord-Trondelag. *J Clin Epidemiol*. 2000;53(11):1150-1157. [EL 3; SS]
606. **Brown JS, Grady D, Ouslander JG, Herzog AR, Varner RE, Posner SF.** Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. *Obstet Gynecol*. 1999;94(1):66-70. [EL 3; SS]
607. **Kuh D, Cardozo L, Hardy R.** Urinary incontinence in middle aged women: childhood enuresis and other lifetime risk factors in a British prospective cohort. *J Epidemiol Community Health*. 1999;53(8):453-458. [EL 3; SS]
608. **Mishra GD, Hardy R, Cardozo L, Kuh D.** Body weight through adult life and risk of urinary incontinence in middle-aged women: results from a British prospective cohort. *Int J Obes (Lond)*. 2008;32(9):1415-1422. [EL 2; PCS]
609. **Waetjen LE, Liao S, Johnson WO, et al.** Factors associated with prevalent and incident urinary incontinence in a cohort of midlife women: a longitudinal analysis of data: study of women's health across the nation. *Am J Epidemiol*. 2007;165(3):309-318. [EL 2; PCS]
610. **Dallosso HM, McGrother CW, Matthews RJ, Donaldson MM. Leicestershire MRC Incontinence Study Group.** The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. *BJU Int*. 2003;92(1):69-77. [EL 3; SS]
611. **Townsend MK, Danforth KN, Rosner B, Curhan GC, Resnick NM, Grodstein F.** Body mass index, weight gain, and incident urinary incontinence in middle-aged women. *Obstet Gynecol*. 2007;110(2 Pt 1):346-353. [EL 3; SS]
612. **Brown JS, Seeley DG, Fong J, Black DM, Ensrud KE, Grady D.** Urinary incontinence in older women: who is at risk? Study of Osteoporotic Fractures Research Group. *Obstet Gynecol*. 1996;87(5 Pt 1):715-721. [EL 3; SS]
613. **Whitcomb EL, Subak LL.** Effect of weight loss on urinary incontinence in women. *Open Access J Urol*. 2011;3:123-132. [EL 2; MNRCT]
614. **Han MO, Lee NY, Park HS.** Abdominal obesity is associated with stress urinary incontinence in Korean women. *Int Urogynecol J Pelvic Floor Dysfunct*. 2006; 17(1):35-39. [EL 3; CCS]
615. **Townsend MK, Curhan GC, Resnick NM, Grodstein F.** BMI, waist circumference, and incident urinary incontinence in older women. *Obesity*. 2008;16(4):881-886. [EL 3; SS]
616. **Kupelian V, McVary KT, Barry MJ, et al.** Association of C-reactive protein and lower urinary tract symptoms in men and women: results from Boston Area Community Health survey. *Urology*. 2009;73(5):950-957. [EL 3; CSS]
617. **Kim IH, Chun H, Kwon JW.** Gender differences in the effect of obesity on chronic diseases among the elderly Koreans. *J Korean Med Sci*. 2011;26(2):250-257. [EL 3; CSS]
618. **Tai HC, Chung SD, Ho CH, et al.** Metabolic syndrome components worsen lower urinary tract symptoms in women with type 2 diabetes. *J Clin Endocrinol Metab*. 2010;95(3):1143-1150. [EL 3; CSS]
619. **Uzun H, Zorba OU.** Metabolic syndrome in female patients with overactive bladder. *Urology*. 2012;79(1):72-75. [EL 3; CSS]
620. **Kirby MG, Wagg A, Cardozo L, et al.** Overactive bladder: is there a link to the metabolic syndrome in men? *Neurourol Urodyn*. 2010;29(8):1360-1364. [EL 4; NE]
621. **Noblett KL, Jensen JK, Ostergard DR.** The relationship of body mass index to intra-abdominal pressure as measured by multichannel cystometry. *Int Urogynecol J Pelvic Floor Dysfunct*. 1997;8(6):323-326. [EL 2; RCCS]
622. **Bump RC, Sugerman HJ, Fantl JA, McClish DK.** Obesity and lower urinary tract function in women: effect of surgically induced weight loss. *Am J Obstet Gynecol*. 1992;167(2):392-397. [EL 2; PCS, N = 12]
623. **Richter HE, Creasman JM, Myers DL, et al.** Urodynamic characterization of obese women with urinary incontinence undergoing a weight loss program: the Program to Reduce Incontinence by Diet and Exercise (PRIDE) trial. *Int Urogynecol J Pelvic Floor Dysfunct*. 2008;19(12):1653-1658. [EL 3; CSS]
624. **Subak LL, Whitcomb E, Shen H, Saxton J, Vittinghoff E, Brown JS.** Weight loss: a novel and effective treatment for urinary incontinence. *J Urol*. 2005;174(1):190-195. [EL 1; RCT, N = 48]
625. **Singh M, Lee J, Gupta N, et al.** Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: a prospective intervention trial. *Obesity (Silver Spring)*. 2013;21(2):284-290. [EL 2; PCS]
626. **Woodman G, Cywes R, Billy H, et al.** Effect of adjustable gastric banding on changes in gastroesophageal reflux disease (GERD) and quality of life. *Curr Med Res Opin*. 2012;28(4):581-589. [EL 2; PCS]
627. **de Jong JR, Besselink MG, van Ramshorst B, Gooszen HG, Smout AJ.** Effects of adjustable gastric banding on gastroesophageal reflux and esophageal motility: a systematic review. *Obes Rev*. 2010;11(4):297-305. [EL 2; MNRCT]
628. **Chiu S, Birch DW, Shi X, Sharma AM, Karmali S.** Effect of sleeve gastrectomy on gastroesophageal reflux disease: a systematic review. *Surg Obes Relat Dis*. 2011; 7(4):510-515. [EL 2; MNRCT]
629. **Carabotti M, Silecchia G, Greco F, et al.** Impact of laparoscopic sleeve gastrectomy on upper gastrointestinal symptoms. *Obes Surg*. 2013;23(10):1551-1557. [EL 3; SS]
630. **Soricelli E, Iossa A, Casella G, Abbatini F, Cali B, Basso N.** Sleeve gastrectomy and crural repair in obese patients with gastroesophageal reflux disease and/or hiatal hernia. *Surg Obes Relat Dis*. 2013;9(3):356-361. [EL 2; PCS]
631. **Daes J, Jimenez ME, Said N, Daza JC, Dennis R.** Laparoscopic sleeve gastrectomy: symptoms of gastroesophageal reflux can be reduced by changes in surgical technique. *Obes Surg*. 2012;22(12):1874-1879. [EL 2; PCS]

632. **Daes J, Jimenez ME, Said N, Dennis R.** Improvement of gastroesophageal reflux symptoms after standardized laparoscopic sleeve gastrectomy. *Obes Surg*. 2014;24(4): 536-540. [EL 2; PCS]
633. **Madalosso CA, Gurski RR, Callegari-Jacques SM, Navarini D, Thiesen V, Fornari F.** The impact of gastric bypass on gastroesophageal reflux disease in patients with morbid obesity: a prospective study based on the Montreal Consensus. *Ann Surg*. 2010;251(2):244-248. [EL 2; PCS]
634. **DuPree CE, Blair K, Steele SR, Martin MJ.** Laparoscopic sleeve gastrectomy in patients with preexisting gastroesophageal reflux disease: a national analysis. *JAMA Surg*. 2014;149(4):328-334. [EL 2; RCCS]
635. **Zalar A, Haddouche B, Antonietti M, et al.** Lack of correlation between morbid obesity and severe gastroesophageal reflux disease in candidates for bariatric surgery: results of a large prospective study. *Obes Surg*. 2013;23(11):1939-1941. [EL 2; PCS]
636. **Chang P, Friedenberg F.** Obesity and GERD. *Gastroenterol Clin North Am*. 2014;43(1):161-173. [EL 4; NE]
637. **Niigaki M, Adachi K, Hirakawa K, Furuta K, Kinoshita Y.** Association between metabolic syndrome and prevalence of gastroesophageal reflux disease in a health screening facility in Japan. *J Gastroenterol*. 2013; 48(4):463-472. [EL 3; CCS]
638. **Kallel L, Bibani N, Fekih M, et al.** Metabolic syndrome is associated with gastroesophageal reflux disease based on a 24-hour ambulatory pH monitoring. *Dis Esophagus*. 2011;24(3):153-159. [EL 3; CSS]
639. **Healy LA, Ryan AM, Pidgeon G, Ravi N, Reynolds JV.** Lack of differential pattern in central adiposity and metabolic syndrome in Barrett's esophagus and gastroesophageal reflux disease. *Dis Esophagus*. 2010; 23(5):386-391. [EL 3; CSS]
640. **Leggett CL, Nelsen EM, Tian J, et al.** Metabolic syndrome as a risk factor for Barrett esophagus: a population-based case-control study. *Mayo Clin Proc*. 2013;88(2):157-165. [EL 2; PCS, case-controlled]
641. **Rubenstein JH, Morgenstern H, Appelman H, et al.** Prediction of Barrett's esophagus among men. *Am J Gastroenterol*. 2013;108(3):353-362. [EL 3; CSS]
642. **Kendall BJ, Macdonald GA, Hayward NK, Prins JB, O'Brien S, Whiteman DC.** Study of Digestive Health. The risk of Barrett's esophagus associated with abdominal obesity in males and females. *Int J Cancer*. 2013;132(9):2192-2199. [EL 2; PCS, case-controlled]
643. **Lagergren J, Mattsson F, Nyrén O.** Gastroesophageal reflux does not alter effects of body mass index on risk of esophageal adenocarcinoma. *Clin Gastroenterol Hepatol*. 2014;12(1):45-51. [EL 2; RCCS]
644. **Springer F, Schwarz M, Machann J, et al.** Quantitative assessment of visceral fat in morbidly obese patients by means of wide-bore MRI and its relation to lower esophageal sphincter pressure and signs of gastroesophageal reflux. *Obes Surg*. 2010;20(6):749-756. [EL 3; CSS, N = 16]
645. **Hajar N, Castell DO, Ghomrawi H, Rackett R, Hila A.** Impedance pH confirms the relationship between GERD and BMI. *Dig Dis Sci*. 2012;57(7):1875-1879. [EL 2; RCCS]
646. **Anggiansah R, Sweis R, Anggiansah A, Wong T, Cooper D, Fox M.** The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2013;37(5):555-563. [EL 2; PCS]
647. **Burgerhart JS, van de Meeberg PC, Siersema PD, Smout AJ.** Nocturnal and daytime esophageal acid exposure in normal-weight, overweight, and obese patients with reflux symptoms. *Eur J Gastroenterol Hepatol*. 2014; 26(1):6-10. [EL 2; RCCS]
648. **Che F, Nguyen B, Cohen A, Nguyen NT.** Prevalence of hiatal hernia in the morbidly obese. *Surg Obes Relat Dis*. 2013;9(6):920-924. [EL 2; RCCS]
649. **Choi JY, Jung HK, Song EM, Shim KN, Jung SA.** Determinants of symptoms in gastroesophageal reflux disease: nonerosive reflux disease, symptomatic, and silent erosive reflux disease. *Eur J Gastroenterol Hepatol*. 2013;25(7):764-771. [EL 2; PCS]
650. **Tai CM, Lee YC, Tu HP, et al.** The relationship between visceral adiposity and the risk of erosive esophagitis in severely obese Chinese patients. *Obesity*. 2010;18(11): 2165-2169. [EL 3; CSS]
651. **Sharma P, Vakil N, Monyak JT, Silberg DG.** Obesity does not affect treatment outcomes with proton pump inhibitors. *J Clin Gastroenterol*. 2013;47(8):672-677. [EL 1; MRCT]
652. **Becker V, Grotz S, Schlag C, et al.** Positive predictors for gastroesophageal reflux disease and the therapeutic response to proton-pump inhibitors. *World J Gastroenterol*. 2014;20(14):4017-4024. [EL 2; RCCS]
653. **Viazis N, Karamanolis GP, Anastasiou J, et al.** Refractory GERD: increased body mass index is associated with persisting acid exposure but not hypersensitive esophagus or functional heartburn. *Eur J Gastroenterol Hepatol*. 2013;25(12):1450-1455. [EL 2; PCS]
654. **Akyuz F, Uyanikoglu A, Ermis F, et al.** Gastroesophageal reflux in asymptomatic obese subjects: an esophageal impedance-pH study. *World J Gastroenterol*. 2015;21(10): 3030-3034. [EL 2; PCS, N = 46]
655. **Tolone S, Limongelli P, del Genio G, et al.** Gastroesophageal reflux disease and obesity: do we need to perform reflux testing in all candidates to bariatric surgery? *Int J Surg*. 2014;12 Suppl 1:S173-S177. [EL 2; PCS]
656. **Robertson EV, Derakhshan MH, Wirz AA, et al.** Central obesity in asymptomatic volunteers is associated with increased intrasphincteric acid reflux and lengthening of the cardiac mucosa. *Gastroenterology*. 2013;145(4):730-739. [EL 2; PCS, N = 24]
657. **Wu YW, Tseng PH, Lee YC, et al.** Association of esophageal inflammation, obesity and gastroesophageal reflux disease: from FDG PET/CT perspective. *PLoS One*. 2014;9(3):e92001. [EL 2; PCS]
658. **American Psychiatric Association DSM-5 Task Force.** *2013 Diagnostic and statistical manual of mental disorders: DSM-5*. 5th ed. 2013. [EL 4; NE]
659. **Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH.** Depression and anxiety among US adults: associations with body mass index. *Int J Obes (Lond)*. 2009;33(2):257-266. [EL 3; SS]
660. **Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW.** Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol*. 2003;158(12):1139-1147. [EL 3; SS]
661. **McElroy SL, Kotwal R, Malhotra S, Nelson EB, Keck PE, Nemeroff CB.** Are mood disorders and obesity related? A review for the mental health professional. *J Clin Psychiatry*. 2004;65(5):634-651. [EL 4; NE]
662. **Pratt LA, Brody DJ.** Depression and obesity in the U.S. adult household population, 2005-2010. *NCHS Data Brief*. 2014;(167):1-8. [EL 4; NE]

663. **Simon GE, Rohde P, Ludman EJ, et al.** Association between change in depression and change in weight among women enrolled in weight loss treatment. *Gen Hosp Psychiatry*. 2010;32(6):583-589. [EL 2; PCS]
664. **Stunkard AJ, Faith MS, Allison KC.** Depression and obesity. *Biol Psychiatry*. 2003;54(3):330-337. [EL 4; NE]
665. **Carpenter KM, Hasin DS, Allison DB, Faith MS.** Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study. *Am J Public Health*. 2000;90(2):251-257. [EL 3; SS]
666. **Luppino FS, de Wit LM, Bouvy PF, et al.** Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220-229. [EL 2; MNRCT]
667. **Kivimäki M, Lawlor DA, Singh-Manoux A, et al.** Common mental disorder and obesity: insight from four repeat measures over 19 years: prospective Whitehall II cohort study. *BMJ*. 2009;339:b3765. [EL 2; PCS]
668. **Blaine B.** Does depression cause obesity?: A meta-analysis of longitudinal studies of depression and weight control. *J Health Psychol*. 2008;13(8):1190-1197. [EL 2; MNRCT]
669. **Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA.** Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes Relat Metab Disord*. 2003;27(4):514-521. [EL 2; PCS]
670. **Dixon JB, Dixon ME, O'Brien PE.** Depression in association with severe obesity: changes with weight loss. *Arch Intern Med*. 2003;163(17):2058-2065. [EL 3; SS]
671. **Khambaty T, Stewart JC, Muldoon MF, Kamarck TW.** Depressive symptom clusters as predictors of 6-year increases in insulin resistance: data from the Pittsburgh Healthy Heart Project. *Psychosom Med*. 2014;76(5):363-369. [EL 2; PCS]
672. **Marazziti D, Rutigliano G, Baroni S, Landi P, Dell'Osso L.** Metabolic syndrome and major depression. *CNS Spectr*. 2014;19(4):293-304. [EL 4; NE]
673. **Vaccarino V, Johnson BD, Sheps DS, et al. National Heart, Lung, and Blood Institute.** Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute-sponsored WISE study. *J Am Coll Cardiol*. 2007;50(21):2044-2050. [EL 2; PCS]
674. **Shelton RC, Falola M, Li L, Zajecka J, Fava M, Papakostas GI.** The pro-inflammatory profile of depressed patients is (partly) related to obesity. *J Psychiatr Res*. 2015;70:91-97. [EL 3; CCS]
675. **Bremmer MA, Beekman AT, Deeg DJ, et al.** Inflammatory markers in late-life depression: results from a population-based study. *J Affect Disord*. 2008;106(3): 249-255. [EL 3; CSS]
676. **Pasquali R, Vicennati V.** Activity of the hypothalamic-pituitary-adrenal axis in different obesity phenotypes. *Int J Obes Relat Metab Disord*. 2000;24 Suppl 2:S47-S49. [EL 4; NE]
677. **Walker BR.** Activation of the hypothalamic-pituitary-adrenal axis in obesity: cause or consequence? *Growth Horm IGF Res*. 2001;11 Suppl A:S91-S95. [EL 4; NE]
678. **Atlantis E, Ball K.** Association between weight perception and psychological distress. *Int J Obes*. 2008; 32(4):715-721. [EL 3; SS]
679. **Derenne JL, Beresin EV.** Body image, media, and eating disorders. *Acad Psychiatry*. 2006;30(3):257-261. [EL 4; NE]
680. **Hoek HW, van Harten PN, Hermans KM, Katzman MA, Matroos GE, Susser ES.** The incidence of anorexia nervosa on Curacao. *Am J Psychiatry*. 2005;162(4):748-752. [EL 3; SS]
681. **Beesdo K, Jacobi F, Hoyer J, Low NC, Höfler M, Wittchen HU.** Pain associated with specific anxiety and depressive disorders in a nationally representative population sample. *Soc Psychiatry Psychiatr Epidemiol*. 2010;45(1):89-104. [EL 3; CSS]
682. **Gadalla T, Piran N.** Psychiatric comorbidity in women with disordered eating behavior: a national study. *Women Health*. 2008;48(4):467-484. [EL 3; SS]
683. **Kahn SE, Hull RL, Utzschneider KM.** Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006;444(7121):840-846. [EL 4; NE]
684. **Garrison RJ, Wilson PW, Castelli WP, Feinleib M, Kannel WB, McNamara PM.** Obesity and lipoprotein cholesterol in the Framingham Offspring Study. *Metabolism*. 1980;29(11):1053-1060. [EL 2; PCS]
685. **Oparil S, Zaman MA, Calhoun DA.** Pathogenesis of hypertension. *Ann Intern Med*. 2003;139(9):761-776. [EL 4; NE]
686. **Ferrannini E, Buzzigoli G, Bonadonna R, et al.** Insulin resistance in essential hypertension. *N Engl J Med*. 1987; 317(6):350-357. [EL 2; PCS, N = 13]
687. **Clark JM, Brancati FL, Diehl AM.** Nonalcoholic fatty liver disease. *Gastroenterology*. 2002;122(6):1649-1657. [EL 4; NE]
688. **Tolman KG, Dalpiaz AS.** Treatment of non-alcoholic fatty liver disease. *Ther Clin Risk Manag*. 2007;3(6):1153-1163. [EL 4; NE]
689. **Bugianesi E, Leone N, Vanni E, et al.** Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology*. 2002;123(1):134-140. [EL 3; CCS, N = 23]
690. **Willner IR, Waters B, Patil SR, Reuben A, Morelli J, Riely CA.** Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. *Am J Gastroenterol*. 2001;96(10): 2957-2961. [EL 2; RCCS]
691. **Struben VM, Hespenheide EE, Caldwell SH.** Nonalcoholic steatohepatitis and cryptogenic cirrhosis within kindreds. *Am J Med*. 2000;108(1):9-13. [EL 3; CCS, retrospective analysis]
692. **Guay AT.** The emerging link between hypogonadism and metabolic syndrome. *J Androl*. 2009;30(4):370-376. [EL 4; NE]
693. **Pasquali R, Casimirri F, Cantobelli S, et al.** Effect of obesity and body fat distribution on sex hormones and insulin in men. *Metabolism*. 1991;40(1):101-104. [EL 2; PCS, case-controlled, N = 52 cases, 20 controls]
694. **Osuna JA, Gómez-Pérez R, Arata-Bellabarba G, Villaroel V.** Relationship between BMI, total testosterone, sex hormone-binding-globulin, leptin, insulin and insulin resistance in obese men. *Arch Androl*. 2006;52(5):355-361. [EL 3; CSS]
695. **Svartberg J, Jorde R, Sundsfjord J, Bønaa KH, Barrett-Connor E.** Seasonal variation of testosterone and waist to hip ratio in men: the Trømso study. *J Clin Endocrinol Metab*. 2003;88(7):3099-3104. [EL 3; CSS]
696. **Svartberg J, von Mühlen D, Sundsfjord J, Jorde R.** Waist circumference and testosterone levels in community dwelling men. The Trømso study. *Eur J Epidemiol*. 2004; 19(7):657-663. [EL 3; CSS]

697. **Carmina E, Chu MC, Longo RA, Rini GB, Lobo RA.** Phenotypic variation in hyperandrogenic women influences the findings of abnormal metabolic and cardiovascular risk parameters. *J Clin Endocrinol Metab*. 2005;90(5):2545-2549. [EL 2; PCS]
698. **Zaadstra BM, Seidell JC, Van Noord PA, et al.** Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. *BMJ*. 1993;306(6876): 484-487. [EL 2; PCS]
699. **Melville JL, Katon W, Delaney K, Newton K.** Urinary incontinence in US women: a population-based study. *Arch Intern Med*. 2005;165(5):537-542. [EL 3; SS]
700. **Barak N, Ehrenpreis ED, Harrison JR, Sitrin MD.** Gastro-oesophageal reflux disease in obesity: pathophysiological and therapeutic considerations. *Obes Rev*. 2002;3(1):9-15. [EL 4; NE]
701. **Ruhl CE, Everhart JE.** Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: the NHANES I Epidemiologic Followup Study. First National Health and Nutrition Examination Survey. *Ann Epidemiol*. 1999;9(7):424-435. [EL 3; SS]
702. **Zhang ZF, Kurtz RC, Yu GP, et al.** Adenocarcinomas of the esophagus and gastric cardia: the role of diet. *Nutr Cancer*. 1997;27(3):298-309. [EL 2; RCCS]
703. **Locke GR, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ.** Risk factors associated with symptoms of gastroesophageal reflux. *Am J Med*. 1999;106(6):642-649. [EL 2; RCCS]
704. **Mittal RK, Balaban DH.** The esophagogastric junction. *N Engl J Med*. 1997;336(13):924-932. [EL 4; NE]
705. **O'Connor HJ.** Review article: Helicobacter pylori and gastro-oesophageal reflux disease-clinical implications and management. *Aliment Pharmacol Ther*. 1999;13(2): 117-127. [EL 4; NE]
706. **Pan XR, Li GW, Hu YH, et al.** Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20(4):537-544. [EL 1; RCT]
707. **Tuomilehto J, Lindström J, Eriksson JG, et al. Finnish Diabetes Prevention Study Group.** Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001; 344(18):1343-1350. [EL 1; RCT]
708. **Knowler WC, Barrett-Connor E, Fowler SE, et al.** Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6): 393-403. [EL 1; RCT]
709. **Ramachandran A, Snehalatha C, Mary S, et al.** The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia*. 2006;49(2):289-297. [EL 1; RCT]
710. **Penn L, White M, Oldroyd J, Walker M, Alberti KG, Mathers JC.** Prevention of type 2 diabetes in adults with impaired glucose tolerance: the European Diabetes Prevention RCT in Newcastle upon Tyne, UK. *BMC Public Health*. 2009;9:342. [EL 1; RCT]
711. **Roumen C, Corpeleijn E, Feskens EJ, Mensink M, Saris WH, Blaak EE.** Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. *Diabet Med*. 2008;25(5):597-605. [EL 1; RCT]
712. **Garvey WT, Ryan DH, Henry R, et al.** Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care*. 2014;37(4):912-921. [EL 1; RCT]
713. **Deedwania PC, Volkova N.** Current treatment options for the metabolic syndrome. *Curr Treat Options Cardiovasc Med*. 2005;7(1):61-74. [EL 4; NE]
714. **Hamman RF, Wing RR, Edelstein SL, et al.** Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care*. 2006;29(9):2102-2107. [EL 2; PCS]
715. **Knowler WC, Fowler SE, Hamman RF, et al.** Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-1686. [EL 1; RCT]
716. **Laaksonen DE, Lindström J, Lakka TA, et al.** Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. *Diabetes*. 2005;54(1):158-165. [EL 1; RCT]
717. **Lindström J, Ilanne-Parikka P, Peltonen M, et al.** Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet*. 2006;368(9548):1673-1679. [EL 1; RCT]
718. **Li G, Zhang P, Wang J, et al.** Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol*. 2014;2(6): 474-480. [EL 1; RCT]
719. **Glechner A, Harreiter J, Gartlehner G, et al.** Sex-specific differences in diabetes prevention: a systematic review and meta-analysis. *Diabetologia*. 2015;58(2):242-254. [EL 1; MRCT]
720. **Barte JC, ter Bogt NC, Bogers RP, et al.** Maintenance of weight loss after lifestyle interventions for overweight and obesity, a systematic review. *Obes Rev*. 2010;11(12):899-906. [EL 1; MRCT]
721. **Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L.** XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27(1): 155-161. [EL 1; RCT]
722. **Garvey WT, Ryan DH, Look M, et al.** Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95(2):297-308. [EL 1; RCT]
723. **Wentworth JM, Hensman T, Playfair J, et al.** Laparoscopic adjustable gastric banding and progression from impaired fasting glucose to diabetes. *Diabetologia*. 2014;57(3):463-468. [EL 2; RCCS]
724. **Sjöholm K, Anveden A, Peltonen M, et al.** Evaluation of current eligibility criteria for bariatric surgery: diabetes prevention and risk factor changes in the Swedish obese subjects (SOS) study. *Diabetes Care*. 2013;36(5):1335-1340. [EL 2; PCS]
725. **Carlsson LM, Peltonen M, Ahlin S, et al.** Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. *N Engl J Med*. 2012;367(8):695-704. [EL 2; NRCT]
726. **Magliano DJ, Barr EL, Zimmet PZ, et al.** Glucose indices, health behaviors, and incidence of diabetes in Australia: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care*. 2008;31(2):267-272. [EL 3; CSS]

727. **Sjöström L, Peltonen M, Jacobson P, et al.** Bariatric surgery and long-term cardiovascular events. *JAMA*. 2012;307(1):56-65. [EL 2; NRCT]
728. **Booth H, Khan O, Prevost T, et al.** Incidence of type 2 diabetes after bariatric surgery: population-based matched cohort study. *Lancet Diabetes Endocrinol*. 2014;2(12):963-968. [EL 2; PCS, case-controlled]
729. **Jeon CY, Lokken RP, Hu FB, van Dam RM.** Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. *Diabetes Care*. 2007;30(3):744-752. [EL 2; MNRCT]
730. **Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW.** Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care*. 2003;26(3):557-562. [EL 2; PCS]
731. **Houmard JA, Tanner CJ, Slentz CA, Duscha BD, McCartney JS, Kraus WE.** Effect of the volume and intensity of exercise training on insulin sensitivity. *J Appl Physiol*. 2004;96(1):101-106. [EL 1; RCT]
732. **Bajpeyi S, Tanner CJ, Slentz CA, et al.** Effect of exercise intensity and volume on persistence of insulin sensitivity during training cessation. *J Appl Physiol*. 2009;106(4):1079-1085. [EL 2; PCS]
733. **Myers VH, McVay MA, Brashear MM, et al.** Exercise training and quality of life in individuals with type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2013;36(7):1884-1890. [EL 1; RCT]
734. **Johannsen NM, Swift DL, Lavie CJ, Earnest CP, Blair SN, Church TS.** Categorical analysis of the impact of aerobic and resistance exercise training, alone and in combination, on cardiorespiratory fitness levels in patients with type 2 diabetes: results from the HART-D study. *Diabetes Care*. 2013;36(10):3305-3312. [EL 1; RCT]
735. **Snowling NJ, Hopkins WG.** Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. *Diabetes Care*. 2006;29(11):2518-2527. [EL 1; MRC, 8 controlled trials with unclear randomization]
736. **Sigal RJ, Kenny GP, Boulé NG, et al.** Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;147(6):357-369. [EL 1; RCT]
737. **Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr.** Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1991;325(3):147-152. [EL 3; SS]
738. **Hu FB, Sigal RJ, Rich-Edwards JW, et al.** Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *JAMA*. 1999;282(15):1433-1439. [EL 2; PCS]
739. **Manson JE, Rimm EB, Stampfer MJ, et al.** Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet*. 1991;338(8770):774-778. [EL 2; PCS]
740. **Katzmarzyk PT, Church TS, Craig CL, Bouchard C.** Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc*. 2009;41(5):998-1005. [EL 2; PCS]
741. **Chiasson JL, Josse RG, Gomis R, et al.** Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359(9323):2072-2077. [EL 1; RCT]
742. **Hu R, Li Y, Lv Q, Wu T, Tong N.** Acarbose monotherapy and type 2 diabetes prevention in eastern and western prediabetes: an ethnicity-specific meta-analysis. *Clin Ther*. 2015;37(8):1798-1812. [EL 1; MRCT]
743. **Zinman B, Harris SB, Neuman J, et al.** Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. *Lancet*. 2010;376(9735):103-111. [EL 1; RCT]
744. **Gerstein HC, Yusuf S, Bosch J, et al. DREAM Trial Investigators.** Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006;368(9541):1096-1105. [EL 1; RCT]
745. **Dagenais GR, Gerstein HC, Holman R, et al. DREAM Trial Investigators.** Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes Care*. 2008;31(5):1007-1014. [EL 1; RCT]
746. **DeFronzo RA, Tripathy D, Schwenke DC, et al.** Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med*. 2011;364(12):1104-1115. [EL 1; RCT]
747. **Hopper I, Billah B, Skiba M, Krum H.** Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: meta-analysis of randomised controlled clinical trials. *Eur J Cardiovasc Prev Rehabil*. 2011;18(6):813-823. [EL 1; MRCT]
748. **Henry RR, Chilton R, Garvey WT.** New options for the treatment of obesity and type 2 diabetes mellitus (narrative review). *J Diabetes Complications*. 2013;27(5):508-518. [EL 4; NE]
749. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients, UKPDS Group. *Metabolism*. 1990;39(9):905-912. [EL 1; RCT]
750. **Bosello O, Armellini F, Zamboni M, Fitchet M.** The benefits of modest weight loss in type II diabetes. *Int J Obes Relat Metab Disord*. 1997;21 Suppl 1:S10-13. [EL 4; NE]
751. **Terranova CO, Brakenridge CL, Lawler SP, Eakin EG, Reeves MM.** Effectiveness of lifestyle-based weight loss interventions for adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2015;17(4):371-378. [EL 1; MRCT]
752. **Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ.** Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. *J Acad Nutr Diet*. 2015;115(9):1447-1463. [EL 1; MRCT]
753. **Norris SL, Zhang X, Avenell A, et al.** Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: a meta-analysis. *Am J Med*. 2004;117(10):762-774. [EL 1; MRCT]
754. **Wing RR, Lang W, Wadden TA, et al. Look AHEAD Research Group.** Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011;34(7):1481-1486. [EL 1; RCT]
755. **Wing RR. Look AHEAD Research Group.** Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med*. 2010;170(17):1566-1575. [EL 1; RCT]
756. **Belalcazar LM, Haffner SM, Lang W, et al. Look AHEAD (Action for Health in Diabetes) Research**

Group. Lifestyle intervention and/or statins for the reduction of C-reactive protein in type 2 diabetes: from the look AHEAD study. *Obesity (Silver Spring)*. 2013; 21(5):944-950. [EL 1; RCT, post-hoc analysis]

757. **Wing RR, Bolin P, Brancati FL, et al. Look AHEAD Research Group.** Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369(2):145-154. [EL 1; RCT]
758. **Gregg EW, Chen H, Wagenknecht LE, et al. Look AHEAD Research Group.** Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA*. 2012;308(23):2489-2496. [EL 1; RCT, secondary observational analysis]
759. **Foster GD, Borradaile KE, Sanders MH, et al. Sleep AHEAD Research Group of Look AHEAD Research Group.** A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med*. 2009;169(17):1619-1626. [EL 1; RCT]
760. **Rejeski WJ, Ip EH, Bertoni AG, et al. Look AHEAD Research Group.** Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med*. 2012;366(13): 1209-1217. [EL 1; RCT, hidden Markov models]
761. **Rubin RR, Wadden TA, Bahnson JL, et al. Look AHEAD Research Group.** Impact of intensive lifestyle intervention on depression and health-related quality of life in type 2 diabetes: the Look AHEAD Trial. *Diabetes Care*. 2014;37(6):1544-1553. [EL 1; RCT, post-hoc analysis]
762. **Look AHEAD Research Group.** Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2014;2(10): 801-809. [EL 1; RCT, secondary analysis]
763. **Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ.** Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA*. 2001;286(10):1218-1227. [EL 1; MRCT]
764. **Colberg SR, Riddell MC.** Physical activity: regulation of glucose metabolism, clinical management strategies, and weight control. In: Peters AL, Laffell LM, eds. *Type I Diabetes Sourcebook*. Alexandria, VA: American Diabetes Association; 2013. [EL 4; NE]
765. **Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ.** Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in Type 2 diabetes mellitus. *Diabetologia*. 2003;46(8):1071-1081. [EL 1; MRCT]
766. **Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C.** Physical activity/exercise and type 2 diabetes. *Diabetes Care*. 2004;27(10):2518-2539. [EL 4; NE]
767. **Church TS, Blair SN, Cocreham S, et al.** Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2010;304(20):2253-2262. [EL 1; RCT]
768. **Umpierre D, Ribeiro PA, Kramer CK, et al.** Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2011;305 (17):1790-1799. [EL 1; MRCT]
769. **Haskell WL, Lee IM, Pate RR, et al.** Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9): 1081-1093. [EL 4; NE]
770. **Colberg SR.** *Exercise and Diabetes: A Clinician's Guide to Prescribing Physical Activity*. 1st ed. Alexandria, VA: American Diabetes Association; 2013. [EL 4; NE]
771. **Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace C.** Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. *Med Sci Sports Exerc*. 2003;35(7):1093-1099. [EL 2; PCS]
772. **Spallone V, Ziegler D, Freeman R, et al.** Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev*. 2011;27(7):639-653. [EL 4; NE]
773. **Pop-Busui R, Evans GW, Gerstein HC, et al.** Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care*. 2010;33(7):1578-1584. [EL 1; RCT, post-hoc analysis]
774. **Hollander PA, Elbein SC, Hirsch IB, et al.** Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care*. 1998;21(8):1288-1294. [EL 1; RCT]
775. **Kelley DE, Bray GA, Pi-Sunyer FX, et al.** Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care*. 2002;25(6): 1033-1041. [EL 1; RCT]
776. **Miles JM, Leiter L, Hollander P, et al.** Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care*. 2002;25(7):1123-1128. [EL 1; RCT]
777. **Garvey WT, Ryan DH, Bohannon NJ, et al.** Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. *Diabetes Care*. 2014;37 (12):3309-3316. [EL 1; RCT]
778. **O'Neil PM, Smith SR, Weissman NJ, et al.** Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)*. 2012;20(7):1426-1436. [EL 1; RCT]
779. **Hollander P, Gupta AK, Plodkowski R, et al. COR-Diabetes Study Group.** Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care*. 2013;36(12):4022-4029. [EL 1; RCT]
780. **Davies MJ, Bergenstal R, Bode B, et al. NN8022-1922 Study Group.** Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA*. 2015;314(7):687-699. [EL 1; RCT]
781. **Ruof J, Golay A, Berne C, Collin C, Lentz J, Maetzel A.** Orlistat in responding obese type 2 diabetic patients: meta-analysis findings and cost-effectiveness as rationales for reimbursement in Sweden and Switzerland. *Int J Obes*. 2005;29(5):517-523. [EL 1; MRCT]
782. **Bray G, Gregg E, Haffner S, et al. Look AHEAD Research Group.** Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res*. 2006; 3(3):202-215. [EL 3; CSS, baseline characteristics of a planned RCT]
783. **Schauer PR, Kashyap SR, Wolski K, et al.** Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med*. 2012;366(17):1567-1576. [EL 1; RCT]
784. **Schauer PR, Bhatt DL, Kirwan JP, et al. STAMPEDE Investigators.** Bariatric surgery versus intensive medical

therapy for diabetes--3-year outcomes. *N Engl J Med*. 2014;370(21):2002-2013. [EL 1; RCT]

785. **Sjöström L, Peltonen M, Jacobson P, et al.** Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA*. 2014;311(22):2297-2304. [EL 2; PCS]
786. **Mingrone G, Panunzi S, De Gaetano A, et al.** Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med*. 2012;366(17):1577-1585. [EL 1; RCT]
787. **Adams TD, Davidson LE, Litwin SE, Hunt SC.** Gastrointestinal surgery: cardiovascular risk reduction and improved long-term survival in patients with obesity and diabetes. *Curr Atheroscler Rep*. 2012;14(6):606-615. [EL 4; NE]
788. **Heneghan HM, Nissen S, Schauer PR.** Gastrointestinal surgery for obesity and diabetes: weight loss and control of hyperglycemia. *Curr Atheroscler Rep*. 2012;14(6):579-587. [EL 4; NE]
789. **Ikramuddin S, Korner J, Lee WJ, et al.** Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA*. 2013;309(21):2240-2249. [EL 1; RCT]
790. **Liang Z, Wu Q, Chen B, Yu P, Zhao H, Ouyang X.** Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: a randomized controlled trial. *Diabetes Res Clin Pract*. 2013;101(1):50-56. [EL 1; RCT]
791. **Courcoulas AP, Goodpaster BH, Eagleton JK, et al.** Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. *JAMA Surg*. 2014; 149(7):707-715. [EL 1; RCT]
792. **Halperin F, Ding SA, Simonson DC, et al.** Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. *JAMA Surg*. 2014;149(7):716-726. [EL 1; RCT]
793. **Gloy VL, Briel M, Bhatt DL, et al.** Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f5934. [EL 1; MRCT]
794. **Buchwald H, Estok R, Fahrbach K, et al.** Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med*. 2009;122(3):248-256.e5. [EL 1; RCT]
795. **Yu J, Zhou X, Li L, et al.** The long-term effects of bariatric surgery for type 2 diabetes: systematic review and meta-analysis of randomized and non-randomized evidence. *Obes Surg*. 2015;25(1):143-158. [EL 1; MRCT]
796. **Gill RS, Birch DW, Shi X, Sharma AM, Karmali S.** Sleeve gastrectomy and type 2 diabetes mellitus: a systematic review. *Surg Obes Relat Dis*. 2010;6(6):707-713. [EL 2; MNRCT]
797. **Yip S, Plank LD, Murphy R.** Gastric bypass and sleeve gastrectomy for type 2 diabetes: a systematic review and meta-analysis of outcomes. *Obes Surg*. 2013;23(12): 1994-2003. [EL 2; MNRCT]
798. **Li P, Fu P, Chen J, Wang LH, Wang DR.** Laparoscopic Roux-en-Y gastric bypass vs. laparoscopic sleeve gastrectomy for morbid obesity and diabetes mellitus: a meta-analysis of sixteen recent studies. *Hepatogastroenterology*. 2013;60(121):132-137. [EL 2; MNRCT]
799. **Cho JM, Kim HJ, Menzo EL, Park S, Szomstein S, Rosenthal RJ.** Effect of sleeve gastrectomy on type 2 diabetes as an alternative treatment modality to Roux-en-Y gastric bypass: systemic review and meta-analysis. *Surg Obes Relat Dis*. 2015;11(6):1273-1280. [EL 2; MNRCT]
800. **Yan YX, Wang GF, Xu N, Wang FL.** Correlation between postoperative weight loss and diabetes mellitus remission: a meta-analysis. *Obes Surg*. 2014;24(11):1862-1869. [EL 2; MNRCT]
801. **Wing RR, Marcus MD, Epstein LH, Salata R.** Type II diabetic subjects lose less weight than their overweight nondiabetic spouses. *Diabetes Care*. 1987;10(5):563-566. [EL 2; NRCT]
802. **National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).** Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421. [EL 4; NE]
803. **Johnson RK, Appel LJ, Brands M, et al.** Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2009; 120(11):1011-1020. [EL 4; NE]
804. **de Souza RJ, Swain JF, Appel LJ, Sacks FM.** Alternatives for macronutrient intake and chronic disease: a comparison of the OmniHeart diets with popular diets and with dietary recommendations. *Am J Clin Nutr*. 2008;88(1):1-11. [EL 4; NE, analysis of diet composition]
805. **Miller M, Stone NJ, Ballantyne C, et al.** Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011; 123(20): 2292-2333. [EL 4; NE]
806. **Mensink RP, Zock PL, Kester AD, Katan MB.** Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77(5):1146-1155. [EL 2; MNRCT, randomization not a stipulated inclusion criterion]
807. **Viljoen A, Wierzbicki AS.** Diagnosis and treatment of severe hypertriglyceridemia. *Expert Rev Cardiovasc Ther*. 2012;10(4):505-514. [EL 4; NE]
808. **Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper References Levels of Nutrients, et al.** *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, D.C.: National Academies Press; 2005. Available at: https://www.nal.usda.gov/fnic/DRI/DRI_Energy/energy_full_report.pdf. Accessed January 16, 2016. [EL 4; NE]
809. **Cao Y, Mauger DT, Pelkman CL, Zhao G, Townsend SM, Kris-Etherton PM.** Effects of moderate (MF) versus lower fat (LF) diets on lipids and lipoproteins: a meta-analysis of clinical trials in subjects with and without diabetes. *J Clin Lipidol*. 2009;3(1):19-32. [EL 2; MNRCT, randomization not a stipulated inclusion criterion]
810. **Welsh JA, Sharma A, Abramson JL, Vaccarino V, Gillespie C, Vos MB.** Caloric sweetener consumption and dyslipidemia among US adults. *JAMA*. 2010;303(15): 1490-1497. [EL 3; CSS]
811. **Livesey G, Taylor R.** Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies. *Am J Clin Nutr*. 2008;88(5):1419-1437. [EL 1; MRCT]
812. **Feinman L, Lieber CS.** Ethanol and lipid metabolism. *Am J Clin Nutr*. 1999;70(5):791-792. [EL 4; NE]

813. **Erkkila AT, Lichtenstein AH.** Fiber and cardiovascular disease risk: how strong is the evidence? *J Cardiovasc Nurs*. 2006;21(1):3-8. [EL 4; NE]
814. **Ylönen K, Saloranta C, Kronberg-Kippilä C, et al.** Associations of dietary fiber with glucose metabolism in nondiabetic relatives of subjects with type 2 diabetes: the Botnia Dietary Study. *Diabetes Care*. 2003;26(7):1979-1985. [EL 3; CSS]
815. **Anderson JW, Randles KM, Kendall CW, Jenkins DJ.** Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. *J Am Coll Nutr.* 2004;23(1):5-17. [EL 2; MNRCT]
816. **Kreisberg RA, Oberman A.** Medical management of hyperlipidemia/dyslipidemia. *J Clin Endocrinol Metab*. 2003;88(6):2445-2461. [EL 4; NE]
817. **Mozaffarian D, Stampfer MJ.** Removing industrial trans fat from foods. *BMJ*. 2010;340:c1826. [EL 4; NE]
818. **Harris WS.** N-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr.* 1997;65(5 Suppl):1645S-1654S. [EL 4; NE, extensive literature review]
819. **Balk E, Chung M, Lichtenstein A, et al.** Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. *Evid Rep Technol Assess (Summ)*. 2004;(93):1-6. [EL 4; NE]
820. **Lungershausen YK, Abbey M, Nestel PJ, Howe PR.** Reduction of blood pressure and plasma triglycerides by omega-3 fatty acids in treated hypertensives. *J Hypertens*. 1994;12(9):1041-1045. [EL 1; RCT]
821. **Appel LJ, Moore TJ, Obarzanek E, et al.** A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336(16):1117-1124. [EL 1; RCT]
822. **Obarzanek E, Sacks FM, Vollmer WM, et al.** Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr.* 2001;74(1):80-89. [EL 1; RCT]
823. **de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N.** Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99(6):779-785. [EL 1; RCT]
824. **Esposito K, Marfella R, Ciotola M, et al.** Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*. 2004;292(12):1440-1446. [EL 1; RCT]
825. **Rumawas ME, Meigs JB, Dwyer JT, McKeown NM, Jacques PF.** Mediterranean-style dietary pattern, reduced risk of metabolic syndrome traits, and incidence in the Framingham Offspring Cohort. *Am J Clin Nutr.* 2009; 90(6):1608-1614. [EL 2; PCS]
826. **Rumawas ME, Dwyer JT, McKeown NM, Meigs JB, Rogers G, Jacques PF.** The development of the Mediterranean-style dietary pattern score and its application to the American diet in the Framingham Offspring Cohort. *J Nutr.* 2009;139(6):1150-1156. [EL 2; PCS]
827. **Vincent-Baudry S, Defoort C, Gerber M, et al.** The Medi-RIVAGE study: reduction of cardiovascular disease risk factors after a 3-mo intervention with a Mediterranean-type diet or a low-fat diet. *Am J Clin Nutr.* 2005;82(5):964-971. [EL 2; PCS]
828. **Salas-Salvadó J, Fernández-Ballart J, Ros E, et al.** PREDIMED Study Investigators. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med*. 2008;168(22):2449-2458. [EL 1; RCT]
829. **Pasanisi F, Contaldo F, de Simone G, Mancini M.** Benefits of sustained moderate weight loss in obesity. *Nutr Metab Cardiovasc Dis*. 2001;11(6):401-406. [EL 4; NE]
830. **Van Gaal LF, Mertens IL, Ballaux D.** What is the relationship between risk factor reduction and degree of weight loss? *Eur Heart J Suppl*. 2005;7(Suppl L): L21-L26. [EL 3; CSS]
831. **Nordmann AJ, Nordmann A, Briel M, et al.** Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166(3):285-293. [EL 1; MRCT]
832. **Poobalan A, Aucott L, Smith WC, et al.** Effects of weight loss in overweight/obese individuals and long-term lipid outcomes--a systematic review. *Obes Rev*. 2004;5(1):43-50. [EL 2; MNRCT]
833. **Anderson JW, Konz EC.** Obesity and disease management: effects of weight loss on comorbid conditions. *Obes Res*. 2001;9 Suppl 4:326S-334S. [EL 2; MNRCT]
834. **Dattilo AM, Kris-Etherton PM.** Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr.* 1992;56(2):320-328. [EL 2; MNRCT]
835. **Morgan LM, Griffin BA, Millward DJ, et al.** Comparison of the effects of four commercially available weight-loss programmes on lipid-based cardiovascular risk factors. *Public Health Nutr.* 2009;12(6):799-807. [EL 1; RCT]
836. **Varady KA, Bhutani S, Klempel MC, Lamarche B.** Improvements in LDL particle size and distribution by short-term alternate day modified fasting in obese adults. *Br J Nutr.* 2011;105(4):580-583. [EL 2; PCS]
837. **Varady KA, Bhutani S, Klempel MC, Kroeger CM.** Comparison of effects of diet versus exercise weight loss regimens on LDL and HDL particle size in obese adults. *Lipids Health Dis*. 2011;10:119. [EL 1; RCT]
838. **Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT.** Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. *Am J Clin Nutr.* 2006;83(5):1025-1031; quiz 1205. [EL 1; RCT]
839. **Wood RJ, Volek JS, Liu Y, Shachter NS, Contois JH, Fernandez ML.** Carbohydrate restriction alters lipoprotein metabolism by modifying VLDL, LDL, and HDL subfraction distribution and size in overweight men. *J Nutr.* 2006;136(2):384-389. [EL 1; RCT]
840. **Richard C, Couture P, Ooi EM, et al.** Effect of Mediterranean diet with and without weight loss on apolipoprotein B100 metabolism in men with metabolic syndrome. *Arterioscler Thromb Vasc Biol*. 2014;34(2): 433-438. [EL 2; PCS]
841. **Sacks FM, Bray GA, Carey VJ, et al.** Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med*. 2009;360(9): 859-873. [EL 1; RCT]
842. **Bonow RO, Eckel RH.** Diet, obesity, and cardiovascular risk. *N Engl J Med*. 2003;348(21):2057-2058. [EL 4; NE]
843. **Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ.** Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA*. 2005; 293(1):43-53. [EL 1; RCT]
844. **Ratner R, Goldberg R, Haffner S, et al.** Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care*. 2005;28(4):888-894. [EL 1; RCT]

845. **Orchard TJ, Temprosa M, Goldberg R, et al.** The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005;142(8):611-619. [EL 1; RCT]
846. **Couillard C, Despres JP, Lamarche B, et al.** Effects of endurance exercise training on plasma HDL cholesterol levels depend on levels of triglycerides: evidence from men of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. *Arterioscler Thromb Vasc Biol*. 2001;21(7):1226-1232. [EL 2; PCS]
847. **Kokkinos PF, Holland JC, Narayan P, Colleran JA, Dotson CO, Papademetriou V.** Miles run per week and high-density lipoprotein cholesterol levels in healthy, middle-aged men. A dose-response relationship. *Arch Intern Med*. 1995;155(4):415-420. [EL 3; CSS]
848. **Kraus WE, Houmard JA, Duscha BD, et al.** Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med*. 2002;347(19):1483-1492. [EL 1; RCT]
849. **Duncan GE, Anton SD, Sydeman SJ, et al.** Prescribing exercise at varied levels of intensity and frequency: a randomized trial. *Arch Intern Med*. 2005;165(20):2362-2369. [EL 1; RCT]
850. **Fontana L, Villareal DT, Weiss EP, et al.** Calorie restriction or exercise: effects on coronary heart disease risk factors. A randomized, controlled trial. *Am J Physiol Endocrinol Metab*. 2007;293(1):E197-202. [EL 1; RCT]
851. **Durstine JL, Grandjean PW, Cox CA, Thompson PD.** Lipids, lipoproteins, and exercise. *J Cardiopulm Rehabil*. 2002;22(6):385-398. [EL 4; NE]
852. **Tambalis K, Panagiotakos DB, Kavouras SA, Sidossis LS.** Responses of blood lipids to aerobic, resistance, and combined aerobic with resistance exercise training: a systematic review of current evidence. *Angiology*. 2009; 60(5):614-632. [EL 4; NE]
853. **Pitsavos C, Panagiotakos DB, Tambalis KD, et al.** Resistance exercise plus to aerobic activities is associated with better lipids' profile among healthy individuals: the ATTICA study. *QJM*. 2009;102(9):609-616. [EL 1; RCT]
854. **Graham TE.** Exercise, postprandial triacylglyceridemia, and cardiovascular disease risk. *Can J Appl Physiol*. 2004; 29(6):781-799. [EL 4; NE]
855. **Dekker MJ, Graham TE, Ooi TC, Robinson LE.** Exercise prior to fat ingestion lowers fasting and postprandial VLDL and decreases adipose tissue IL-6 and GIP receptor mRNA in hypertriacylglycerolemic men. *J Nutr Biochem*. 2010;21(10):983-990. [EL 1; RCT]
856. **Rössner S, Sjöström L, Noack R, Meinders AE, Noseda G.** Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. *Obes Res*. 2000;8(1):49-61. [EL 1; RCT]
857. **Smith SR, Weissman NJ, Anderson CM, et al.** Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med*. 2010;363(3):245-256. [EL 1; RCT]
858. **Allison DB, Gadde KM, Garvey WT, et al.** Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)*. 2012;20(2):330-342. [EL 1; RCT]
859. **Wadden TA, Foreyt JP, Foster GD, et al.** Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)*. 2011;19(1):110-120. [EL 1; RCT]
860. **Tailleux A, Rouskas K, Pattou F, Staels B.** Bariatric surgery, lipoprotein metabolism and cardiovascular risk. *Curr Opin Lipidol*. 2015;26(4):317-324. [EL 4; NE]
861. **Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB.** Bariatric surgery and cardiovascular outcomes: a systematic review. *Heart*. 2012;98(24):1763-1777. [EL 2; MNRCT]
862. **Puzziferri N, Roshek TB, Mayo HG, Gallagher R, Belle SH, Livingston EH.** Long-term follow-up after bariatric surgery: a systematic review. *JAMA*. 2014;312(9):934-942. [EL 2; MNRCT]
863. **Adams TD, Davidson LE, Litwin SE, et al.** Health benefits of gastric bypass surgery after 6 years. *JAMA*. 2012;308(11):1122-1131. [EL 1; RCT]
864. **Heffron SP, Singh A, Zagzag J, et al.** Laparoscopic gastric banding resolves the metabolic syndrome and improves lipid profile over five years in obese patients with body mass index 30-40 kg/m(2.). *Atherosclerosis*. 2014;237(1):183-190. [EL 2; PCS]
865. **Aminian A, Zelisko A, Kirwan JP, Brethauer SA, Schauer PR.** Exploring the impact of bariatric surgery on high density lipoprotein. *Surg Obes Relat Dis*. 2015;11(1):238-247. [EL 4; NE]
866. **Julve J, Pardina E, Pérez-Cuéllar M, et al.** Bariatric surgery in morbidly obese patients improves the atherogenic qualitative properties of the plasma lipoproteins. *Atherosclerosis*. 2014;234(1):200-205. [EL 2; PCS]
867. **United States Department of Agriculture, Department of Health and Human Services.** Scientific report of the 2015 dietary guidelines advisory committee: advisory report to the secretary of health and human services and the secretary of agriculture. Available at: http://www.health.gov/dietaryguidelines/2015-scientific-report/PDFs/Scientific-Report-of-the-2015-Dietary-Guidelines-Advisory-Committee.pdf. Health.gov. 2015. [EL 4; NE]
868. **Ridker PM, Danielson E, Fonseca FA, et al.** Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207. [EL 1; RCT]
869. **Pal S, Khossousi A, Binns C, Dhaliwal S, Radavelli-Bagatini S.** The effects of 12-week psyllium fibre supplementation or healthy diet on blood pressure and arterial stiffness in overweight and obese individuals. *Br J Nutr*. 2012;107(5):725-734. [EL 1; RCT]
870. **Hu X, Gao J, Zhang Q, et al.** Soy fiber improves weight loss and lipid profile in overweight and obese adults: a randomized controlled trial. *Mol Nutr Food Res*. 2013; 57(12):2147-2154. [EL 1; RCT]
871. **Sharafedtinov KK, Plotnikova OA, Alexeeva RI, et al.** Hypocaloric diet supplemented with probiotic cheese improves body mass index and blood pressure indices of obese hypertensive patients--a randomized double-blind placebo-controlled pilot study. *Nutr J*. 2013;12:138. [EL 1; RCT]
872. **Lopes HF, Martin KL, Nashar K, Morrow JD, Goodfriend TL, Egan BM.** DASH diet lowers blood pressure and lipid-induced oxidative stress in obesity. *Hypertension*. 2003;41(3):422-430. [EL 1; RCT, N = 24]
873. **Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L.** Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases--incidence: a systematic review and meta-analysis on observational prospective studies. *Nutrition*. 2013;29(4):611-618. [EL 2; MNRCT]
874. **Parikh A, Lipsitz SR, Natarajan S.** Association between a DASH-like diet and mortality in adults with hypertension:

findings from a population-based follow-up study. *Am J Hypertens*. 2009;22(4):409-416. [EL 2; PCS]

875. **Al-Solaiman Y, Jesri A, Mountford WK, Lackland DT, Zhao Y, Egan BM.** DASH lowers blood pressure in obese hypertensives beyond potassium, magnesium and fibre. *J Hum Hypertens*. 2010;24(4):237-246. [EL 1; RCT]
876. **Sánchez-Taínta A, Estruch R, Bulló M, et al.** Adherence to a Mediterranean-type diet and reduced prevalence of clustered cardiovascular risk factors in a cohort of 3,204 high-risk patients. *Eur J Cardiovasc Prev Rehabil*. 2008;15(5):589-593. [EL 3; CSS, baseline for RCT]
877. **Siebenhofer A, Jeitler K, Berghold A, et al.** Long-term effects of weight-reducing diets in hypertensive patients. *Cochrane Database Syst Rev*. 2011;(9):CD008274. [EL 1; MRCT]
878. **Staessen J, Fagard R, Amery A.** The relationship between body weight and blood pressure. *J Hum Hypertens*. 1988;2(4):207-217. [EL 4; NE]
879. **Blumenthal JA, Babyak MA, Hinderliter A, et al.** Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Arch Intern Med*. 2010;170(2):126-135. [EL 1; RCT]
880. **Fogari R, Zoppi A, Corradi L, et al.** Effect of body weight loss and normalization on blood pressure in overweight non-obese patients with stage 1 hypertension. *Hypertens Res*. 2010;33(3):236-242. [EL 2; PCS]
881. **Metz JA, Stern JS, Kris-Etherton P, et al.** A randomized trial of improved weight loss with a prepared meal plan in overweight and obese patients: impact on cardiovascular risk reduction. *Arch Intern Med*. 2000;160(14):2150-2158. [EL 1; RCT]
882. **Brehm BJ, Lattin BL, Summer SS, et al.** One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. *Diabetes Care*. 2009;32(2):215-220. [EL 1; RCT]
883. **Davis NJ, Tomuta N, Schechter C, et al.** Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. *Diabetes Care*. 2009;32(7):1147-1152. [EL 1; RCT]
884. **Larsen RN, Mann NJ, Maclean E, Shaw JE.** The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. *Diabetologia*. 2011;54(4):731-740. [EL 1; RCT]
885. **Krebs JD, Elley CR, Parry-Strong A, et al.** The Diabetes Excess Weight Loss (DEWL) Trial: a randomised controlled trial of high-protein versus high-carbohydrate diets over 2 years in type 2 diabetes. *Diabetologia*. 2012;55(4):905-914. [EL 1; RCT]
886. **Guldbrand H, Dizdar B, Bunjaku B, et al.** In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. *Diabetologia*. 2012;55(8):2118-2127. [EL 1; RCT]
887. **Esposito K, Maiorino MI, Ciotola M, et al.** Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med*. 2009;151(5):306-314. [EL 1; RCT]
888. **Pi-Sunyer X, Blackburn G, Brancati FL, et al.** Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care*. 2007;30(6):1374-1383. [EL 1; RCT]
899. **Croymans DM, Krell SL, Oh CS, et al.** Effects of resistance training on central blood pressure in obese young men. *J Hum Hypertens*. 2014;28(3):157-164. [EL 1; RCT]
890. **Ho SS, Radavelli-Bagatini S, Dhaliwal SS, Hills AP, Pal S.** Resistance, aerobic, and combination training on vascular function in overweight and obese adults. *J Clin Hypertens*. 2012;14(12):848-854. [EL 1; RCT]
891. **Cornelissen VA, Smart NA.** Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc*. 2013;2(1):e004473. [EL 1; MRCT]
892. **Kokkinos P.** Cardiorespiratory fitness, exercise, and blood pressure. *Hypertension*. 2014;64(6):1160-1164. [EL 4; NE]
893. **Barlow CE, LaMonte MJ, Fitzgerald SJ, Kampert JB, Perrin JL, Blair SN.** Cardiorespiratory fitness is an independent predictor of hypertension incidence among initially normotensive healthy women. *Am J Epidemiol*. 2006;163(2):142-150. [EL 2; PCS, N = 4884]
894. **Huai P, Xun H, Reilly KH, Wang Y, Ma W, Xi B.** Physical activity and risk of hypertension: a meta-analysis of prospective cohort studies. *Hypertension*. 2013;62(6):1021-1026. [EL 2; MNRCT]
895. **Bushman B.** Promoting exercise as medicine for prediabetes and prehypertension. *Curr Sports Med Rep*. 2014;13(4):233-239. [EL 4; NE]
896. **Donnelly JE, Blair SN, Jakicic JM, et al.** American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc*. 2009;41(2):459-471. [EL 4; NE]
897. **Astrup A, Carraro R, Finer N, et al.** Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes*. 2012;36(6):843-854. [EL 1; RCT]
898. **Pontiroli AE, Folli F, Paganelli M, et al.** Laparoscopic gastric banding prevents type 2 diabetes and arterial hypertension and induces their remission in morbid obesity: a 4-year case-controlled study. *Diabetes Care*. 2005;28(11):2703-2709. [EL 2; NRCT]
899. **Wilhelm SM, Young J, Kale-Pradhan PB.** Effect of bariatric surgery on hypertension: a meta-analysis. *Ann Pharmacother*. 2014;48(6):674-682. [EL 2; MNRCT]
900. **Müller-Stich BP, Senft JD, Warschkow R, et al.** Surgical versus medical treatment of type 2 diabetes mellitus in nonseverely obese patients: a systematic review and meta-analysis. *Ann Surg*. 2015;261(3):421-429. [EL 2; MNRCT]
901. **Lemanu DP, Singh PP, Rahman H, Hill AG, Babor R, MacCormick AD.** Five-year results after laparoscopic sleeve gastrectomy: a prospective study. *Surg Obes Relat Dis*. 2015;11(3):518-524. [EL 2; PCS]
902. **Marceau P, Biron S, Marceau S, et al.** Long-term metabolic outcomes 5 to 20 years after biliopancreatic diversion. *Obes Surg*. 2015;25(9):1584-1593. [EL 3; SS, N = 2,615]
903. **Thereaux J, Czernichow S, Corigliano N, Poitou C, Oppert JM, Bouillot JL.** Five-year outcomes of gastric bypass for super-super-obesity (BMI ≥60 kg/m^2): a case matched study. *Surg Obes Relat Dis*. 2015;11(1):32-37. [EL 2; RCCS]
904. **Golomb I, Ben David M, Glass A, Kolitz T, Keidar A.** Long-term metabolic effects of laparoscopic sleeve gastrectomy. *JAMA Surg*. 2015;150(11):1051-1057. [EL 2; PCS, retrospective analysis]

905. **Young MT, Gebhart A, Khalaf R, et al.** One-year outcomes of laparoscopic sleeve gastrectomy versus laparoscopic adjustable gastric banding for the treatment of morbid obesity. *Am Surg*. 2014;80(10):1049-1053. [EL 3; SS, retrospective matched cohort]
906. **Benaiges D, Sagué M, Flores-Le Roux JA, et al.** Predictors of hypertension remission and recurrence after bariatric surgery. *Am J Hypertens*. 2015; 29(5):653-659. [EL 2; PCS]
907. **de Barros F, Setúbal S, Martinho JM, Monteiro AB.** Early endocrine and metabolic changes after bariatric surgery in grade III morbidly obese patients: a randomized clinical trial comparing sleeve gastrectomy and gastric bypass. *Metab Syndr Relat Disord*. 2015;13(6):264-271. [EL 1; RCT]
908. **Huang CK, Garg A, Kuao HC, Chang PC, Hsin MC.** Bariatric surgery in old age: a comparative study of laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy in an Asia centre of excellence. *J Biomed Res*. 2015;29(2):118-124. [EL 2; PCS, retrospective analysis]
909. **Batsis JA, Miranda WR, Prasad C, et al.** Effect of bariatric surgery on cardiometabolic risk in elderly patients: a population-based study. *Geriatr Gerontol Int*. 2016;16(5):618-624. [EL 2; PCS]
910. **Abbas M, Cumella L, Zhang Y, et al.** Outcomes of laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass in patients older than 60. *Obes Surg*. 2015;25(12): 2251-2256. [EL 3; SS]
911. **Pequignot A, Prevot F, Dhahri A, Rebibo L, Badaoui R, Regimbeau JM.** Is sleeve gastrectomy still contraindicated for patients aged ≥60 years? A case-matched study with 24 months of follow-up. *Surg Obes Relat Dis*. 2015;11(5):1008-1013. [EL 2; PCS, retrospective analysis]
912. **Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C.** Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged 40-64 years. *Am J Epidemiol*. 1995;141(12):1128-1141. [EL 2; PCS, retrospective analysis, N = 43,457]
913. **Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C.** Prospective study of intentional weight loss and mortality in overweight white men aged 40-64 years. *Am J Epidemiol*. 1999;149(6):491-503. [EL 2; PCS, retrospective analysis, N = 43,457]
914. **Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T.** Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care*. 2000;23(10):1499-1504. [EL 2; PCS]
915. **Kritchevsky SB, Beavers KM, Miller ME, et al.** Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. *PLoS One*. 2015;10(3):e0121993. [EL 1; MRCT]
916. **Pack QR, Rodriguez-Escudero JP, Thomas RJ, et al.** The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. *Mayo Clin Proc*. 2014;89(10):1368-1377. [EL 2; MNRCT]
917. **Sjöström L, Narbro K, Sjöström CD, et al.** Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357(8):741-752. [EL 2; PCS]
918. **Adams TD, Gress RE, Smith SC, et al.** Long-term mortality after gastric bypass surgery. *N Engl J Med*. 2007;357(8):753-761. [EL 3; SS, retrospective cohort, matched for age, sex, and BMI, N = 9.949]
919. **Flum DR, Dellinger EP.** Impact of gastric bypass operation on survival: a population-based analysis. *J Am Coll Surg*. 2004;199(4):543-551. [EL 2; PCS]
920. **Maciejewski ML, Livingston EH, Smith VA, et al.** Survival among high-risk patients after bariatric surgery. *JAMA*. 2011;305(23):2419-2426. [EL 3; SS, retrospective cohort]
921. **Arterburn DE, Olsen MK, Smith VA, et al.** Association between bariatric surgery and long-term survival. *JAMA*. 2015;313(1):62-70. [EL 3; SS, retrospective cohort]
922. **Kwok CS, Pradhan A, Khan MA, et al.** Bariatric surgery and its impact on cardiovascular disease and mortality: a systematic review and meta-analysis. *Int J Cardiol*. 2014;173(1):20-28. [EL 2; MNRCT]
923. **Pontiroli AE, Morabito A.** Long-term prevention of mortality in morbid obesity through bariatric surgery. a systematic review and meta-analysis of trials performed with gastric banding and gastric bypass. *Ann Surg*. 2011;253(3):484-487. [EL 2; MNRCT]
924. **Williamson DF.** Weight loss and mortality in persons with type-2 diabetes mellitus: a review of the epidemiological evidence. *Exp Clin Endocrinol Diabetes*. 1998;(106 Suppl 2):14-21. [EL 4; NE]
925. **Harrington M, Gibson S, Cottrell RC.** A review and meta-analysis of the effect of weight loss on all-cause mortality risk. *Nutr Res Rev*. 2009;22(1):93-108. [EL 2; MNRCT]
926. **Romeo S, Maglio C, Burza MA, et al.** Cardiovascular events after bariatric surgery in obese subjects with type 2 diabetes. *Diabetes Care*. 2012;35(12):2613-2617. [EL 2; PCS]
927. **Alpert MA, Terry BE, Mulekar M, et al.** Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. *Am J Cardiol*. 1997;80(6):736-740. [EL 2; PCS]
928. **Alexander JK, Peterson KL.** Cariovascular effects of weight reduction. *Circulation*. 1972;45(2):310-318. [EL 2; PCS, N = 9]
929. **Alpert MA, Terry BE, Kelly DL.** Effect of weight loss on cardiac chamber size, wall thickness and left ventricular function in morbid obesity. *Am J Cardiol*. 1985;55(6):783-786. [EL 2; PCS]
930. **Alpert MA, Terry BE, Lambert CR, et al.** Factors influencing left ventricular systolic function in nonhypertensive morbidly obese patients, and effect of weight loss induced by gastroplasty. *Am J Cardiol*. 1993; 71(8):733-737. [EL 2; PCS]
931. **Kunju SU, Badarudeen S, Schwarz ER.** Impact of obesity in patients with congestive heart failure. *Rev Cardiovasc Med*. 2009;10(3):142-151. [EL 4; NE]
932. **Alpert MA, Fraley MA, Birchem JA, Senkottaiyan N.** Management of obesity cardiomyopathy. *Expert Rev Cardiovasc Ther*. 2005;3(2):225-230. [EL 4; NE]
933. **Guglin M, Verma S, Chen R.** Association between weight loss and improvement of ventricular systolic function in advanced heart failure. *Congest Heart Fail*. 2013;19(4):186-191. [EL 2; PCS]
934. **Alsabrook GD, Goodman HR, Alexander JW.** Gastric bypass for morbidly obese patients with established cardiac disease. *Obes Surg*. 2006;16(10):1272-1277. [EL 2; PCS]
935. **Ristow B, Rabkin J, Haeusslein E.** Improvement in dilated cardiomyopathy after bariatric surgery. *J Card Fail*. 2008;14(3):198-202. [EL 3; SCR]
936. **MacMahon SW, Wilcken DE, Macdonald GJ.** The effect of weight reduction on left ventricular mass. A

randomized controlled trial in young, overweight hypertensive patients. *N Engl J Med*. 1986;314(6):334-339. [EL 1; RCT]

937. **Reid CM, Dart AM, Dewar EM, Jennings GL.** Interactions between the effects of exercise and weight loss on risk factors, cardiovascular haemodynamics and left ventricular structure in overweight subjects. *J Hypertens*. 1994;12(3):291-301. [EL 1; RCT]
938. Pocock SJ, McMurray JJ, Dobson J, et al. Weight loss and mortality risk in patients with chronic heart failure in the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) programme. *Eur Heart J*. 2008;29(21):2641-2650. [EL 3; SS]
939. **Yancy CW, Jessup M, Bozkurt B, et al.** 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239. [EL 4; NE]
940. **Remme WJ, Swedberg K, Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology.** Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J*. 2001; 22(17):1527-1560. [EL 4; NE]
941. **McMurray JJ, Adamopoulos S, Anker SD, et al.** ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012; 14(8):803-869. [EL 4; NE]
942. **Suzuki A, Lindor K, St Saver J, et al.** Effect of changes on body weight and lifestyle in nonalcoholic fatty liver disease. *J Hepatol*. 2005;43(6):1060-1066. [EL 3; SS]
943. **Lazo M, Solga SF, Horska A, et al.** Fatty Liver Subgroup of the Look AHEAD Research Group. Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. *Diabetes Care*. 2010;33(10):2156-2163. [EL 1; RCT, post-hoc analysis]
944. **Bacchi E, Negri C, Targher G, et al.** Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 Randomized Trial). *Hepatology*. 2013;58(4):1287-1295. [EL 1; RCT]
945. **Sullivan S, Kirk EP, Mittendorfer B, Patterson BW, Klein S.** Randomized trial of exercise effect on intrahepatic triglyceride content and lipid kinetics in nonalcoholic fatty liver disease. *Hepatology*. 2012;55(6):1738-1745. [EL 1; RCT]
946. **Oh S, Tanaka K, Tsujimoto T, So R, Shida T, Shoda J.** Regular exercise coupled to diet regimen accelerates reduction of hepatic steatosis and associated pathological conditions in nonalcoholic fatty liver disease. *Metab Syndr Relat Disord*. 2014;12(5):290-298. [EL 2; PCS]
947. **Goodpaster BH, Delany JP, Otto AD, et al.** Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: a randomized trial. *JAMA*. 2010;304(16):1795-1802. [EL 1; RCT]
948. **Copaci I, Lupescu I, Caceaune E, Chiriac G, Ismail G.** Noninvasive markers of improvement of liver steatosis achieved by weight reduction in patients with nonalcoholic fatty liver disease. *Rom J Intern Med*. 2015; 53(1):54-62. [EL 2; PCS]
949. **Montesi L, Caselli C, Centis E, et al.** Physical activity support or weight loss counseling for nonalcoholic fatty liver disease? *World J Gastroenterol*. 2014;20(29):10128-10136. [EL 2; NRCT]
950. **Elias MC, Parise ER, de Carvalho L, Szejnfeld D, Netto JP.** Effect of 6-month nutritional intervention on non-alcoholic fatty liver disease. *Nutrition*. 2010;26(11-12):1094-1099. [EL 2; PCS]
951. **Kani AH, Alavian SM, Esmaillzadeh A, Adibi P, Azadbakht L.** Effects of a novel therapeutic diet on liver enzymes and coagulating factors in patients with non-alcoholic fatty liver disease: a parallel randomized trial. *Nutrition*. 2014;30(7-8):814-821. [EL 1; RCT]
952. **Hickman IJ, Jonsson JR, Prins JB, et al.** Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut*. 2004;53(3):413-419. [EL 2; PCS]
953. **Aller R, de Luis DA, Izaola O, de la Fuente B, Bachiller R.** Effect of a high monounsaturated vs high polyunsaturated fat hypocaloric diets in nonalcoholic fatty liver disease. *Eur Rev Med Pharmacol Sci*. 2014; 18(7):1041-1047. [EL 1; RCT]
954. **Oh S, Shida T, Yamagishi K, et al.** Moderate to vigorous physical activity volume is an important factor for managing nonalcoholic fatty liver disease: a retrospective study. *Hepatology*. 2015;61(4):1205-1215. [EL 3; SS]
955. **Yoshimura E, Kumahara H, Tobina T, et al.** Lifestyle intervention involving calorie restriction with or without aerobic exercise training improves liver fat in adults with visceral adiposity. *J Obes*. 2014;2014:197216. [EL 1; RCT]
956. **Zelber-Sagi S, Buch A, Yeshua H, et al.** Effect of resistance training on non-alcoholic fatty-liver disease a randomized-clinical trial. *World J Gastroenterol*. 2014; 20(15):4382-4392. [EL 1; RCT]
957. **Kechagias S, Ernersson A, Dahlqvist O, et al.** Fast-food-based hyper-alimentation can induce rapid and profound elevation of serum alanine aminotransferase in healthy subjects. *Gut*. 2008;57(5):649-654. [EL 2; PCS]
958. **Wong VW, Chan RS, Wong GL, et al.** Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. *J Hepatol*. 2013;59(3):536-542. [EL 1; RCT]
959. **Nigam P, Bhatt S, Misra A, et al.** Effect of a 6-month intervention with cooking oils containing a high concentration of monounsaturated fatty acids (olive and canola oils) compared with control oil in male Asian Indians with nonalcoholic fatty liver disease. *Diabetes Technol Ther*. 2014;16(4):255-261. [EL 1; RCT]
960. **Lewis MC, Phillips ML, Slavotinek JP, Kow L, Thompson CH, Toouli J.** Change in liver size and fat content after treatment with Optifast very low calorie diet. *Obes Surg*. 2006;16(6):697-701. [EL 2; PCS]
961. **Del Ben M, Polimeni L, Baratta F, Pastori D, Loffredo L, Angelico F.** Modern approach to the clinical management of non-alcoholic fatty liver disease. *World J Gastroenterol*. 2014;20(26):8341-8350. [EL 4; NE]
962. **Chang HC, Huang CN, Yeh DM, Wang SJ, Peng CH, Wang CJ.** Oat prevents obesity and abdominal fat distribution, and improves liver function in humans. *Plant Foods Hum Nutr*. 2013;68(1):18-23. [EL 1; RCT, N = 34]
963. **Parnell JA, Raman M, Rioux KP, Reimer RA.** The potential role of prebiotic fibre for treatment and management of non-alcoholic fatty liver disease and associated obesity and insulin resistance. *Liver Int*. 2012; 32(5):701-711. [EL 4; NE]

964. **Magosso E, Ansari MA, Gopalan Y, et al.** Tocotrienols for normalisation of hepatic echogenic response in nonalcoholic fatty liver: a randomised placebo-controlled clinical trial. *Nutr J*. 2013;12(1):166. [EL 1; RCT]
965. **Athyros VG, Mikhailidis DP, Didangelos TP, et al.** Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study. *Curr Med Res Opin*. 2006;22(5):873-883. [EL 1; RCT]
966. **Shao N, Kuang HY, Hao M, Gao XY, Lin WJ, Zou W.** Benefits of exenatide on obesity and non-alcoholic fatty liver disease with elevated liver enzymes in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2014;30(6):521-529. [EL 1; RCT]
967. **Promrat K, Kleiner DE, Niemeier HM, et al.** Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology*. 2010; 51(1):121-129. [EL 1; RCT]
968. **Assy N, Hussein O, Abassi Z.** Weight loss induced by orlistat reverses fatty infiltration and improves hepatic fibrosis in obese patients with non-alcoholic steatohepatitis. *Gut*. 2007;56(3):443-444. [EL 2; PCS]
969. **Armstrong MJ, Gaunt P, Aithal GP, et al. LEAN trial team.** Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387(10019):679-690. [EL 1; RCT]
970. **Armstrong MJ, Hull D, Guo K, et al.** Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. *J Hepatol*. 2016;64(2):399-408. [EL 1; RCT, small N = 14]
971. **Eguchi Y, Kitajima Y, Hyogo H, et al.** Pilot study of liraglutide effects in non-alcoholic steatohepatitis and non-alcoholic fatty liver disease with glucose intolerance in Japanese patients (LEAN-J). *Hepatol Res*. 2015;45(3):269-278. [EL 2; PCS]
972. **Cuthbertson DJ, Irwin A, Gardner CJ, et al.** Improved glycaemia correlates with liver fat reduction in obese, type 2 diabetes, patients given glucagon-like peptide-1 (GLP-1) receptor agonists. *PLoS One*. 2012;7(12):e50117. [EL 2; PCS]
973. **Armstrong MJ, Houlihan DD, Rowe IA, et al.** Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. *Aliment Pharmacol Ther*. 2013;37(2):234-242. [EL 1; MRCT]
974. **Ohki T, Isogawa A, Iwamoto M, et al.** The effectiveness of liraglutide in nonalcoholic fatty liver disease patients with type 2 diabetes mellitus compared to sitagliptin and pioglitazone. *Scientific World J*. 2012;2012:496453. [EL 3; SS]
975. **Liu X, Lazenby AJ, Clements RH, Jhala N, Abrams GA.** Resolution of nonalcoholic steatohepatits after gastric bypass surgery. *Obes Surg*. 2007;17(4):486-492. [EL 3; SS]
976. **Barker KB, Palekar NA, Bowers SP, Goldberg JE, Pulcini JP, Harrison SA.** Non-alcoholic steatohepatitis: effect of Roux-en-Y gastric bypass surgery. *Am J Gastroenterol*. 2006;101(2):368-373. [EL 2; PCS]
977. **Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK.** Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2008;6(12):1396-1402. [EL 2; MNRCT]
978. **Pasquali R, Antenucci D, Casimirri F, et al.** Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. *J Clin Endocrinol Metab*. 1989;68(1):173-179. [EL 2; PCS, N = 20]
979. **Pasquali R, Fabbri R, Venturoli S, Paradisi R, Antenucci D, Melchionda N.** Effect of weight loss and antiandrogenic therapy on sex hormone blood levels and insulin resistance in obese patients with polycystic ovaries. *Am J Obstet Gynecol*. 1986;154(1):139-144. [EL 1; RCT]
980. **Pasquali R, Gambineri A, Biscotti D, et al.** Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2000;85(8):2767-2774. [EL 1; RCT]
981. **Kiddy DS, Hamilton-Fairley D, Bush A, et al.** Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol*. 1992;36(1):105-111. [EL 2; PCS]
982. **Kiddy DS, Hamilton-Fairley D, Seppälä M, et al.** Diet-induced changes in sex hormone binding globulin and free testosterone in women with normal or polycystic ovaries: correlation with serum insulin and insulin-like growth factor-I. *Clin Endocrinol*. 1989;31(6):757-763. [EL 1; RCT, small N = 11]
983. **Hamilton-Fairley D, Kiddy D, Anyaoku V, Koistinen R, Seppälä M, Franks S.** Response of sex hormone binding globulin and insulin-like growth factor binding protein-1 to an oral glucose tolerance test in obese women with polycystic ovary syndrome before and after calorie restriction. *Clin Endocrinol*. 1993;39(3):363-367. [EL 2; PCS]
984. **Andersen P, Seljeflot I, Abdelnoor M, et al.** Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome. *Metabolism*. 1995;44(5):611-616. [EL 2; PCS]
985. **Holte J, Bergh T, Berne C, Wide L, Lithell H.** Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 1995;80(9):2586-2593. [EL 2; PCS, BMI matched]
986. **Jakubowicz DJ, Nestler JE.** 17 alpha-Hydroxy-progesterone responses to leuprolide and serum androgens in obese women with and without polycystic ovary syndrome offer dietary weight loss. *J Clin Endocrinol Metab*. 1997;82(2):556-560. [EL 2; PCS]
987. **Wahrenberg H, Ek I, Reynisdottir S, Carlström K, Bergqvist A, Arner P.** Divergent effects of weight reduction and oral anticonception treatment on adrenergic lipolysis regulation in obese women with the polycystic ovary syndrome. *J Clin Endocrinol Metab*. 1999;84(6): 2182-2187. [EL 2; PCS]
988. **Van Dam EW, Roelfsema F, Veldhuis JD, et al.** Increase in daily LH secretion in response to short-term calorie restriction in obese women with PCOS. *Am J Physiol Endocrinol Metab*. 2002;282(4):E865-E672. [EL 2; PCS]
989. **van Dam EW, Roelfsema F, Veldhuis JD, et al.** Retention of estradiol negative feedback relationship to LH predicts ovulation in response to caloric restriction and weight loss in obese patients with polycystic ovary syndrome. *Am J Physiol Endocrinol Metab*. 2004;286(4):E615-E620. [EL 2; PCS]
990. **Tolino A, Gambardella V, Caccavale C, et al.** Evaluation of ovarian functionality after a dietary treatment in obese women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol*. 2005;119(1):87-93. [EL 2; PCS]

991. **Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ.** Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2003;88(2):812-819. [EL 1; RCT]
992. **Moran LJ, Noakes M, Clifton PM, Wittert GA, Williams G, Norman RJ.** Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome. *Am J Clin Nutr*. 2006;84(1):77-87. [EL 2; PCS]
993. **Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS.** A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. *Fertil Steril*. 2004;81(3):630-637. [EL 1; RCT]
994. **Hays JH, DiSabatino A, Gorman RT, Vincent S, Stillabower ME.** Effect of a high saturated fat and no-starch diet on serum lipid subfractions in patients with documented atherosclerotic cardiovascular disease. *Mayo Clin Proc*. 2003;78(11):1331-1336. [EL 2; PCS]
995. **Mavropoulos JC, Yancy WS, Hepburn J, Westman EC.** The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: a pilot study. *Nutr Metab*. 2005;2:35. [EL 2; PCS]
996. **Palomba S, Giallauria F, Falbo A, et al.** Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. *Hum Reprod*. 2008;23(3):642-650. [EL 2; PCS]
997. **Vigorito C, Giallauria F, Palomba S, et al.** Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2007;92(4):1379-1384. [EL 1; RCT]
998. **Bruner B, Chad K, Chizen D.** Effects of exercise and nutritional counseling in women with polycystic ovary syndrome. *Appl Physiol Nutr Metab*. 2006;31(4):384-391. [EL 1; RCT, small N = 12]
999. **Randeva HS, Lewandowski KC, Drzewoski J, et al.** Exercise decreases plasma total homocysteine in overweight young women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2002;87(10):4496-4501. [EL 2; PCS]
1000. **Guzick DS, Wing R, Smith D, Berga SL, Winters SJ.** Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. *Fertil Steril*. 1994;61(4):598-604. [EL 1; RCT]
1001. **Clark AM, Ledger W, Galletly C, et al.** Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod*. 1995;10(10):2705-2712. [EL 2; PCS]
1002. **Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ.** Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod*. 1998;13(6):1502-1505. [EL 2; PCS]
1003. **Huber-Buchholz MM, Carey DG, Norman RJ.** Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab*. 1999;84(4):1470-1474. [EL 2; PCS]
1004. **Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS.** A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. *Fertil Steril*. 2004; 82(2): 421-429. [EL 1; RCT]
1005. **Tang T, Glanville J, Hayden CJ, White D, Barth JH, Balen AH.** Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. *Hum Reprod*. 2006;21(1):80-89. [EL 1; RCT]
1006. **Jayagopal V, Kilpatrick ES, Holding S, Jennings PE, Atkin SL.** Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. *J Clin Endocrinol Metab*. 2005;90(2):729-733. [EL 1; RCT]
1007. **Diamanti-Kandarakis E, Katsikis I, Piperi C, Alexandraki K, Panidis D.** Effect of long-term orlistat treatment on serum levels of advanced glycation end-products in women with polycystic ovary syndrome. *Clin Endocrinol*. 2007;66(1):103-109. [EL 2; PCS]
1008. **Panidis D, Farmakiotis D, Rousso D, Kourtis A, Katsikis I, Krassas G.** Obesity, weight loss, and the polycystic ovary syndrome: effect of treatment with diet and orlistat for 24 weeks on insulin resistance and androgen levels. *Fertil Steril*. 2008;89(4):899-906. [EL 2; PCS]
1009. **Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millán JL.** The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *J Clin Endocrinol Metab*. 2005;90(12):6364-6369. [EL 2; PCS]
1010. **Eid GM, Cottam DR, Velcu LM, et al.** Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2005;1(2):77-80. [EL 3; SS]
1011. **Jamal M, Gunay Y, Capper A, Eid A, Heitshusen D, Samuel I.** Roux-en-Y gastric bypass ameliorates polycystic ovary syndrome and dramatically improves conception rates: a 9-year analysis. *Surg Obes Relat Dis*. 2012;8(4):440-444. [EL 3; CSS]
1012. **Gomez-Meade CA, Lopez-Mitnik G, Messiah SE, Arheart KL, Carrillo A, de la Cruz-Muñoz N.** Cardiometabolic health among gastric bypass surgery patients with polycystic ovarian syndrome. *World J Diabetes*. 2013;4(3):64-69. [EL 3; SS]
1013. **Kuchenbecker WK, Groen H, van Asselt SJ, et al.** In women with polycystic ovary syndrome and obesity, loss of intra-abdominal fat is associated with resumption of ovulation. *Hum Reprod*. 2011;26(9):2505-2512. [EL 2; PCS]
1014. **Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD.** The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;93(9):3373-3380. [EL 1; RCT]
1015. **Pasquali R, Gambineri A, Cavazza C, et al.** Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. *Eur J Endocrinol*. 2011; 164(1):53-60. [EL 2; RCT]
1016. **Panidis D, Tziomalos K, Papadakis E, et al.** The role of orlistat combined with lifestyle changes in the management of overweight and obese patients with polycystic ovary syndrome. *Clin Endocrinol*. 2014;80(3): 432-438. [EL 2; PCS]
1017. **Cho LW, Kilpatrick ES, Keevil BG, Coady AM, Atkin SL.** Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary syndrome. *Clin Endocrinol*. 2009;70(2):233-237. [EL 1; RCT]
1018. **Ghandi S, Aflatoonian A, Tabibnejad N, Moghaddam MH.** The effects of metformin or orlistat on obese women

with polycystic ovary syndrome: a prospective randomized open-label study. *J Assist Reprod Genet*. 2011;28(7):591-596. [EL 1; RCT]

1019. **Metwally M, Amer S, Li TC, Ledger WL.** An RCT of metformin versus orlistat for the management of obese anovulatory women. *Hum Reprod*. 2009;24(4):966-975. [EL 1; RCT]
1020. **Sabuncu T, Harma M, Harma M, Nazligul Y, Kilic F.** Sibutramine has a positive effect on clinical and metabolic parameters in obese patients with polycystic ovary syndrome. *Fertil Steril*. 2003;80(5):1199-1204. [EL 1; RCT]
1021. **Florakis D, Diamanti-Kandarakis E, Katsikis I, et al.** Effect of hypocaloric diet plus sibutramine treatment on hormonal and metabolic features in overweight and obese women with polycystic ovary syndrome: a randomized, 24-week study. *Int J Obes*. 2008;32(4):692-699. [EL 1; RCT]
1022. **Sathyapalan T, Cho LW, Kilpatrick ES, Coady AM, Atkin SL.** A comparison between rimonabant and metformin in reducing biochemical hyperandrogenaemia and insulin resistance in patients with polycystic ovary syndrome (PCOS): a randomized open-label parallel study. *Clin Endocrinol*. 2008;69(6):931-935. [EL 1; RCT]
1023. **Rasmussen CB, Lindenberg S.** The effect of liraglutide on weight loss in women with polycystic ovary syndrome: an observational study. *Front Endocrinol*. 2014;5:140. [EL 2; PCS]
1024. **Jensterle Sever M, Kocjan T, Pfeifer M, Kravos NA, Janez A.** Short-term combined treatment with liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary syndrome and previous poor response to metformin. *Eur J Endocrinol*. 2014;170(3):451-459. [EL 1; RCT]
1025. **Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH.** Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev*. 2010;(1):CD003053. [EL 1; MRCT]
1026. **Palomba S, Falbo A, La Sala GB.** Metformin and gonadotropins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials. *Reprod Biol Endocrinol*. 2014;12:3. [EL 1; MRCT]
1027. **Xiao J, Chen S, Zhang C, Chang S.** The effectiveness of metformin ovulation induction treatment in patients with PCOS: a systematic review and meta-analysis. *Gynecol Endocrinol*. 2012;28(12):956-960. [EL 1; MRCT]
1028. **Siebert TI, Viola MI, Steyn DW, Kruger TF.** Is metformin indicated as primary ovulation induction agent in women with PCOS? A systematic review and meta-analysis. *Gynecol Obstet Invest*. 2012;73(4):304-313. [EL 2; MNRCT]
1029. **Johnson N.** Metformin is a reasonable first-line treatment option for non-obese women with infertility related to anovulatory polycystic ovary syndrome--a meta-analysis of randomised trials. *Aust N Z J Obstet Gynaecol*. 2011;51(2):125-129. [EL 1; MRCT]
1030. **Du Q, Yang S, Wang YJ, Wu B, Zhao YY, Fan B.** Effects of thiazolidinediones on polycystic ovary syndrome: a meta-analysis of randomized placebo-controlled trials. *Adv Ther*. 2012;29(9):763-774. [EL 1; MRCT]
1031. **Li XJ, Yu YX, Liu CQ, et al.** Metformin vs thiazolidinediones for treatment of clinical, hormonal and metabolic characteristics of polycystic ovary syndrome: a meta-analysis. *Clin Endocrinol*. 2011;74(3):332-339. [EL 1; MRCT]
1032. **Kort JD, Winget C, Kim SH, Lathi RB.** A retrospective cohort study to evaluate the impact of meaningful weight loss on fertility outcomes in an overweight population with infertility. *Fertil Steril*. 2014;101(5):1400-1403. [EL 3; SS, retrospective cohort]
1033. **Hollmann M, Runnebaum B, Gerhard I.** Effects of weight loss on the hormonal profile in obese, infertile women. *Hum Reprod*. 1996;11(9):1884-1891. [EL 2; PCS]
1034. **Chavarro JE, Ehrlich S, Colaci DS, et al.** Body mass index and short-term weight change in relation to treatment outcomes in women undergoing assisted reproduction. *Fertil Steril*. 2012;98(1):109-116. [EL 2; PCS]
1035. **Moran L, Tsagareli V, Norman R, Noakes M.** Diet and IVF pilot study: short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF. *Aust N Z J Obstet Gynaecol*. 2011;51(5):455-459. [EL 1; RCT]
1036. **Sim KA, Dezarnaulds GM, Denyer GS, Skilton MR, Caterson ID.** Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. *Clin Obes*. 2014;4(2):61-68. [EL 1; RCT]
1037. **Hoeger K.** Obesity and weight loss in polycystic ovary syndrome. *Obstet Gynecol Clin North Am*. 2001;28(1):85-97. [EL 4; NE]
1038. **Sheiner E, Menes TS, Silverberg D, et al.** Pregnancy outcome of patients with gestational diabetes mellitus following bariatric surgery. *Am J Obstet Gynecol*. 2006;194(2):431-435. [EL 3; SS]
1039. **Deitel M, Stone E, Kassam HA, Wilk EJ, Sutherland DJ.** Gynecologic-obstetric changes after loss of massive excess weight following bariatric surgery. *J Am Coll Nutr*. 1988;7(2):147-153. [EL 2; PCS]
1040. **Bilenka B, Ben-Shlomo I, Cozacov C, Gold CH, Zohar S.** Fertility, miscarriage and pregnancy after vertical banded gastroplasty operation for morbid obesity. *Acta Obstet Gynecol Scand*. 1995;74(1):42-44. [EL 3; SS]
1041. **Martin LF, Finigan KM, Nolan TE.** Pregnancy after adjustable gastric banding. *Obstet Gynecol*. 2000;95(6 Pt 1):927-930. [EL 2; PCS]
1042. **Marceau P, Kaufman D, Biron S, et al.** Outcome of pregnancies after biliopancreatic diversion. *Obes Surg*. 2004;14(3):318-324. [EL 3; CSS]
1043. **Gerrits EG, Ceulemans R, van Hee R, Hendrickx L, Totté E.** Contraceptive treatment after biliopancreatic diversion needs consensus. *Obes Surg*. 2003;13(3):378-382. [EL 2; PCS]
1044. **Legro RS, Dodson WC, Gnatuk CL, et al.** Effects of gastric bypass surgery on female reproductive function. *J Clin Endocrinol Metab*. 2012;97(12):4540-4548. [EL 2; PCS]
1045. **Dixon JB, Dixon ME, O'Brien PE.** Pregnancy after Lap-Band surgery: management of the band to achieve healthy weight outcomes. *Obes Surg*. 2001;11(1):59-65. [EL 2; PCS]
1046. **Tan O, Carr BR.** The impact of bariatric surgery on obesity-related infertility and in vitro fertilization outcomes. *Semin Reprod Med*. 2012;30(6):517-528. [EL 4; NE]
1047. **Practice Committee of the American Society for Reproductive Medicine.** Obesity and reproduction: a committee opinion. *Fertil Steril*. 2015;104(5):1116-1126. [EL 4; NE]
1048. **Maggard MA, Yermilov I, Li Z, et al.** Pregnancy and fertility following bariatric surgery: a systematic review. *JAMA*. 2008;300(19):2286-2296. [EL 4; NE]
1049. **Ducarme G, Revaux A, Rodrigues A, Aissaoui F, Pharisien I, Uzan M.** Obstetric outcome following laparoscopic adjustable gastric banding. *Int J Gynaecol Obstet*. 2007;98(3):244-247. [EL 2; RCCS]
1050. **Patel JA, Patel NA, Thomas RL, Nelms JK, Colella JJ.** Pregnancy outcomes after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2008;4(1):39-45. [EL 3; SS]

1051. **Wax JR, Cartin A, Wolff R, Lepich S, Pinette MG, Blackstone J.** Pregnancy following gastric bypass for morbid obesity: effect of surgery-to-conception interval on maternal and neonatal outcomes. *Obes Surg*. 2008;18(12):1517-1521. [EL 3; SS]
1052. **Guelinckx I, Devlieger R, Vansant G.** Reproductive outcome after bariatric surgery: a critical review. *Hum Reprod Update*. 2009;15(2):189-201. [EL 4; NE]
1053. **Galletly C, Clark A, Tomlinson L, Blaney F.** A group program for obese, infertile women: weight loss and improved psychological health. *J Psychosom Obstet Gynaecol*. 1996;17(2):125-128. [EL 3; SS]
1054. **Awartani KA, Al-Sahan N, Al-Hassan SH, Coskun S.** Effect of weight loss in morbidly obese infertile women on IVF outcome. *Fertil Steril*. 2012;98(3);S204. [EL 3; SS, abstract]
1055. **van Veen LJ, van den Dool GC, Rijnsaardt HGM, Lambers MDA.** The development of a life style program aimed at weight reduction in obese patients with subfertility in a large district hospital, results after five years. In: 27th Annual Meeting of the European Society of Human Reproduction and Embryology, July 3-6, 2011. Stockholm, Sweden. Abstract. [EL 4; abstract]
1056. **Tsagareli V, Noakes M, Norman RJ.** Effect of a very-low-calorie diet on in vitro fertilization outcomes. *Fertil Steril*. 2006;86(1):227-229. [EL 2; PCS, very small N = 10]
1057. **Doblado MA, Lewkowksi BM, Odem RR, Jungheim ES.** In vitro fertilization after bariatric surgery. *Fertil Steril*. 2010;94(7):2812-2814. [EL 3; CCS]
1058. **Hirshfeld-Cytron J, Kim HH.** Empty follicle syndrome in the setting of dramatic weight loss after bariatric surgery: case report and review of available literature. *Fertil Steril*. 2008;90(4):1199.e21-e23. [EL 3; SCR]
1059. **Musella M, Milone M, Bellini M, et al.** The potential role of intragastric balloon in the treatment of obese-related infertility: personal experience. *Obes Surg*. 2011; 21(4):426-430. [EL 3; SS]
1060. **Sim KA, Partridge SR, Sainsbury A.** Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obes Rev*. 2014;15(10):839-850. [EL 4; NE]
1061. **Kashyap SR, Schaue P, Bhatt DL, et al.** Increased free testosterone levels following bariatric surgery are related to weight loss and glycaemic control in men with type 2 diabetes: analysis from a RCT. In: 49th European Association for the Study of Diabetes Annual Meeting, September 24-27, 2013; Barcelona, Spain. Abstract. [EL 1; RCT]
1062. **Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P. BLAST Study Group.** Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. *J Sex Med*. 2014;11(3):840-856. [EL 1; RCT]
1063. **Seftel A.** Re: effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Urol*. 2011;185(2):634. [EL 1; RCT]
1064. **Francomano D, Bruzziches R, Barbaro G, Lenzi A, Aversa A.** Effects of testosterone undecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: a pilot study. *J Endocrinol Invest*. 2014;37(4):401-411. [EL 2; PCS]
1065. **Saad F, Haider A, Doros G, Traish A.** Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. *Obesity (Silver Spring)*. 2013;21(10):1975-1981. [EL 2; PCS]
1066. **Yassin A, Doros G.** Testosterone therapy in hypogonadal men results in sustained and clinically meaningful weight loss. *Clin Obes*. 2013;3(3-4):73-83. [EL 2; PCS]
1067. **Saad F, Haider A, Yassin A, et al.** 156 hypogonadal men with obesity and type 2 diabetes achieve weight loss and improved glycaemic control upon treatment with testosterone undecanoate up to 6 years: a subgroup analysis from two observational registry studies. In: 39th Amercian Society of Andrology Annual Meeting, April 5-8, 2014; Atlanta, GA. Abstract. [EL 2; PCS]
1068. **Yassin DJ, Doros G, Hammerer PG, Yassin AA.** Long-term testosterone treatment in elderly men with hypogonadism and erectile dysfunction reduces obesity parameters and improves metabolic syndrome and health-related quality of life. *J Sex Med*. 2014;11(6):1567-1576. [EL 2; PCS]
1069. **Traish AM, Haider A, Doros G, Saad F.** Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study. *Int J Clin Pract*. 2014;68(3):314-329. [EL 2; PCS]
1070. **Haider A, Gooren LJ, Padungtod P, Saad F.** Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate. *Exp Clin Endocrinol Diabetes*. 2010;118(3):167-171. [EL 2; PCS]
1071. **Zitzmann M, Saad F, Kliesch S.** Weight loss and beneficial effects on the metabolic syndrome as a result of testosterone treatment for up to 16 years in 381 hypogonadal men. In: 49th European Association for the Study of Diabetes Annual Meeting, September 24-27, 2013; Barcelona, Spain. Abstract. [EL 4; NE, abstract]
1072. **Zitzmann M, Saad F.** Differential effects of intramuscular testosterone undecanoate in hypogonadal men on body weight and waist circumference during 16 years of treatment. In: The Endocrine Society's 95th Annual Meeting and Expo, June 15-18, 2013; San Francisco, CA. Abstract. [EL 4; NE, abstract]
1073. **Yassin A, Yassin DJ, Hammerer PG, et al.** Long-term testosterone treatment has favourable effects in obese hypogonadal men on body weight and prostate health parameters. In: Program of the 29th Annual EAU Congress, April 14, 2014; Stockholm, Sweden. Abstract. [EL 4; NE, abstract]
1074. **Haider A, Traish A.** Effects of long-term testosterone treatment in obese hypogonadal men on body weight and prostate parameters. *Urology*. 2013(1):S30-S31. [EL 4; NE, abstract]
1075. **Francomano D, Ilacqua A, Bruzziches R, Lenzi A, Aversa A.** Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome. *Urology*. 2014;83(1):167-173. [EL 2; NRCT]
1076. **Buvat J, Maggi M, Guay A, Torres LO.** Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. *J Sex Med*. 2013;10(1):245-284. [EL 4; NE]
1077. **Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK.** Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2012;5(5):720-728. [EL 2; MNRCT]
1078. **Johansson K, Neovius M, Lagerros YT, et al.** Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial. *BMJ*. 2009;339:b4609. [EL 1; RCT]

1079. **Johansson K, Hemmingsson E, Harlid R, et al.** Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study. *BMJ*. 2011;342:d3017. [EL 2; PCS]
1080. **Tuomilehto H, Gylling H, Peltonen M, et al.** Sustained improvement in mild obstructive sleep apnea after a diet- and physical activity-based lifestyle intervention: postintervential follow-up. *Am J Clin Nutr.* 2010;92(4): 688-696. [EL 1; RCT, post-intervention follow-up data]
1081. **Kajaste S, Telakivi T, Mustajoki P, Pihl S, Partinen M.** Effects of a cognitive-behavioural weight loss programme on overweight obstructive sleep apnoea patients. *J Sleep Res*. 1994;3(4):245-249. [EL 2; PCS]
1082. **Kansanen M, Vanninen E, Tuunainen A, et al.** The effect of a very low-calorie diet-induced weight loss on the severity of obstructive sleep apnoea and autonomic nervous function in obese patients with obstructive sleep apnoea syndrome. *Clin Physiol*. 1998;18(4):377-385. [EL 2; PCS]
1083. **Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER.** Weight loss in mildly to moderately obese patients with obstructive sleep apnea. *Ann Intern Med*. 1985;103(6 Pt 1):850-855. [EL 2; RCCS]
1084. **Suratt PM, McTier RF, Findley LJ, Pohl SL, Wilhoit SC.** Effect of very-low-calorie diets with weight loss on obstructive sleep apnea. *Am J Clin Nutr.* 1992;56(1 Suppl):182S-184S. [EL 2; PCS, small N = 8]
1085. **Kajaste S, Brander PE, Telakivi T, Partinen M, Mustajoki P.** A cognitive-behavioral weight reduction program in the treatment of obstructive sleep apnea syndrome with or without initial nasal CPAP: a randomized study. *Sleep Med*. 2004;5(2):125-131. [EL 1; RCT]
1086. **Dixon JB, Schachter LM, O'Brien PE.** Polysomnography before and after weight loss in obese patients with severe sleep apnea. *Int J Obes*. 2005;29(9):1048-1054. [EL 2; PCS]
1087. **Lettieri CJ, Eliasson AH, Greenburg DL.** Persistence of obstructive sleep apnea after surgical weight loss. *J Clin Sleep Med*. 2008;4(4):333-338. [EL 2; PCS]
1088. **Schwartz AR, Gold AR, Schubert N, et al.** Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis*. 1991;144(3 Pt 1):494-498. [EL 2; NRCT]
1089. **Barnes M, Goldsworthy UR, Cary BA, Hill CJ.** A diet and exercise program to improve clinical outcomes in patients with obstructive sleep apnea--a feasibility study. *J Clin Sleep Med*. 2009;5(5):409-415. [EL 2; PCS]
1090. **Noseda A, Kempenaers C, Kerkhofs M, Houben JJ, Linkowski P.** Sleep apnea after 1 year domiciliary nasal-continuous positive airway pressure and attempted weight reduction. Potential for weaning from continuous positive airway pressure. *Chest*. 1996;109(1):138-143. [EL 2; PCS]
1091. **Sugerman HJ, Fairman RP, Sood RK, Engle K, Wolfe L, Kellum JM.** Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. *Am J Clin Nutr.* 1992;55(2 Suppl):597S-601S. [EL 2; PCS]
1092. **Charuzi I, Lavie P, Peiser J, Peled R.** Bariatric surgery in morbidly obese sleep-apnea patients: short- and long-term follow-up. *Am J Clin Nutr.* 1992;55(2 Suppl):594S-596S. [EL 2; PCS]
1093. **Peiser J, Lavie P, Ovnat A, Charuzi I.** Sleep apnea syndrome in the morbidly obese as an indication for weight reduction surgery. *Ann Surg*. 1984;199(1):112-115. [EL 2; PCS]
1094. **Harman EM, Wynne JW, Block AJ.** The effect of weight loss on sleep-disordered breathing and oxygen desaturation in morbidly obese men. *Chest*. 1982;82(3):291-294. [EL 2; PCS, only 4 patients in cohort]
1095. **Araghi MH, Chen YF, Jagielski A, et al.** Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis. *Sleep*. 2013;36(10): 1553-1562. [EL 2; MNRCT]
1096. **Winslow DH, Bowden CH, DiDonato KP, McCullough PA.** A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. *Sleep*. 2012;35(11):1529-1539. [EL 1; RCT]
1097. **Gomez-Peralta F, Abreu C, Castro JC, et al.** An association between liraglutide treatment and reduction in excessive daytime sleepiness in obese subjects with type 2 diabetes. *BMC Endocr Disord*. 2015;15(1):78. [EL 3; SS]
1098. **Fusco M, James S, Cornell C, Okerson T.** Weight loss through adjustable gastric banding and improvement in daytime sleepiness: 2 year interim results of APEX study. *Curr Med Res Opin*. 2014;30(5):849-855. [EL 2; PCS]
1099. **Dixon JB, Schachter LM, O'Brien PE, et al.** Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;308(11):1142-1149. [EL 1; RCT]
1100. **Sahlman J, Seppä J, Herder C, et al.** Effect of weight loss on inflammation in patients with mild obstructive sleep apnea. *Nutr Metab Cardiovasc Dis*. 2012;22(7):583-590. [EL 1; RCT]
1101. **Kuna ST, Reboussin DM, Borradaile KE, et al. Sleep AHEAD Research Group of the Look AHEAD Research Group.** Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. *Sleep*. 2013;36(5):641-649A. [EL 1; RCT]
1102. **Johnson JB, Summer W, Cutler RG, et al.** Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radic Biol Med*. 2007;42(5):665-674. [EL 2; PCS]
1103. **Dandona P, Ghanim H, Monte SV, et al.** Increase in the mediators of asthma in obesity and obesity with type 2 diabetes: reduction with weight loss. *Obesity (Silver Spring)*. 2014;22(2):356-362. [EL 2; PCS]
1104. **Leão da Silva P, de Mello MT, Cheik NC, et al.** Reduction in the leptin concentration as a predictor of improvement in lung function in obese adolescents. *Obes Facts*. 2012;5(6):806-820. [EL 2; PCS]
1105. **Dias-Júnior SA, Reis M, de Carvalho-Pinto RM, Stelmach R, Halpern A, Cukier A.** Effects of weight loss on asthma control in obese patients with severe asthma. *Eur Respir J*. 2014;43(5):1368-1377. [EL 1; RCT, relatively small sample size N = 22]
1106. **Christensen R, Astrup A, Bliddal H.** Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. *Osteoarthr Cartil*. 2005;13(1):20-27. [EL 1; RCT]
1107. **Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ.** Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. *Ann Intern Med*. 1992;116(7):535-539. [EL 2; PCS]
1108. **Toda Y, Toda T, Takemura S, Wada T, Morimoto T, Ogawa R.** Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of obese patients with knee osteoarthritis after a weight control program. *J Rheumatol*. 1998;25(11):2181-2186. [EL 2; PCS]
1109. **Riecke BF, Christensen R, Christensen P, et al.** Comparing two low-energy diets for the treatment of knee osteoarthritis symptoms in obese patients: a pragmatic randomized clinical trial. *Osteoarthr Cartil*. 2010;18(6):746-754. [EL 1; RCT]

1110. **Messier SP, Loeser RF, Mitchell MN, et al.** Exercise and weight loss in obese older adults with knee osteoarthritis: a preliminary study. *J Am Geriatr Soc*. 2000;48(9):1062-1072. [EL 1; RCT]
1111. **Messier SP, Loeser RF, Miller GD, et al.** Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum*. 2004;50(5):1501-1510. [EL 1; RCT, single-blinded]
1112. **Messier SP, Gutekunst DJ, Davis C, DeVita P.** Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis Rheum*. 2005;52(7):2026-2032. [EL 1; RCT, single-blinded]
1113. **Messier SP, Mihalko SL, Legault C, et al.** Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. *JAMA*. 2013;310(12):1263-1273. [EL 1; RCT, single-blinded]
1114. **Christensen R, Bartels EM, Astrup A, Bliddal H.** Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis*. 2007;66(4):433-439. [EL 1; MRCT]
1115. **Maly MR, Robbins SM.** Osteoarthritis year in review 2014: rehabilitation and outcomes. *Osteoarthr Cartil*. 2014;22(12):1958-1988. [EL 4; NE]
1116. **Hochberg MC, Altman RD, April KT, et al.** American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64(4):465-474. [EL 4; NE]
1117. **Fernandes L, Hagen KB, Bijlsma JW, et al.** EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis*. 2013;72(7):1125-1135. [EL 4; NE]
1118. **Jevsevar DS, Brown GA, Jones DL, et al.** The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition. *J Bone Joint Surg Am*. 2013;95(20):1885-1886. [EL 4; NE]
1119. **Zhang W, Moskowitz RW, Nuki G, et al.** OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthr Cartil*. 2008;16(2):137-162. [EL 4; NE]
1120. **Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM.** A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. Bone and Joint Initiative. *Semin Arthritis Rheum*. 2014;43(6):701-712. [EL 4; NE]
1121. **Willims RA, Foulsham BM.** Weight reduction in osteoarthritis using phentermine. *Practitioner.* 1981;225(1352):231-232. [EL 4; NE]
1122. **Abu-Abeid S, Wishnitzer N, Szold A, Liebergall M, Manor O.** The influence of surgically-induced weight loss on the knee joint. *Obes Surg*. 2005;15(10):1437-1442. [EL 2; PCS]
1123. **Groen VA, van de Graaf VA, Scholtes VA, Sprague S, van Wagensveld BA, Poolman RW.** Effects of bariatric surgery for knee complaints in (morbidly) obese adult patients: a systematic review. *Obes Rev*. 2015;16(2):161-170. [EL 4; NE]
1124. **Peltonen M, Lindroos AK, Torgerson JS.** Musculoskeletal pain in the obese: a comparison with a general population and long-term changes after conventional and surgical obesity treatment. *Pain*. 2003;104(3):549-557. [EL 3; SS, post-hoc comparison of random sample with previously published sample]
1125. **Gill RS, Al-Adra DP, Shi X, Sharma AM, Birch DW, Karmali S.** The benefits of bariatric surgery in obese patients with hip and knee osteoarthritis: a systematic review. *Obes Rev*. 2011;12(12):1083-1089. [EL 4; NE]
1126. **Fehring TK, Odum SM, Griffin WL, Mason JB, McCoy TH.** The obesity epidemic: its effect on total joint arthroplasty. *J Arthroplasty*. 2007;22(6 Suppl 2):71-76. [EL 3; SS]
1127. **Manninen P, Riihimaki H, Heliövaara M, Suomalainen O.** Weight changes and the risk of knee osteoarthritis requiring arthroplasty. *Ann Rheum Dis*. 2004;63(11):1434-1437. [EL 3; SS]
1128. **Krushell RJ, Fingeroth RJ.** Primary total knee arthroplasty in morbidly obese patients: a 5- to 14-year follow-up study. *J Arthroplasty*. 2007;22(6 Suppl 2):77-80. [EL 3; SS]
1129. **Winiarsky R, Barth P, Lotke P.** Total knee arthroplasty in morbidly obese patients. *J Bone Joint Surg Am*. 1998;80(12):1770-1774. [EL 3; SS]
1130. **Rajgopal V, Bourne RB, Chesworth BM, MacDonald SJ, McCalden RW, Rorabeck CH.** The impact of morbid obesity on patient outcomes after total knee arthroplasty. *J Arthroplasty*. 2008;23(6):795-800. [EL 2; RCCS]
1131. **Spicer DD, Pomeroy DL, Badenhausen WE, et al.** Body mass index as a predictor of outcome in total knee replacement. *Int Orthop*. 2001;25(4):246-249. [EL 3; SS]
1132. **Samson AJ, Mercer GE, Campbell DG.** Total knee replacement in the morbidly obese: a literature review. *ANZ J Surg*. 2010;80(9):595-599. [EL 4; NE]
1133. **Amin AK, Clayton RA, Patton JT, Gaston M, Cook RE, Brenkel IJ.** Total knee replacement in morbidly obese patients. Results of a prospective, matched study. *J Bone Joint Surg Br.* 2006;88(10):1321-1326. [EL 2; PCS]
1134. **Vazquez-Vela Johnson G, Worland RL, Keenan J, Norambuena N.** Patient demographics as a predictor of the ten-year survival rate in primary total knee replacement. *J Bone Joint Surg Br.* 2003;85(1):52-56. [EL 3; SS]
1135. **Foran JR, Mont MA, Etienne G, Jones LC, Hungerford DS.** The outcome of total knee arthroplasty in obese patients. *J Bone Joint Surg Am*. 2004;86-A(8): 1609-1615. [EL 3; SS]
1136. **Kuipers BM, Kollen BJ, Bots PC, et al.** Factors associated with reduced early survival in the Oxford phase III medial unicompartment knee replacement. *Knee*. 2010;17(1):48-52. [EL 3; SS]
1137. **Santaguida PL, Hawker GA, Hudak PL, et al.** Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: a systematic review. *Can J Surg*. 2008;51(6):428-436. [EL 4; NE]
1138. **Subak LL, Johnson C, Whitcomb E, Boban D, Saxton J, Brown JS.** Does weight loss improve incontinence in moderately obese women? *Int Urogynecol J Pelvic Floor Dysfunct*. 2002;13(1):40-43. [EL 2; PCS]
1139. **Auwad W, Steggles P, Bombieri L, Waterfield M, Wilkin T, Freeman R.** Moderate weight loss in obese women with urinary incontinence: a prospective longitudinal study. *Int Urogynecol J Pelvic Floor Dysfunct*. 2008;19(9):1251-1259. [EL 2; PCS]
1140. **Brown JS, Wing R, Barrett-Connor E, et al.** Lifestyle intervention is associated with lower prevalence of urinary incontinence: the Diabetes Prevention Program. *Diabetes Care*. 2006;29(2):385-390. [EL 1; RCT, post-hoc analysis]
1141. **Phelan S, Kanaya AM, Subak LL, et al. Look AHEAD Research Group.** Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD trial. *J Urol*. 2012;187(3):939-944. [EL 1; RCT, post-intervention followup data]

1142. **Subak LL, Wing R, West DS, et al.** Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med*. 2009;360(5):481-490. [EL 1; RCT]
1143. **Wing RR, West DS, Grady D, et al.** Program to Reduce Incontinence by Diet and Exercise Group. Effect of weight loss on urinary incontinence in overweight and obese women: results at 12 and 18 months. *J Urol*. 2010;184(3): 1005-1010. [EL 1; RCT]
1144. **Burgio KL, Richter HE, Clements RH, Redden DT, Goode PS.** Changes in urinary and fecal incontinence symptoms with weight loss surgery in morbidly obese women. *Obstet Gynecol*. 2007;110(5):1034-1040. [EL 2; PCS]
1145. **Sugerman HJ, Sugerman EL, DeMaria EJ, et al.** Bariatric surgery for severely obese adolescents. *J Gastrointest Surg*. 2003;7(1):102-107. [EL 3; SS]
1146. **Ahroni JH, Montgomery KF, Watkins BM.** Laparoscopic adjustable gastric banding: weight loss, co-morbidities, medication usage and quality of life at one year. *Obes Surg*. 2005;15(5):641-647. [EL 2; PCS]
1147. **Sugerman H, Windsor A, Bessos M, Kellum J, Reines H, DeMaria E.** Effects of surgically induced weight loss on urinary bladder pressure, sagittal abdominal diameter and obesity co-morbidity. *Int J Obes Relat Metab Disord*. 1998;22(3):230-235. [EL 2; PCS]
1148. **Kuruba R, Almahmeed T, Martinez F, et al.** Bariatric surgery improves urinary incontinence in morbidly obese individuals. *Surg Obes Relat Dis*. 2007;3(6):586-90; discussion 590-591. [EL 2; PCS]
1149. **Bredenoord AJ, Pandolfino JE, Smout AJ.** Gastro-oesophageal reflux disease. *Lancet*. 2013;381(9881):1933-1942. [EL 4; NE]
1150. **Eherer AJ, Netolitzky F, Högenauer C, et al.** Positive effect of abdominal breathing exercise on gastroesophageal reflux disease: a randomized, controlled study. *Am J Gastroenterol*. 2012;107(3):372-378. [EL 2; PCS]
1151. **Kaltenbach T, Crockett S, Gerson LB.** Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med*. 2006;166(9):965-971. [EL 4; NE]
1152. **Nadaleto BF, Herbella FA, Patti MG.** Gastroesophageal reflux disease in the obese: pathophysiology and treatment. *Surgery*. 2016;159(2):475-486. [EL 4; NE]
1153. **Austin GL, Thiny MT, Westman EC, Yancy WS,Jr, Shaheen NJ.** A very low-carbohydrate diet improves gastroesophageal reflux and its symptoms. *Dig Dis Sci*. 2006;51(8):1307-1312. [EL 2; PCS]
1154. **Mathus-Vliegen LM, Tytgat GN.** Twenty-four-hour pH measurements in morbid obesity: effects of massive overweight, weight loss and gastric distension. *Eur J Gastroenterol Hepatol*. 1996;8(7):635-640. [EL 1; RCT]
1155. **Mathus-Vliegen EM, van Weeren M, van Eerten PV.** Los function and obesity: the impact of untreated obesity, weight loss, and chronic gastric balloon distension. *Digestion*. 2003;68(2-3):161-168. [EL 1; RCT]
1156. **Fraser-Moodie CA, Norton B, Gornall C, Magnago S, Weale AR, Holmes GK.** Weight loss has an independent beneficial effect on symptoms of gastro-oesophageal reflux in patients who are overweight. *Scand J Gastroenterol*. 1999;34(4):337-340. [EL 2; PCS]
1157. **Smith JE, Morjaria JB, Morice AH.** Dietary intervention in the treatment of patients with cough and symptoms suggestive of airways reflux as determined by Hull airways Reflux Questionnaire. *Cough*. 2013;9(1):27. [EL 1; RCT]
1158. **Ness-Jensen E, Lindam A, Lagergren J, Hveem K.** Weight loss and reduction in gastroesophageal reflux. A prospective population-based cohort study: the HUNT study. *Am J Gastroenterol*. 2013;108(3):376-382. [EL 2; PCS]
1159. **Mathus-Vliegen EM, Tygat GN.** Gastro-oesophageal reflux in obese subjects: influence of overweight, weight loss and chronic gastric balloon distension. *Scand J Gastroenterol*. 2002;37(11):1246-1252. [EL 1; RCT]
1160. **Frederiksen SG, Johansson J, Johnsson F, Hedenbro J.** Neither low-calorie diet nor vertical banded gastroplasty influence gastro-oesophageal reflux in morbidly obese patients. *Eur J Surg*. 2000;166(4):296-300. [EL 2; PCS]
1161. **Kjellin A, Ramel S, Rössner S, Thor K.** Gastroesophageal reflux in obese patients is not reduced by weight reduction. *Scand J Gastroenterol*. 1996;31(11):1047-1051. [EL 1; RCT, small N = 20]
1162. **Dickman R, Boaz M, Aizic S, Beniashvili Z, Fass R, Niv Y.** Comparison of clinical characteristics of patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy versus those who fully responded. *J Neurogastroenterol Motil*. 2011;17(4):387-394. [EL 3; SS]
1163. **Heading RC, Mönnikes H, Tholen A, Schmitt H.** Prediction of response to PPI therapy and factors influencing treatment outcome in patients with GORD: a prospective pragmatic trial using pantoprazole. *BMC Gastroenterol*. 2011;11:52. [EL 2; PCS]
1164. **Fletcher J, Derakhshan MH, Jones GR, Wirz AA, McColl KE.** BMI is superior to symptoms in predicting response to proton pump inhibitor: randomised trial in patients with upper gastrointestinal symptoms and normal endoscopy. *Gut*. 2011;60(4):442-448. [EL 1; RCT]
1165. **Belhocine K, Vavasseur F, Volteau C, Flet L, Touchefeu Y, Bruley des Varannes S.** Controlling on-demand gastric acidity in obese subjects: a randomized, controlled trial comparing a single dose of 20 mg rabeprazole and 20 mg omeprazole. *BMC Gastroenterol*. 2014;14:128. [EL 1; RCT]
1166. **Bruley des Varannes S, Coudsy B, Waechter S, et al.** On-demand proton pump inhibitory treatment in overweight/obese patients with gastroesophageal reflux disease: are there pharmacodynamic arguments for using higher doses? *Digestion*. 2013;88(1):56-63. [EL 1; RCT, post-hoc analysis]
1167. **Pace F, Coudsy B, DeLemos B, et al.** Does BMI affect the clinical efficacy of proton pump inhibitor therapy in GERD? The case for rabeprazole. *Eur J Gastroenterol Hepatol*. 2011;23(10):845-851. [EL 1; RCT, post-hoc analysis]
1168. **El-Hadi M, Birch DW, Gill RS, Karmali S.** The effect of bariatric surgery on gastroesophageal reflux disease. *Can J Surg*. 2014;57(2):139-144. [EL 4; NE]
1169. **Rebecchi F, Rocchietto S, Giaccone C, Talha A, Morino M.** Gastroesophageal reflux disease and esophageal motility in morbidly obese patients submitted to laparoscopic adjustable silicone gastric banding or laparoscopic vertical banded gastroplasty. *Surg Endosc*. 2011;25(3):795-803. [EL 1; RCT]
1170. **Howard DD, Caban AM, Cendan JC, Ben-David K.** Gastroesophageal reflux after sleeve gastrectomy in morbidly obese patients. *Surg Obes Relat Dis*. 2011;7(6): 709-713. [EL 3; SS]
1171. **Rebecchi F, Allaix ME, Giaccone C, Ugliono E, Scozzari G, Morino M.** Gastroesophageal reflux disease and laparoscopic sleeve gastrectomy: a physiopathologic evaluation. *Ann Surg*. 2014;260(5):909-914. [EL 2; PCS]
1172. **Tai CM, Huang CK, Lee YC, Chang CY, Lee CT, Lin JT.** Increase in gastroesophageal reflux disease symptoms and erosive esophagitis 1 year after laparoscopic sleeve gastrectomy among obese adults. *Surg Endosc*. 2013; 27(4):1260-1266. [EL 2; PCS]
1173. **Santonicola A, Angrisani L, Cutolo P, Formisano G, Iovino P.** The effect of laparoscopic sleeve gastrectomy with or without hiatal hernia repair on gastroesophageal

reflux disease in obese patients. *Surg Obes Relat Dis*. 2014;10(2):250-255. [EL 2; PCS]

1174. **Toro JP, Lin E, Patel AD, et al.** Association of radiographic morphology with early gastroesophageal reflux disease and satiety control after sleeve gastrectomy. *J Am Coll Surg*. 2014;219(3):430-438. [EL 2; PCS]
1175. **Lazoura O, Zacharoulis D, Triantafyllidis G, et al.** Symptoms of gastroesophageal reflux following laparoscopic sleeve gastrectomy are related to the final shape of the sleeve as depicted by radiology. *Obes Surg*. 2011;21(3):295-299. [EL 2; PCS]
1176. **Frezza EE, Ikramuddin S, Gourash W, et al.** Symptomatic improvement in gastroesophageal reflux disease (GERD) following laparoscopic Roux-en-Y gastric bypass. *Surg Endosc*. 2002;16(7):1027-1031. [EL 3; SS]
1177. **Tai CM, Lee YC, Wu MS, et al.** The effect of Roux-en-Y gastric bypass on gastroesophageal reflux disease in morbidly obese Chinese patients. *Obes Surg*. 2009;19(5):565-570. [EL 2; PCS]
1178. **Mejía-Rivas MA, Herrera-López A, Hernández-Calleros J, Herrera MF, Valdovinos MA.** Gastroesophageal reflux disease in morbid obesity: the effect of Roux-en-Y gastric bypass. *Obes Surg*. 2008;18(10):1217-1224. [EL 2; PCS]
1179. **Nelson LG, Gonzalez R, Haines K, Gallagher SF, Murr MM.** Amelioration of gastroesophageal reflux symptoms following Roux-en-Y gastric bypass for clinically significant obesity. *Am Surg*. 2005;71(11):950-953. [EL 2; PCS]
1180. **Pallati PK, Shaligram A, Shostrom VK, Oleynikov D, McBride CL, Goede MR.** Improvement in gastroesophageal reflux disease symptoms after various bariatric procedures: review of the Bariatric Outcomes Longitudinal Database. *Surg Obes Relat Dis*. 2014; 10(3):502-507. [EL 2; PCS]
1181. **Ekelund M, Oberg S, Peterli R, Frederiksen SG, Hedenbro JL.** Gastroesophageal reflux after vertical banded gastroplasty is alleviated by conversion to gastric bypass. *Obes Surg*. 2012;22(6):851-854. [EL 2; PCS, only 8 patients]
1182. **Gautier T, Sarcher T, Contival N, Le Roux Y, Alves A.** Indications and mid-term results of conversion from sleeve gastrectomy to Roux-en-Y gastric bypass. *Obes Surg*. 2013;23(2):212-215. [EL 3; SS]
1183. **Yamamoto SR, Hoshino M, Nandipati KC, Lee TH, Mittal SK.** Long-term outcomes of reintervention for failed fundoplication: redo fundoplication versus Roux-en-Y reconstruction. *Surg Endosc*. 2014;28(1):42-48. [EL 2; PCS, retrospective review of database]
1184. **Awais O, Luketich JD, Reddy N, et al.** Roux-en-Y near esophagojejunostomy for failed antireflux operations: outcomes in more than 100 patients. *Ann Thorac Surg*. 2014;98(6):1905-1911. [EL 3; SS]
1185. **Braghetto I, Korn O, Csendes A, Gutiérrez L, Valladares H, Chacon M.** Laparoscopic treatment of obese patients with gastroesophageal reflux disease and Barrett's esophagus: a prospective study. *Obes Surg*. 2012;22(5):764-772. [EL 2; PCS]
1186. **Stunkard AJ.** The dieting depression; incidence and clinical characteristics of untoward responses to weight reduction regimens. *Am J Med*. 1957;23(1):77-86. [EL 2; PCS]
1187. **Keys A.** The residues of malnutrition and starvation. *Science*. 1950;112(2909):371-373. [EL 4; NE]
1188. **Smoller JW, Wadden TA, Stunkard AJ.** Dieting and depression: a critical review. *J Psychosom Res*. 1987; 31(4):429-440. [EL 4; NE]
1189. **Wing RR, Epstein LH, Marcus MD, Kupfer DJ.** Mood changes in behavioral weight loss programs. *J Psychosom Res*. 1984;28(3):189-196. [EL 4; NE]
1190. **Fabricatore AN, Wadden TA, Higginbotham AJ, et al.** Intentional weight loss and changes in symptoms of depression: a systematic review and meta-analysis. *Int J Obes*. 2011;35(11):1363-1376. [EL 1; MRCT]
1191. **Klem ML, Wing RR, Simkin-Silverman L, Kuller LH.** The psychological consequences of weight gain prevention in healthy, premenopausal women. *Int J Eat Disord*. 1997;21(2):167-174. [EL 1; RCT]
1192. **Andersen RE, Wadden TA, Bartlett SJ, Zemel B, Verde TJ, Franckowiak SC.** Effects of lifestyle activity vs structured aerobic exercise in obese women: a randomized trial. *JAMA*. 1999;281(4):335-340. [EL 1; RCT]
1193. **Dennis KE, Pane KW, Adams BK, Qi BB.** The impact of a shipboard weight control program. *Obes Res*. 1999;7 (1):60-67. [EL 1; RCT]
1194. **Sbrocco T, Nedegaard RC, Stone JM, Lewis EL.** Behavioral choice treatment promotes continuing weight loss: preliminary results of a cognitive-behavioral decision-based treatment for obesity. *J Consult Clin Psychol*. 1999;67(2):260-266. [EL 1; RCT, N = 24]
1195. **Bacon L, Keim NL, Van Loan MD, et al.** Evaluating a 'non-diet' wellness intervention for improvement of metabolic fitness, psychological well-being and eating and activity behaviors. *Int J Obes Relat Metab Disord*. 2002;26(6):854-865. [EL 1; RCT]
1196. **Evangelista LS, Doering LV, Lennie T, et al.** Usefulness of a home-based exercise program for overweight and obese patients with advanced heart failure. *Am J Cardiol*. 2006;97(6):886-890. [EL 2; PCS]
1197. **Carels RA, Darby LA, Cacciapaglia HM, Douglass OM.** Reducing cardiovascular risk factors in postmenopausal women through a lifestyle change intervention. *J Womens Health*. 2004;13(4):412-426. [EL 1; RCT]
1198. **Fontaine KR, Barofsky I, Andersen RE, et al.** Impact of weight loss on health-related quality of life. *Qual Life Res*. 1999;8(3):275-277. [EL 1; RCT]
1199. **Annesi JJ, Unruh JL.** Relations of exercise, self-appraisal, mood changes and weight loss in obese women: testing propositions based on Baker and Brownell's (2000) model. *Am J Med Sci*. 2008;335(3):198-204. [EL 2; PCS]
1200. **Kerr J, Patrick K, Norman G, et al.** Randomized control trial of a behavioral intervention for overweight women: impact on depressive symptoms. *Depress Anxiety*. 2008;25(7):555-558. [EL 1; RCT]
1201. **Galletly C, Moran L, Noakes M, Clifton P, Tomlinson L, Norman R.** Psychological benefits of a high-protein, low-carbohydrate diet in obese women with polycystic ovary syndrome--a pilot study. *Appetite*. 2007;49(3):590-593. [EL 1; RCT, N = 25]
1202. **Halyburton AK, Brinkworth GD, Wilson CJ, et al.** Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. *Am J Clin Nutr*. 2007;86(3):580-587. [EL 1; RCT]
1203. **Nieman DC, Custer WF, Butterworth DE, Utter AC, Henson DA.** Psychological response to exercise training and/or energy restriction in obese women. *J Psychosom Res*. 2000;48(1):23-29. [EL 1; RCT]
1204. **Tanco S, Linden W, Earle T.** Well-being and morbid obesity in women: a controlled therapy evaluation. *Int J Eat Disord*. 1998;23(3):325-339. [EL 1; RCT]
1205. **Wing RR, Marcus MD, Blair EH, Burton LR.** Psychological responses of obese type II diabetic subjects to very-low-calorie diet. *Diabetes Care*. 1991;14(7):596-599. [EL 1; RCT]
1206. **Melanson KJ, Dell'Olio J, Carpenter MR, Angelopoulos TJ.** Changes in multiple health outcomes at 12 and 24 weeks resulting from 12 weeks of exercise counseling with or without dietary counseling in obese adults. *Nutrition*. 2004;20(10):849-856. [EL 1; RCT]

1207. **Wadden TA, Foster GD, Sarwer DB, et al.** Dieting and the development of eating disorders in obese women: results of a randomized controlled trial. *Am J Clin Nutr*. 2004;80(3):560-568. [EL 1; RCT]
1208. **Smith PJ, Blumenthal JA, Babyak MA, Georgiades A, Hinderliter A, Sherwood A.** Effects of exercise and weight loss on depressive symptoms among men and women with hypertension. *J Psychosom Res*. 2007;63(5): 463-469. [EL 1; RCT]
1209. **Rapoport L, Clark M, Wardle J.** Evaluation of a modified cognitive-behavioural programme for weight management. *Int J Obes Relat Metab Disord*. 2000; 24(12):1726-1737. [EL 1; RCT]
1210. **Sarsan A, Ardiç F, Ozgen M, Topuz O, Sermez Y.** The effects of aerobic and resistance exercises in obese women. *Clin Rehabil*. 2006;20(9):773-782. [EL 1; RCT]
1211. **Wadden TA, Mason G, Foster GD, Stunkard AJ, Prange AJ.** Effects of a very low calorie diet on weight, thyroid hormones and mood. *Int J Obes*. 1990;14(3):249-258. [EL 1; RCT]
1212. **Williamson DA, Martin CK, Anton SD, et al.** Is caloric restriction associated with development of eating-disorder symptoms? Results from the CALERIE trial. *Health Psychol*. 2008;27(1 Suppl):S32-S42. [EL 1; RCT]
1213. **Wal JS, McBurney MI, Cho S, Dhurandhar NV.** Ready-to-eat cereal products as meal replacements for weight loss. *Int J Food Sci Nutr*. 2007;58(5):331-340. [EL 1; RCT]
1214. **Karlsson J, Taft C, Rydén A, Sjöström L, Sullivan M.** Ten-year trends in health-related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study. *Int J Obes*. 2007;31(8):1248-1261. [EL 2; PCS, post-hoc analysis]
1215. **Stapleton P, Church D, Sheldon T, Porter B, Carlopio C.** Depression symptoms improve after successful weight loss with emotional freedom techniques. *ISRN Psychiatry*. 2013;2013:573532. [EL 1; RCT]
1216. **Faulconbridge LF, Wadden TA, Berkowitz RI, et al.** Changes in symptoms of depression with weight loss: results of a randomized trial. *Obesity (Silver Spring)*. 2009;17(5):1009-1016. [EL 1; RCT]
1217. **Faulconbridge LF, Wadden TA, Rubin RR, et al.** One-year changes in symptoms of depression and weight in overweight/obese individuals with type 2 diabetes in the Look AHEAD study. *Obesity (Silver Spring)*. 2012; 20(4):783-793. [EL 1; RCT, post-hoc analysis]
1218. **Rubin RR, Peyrot M, Wang NY, et al.** Patient-reported outcomes in the practice-based opportunities for weight reduction (POWER) trial. *Qual Life Res*. 2013;22(9):2389-2398. [EL 1; RCT]
1219. **Rubin RR, Knowler WC, Ma Y, et al.** Diabetes Prevention Program Research Group. Depression symptoms and antidepressant medicine use in Diabetes Prevention Program participants. *Diabetes Care*. 2005; 28(4):830-837. [EL 1; RCT, post-hoc analysis]
1220. **Jackson SE, Steptoe A, Beeken RJ, Kivimaki M, Wardle J.** Psychological changes following weight loss in overweight and obese adults: a prospective cohort study. *PLoS One*. 2014;9(8):e104552. [EL 2; PCS]
1221. **Schowalter M, Benecke A, Lager C, et al.** Changes in depression following gastric banding: a 5- to 7-year prospective study. *Obes Surg*. 2008;18(3):314-320. [EL 2; PCS]
1222. **Thonney B, Pataky Z, Badel S, Bobbioni-Harsch E, Golay A.** The relationship between weight loss and psychosocial functioning among bariatric surgery patients. *Am J Surg*. 2010;199(2):183-188. [EL 2; PCS]
1223. **Brancatisano A, Wahlroos S, Brancatisano R.** Improvement in comorbid illness after placement of the Swedish Adjustable Gastric Band. *Surg Obes Relat Dis*. 2008;4(3 Suppl):S39-46. [EL 2; PCS]
1224. **Tindle HA, Omalu B, Courcoulas A, Marcus M, Hammers J, Kuller LH.** Risk of suicide after long-term follow-up from bariatric surgery. *Am J Med*. 2010; 123(11):1036-1042. [EL 3; SS]
1225. **Bhatti JA, Nathens AB, Thiruchelvam D, Grantcharov T, Goldstein BI, Redelmeier DA.** Self-harm emergencies after bariatric surgery: a population-based cohort study. *JAMA Surg*. 2016;151(3):226-232. [EL 2; PCS]
1226. **Heinberg LJ, Ashton K, Coughlin J.** Alcohol and bariatric surgery: review and suggested recommendations for assessment and management. *Surg Obes Relat Dis*. 2012;8(3):357-363. [EL 4; NE]
1227. **Wadden TA, Sarwer DB, Fabricatore AN, Jones L, Stack R, Williams NS.** Psychosocial and behavioral status of patients undergoing bariatric surgery: what to expect before and after surgery. *Med Clin North Am*. 2007; 91(3):451-469. [EL 4; NE]
1228. **Yen Y, Huang C, Tai C.** Psychiatric aspects of bariatric surgery. *Curr Opin Psychiatry*. 2014;27(5):374-379. [EL 4; NE]
1229. **Mitchell JE, Crosby R, de Zwaan M, et al.** Possible risk factors for increased suicide following bariatric surgery. *Obesity (Silver Spring)*. 2013;21(4):665-672. [EL 4; NE]
1230. **Steinberg DM, Askew S, Lanpher MG, Foley PB, Levine EL, Bennett GG.** The effect of a "maintain, don't gain" approach to weight management on depression among black women: results from a randomized controlled trial. *Am J Public Health*. 2014;104(9):1766-1773. [EL 1; RCT]
1231. **Gow ML, Ho M, Burrows TL, et al.** Impact of dietary macronutrient distribution on BMI and cardiometabolic outcomes in overweight and obese children and adolescents: a systematic review. *Nutr Rev*. 2014;72(7): 453-470. [EL 4; NE]
1232. **Svetkey LP, Simons-Morton D, Vollmer WM, et al.** Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Arch Intern Med*. 1999;159(3):285-293. [EL 1; RCT]
1233. **Sacks FM, Svetkey LP, Vollmer WM, et al.** Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344(1):3-10. [EL 1; RCT]
1234. **Elder CR, Gullion CM, Funk KL, Debar LL, Lindberg NM, Stevens VJ.** Impact of sleep, screen time, depression and stress on weight change in the intensive weight loss phase of the LIFE study. *Int J Obes*. 2012;36(1):86-92. [EL 2; NRCT, post-hoc analysis of phase I: non-randomized]
1235. **Appel LJ, Champagne CM, Harsha DW, et al.** Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA*. 2003;289(16):2083-2093. [EL 1; RCT]
1236. **Itsiopoulos C, Brazionis L, Kaimakamis M, et al.** Can the Mediterranean diet lower HbA1c in type 2 diabetes? Results from a randomized cross-over study. *Nutr Metab Cardiovasc Dis*. 2011;21(9):740-747. [EL 1; RCT]
1237. **Estruch R, Ros E, Salas-Salvadó J, et al.** Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368(14):1279-1290. [EL 1; RCT]
1238. **Shai I, Schwarzfuchs D, Henkin Y, et al.** Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med*. 2008;359(3):229-241. [EL 1; RCT]
1239. **Martinez-Gonzalez MA, Bes-Rastrollo M.** Dietary patterns, Mediterranean diet, and cardiovascular disease. *Curr Opin Lipidol*. 2014;25(1):20-26. [EL 4; NE]

1240. **Hoevenaar-Blom MP, Nooyens AC, Kromhout D, et al.** Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. *PLoS One*. 2012;7(9):e45458. [EL 2; PCS]

1241. **Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB.** The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol*. 2011;57(11):1299-1313. [EL 2; MNRCT]

1242. **Esposito K, Maiorino MI, Ceriello A, Giugliano D.** Prevention and control of type 2 diabetes by Mediterranean diet: a systematic review. *Diabetes Res Clin Pract*. 2010; 89(2):97-102. [EL 4; NE]

1243. **Salas-Salvadó J, Bulló M, Babio N, et al.** Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care*. 2011;34(1):14-19. [EL 1; RCT]

1244. **Martinez-González MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, et al.** Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. *BMJ*. 2008;336(7657):1348-1351. [EL 1; RCT]

1245. **Ross LJ, Tapsell LC, Probst Y.** Optimizing dietary fat in a weight-loss trial requires advice based on a structured "whole-of-diet" model. *Nutr Res*. 2011;31(9):683-690. [EL 1; RCT]

1246. **Anton SD, Gallagher J, Carey VJ, et al.** Diet type and changes in food cravings following weight loss: findings from the POUNDS LOST Trial. *Eat Weight Disord*. 2012;17(2):e101-8. [EL 1; RCT, post-hoc analysis]

1247. **Bray GA, Smith SR, DeJonge L, et al.** Effect of diet composition on energy expenditure during weight loss: the POUNDS LOST Study. *Int J Obes*. 2012;36(3):448-455. [EL 1; RCT, post-hoc analysis]

1248. **Canfi A, Gepner Y, Schwarzfuchs D, et al.** Effect of changes in the intake of weight of specific food groups on successful body weight loss during a multi-dietary strategy intervention trial. *J Am Coll Nutr.* 2011;30(6):491-501. [EL 1; RCT, post-hoc analysis]

1249. **Bédard A, Goulet J, Riverin M, Lamarche B, Lemieux S.** Effects of a dietary intervention promoting the adoption of a Mediterranean food pattern on fast-food consumption among healthy French-Canadian women. *Br J Nutr.* 2010; 104(11):1662-1665. [EL 2; NRCT]

1250. **Abete I, Astrup A, Martinez JA, Thorsdottir I, Zulet MA.** Obesity and the metabolic syndrome: role of different dietary macronutrient distribution patterns and specific nutritional components on weight loss and maintenance. *Nutr Rev.* 2010;68(4):214-231. [EL 4; NE]

1251. **Lin PH, Wang Y, Grambow SC, Goggins W, Almirall D.** Dietary saturated fat intake is negatively associated with weight maintenance among the PREMIER participants. *Obesity (Silver Spring)*. 2012;20(3):571-575. [EL 1; RCT, post-intervention observational data]

1252. **Shay CM, Van Horn L, Stamler J, et al.** Food and nutrient intakes and their associations with lower BMI in middle-aged US adults: the International Study of Macro-/Micronutrients and Blood Pressure (INTERMAP). *Am J Clin Nutr.* 2012;96(3):483-491. [EL 3; CSS]

1253. **Morenga LT, Williams S, Brown R, Mann J.** Effect of a relatively high-protein, high-fiber diet on body composition and metabolic risk factors in overweight women. *Eur J Clin Nutr.* 2010;64(11):1323-1331. [EL 1; RCT]

1254. **Stimson RH, Johnstone AM, Homer NZ, et al.** Dietary macronutrient content alters cortisol metabolism independently of body weight changes in obese men. *J Clin Endocrinol Metab*. 2007;92(11):4480-4484. [EL 1; RCT]

1255. **Qi Q, Xu M, Wu H, et al.** IRS1 genotype modulates metabolic syndrome reversion in response to 2-year weight-loss diet intervention: the POUNDS LOST trial. *Diabetes Care*. 2013;36(11):3442-3447. [EL 1; RCT]

1256. **Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee YC, Ordovas JM, Scheer FA.** Timing of food intake predicts weight loss effectiveness. *Int J Obes*. 2013; 37(4):604-611. [EL 2; PCS]

1257. **Garaulet M, Esteban Tardido A, Lee YC, Smith CE, Parnell LD, Ordovas JM.** SIRT1 and CLOCK 3111T> C combined genotype is associated with evening preference and weight loss resistance in a behavioral therapy treatment for obesity. *Int J Obes*. 2012;36(11):1436-1441. [EL 2; PCS]

1258. **Garaulet M, Sánchez-Moreno C, Smith CE, Lee YC, Nicolás F, Ordovás JM.** Ghrelin, sleep reduction and evening preference: relationships to CLOCK 3111 T/C SNP and weight loss. *PLoS One*. 2011;6(2):e17435. [EL 2; PCS]

1259. **Mattei J, Qi Q, Hu FB, Sacks FM, Qi L.** TCF7L2 genetic variants modulate the effect of dietary fat intake on changes in body composition during a weight-loss intervention. *Am J Clin Nutr.* 2012;96(5):1129-1136. [EL 1; RCT]

1260. **Stocks T, Ängquist L, Hager J, et al.** TFAP2B -dietary protein and glycemic index interactions and weight maintenance after weight loss in the DiOGenes trial. *Hum Hered*. 2013;75(2-4):213-219. [EL 1; RCT]

1261. **de Luis DA, Aller R, Izaola O, et al.** Evaluation of weight loss and adipocytokine levels after two hypocaloric diets with different macronutrient distribution in obese subjects with the rs6923761 gene variant of glucagon-like peptide 1 receptor. *Ann Nutr Metab*. 2013;63(4):277-282. [EL 1; RCT]

1262. **Grau K, Hansen T, Holst C, et al.** Macronutrient-specific effect of FTO rs9939609 in response to a 10-week randomized hypo-energetic diet among obese Europeans. *Int J Obes*. 2009;33(11):1227-1234. [EL 1; RCT]

1263. **Sakr M, Hamdy O.** Cardiometabolic risk factors and the metabolic syndrome. In: Mechanick JI, Via MA, Zhou S, eds. *Molecular Nutrition*. Washington, D.C.: Endocrine Press; 2015: 223-233 [EL 4; NE]

1264. **Capel F, Viguerie N, Vega N, et al.** Contribution of energy restriction and macronutrient composition to changes in adipose tissue gene expression during dietary weight-loss programs in obese women. *J Clin Endocrinol Metab*. 2008;93(11):4315-4322. [EL 1; RCT]

1265. **Irwin ML, Yasui Y, Ulrich CM, et al.** Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. *JAMA*. 2003;289(3): 323-330. [EL 1; RCT]

1266. **Ross R, Janssen I, Dawson J, et al.** Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. *Obes Res*. 2004;12(5):789-798. [EL 1; RCT]

1267. **Blumenthal JA, Sherwood A, Gullette EC, et al.** Exercise and weight loss reduce blood pressure in men and women with mild hypertension: effects on cardiovascular, metabolic, and hemodynamic functioning. *Arch Intern Med*. 2000;160(13):1947-1958. [EL 1; RCT]

1268. **Donnelly JE, Hill JO, Jacobsen DJ, et al.** Effects of a 16-month randomized controlled exercise trial on body weight and composition in young, overweight men and women: the Midwest Exercise Trial. *Arch Intern Med*. 2003;163(11):1343-1350. [EL 1; RCT]

1269. **Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, Blair SN.** Changes in weight, waist circumference and compensatory responses with different doses of exercise among sedentary, overweight postmenopausal women. *PLoS One*. 2009;4(2):e4515. [EL 1; RCT]

1270. **Shaw K, Gennat H, O'Rourke P, Del Mar C.** Exercise for overweight or obesity. *Cochrane Database Syst Rev*. 2006;(4):CD003817. [EL 4; NE]
1271. **Thorogood A, Mottillo S, Shimony A, et al.** Isolated aerobic exercise and weight loss: a systematic review and meta-analysis of randomized controlled trials. *Am J Med*. 2011;124(8):747-755. [EL 1; MRCT]
1272. **Ismail I, Keating SE, Baker MK, Johnson NA.** A systematic review and meta-analysis of the effect of aerobic vs. resistance exercise training on visceral fat. *Obes Rev*. 2012;13(1):68-91. [EL 1; MRCT]
1273. **Ross R, Hudson R, Stotz PJ, Lam M.** Effects of exercise amount and intensity on abdominal obesity and glucose tolerance in obese adults: a randomized trial. *Ann Intern Med*. 2015;162(5):325-334. [EL 1; RCT]
1274. **Slentz CA, Duscha BD, Johnson JL, et al.** Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE--a randomized controlled study. *Arch Intern Med*. 2004;164(1):31-39. [EL 1; RCT]
1275. **Friedenreich CM, Neilson HK, O'Reilly R, et al.** Effects of a high vs moderate volume of aerobic exercise on adiposity outcomes in postmenopausal women: a randomized clinical trial. *JAMA Oncol*. 2015;1(6):766-776. [EL 1; RCT]
1276. **Richardson CR, Newton TL, Abraham JJ, Sen A, Jimbo M, Swartz AM.** A meta-analysis of pedometer-based walking interventions and weight loss. *Ann Fam Med*. 2008;6(1):69-77. [EL 2; MNRCT]
1277. **Vissers D, Hens W, Taeymans J, Baeyens JP, Poortmans J, Van Gaal L.** The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. *PLoS One*. 2013;8(2):e56415. [EL 2; MNRCT]
1278. **Wu T, Gao X, Chen M, van Dam RM.** Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. *Obes Rev*. 2009;10(3):313-323. [EL 1; MRCT]
1279. **Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P.** Behavioural Weight Management Review Group. Diet or exercise interventions vs combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. *J Acad Nutr Diet*. 2014;114(10):1557-1568. [EL 2; MNRCT]
1280. **Ross R, Dagnone D, Jones PJ, et al.** Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. *Ann Intern Med*. 2000;133(2):92-103. [EL 1; RCT]
1281. **Jakicic JM, Marcus BH, Gallagher KI, Napolitano M, Lang W.** Effect of exercise duration and intensity on weight loss in overweight, sedentary women: a randomized trial. *JAMA*. 2003;290(10):1323-1330. [EL 1; RCT]
1282. **Jakicic JM, Winters C, Lang W, Wing RR.** Effects of intermittent exercise and use of home exercise equipment on adherence, weight loss, and fitness in overweight women: a randomized trial. *JAMA*. 1999;282(16):1554-1560. [EL 1; RCT]
1283. **Miller WC, Koceja DM, Hamilton EJ.** A meta-analysis of the past 25 years of weight loss research using diet, exercise or diet plus exercise intervention. *Int J Obes Relat Metab Disord*. 1997;21(10):941-947. [EL 2; MNRCT]
1284. **Chomentowski P, Dubé JJ, Amati F, et al.** Moderate exercise attenuates the loss of skeletal muscle mass that occurs with intentional caloric restriction-induced weight loss in older, overweight to obese adults. *J Gerontol A Biol Sci Med Sci*. 2009;64(5):575-580. [EL 1; RCT]
1285. **Beavers KM, Beavers DP, Nesbit BA, et al.** Effect of an 18-month physical activity and weight loss intervention on body composition in overweight and obese older adults. *Obesity (Silver Spring)*. 2014;22(2):325-331. [EL 1; RCT]
1286. **Garrow J, Summerbell C.** Meta-analysis on the effect of exercise on the composition of weight loss. *Int J Obes Relat Metab Disord*. 1994;18(7):516-517. [EL 4; NE]
1287. **Ballor DL, Poehlman ET.** Exercise-training enhances fat-free mass preservation during diet-induced weight loss: a meta-analytical finding. *Int J Obes Relat Metab Disord*. 1994;18(1):35-40. [EL 2; MNRCT]
1288. **Garrow JS, Summerbell CD.** Meta-analysis: effect of exercise, with or without dieting, on the body composition of overweight subjects. *Eur J Clin Nutr*. 1995;49(1):1-10. [EL 2; MNRCT]
1289. **Weinheimer EM, Sands LP, Campbell WW.** A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: implications for sarcopenic obesity. *Nutr Rev*. 2010;68(7):375-388. [EL 4; NE]
1290. **Nascimento SL, Pudwell J, Surita FG, Adamo KB, Smith GN.** The effect of physical exercise strategies on weight loss in postpartum women: a systematic review and meta-analysis. *Int J Obes*. 2014;38(5):626-635. [EL 1; MRCT]
1291. **Curioni CC, Lourenço PM.** Long-term weight loss after diet and exercise: a systematic review. *Int J Obes*. 2005; 29(10):1168-1174. [EL 1; MRCT]
1292. **Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF.** Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2014;348:g2646. [EL 1; MRCT]
1293. **McTiernan A, Sorensen B, Irwin ML, et al.** Exercise effect on weight and body fat in men and women. *Obesity (Silver Spring)*. 2007;15(6):1496-1512. [EL 1; RCT]
1294. **Jakicic JM, Marcus BH, Lang W, Janney C.** Effect of exercise on 24-month weight loss maintenance in overweight women. *Arch Intern Med*. 2008;168(14):1550-1559. [EL 1; RCT]
1295. **Tate DF, Jeffery RW, Sherwood NE, Wing RR.** Long-term weight losses associated with prescription of higher physical activity goals. Are higher levels of physical activity protective against weight regain? *Am J Clin Nutr*. 2007;85(4):954-959. [EL 1; RCT]
1296. **Fogelholm M, Kukkonen-Harjula K, Nenonen A, Pasanen M.** Effects of walking training on weight maintenance after a very-low-energy diet in premenopausal obese women: a randomized controlled trial. *Arch Intern Med*. 2000;160(14):2177-2184. [EL 1; RCT]
1297. **Johansson K, Neovius M, Hemmingsson E.** Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2014;99(1):14-23. [EL 1; MRCT]
1298. **Leermakers EA, Perri MG, Shigaki CL, Fuller PR.** Effects of exercise-focused versus weight-focused maintenance programs on the management of obesity. *Addict Behav*. 1999;24(2):219-227. [EL 1; RCT]
1299. **Avenell A, Brown TJ, McGee MA, et al.** What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions. *J Hum Nutr Diet*. 2004;17(4):293-316. [EL 1; MRCT]
1300. **Mekary RA, Feskanich D, Hu FB, Willett WC, Field AE.** Physical activity in relation to long-term weight maintenance after intentional weight loss in premenopausal women. *Obesity (Silver Spring)*. 2010; 18(1):167-174. [EL 2; PCS]

1301. **Vanderwood KK, Hall TO, Harwell TS, et al.** Factors associated with the maintenance or achievement of the weight loss goal at follow-up among participants completing an adapted diabetes prevention program. *Diabetes Res Clin Pract*. 2011;91(2):141-147. [EL 1; RCT, post-intervention survey]
1302. **Wadden TA, Neiberg RH, Wing RR, et al. Look AHEAD Research Group.** Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring)*. 2011;19(10):1987-1998. [EL 1; RCT]
1303. **Catenacci VA, Ogden LG, Stuht J, et al.** Physical activity patterns in the National Weight Control Registry. *Obesity (Silver Spring)*. 2008;16(1):153-161. [EL 3; SS]
1304. **Catenacci VA, Grunwald GK, Ingebrigtsen JP, et al.** Physical activity patterns using accelerometry in the National Weight Control Registry. *Obesity (Silver Spring)*. 2011;19(6):1163-1170. [EL 3; SS]
1305. **Lee IM, Djoussé L, Sesso HD, Wang L, Buring JE.** Physical activity and weight gain prevention. *JAMA*. 2010;303(12):1173-1179. [EL 2; PCS]
1306. **Hankinson AL, Daviglus ML, Bouchard C, et al.** Maintaining a high physical activity level over 20 years and weight gain. *JAMA*. 2010;304(23):2603-2610. [EL 2; PCS]
1307. **Moholdt T, Wisløff U, Lydersen S, Nauman J.** Current physical activity guidelines for health are insufficient to mitigate long-term weight gain: more data in the fitness versus fatness debate (The HUNT study, Norway). *Br J Sports Med*. 2014;48(20):1489-1496. [EL 2; PCS]
1308. **Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J.** Long-term non-pharmacological weight loss interventions for adults with prediabetes. *Cochrane Database Syst Rev*. 2005;(2):CD005270. [EL 1; MRCT]
1309. **Norris SL, Zhang X, Avenell A, et al.** Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. *Cochrane Database Syst Rev*. 2005;(2):CD004095. [EL 1; MRCT]
1310. **Colberg SR, Sigal RJ, Fernhall B, et al.** Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. *Diabetes Care*. 2010;33(12):2692-2696. [EL 4; NE]
1311. **American Diabetes Association.** Foundations of care: education, nutrition, physical activity, smoking cessation, psychosocial care, and immunization. *Diabetes Care*. 2015;38 Suppl:S20-S30. [EL 4; NE]
1312. **Livhits M, Mercado C, Yermilov I, et al.** Exercise following bariatric surgery: systematic review. *Obes Surg*. 2010;20(5):657-665. [EL 2; MNRCT]
1313. **Egberts K, Brown WA, Brennan L, O'Brien PE.** Does exercise improve weight loss after bariatric surgery? A systematic review. *Obes Surg*. 2012;22(2):335-341. [EL 2; MNRCT]
1314. **Ahmed SM, Sho S, Changchien E, et al.** Do Pedometers Increase Physical Activity Following RYGB? *Obesity*. 2011;19:S57. In: Program of the 29th Annual Meeting of the Obesity Society, October 3, 2011; Orlando, Florida. Abstract. [EL 4; NE, abstract]
1315. **Ballor DL, Keesey RE.** A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. *Int J Obes*. 1991;15(11):717-726. [EL 2; MNRCT]
1316. **Schwingshackl L, Dias S, Strasser B, Hoffmann G.** Impact of different training modalities on anthropometric and metabolic characteristics in overweight/obese subjects: a systematic review and network meta-analysis. *PLoS One*. 2013;8(12):e82853. [EL 1; MRCT]
1317. **Villareal DT, Chode S, Parimi N, et al.** Weight loss, exercise, or both and physical function in obese older adults. *N Engl J Med*. 2011;364(13):1218-1229. [EL 1; RCT]
1318. **Ballor DL, Katch VL, Becque MD, Marks CR.** Resistance weight training during caloric restriction enhances lean body weight maintenance. *Am J Clin Nutr*. 1988;47(1):19-25. [EL 1; RCT, N = 40]
1319. **Hunter GR, Byrne NM, Sirikul B, et al.** Resistance training conserves fat-free mass and resting energy expenditure following weight loss. *Obesity (Silver Spring)*. 2008;16(5):1045-1051. [EL 1; RCT]
1320. **Borg P, Kukkonen-Harjula K, Fogelholm M, Pasanen M.** Effects of walking or resistance training on weight loss maintenance in obese, middle-aged men: a randomized trial. *Int J Obes Relat Metab Disord*. 2002;26(5):676-683. [EL 1; RCT]
1321. **Schmitz KH, Jensen MD, Kugler KC, Jeffery RW, Leon AS.** Strength training for obesity prevention in midlife women. *Int J Obes Relat Metab Disord*. 2003;27(3):326-333. [EL 1; RCT]
1322. **Balducci S, Zanuso S, Nicolucci A, et al.** Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). *Arch Intern Med*. 2010;170(20):1794-1803. [EL 1; RCT]
1323. **Bacchi E, Negri C, Zanolin ME, et al.** Metabolic effects of aerobic training and resistance training in type 2 diabetic subjects: a randomized controlled trial (the RAED2 study). *Diabetes Care*. 2012;35(4):676-682. [EL 1; RCT]
1324. **Marzolini S, Oh PI, Brooks D.** Effect of combined aerobic and resistance training versus aerobic training alone in individuals with coronary artery disease: a meta-analysis. *Eur J Prev Cardiol*. 2012;19(1):81-94. [EL 1; MRCT]
1325. **Willis LH, Slentz CA, Bateman LA, et al.** Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. *J Appl Physiol*. 2012;113(12):1831-1837. [EL 1; RCT]
1326. **Aguiar EJ, Morgan PJ, Collins CE, Plotnikoff RC, Callister R.** Efficacy of interventions that include diet, aerobic and resistance training components for type 2 diabetes prevention: a systematic review with meta-analysis. *Int J Behav Nutr Phys Act*. 2014;11:2. [EL 2; MNRCT]
1327. **Strasser B, Siebert U, Schobersberger W.** Resistance training in the treatment of the metabolic syndrome: a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. *Sports Med*. 2010;40(5):397-415. [EL 1; MRCT]
1328. **Mekary RA, Grøntved A, Despres JP, et al.** Weight training, aerobic physical activities, and long-term waist circumference change in men. *Obesity (Silver Spring)*. 2015;23(2):461-467. [EL 2; PCS]
1329. **Haltom RW, Kraemer RR, Sloan RA, Hebert EP, Frank K, Tryniecki JL.** Circuit weight training and its effects on excess postexercise oxygen consumption. *Med Sci Sports Exerc*. 1999;31(11):1613-1618. [EL 1; RCT, very small study of only 7 subjects]
1330. **Braun WA, Hawthorne WE, Markofski MM.** Acute EPOC response in women to circuit training and treadmill exercise of matched oxygen consumption. *Eur J Appl Physiol*. 2005;94(5-6):500-504. [EL 2; PCS, very small study of only 8 subjects]
1331. **Levine JA.** Non-exercise activity thermogenesis (NEAT). *Best Pract Res Clin Endocrinol Metab*. 2002;16(4):679-702. [EL 4; NE]
1332. **Martíinez-González MA, Martínez JA, Hu FB, Gibney MJ, Kearney J.** Physical inactivity, sedentary lifestyle and obesity in the European Union. *Int J Obes Relat Metab*

Disord. 1999;23(11):1192-1201. [EL 3; SS, large N: questionnaires to 15,239 subjects]

1333. **Hu FB, Li TY, Colditz GA, Willett WC, Manson JE.** Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA*. 2003;289(14):1785-1791. [EL 2; PCS, large study N = 50,277]
1334. **Healy GN, Wijndaele K, Dunstan DW, et al.** Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Diabetes Care*. 2008;31(2):369-371. [EL 3; CSS, substudy]
1335. **Inoue S, Sugiyama T, Takamiya T, Oka K, Owen N, Shimomitsu T.** Television viewing time is associated with overweight/obesity among older adults, independent of meeting physical activity and health guidelines. *J Epidemiol*. 2012;22(1):50-56. [EL 3; CSS]
1336. **Maher CA, Mire E, Harrington DM, Staiano AE, Katzmarzyk PT.** The independent and combined associations of physical activity and sedentary behavior with obesity in adults: NHANES 2003-06. *Obesity (Silver Spring)*. 2013;21(12):E730-E737. [EL 3; CSS]
1337. **Van Dyck D, Cerin E, De Bourdeaudhuij I, et al.** International study of objectively measured physical activity and sedentary time with body mass index and obesity: IPEN adult study. *Int J Obes*. 2015;39(2):199-207. [EL 3; CSS]
1338. **Arsenault BJ, Rana JS, Lemieux I, et al.** Physical inactivity, abdominal obesity and risk of coronary heart disease in apparently healthy men and women. *Int J Obes*. 2010;34(2):340-347. [EL 2; PCS]
1339. **Thorp AA, Owen N, Neuhaus M, Dunstan DW.** Sedentary behaviors and subsequent health outcomes in adults a systematic review of longitudinal studies, 1996-2011. *Am J Prev Med*. 2011;41(2):207-215. [EL 2; MNRCT]
1340. **van Baak MA, van Mil E, Astrup AV, et al.** Leisure-time activity is an important determinant of long-term weight maintenance after weight loss in the Sibutramine Trial on Obesity Reduction and Maintenance (STORM trial). *Am J Clin Nutr*. 2003;78(2):209-214. [EL 1; RCT]
1341. **Bravata DM, Smith-Spangler C, Sundaram V, et al.** Using pedometers to increase physical activity and improve health: a systematic review. *JAMA*. 2007; 298(19): 2296-2304. [EL 2; MNRCT]
1342. **Freak-Poli RL, Cumpston M, Peeters A, Clemes SA.** Workplace pedometer interventions for increasing physical activity. *Cochrane Database Syst Rev*. 2013;(4): CD009209. [EL 1; MRCT]
1343. **Shrestha N, Ijaz S, Kukkonen-Harjula KT, Kumar S, Nwankwo CP.** Workplace interventions for reducing sitting at work. *Cochrane Database Syst Rev*. 2015;(1): CD010912. [EL 2; MNRCT]
1344. **Jeffery RW, Wing RR, Thorson C, Burton LR.** Use of personal trainers and financial incentives to increase exercise in a behavioral weight-loss program. *J Consult Clin Psychol*. 1998;66(5):777-783. [EL 1; RCT]
1345. **Roddy E, Zhang W, Doherty M, et al.** Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee--the MOVE consensus. *Rheumatology*. 2005;44(1):67-73. [EL 4; NE]
1346. **Mazzetti SA, Kraemer WJ, Volek JS, et al.** The influence of direct supervision of resistance training on strength performance. *Med Sci Sports Exerc*. 2000;32(6): 1175-1184. [EL 1; RCT, N = 20]
1347. **McClaran SR.** The effectiveness of personal training on changing attitudes towards physical activity. *J Sports Sci Med*. 2003;2(1):10-14. [EL 2; PCS]
1348. **Wing RR, Jeffery RW, Pronk N, Hellerstedt WL.** Effects of a personal trainer and financial incentives on exercise adherence in overweight women in a behavioral weight loss program. *Obes Res*. 1996;4(5):457-462. [EL 2; PCS]
1349. **Baker RC, Kirschenbaum DS.** Self-monitoring may be necessary for successful weight control. *Behav Ther*. 1993;24(3):377-394. [EL 2; PCS]
1350. **O'Neil PM.** Assessing dietary intake in the management of obesity. *Obes Res*. 2001;9 Suppl 5:361S-366S. [EL 4; NE]
1351. **Jakicic JM.** Exercise in the treatment of obesity. *Endocrinol Metab Clin North Am*. 2003;32:967-980. [EL 4; NE]
1352. **Guare JC, Wing RR, Marcus MD, Epstein LH, Burton LR, Gooding WE.** Analysis of changes in eating behaviour and weight loss in type II diabetic patients. Which behaviours to change. *Diabetes Care*. 1989;12: 500-512. [EL 2; PCS]
1353. **Wadden TA, Berkowitz RI, Womble LG, et al.** Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med*. 2005;353 (20):2111-2120. [EL 1; RCT]
1354. **Wansink B, Cheney MM.** Super Bowls: serving bowl size and food consumption. *JAMA*. 2005;293(14):1727-1728. [EL 2; NRCT]
1355. **Pedersen SD, Kang J, Kline GA.** Portion control plate for weight loss in obese patients with type 2 diabetes mellitus: a controlled clinical trial. *Arch Intern Med*. 2007;167(12):1277-1283. [EL 1; RCT]
1356. **Hannum SM, Carson L, Evans EM, et al.** Use of portion-controlled entrees enhances weight loss in women. *Obes Res*. 2004;12(3):538-546. [EL 1; RCT]
1357. **Ryan DH, Espeland MA, Foster GD, et al.** Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials*. 2003;24(5):610-628. [EL 4; NE]
1358. **Ditschuneit HH, Flechtner-Mors M.** Value of structured meals for weight management: risk factors and long-term weight maintenance. *Obes Res*. 2001;(9 Suppl 4):284S-289S. [EL 1; RCT]
1359. **Rothacker DQ, Staniszewski BA, Ellis PK.** Liquid meal replacement vs traditional food: a potential model for women who cannot maintain eating habit change. *J Am Diet Assoc*. 2001;101(3):345-347. [EL 1; RCT]
1360. **Noakes M, Foster PR, Keogh JB, Clifton PM.** Meal replacements are as effective as structured weight-loss diets for treating obesity in adults with features of metabolic syndrome. *J Nutr*. 2004;134(8):1894-1899. [EL 1; RCT]
1361. **Heymsfield SB, van Mierlo CAJ, van der Knaap HCM, Heo M, Frier HI.** Weight management using meal replacement strategy: meta and pooling analysis from six studies. *Int J Obes*. 2003;27:537-549. [EL 1; MRCT]
1362. **Wing RR, Phelan S.** Long-term weight loss maintenance. *Am J Clin Nutr*. 2005;82(1 Suppl):222S-225S. [EL 4; NE]
1363. **Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G.** Financial incentive-based approaches for weight loss: a randomized trial. *JAMA*. 2008;300(22): 2631-2637. [EL 1; RCT]
1364. **Avenell A, Broom J, Brown TJ, et al.** Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess*. 2004;8(21):iii-iv, 1-182. [EL 1; MNRCT]
1365. **Blaine B, Rodman J.** Responses to weight loss treatment among obese individuals with and without BED: a matched-study meta-analysis. *Eat Weight Disord*. 2007;

12(2):54-60. [EL 2; MNRCT, matched-study analysis, non-exhaustive literature search]
1366. **Berkel LA, Poston WS, Reeves RS, Foreyt JP.** Behavioral interventions for obesity. *J Am Diet Assoc*. 2005;105(5 Suppl 1):S35-S43. [EL 4; NE]
1367. **Wadden TA, Foster GD.** Behavioral treatment of obesity. *Med Clin North Am*. 2000;84(2):441-461. [EL 4; NE]
1368. **Wing RR.** Behavioral weight control. In: Wadden TA, Stunkard AJ, eds. *Handbook of obesity treatment*. New York, NY: Guilford Press; 2002: 301-316. [EL 4; NE]
1369. **Brownell KD.** *The LEARN Program for Weight Management 2000*. Dallas, TX: American Health Publisher Co.; 2000. [EL 4; NE]
1370. **Perri MG, Limacher MC, von Castel-Roberts K, et al.** Comparative effectiveness of three doses of weight-loss counseling: two-year findings from the rural LITE trial. *Obesity (Silver Spring)*. 2014;22(11):2293-2300. [EL 1; RCT]
1371. **Lucini D, Cesana G, Vigo C, Malacarne M, Pagani M.** Reducing weight in an internal medicine outpatient clinic using a lifestyle medicine approach: a proof of concept. *Eur J Intern Med*. 2015;26(9):680-684. [EL 2; PCS]
1372. **Wadden TA, Butryn ML, Hong PS, Tsai AG.** Behavioral treatment of obesity in patients encountered in primary care settings: a systematic review. *JAMA*. 2014;312(17):1779-1791. [EL 1; RCT]
1373. **Booth HP, Prevost TA, Wright AJ, Gulliford MC.** Effectiveness of behavioural weight loss interventions delivered in a primary care setting: a systematic review and meta-analysis. *Fam Pract*. 2014;31(6):643-653. [EL 1; MRCT]
1374. **Hartmann-Boyce J, Johns DJ, Jebb SA, Summerbell C, Aveyard P, Behavioural Weight Management Review Group.** Behavioural weight management programmes for adults assessed by trials conducted in everyday contexts: systematic review and meta-analysis. *Obes Rev*. 2014; 15(11):920-932. [EL 2; MNRCT]
1375. **Teixeira PJ, Carraça EV, Marques MM, et al.** Successful behavior change in obesity interventions in adults: a systematic review of self-regulation mediators. *BMC Med*. 2015;13:84. [EL 2; MNRCT]
1376. **Franz MJ, VanWormer JJ, Crain AL, et al.** Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc*. 2007;107(10):1755-1767. [EL 1; MRCT]
1377. **O'Brien MJ, Whitaker RC, Yu D, Ackermann RT.** The comparative efficacy of lifestyle intervention and metformin by educational attainment in the Diabetes Prevention Program. *Prev Med*. 2015;77:125-130. [EL 1; RCT, post-hoc analysis]
1378. **Wing RR, Hamman RF, Bray GA, et al. Diabetes Prevention Program Research Group.** Achieving weight and activity goals among diabetes prevention program lifestyle participants. *Obes Res*. 2004;12(9):1426-1434. [EL 1; RCT, post-hoc analysis]
1379. **Miller CK, Nagaraja HN, Weinhold KR.** Early weight-loss success identifies nonresponders after a lifestyle intervention in a worksite diabetes prevention trial. *J Acad Nutr Diet*. 2015;115(9):1464-1471. [EL 1; RCT]
1380. **Carels RA, Darby L, Cacciapaglia HM, et al.** Applying a stepped-care approach to the treatment of obesity. *J Psychosom Res*. 2005;59(6):375-383. [EL 1; RCT]
1381. **Wadden TA, Foster GD, Wang J, et al.** Clinical correlates of short- and long-term weight loss. *Am J Clin Nutr*. 1992;56(1 Suppl):271S-274S. [EL 1; RCT]
1382. **Hadžiabdić MO, Mucalo I, Hrabač P, Matić T, Rahelić D, Božikov V.** Factors predictive of drop-out and weight loss success in weight management of obese patients. *J Hum Nutr Diet*. 2015;(28 Suppl 2):24-32. [EL 1; RCT, single-blinded primary study, secondary subset analysis]
1383. **Stotland SC, Larocque M.** Early treatment response as a predictor of ongoing weight loss in obesity treatment. *Br J Health Psychol*. 2005;10(Pt 4):601-614. [EL 2; PCS]
1384. **Greenberg I, Stampfer MJ, Schwarzfuchs D, Shai I, DIRECT Group.** Adherence and success in long-term weight loss diets: the dietary intervention randomized controlled trial (DIRECT). *J Am Coll Nutr*. 2009;28(2): 159-168. [EL 1; RCT]
1385. **Feldstein AC, Nichols GA, Smith DH, et al.** Weight change in diabetes and glycemic and blood pressure control. *Diabetes Care*. 2008;31(10):1960-1965. [EL 3; SS, retrospective cohort N = 2,574]
1386. **Rock CL, Flatt SW, Byers TE, et al.** Results of the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial: a behavioral weight loss intervention in overweight or obese breast cancer survivors. *J Clin Oncol*. 2015;33(28):3169-3176. [EL 1; RCT]
1387. **Chow CK, Redfern J, Hillis GS, et al.** Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. *JAMA*. 2015;314(12):1255-1263. [EL 1; RCT]
1388. **Lin M, Mahmooth Z, Dedhia N, et al.** Tailored, interactive text messages for enhancing weight loss among African American adults: the TRIMM randomized controlled trial. *Am J Med*. 2015;128(8):896-904. [EL 1; RCT]
1389. **Hall AK, Cole-Lewis H, Bernhardt JM.** Mobile text messaging for health: a systematic review of reviews. *Annu Rev Public Health*. 2015;36:393-415. [EL 4; NE]
1390. **Fukuoka Y, Gay CL, Joiner KL, Vittinghoff E.** A novel diabetes prevention intervention using a mobile app: a randomized controlled trial with overweight adults at risk. *Am J Prev Med*. 2015;49(2):223-237. [EL 1; RCT]
1391. **Block G, Azar KM, Romanelli RJ, et al.** Diabetes prevention and weight loss with a fully automated behavioral intervention by email, web, and mobile phone: a randomized controlled trial among persons with prediabetes. *J Med Internet Res*. 2015;17(10):e240. [EL 1; RCT]
1392. **Flores Mateo G, Granado-Font E, Ferré-Grau C, Montaña-Carreras X.** Mobile phone apps to promote weight loss and increase physical activity: a systematic review and meta-analysis. *J Med Internet Res*. 2015;17 (11):e253. [EL 2; MNRCT]
1393. **Watson S, Woodside JV, Ware LJ, et al.** Effect of a web-based behavior change program on weight loss and cardiovascular risk factors in overweight and obese adults at high risk of developing cardiovascular disease: randomized controlled trial. *J Med Internet Res*. 2015;17(7):e177. [EL 1; RCT]
1394. **Svensson M, Hult M, van der Mark M, et al.** The change in eating behaviors in a Web-based weight loss program: a longitudinal analysis of study completers. *J Med Internet Res*. 2014;16(11):e234. [EL 2; PCS]
1395. **Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR.** Weight-loss maintenance for 10 years in the National Weight Control Registry. *Am J Prev Med*. 2014;46(1):17-23. [EL 3; SS, registry analysis]
1396. **Catenacci VA, Odgen L, Phelan S, et al.** Dietary habits and weight maintenance success in high versus low exercisers in the National Weight Control Registry. *J Phys Act Health*. 2014;11(8):1540-1548. [EL 3; SS, registry analysis]
1397. **Catenacci VA, Pan Z, Thomas JG, et al.** Low/no calorie sweetened beverage consumption in the National Weight Control Registry. *Obesity (Silver Spring)*. 2014;22(10):2244-2251. [EL 3; SS, registry analysis]

1398. **Raynor DA, Phelan S, Hill JO, Wing RR.** Television viewing and long-term weight maintenance: results from the National Weight Control Registry. *Obesity (Silver Spring)*. 2006;14(10):1816-1824. [EL 3; SS, registry analysis]
1399. **Shea MK, Houston DK, Nicklas BJ, et al.** The effect of randomization to weight loss on total mortality in older overweight and obese adults: the ADAPT Study. *J Gerontol A Biol Sci Med Sci*. 2010;65(5):519-525. [EL 1; RCT]
1400. **Whelton PK, Appel LJ, Espeland MA, et al.** TONE Collaborative Research Group. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled Trial of Non-pharmacologic Interventions in the Elderly (TONE). *JAMA*. 1998;279(11):839-846. [EL 1; RCT]
1401. **Gudzune KA, Doshi RS, Mehta AK, et al.** Efficacy of commercial weight-loss programs: an updated systematic review. *Ann Intern Med*. 2015;162(7):501-512. [EL 2; MNRCT]
1402. **Heshka S, Greenway F, Anderson JW, et al.** Self-help weight loss versus a structured commercial program after 26 weeks: a randomized controlled study. *Am J Med*. 2000; 109(4):282-287. [EL 1; RCT]
1403. **Rock CL, Pakiz B, Flatt SW, Quintana EL.** Randomized trial of a multifaceted commercial weight loss program. *Obesity (Silver Spring)*. 2007;15(4):939-949. [EL 1; RCT]
1404. **Foster GD, Borradaile KE, Vander Veur SS, et al.** The effects of a commercially available weight loss program among obese patients with type 2 diabetes: a randomized study. *Postgrad Med*. 2009;121(5):113-118. [EL 1; RCT]
1405. **Ackermann RT, Finch EA, Caffrey HM, Lipscomb ER, Hays LM, Saha C.** Long-term effects of a community-based lifestyle intervention to prevent type 2 diabetes: the DEPLOY extension pilot study. *Chronic Illn*. 2011;7(4): 279-290. [EL 1; RCT, extension study]
1406. **Wadden TA, Webb VL, Moran CH, Bailer BA.** Lifestyle modification for obesity: new developments in diet, physical activity, and behavior therapy. *Circulation*. 2012;125(9):1157-1170. [EL 4; NE]
1407. **Schapiro MM, Bogran N.** Dietless weight loss with benzphetamine (didrex): a controlled comparison with phenmetrazine and placebo. *Curr Ther Res Clin Exp*. 1960;2:333-345. [EL 2; RCCS]
1408. **Wadden TA, Berkowitz RI, Sarwer DB, Prus-Wisniewski R, Steinberg C.** Benefits of lifestyle modification in the pharmacologic treatment of obesity: a randomized trial. *Arch Intern Med*. 2001;161(2):218-227. [EL 1; RCT]
1409. **Craighead LW.** Sequencing of behavior therapy and pharmacotherapy for obesity. *J Consult Clin Psychol*. 1984;52(2):190-199. [EL 1; RCT]
1410. **Craighead LW, Stunkard AJ, O'Brien RM.** Behavior therapy and pharmacotherapy for obesity. *Arch Gen Psychiatry*. 1981;38(7):763-768. [EL 2; PCS]
1411. **Poston WS, Haddock CK, Pinkston MM, et al.** Evaluation of a primary care-oriented brief counselling intervention for obesity with and without orlistat. *J Intern Med*. 2006;260(4):388-398. [EL 1; RCT]
1412. **Tong PC, Lee ZS, Sea MM, et al.** The effect of orlistat-induced weight loss, without concomitant hypocaloric diet, on cardiovascular risk factors and insulin sensitivity in young obese Chinese subjects with or without type 2 diabetes. *Arch Intern Med*. 2002;162(21):2428-2435. [EL 2; PCS]
1413. **James WP, Avenell A, Broom J, Whitehead J.** A one-year trial to assess the value of orlistat in the management of obesity. *Int J Obes Relat Metab Disord*. 1997;(21 Suppl 3):S24-S30. [EL 2; MNRCT]
1414. **Davidson MH, Hauptman J, DiGirolamo M, et al.** Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA*. 1999;281(3):235-242. [EL 1; RCT]
1415. **Krempf M, Louvet JP, Allanic H, Miloradovich T, Joubert JM, Attali JR.** Weight reduction and long-term maintenance after 18 months treatment with orlistat for obesity. *Int J Obes Relat Metab Disord*. 2003;27(5):591-597. [EL 1; RCT]
1416. **Lindgärde F.** The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: the Swedish Multimorbidity Study. *J Intern Med*. 2000;248 (3):245-254. [EL 1; RCT]
1417. **O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.** A systematic review of the clinical effectiveness of orlistat used for the management of obesity. *Obes Rev*. 2004;5(1):51-68. [EL 1; MRCT]
1418. **Sjöström L, Rissanen A, Andersen T, et al.** Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet*. 1998; 352(9123):167-172. [EL 1; RCT]
1419. **Derosa G, Cicero AF, D'Angelo A, Fogari E, Maffioli P.** Effects of 1-year orlistat treatment compared to placebo on insulin resistance parameters in patients with type 2 diabetes. *J Clin Pharm Ther*. 2012;37(2):187-195. [EL 1; RCT]
1420. **Finer N, James WP, Kopelman PG, Lean ME, Williams G.** One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. *Int J Obes Relat Metab Disord*. 2000;24(3):306-313. [EL 1; RCT]
1421. **Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM.** Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity (Silver Spring)*. 2013;21(11):2163-2171. [EL 1; RCT]
1422. **Apovian CM, Aronne L, Rubino D, et al.** A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)*. 2013;21(5):935-943. [EL 1; RCT]
1423. **van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH.** Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes*. 2014;38(6):784-793. [EL 1; RCT]
1424. **Wadden TA, Hollander P, Klein S, et al.** NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes*. 2013;37(11):1443-1451. [EL 1; RCT]
1425. **Kushner RF, Ryan DH.** Assessment and lifestyle management of patients with obesity: clinical recommendations from systematic reviews. *JAMA*. 2014; 312(9):943-952. [EL 4; NE]
1426. **Pi-Sunyer X.** The medical risks of obesity. *Postgrad Med*. 2009;121(6):21-33. [EL 4; NE]
1427. **Lean ME, Carraro R, Finer N, et al.** Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. *Int J Obes*. 2014;38(5):689-697. [EL 1; RCT]
1428. **Pi-Sunyer FX.** Short-term medical benefits and adverse effects of weight loss. *Ann Intern Med*. 1993;119(7 Pt 2): 722-726. [EL 4; NE]
1429. **Haddock CK, Poston WS, Dill PL, Foreyt JP, Ericsson M.** Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord*. 2002;26(2):262-273. [EL 1; MRCT]

1430. **Kim KK, Cho HJ, Kang HC, Youn BB, Lee KR.** Effects on weight reduction and safety of short-term phentermine administration in Korean obese people. *Yonsei Med J*. 2006;47(5):614-625. [EL 1; RCT]
1431. **Parsons WB.** Controlled-release diethylpropion hydrochloride used in a program for weight reduction. *Clin Ther*. 1981;3(5):329-335. [EL 1; RCT, small group sizes: 12-13 for each of 3 groups]
1432. **Carney DE, Tweddell ED.** Double blind evaluation of long acting diethylpropion hydrochloride in obese patients from a general practice. *Med J Aust*. 1975;1(1):13-15. [EL 1; RCT]
1433. **Munro JF, MacCuish AC, Wilson EM, Duncan LJ.** Comparison of continuous and intermittent anorectic therapy in obesity. *Br Med J*. 1968;1(5588):352-354. [EL 2; NRCT, allocation concealment]
1434. **Silverstone T.** Intermittent treatment with anorectic drugs. *Practitioner*. 1974;213(1274):245-252. [EL 2; NRCT, allocation concealment]
1435. **Kaya A, Aydin N, Topsever P, et al.** Efficacy of sibutramine, orlistat and combination therapy on short-term weight management in obese patients. *Biomed Pharmacother*. 2004;58(10):582-587. [EL 1; RCT]
1436. **Redman LM, Heilbronn LK, Martin CK, et al.** Metabolic and behavioral compensations in response to caloric restriction: implications for the maintenance of weight loss. *PLoS One*. 2009;4(2):e4377. [EL 1; RCT]
1437. **Rosenbaum M, Hirsch J, Gallagher DA, Leibel RL.** Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. *Am J Clin Nutr*. 2008;88(4):906-912. [EL 2; PCS, weight-matched subjects]
1438. **Baldwin KM, Joanisse DR, Haddad F, et al.** Effects of weight loss and leptin on skeletal muscle in human subjects. *Am J Physiol Regul Integr Comp Physiol*. 2011;301(5):R1259-66. [EL 1; RCT, only 10 subjects]
1439. **Sumithran P, Prendergast LA, Delbridge E, et al.** Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med*. 2011;365(17):1597-1604. [EL 2; PCS]
1440. **Rueda-Clausen CF, Padwal RS, Sharma AM.** New pharmacological approaches for obesity management. *Nat Rev Endocrinol*. 2013;9(8):467-478. [EL 4; NE]
1441. **Drent ML, van der Veen EA.** Lipase inhibition: a novel concept in the treatment of obesity. *Int J Obes Relat Metab Disord*. 1993;17(4):241-244. [EL 1; RCT]
1442. XENICAL (orlistat) [package insert]. South San Francisco, CA: Genentech; 2015. [EL 4; NE]
1443. **Gilman AG, Rall TW, Nies AS, Taylor P, eds.** *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 8th ed. New York, NY: Pergamon Press; 1990. [EL 4; NE]
1444. Qsymia (phentermine and topiramate extended-release) capsules, for oral use, CIV, [package insert]. Mountain View, CA: Vivus, Inc; 2014. [EL 4; NE]
1445. Belviq (lorcaserin HCl) [package insert]. Woodcliffe, NJ: Eisai Inc; 2014. [EL 4; NE]
1446. **Plodkowski RA, Nguyen Q, Sundaram U, Nguyen L, Chau DL, St Jeor S.** Bupropion and naltrexone: a review of their use individually and in combination for the treatment of obesity. *Expert Opin Pharmacother*. 2009;10(6):1069-1081. [EL 4; NE]
1447. **Greenway FL, Whitehouse MJ, Guttadauria M, et al.** Rational design of a combination medication for the treatment of obesity. *Obesity (Silver Spring)*. 2009;17(1):30-39. [EL 1; RCT, human proof-of-concept trial; note there are also preclinical studies in this paper]
1448. Contrave (naltrexone HCl and bupropion HCl) extended-release tablets [package insert]. Deerfield, IL: Takeda Pharmaceuticals; 2014. [EL 4; NE]
1449. SAXENDA® (liraglutide [rDNA origin] injection), solution for subcutaneous use, [package insert]. Plainsboro, NJ: Novo Nordisk; 2014, rev 2015. [EL 4; NE]
1450. **Thomsen RW, Pedersen L, Møller N, Kahlert J, Beck-Nielsen H, Sørensen HT.** Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case-control study. *Diabetes Care*. 2015;38(6):1089-1098. [EL 2; RCCS]
1451. **Cosentino G, Conrad AO, Uwaifo GI.** Phentermine and topiramate for the management of obesity: a review. *Drug Des Devel Ther*. 2011;7:267-278. [EL 4; NE]
1452. **Rothman RB.** Treatment of obesity with "combination" pharmacotherapy. *Am J Ther*. 2010;17(6):596-603. [EL 4; NE]
1453. **Hussain HT, Parker JL, Sharma AM.** Clinical trial success rates of anti-obesity agents: the importance of combination therapies. *Obes Rev*. 2015;16(9):707-714. [EL 4; NE]
1454. **Greenway FL, Bray GA.** Combination drugs for treating obesity. *Curr Diab Rep*. 2010;10(2):108-115. [EL 4; NE]
1455. **Schmidt SL, Bryman D, Greenway FL, Hendricks EJ.** How physician obesity medicine specialists treated obesity before 2012 new drug approvals. *Obes Surg*. 2015;25(1):186-190. [EL 3; SS]
1456. **Weintraub M, Hasday JD, Mushlin AI, Lockwood DH.** A double-blind clinical trial in weight control. Use of fenfluramine and phentermine alone and in combination. *Arch Intern Med*. 1984;144(6):1143-1148. [EL 1; RCT]
1457. **Weintraub M, Sundaresan PR, Madan M, et al.** Long-term weight control study. I (weeks 0 to 34). The enhancement of behavior modification, caloric restriction, and exercise by fenfluramine plus phentermine versus placebo. *Clin Pharmacol Ther*. 1992;51(5):586-594. [EL 1; RCT]
1458. **Wellman PJ, Maher TJ.** Synergistic interactions between fenfluramine and phentermine. *Int J Obes Relat Metab Disord*. 1999;23(7):723-732. [EL 4; NE]
1459. **Smith SR, Garvey WT, Greenway FL, et al.** Combination weight management pharmacotherapy with lorcaserin and immediate release phentermine. In: Obesity Week 2014, November 2-7, 2014; Boston, MA. Abstract. [EL 4; NE, abstract]
1460. **Filippatos TD, Derdemezis CS, Gazi IF, Nakou ES, Mikhailidis DP, Elisaf MS.** Orlistat-associated adverse effects and drug interactions: a critical review. *Drug Saf*. 2008;31(1):53-65. [EL 4; NE]
1461. **Kambia K, Bah S, Dine T, et al.** High-performance liquid chromatographic determination of naltrexone in plasma of hemodialysis patients. *Biomed Chromatogr*. 2000;14(3):151-155. [EL 2; PCS, N = 8: HPLC methods paper]
1462. **Turpeinen M, Koivuviita N, Tolonen A, et al.** Effect of renal impairment on the pharmacokinetics of bupropion and its metabolites. *Br J Clin Pharmacol*. 2007;64(2):165-173. [EL 2; PCS, N = 27]
1463. **Davidson JA, Brett J, Falahati A, Scott D.** Mild renal impairment and the efficacy and safety of liraglutide. *Endocr Pract*. 2011;17(3):345-355. [EL 1; MRCT]
1464. **Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M.** Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. *Br J Clin Pharmacol*. 2009;68(6):898-905. [EL 2; PCS]
1465. **Scheen AJ.** Pharmacokinetics and clinical use of incretin-based therapies in patients with chronic kidney disease and type 2 diabetes. *Clin Pharmacokinet*. 2015;54(1):1-21. [EL 4; NE]
1466. **Kaakeh Y, Kanjee S, Boone K, Sutton J.** Liraglutide-induced acute kidney injury. *Pharmacotherapy*. 2012;32(1):e7-e11. [EL 3; SCR]

1467. **Idorn T, Knop FK, Jørgensen MB, et al.** Safety and efficacy of liraglutide in patients with type 2 diabetes and end-stage renal disease: an investigator-initiated, placebo-controlled, double-blinded, parallel group, randomized trial. *Diabetes Care*. 2016;39(2):206-213. [EL 1; RCT]
1468. **Weir MA, Beyea MM, Gomes T, et al.** Orlistat and acute kidney injury: an analysis of 953 patients. *Arch Intern Med*. 2011;171(7):703-704. [EL 3; SS]
1469. **Coutinho AK, Glancey GR.** Orlistat, an under-recognised cause of progressive renal impairment. *Nephrol Dial Transplant*. 2013;28 Suppl 4:iv172-4. [EL 3; SCR]
1470. **Manitpisitkul P, Curtin CR, Shalayda K, Wang SS, Ford L, Heald DL.** Pharmacokinetics of topiramate in patients with renal impairment, end-stage renal disease undergoing hemodialysis, or hepatic impairment. *Epilepsy Res*. 2014;108(5):891-901. [EL 2; PCS, age/sex/weight-matched]
1471. **Welch BJ, Graybeal D, Moe OW, Maalouf NM, Sakhaee K.** Biochemical and stone-risk profiles with topiramate treatment. *Am J Kidney Dis*. 2006;48(4):555-563. [EL 3; CSS]
1472. **Dell'Orto VG, Belotti EA, Goeggel-Simonetti B, et al.** Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review. *Br J Clin Pharmacol*. 2014;77(6):958-964. [EL 2; MNRCT]
1473. **Kossoff EH, Pyzik PL, Furth SL, Hladky HD, Freeman JM, Vining EP.** Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. *Epilepsia*. 2002;43(10):1168-1171. [EL 3; SS, retrospective cohort]
1474. **Ahmed MH.** Orlistat and calcium oxalate crystalluria: an association that needs consideration. *Ren Fail*. 2010; 32(8):1019-1021. [EL 4; NE]
1475. **Yen MH, Ko HC, Tang FI, Lu RB, Hong JS.** Study of hepatotoxicity of naltrexone in the treatment of alcoholism. *Alcohol*. 2006;38(2):117-120. [EL 4; NE]
1476. **Smith SR, Prosser WA, Donahue DJ, et al.** Lorcaserin (APD356), a selective 5-HT(2C) agonist, reduces body weight in obese men and women. *Obesity (Silver Spring)*. 2009;17(3):494-503. [EL 1; RCT]
1477. **Umemura T, Ichijo T, Matsumoto A, Kiyosawa K.** Severe hepatic injury caused by orlistat. *Am J Med*. 2006;119(8):e7. [EL 3; SCR]
1478. **Sall D, Wang J, Rashkin M, Welch M, Droege C, Schauer D.** Orlistat-induced fulminant hepatic failure. *Clin Obes*. 2014;4(6):342-347. [EL 3; SCR]
1479. **Erlinger S.** Gallstones in obesity and weight loss. *Eur J Gastroenterol Hepatol*. 2000;12(12):1347-1352. [EL 4; NE]
1480. **Everhart JE.** Contributions of obesity and weight loss to gallstone disease. *Ann Intern Med*. 1993;119(10):1029-1035. [EL 4; NE]
1481. **Stinton LM, Myers RP, Shaffer EA.** Epidemiology of gallstones. *Gastroenterol Clin North Am*. 2010;39(2):157-169. [EL 4; NE]
1482. **Stokes CS, Gluud LL, Casper M, Lammert F.** Ursodeoxycholic acid and diets higher in fat prevent gallbladder stones during weight loss: a meta-analysis of randomized controlled trials. *Clin Gastroenterol Hepatol*. 2014;12(7):1090-1100. [EL 1; MRCT]
1483. **Uy MC, Talingdan-Te MC, Espinosa WZ, Daez ML, Ong JP.** Ursodeoxycholic acid in the prevention of gallstone formation after bariatric surgery: a meta-analysis. *Obes Surg*. 2008;18(12):1532-1538. [EL 1; MRCT]
1484. **Miller K, Hell E, Lang B, Lengauer E.** Gallstone formation prophylaxis after gastric restrictive procedures for weight loss: a randomized double-blind placebo-controlled trial. *Ann Surg*. 2003;238(5):697-702. [EL 1; RCT]
1485. **Shiffman ML, Kaplan GD, Brinkman-Kaplan V, Vickers FF.** Prophylaxis against gallstone formation with ursodeoxycholic acid in patients participating in a very-low-calorie diet program. *Ann Intern Med*. 1995; 122(12):899-905. [EL 1; RCT]
1486. **Sugerman HJ, Brewer WH, Shiffman ML, et al.** A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypass-induced rapid weight loss. *Am J Surg*. 1995;169(1):91-96. [EL 1; RCT]
1487. **Drøyvold WB, Midthjell K, Nilsen TI, Holmen J.** Change in body mass index and its impact on blood pressure: a prospective population study. *Int J Obes*. 2005;29(6):650-655. [EL 3; CSS, N = 15,971 women and 13,846 men]
1488. **Adler C, Schaffrath Rosario A, Diederichs C, Neuhauser HK.** Change in the association of body mass index and systolic blood pressure in Germany - national cross-sectional surveys 1998 and 2008-2011. *BMC Public Health*. 2015;15:705. [EL 3; CSS, N = 6,931 in 1998 and 6,861 2008-2011]
1489. **Roth EM, Oparil S, Melino M, Lee J, Fernandez V, Heyrman R.** Olmesartan/amlodipine/hydrochlorothiazide in obese participants with hypertension: a TRINITY subanalysis. *J Clin Hypertens*. 2013;15(8):584-592. [EL 1; RCT, subgroup analysis]
1490. **Jordan J, Yumuk V, Schlaich M, et al.** Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: obesity and difficult to treat arterial hypertension. *J Hypertens*. 2012;30(6):1047-1055. [EL 4; NE]
1491. **Siebenhofer A, Jeitler K, Horvath K, Berghold A, Siering U, Semlitsch T.** Long-term effects of weight-reducing drugs in hypertensive patients. *Cochrane Database Syst Rev*. 2013;(3):CD007654. [EL 1; MRCT]
1492. **James WP, Caterson ID, Coutinho W, et al.** Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med*. 2010;363(10):905-917. [EL 1; RCT]
1493. **Zavoral JH.** Treatment with orlistat reduces cardiovascular risk in obese patients. *J Hypertens*. 1998; 16(12 Pt 2):2013-2017. [EL 1; MRCT]
1494. **Broom I, Wilding J, Stott P, Myers N. UK Multimorbidity Study Group.** Randomised trial of the effect of orlistat on body weight and cardiovascular disease risk profile in obese patients: UK Multimorbidity Study. *Int J Clin Pract*. 2002;56(7):494-499. [EL 1; RCT]
1495. **Didangelos TP, Thanopoulou AK, Bousboulas SH, et al.** The ORLIstat and CArdiovascular risk profile in patients with metabolic syndrome and type 2 DIAbetes (ORLICARDIA) Study. *Curr Med Res Opin*. 2004;20(9): 1393-1401. [EL 1; RCT]
1496. **Swinburn BA, Carey D, Hills AP, et al.** Effect of orlistat on cardiovascular disease risk in obese adults. *Diabetes Obes Metab*. 2005;7(3):254-262. [EL 1; RCT]
1497. **Rosenstock J, Hollander P, Gadde KM, et al.** A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients. *Diabetes Care*. 2007;30(6):1480-1486. [EL 1; RCT]
1498. **Tonstad S, Tykarski A, Weissgarten J, et al.** Efficacy and safety of topiramate in the treatment of obese subjects with essential hypertension. *Am J Cardiol*. 2005;96(2):243-251. [EL 1; RCT]
1499. **Sun F, Wu S, Guo S, et al.** Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Res Clin Pract*. 2015;110(1):26-37. [EL 1; MRCT]

1500. **Byrd JB, Brook RD.** A critical review of the evidence supporting aldosterone in the etiology and its blockade in the treatment of obesity-associated hypertension. *J Hum Hypertens*. 2014;28(1):3-9. [EL 4; NE]
1501. **Ofili EO, Zappe DH, Purkayastha D, Samuel R, Sowers JR.** Antihypertensive and metabolic effects of Angiotensin receptor blocker/diuretic combination therapy in obese, hypertensive African American and white patients. *Am J Ther*. 2013;20(1):2-12. [EL 1; RCT, post-hoc analysis]
1502. **Dorresteijn JA, Schrover IM, Visseren FL, et al.** Differential effects of renin-angiotensin-aldosterone system inhibition, sympathoinhibition and diuretic therapy on endothelial function and blood pressure in obesity-related hypertension: a double-blind, placebo-controlled cross-over trial. *J Hypertens*. 2013;31(2):393-403. [EL 1; RCT]
1503. **Marinik EL, Frisard MI, Hulver MW, et al.** Angiotensin II receptor blockade and insulin sensitivity in overweight and obese adults with elevated blood pressure. *Ther Adv Cardiovasc Dis*. 2013;7(1):11-20. [EL 1; RCT]
1504. **Sowers JR, Raij L, Jialal I, et al.** Angiotensin receptor blocker/diuretic combination preserves insulin responses in obese hypertensives. *J Hypertens*. 2010;28(8):1761-1769. [EL 1; RCT]
1505. **Scholze J, Grimm E, Herrmann D, Unger T, Kintscher U.** Optimal treatment of obesity-related hypertension: the Hypertension-Obesity-Sibutramine (HOS) study. *Circulation*. 2007;115(15):1991-1998. [EL 1; RCT]
1506. **Lee P, Kengne AP, Greenfield JR, Day RO, Chalmers J, Ho KK.** Metabolic sequelae of beta-blocker therapy: weighing in on the obesity epidemic? *Int J Obes*. 2011;35(11):1395-1403. [EL 3; CSS, 2 studies]
1507. **Domecq JP, Prutsky G, Leppin A, et al.** Clinical review: Drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2015;100(2):363-370. [EL 1; MRCT]
1508. **Gerdts E, de Simone G, Lund BP, et al.** Impact of overweight and obesity on cardiac benefit of antihypertensive treatment. *Nutr Metab Cardiovasc Dis*. 2013;23(2):122-129. [EL 1; RCT, post-hoc analysis]
1509. **Zhang K, Huang F, Chen J, et al.** Independent influence of overweight and obesity on the regression of left ventricular hypertrophy in hypertensive patients: a meta-analysis. *Medicine*. 2014;93(25):e130. [EL 1; MRCT]
1510. **Caterson ID, Finer N, Coutinho W, et al.** Maintained intentional weight loss reduces cardiovascular outcomes: results from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial. *Diabetes Obes Metab*. 2012;14(6):523-530. [EL 1; RCT]
1511. **Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EG.** Cardiovascular effects of bupropion in depressed patients with heart disease. *Am J Psychiatry*. 1991;148(4):512-516. [EL 2; NRCT, allocation concealment]
1512. **Thase ME, Haight BR, Johnson MC, et al.** A randomized, double-blind, placebo-controlled study of the effect of sustained-release bupropion on blood pressure in individuals with mild untreated hypertension. *J Clin Psychopharmacol*. 2008;28(3):302-307. [EL 1; RCT]
1513. **Tonstad S, Farsang C, Klaene G, et al.** Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. *Eur Heart J*. 2003;24(10):946-955. [EL 1; RCT]
1514. **Planer D, Lev I, Elitzur Y, et al.** Bupropion for smoking cessation in patients with acute coronary syndrome. *Arch Intern Med*. 2011;171(12):1055-1060. [EL 1; RCT]
1515. **Eisenberg MJ, Grandi SM, Gervais A, et al.** Bupropion for smoking cessation in patients hospitalized with acute myocardial infarction: a randomized, placebo-controlled trial. *J Am Coll Cardiol*. 2013;61(5):524-532. [EL 1; RCT]
1516. **Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ.** Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation*. 2014;129(1):28-41. [EL 1; MRCT]
1517. **Rothman RB, Baumann MH, Dersch CM, et al.** Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*. 2001;39(1):32-41. [EL 4; NE, preclinical]
1518. **Kang JG, Park CY, Kang JH, Park YW, Park SW.** Randomized controlled trial to investigate the effects of a newly developed formulation of phentermine diffuse-controlled release for obesity. *Diabetes Obes Metab*. 2010;12(10):876-882. [EL 1; RCT]
1519. **Vallé-Jones JC, Brodie NH, O'Hara H, O'Hara J, McGhie RL.** A comparative study of phentermine and diethylpropion in the treatment of obese patients in general practice. *Pharmatherapeutica*. 1983;3(5):300-304. [EL 1; RCT]
1520. **Hendricks EJ, Greenway FL, Westman EC, Gupta AK.** Blood pressure and heart rate effects, weight loss and maintenance during long-term phentermine pharmacotherapy for obesity. *Obesity (Silver Spring)*. 2011;19(12):2351-2360. [EL 3; SS]
1521. **Danielsson BR, Lansdell K, Patmore L, Tomson T.** Effects of the antiepileptic drugs lamotrigine, topiramate and gabapentin on hERG potassium currents. *Epilepsy Res*. 2005;63(1):17-25. [EL 4; NE, preclinical]
1522. **Lathers CM, Schraeder PL.** Clinical pharmacology: drugs as a benefit and/or risk in sudden unexpected death in epilepsy? *J Clin Pharmacol*. 2002;42(2):123-136. [EL 4; NE]
1523. **Astrup A, Caterson I, Zelissen P, et al.** Topiramate: long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obes Res*. 2004;12(10): 1658-1669. [EL 1; RCT]
1524. **Bray GA, Hollander P, Klein S, et al.** A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes Res*. 2003;11(6):722-733. [EL 1; RCT]
1525. **Stenlöf K, Rössner S, Vercruysse F, et al.** Topiramate in the treatment of obese subjects with drug-naive type 2 diabetes. *Diabetes Obes Metab*. 2007;9(3):360-368. [EL 1; RCT]
1526. **Toplak H, Hamann A, Moore R, et al.** Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Int J Obes*. 2007;31(1):138-146. [EL 1; RCT]
1527. **Davidson MH, Tonstad S, Oparil S, Schwiers M, Day WW, Bowden CH.** Changes in cardiovascular risk associated with phentermine and topiramate extended-release in participants with comorbidities and a body mass index ≥27 kg/m(2). *Am J Cardiol*. 2013;111(8):1131-1138. [EL 1; RCT]
1528. U.S. Food and Drug Administration. Briefing information for the February 22, 2012 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. Available at:http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm292314.htm. U.S. Food and Drug Administration; 2012. Accessed 2015. [EL 4; NE]
1529. **Jordan J, Astrup A, Engeli S, Narkiewicz K, Day WW, Finer N.** Cardiovascular effects of phentermine and topiramate: a new drug combination for the treatment of obesity. *J Hypertens*. 2014;32(6):1178-1188. [EL 4; NE]

1530. **Monami M, Cremasco F, Lamanna C, et al.** Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. *Exp Diabetes Res*. 2011;2011:215764. [EL 1; MRCT]
1531. **Wu S, Sun F, Zhang Y, et al.** The cardiovascular effects of glucagon-like peptide-1 receptor agonists: a trial sequential analysis of randomized controlled trials. *J Clin Pharm Ther.* 2014;39(1):7-13. [EL 1; MRCT]
1532. **Seshasai SR, Bennett RL, Petrie JR, et al.** Cardiovascular safety of the glucagon-like peptide-1 receptor agonist taspoglutide in people with type 2 diabetes: an individual participant data meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2015;17(5):505-510. [EL 1; MRCT]
1533. **Fisher M, Petrie MC, Ambery PD, Donaldson J, Ye J, McMurray JJ.** Cardiovascular safety of albiglutide in the Harmony programme: a meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3(9):697-703. [EL 1; MRCT]
1534. **Sun F, Wu S, Wang J, et al.** Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis. *Clin Ther.* 2015;37(1):225-241.e8. [EL 1; MRCT]
1535. **Marso SP, Lindsey JB, Stolker JM, et al.** Cardiovascular safety of liraglutide assessed in a patient-level pooled analysis of phase 2: 3 liraglutide clinical development studies. *Diab Vasc Dis Res*. 2011;8(3):237-240. [EL 1; MRCT]
1536. **Smilowitz NR, Donnino R, Schwartzbard A.** Glucagon-like peptide-1 receptor agonists for diabetes mellitus: a role in cardiovascular disease. *Circulation*. 2014;129(22): 2305-2312. [EL 4; NE]
1537. **Margulies KB, Anstrom KJ, Hernandez AF, et al.** GLP-1 agonist therapy for advanced heart failure with reduced ejection fraction: design and rationale for the functional impact of GLP-1 for heart failure treatment study. *Circ Heart Fail*. 2014;7(4):673-679. [EL 4; NE]
1538. **Marso SP, Poulter NR, Nissen SE, et al.** Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. *Am Heart J*. 2013;166(5):823-830.e5. [EL 1; RCT]
1539. **Boyer EW, Shannon M.** The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112-1120. [EL 4; NE]
1540. **Nichols DE.** Hallucinogens. *Pharmacol Ther.* 2004;101(2): 131-181. [EL 4; NE]
1541. **Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM.** Suicide-related events in patients treated with antiepileptic drugs. *N Engl J Med*. 2010;363(6):542-551. [EL 2; MNRCT, meta-analysis of observational data, N = 5,130,795]
1542. **Kessler RC, Wang PS.** The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annu Rev Public Health*. 2008;29:115-129. [EL 4; NE]
1543. **Gariepy G, Nitka D, Schmitz N.** The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. *Int J Obes*. 2010; 34(3):407-419. [EL 2; MNRCT]
1544. **Bjerkeset O, Romundstad P, Evans J, Gunnell D.** Association of adult body mass index and height with anxiety, depression, and suicide in the general population: the HUNT study. *Am J Epidemiol*. 2008;167(2):193-202. [EL 2; PCS, N = 74,332]
1545. **Kasen S, Cohen P, Chen H, Must A.** Obesity and psychopathology in women: a three decade prospective study. *Int J Obes*. 2008;32(3):558-566. [EL 2; PCS]
1546. **Bradshaw T, Mairs H.** Obesity and serious mental ill health: a critical review of the literature. *Healthcare*. 2014; 2(2):166-182. [EL 4; NE]
1547. **Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M.** Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. *Schizophr Bull*. 2013;39(2):306-318. [EL 2; MNRCT]
1548. **Allison DB, Newcomer JW, Dunn AL, et al.** Obesity among those with mental disorders: a National Institute of Mental Health meeting report. *Am J Prev Med*. 2009; 36(4):341-350. [EL 4; NE]
1549. **Allison DB, Fontaine KR, Heo M, et al.** The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry*. 1999;60(4):215-220. [EL 3; SS]
1550. **Correll CU, Druss BG, Lombardo I, et al.** Findings of a U.S. national cardiometabolic screening program among 10,084 psychiatric outpatients. *Psychiatr Serv*. 2010; 61(9):892-898. [EL 3; SS]
1551. **Galletly CA, Foley DL, Waterreus A, et al.** Cardiometabolic risk factors in people with psychotic disorders: the second Australian national survey of psychosis. *Aust N Z J Psychiatry*. 2012;46(8):753-761. [EL 3; CSS]
1552. **Limosin F, Gasquet I, Leguay D, Azorin JM, Rouillon F.** Body mass index and prevalence of obesity in a French cohort of patients with schizophrenia. *Acta Psychiatr Scand*. 2008;118(1):19-25. [EL 3; SS]
1553. **Holt RI, Peveler RC.** Obesity, serious mental illness and antipsychotic drugs. *Diabetes Obes Metab*. 2009;11(7): 665-679. [EL 4; NE]
1554. **Alvarez-Jiménez M, González-Blanch C, Crespo-Facorro B, et al.** Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. *CNS Drugs*. 2008;22(7):547-562. [EL 1; MRCT]
1555. **McCloughen A, Foster K.** Weight gain associated with taking psychotropic medication: an integrative review. *Int J Ment Health Nurs*. 2011;20(3):202-222. [EL 2; MNRCT]
1556. **Sicras-Mainar A, Navarro-Artieda R, Rejas-Gutiérrez J, Blanca-Tamayo M.** Relationship between obesity and antipsychotic drug use in the adult population: a longitudinal, retrospective claim database study in primary care settings. *Neuropsychiatr Dis Treat*. 2008;4(1):219-226. [EL 3; SS, N = 42,437]
1557. **American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity.** Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596-601. [EL 4; NE]
1558. **Mukundan A, Faulkner G, Cohn T, Remington G.** Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. *Cochrane Database Syst Rev*. 2010;(12): CD006629. [EL 1; MRCT]
1559. **Daumit GL, Dickerson FB, Wang NY, et al.** A behavioral weight-loss intervention in persons with serious mental illness. *N Engl J Med*. 2013;368(17):1594-1602. [EL 1; RCT]
1560. **Alvarez-Jiménez M, González-Blanch C, Vázquez-Barquero JL, et al.** Attenuation of antipsychotic-induced weight gain with early behavioral intervention in drug-naive first-episode psychosis patients: a randomized controlled trial. *J Clin Psychiatry*. 2006;67(8):1253-1260. [EL 1; RCT]
1561. **Brown S, Chan K.** A randomized controlled trial of a brief health promotion intervention in a population with serious mental illness. *J Ment Health*. 2006;15:543-549. [EL 1; RCT]
1562. **Forsberg KA, Björkman T, Sandman PO, Sandlund M.** Physical health--a cluster randomized controlled lifestyle intervention among persons with a psychiatric disability

and their staff. *Nord J Psychiatry*. 2008;62(6):486-495. [EL 1; RCT]

1563. **Brar JS, Ganguli R, Pandina G, Turkoz I, Berry S, Mahmoud R.** Effects of behavioral therapy on weight loss in overweight and obese patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry*. 2005;66(2): 205-212. [EL 1; RCT]
1564. **Wu RR, Zhao JP, Jin H, et al.** Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA*. 2008; 299(2): 185-193. [EL 1; RCT]
1565. **Jean-Baptiste M, Tek C, Liskov E, et al.** A pilot study of a weight management program with food provision in schizophrenia. *Schizophr Res*. 2007;96(1-3):198-205. [EL 1; RCT, pilot study, N = 18]
1566. **Poulin MJ, Chaput JP, Simard V, et al.** Management of antipsychotic-induced weight gain: prospective naturalistic study of the effectiveness of a supervised exercise programme. *Aust N Z J Psychiatry*. 2007;41(12): 980-989. [EL 2; PCS]
1567. **Evans S, Newton R, Higgins S.** Nutritional intervention to prevent weight gain in patients commenced on olanzapine: a randomized controlled trial. *Aust N Z J Psychiatry*. 2005;39(6):479-486. [EL 1; RCT]
1568. **Skrinar GS, Huxley NA, Hutchinson DS, Menninger E, Glew P.** The role of a fitness intervention on people with serious psychiatric disabilities. *Psychiatr Rehabil J*. 2005;29(2):122-127. [EL 1; RCT]
1569. **Scheewe TW, Backx FJ, Takken T, et al.** Exercise therapy improves mental and physical health in schizophrenia: a randomised controlled trial. *Acta Psychiatr Scand*. 2013; 127(6):464-473. [EL 1; RCT]
1570. **Bruins J, Jörg F, Bruggeman R, Slooff C, Corpeleijn E, Pijnenborg M.** The effects of lifestyle interventions on (long-term) weight management, cardiometabolic risk and depressive symptoms in people with psychotic disorders: a meta-analysis. *PLoS One*. 2014;9(12):e112276. [EL 1; MRCT]
1571. **Mizuno Y, Suzuki T, Nakagawa A, et al.** Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull*. 2014;40(6):1385-1403. [EL 1; MRCT]
1572. **Baptista T, Martinez J, Lacruz A, et al.** Metformin for prevention of weight gain and insulin resistance with olanzapine: a double-blind placebo-controlled trial. *Can J Psychiatry*. 2006;51(3):192-196. [EL 1; RCT]
1573. **Baptista T, Rangel N, Fernández V, et al.** Metformin as an adjunctive treatment to control body weight and metabolic dysfunction during olanzapine administration: a multicentric, double-blind, placebo-controlled trial. *Schizophr Res*. 2007;93(1-3):99-108. [EL 1; RCT]
1574. **Wu RR, Zhao JP, Guo XF, et al.** Metformin addition attenuates olanzapine-induced weight gain in drug-naive first-episode schizophrenia patients: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2008;165(3): 352-358. [EL 1; RCT]
1575. **Jarskog LF, Hamer RM, Catellier DJ, et al.** Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder. *Am J Psychiatry*. 2013;170(9):1032-1040. [EL 1; RCT]
1576. **Arman S, Sadramely MR, Nadi M, Koleini N.** A randomized, double-blind, placebo-controlled trial of metformin treatment for weight gain associated with initiation of risperidone in children and adolescents. *Saudi Med J*. 2008;29(8):1130-1134. [EL 1; RCT]
1577. **Carrizo E, Fernández V, Connell L, et al.** Extended release metformin for metabolic control assistance during prolonged clozapine administration: a 14 week, double-blind, parallel group, placebo-controlled study. *Schizophr Res*. 2009;113(1):19-26. [EL 1; RCT]
1578. **Wang M, Tong JH, Zhu G, Liang GM, Yan HF, Wang XZ.** Metformin for treatment of antipsychotic-induced weight gain: a randomized, placebo-controlled study. *Schizophr Res*. 2012;138(1):54-57. [EL 1; RCT]
1579. **Wu RR, Jin H, Gao K, et al.** Metformin for treatment of antipsychotic-induced amenorrhea and weight gain in women with first-episode schizophrenia: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry*. 2012;169(8):813-821. [EL 1; RCT]
1580. **Chen CH, Huang MC, Kao CF, et al.** Effects of adjunctive metformin on metabolic traits in nondiabetic clozapine-treated patients with schizophrenia and the effect of metformin discontinuation on body weight: a 24-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2013;74(5):e424-30. [EL 1; RCT]
1581. **Narula PK, Rehan HS, Unni KE, Gupta N.** Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. *Schizophr Res*. 2010;118(1-3): 218-223. [EL 1; RCT]
1582. **Ko YH, Joe SH, Jung IK, Kim SH.** Topiramate as an adjuvant treatment with atypical antipsychotics in schizophrenic patients experiencing weight gain. *Clin Neuropharmacol*. 2005;28(4):169-175. [EL 1; RCT]
1583. **Afshar H, Roohafza H, Mousavi G, et al.** Topiramate add-on treatment in schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. *J Psychopharmacol*. 2009;23(2):157-162. [EL 1; RCT]
1584. **Kim JH, Yim SJ, Nam JH.** A 12-week, randomized, open-label, parallel-group trial of topiramate in limiting weight gain during olanzapine treatment in patients with schizophrenia. *Schizophr Res*. 2006;82(1):115-117. [EL 1; RCT]
1585. **Tek C, Ratliff J, Reutenauer E, Ganguli R, O'Malley SS.** A randomized, double-blind, placebo-controlled pilot study of naltrexone to counteract antipsychotic-associated weight gain: proof of concept. *J Clin Psychopharmacol*. 2014;34(5):608-612. [EL 1; RCT]
1586. **Tek C, Guloksuz S, Srihari VH, Reutenauer EL.** Investigating the safety and efficacy of naltrexone for antipsychotic induced weight gain in severe mental illness: study protocol of a double-blind, randomized, placebo-controlled trial. *BMC Psychiatry*. 2013;13:176. [EL 1; RCT]
1587. **Joffe G, Takala P, Tchoukhine E, et al.** Orlistat in clozapine- or olanzapine-treated patients with overweight or obesity: a 16-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2008;69(5):706-711. [EL 1; RCT]
1588. **Chukhin E, Takala P, Hakko H, et al.** In a randomized placebo-controlled add-on study orlistat significantly reduced clozapine-induced constipation. *Int Clin Psychopharmacol*. 2013;28(2):67-70. [EL 1; RCT]
1589. **Nguyen C, Suzuki A, Bera K.** Use of lorcaserin, a 5-HT2c agonist, in the management of olanzapine-induced weight gain. *J Metabolic Synd*. 2015;4(4). [EL 3; SCR]
1590. **Stunkard AJ, Allison KC.** Two forms of disordered eating in obesity: binge eating and night eating. *Int J Obes Relat Metab Disord*. 2003;27(1):1-12. [EL 4; NE]
1591. **McElroy SL, Guerdjikova AI, Mori N, O'Melia AM.** Current pharmacotherapy options for bulimia nervosa and binge eating disorder. *Expert Opin Pharmacother*. 2012;13(14):2015-2026. [EL 4; NE]
1592. **Hudson JI, Hiripi E, Pope HG, Kessler RC.** The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry*. 2007; 61(3):348-358. [EL 3; SS]

1593. **Schag K, Schönleber J, Teufel M, Zipfel S, Giel KE.** Food-related impulsivity in obesity and binge eating disorder--a systematic review. *Obes Rev*. 2013;14(6):477-495. [EL 4; NE]
1594. **Grilo CM, Masheb RM, Wilson GT, Gueorguieva R, White MA.** Cognitive-behavioral therapy, behavioral weight loss, and sequential treatment for obese patients with binge-eating disorder: a randomized controlled trial. *J Consult Clin Psychol*. 2011;79(5):675-685. [EL 1; RCT]
1595. **Brownley KA, Berkman ND, Sedway JA, Lohr KN, Bulik CM.** Binge eating disorder treatment: a systematic review of randomized controlled trials. *Int J Eat Disord*. 2007;40(4):337-348. [EL 1; MRCT]
1596. **Reas DL, Grilo CM.** Current and emerging drug treatments for binge eating disorder. *Expert Opin Emerg Drugs*. 2014;19(1):99-142. [EL 4; NE]
1597. **Wilson GT, Wilfley DE, Agras WS, Bryson SW.** Psychological treatments of binge eating disorder. *Arch Gen Psychiatry*. 2010;67(1):94-101. [EL 1; RCT]
1598. **Gorin AA, Niemeier HM, Hogan P, et al.** Binge eating and weight loss outcomes in overweight and obese individuals with type 2 diabetes: results from the Look AHEAD trial. *Arch Gen Psychiatry*. 2008;65(12):1447-1455. [EL 1; RCT]
1599. **Sherwood NE, Jeffery RW, Wing RR.** Binge status as a predictor of weight loss treatment outcome. *Int J Obes Relat Metab Disord*. 1999;23(5):485-493. [EL 3; CSS]
1600. **Gladis MM, Wadden TA, Vogt R, Foster G, Kuehnel RH, Bartlett SJ.** Behavioral treatment of obese binge eaters: do they need different care? *J Psychosom Res*. 1998;44(3-4):375-384. [EL 1; RCT]
1601. **Bishop-Gilyard CT, Berkowitz RI, Wadden TA, Gehrman CA, Cronquist JL, Moore RH.** Weight reduction in obese adolescents with and without binge eating. *Obesity (Silver Spring)*. 2011;19(5):982-987. [EL 1; RCT]
1602. **Golay A, Laurent-Jaccard A, Habicht F, et al.** Effect of orlistat in obese patients with binge eating disorder. *Obes Res*. 2005;13(10):1701-1708. [EL 1; RCT]
1603. **Grilo CM, Masheb RM, Salant SL.** Cognitive behavioral therapy guided self-help and orlistat for the treatment of binge eating disorder: a randomized, double-blind, placebo-controlled trial. *Biol Psychiatry*. 2005; 57(10):1193-1201. [EL 1; RCT]
1604. **Grilo CM, White MA.** Orlistat with behavioral weight loss for obesity with versus without binge eating disorder: randomized placebo-controlled trial at a community mental health center serving educationally and economically disadvantaged Latino/as. *Behav Res Ther*. 2013;51(3):167-175. [EL 1; RCT]
1605. **Robert SA, Rohana AG, Shah SA, Chinna K, Wan Mohamud WN, Kamaruddin NA.** Improvement in binge eating in non-diabetic obese individuals after 3 months of treatment with liraglutide - a pilot study. *Obes Res Clin Pract*. 2015;9(3):301-304. [EL 1; RCT]
1606. **Billes SK, Sinnayah P, Cowley MA.** Naltrexone/bupropion for obesity: an investigational combination pharmacotherapy for weight loss. *Pharmacol Res*. 2014; 84:1-11. [EL 4; NE]
1607. **Mason AE, Laraia B, Daubenmier J, et al.** Putting the brakes on the "drive to eat": pilot effects of naltrexone and reward-based eating on food cravings among obese women. *Eat Behav*. 2015;19:53-56. [EL 1; RCT]
1608. **Murray E, Brouwer S, McCutcheon R, Harmer CJ, Cowen PJ, McCabe C.** Opposing neural effects of naltrexone on food reward and aversion: implications for the treatment of obesity. *Psychopharmacology*. 2014;231(22):4323-4335. [EL 1; RCT, N = 20]
1609. **White MA, Grilo CM.** Bupropion for overweight women with binge-eating disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2013;74(4):400-406. [EL 1; RCT]
1610. **Claudino AM, de Oliveira IR, Appolinario JC, et al.** Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. *J Clin Psychiatry*. 2007;68(9):1324-1332. [EL 1; RCT]
1611. **McElroy SL, Arnold LM, Shapira NA, et al.** Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. *Am J Psychiatry*. 2003;160(2):255-261. [EL 1; RCT]
1612. **McElroy SL, Hudson JI, Capece JA, et al.** Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. *Biol Psychiatry*. 2007; 61(9):1039-1048. [EL 1; RCT]
1613. **McElroy SL, Kotwal R, Guerdjikova AI, et al.** Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial. *J Clin Psychiatry*. 2006;67(12):1897-1906. [EL 1; RCT]
1614. **Gluck ME, Geliebter A, Satov T.** Night eating syndrome is associated with depression, low self-esteem, reduced daytime hunger, and less weight loss in obese outpatients. *Obes Res*. 2001;9(4):264-267. [EL 2; PCS]
1615. **Stunkard AJ, Grace WJ, Wolff HG.** The night-eating syndrome; a pattern of food intake among certain obese patients. *Am J Med*. 1955;19(1):78-86. [EL 3; CCS]
1616. **Dalle Grave R, Calugi S, Ruocco A, Marchesini G.** Night eating syndrome and weight loss outcome in obese patients. *Int J Eat Disord*. 2011;44(2):150-156. [EL 2; PCS, case-controlled]
1617. **O'Reardon JP, Allison KC, Martino NS, Lundgren JD, Heo M, Stunkard AJ.** A randomized, placebo-controlled trial of sertraline in the treatment of night eating syndrome. *Am J Psychiatry*. 2006;163(5):893-898. [EL 1; RCT]
1618. **Vander Wal JS, Gang CH, Griffing GT, Gadde KM.** Escitalopram for treatment of night eating syndrome: a 12-week, randomized, placebo-controlled trial. *J Clin Psychopharmacol*. 2012;32(3):341-345. [EL 1; RCT]
1619. **McElroy SL, Hudson JI, Mitchell JE, et al.** Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry*. 2015;72(3):235-246. [EL 1; RCT]
1620. **McElroy SL, Guerdjikova A, Kotwal R, et al.** Atomoxetine in the treatment of binge-eating disorder: a randomized placebo-controlled trial. *J Clin Psychiatry*. 2007;68(3):390-398. [EL 1; RCT]
1621. **Arnold LM, McElroy SL, Hudson JI, Welge JA, Bennett AJ, Keck PE.** A placebo-controlled, randomized trial of fluoxetine in the treatment of binge-eating disorder. *J Clin Psychiatry*. 2002;63(11):1028-1033. [EL 1; RCT]
1622. **Devlin MJ, Goldfein JA, Petkova E, et al.** Cognitive behavioral therapy and fluoxetine as adjuncts to group behavioral therapy for binge eating disorder. *Obes Res*. 2005;13(6):1077-1088. [EL 1; RCT]
1623. **Grilo CM, Masheb RM, Wilson GT.** Efficacy of cognitive behavioral therapy and fluoxetine for the treatment of binge eating disorder: a randomized double-blind placebo-controlled comparison. *Biol Psychiatry*. 2005;57(3):301-309. [EL 1; RCT]
1624. **Grilo CM, Crosby RD, Wilson GT, Masheb RM.** 12-month follow-up of fluoxetine and cognitive behavioral therapy for binge eating disorder. *J Consult Clin Psychol*. 2012;80(6):1108-1113. [EL 1; RCT, post-intervention followup]
1625. **Ricca V, Mannucci E, Mezzani B, et al.** Fluoxetine and fluvoxamine combined with individual cognitive-behaviour therapy in binge eating disorder: a one-year follow-up

study. *Psychother Psychosom*. 2001;70(6):298-306. [EL 1; RCT]

1626. **McElroy SL, Casuto LS, Nelson EB, et al.** Placebo-controlled trial of sertraline in the treatment of binge eating disorder. *Am J Psychiatry*. 2000;157(6):1004-1006. [EL 1; RCT]
1627. **McElroy SL, Hudson JI, Malhotra S, Welge JA, Nelson EB, Keck PE.** Citalopram in the treatment of binge-eating disorder: a placebo-controlled trial. *J Clin Psychiatry*. 2003;64(7):807-813. [EL 1; RCT]
1628. **Guerdjikova AI, McElroy SL, Kotwal R, et al.** High-dose escitalopram in the treatment of binge-eating disorder with obesity: a placebo-controlled monotherapy trial. *Hum Psychopharmacol*. 2008;23(1):1-11. [EL 1; RCT]
1629. **Guerdjikova AI, McElroy SL, Winstanley EL, et al.** Duloxetine in the treatment of binge eating disorder with depressive disorders: a placebo-controlled trial. *Int J Eat Disord*. 2012;45(2):281-289. [EL 1; RCT]
1630. **Laederach-Hofmann K, Graf C, Horber F, et al.** Imipramine and diet counseling with psychological support in the treatment of obese binge eaters: a randomized, placebo-controlled double-blind study. *Int J Eat Disord*. 1999;26(3):231-244. [EL 1; RCT]
1631. **Denis P, Charpentier D, Berros P, Touameur S.** Bilateral acute angle-closure glaucoma after dexfenfluramine treatment. *Ophthalmologica*. 1995;209(4):223-224. [EL 3; SCR]
1632. **Fraunfelder FW, Fraunfelder FT, Keates EU.** Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology*. 2004;111(1):109-111. [EL 3; SS]
1633. **Grewal DS, Goldstein DA, Khatana AK, Tanna AP.** Bilateral angle closure following use of a weight loss combination agent containing topiramate. *J Glaucoma*. 2015;24(5):e132-6. [EL 3; SCR]
1634. **Etminan M, Maberley D, Mikelberg FS.** Use of topiramate and risk of glaucoma: a case-control study. *Am J Ophthalmol*. 2012;153(5):827-830. [EL 2; RCCS]
1635. **Ho JD, Keller JJ, Tsai CY, Liou SW, Chang CJ, Lin HC.** Topiramate use and the risk of glaucoma development: a population-based follow-up study. *Am J Ophthalmol*. 2013;155(2):336-341.e1. [EL 3; SS]
1636. **Abtahi MA, Abtahi SH, Fazel F, et al.** Topiramate and the vision: a systematic review. *Clin Ophthalmol*. 2012;6:117-131. [EL 2; MNRCT]
1637. ADIPEX-P (phentermine hydrochloride USP) CIV for oral use [package insert]. Sellersville, PA: Teva Pharmaceuticals; 2012. [EL 4; NE]
1638. **Koo SH, Choi WS, Lee JW, Park YJ, Lee KW.** A case of phentermine hydrochloride induced acute myopia and acute angle closure. *J Korean Ophthalmol Soc*. 2011; 52(7):881-886. [EL 3; SCR]
1639. **Symes RJ, Etminan M, Mikelberg FS.** Risk of angle-closure glaucoma with bupropion and topiramate. *JAMA Ophthalmol*. 2015;133(10):1187-1189. [EL 2; RCCS]
1640. **Ghibellini G, Park J, Brittain CF, et al.** Bupropion has no effect on intraocular pressure or other ophthalmologic parameters after single or repeat doses in healthy volunteers. *J Clin Pharmacol*. 2009;49(4):489-495. [EL 1; RCT]
1641. **Stein JD, Talwar N, Kang JH, Okereke OI, Wiggs JL, Pasquale LR.** Bupropion use and risk of open-angle glaucoma among enrollees in a large U.S. managed care network. *PLoS One*. 2015;10(4):e0123682. [EL 3; SS]
1642. **Carroll FI, Blough BE, Mascarella SW, Navarro HA, Lukas RJ, Damaj MI.** Bupropion and bupropion analogs as treatments for CNS disorders. *Adv Pharmacol*. 2014;69:177-216. [EL 4; NE]
1643. **Jefferson JW, Pradko JF, Muir KT.** Bupropion for major depressive disorder: pharmacokinetic and formulation considerations. *Clin Ther*. 2005;27(11):1685-1695. [EL 4; NE]
1644. **Peck AW, Stern WC, Watkinson C.** Incidence of seizures during treatment with tricyclic antidepressant drugs and bupropion. *J Clin Psychiatry*. 1983;44(5 Pt 2): 197-201. [EL 4; NE]
1645. **Johnston JA, Lineberry CG, Ascher JA, et al.** A 102-center prospective study of seizure in association with bupropion. *J Clin Psychiatry*. 1991;52(11):450-456. [EL 2; PCS]
1646. **Dunner DL, Zisook S, Billow AA, Batey SR, Johnston JA, Ascher JA.** A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. *J Clin Psychiatry*. 1998;59(7):366-373. [EL 2; PCS]
1647. **Cahill K, Stevens S, Perera R, Lancaster T.** Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013;(5):CD009329. [EL 1; MRCT]
1648. **Christou GA, Kiortsis DN.** The efficacy and safety of the naltrexone/bupropion combination for the treatment of obesity: an update. *Hormones*. 2015;14(3):370-375. [EL 4; NE]
1649. **Sadr-Azodi O, Orsini N, Andrén-Sandberg Å, Wolk A.** Abdominal and total adiposity and the risk of acute pancreatitis: a population-based prospective cohort study. *Am J Gastroenterol*. 2013;108(1):133-139. [EL 2; PCS]
1650. **Banim PJ, Luben RN, Bulluck H, et al.** The aetiology of symptomatic gallstones quantification of the effects of obesity, alcohol and serum lipids on risk. Epidemiological and biomarker data from a UK prospective cohort study (EPIC-Norfolk). *Eur J Gastroenterol Hepatol*. 2011; 23(8):733-740. [EL 2; PCS]
1651. **Bonfrate L, Wang DQ, Garruti G, Portincasa P.** Obesity and the risk and prognosis of gallstone disease and pancreatitis. *Best Pract Res Clin Gastroenterol*. 2014; 28(4):623-635. [EL 4; NE]
1652. **Mery CM, Rubio V, Duarte-Rojo A, et al.** Android fat distribution as predictor of severity in acute pancreatitis. *Pancreatology*. 2002;2(6):543-549. [EL 3; CSS]
1653. **Hong S, Qiwen B, Ying J, Wei A, Chaoyang T.** Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis. *Eur J Gastroenterol Hepatol*. 2011; 23(12):1136-1143. [EL 2; MNRCT]
1654. **Sempere L, Martinez J, de Madaria E, et al.** Obesity and fat distribution imply a greater systemic inflammatory response and a worse prognosis in acute pancreatitis. *Pancreatology*. 2008;8(3):257-264. [EL 2; PCS]
1655. **Papachristou GI, Papachristou DJ, Avula H, Slivka A, Whitcomb DC.** Obesity increases the severity of acute pancreatitis: performance of APACHE-O score and correlation with the inflammatory response. *Pancreatology*. 2006;6(4):279-285. [EL 2; PCS]
1656. **Gukovsky I, Li N, Todoric J, Gukovskaya A, Karin M.** Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144(6):1199-209.e4. [EL 4; NE]
1657. **Blomgren KB, Sundström A, Steineck G, Wiholm BE.** Obesity and treatment of diabetes with glyburide may both be risk factors for acute pancreatitis. *Diabetes Care*. 2002;25(2):298-302. [EL 2; RCCS]
1658. **Napier S, Thomas M.** 36 year old man presenting with pancreatitis and a history of recent commencement of Orlistat case report. *Nutr J*. 2006;5:19. [EL 3; SCR]
1659. **Ahmad FA, Mahmud S.** Acute pancreatitis following orlistat therapy: report of two cases. *JOP*. 2010;11(1):61-63. [EL 3; SCR]

1660. **Faillie JL, Babai S, Crépin S, et al.** Pancreatitis associated with the use of GLP-1 analogs and DPP-4 inhibitors: a case/non-case study from the French Pharmacovigilance Database. *Acta Diabetol*. 2014;51(3):491-497. [EL 3; SS]
1661. **Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB.** Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med*. 2013;173(7):534-539. [EL 2; RCCS]
1662. **Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC.** Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes*. 2013;62(7):2595-2604. [EL 2; RCCS]
1663. **Labuzek K, Kozłowski M, Szkudłapski D, Sikorska P, Kozłłowska M, Okopien B.** Incretin-based therapies in the treatment of type 2 diabetes--more than meets the eye? *Eur J Intern Med*. 2013;24(3):207-212. [EL 4; NE]
1664. **Ryder REJ, Thong KY. ABCD nationwide exenatide audit contributors.** Incidence of acute pancreatitis in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit. Available at: http://www.diabetologists-abcd.org.uk/GLP1_Audits/pancreatitis_incidence_exenatide_audit.pdf. Association of British Clinical Diabetologists; 2013. Accessed January 20, 2016. [EL 3; SS]
1665. **Ryder RE.** The potential risks of pancreatitis and pancreatic cancer with GLP-1-based therapies are far outweighed by the proven and potential (cardiovascular) benefits. *Diabet Med*. 2013;30(10):1148-1155. [EL 1; MRCT, this represents the highest level substudy in report]
1666. **Ryder REJ, Thong KY, Blann AD, et al.** ABCD nationwide liraglutide audit contributors. Liraglutide pancreatitis: the ABCD nationwide liraglutide audit. *Br J Diabetes Vasc Dis*. 2013;13(5-6):253-259. [EL 3; SS]
1667. **Ryder RE, Sen Gupta P, Thong KY, ABCD nationwide exenatide and liraglutide audit contributors.** The Association of British Clinical Diabetologists nationwide exenatide and liraglutide audits suggest a low incidence of acute pancreatitis. Response to Robson. Incretins and pancreatitis--what happens next? A personal viewpoint. *Diabet Med*. 2013;30(12):1510-1511. [EL 4; NE]
1668. **Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E.** Glucagon-like peptide-1 receptor agonists and pancreatitis: a meta-analysis of randomized clinical trials. *Diabetes Res Clin Pract*. 2014;103(2):269-275. [EL 1; MRCT]
1669. **Shyangdan DS, Royle PL, Clar C, Sharma P, Waugh NR.** Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis. *BMC Endocr Disord*. 2010;10:20. [EL 1; MRCT]
1670. **Monami M, Dicembrini I, Mannucci E.** Dipeptidyl peptidase-4 inhibitors and pancreatitis risk: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2014;16(1):48-56. [EL 1; MRCT]
1671. **de Leon J, Santoro V, D'Arrigo C, Spina E.** Interactions between antiepileptics and second-generation antipsychotics. *Expert Opin Drug Metab Toxicol*. 2012; 8(3):311-334. [EL 4; NE]
1672. **Suazo-Baráhona J, Carmona-Sánchez R, Robles-Díaz G, et al.** Obesity: a risk factor for severe acute biliary and alcoholic pancreatitis. *Am J Gastroenterol*. 1998;93(8): 1324-1328. [EL 3; SS]
1673. **Frossard JL, Lescuyer P, Pastor CM.** Experimental evidence of obesity as a risk factor for severe acute pancreatitis. *World J Gastroenterol*. 2009;15(42):5260-5265. [EL 4; NE]
1674. **Wu D, Xu Y, Zeng Y, Wang X.** Endocrine pancreatic function changes after acute pancreatitis. *Pancreas*. 2011;40(7):1006-1011. [EL 3; CSS]
1675. **Johnson CD, Toh SK, Campbell MJ.** Combination of APACHE-II score and an obesity score (APACHE-O) for the prediction of severe acute pancreatitis. *Pancreatology*. 2004;4(1):1-6. [EL 2; PCS]
1676. **Martínez J, Johnson CD, Sánchez-Payá J, de Madaria E, Robles-Díaz G, Pérez-Mateo M.** Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. *Pancreatology*. 2006;6(3):206-209. [EL 2; MNRCT]
1677. **Katuchova J, Bober J, Harbulak P, et al.** Obesity as a risk factor for severe acute pancreatitis patients. *Wien Klin Wochenschr*. 2014;126(7-8):223-227. [EL 2; PCS, post-hoc analysis]
1678. **Sawalhi S, Al-Maramhy H, Abdelrahman AI, Allah SE, Al-Jubori S.** Does the presence of obesity and/or metabolic syndrome affect the course of acute pancreatitis? A prospective study. *Pancreas*. 2014;43(4):565-570. [EL 2; PCS]
1679. **Cone RD.** Anatomy and regulation of the central melanocortin system. *Nat Neurosci*. 2005;8(5):571-578. [EL 4; NE]
1680. **Cowley MA, Smart JL, Rubinstein M, et al.** Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature*. 2001; 411(6836): 480-484. [EL 4; NE]
1681. **Ibrahim N, Bosch MA, Smart JL, et al.** Hypothalamic proopiomelanocortin neurons are glucose responsive and express K(ATP) channels. *Endocrinology*. 2003;144(4): 1331-1340. [EL 4; NE, preclinical]
1682. **Kelly MJ, Loose MD, Ronnekleiv OK.** Opioids hyperpolarize beta-endorphin neurons via mu-receptor activation of a potassium conductance. *Neuroendocrinology*. 1990;52(3):268-275. [EL 4; NE, preclinical]
1683. **Verebey K.** The clinical pharmacology of naltrexone: pharmacology and pharmacodynamics. *NIDA Res Monogr*. 1981;28:147-158. [EL 4; NE]
1684. **Yoburn BC, Luke MC, Pasternak GW, Inturrisi CE.** Upregulation of opioid receptor subtypes correlates with potency changes of morphine and DADLE. *Life Sci*. 1988;43(16):1319-1324. [EL 4; NE, preclinical]
1685. **Rösner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M.** Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev*. 2010; (12):CD001867. [EL 1; MRCT]
1686. **Van Gaal LF, Broom JI, Enzi G, Toplak H.** Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. Orlistat Dose-Ranging Study Group. *Eur J Clin Pharmacol*. 1998;54(2):125-132. [EL 1; RCT]
1687. **Astrup A, Rössner S, Van Gaal L, et al.** Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 2009; 374(9701):1606-1616. [EL 1; RCT]
1688. **Källén BA.** Antiobesity drugs in early pregnancy and congenital malformations in the offspring. *Obes Res Clin Pract*. 2014;8(6):e571-6. [EL 3; SS]
1689. **Alsaad AM, Chaudhry SA, Koren G.** First trimester exposure to topiramate and the risk of oral clefts in the offspring: a systematic review and meta-analysis. *Reprod Toxicol*. 2015;53:45-50. [EL 2; MNRCT]
1690. **Green MW, Seeger JD, Peterson C, Bhattacharyya A.** Utilization of topiramate during pregnancy and risk of birth defects. *Headache*. 2012;52(7):1070-1084. [EL 3; SS]
1691. **Hunt S, Russell A, Smithson WH, et al.** Topiramate in pregnancy: preliminary experience from the UK Epilepsy

and Pregnancy Register. *Neurology*. 2008;71(4):272-276. [EL 3; SS]

1692. **Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM.** Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf*. 2007;16(5):474-484. [EL 3; SS]
1693. **Alwan S, Reefhuis J, Botto LD, et al.** Maternal use of bupropion and risk for congenital heart defects. *Am J Obstet Gynecol*. 2010;203(1):52.e1-52.e6. [EL 2; RCCS]
1694. **Chun-Fai-Chan B, Koren G, Fayez I, et al.** Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol*. 2005;192(3):932-936. [EL 2; PCS]
1695. **Einarson TR, Einarson A.** Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. *Pharmaco-epidemiol Drug Saf*. 2005;14(12):823-827. [EL 2; MNRCT]
1696. **Greco D.** Normal pregnancy outcome after first-trimester exposure to liraglutide in a woman with Type 2 diabetes. *Diabet Med*. 2015;32(10):e29-30. [EL 3; SCR]
1697. **Kumar P, Arora S.** Orlistat in polycystic ovarian syndrome reduces weight with improvement in lipid profile and pregnancy rates. *J Hum Reprod Sci*. 2014;7(4):255-261. [EL 1; RCT]
1698. **Jensterle M, Kravos NA, Pfeifer M, Kocjan T, Janez A.** A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome. *Hormones*. 2015;14(1):81-90. [EL 1; RCT]
1699. **Jensterle M, Kocjan T, Kravos NA, Pfeifer M, Janez A.** Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome. *Endocr Res*. 2015;40(3):133-138. [EL 2; PCS]
1700. **Dorner TE, Rieder A.** Obesity paradox in elderly patients with cardiovascular diseases. *Int J Cardiol*. 2012;155(1):56-65. [EL 4; NE]
1701. **McTigue KM, Hess R, Ziouras J.** Obesity in older adults: a systematic review of the evidence for diagnosis and treatment. *Obesity (Silver Spring)*. 2006;14(9):1485-1497. [EL 2; MNRCT]
1702. **Zamboni M, Mazzali G, Zoico E, et al.** Health consequences of obesity in the elderly: a review of four unresolved questions. *Int J Obes*. 2005;29(9):1011-1029. [EL 4; NE]
1703. **Villareal DT, Apovian CM, Kushner RF, Klein S, American Society for Nutrition, NAASO TOS.** Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. *Am J Clin Nutr*. 2005;82(5):923-934. [EL 4; NE]
1704. **Baumgartner RN, Koehler KM, Gallagher D, et al.** Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol*. 1998;147(8):755-763. [EL 3; SS]
1705. **Baumgartner RN.** Body composition in healthy aging. *Ann NY Acad Sci*. 2000;904:437-448. [EL 4; NE]
1706. **Goodpaster BH, Carlson CL, Visser M, et al.** Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. *J Appl Physiol*. 2001;90(6):2157-2165. [EL 2; PCS]
1707. **Cree MG, Newcomer BR, Katsanos CS, et al.** Intramuscular and liver triglycerides are increased in the elderly. *J Clin Endocrinol Metab*. 2004;89(8):3864-3871. [EL 3; CSS]
1708. **Bales CW, Ritchie CS.** Sarcopenia, weight loss, and nutritional frailty in the elderly. *Annu Rev Nutr*. 2002;22:309-323. [EL 4; NE]
1709. **Morley JE.** Sarcopenia: diagnosis and treatment. *J Nutr Health Aging*. 2008;12(7):452-456. [EL 4; NE]
1710. **Ryan AS, Pratley RE, Elahi D, Goldberg AP.** Resistive training increases fat-free mass and maintains RMR despite weight loss in postmenopausal women. *J Appl Physiol*. 1995;79(3):818-823. [EL 2; NRCT, allocation concealment]
1711. **Pavlou KN, Krey S, Steffee WP.** Exercise as an adjunct to weight loss and maintenance in moderately obese subjects. *Am J Clin Nutr*. 1989;49(5 Suppl):1115-1123. [EL 1; RCT]
1712. **Stenholm S, Rantanen T, Heliövaara M, Koskinen S.** The mediating role of C-reactive protein and handgrip strength between obesity and walking limitation. *J Am Geriatr Soc*. 2008;56(3):462-469. [EL 3; CSS]
1713. **Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L.** Sarcopenic obesity: definition, cause and consequences. *Curr Opin Clin Nutr Metab Care*. 2008;11(6):693-700. [EL 4; NE]
1714. **Slemenda CW, Hui SL, Longcope C, Wellman H, Johnston CC.** Predictors of bone mass in perimenopausal women. A prospective study of clinical data using photon absorptiometry. *Ann Intern Med*. 1990;112(2):96-101. [EL 2; PCS, post-hoc cross-sectional study of the cohort]
1715. **Melton LJ, Kan SH, Frye MA, Wahner HW, O'Fallon WM, Riggs BL.** Epidemiology of vertebral fractures in women. *Am J Epidemiol*. 1989;129(5):1000-1011. [EL 3; SS]
1716. **Pocock N, Eisman J, Gwinn T, et al.** Muscle strength, physical fitness, and weight but not age predict femoral neck bone mass. *J Bone Miner Res*. 1989;4(3):441-448. [EL 3; CSS]
1717. **Seeman E, Melton LJ, O'Fallon WM, Riggs BL.** Risk factors for spinal osteoporosis in men. *Am J Med*. 1983;75(6):977-983. [EL 2; PCS]
1718. **Felson DT, Zhang Y, Hannan MT, Anderson JJ.** Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. *J Bone Miner Res*. 1993;8(5):567-573. [EL 2; PCS]
1719. **Compston JE, Laskey MA, Croucher PI, Coxon A, Kreitzman S.** Effect of diet-induced weight loss on total body bone mass. *Clin Sci*. 1992;82(4):429-432. [EL 2; PCS]
1720. **Hyldstrup L, Andersen T, McNair P, Breum L, Transbøl I.** Bone metabolism in obesity: changes related to severe overweight and dietary weight reduction. *Acta Endocrinol*. 1993;129(5):393-398. [EL 2; PCS]
1721. **Schott AM, Cormier C, Hans D, et al.** How hip and whole-body bone mineral density predict hip fracture in elderly women: the EPIDOS Prospective Study. *Osteoporos Int*. 1998;8(3):247-254. [EL 2; PCS]
1722. **Ensrud KE, Cauley J, Lipschutz R, Cummings SR.** Weight change and fractures in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med*. 1997;157(8):857-863. [EL 2; PCS]
1723. **Wedick NM, Barrett-Connor E, Knoke JD, Wingard DL.** The relationship between weight loss and all-cause mortality in older men and women with and without diabetes mellitus: the Rancho Bernardo study. *J Am Geriatr Soc*. 2002;50(11):1810-1815. [EL 2; PCS]
1724. **Andres R, Muller DC, Sorkin JD.** Long-term effects of change in body weight on all-cause mortality. A review. *Ann Intern Med*. 1993;119(7 Pt 2):737-743. [EL 4; NE]
1725. **Williamson DF, Pamuk ER.** The association between weight loss and increased longevity. A review of the evidence. *Ann Intern Med*. 1993;119(7 Pt 2):731-736. [EL 4; NE]

1726. **Lee IM, Paffenbarger RS.** Is weight loss hazardous? *Nutr Rev*. 1996;54(4 Pt 2):S116-24. [EL 4; NE]
1727. **Lissner L, Odell PM, D'Agostino RB, et al.** Variability of body weight and health outcomes in the Framingham population. *N Engl J Med*. 1991;324(26):1839-1844. [EL 2; PCS]
1728. **Blair SN, Shaten J, Brownell K, Collins G, Lissner L.** Body weight change, all-cause mortality, and cause-specific mortality in the Multiple Risk Factor Intervention Trial. *Ann Intern Med*. 1993;119(7 Pt 2):749-757. [EL 2; PCS]
1729. **Yaari S, Goldbourt U.** Voluntary and involuntary weight loss: associations with long term mortality in 9,228 middle-aged and elderly men. *Am J Epidemiol*. 1998;148(6):546-555. [EL 2; PCS]
1730. **French SA, Folsom AR, Jeffery RW, Williamson DF.** Prospective study of intentionality of weight loss and mortality in older women: the Iowa Women's Health Study. *Am J Epidemiol*. 1999;149(6):504-514. [EL 2; PCS]
1731. **Diehr P, Bild DE, Harris TB, Duxbury A, Siscovick D, Rossi M.** Body mass index and mortality in nonsmoking older adults: the Cardiovascular Health Study. *Am J Public Health*. 1998;88(4):623-629. [EL 2; PCS]
1732. **Shea MK, Nicklas BJ, Houston DK, et al.** The effect of intentional weight loss on all-cause mortality in older adults: results of a randomized controlled weight-loss trial. *Am J Clin Nutr*. 2011;94(3):839-846. [EL 1; RCT]
1733. **Binder EF, Schechtman KB, Ehsani AA, et al.** Effects of exercise training on frailty in community-dwelling older adults: results of a randomized, controlled trial. *J Am Geriatr Soc*. 2002;50(12):1921-1928. [EL 1; RCT]
1734. **Fiatarone MA, O'Neill EF, Ryan ND, et al.** Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. 1994;330(25):1769-1775. [EL 1; RCT]
1735. **Crandall J, Schade D, Ma Y, et al. Diabetes Prevention Program Research Group.** The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Sci Med Sci*. 2006;61(10):1075-1081. [EL 1; RCT, post-hoc analysis]
1736. **Colman E, Katzel LI, Rogus E, Coon P, Muller D, Goldberg AP.** Weight loss reduces abdominal fat and improves insulin action in middle-aged and older men with impaired glucose tolerance. *Metabolism*. 1995;44(11):1502-1508. [EL 2; PCS]
1737. **Katzel LI, Bleecker ER, Colman EG, Rogus EM, Sorkin JD, Goldberg AP.** Effects of weight loss vs aerobic exercise training on risk factors for coronary disease in healthy, obese, middle-aged and older men. A randomized controlled trial. *JAMA*. 1995;274(24):1915-1921. [EL 1; RCT]
1738. **Dengel DR, Pratley RE, Hagberg JM, Rogus EM, Goldberg AP.** Distinct effects of aerobic exercise training and weight loss on glucose homeostasis in obese sedentary men. *J Appl Physiol*. 1996;81(1):318-325. [EL 2; PCS]
1739. **Purnell JQ, Kahn SE, Albers JJ, Nevin DN, Brunzell JD, Schwartz RS.** Effect of weight loss with reduction of intra-abdominal fat on lipid metabolism in older men. *J Clin Endocrinol Metab*. 2000;85(3):977-982. [EL 2; PCS]
1740. **Kumanyika SK, Espeland MA, Bahnson JL, et al. TONE Cooperative Research Group.** Ethnic comparison of weight loss in the Trial of Nonpharmacologic Interventions in the Elderly. *Obes Res*. 2002;10(2):96-106. [EL 1; RCT]
1741. **Womack CJ, Harris DL, Katzel LI, Hagberg JM, Bleecker ER, Goldberg AP.** Weight loss, not aerobic exercise, improves pulmonary function in older obese men. *J Gerontol A Biol Sci Med Sci*. 2000;55(8):M453-M457. [EL 1; RCT]
1742. **Rejeski WJ, Focht BC, Messier SP, Morgan T, Pahor M, Penninx B.** Obese, older adults with knee osteoarthritis: weight loss, exercise, and quality of life. *Health Psychol*. 2002;21(5):419-426. [EL 1; RCT]
1743. **Focht BC, Rejeski WJ, Ambrosius WT, Katula JA, Messier SP.** Exercise, self-efficacy, and mobility performance in overweight and obese older adults with knee osteoarthritis. *Arthritis Rheum*. 2005;53(5):659-665. [EL 1; RCT]
1744. **Bales CW, Buhr G.** Is obesity bad for older persons? A systematic review of the pros and cons of weight reduction in later life. *J Am Med Dir Assoc*. 2008;9(5):302-312. [EL 1; MRCT]
1745. **Mathus-Vliegen EM. Obesity Management Task Force of the European Association for the Study of Obesity.** Prevalence, pathophysiology, health consequences and treatment options of obesity in the elderly: a guideline. *Obes Facts*. 2012;5(3):460-483. [EL 4; NE]
1746. **Han TS, Tajar A, Lean ME.** Obesity and weight management in the elderly. *Br Med Bull*. 2011;97:169-196. [EL 4; NE]
1747. **Perna S, Guido D, Bologna C, et al.** Liraglutide and obesity in elderly: efficacy in fat loss and safety in order to prevent sarcopenia. A perspective case series study. *Aging Clin Exp Res*. 2016. [EL 2; PCS]
1748. **Segal KR, Lucas C, Boldrin M, Hauptman J.** Weight loss efficacy of orlistat in obese elderly adults. *Obes Res*. 1999;7(suppl):26A (abstract). [EL 4; NE, abstract]
1749. **Abu-Abeid S, Keidar A, Szold A.** Resolution of chronic medical conditions after laparoscopic adjustable silicone gastric banding for the treatment of morbid obesity in the elderly. *Surg Endosc*. 2001;15(2):132-134. [EL 3; SS]
1750. **Quebbemann B, Engstrom D, Siegfried T, Garner K, Dallal R.** Bariatric surgery in patients older than 65 years is safe and effective. *Surg Obes Relat Dis*. 2005;1(4):389-392. [EL 3; SS]
1751. **Sugerman HJ, DeMaria EJ, Kellum JM, Sugerman EL, Meador JG, Wolfe LG.** Effects of bariatric surgery in older patients. *Ann Surg*. 2004;240(2):243-247. [EL 3; SS]
1752. **Sosa JL, Pombo H, Pallavicini H, Ruiz-Rodriguez M.** Laparoscopic gastric bypass beyond age 60. *Obes Surg*. 2004;14(10):1398-1401. [EL 3; SS, prospectively collected database]
1753. **St Peter SD, Craft RO, Tiede JL, Swain JM.** Impact of advanced age on weight loss and health benefits after laparoscopic gastric bypass. *Arch Surg*. 2005;140(2):165-168. [EL 3; SS]
1754. **Varela JE, Wilson SE, Nguyen NT.** Outcomes of bariatric surgery in the elderly. *Am Surg*. 2006;72(10):865-869. [EL 3; SS]
1755. **Dorman RB, Abraham AA, Al-Refaie WB, Parsons HM, Ikramuddin S, Habermann EB.** Bariatric surgery outcomes in the elderly: an ACS NSQIP study. *J Gastrointest Surg*. 2012;16(1):35-44. [EL 3; SS]
1756. **Weygandt M, Mai K, Dommes E, et al.** The role of neural impulse control mechanisms for dietary success in obesity. *Neuroimage*. 2013;83:669-678. [EL 2; PCS]
1757. **Baik JH.** Dopamine signaling in food addiction: role of dopamine D2 receptors. *BMB Rep*. 2013;46(11):519-526. [EL 4; NE]
1758. **Carr KD.** Food scarcity, neuroadaptations, and the pathogenic potential of dieting in an unnatural ecology: binge eating and drug abuse. *Physiol Behav*. 2011;104(1): 162-167. [EL 4; NE]
1759. **Vengeliene V.** The role of ghrelin in drug and natural reward. *Addict Biol*. 2013;18(6):897-900. [EL 4; NE]

1760. **Del Re AC, Gordon AJ, Lembke A, Harris AH.** Prescription of topiramate to treat alcohol use disorders in the Veterans Health Administration. *Addict Sci Clin Pract*. 2013;8:12. [EL 3; SS, large retrospective cohort N = 375,777]
1761. **Blodgett JC, Del Re AC, Maisel NC, Finney JW.** A meta-analysis of topiramate's effects for individuals with alcohol use disorders. *Alcohol Clin Exp Res*. 2014;38(6):1481-1488. [EL 1; MRCT, relatively small number of studies N = 7]
1762. **Atkinson RL.** Opioid regulation of food intake and body weight in humans. *Fed Proc*. 1987;46(1):178-182. [EL 4; NE]
1763. **Mysels DJ, Vosburg SK, Benga I, Levin FR, Sullivan MA.** Course of weight change during naltrexone versus methadone maintenance for opioid-dependent patients. *J Opioid Manag*. 2011;7(1):47-53. [EL 3; SS]
1764. **Wang GJ, Tomasi D, Volkow ND, et al.** Effect of combined naltrexone and bupropion therapy on the brain's reactivity to food cues. *Int J Obes*. 2014;38(5):682-688. [EL 1; RCT]
1765. **Cambridge VC, Ziauddeen H, Nathan PJ, et al.** Neural and behavioral effects of a novel mu opioid receptor antagonist in binge-eating obese people. *Biol Psychiatry*. 2013;73(9):887-894. [EL 2; NRCT]
1766. **Horne RL, Ferguson JM, Pope HG, et al.** Treatment of bulimia with bupropion: a multicenter controlled trial. *J Clin Psychiatry*. 1988;49(7):262-266. [EL 1; RCT]
1767. **Shepherd G, Velez LI, Keyes DC.** Intentional bupropion overdoses. *J Emerg Med*. 2004;27(2):147-151. [EL 3; SS]
1768. **Davidson J.** Seizures and bupropion: a review. *J Clin Psychiatry*. 1989;50(7):256-261. [EL 4; NE]
1769. **Johnson BA, Ait-Daoud N, Bowden CL, et al.** Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet*. 2003;361(9370): 1677-1685. [EL 1; RCT]
1770. **Anthenelli RM, Blom TJ, McElroy SL, Keck PE.** Preliminary evidence for gender-specific effects of topiramate as a potential aid to smoking cessation. *Addiction*. 2008;103(4):687-694. [EL 1; RCT]
1771. **Ma JZ, Johnson BA, Yu E, et al.** Fine-grain analysis of the treatment effect of topiramate on methamphetamine addiction with latent variable analysis. *Drug Alcohol Depend*. 2013;130(1-3):45-51. [EL 1; RCT, secondary analysis]
1772. **Elkashef A, Kahn R, Yu E, et al.** Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. *Addiction*. 2012;107(7):1297-1306. [EL 1; RCT]
1773. **Johnson BA, Ait-Daoud N, Wang XQ, et al.** Topiramate for the treatment of cocaine addiction: a randomized clinical trial. *JAMA Psychiatry*. 2013;70(12):1338-1346. [EL 1; RCT]
1774. **Kampman KM, Pettinati HM, Lynch KG, Spratt K, Wierzbicki MR, O'Brien CP.** A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. *Drug Alcohol Depend*. 2013;133(1):94-99. [EL 1; RCT]
1775. **Johnson BA.** Recent advances in the development of treatments for alcohol and cocaine dependence: focus on topiramate and other modulators of GABA or glutamate function. *CNS Drugs*. 2005;19(10):873-896. [EL 4; NE]
1776. **Blumenthal DM, Gold MS.** Neurobiology of food addiction. *Curr Opin Clin Nutr Metab Care*. 2010;13(4): 359-365. [EL 4; NE]
1777. **Greene WM, Sylvester M, Abraham J.** Addiction liability of pharmacotherapeutic interventions in obesity. *Curr Pharm Des*. 2011;17(12):1188-1192. [EL 4; NE]
1778. **Dodds CM, O'Neill B, Beaver J, et al.** Effect of the dopamine D3 receptor antagonist GSK598809 on brain responses to rewarding food images in overweight and obese binge eaters. *Appetite*. 2012;59(1):27-33. [EL 1; RCT]
1779. **Cooper TC, Simmons EB, Webb K, Burns JL, Kushner RF.** Trends in weight egain following Roux-en-Y gastric bypass (RYGB) bariatric surgery. *Obes Surg*. 2015;25(8):1474-1481. [EL 2; PCS]
1780. **Conceição E, Mitchell JE, Vaz AR, et al.** The presence of maladaptive eating behaviors after bariatric surgery in a cross sectional study: importance of picking or nibbling on weight regain. *Eat Behav*. 2014;15(4):558-562. [EL 3; CSS]
1781. **DiGiorgi M, Rosen DJ, Choi JJ, et al.** Re-emergence of diabetes after gastric bypass in patients with mid- to long-term follow-up. *Surg Obes Relat Dis*. 2010;6(3):249-253. [EL 3; SS]
1782. **Johnson Stoklossa C, Atwal S.** Nutrition care for patients with weight regain after bariatric surgery. *Gastroenterol Res Pract*. 2013;2013:256145. [EL 4; NE]
1783. **Mann JP, Jakes AD, Hayden JD, Barth JH.** Systematic review of definitions of failure in revisional bariatric surgery. *Obes Surg*. 2015;25(3):571-574. [EL 4; NE]
1784. **Pajecki D, Halpern A, Cercato C, Mancini M, de Cleva R, Santo MA.** Short-term use of liraglutide in the management of patients with weight regain after bariatric surgery. *Rev Col Bras Cir*. 2013;40(3):191-195. [EL 3; SS]
1785. **Guthrie H, Tetley D, Hill AJ.** Quasi-prospective, real-life monitoring of food craving post-bariatric surgery: comparison with overweight and normal weight women. *Clin Obes*. 2014;4(3):136-142. [EL 3; CSS]
1786. **Rosenbaum M, Goldsmith R, Bloomfield D, et al.** Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *J Clin Invest*. 2005;115(12):3579-3586. [EL 2; PCS, small cohort N = 10]
1787. **Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J.** Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest*. 2008;118(7):2583-2591. [EL 2; PCS, small cohort N = 6]
1788. **Kissileff HR, Thornton JC, Torres MI, et al.** Leptin reverses declines in satiation in weight-reduced obese humans. *Am J Clin Nutr*. 2012;95(2):309-317. [EL 2; PCS, small cohort N = 10]

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AACE/ACE ALGORITHM FOR THE MEDICAL CARE OF PATIENTS WITH OBESITY

Patient Presentation	Screen positive for overweight or obesity BMI ≥25 kg/m² (≥23 kg/m² in some ethnicities)	Presence of weight-related disease or complication that could be improved by weight-loss therapy

Diagnosis

Evaluation

- Medical history • Physical examination • Clinical laboratory
- Review of systems, emphasizing weight-related complications
- Obesity history: graph weight vs age, lifestyle patterns/preferences, previous interventions

Anthropometric Diagnosis

- Confirm that elevated BMI represents excess adiposity
- Measure waist circumference to evaluate cardiometabolic disease risk

BMI kg/m²

<25 NORMAL WEIGHT <23 in certain ethnicities Waist circumference below regional/ethnic cutoffs	25–29.9 OVERWEIGHT | ≥30 OBESITY	
Clinical Diagnosis	**Checklist of Obesity-Related Complications** (staging and risk stratification based on complication-specific criteria)	
	None	**Mild to Moderate**	**Severe**

Diagnostic Categories	**NORMAL WEIGHT (no obesity)**	**STAGE 0**	**STAGE 1**	**STAGE 2**
		No complications	One or more mild-to-moderate complications or may be treated effectively with moderate weight loss	At least one severe complication or requires significant weight loss for effective treatment
		OVERWEIGHT **BMI 25–29.9** OBESITY **BMI ≥30**	**BMI ≥25**	**BMI ≥25**
Phases of Chronic Disease Prevention and Treatment Goals	**PRIMARY** Prevent overweight/obesity	**SECONDARY** Prevent progressive weight gain or achieve weight loss to prevent complications	**TERTIARY** Achieve weight loss sufficient to ameliorate the complications and prevent further deterioration	
Treatment Based on Clinical Judgment	• Healthy meal plan • Physical activity • Health education • Built environment	• Lifestyle/behavioral therapy • Consider pharmacotherapy if lifestyle alone not effective	• Lifestyle/behavioral therapy • Consider pharmacotherapy (BMI ≥27)	• Lifestyle/behavioral therapy • Add pharmacotherapy (BMI ≥27) • Consider bariatric surgery (BMI ≥35)

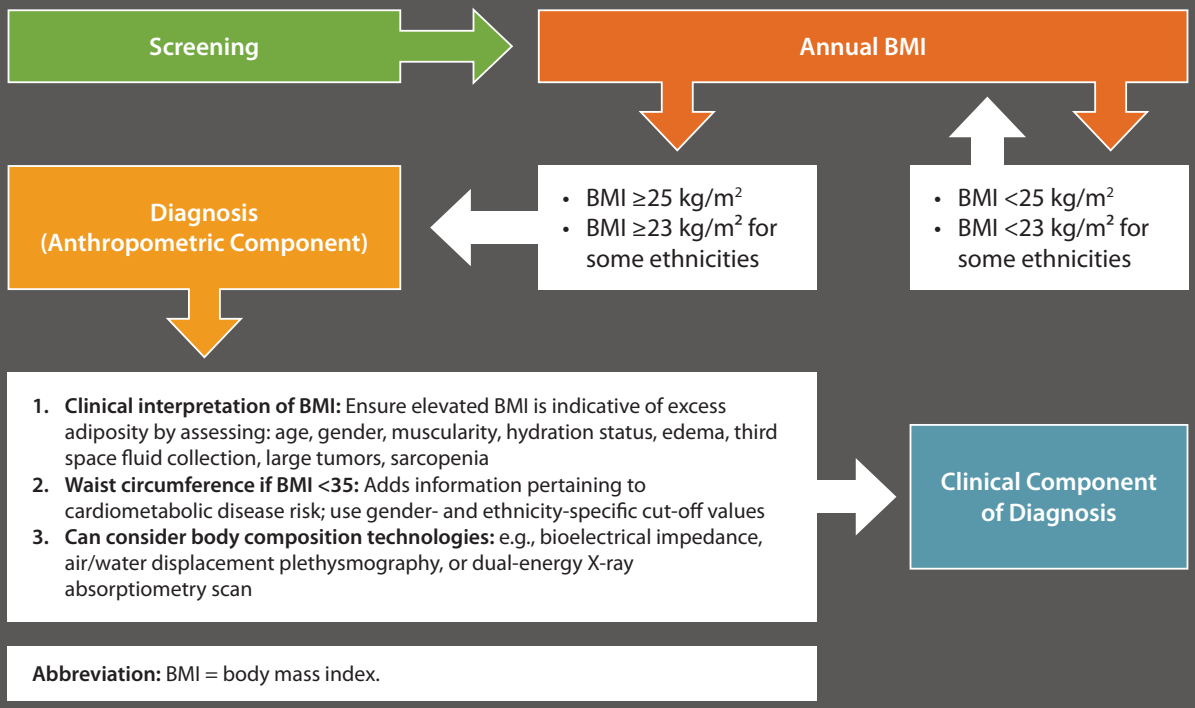
Follow-Up

- Once the plateau for weight loss has been achieved, re-evaluate the weight-related complications. If the complications have not been ameliorated, weight-loss therapy should be intensified or complication-specific interventions need to be employed.
- Obesity is a chronic disease and the diagnostic categories for obesity may not be static. Therefore, patients require ongoing follow-up, re-evaluation and long-term treatment.

Abbreviation: BMI = body mass index

ANTHROPOMETRIC COMPONENT OF THE MEDICAL DIAGNOSIS OF OBESITY

Evidence-based screening and diagnosis for excess adiposity in clinical settings



CLINICAL COMPONENT OF THE MEDICAL DIAGNOSIS OF OBESITY

Evaluation of a checklist of weight-related complications. Candidates for weight-loss therapy can present with either excess adiposity (i.e., the anthropometric component) or weight-related complications (i.e., the clinical component)

Patients Present with Overweight or Obesity (Anthropometric Component)	Candidates for Weight Loss Therapy	Patients Present with Weight-Related Disease or Complication (Clinical Component)
Patients present with BMI ≥25 kg/m², or ≥23 kg/m² in certain ethnicities, and excess adiposity	Evaluate for weight-related complications → / Evaluate for overweight or obesity ←	Prediabetes
		Metabolic Syndrome
		Type 2 Diabetes
		Dyslipidemia
		Hypertension
		Cardiovascular Disease
		Nonalcoholic Fatty Liver Disease
		Polycystic Ovary Syndrome
		Female Infertility
		Male Hypogonadism
		Obstructive Sleep Apnea
		Asthma/Reactive Airway Disease
		Osteoarthritis
		Urinary Stress Incontinence
		Gastroesophageal Reflux Disease
		Depression

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CHECKLIST OF WEIGHT-RELATED COMPLICATIONS: SCREENING AND DIAGNOSES IN PATIENTS WITH OVERWEIGHT/OBESITY

Weight-Related Complication	Basis for Screening and/or Diagnosis	Suggested Secondary Testing When Needed To Confirm Diagnosis, Stage Severity, or Guide Therapy
Prediabetes	Fasting glucose; A1C; 2-hour OGTT glucose	If fasting glucose is 100-125 mg/dL, a repeat elevated fasting glucose completes diagnosis of IFG; however, 2-hour OGTT should also be performed to exclude diabetes and IGT. Fasting and 2-hour OGTT should be performed if initial fasting glucose is normal and A1C is elevated, or in high-risk patients based on family history or metabolic syndrome.
Metabolic Syndrome	Waist circumference, blood pressure, fasting glucose, triglycerides, HDL-c	Initial evaluation completes diagnosis; use OGTT to test for IGT or diabetes.
Type 2 Diabetes	Fasting glucose; A1C; 2-hour OGTT glucose; symptoms of hyperglycemia	Overtly elevated (i.e., ≥200 mg/dL) or a repeat fasting glucose ≥126 mg/dL completes diagnosis. If fasting glucose and/or A1C is consistent with prediabetes, 2-hour OGTT should be performed to test for diabetes. A1C should be performed to help guide therapy.
Dyslipidemia	Lipid panel (total cholesterol, HDL-c, triglycerides, LDL-c, non-HDL-c)	Lipid panel completes diagnosis; lipoprotein subclasses, apoB100 may further define risk.
Hypertension	Sitting blood pressure	Repeat elevated blood pressure measurements to complete diagnosis; home blood pressure or ambulatory blood pressure monitoring may help complete testing.
Cardiovascular Disease	Physical exam; ROS; history and medical records	Additional testing based on findings and risk status (e.g., ankle-brachial index, stress testing, coronary artery calcium score and the MESA risk score calculator, arteriography, carotid ultrasound).
NAFLD / NASH	Physical exam; LFTs	Imaging (e.g., ultrasound, MRI, elastography) and/or liver biopsy needed to complete diagnosis.
PCOS and Female Infertility	Physical exam; ROS; menstrual and reproductive history	Hormonal testing (e.g., androgen levels, SHBG, LH/FSH, estradiol), ovulation testing, imaging of ovaries, may be needed to complete diagnosis.
Male Hypogonadism	Physical exam; ROS	Hormonal testing (total and free testosterone, SHBG, LH/FSH, prolactin) as needed to complete diagnosis.
Obstructive Sleep Apnea	Physical exam; neck circumference; ROS	Polysomnography needed to complete diagnosis.
Asthma / Respiratory Disease	Physical exam; ROS	Chest X-ray and spirometry may be needed to complete diagnosis.
Osteoarthritis	Physical exam; ROS	Radiographic imaging may be needed to complete diagnosis.
Urinary Stress Incontinence	Physical exam; ROS	Urine culture, urodynamic testing may be needed to complete diagnosis.
GERD	Physical exam; ROS	Endoscopy, esophageal motility study may be needed to complete diagnosis.
Depression, Anxiety, Binge Eating Disorder, Stigmatization	History; ROS	Screening/diagnostic evaluation or questionnaires based on criteria in Diagnostic and Statistical Manual of Mental Disorders; referral to clinical psychologist or psychiatrist.
Disability	Physical exam; ROS	Functional testing may be helpful.
Additional Evaluation Relevant to the Differential Diagnosis of Obesity		
Interpretation of BMI	Physical exam to ensure that BMI value is indicative of excess adiposity	Assess muscularity, edema, volume status, pregnancy, third space fluid accumulation, sarcopenia, large tumors, lipodystrophy, etc. Bioelectric impedance, air/water displacement plethysmography, or dual-energy absorptiometry scan may be considered.
Obesity Secondary to Hormonal Disorder	Physical exam; ROS	TSH for suspected hypothyroidism; salivary/serum/urine cortisol for hypercortisolism if clinical findings or symptoms present.
Iatrogenic Obesity (e.g., secondary to medications)	Review current medications and medication history	Withdraw offending medication and/or substitute with weight-neutral alternative. Follow-up assessment may be needed to complete diagnosis.
Genetic Syndrome	Physical exam; ROS; family history	If clinical findings are suggestive, genetic testing of patient and perhaps family members may be needed to complete diagnosis.

Abbreviations: A1C = glycated hemoglobin; BMI = body mass index; FSH = follicle-stimulating hormone; GERD = gastroesophageal reflux disease; HDL-c = high-density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LFTs = liver function tests; LDL-c = low-density lipoprotein cholesterol; LH = luteinizing hormone; MRI = magnetic resonance imaging; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; OGTT = oral glucose tolerance test; PCOS = polycystic ovarian syndrome; ROS = review of symptoms; SHBG = sex hormone-binding globulin; TSH = thyroid-stimulating hormone.

LIFESTYLE THERAPY

Evidence-based lifestyle therapy for treatment of obesity should include three components

MEAL PLAN	PHYSICAL ACTIVITY	BEHAVIOR
• Reduced-calorie healthy meal plan • ~500–750 kcal daily deficit • Individualize based on personal and cultural preferences • Meal plans can include: Mediterranean, DASH, low-carb, low-fat, volumetric, high protein, vegetarian • Meal replacements • Very low-calorie diet is an option for selected patients and requires medical supervision Team member or expertise: dietitian, health educator	• Voluntary aerobic physical activity progressing to >150 minutes/week performed on 3–5 separate days per week • Resistance exercise: single-set repetitions involving major muscle groups, 2–3 times per week • Reduce sedentary behavior • Individualize program based on preferences and take into account physical limitations Team member or expertise: exercise trainer, physical activity coach, physical/occupational therapist	An interventional package that includes any number of the following: • Self-monitoring (food intake, exercise, weight) • Goal setting • Education (face-to-face meetings, group sessions, remote technologies) • Problem-solving strategies • Stimulus control • Behavioral contracting • Stress reduction • Psychologic evaluation, counseling, and treatment when needed • Cognitive restructuring • Motivational interviewing • Mobilization of social support structures Team member or expertise: health educator, behaviorist, clinical psychologist, psychiatrist

WHEN TO INITIATE WEIGHT-LOSS MEDICATIONS IN PATIENTS WITH OVERWEIGHT/OBESITY

INITIATE LIFESTYLE THERAPY

1. No Complications.
Patients with overweight or obesity who have no clinically significant weight-related complications (secondary prevention)

2. Mild to Moderate Complications.
- Patient with mild to moderate weight-related complications when lifestyle therapy is anticipated to achieve sufficient weight loss to ameliorate the complication (tertiary prevention)
- Note: weight-loss medications may also be indicated based on clinical judgment

INITIATE WEIGHT LOSS MEDICATION AS AN ADJUNCT TO LIFESTYLE THERAPY

1. Failure to lose weight.
Add medication for patients who have progressive weight gain or who have not achieved clinical improvement in weight-related complications on lifestyle therapy alone.

2. Weight Regain on Lifestyle Therapy.
Add medication for patients with overweight (BMI 25 to 29.9 kg/m^2) or obesity who are experiencing weight regain following initial success on lifestyle therapy alone.

3. Presence of Weight-Related Complications.
Initiate medication concurrent with lifestyle therapy for patients with overweight (BMI to 29.9 kg/m^2) or obesity who have weight-related complications, particularly if severe, in order to achieve sufficient weight loss to ameliorate the complication (tertiary prevention).

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TREATMENT GOALS BASED ON DIAGNOSIS IN THE MEDICAL MANAGEMENT OF PATIENTS WITH OBESITY

	DIAGNOSIS		TREATMENT GOALS	
	Anthropometric Component	**Clinical Component**	**Intervention/ Weight-Loss Goal**	**Clinical Goals**
PRIMARY PREVENTION				
Primordial Prevention	BMI ≤25 (≤23 in certain ethnicities)	Obesogenic environment	• Public education • Built environment • Access to healthy foods	Decreased incidence of overweight/obesity in populations
Primary Prevention	BMI ≤25 (≤23 in certain ethnicities)	High-risk individuals or subgroups based on individual or cultural behaviors, ethnicity, family history, biomarkers, or genetics	• Annual BMI screening • Healthy meal plan • Increased physical activity	Decreased incidence of overweight/obesity in high-risk individuals or identifiable subgroups
SECONDARY PREVENTION				
Overweight	BMI 25–29.9 (BMI 23–24.9 in certain ethnicities)	No clinically significant or detectable weight-related complications	• Prevent progressive weight gain or • Weight loss	• Prevent progression to obesity • Prevent the development of weight-related complications
Obesity	BMI ≥30 (≥25 in certain ethnicities)	No clinically significant or detectable weight-related complications	• Weight loss or • Prevent progressive weight gain	Prevent the development of weight-related complications
TERTIARY PREVENTION				
Overweight or Obesity	BMI ≥25 (≥23 in certain ethnicities)	Metabolic syndrome	10%	Prevention of T2DM
		Prediabetes	10%	Prevention of T2DM
		T2DM	5-15% or more	• Reduction in A1C • Reduction in number and/or doses of glucose-lowering medications • Diabetes remission especially when diabetes duration is short
		Dyslipidemia	5-15% or more	• Lower triglycerides • Raise HDL-c • Lower non-HDL-c
		Hypertension	5-15% or more	• Lower systolic and diastolic BP • Reductions in number and/or doses of antihypertensive medications
		Nonalcoholic fatty liver disease: Steatosis	5% or more	Reduction in intrahepatocellular lipid
		Nonalcoholic fatty liver disease: Steatohepatitis	10-40%	Reduction in inflammation and fibrosis
		Polycystic ovary syndrome	5-15% or more	• Ovulation • Regularization of menses • Reduction in hirsutism • Enhanced insulin sensitivity • Reduced serum androgen levels
		Female infertility	10% or more	• Ovulation • Pregnancy and live birth
		Male hypogonadism	5-10% or more	Increase in serum testosterone
		Obstructive sleep apnea	7-11% or more	• Improved symptomatology • Decreased apnea-hypopnea index
		Asthma/reactive airway disease	7-8% or more	• Improvement in forced expiratory volume at 1 second • Improved symptomatology
		Osteoarthritis	• ≥10% • 5-10% or more when coupled with exercise	• Improved symptomatology • Increased function
		Urinary stress incontinence	5-10% or more	Reduced frequency of incontinence
		Gastroesophageal reflux disease	10% or more	Improved symptomatology
		Depression	Uncertain	• Improved symptomatology • Improvement in depression scores

Abbreviations: A1C = hemoglobin A1c; BMI = body mass index; BP = blood pressure; HDL-c = high-density lipoprotein cholesterol; T2DM = type 2 diabetes mellitus.

PREFERRED WEIGHT-LOSS MEDICATIONS: INDIVIDUALIZATION OF THERAPY

KEY: PREFERRED DRUG | USE WITH CAUTION | AVOID

CLINICAL CHARACTERISTICS OR CO-EXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	**Lorcaserin**	**Phentermine/ topiramate ER**	**Naltrexone ER/ bupropion ER**	**Liraglutide 3 mg**
Diabetes Prevention (metabolic syndrome, prediabetes)			Insufficient data for T2DM prevention		Insufficient data for T2DM prevention	
Type 2 Diabetes Mellitus						
Hypertension				Monitor heart rate	Monitor BP and heart rate Contraindicated in uncontrolled HTN	Monitor heart rate
Cardiovascular Disease	**CAD**			Monitor heart rate	Monitor heart rate, BP	Monitor heart rate
	Arrhythmia		Monitor for bradycardia	Monitor heart rate, rhythm	Monitor heart rate, rhythm, BP	Monitor heart rate, rhythm
	CHF	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Chronic Kidney Disease	**Mild (50–79 mL/min)**					
	Moderate (30–49 mL/min)			Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg bid	
	Severe (<30 mL/min)	Watch for oxalate nephropathy	Urinary clearance of drug metabolites	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion
Nephrolithiasis		Calcium oxalate stones		Calcium phosphate stones		
Hepatic Impairment	**Mild-Moderate (Child-Pugh 5–9)**	Watch for cholelithiasis	Hepatic metabolism of drug	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg in AM	Watch for cholelithiasis
	Severe (Child-Pugh >9)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Depression			Insufficient safety data Avoid combinations of serotonergic drugs	Avoid maximum dose: 15 mg/92 mg per day	Insufficient safety data Avoid in adolescents and young adults	
Anxiety				Avoid max dose: 15 mg/92 mg per day		
Psychoses		Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Binge Eating Disorder			Insufficient data; however, possible benefit based on reduction in food cravings	Insufficient data; however, possible benefit based on studies with topiramate	Insufficient data, though possible benefit based on studies with bupropion Avoid in patients with purging or bulimia nervosa	Insufficient data
Glaucoma				Contraindicated, may trigger angle closure	May trigger angle closure	
Seizure Disorder				If discontinuing from max dose, taper slowly	Bupropion lowers seizure threshold	
Pancreatitis		Monitor for symptoms				Monitor for symptoms Avoid if prior or current disease
Opioid Use					Will antagonize opioids and opiates	
Women of Reproductive Potential	**Pregnancy**	Use contraception and discontinue orlistat should pregnancy occur	Use contraception and discontinue lorcaserin should pregnancy occur	Use contraception and discontinue phentermine/topiramate should pregnancy occur (perform monthly pregnacy checks to identify early pregnancy)	Use contraception and discontinue naltrexone ER/bupropion ER should pregnancy occur	Use contraception and discontinue liraglutide 3 mg should pregnancy occur
	Breast-feeding	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Age ≥65 years *		Limited data available	Insufficient data	Limited data available	Insufficient data	Limited data available
Alcoholism/ Addiction			Might have abuse potential due to euphoria at high doses	Insufficient data, though topiramate might exert therapeutic benefits	Avoid due to seizure risk and lower seizure threshold on bupropion	
Post-Bariatric Surgery		Insufficient data	Insufficient data	Limited data available	Insufficient data	Data available at 1.8 – 3.0 mg/day

* Use medications only with clear health-related goals in mind; assess patient for osteoporosis and sarcopenia.

Abbreviations: BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; HTN = hypertension; T2DM = Type 2 Diabetes Mellitus.

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DIAGNOSIS AND MEDICAL MANAGEMENT OF OBESITY

DIAGNOSIS		COMPLICATION-SPECIFIC STAGING AND TREATMENT		
Anthropometric Component (BMI kg/m²)	**Clinical Component**	**Disease Stage**	**Chronic Disease Phase of Prevention**	**Suggested Therapy (based on clinical judgment)**
<25 **<23 in certain ethnicities** **waist circumference below regional/ ethnic cutoffs**		**Normal weight** (no obesity)	**Primary**	• **Healthy lifestyle:** healthy meal plan/ physical activity
25–29.9 **23–24.9 in certain ethnicities**	Evaluate for presence or absence of adiposity-related complications and severity of complications • Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease • Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Female infertility • Male hypogonadism • Obstructive sleep apnea • Asthma/reactive airway disease • Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Depression	**Overweight stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions
≥30 **≥25 in certain ethnicities**		**Obesity stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to prevent progressive weight gain (BMI ≥27)
≥25 **≥23 in certain ethnicties**		**Obesity stage 1** (1 or more mild to moderate complications)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to achieve therapeutic target or initiate concurrently with lifestyle therapy (BMI ≥27)
≥25 **≥23 in certain ethnicties**		**Obesity stage 2** (at least 1 severe complication)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Add weight-loss medication:** Initiate concurrently with lifestyle therapy (BMI ≥27) • **Consider bariatric surgery:** (BMI ≥35)

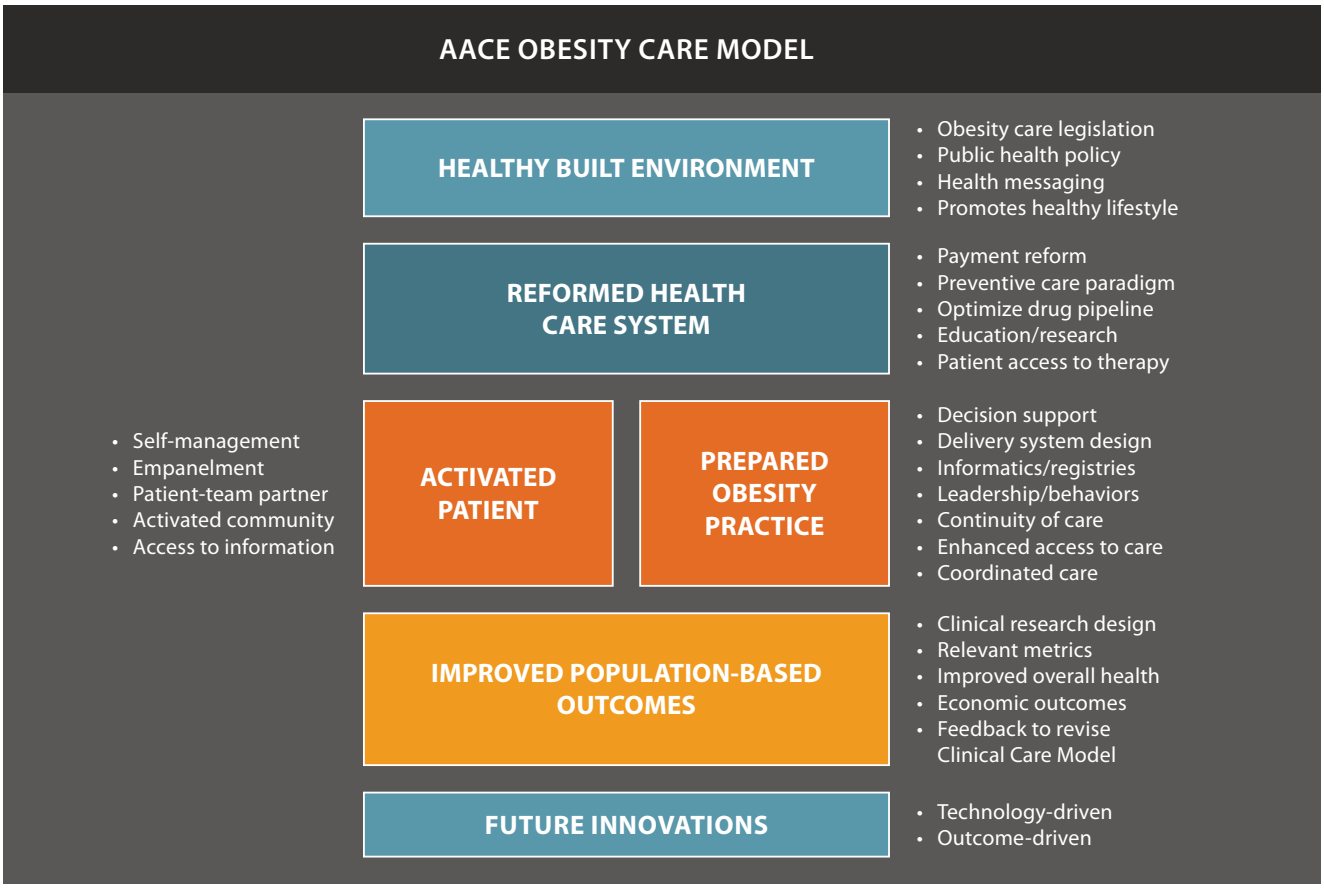
a. All patients with BMI ≥25 have either overweight or obesity stage 0 or higher, depending on the initial clinical evaluation for presence and severity of complications. These patients should be followed over time and evaluated for changes in both anthropometric and clinical diagnostic components. The diagnoses of overweight/obesity stage 0, obesity stage 1, and obesity stage 2 are not static, and disease progression may warrant more aggressive weight-loss therapy in the future. BMI values ≥25 have been clinically confirmed to represent excess adiposity after evaluation for muscularity, edema, sarcopenia, etc.

b. Stages are determined using criteria specific to each obesity-related complication; stage 0 = no complication; stage 1 = mild to moderate; stage 2 = severe.

c. Treatment plans should be individualized; suggested interventions are appropriate for obtaining the sufficient degree of weight loss generally required to treat the obesity-related complication(s) at the specified stage of severity.

d. BMI ≥27 is consistent with the recommendations established by the US Food and Drug Administration for weight-loss medications.

Abbreviation: BMI = body mass index.


AACE OBESITY CARE MODEL
HEALTHY BUILT ENVIRONMENT
• Obesity care legislation
• Public health policy
• Health messaging
• Promotes healthy lifestyle
REFORMED HEALTH CARE SYSTEM
• Payment reform
• Preventive care paradigm
• Optimize drug pipeline
• Education/research
• Patient access to therapy
• Self-management
• Empanelment
• Patient-team partner
• Activated community
• Access to information
ACTIVATED PATIENT
PREPARED OBESITY PRACTICE
• Decision support
• Delivery system design
• Informatics/registries
• Leadership/behaviors
• Continuity of care
• Enhanced access to care
• Coordinated care
IMPROVED POPULATION-BASED OUTCOMES
• Clinical research design
• Relevant metrics
• Improved overall health
• Economic outcomes
• Feedback to revise Clinical Care Model
FUTURE INNOVATIONS
• Technology-driven
• Outcome-driven

WEIGHT-LOSS MEDICATIONS APPROVED BY THE FDA FOR LONG-TERM TREATMENT OF OBESITY

Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments

Orlistat
 	
(Xenical™)
(Alli™) – OTC
 	
1999
	Lipase inhibitor
	
	XENDOS
	
	1 yr: 4.0%
	4 yr: 2.6%
		120 mg PO TID (before meals)
		
		OTC: 60 mg PO TID (before meals)
			• Steatorrhea
			• Fecal urgency
			• Incontinence
			• Flatulence
			• Oily spotting
			• Frequent bowel movements
			• Abdominal pain
			• Headache
				✓ Pregnancy and breastfeeding
				✓ Chronic malabsorption syndrome
				✓ Cholestasis
				✓ Oxalate nephrolithiasis
				• Rare severe liver injury
				• Cholelithiasis
				• Malabsorption of fat-soluble vitamins
				• Effects on other medications:
				  • Warfarin (enhance)
				  • Anti-epileptics (decrease)
				  • Levothyroxine (decrease)
				  • Cyclosporine (decrease)
					Monitor for:
					• Cholelithiasis
					• Nephrolithiasis
					
					- Recommend standard multivitamin (to include vitamins A, D, E, and K) at bedtime or 2 hours after orlistat dose
					- Eating >30% kcal from fat results in greater GI side effects
					- FDA-approved for children ≥12 years old
					- Administer levothyroxine and orlistat 4 hours apart

Lorcaserin (Belviq®) 2012	Serotonin (5HT2c) receptor agonist BLOSSOM BLOOM **1 yr: 3.0%-3.6%** **2 yr: 3.1%**	10 mg PO BID	• Headache • Nausea • Dizziness • Fatigue • Xerostomia • Dry eye • Constipation • Diarrhea • Back pain • Nasopharyngitis • Hyperprolactinemia	✓ Pregnancy and breastfeeding ✓ Serotonin syndrome or neuroleptic malignant syndrome • Safety data lacking in patients who have depression • Concomitant use of SSRI, SNRI, MAOI, bupropion, St. John's wort as may increase risk of developing serotonin syndrome • Uncontrolled mood disorder • Cognitive impairment • Avoid in patients with severe liver injury or renal insufficiency • Caution for patients with bradycardia, heart block, or heart failure • Unproven concern for potential cardiac valvulopathy • Leukopenia	**Monitor for:** • Symptoms of cardiac valve disease • Bradycardia • Serotonin syndrome • Neuroleptic malignant syndrome • Depression • Severe mood alteration, euphoria, dissociative state • Confusion/somnolence • Priapism • Leukopenia • Euphoria at high doses could predispose to abuse • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas
Phentermine/ Topiramate ER (Qsymia®) 2012	NE-releasing agent (phentermine) GABA receptor modulation (topiramate) EQUIP CONQUER SEQUEL **1 yr: 8.6%-9.3% on high dose; 6.6% on treatment dose** **2 yr: 8.7% on high dose; 7.5% on treatment dose**	**Starting dose:** 3.75/23 mg PO QD for 2 weeks **Recommended dose:** 7.5/46 mg PO QD **Escalation dose:** 11.25/69 mg PO QD **Maximum dose:** 15/92 mg PO QD	• Headache • Paresthesia • Insomnia • Decreased bicarbonate • Xerostomia • Constipation • Nasopharyngitis • Anxiety • Depression • Cognitive impairment (concentration and memory) • Dizziness • Nausea • Dysgeusia	✓ Pregnancy and breastfeeding (topiramate teratogenicity) ✓ Hyperthyroidism ✓ Acute angle-closure glaucoma ✓ Concomitant MAOI use (within 14 days) • Tachyarrhythmia • Decreased cognition • Seizure disorder • Anxiety and panic attacks • Nephrolithiasis • Hyperchloremic metabolic acidosis • Dose adjustment with hepatic or renal impairment • Concern for abuse potential • Combined use with alcohol or depressant drugs can worsen cognitive impairment	**Monitor for:** • Increased heart rate • Depressive symptomatology or worsening depression especially on maximum dose • Hypokalemia (especially with HCTZ or furosemide) • Acute myopia and/or ocular pain • Acute kidney stone formation • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas - Potential for lactic acidosis (hyperchloremic non-anion gap) in combination with metformin - MAOI (allow ≥14 days between discontinuation) - 15 mg/92 mg dose should not be discontinued abruptly (increased risk of seizure); taper over at least 1 week - Health care professional should check ßHCG before initiating, followed by monthly self-testing at home - Monitor electrolytes and creatinine before and during treatment - Can cause menstrual spotting in women taking birth control pills due to altered metabolism of estrogen and progestins

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Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments
Naltrexone ER/ Bupropion ER (Contrave®) 2014	Opiate antagonist (naltrexone) Reuptake inhibitor of DA and NE (bupropion) COR-I COR-II COR-BMOD **1 yr: 4.2%-5.2%**	**Titrate dose:** **Week 1:** 1 tab (8/90 mg) PO QAM **Week 2:** 1 tab (8/90 mg) PO BID **Week 3:** 2 tabs (total 16/180 mg) PO QAM and 1 tab (8/90 mg) PO QHS **Week 4:** 2 tabs (total 16/180 mg) PO QHS	• Nausea • Headache • Insomnia • Vomiting • Constipation • Diarrhea • Dizziness • Anxiety • Xerostomia	✓ Pregnancy and breastfeeding ✓ Uncontrolled hypertension ✓ Seizure disorder ✓ Anorexia nervosa ✓ Bulimia nervosa ✓ Severe depression ✓ Drug or alcohol withdrawal ✓ Concomitant MAOI (within 14 days) ✓ Chronic opioid use • Cardiac arrhythmia • Dose adjustment for liver or kidney impairment • Narrow-angle glaucoma • Uncontrolled migraine disorder • Generalized anxiety disorder • Bipolar disorder • Safety data lacking in patients who have depression • Seizures (bupropion lowers seizure threshold)	**Monitor for:** • Increased heart rate and blood pressure • Worsening depression or suicidal ideation • Worsening of migraines • Liver injury (naltrexone) • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Seizures (bupropion lowers seizure threshold) - MAOI (allow ≥14 days between discontinuation) - Dose adjustment for patients with renal and hepatic impairment - Avoid taking medication with a high-fat meal - Can cause false positive urine test for amphetamine - Bupropion inhibits CYP2D6
Liraglutide 3 mg (Saxenda®) 2014	GLP-1 analog SCALE Obesity & Prediabetes **1 yr: 5.6%**	**Titrate dose weekly by 0.6 mg as tolerated by patient (side effects):** 0.6 mg SC QD→ 1.2 mg SC QD→ 1.8 mg SC QD→ 2.4 mg SC QD→ 3.0 mg SC QD	• Nausea • Vomiting • Diarrhea • Constipation • Headache • Dyspepsia • Increased heart rate	✓ Pregnancy and breastfeeding ✓ Personal or family history of medullary thyroid cancer or MEN2 ✓ Pancreatitis ✓ Acute gallbladder disease • Gastroparesis • Severe renal impairment can result from vomiting and dehydration • Use caution in patients with history of pancreatitis • Use caution in patients with cholelithiasis • Suicidal ideation and behavior • Injection site reactions	**Monitor for:** • Pancreatitis • Cholelithiasis and cholecystitis • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Increased heart rate • Dehydration from nausea/vomiting • Injection site reactions - Titrate dose based on tolerability (nausea and GI side effects)

Abbreviations: BID = twice daily; CYP2D6 = cytochrome P450 2D6; DA = dopamine; FDA = US Food and Drug Administration; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; HCTZ = hydrochlorothiazide; MAOI = monoxidase inhibitor; MEN2 = multiple endocrine neoplasia type 2; NE = norepinephrine; OTC = over-the-counter medication; % TBWL = percent total body weight loss from baseline over that observed in the placebo group; PO = oral; QAM = every morning; QD = daily; QHS = every bedtime; SC = subcutaneous; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TID = 3 times a day; T2DM = type 2 diabetes mellitus.

FDA indication for all medications: BMI >30 kg/m^2 or BMI ≥27kg/m^2 with significant comorbidity.

After 3 to 4 months of treatment with anti-obesity medication:

- **For naltrexone ER/bupropion ER and lorcaserin:**
  If the patient has not lost at least 5% of their baseline body weight at 12 weeks on the maintenance dose, the medication should be discontinued.
- **For phentermine/topiramate ER:**
  Continue medication if the patient has lost >5% body weight after 12 weeks on recommended dose (7.5 mg/42 mg); if the patient has not lost at least 3% of body weight after being on the recommended dose for 12 weeks then the medication should be discontinued, or the patient can be transitioned to maximum dose (15 mg/92 mg); if patient has not lost at least 5% after 12 additional weeks on the maximum dose, the medication should be discontinued.
- **For liraglutide 3 mg:**
  If the patient has not lost at least 4% of body weight 16 weeks after initiation, the medication should be discontinued.

References:

1–4 and package inserts for each medication

1. Wyatt HR. Update on treatment strategies for obesity. *J Clin Endocrinol Metab*. 2013;98(4):1299-1306.
2. Garvey WT, Garber AJ, Mechanick JI, Bray GA, Dagogo-Jack S, Einhorn D, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocr Pract*. 2014;20(9):977-989.
3. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311(1):74-86.
4. Fujioka K. Current and emerging medications for overweight and obesity in people with comorbidities. *Diabetes Obes Metab*. 2015;17(11):1021-1032.

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Appendix 3

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY

OBESITY CHRONIC CARE MODEL

Obesity is a chronic disease that has become increasingly responsible for patient suffering and social costs worldwide. The conceptualization of obesity as a lifestyle choice and primarily a cosmetic concern is not only debunked by scientific evidence, but has failed our patients and our societies. With improved efficacy and an increased range of treatment options, it is incumbent that the full force of our medical chronic care model (CCM) be brought to focus on obesity prevention and treatment. This shift can only be achieved through activated health care systems, as well as regulatory and legislative measures that ensure patient access to therapies of proven benefit. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity represent an evidence-based CCM that emphasizes weight-loss therapy directed at the prevention and treatment of obesity-related complications. This clinical practice guideline (CPG) approaches obesity as a chronic medical illness that is a source of morbidity, mortality, and compromised quality of life. The guidelines target more aggressive treatment for patients with weight-related complications who benefit most from weight loss and as such, optimize benefit/risk ratios and cost-effectiveness (i.e., the "complications-centric" approach). The medical CCM promulgated by these guidelines is not isolated but exists within the context of our larger health care system, communities, governments, and societies. Therefore, a CCM for obesity must become an operational, integral component of the health care system and be embraced by the larger society to optimally benefit patients in particular and public health in general.

Introduced in the 1990s, the general concept of the CCM for disease management was designed for primary care practice settings and credited with improving clinical outcomes (1,2). The core aspiration is that patients become activated and empowered, while health care systems become prepared and proactive. In general, there are 3 interrelated settings for the CCM: community, health care system, and provider organization (private practice, health center, integrated system, etc) (3). The 6 integrated components of the AACE/ACE Obesity CCM are as follows:

- Component 1: **Built Environment** (contextualization; community resources, laws, and policies; safe public spaces for physical activity, lifestyle education, self-help, and socialization; and minimization of adverse obesogenic drivers; includes home and workplace)
- Component 2: **Healthcare System** (recognition and prioritization of health promotion and obesity prevention, with a favorable economic model [payment reform] that engages health care professionals [primary care and specialists] and patients, while making comprehensive, evidence-based obesity care affordable and accessible)
- Component 3: **Decision Support** (creation and electronic implementation of evidence-based CPGs for comprehensive, complications-centric obesity care)
- Component 4: **Delivery System Design** (creation and coordination of an obesity care team that is available for routine patient encounters and oriented toward management of both acute and chronic issues; includes lifestyle, pharmacotherapy, and bariatric procedures)
- Component 5: **Clinical Information Systems** (routine patient care, CPGs, interactive/feedback, and registries)
- Component 6: **Self-Management Support** (education, behavioral medicine, follow-up, and feedback regarding obesity care; recognition by the patient of need for obesity prevention and care)

Effective integration of the components of this CCM is central to successful implementation and realization of superior clinical outcomes in comprehensive, complications-centric obesity care. The specific processes for a CCM have been described as building blocks (4) and are described here in the context of the AACE and ACE Obesity CCM:

- Block 1: **Engaged Leadership** (commitment to transformative care and focus on health promotion, obesity prevention, and comprehensive, complications-centric obesity management to improve patient health)
- Block 2: **Data-Driven Improvement** (evidence-based interventions and metrics; use of registries; properly designed clinical trials)
- Block 3: **Empanelment** (linking patients with an obesity care team and primary care clinician; basis for performance metrics)
- Block 4: **Team-Based Care** (team leaders [primary care physician, endocrinologist, or other obesity specialist AND advanced practice professional] and support [nurse, registered dietitian, behaviorist, psychologist, pharmacist, physical activity trainer, social worker, etc])
- Block 5: **Patient-Team Partnership** (empowered, activated patient with a prepared, proactive practice that is empathetic and supportive; physician that promotes personal health behaviors; motivational interviewing, shared decision-making, and trustworthy relationships)

- Block 6: **Population-Based Care** (routine health promotion and coaching with preventive services; use of specialized teams for patients with specific weight-related complications; family-oriented care that addresses childhood obesity; identification of relevant metrics [e.g., weight, body mass index, waist circumference, target blood pressure, target lipids, target renal and liver function, symptom relief, performance, and reduction of major adverse cardiac events])
- Block 7: **Continuity of Care** (linked to all blocks and necessary for effective CCM; requires payment reform)
- Block 8: **Enhanced Access to Care** (includes nights and weekends and adds capacity to meet demand; uses e-visits, phone visits, group visits, telemedicine visits, efficient use of obesity team members, and payment reform)
- Block 9: **Comprehensive Coordinated Care** (primary care, weight loss, weight-related complications, other specialized care; accountability by primary care; includes outpatient, inpatient, and long-term care; infrastructure for appointment logistics, transportation, interpretation, comfort and safety, electronic connectivity, and information-sharing)
- Block 10: **Alternative Encounters** (payment reforms to drive and facilitate novel modalities for each of the above blocks to optimize obesity care)

In conclusion, a contemporary AACE/ACE Obesity CCM focuses on an upstream approach (3) that promotes general health and prevents obesity as a disease state while providing downstream comprehensive, complications-centric, disease management. The CCM uses evidence-based treatment guidelines for obesity to define a concerted approach, which is required to stem the increasing suffering and social costs of this disease. The above text, recommendations in the Executive Summary, explanations and evidence base in Appendix 1, and the pictorial algorithm in Appendix 2 contribute detail to the AACE/ACE Obesity CCM provided in Figure 1.

REFERENCES

1. **Bodenheimer T, Wagner EH, Grumbach K.** Improving primary care for patients with chronic illness, parts 1 and 2. *JAMA*. 2002;288:1775-1779, 1909-1914.
2. **Barr VJ, Robinson S, Marin-Link B, et al.** The expanded chronic care model: an integration of concepts and strategies from population health promotion and the chronic care model. *Hosp Q*. 2003;7:73-82.
3. **Bodenheimer T, Willard-Grace R.** The chronic care model and the transformation of primary care. In: Mechanick JI, Kushner RF, eds. *Lifestyle Medicine: A Manual for Clinical Practice*. New York, NY: Springer International; 2016: 89-96.
4. **Bodenheimer T, Ghorob A, Willard-Grace R, Grumbach K.** The 10 building blocks of high-performing primary care. *Ann Fam Med*. 2014;12:166-171.

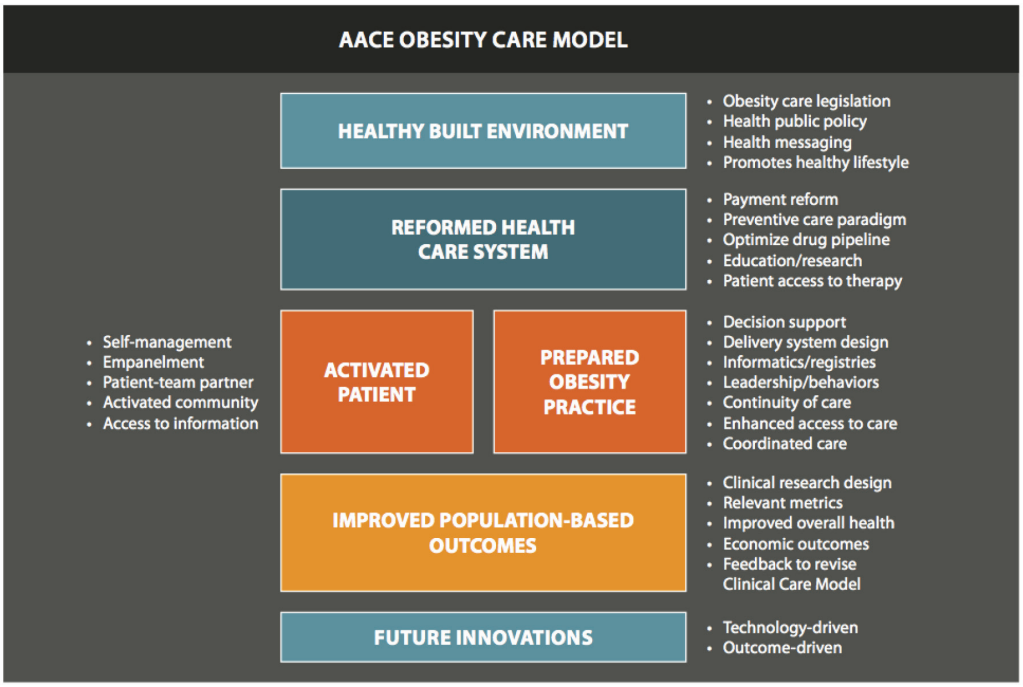

Fig. 1. The AACE/ACE Obesity Chronic Care Model*

**See text for details.*