Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study

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See Online for appendix

Summary

Background Effective prevention is needed to combat the worldwide epidemic of type 2 diabetes. We investigated the long-term extent of beneficial effects of lifestyle intervention and metformin on diabetes prevention, originally shown during the 3-year Diabetes Prevention Program (DPP), and assessed whether these interventions reduced diabetes-associated microvascular complications.

Methods The DPP (1996–2001) was a randomised trial comparing an intensive lifestyle intervention or masked metformin with placebo in a cohort selected to be at very high risk of developing diabetes. All participants were offered lifestyle training at the end of the DPP. 2776 (88%) of the surviving DPP cohort were followed up in the DPP Outcomes Study (DPPOS, Sept 1, 2002, to Jan 2, 2014) and analysed by intention to treat on the basis of their original DPP assignment. During DPPOS, the original lifestyle intervention group was offered lifestyle reinforcement semi-annually and the metformin group received unmasked metformin. The primary outcomes were the development of diabetes and the prevalence of microvascular disease. For the assessment of microvascular disease, we used an aggregate microvascular outcome, composed of nephropathy, retinopathy, and neuropathy.

Findings During a mean follow-up of 15 years, diabetes incidence was reduced by 27% in the lifestyle intervention group (hazard ratio 0·73, 95% CI 0·65–0·83; p<0·0001) and by 18% in the metformin group (0·82, 0·72–0·93; p=0·001), compared with the placebo group, with declining between-group differences over time. At year 15, the cumulative incidences of diabetes were 55% in the lifestyle group, 56% in the metformin group, and 62% in the placebo group. The prevalences at the end of the study of the aggregate microvascular outcome were not significantly different between the treatment groups in the total cohort (placebo 12·4%, 95% CI 11·1–13·8; metformin 13·0%, 11·7–14·5; lifestyle intervention 11·3%, 10·1–12·7). However, in women (n=1887) the lifestyle intervention was associated with a lower prevalence (8·7%, 95% CI 7·4–10·2) than in the placebo (11·0%, 9·6–12·6) and metformin (11·2%, 9·7–12·9) groups, with reductions in the lifestyle intervention group of 21% (p=0·03) compared with placebo and 22% (p=0·02) compared with metformin. Compared with participants who developed diabetes, those who did not develop diabetes had a 28% lower prevalence of microvascular complications (relative risk 0·72, 95% CI 0·63–0·83; p<0·0001).

Interpretation Lifestyle intervention or metformin significantly reduced diabetes development over 15 years. There were no overall differences in the aggregate microvascular outcome between treatment groups; however, those who did not develop diabetes had a lower prevalence of microvascular complications than those who did develop diabetes. This result supports the importance of diabetes prevention.

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Introduction

In the USA, 12·3% of the adult population has diabetes, with 1·7 million new cases diagnosed per year.[1] Most have type 2 diabetes. The economic cost of diabetes and prediabetes was estimated to be US$322 billion in 2012.[2] When the Diabetes Prevention Program (DPP; 1996–2001) was planned in the mid-1990s,[3] the goal was to determine whether a behavioural lifestyle intervention programme designed to address the two major environmental risk factors for type 2 diabetes, overweight or obesity and sedentary lifestyle, or the most commonly used drug to treat diabetes, metformin, would reduce the development of the disease in a population selected to be at very high risk. The large beneficial short-term effects, and especially the lifestyle intervention, shown in DPP[4] and in other studies[5,6] prompted many translation projects internationally.[7]

The ultimate worth of diabetes prevention is in the reduction of long-term morbidity or mortality, compared with waiting for the disease to develop and then treating it. The DPP Outcomes Study (DPPOS; Sept 1, 2002, to Jan 2, 2014) was designed to examine the effects of the original DPP interventions, beyond the 3-year average treatment during DPP, on the further development of diabetes and on microvascular complications.[8]

Research in context

Evidence before this study

The US Diabetes Prevention Program (DPP, 1996–2001) was initiated at a time when the worldwide epidemic of type 2 diabetes was increasing at a rapid rate. A fairly small study of lifestyle interventions to prevent diabetes in China, the Da Qing Study, had been completed and another small study in Finland (Finnish Diabetes Prevention Program) was underway when the DPP was initiated. The DPP was the largest and most comprehensive study of diabetes prevention. It was done in a diverse cohort representative of the population at very high risk for diabetes in the USA and included both lifestyle intervention and drug treatment (metformin) groups, with the aim of preventing or delaying the onset of diabetes. After 3 years, the DPP results showed a 58% reduction in the development of diabetes with the lifestyle intervention and a 31% reduction with metformin. The DPP lifestyle intervention results extended the previous findings from the Chinese and Finnish populations.

Added value of this study

The DPP Outcomes Study (DPPOS; 2002–13) was a continuation of the DPP. DPPOS was initiated to establish the longer-term effects of the DPP interventions on the development of diabetes and on the downstream microvascular complications of diabetes and cardiovascular risk factors. We published an interim report in 2009 reflecting 10 years of total follow-up. It showed continued reduction in diabetes development, albeit with reduced efficacy, and a reduction of cardiovascular risk factors in the lifestyle intervention group. In the current report, we show that diabetes prevention persists over as long as 15 years. Although microvascular complications were not reduced in the total cohort with either intervention, they were significantly reduced in the women in the lifestyle intervention group. Moreover, microvascular complications were significantly less frequent in those patients who did not develop diabetes compared with those who did.

Implications of all the available evidence

Understanding the effects of prevention, beyond the reduction in biochemical diabetes, is crucial for identifying whether prevention efforts will reduce the long-term public health burden of diabetes. DPPOS has shown the long-term prevention of diabetes and other added benefits of the lifestyle intervention and metformin, such as reduced cardiovascular risk factors, improved quality of life, and even cost savings (with metformin); however, establishing whether long-term microvascular or cardiovascular complications are reduced by the interventions will need further study.

The limited 3-year duration of the DPP precluded an understanding of longer-term effects of the interventions on diabetes prevention or on the development of complications associated with diabetes. Understanding the timecourse of the development of complications has been hampered in previous studies by a poor ascertainment of the actual time of diabetes onset, since the prevalence of complications is related to diabetes duration and exposure to hyperglycaemia. Longer follow-up of the DPP cohort was necessary to determine whether preventing or delaying diabetes onset would reduce the development of complications. Interim analyses of the 10-year combined DPP and DPPOS follow-up revealed a continued reduction of diabetes development with the lifestyle intervention and metformin, albeit with decreased efficacy.[8]

Here we report the main outcomes of the DPPOS, focusing on the long-term prevention of diabetes and the effects of the original, randomly assigned DPP interventions and the development of diabetes on microvascular complications over a mean follow-up of 15 years.

Methods

Study design and participants

The DPP was a randomised controlled clinical trial, done in 27 centres in the USA.[4] All surviving members of the three original DPP treatment groups (placebo, metformin, and intensive lifestyle intervention) who had not withdrawn consent were invited to join the DPPOS, irrespective of diabetes status.[8] A similar proportion of each DPP treatment group joined DPPOS (figure 1), and there were no significant differences in the baseline characteristics of those who joined DPPOS and those who did not.[8] Written informed consent was obtained from all participants and the studies were approved by each clinical centre's institutional review board. An independent data safety monitoring board, appointed by the funder (the US National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]), oversaw the study.

Procedures

In the DPP study, participants were randomly assigned to receive metformin (850 mg twice per day), an individual behavioural lifestyle intervention programme, or placebo (meant to resemble metformin in appearance and frequency of administration). Randomisation procedures have been described previously.[3,4] The lifestyle programme included a 16-session curriculum with individual sessions aimed at achieving a 7% weight loss through a healthy, low-fat, low-calorie diet and 150 min per week of moderate-intensity physical activity. After the first 24 weeks, individual and group sessions were used to reinforce the lifestyle modification behaviours.[9] The metformin and placebo treatment groups were double-masked, but, for practical reasons, the lifestyle group was not.[3,9] If diabetes was diagnosed by oral glucose tolerance test (OGTT) or fasting plasma glucose (FPG), and confirmed with a repeat test, participants and their health-care providers were informed. Study metformin or

placebo was still provided until hyperglycaemia worsened to an FPG of 7·78 mmol/L or more, at which time study drugs were discontinued and diabetes management transferred to the participant's own health-care provider. At the end of the DPP, after a brief metformin and placebo washout study,[10] the participants in the placebo and metformin groups were subsequently unmasked to their treatment assignment and placebo was stopped. In view of the clear evidence of benefit of the lifestyle intervention,[4] all participants were offered the lifestyle intervention in a group format during a 1-year bridge period between DPP and DPPOS.[11]

During DPPOS, as in DPP, metformin was provided to the group originally assigned to it; however, metformin was now unmasked. The same transfer from study drug and care to the patient's care provider upon the development of diabetes occurred as during DPP except that study metformin was continued until HbA_{1c} was 7% or higher. Maintenance group lifestyle sessions, offered quarterly to all DPPOS participants, reinforced the basic lifestyle content and the weight loss and physical activity goals. In addition to the maintenance sessions, participants who had original been randomly assigned to the lifestyle intervention in DPP were offered supplementary group programmes, reinforcing behavioural self-management activities, and an individual lifestyle check-in, each twice per year.

Outcomes

The primary DPPOS analytical outcomes, defined a priori, were development of diabetes and the prevalence of microvascular disease.

As in the DPP, development of diabetes was determined with 75 g OGTT done annually and FPG tests every 6 months.[3] For diagnosis of diabetes, FPG of 7·0 mmol/L or more or 2 h concentration of 11·1 mmol/L or more had to be confirmed by a repeat test within 6 weeks. HbA_{1c} concentrations were measured annually by high-performance liquid chromatography, but were not used to diagnose diabetes.

We also assessed the effect of the interventions on microvascular complications using an aggregate outcome. The aggregate microvascular disease outcome was defined by protocol to include three components: nephropathy, retinopathy, and neuropathy. Nephropathy was defined as albuminuria of 30 mg/g creatinine or more in a spot urine collection on two consecutive tests, an estimated glomerular filtration rate (GFR) of less than 45 mL/min per 1·73 m² (based on annual serum creatinine as estimated with the Chronic Kidney Disease Epidemiology Collaboration equation)[12] on two consecutive tests, or renal failure (end-stage renal disease, dialysis, or transplantation). Participants taking antihypertensive drugs at the final assessment who did not meet albuminuria or estimated GFR criteria at that time were regarded as having reached the nephropathy outcome if the nephropathy criteria were met previously at two consecutive visits. Retinopathy was diagnosed with seven-field stereoscopic fundus photography if the Early Treatment Diabetic Retinopathy Study grade was 20 or greater[13] in either eye or with treatment of retinopathy with laser or intravitreal injections. Presence of neuropathy was based on loss of light touch sensation (less than eight of ten applications detected on the dorsum of the great toe in either foot),

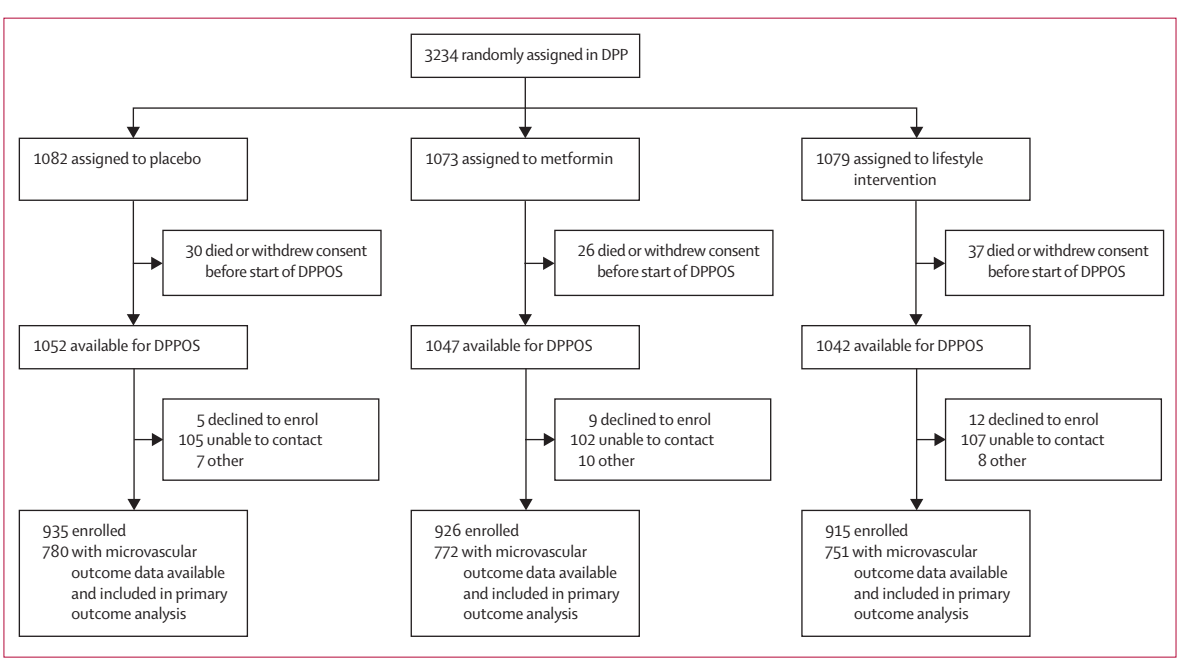

Figure 1: **Trial profile**
DPP=Diabetes Prevention Program. DPPOS=DPP Outcomes Study.

	DPP baseline (total, n=2776)	DPP-end (2001)			DPPOS-end (2013)				
		Placebo group (n=935)	Metformin group (n=926)	Lifestyle intervention group (n=915)	Placebo group (n=780)	Metformin group (n=772)	Lifestyle intervention group (n=751)	Non-diabetes (n=1226)	Diabetes (n=1550)
Age (years)	51 (10)	54 (10)	54 (10)	54 (11)	65 (10)	66 (9)*	66 (11)*	67 (10)	65 (10)*
Sex (women)	1887 (68%)	644 (69%)	619 (67%)	624 (68%)	538 (69%)	525 (68%)	513 (68%)	838 (68%)	1049 (68%)
Race or ethnic origin									
White	1508 (54%)	501 (54%)	516 (56%)	491 (54%)	411 (53%)	420 (54%)	396 (53%)	713 (58%)	795 (51%)*
African-American	561 (20%)	193 (21%)	191 (21%)	177 (19%)	162 (21%)	166 (22%)	148 (20%)	208 (17%)	353 (23%)
Hispanic American	426 (15%)	145 (16%)	141 (15%)	140 (15%)	119 (15%)	118 (15%)	109 (15%)	183 (15%)	243 (16%)
American Indian	156 (6%)	55 (6%)	47 (5%)	54 (6%)	52 (7%)	43 (6%)	50 (7%)	70 (6%)	86 (6%)
Asian American–Pacific Islanders	125 (5%)	41 (4%)	47 (3%)	53 (6%)	36 (5%)	25 (3%)	48 (6%)	52 (4%)	73 (5%)
Weight (kg)	94 (20)	94 (20)	92 (21)*	89 (21)*†	91 (20)	90 (19)	89 (19)*	87 (18)	92 (20)*
BMI (kg/m^2)	34 (7)	34 (7)	33 (7)*	32 (7)*†	33 (7)	32 (7)*	32 (6)*	31 (6)	33 (7)*
Diabetes cases	0	278 (30%)	199 (21%)*	132 (14%)*†	564 (60%)	506 (55%)*	480 (52%)*	0	100%
Diabetes duration (years)									
Total cohort‡	0	0·5 (0·9)	0·3 (0·8)*	0·2 (0·6)*†	6·5 (6·0)	5·5 (5·8)*	4·8 (5·3)*†	0	5·6 (5·8)
Participants who developed diabetes	0	1·5 (1·0)	1·5 (1·0)	1·3 (1·1)*	10·3 (4·3)	9·7 (4·3)	8·6 (4·3)*†	0	9·6 (4·4)
FPG (mmol/L)	5·9 (0·5)	6·2 (1·1)	5·9 (0·8)*	5·9 (0·8)*	6·8 (1·9)	6·5 (1·9)*	6·8 (2·0)†	5·7 (0·5)	7·4 (2·3)*
HbA_{1c} (%)									
Total cohort	5·9% (0·5)	6·1% (0·7)	6·0% (0·5)*	5·9% (0·5)*†	6·3% (1·2)	6·1% (1·1)*	6·2% (1·2)†	5·6% (0·4)	6·6% (1·4)*
Participants who developed diabetes	..	6·5% (0·9)	6·3% (0·7)*	6·4% (0·7)*	6·7% (1·4)	6·5% (1·3)	6·7% (1·4)†	..	6·6% (1·4)*

Data are mean (SD) of continuous variables or n (%). DPP-end is the last annual visit of the Diabetes Prevention Program (DPP). DPPOS-end includes data from the final annual visit of the DPP Outcomes Study (DPPOS) except for the diabetes cases which include patients who developed diabetes at any time during the study. Statistical comparisons are based on χ^2 tests for categorical variables and *t* tests for continuous variables for the lifestyle intervention group or the metformin group versus the placebo group. *p<0·05 for the lifestyle intervention group or the metformin group versus the placebo group, or diabetes versus non-diabetes. †p<0·05, versus the metformin group. ‡Diabetes duration for participants who remain non-diabetic calculated as 0 years.

Table 1: **Characteristics of the Diabetes Prevention Program Outcomes Study cohort**

measured with a 10 g Semmes-Weinstein monofilament.[14] Kidney function and neuropathy were measured annually during DPPOS, whereas retinopathy was measured during the final year of DPPOS (2012–13).

Adverse events were documented at semi-annual visits using a standard questionnaire. Sprains or fractures needing medical attention were predefined as a non-severe adverse event of special interest because of the increased activity and exercise in the lifestyle intervention group.

Statistical analysis

The outcomes reported in these analyses are based on data entered as of Jan 2, 2014, for the 2776 DPP participants who enrolled in DPPOS. Development of diabetes and the prevalence of microvascular disease were analysed by intention to treat. Time to diabetes compared each intervention with placebo on a modified product-limit life-table distribution with a log-rank test statistic.[15] Follow-up was censored at a participant's last visit if diabetes had not developed.

As specified in the protocol, the aggregate microvascular outcomes were analysed with the global test using general estimating equation (GEE) models[16] to estimate average prevalence and account for correlations among the three components. The study was powered based on the global test[17,18] which provided 91% power to detect a 25% reduction in microvascular complications due to an intervention, with two-sided α of 0·025, from a projected placebo group average prevalence of 12·1%. Each of the two pairwise comparisons (lifestyle group *vs* placebo group and metformin group *vs* placebo group) were set at an α of 0·025 to maintain an overall α of 0·05 for multiple comparisons by use of Bonferroni adjustment. Secondary analyses were not adjusted for multiple comparisons and are nominally significant at an α of 0·05. A detailed explanation of the analyses is in the appendix. We also used GEE models to assess differences in intervention effects using interactions across prespecified subgroups that included sex, age, race, ethnic origin, and glycaemia. Fixed-effects models with the assumption of normally distributed errors[19] were used to assess differences in bodyweight over time between the three groups.

An important issue in assessing any treatment comparison is the amount of missing data. DPP and DPPOS generally have had low rates of missing data. The completion rates (87% of those enrolled) of the microvascular components did not differ among the three treatment groups and missing data were assumed to be

missing at random. The global test[17] used to test the composite microangiopathy outcome is less affected by incomplete ascertainment of one or more of its components than is a traditional collapsed test. All analyses were done with SAS version 9.3.

Role of the funding source

The funder was represented on the study steering committee and played a part in the study design and how the study was done. The funder was not represented in the writing group. All authors had full access to all of the data related to this publication and had final responsibility for the decision to submit for publication.

Results

Of the 3149 surviving members of the three original DPP treatment groups (placebo, metformin, and intensive lifestyle intervention), 2776 (88%) joined DPPOS (figure 1). An additional ten former DPP participants joined DPPOS after the publication of the 10-year report,[8] explaining the discrepancy between the study population in that publication (n=2766) and in the current report (n=2776). The characteristics of the DPPOS cohort at DPP baseline, the end of the DPP, and at the final annual visit of the DPPOS are shown in table 1.

The DPPOS cohort continued to maintain substantial differences in weight loss between the three treatment groups until about 4 years after randomisation (appendix). Subsequently, weight regain in the lifestyle intervention group and sustained long-term weight loss with metformin led to almost identical weight loss in these two groups, compared with the original placebo group, by 5 years after the start of the DPP. Weight in the placebo group fell slightly after the introduction of the group lifestyle intervention during the bridge between DPP and DPPOS and began to fall from DPP levels after 8–9 years of combined follow-up. Adherence to metformin in the metformin group, measured by pill count and defined as taking at least 80% of the pills assigned, was about 70% during DPP and fell to an average of 49% over the entire DPPOS. By DPPOS-end, 33% (258/780) of the placebo and 27% (205/751) of the lifestyle intervention groups were treated with metformin by their health-care providers, almost all in the setting of diabetes development. The mean exposure to metformin, including study and non-study treatment, remained widely separated during the combined DPP and DPPOS, with 10·7 metformin-years in the metformin group, 2·3 metformin-years in the placebo group, and 1·7 metformin-years in the lifestyle intervention group.

Among the 2776 DPPOS participants, 609 developed diabetes during DPP and 941 developed diabetes during DPPOS; 1226 participants did not develop diabetes during the entire study period. Over the entire 15-year study, the average annual incidence was 7%, 5·7%, and 5·2% in the placebo, metformin, and lifestyle intervention groups,

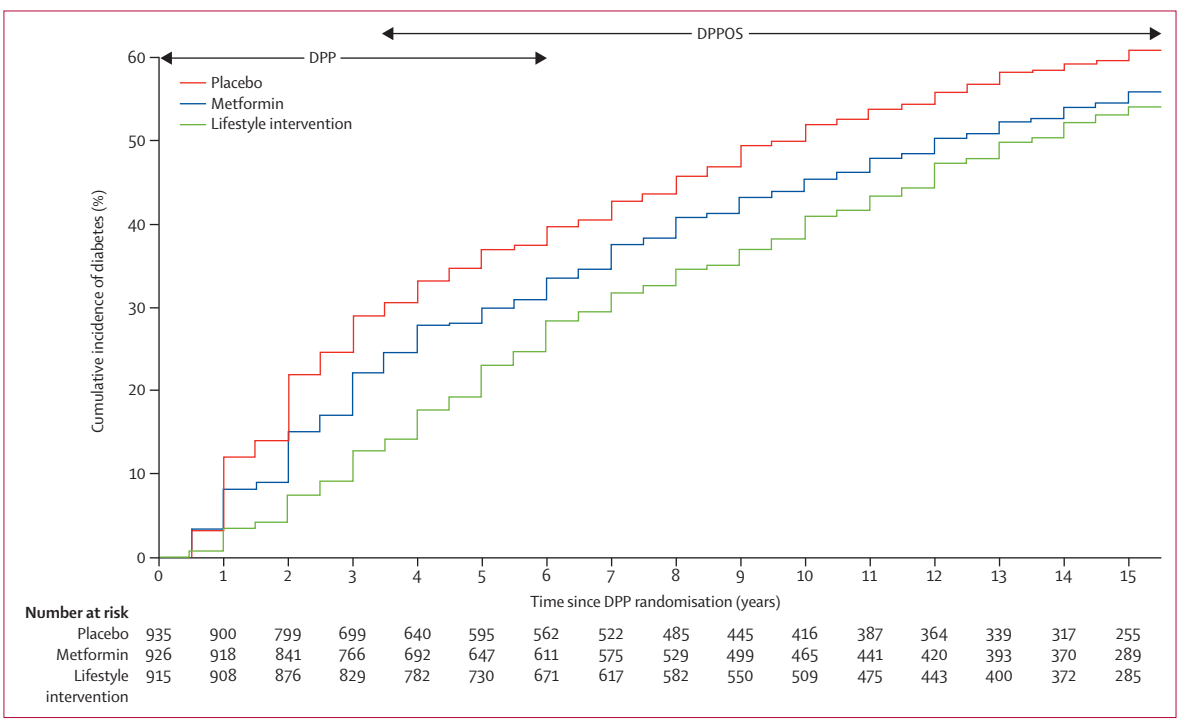

Figure 2: **Cumulative incidence of diabetes by treatment group in the 2776 DPP–DPPOS participants**
The Diabetes Prevention Program (DPP) and DPP Outcomes Study (DPPOS) periods, and the overlap between them, are shown. Over the entire study, the cumulative incidence was 27% lower for the lifestyle group than for the placebo group (p<0·0001) and 18% lower for the metformin group than for the placebo group (p<0·0001). The difference between the lifestyle and metformin groups was not significant (p=0·10).

respectively. Diabetes incidence was significantly lower by 27% in the lifestyle intervention group (hazard ratio 0·73, 95% CI 0·65–0·83) and by 18% in the metformin group (0·82, 0·72–0·93), compared with the placebo group (table 1, figure 2). These reductions are lower than the 58% seen with the lifestyle intervention and 31% with metformin after the first 2·8 years of DPP[4] (58% and 32%, respectively, in the subgroup of the DPP cohort that continued into DPPOS). The reduced differences during DPPOS represent a reduction in the incidence of diabetes in the placebo and metformin groups to about 5% per year, the rate recorded in the lifestyle group, which remained fairly constant during the entire DPP and DPPOS study periods. The number of cases of diabetes and cumulative incidence calculated from the lifetables by year 15 were 560 (62%) in the placebo group, 499 (56%) in the metformin group, and 480 (55%) in the lifestyle group. The diabetes outcome did not include nine people who had a diabetes diagnosis trigger (ie, initial positive test result) without a confirmation visit (because of death or refusal). Including these as diabetes cases in a sensitivity analysis had no effect on the results (data not shown). The mean duration of diabetes in those who developed diabetes was 10·3 years (SD 4·3) in the placebo group, 9·7 years (4·3) in the metformin group, and 8·6 years (4·3) in the lifestyle intervention group (table 1). The incidence rates over time among the three treatment groups were similar for men and women (appendix), with no significant interaction between treatment and sex.

The average prevalence of the microvascular outcomes at the DPPOS-end did not differ significantly among the three treatment groups (figure 3, table 2), despite the group differences in diabetes incidence. The aggregate microvascular outcome prevalence was about 58% higher in men than women (figure 3), and increased with increasing age, but was similar across race and ethnic groups (table 2). The prespecified sex-specific analysis showed a significant sex interaction for lifestyle intervention versus placebo treatment, with a benefit only in women (table 2, figure 3). This sex interaction was not seen with metformin, which did not reduce microvascular disease in either sex (table 2). In women but not in men, lifestyle intervention reduced microvascular disease significantly by 21% (relative risk [RR] 0·79, 95% CI 0·64–0·98) compared with placebo and 22% (RR 0·78, 0·62–0·96) compared with metformin (table 2, figure 3). There were no differences in the treatment effects on aggregate microvascular complications in other prespecified subgroups defined by age, race, and ethnic origin, except that Hispanic Americans had a significantly lower microvascular disease prevalence in the lifestyle intervention group than in the metformin (RR 0·42, 95% CI 0·19–0·90) and placebo groups (RR 0·43, 0·20–0·91; table 2). Participants who did not develop diabetes during DPP and DPPOS had a significant 28% lower (RR 0·72, 95% CI 0·63–0·83; p<0·0001) aggregate microvascular disease prevalence than those who did develop diabetes for all treatment groups combined, with similar patterns in all treatment groups (table 2, figure 3).

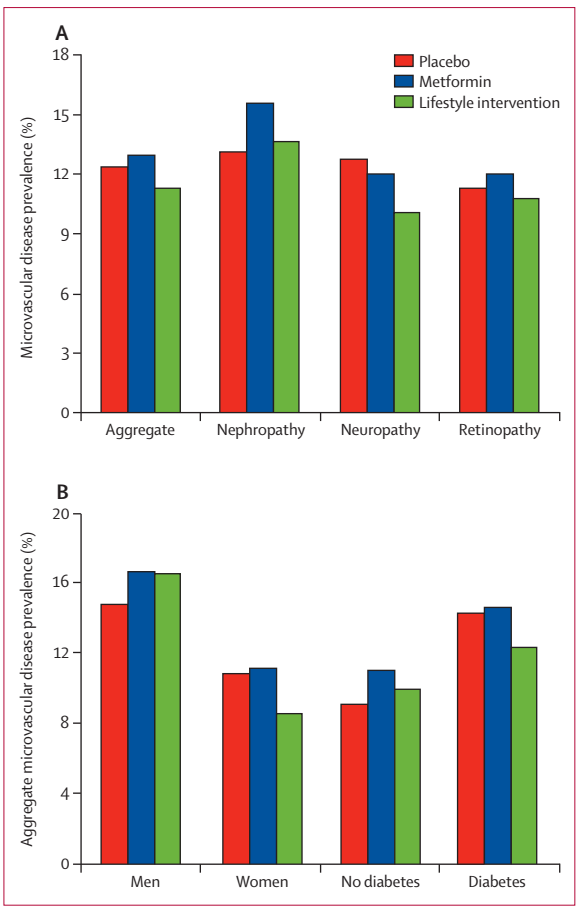

Figure 3: **Prevalence of aggregate microvascular complications and individual microvascular components at DPPOS-end**
(A) All participants. None of the treatment group differences were significant for the aggregate or the microvascular components. The aggregate microvascular complications outcome is expressed as the average prevalence among the three components of nephropathy, retinopathy, and neuropathy. (B) Sex and diabetes subgroups. When assessed by prespecified sex and diabetes status subgroups, prevalence was significantly (p<0·0001) greater in men than in women and was consistent for each of the three treatment groups. In women, the prevalence of the aggregate microvascular outcome was 22% lower in the lifestyle intervention group than in the metformin group (relative risk 0·78, 95% CI 0·62–0·96; p=0·02) and 21% lower in the lifestyle intervention group than in the placebo group (relative risk 0·79, 0·64–0·98; p=0·03). The prevalence of microvascular disease in participants who did not develop diabetes was 28% lower than that in those who developed diabetes in a treatment group-adjusted model (p<0·0001).

Higher concentrations of baseline fasting glucose and HbA_{1c} were associated with higher prevalence of microvascular complications (table 2). During the DPP and DPPOS combined, mean HbA_{1c} concentrations, although significantly different between the placebo group and each of the active intervention groups, were generally low, with mean concentrations of 6·1% in the placebo group, 5·9% in the metformin group, and 6·0% in the lifestyle intervention group. Mean glycaemia was higher in participants who developed diabetes than in

	Pooled RR in subgroups*	Model-based prevalence of aggregate microvascular disease			RR† for aggregate microvascular disease		
		Placebo group	Metformin group	Lifestyle intervention group	Lifestyle intervention group *vs* metformin group	Lifestyle intervention group *vs* placebo group	Metformin group *vs* placebo group
Overall	..	12·4% (11·1–13·8)	13·0% (11·7–14·5)	11·3% (10·1–12·7)	0·87 (0·74–1·02); p=0·08	0·91 (0·78–1·07); p=0·28	1·05 (0·91–1·23); p=0·50
Sex	p<0·0001				p=0·14	p=0·04	p=0·55
Female	1·0	11·0% (9·6–12·6)	11·2% (9·7–12·9)	8·7% (7·4–10·2)	0·78 (0·62–0·96)‡	0·79 (0·64–0·98)‡	1·02 (0·84–1·24)
Male	1·58 (1·38–1·80)‡	15·1% (12·5–18·2)	16·8% (14·3–19·7)	16·6% (14·0–19·7)	0·99 (0·78–1·25)	1·10 (0·86–1·42)	1·11 (0·87–1·43)
Age at randomisation (years)	p<0·0001				p=0·86	p=0·47	p=0·18
25–44	1·0	8·9% (6·8–11·7)	7·7% (5·7–10·5)	6·9% (4·9–9·5)	0·89 (0·57–1·39)	0·77 (0·50–1·18)	0·87 (0·58–1·30)
45–59	1·40 (1·15–1·70)‡	11·8% (10·2–13·7)	11·7% (10·0–13·7)	9·5% (7·9–11·5)	0·82 (0·64–1·04)	0·81 (0·64–1·03)	0·99 (0·80–1·23)
≥60	2·40 (1·94–2·94)‡	16·9% (13·5–21·3)	22·2% (18·8–26·3)	17·1% (13·9–21·1)	0·77 (0·59–1·01)	1·01 (0·74–1·38)	1·31 (0·99–1·74)
Race or ethnic origin§	p<0·0001				p=0·29	p=0·20	p=0·92
White	1·0	13·5% (11·7–15·6)	14·3% (12·4–16·4)	13·0% (11·1–15·1)	0·91 (0·74–1·12)	0·96 (0·78–1·19)	1·06 (0·87–1·29)
African-American	0·85 (0·71–1·0)	12·5% (9·9–15·7)	11·6% (8·8–15·2)	10·2% (7·5–13·9)	0·89 (0·59–1·34)	0·82 (0·56–1·21)	0·93 (0·65–1·33)
Hispanic	0·63 (0·51–0·79)‡	10·5% (7·7–14·2)	10·7% (7·7–14·9)	4·5% (2·2–8·9)	0·42 (0·19–0·90)‡	0·43 (0·20–0·91)‡	1·02 (0·65–1·60)
Asian	0·83 (0·59–1·17)	9·7% (4·7–19·9)	11·8% (6·1–22·6)	11·0% (6·6–18·4)	0·94 (0·41–2·15)	1·14 (0·47–2·78)	1·22 (0·46–3·23)
Baseline BMI (kg/m^2)	p=0·27				p=0·62	p=0·12	p=0·08
22–<30	1·0	10·1% (8·1–12·6)	12·8% (10·6–15·4)	11·7% (9·7–14·2)	0·91 (0·70–1·20)	1·15 (0·86–1·54)	1·26 (0·94–1·69)
30–<35	1·0 (0·85–1·19)	11·1% (8·9–13·8)	13·6% (11·3–16·3)	10·3% (8·2–13·0)	0·76 (0·57–1·02)	0·93 (0·68–1·27)	1·23 (0·92–1·63)
≥35	1·12 (0·96–1·31)	14·9% (12·8–17·3)	12·8% (10·6–15·5)	11·4% (9·2–14·0)	0·89 (0·67–1·17)	0·76 (0·59–0·99)‡	0·86 (0·68–1·10)
Baseline fasting glucose (mmol/L)	p=0·0002				p=0·34	p=0·16	p=0·65
5·3–6·0	1·0	11·7% (10·2–13·4)	11·9% (10·4–13·7)	9·8% (8·4–11·5)	0·82 (0·67–1·01)	0·84 (0·68–1·04)	1·02 (0·84–1·24)
6·1–6·9	1·29 (1·13–1·47)‡	13·5% (11·3–16·1)	15·1% (12·7–18·1)	14·0% (11·6–16·8)	0·92 (0·72–1·19)	1·04 (0·80–1·34)	1·12 (0·87–1·44)
Baseline 2 h glucose (mmol/L)	p=0·42				p=0·86	p=0·93	p=0·74
7·8–8·5	1·0	11·8% (9·7–14·4)	13·2% (10·9–16·1)	10·8% (8·8–13·3)	0·82 (0·62–1·08)	0·92 (0·69–1·22)	1·12 (0·85–1·48)
8·6–9·5	0·97 (0·83–1·14)	11·5% (9·5–14·0)	12·5% (10·3–15·1)	11·0% (9·0–13·5)	0·89 (0·67–1·17)	0·96 (0·72–1·27)	1·08 (0·82–1·42)
9·6–11·0	1·08 (0·92–1·26)	13·6% (11·4–16·2)	13·2% (11·1–15·8)	12·0% (9·7–14·7)	0·91 (0·69–1·19)	0·88 (0·67–1·16)	0·97 (0·76–1·25)
Baseline HbA_{1c} (%)	p<0·0001				p=0·52	p=0·25	p=0·44
3·2–<5·7	1·0	8·3% (6·4–10·7)	9·8% (7·8–12·4)	9 ·8% (7·7–12·6)	1·00 (0·71–1·40)	1·19 (0·83–1·69)	1·19 (0·84–1·67)
5·7–<6·0	1·33 (1·10–1·60)‡	12·2% (9·9–15·2)	14·4% (11·8–17·5)	11·0% (8·7–13·9)	0·77 (0·56–1·04)	0·90 (0·65–1·24)	1·17 (0·87–1·57)
6·0–8·5	1·46 (1·24–1·73)‡	14·7% (12·7–17·0)	14·2% (12·1–16·6)	12·3% (10·4–14·5)	0·86 (0·69–1·09)	0·83 (0·67–1·04)	0·96 (0·78–1·19)
Diabetes at assessment	p<0·0001				p=0·61	p=0·07	p=0·17
Diabetes	1·0	14·4% (12·7–16·4)	14·5% (12·6–16·6)	12·3% (10·5–14·4)	0·85 (0·69–1·04)	0·85 (0·70–1·04)	1·00 (0·83–1·21)
No diabetes	0·72 (0·63–0·83)‡	8·6% (7·0–10·7)	10·9% (9·1–13·0)	10·0% (8·3–12·0)	0·92 (0·71–1·18)	1·16 (0·88–1·54)	1·27 (0·96–1·67)

Data are point estimates (95% CI) of relative risk (RR) and prevalence from general estimating equation models with age, BMI, fasting glucose, 2 h glucose, and HbA_{1c} concentrations analysed as continuous variables. *Since there was no significant heterogeneity among treatment groups based on the interaction term for treatment by subgroup, the RRs among subgroups were assessed using treatment group-adjusted estimates of the aggregate prevalence (the reference group is noted with an RR of 1·0 and p value noted). †RRs were compared across subgroups using an interaction for the treatment effect by subgroup and the resulting p value is listed. ‡p<0·05 for RRs among subgroups and treatment groups. §The number of events among Ameican Indian participants was too small to allow models to be assessed.

Table 2: **Model-based prevalence and relative risk of the aggregate microvascular outcome at the final annual visit of the DPPOS in treatment groups, stratified by baseline DPP characteristics and diabetes status at the time of the microvascular outcomes assessment**

those who had not, and differed by treatment group assignment (table 1). Diabetes duration and mean HbA_{1c} concentrations were associated with retinopathy and nephropathy, but not with neuropathy (figure 4). The aggregate microvascular outcome had a non-linear association with HbA_{1c}, with a suggestion of an inflection point at an HbA_{1c} of about 6·2%. In a post-hoc analysis among participants whose most recent HbA_{1c} measurement was 6·5% or more, representing about 26% (607/2303) of the cohort, the lifestyle intervention group showed significant reductions compared with placebo in the aggregate microvascular outcome (RR 0·59, 95% CI 0·42–0·81; p=0·002), retinopathy (RR 0·61, 0·37–1·01; p=0·05), and neuropathy (0·38, 0·19–0·75; p=0·01) and compared with metformin in the aggregate microvascular outcome (0·58, 0·40–0·82; p=0·002), retinopathy (0·51, 0·30–0·84; p=0·01), and neuropathy (0·39, 0·19–0·79; p=0·01), with no significant differences between the metformin and placebo groups (appendix).

The lifestyle intervention was not associated with an increase in risk for sprains or fractures needing medical attention compared with the placebo or metformin

groups (3·7 events per 100 patient-years in the placebo group, 4·3 events per 100 patient-years in the lifestyle group, and 4·1 events per 100 patient-years in the metformin group). No cases of lactic acidosis were reported in about 40 000 patient-years of follow-up. We noted no significant differences between the three treatment groups in any of the other severe adverse events documented over the course of the study.

Discussion

The results of DPPOS have shown durable effects of the original DPP interventions on the cumulative incidence of diabetes, with the majority of the prevention or delay having occurred during the first 3 years of DPP, but with between-group differences persisting over the subsequent 12 years of follow-up. Despite the difference in diabetes development with the lifestyle and metformin interventions and a significantly lower prevalence of the aggregate microvascular outcome in those who remained free of diabetes compared with those who developed diabetes, we noted no significant differences in the aggregate microvascular outcome between the three treatment groups. We did identify a significant reduction in this outcome with the lifestyle intervention compared with placebo or metformin in a prespecified analysis in women participants.

The similar annual incidence of diabetes among the three treatment groups during DPPOS, with the original metformin and placebo groups achieving similar rates to the lifestyle intervention group, suggests that offering the group lifestyle intervention to all of the participants was effective in reducing the further development of diabetes. An alternative explanation is that the most susceptible subset of patients at risk for developing diabetes did so during DPP, leaving only a smaller fraction at risk during DPPOS.[20] Despite the reduction in relative efficacy of the interventions over time, the long-term reduction in diabetes development remains substantial.

The ultimate benefits of prevention or delay of diabetes, or of earlier intervention during the course of dysglycaemia, include potential reduction of the development of long-term complications, which cause major morbidity and mortality and contribute the largest proportion of total diabetes costs.[21] Our results do not show a difference between the three groups in the prevalence of aggregate microvascular outcome in the total cohort 15 years after randomisation. However, men had a substantially higher prevalence of microvascular complications than women, and in women the lifestyle intervention was associated with a 21% reduction in microvascular outcomes compared with placebo. These sex-specific findings, for which we have no explanation, are of great interest. Results of some,[22,23] but not all,[24] previous studies in type 1 and type 2 diabetes have shown sex differences in the incidence or prevalence of diabetic nephropathy or retinopathy. The Look AHEAD clinical trial used a lifestyle intervention based on the DPP lifestyle progamme, but in adults with type 2 diabetes. It identified sex effects and interactions for nephropathy, similar to the DPPOS results, with a treatment benefit seen only in women.[23]

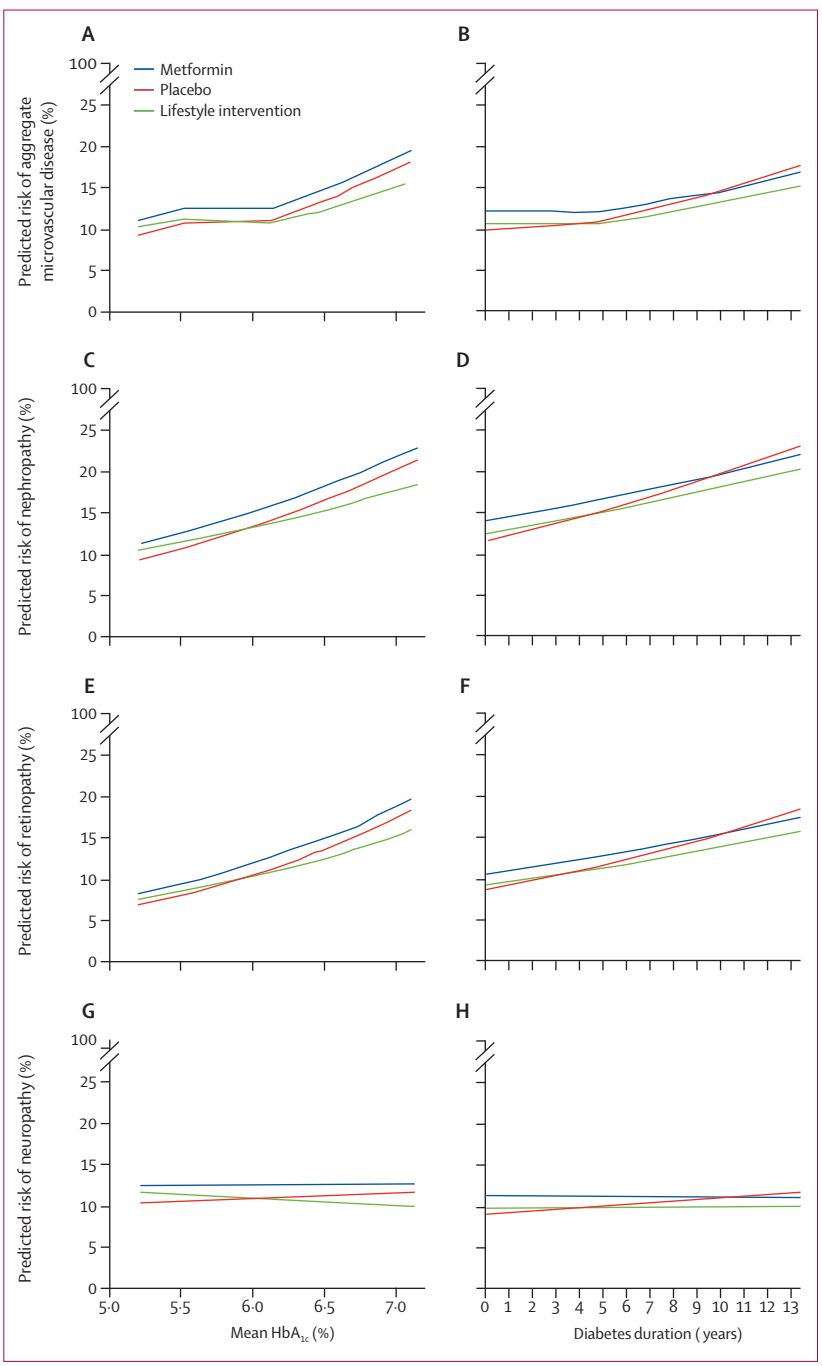

Figure 4: **Role of HbA_{1c} and diabetes duration on microvascular disease and its components**
Separate general estimating equation models were used and included two interaction terms for treatment group by glycaemia measure and microvascular component by glycaemia measure. The interactions of HbA_{1c} with the individual microvascular components were significantly different (p<0.0001). HbA_{1c} (A, C, E, G) was associated with nephropathy and retinopathy (both p<0·0001), but not neuropathy (p=0·69). The interactions of diabetes duration also differed (p=0·01) in the microvascular components (B, D, F, H), with longer diabetes duration associated with nephropathy and retinopathy (both p<0·0001), but not with neuropathy (p=0·57).

Also notable is the 28% lower prevalence of the aggregate microvascular outcome in participants who did not develop diabetes compared with those who did. The absence of an effect of the active treatments on the microvascular outcome in the total cohort, even though diabetes development was significantly reduced, might be because of low study power, the sex disparity in the effects, or the small differences in HbA_{1c} concentrations among the three treatment groups.

The prevalence of individual microvascular complications was related (retinopathy and nephropathy) or unrelated (neuropathy) to the extent of hyperglycaemia present in our population, with the aggregate microvascular complications more strongly related to glycaemia in participants with an HbA_{1c} concentration of 6·5% and above than in those with an HbA_{1c} concentration of less than 6·5%. Notably, in the post-hoc analysis of the cohort based on this HbA_{1c} threshold, participants with an HbA_{1c} concentration of 6·5% and above had significantly reduced microvascular disease when treated with the lifestyle intervention (appendix), consistent with the differences in aggregate microvascular complications by diabetes status in year 15.

The strong relation between duration of diabetes and HbA_{1c} concentrations with the prevalence of complications in this study and in others[25] suggests that further follow-up could show a differential effect of the original DPP interventions on complications. In the Da Qing study,[26] benefits of lifestyle interventions on diabetes prevention, retinopathy, and cardiovascular and all-cause mortality were seen after 23 years of follow-up, with the mortality benefits seen only in women.

Benefits of the lifestyle intervention and metformin in the DPPOS cohort, in addition to the prevention or delay of diabetes, include a reduction in cardiovascular disease risk factors[27] and metabolic syndrome,[28] reduced prevalence of lower urinary tract symptoms associated with obesity and diabetes,[29] and improved quality of life.[30] An economic analysis after 10 years, accounting for all out-of-study medical costs and the costs of the interventions, revealed that metformin was cost-saving and lifestyle intervention was cost-effective.[31] Longer-term follow-up of the DPP–DPPOS cohort is planned and should help to elucidate the effects of the interventions on cardiovascular disease and mortality, and provide a more complete assessment of the economic effect of diabetes prevention.

Although the DPPOS had many strengths, including a highly engaged cohort and consistent follow-up with standardised interventions and complete data collection, it also had some limitations. These limitations included the therapeutic crossover through the offering of lifestyle change instruction to all three groups during the 1-year bridge period at the end of DPP. This design feature might have reduced the relative effects of our intervention on both diabetes and microvascular disease. Moreover, the application of the lifestyle intervention after the first 24 weeks of DPP and during DPPOS was less intensive, probably contributing to the weight regain in that group. The use of metformin by participants in the DPP lifestyle intervention and placebo groups might have diminished the relative effects of metformin; however, the difference in metformin exposure between the original metformin group and the other two groups remained substantial. These factors might have reduced the size of putative microvascular benefits in the three original treatment groups.

Another limitation could be the combination of three different microvascular outcomes in the aggregate outcome, two of which are objective measurements and masked and one of which, neuropathy measured by monofilament, is more subjective and relatively insensitive for early neuropathy. The combination of these outcomes to improve study power was based on their being in the same pathogenic stream for diabetes complications. Finally, the generalisability of the findings of any clinical trial, with selected populations and protocol-driven interventions often implemented in academic clinical centres, could be questioned. However, the DPP protocol has been translated successfully into numerous settings[7] and for the first time in several decades the annual incidence of diabetes in the USA has begun to fall,[32] suggesting that the DPP findings are generalisable.

The results of the DPPOS have shown very long-term effects of lifestyle intervention and metformin to reduce the incidence of diabetes in a population at very high risk. However, most participants in each treatment group developed diabetes 15 years after enrolment. Therefore, interventions with greater long-term efficacy for diabetes prevention are still needed. The two interventions assessed did not reduce the prevalence of aggregate microvascular complications compared with placebo after a total of 15 years of follow-up in the total cohort, although there was a significant 21–22% reduction with the lifestyle intervention compared with placebo and metformin in women. Participants who did not develop diabetes had a 28% lower prevalence of the aggregate microvascular complications outcome compared with participants who did. This result supports the importance of diabetes prevention.

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Contributors

The entire Diabetes Prevention Program Research Group, including the members of the writing group, designed and approved the study. DMN, SLE, and MT prepared the initial draft of the manuscript. The other members of the writing group provided critical revisions and all members of the writing group approved the final manuscript.

Declaration of interests

We declare no competing interests.

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