Effect of Metformin and Lifestyle Interventions on Mortality in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study

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OBJECTIVE

To determine whether metformin or lifestyle modification can lower rates of all-cause and cause-specific mortality in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study.

RESEARCH DESIGN AND METHODS

From 1996 to 1999, 3,234 adults at high risk for type 2 diabetes were randomized to an intensive lifestyle intervention, masked metformin, or placebo. Placebo and lifestyle interventions stopped in 2001, and a modified lifestyle program was offered to everyone, but unmasked study metformin continued in those originally randomized. Causes of deaths through 31 December 2018 were adjudicated by blinded reviews. All-cause and cause-specific mortality hazard ratios (HRs) were estimated from Cox proportional hazards regression models and Fine-Gray models, respectively.

RESULTS

Over a median of 21 years (interquartile range 20–21), 453 participants died. Cancer was the leading cause of death (*n* = 170), followed by cardiovascular disease (*n* = 131). Compared with placebo, metformin did not influence mortality from all causes (HR 0.99 [95% CI 0.79, 1.25]), cancer (HR 1.04 [95% CI 0.72, 1.52]), or cardiovascular disease (HR 1.08 [95% CI 0.70, 1.66]). Similarly, lifestyle modification did not impact all-cause (HR 1.02 [95% CI 0.81, 1.28]), cancer (HR 1.07 [95% CI 0.74, 1.55]), or cardiovascular disease (HR 1.18 [95% CI 0.77, 1.81]) mortality. Analyses adjusted for diabetes status and duration, BMI, cumulative glycemic exposure, and cardiovascular risks yielded results similar to those for all-cause mortality.

CONCLUSIONS

Cancer was the leading cause of mortality among adults at high risk for type 2 diabetes. Although metformin and lifestyle modification prevented diabetes, neither strategy reduced all-cause, cancer, or cardiovascular mortality rates.

Adults with prediabetes are at a higher risk for all-cause, cardiovascular, and cancer mortality (1–3). While metformin and lifestyle interventions to achieve weight loss

and increase physical activity have been shown to lower the risk of type 2 diabetes in adults with impaired glucose tolerance (4), limited data from randomized clinical trials exist on whether these interventions can reduce mortality rates.

Both metformin and lifestyle interventions have evidence for life span and health span extension in animal models, potentially through nutrient-sensing and stress-response pathways (5). In addition, numerous observational studies suggest that metformin may lower the risk of all-cause, cardiovascular, and cancer mortality among populations with type 2 diabetes (6–14). There are also observational studies that suggest that self-reported intentional weight loss in people with overweight and obesity is associated with lower mortality rates (15–17). However, evidence for mortality benefits of metformin and lifestyle modification from clinical trials is more limited.

The UK Prospective Diabetes Study (UKPDS) is a clinical trial of adults with newly diagnosed diabetes that demonstrated the efficacy of metformin in lowering the risk of all-cause mortality compared with conventional control or intensive control with chlorpropamide, glibenclamide, or insulin (18). However, no trial has evaluated the effect of metformin on all-cause or cause-specific mortality in a population of adults at high risk for developing type 2 diabetes. A meta-analysis of randomized behavioral weight loss trials in adults with obesity concluded that weight loss is associated with a lower risk of all-cause mortality, but many of the trials were of limited duration (19). In the Da Qing Diabetes Prevention Outcome Study, a randomized controlled trial of lifestyle interventions administered over 6 years to Chinese adults with impaired glucose tolerance and a mean baseline BMI of 26 kg/m^2, all-cause and cardiovascular mortality rates were reduced after 20–30 years' follow-up (20,21). However, it is unknown whether these findings will be replicated in the Diabetes Prevention Program (DPP) study population with higher mean age and BMI at baseline after 21 years' follow-up. Impaired glucose tolerance is associated with a higher risk of cancer and cancer deaths, the second leading cause of mortality in the U.S (3,22). No trials exist, however, to evaluate the efficacy of lifestyle modification in lowering the risk of cancer mortality among adults with impaired glucose tolerance.

DPP was designed to evaluate the efficacy of metformin and intensive lifestyle interventions to prevent diabetes, and the long-term follow-up of enrolled DPP participants in the Diabetes Prevention Program Outcomes Study (DPPOS) focused on their effects on development of microvascular complications, cancer, and cardiovascular disease. Because obesity and diabetes increase the risk for all-cause, cancer, and cardiovascular disease mortality (23,24), and because metformin and lifestyle interventions were effective in lowering weight and preventing diabetes in the DPP (4), we hypothesized that metformin and lifestyle modification may also lower the risk for all-cause, cancer, and cardiovascular disease mortality. While mortality was not a primary outcome in DPP or DPPOS, mortality was assessed with rigorous adjudication of causes to account for the competing risk of deaths on key outcomes measured in DPPOS. Therefore, these high-quality mortality data, the long duration of the metformin intervention, and the long follow-up period in DPPOS provide a unique opportunity to conduct a secondary data analysis to evaluate the effects of metformin and intensive lifestyle modification interventions on all-cause and cause-specific mortality in a population of adults at high risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Population

From 1996 to 1999, 3,234 adults ages ≥25 years were enrolled in DPP at 27 clinical sites in the U.S. Written informed consent was obtained from all participants before screening, consistent with the Declaration of Helsinki and the guidelines of each center's institutional review board. For inclusion of a study population at high risk for developing type 2 diabetes, inclusion criteria included a BMI ≥24 kg/m^2 (≥22 kg/m^2 for Asian Americans), fasting plasma glucose 95–125 mg/dL (≤125 mg/dL for American Indians), and 2-h glucose 140–199 mg/dL after a 75-g oral glucose load. Key exclusions were significant cardiovascular or renal disease, cancer requiring treatment in the past 5 years (except cancer considered cured or associated with a good prognosis, such as nonmelanoma skin cancer, papillary thyroid carcinoma, and cervical carcinoma in situ), hepatitis, and other medical conditions likely to limit life span or increase the risk of the interventions, as previously described (25).

Study Design and Interventions

Participants were randomized to one of three groups: an intensive lifestyle intervention (lifestyle) focused on achieving at least 150 min physical activity weekly and ≥7% body weight loss, metformin 850 mg twice daily with standard diet and exercise recommendations, or a placebo twice daily with standard diet and exercise recommendations, as previously described (Consolidated Standards of Reporting Trials [CONSORT] diagram [Supplementary Fig. 1]) (26). The masked intervention phase of the study was stopped on 1 July 2001 when efficacy for the primary outcome of diabetes prevention was achieved. In 2002, after a bridge period during which all participants received a modified group lifestyle intervention, 2,779 participants continued in DPPOS and were offered quarterly lifestyle sessions. Those originally randomized to lifestyle were offered additional lifestyle reinforcement semiannually, and those randomized to metformin continued to receive open-label metformin 850 mg twice daily. Study metformin and instructions to take it were provided if participants did not develop a contraindication to the study drug, until plasma glucose worsened to ≥140 mg/dL in the DPP, or when hemoglobin A_{1c} (HbA_{1c}) was ≥7% during the DPPOS, at which time study metformin was discontinued and diabetes management was transferred to the participant's health care provider. Participants were instructed to bring any unused study metformin to study visits for pill counts to track adherence, as previously described (27).

Outcomes

The primary outcome of all-cause mortality was ascertained for all participants enrolled in DPP through regular surveillance of the study population at annual

visits and two National Death Index (NDI) searches through 31 December 2018. No deaths were counted after that date, and anyone not known to be deceased or found in the NDI search by that closing date was considered to be alive. An adjudication committee that was blinded to treatment assignment used medical records, death certificates, and NDI cause of death codes to assign the underlying cause of death for the secondary outcomes of cause-specific mortality. Participants had previously signed medical release forms allowing for the acquisition of their medical records. Categories of cause-specific mortality for this manuscript comprise cardiovascular disease, cancer, and other causes. Demographics, medical history, and lifestyle factors were assessed via questionnaire; standardized exams that included weight, height, and blood pressure; and laboratory specimens from fasting subjects that were assayed for glucose, lipids, and HbA_{1c}, as previously described (26). In addition, all participants were instructed to bring medications (lists, prescriptions, and containers) to their annual study visit for an inventory of concomitant medications taken within the prior 2 weeks, on the basis of which use of antihypertensive medications, lipid-lowering agents, and out-of-study metformin use was assessed.

Statistical Analysis

Hazard ratios (HRs) for all-cause mortality associated with metformin and lifestyle compared with placebo were estimated from Cox proportional hazards regression models with adjustments for baseline age, race/ethnicity, and sex, and the assumption of proportional hazards was confirmed. Time-to-event Fine-Gray models accounting for the competing risk of other causes of mortality were used to determine the risk for cause-specific mortality associated with metformin and lifestyle compared with placebo with adjustments for baseline age, race/ethnicity, and sex for causes with $\geq$50 deaths. Differences in the effects of the DPP randomized interventions on mortality in prespecified subgroups were explored by testing of interactions by age, sex, race/ethnicity, and BMI in these models without adjustment for multiplicity, and *P* values $<$0.05 were considered statistically significant. Sensitivity analyses using alternative models were performed to account for potential factors that may have affected the effects of treatment: *1*) multivariable models to account for time-varying characteristics collecting during follow-up (including diabetes status and duration, BMI, glycemic exposure, and cardiovascular risk factors), since these covariates are influenced by DPP interventions and are risk factors for mortality; *2*) multivariable models to account for drop-in use of out-of-study metformin in the three arms of DPP with adjustment for time-varying, out-of-study metformin use in the above time-to-event Fine-Gray models; and *3*) marginal structural models with truncated inverse probability stability weights to estimate the etiologic effect of metformin use on all-cause mortality in the presence of out-of-study metformin and discontinuation of and adherence to randomized metformin (28). All statistical analyses were performed with SAS 9.4 and R 3.5.2.

Data and Resource Availability

In accordance with the National Institutes of Health (NIH) Public Access Policy, we continue to provide all manuscripts to PubMed Central including this manuscript. DPP/DPPOS has provided the protocols and lifestyle and medication intervention manuals to the public through its public website (https://www.dppos.org). The DPPOS abides by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) data sharing policy and implementation guidance as required by the NIH/NIDDK (https://www.niddkrepository.org/studies/dppos/).

RESULTS

The study population enrolled in the DPP had a mean ± SD age of 50.6 ± 10.7 years and BMI 34.0 ± 6.7 kg/m^2, 68% were female, and 55% were non-Hispanic White. With regard to other cardiovascular risk factors at baseline, 41% were former or current smokers, 29% had hypertension or were treated for hypertension, and 69% had hyperlipidemia or were on treatment with lipid-lowering medications. There were no significant differences in baseline demographic or clinical characteristics across the three randomized groups (Table 1). However, by 31 December 2018, there were differences in the prevalence of diabetes in the metformin (55%), lifestyle (53%), and placebo (60%) groups (*P* = 0.003).

Over a median follow-up of 21 years (interquartile range 20–21), 453 (14%) of the 3,234 participants died. The cause of death was unknown in 7% due to missing records or other documentation needed for accurate adjudication of the cause. Cancer was the most common cause of death (37%), followed by cardiovascular disease (29%). The fractions of deaths from chronic respiratory diseases, infection, neurologic disease, renal disease, trauma, and other causes were all $<$10% (Table 2).

Mortality rates were similar across groups randomized to metformin (7.1 deaths/1,000 person-years), lifestyle (7.4 deaths/1,000 person-years), and placebo (6.6 deaths/1,000 person-years (Fig. 1). There was no difference between metformin and placebo groups in the risk of all-cause (HR 0.99 [95% CI 0.79, 1.25]), cardiovascular (HR 1.08 [95% CI 0.70], 1.66), cancer (HR 1.04, [95% CI 0.72, 1.52]), or other (HR 0.94 [95% CI 0.64, 1.38]) mortality (Table 3). There was also no difference between lifestyle and placebo groups in the risk of all-cause (HR 1.02 [95% CI 0.81, 1.28]), cardiovascular (HR 1.18 [95% CI 0.77, 1.81]), cancer (HR 1.07 [95% CI 0.74, 1.55]) or other (HR 0.85 [95% CI 0.58, 1.26]) mortality (Table 3).

The risks of all-cause mortality associated with metformin or lifestyle compared with placebo did not differ by age, sex, race/ethnicity, or BMI (Supplementary Table 1). In sensitivity analyses with adjustment for time-varying out-of-study metformin use in all three randomized groups, the risk of all-cause mortality associated with metformin compared with placebo remained unchanged (HR 0.97 [95% CI 0.77, 1.23] [Supplementary Table 2]). Multivariable models exploring the potential mediating effects of diabetes status and duration, changes in BMI, cumulative glycemic exposure, and cardiovascular risk factors also did not materially change the risk for all-cause mortality associated with lifestyle or metformin compared with placebo (Supplementary Table 2). With use of a marginal structural model to account for metformin

Table 1—Baseline characteristics of participants by DPP randomized groups

Characteristic	Total (*n* = 3,234)	Placebo (*n* = 1,082)	Metformin (*n* = 1,073)	Lifestyle (*n* = 1,079)
Age (years)	50.6 ± 10.7	50.3 ± 10.4	50.9 ± 10.3	50.6 ± 11.3
Women	2,191 (68)	747 (69)	710 (66)	734 (68)
Race/ethnicity				
White	1,768 (55)	586 (54)	602 (56)	580 (54)
African American	645 (20)	220 (20)	221 (21)	204 (19)
Hispanic	508 (16)	168 (16)	162 (15)	178 (16)
American Indian	171 (5)	59 (6)	52 (5)	60 (6)
Asian American	142 (4)	49 (4)	36 (3)	57 (5)
Education				
Primary	130 (4)	51 (5)	36 (3)	43 (4)
High school	704 (22)	234 (22)	233 (22)	237 (22)
College	1,556 (48)	520 (48)	514 (48)	522 (48)
Graduate school	844 (26)	277 (26)	290 (27)	277 (26)
Income >$50,000	1,328 (41)	429 (40)	463 (43)	436 (40)
Smoking				
Never	1,897 (59)	635 (59)	634 (59)	628 (58)
Former	1,111 (34)	363 (34)	367 (34)	381 (35)
Current	226 (7)	84 (8)	72 (7)	70 (7)
Weekly alcohol use				
<1 drink	2,380 (75)	796 (75)	784 (74)	800 (76)
1–7 drinks	647 (20)	224 (21)	220 (21)	203 (19)
>7 drinks	148 (5)	44 (4)	53 (5)	51 (5)
BMI (kg/m^2)	34.0 ± 6.7	34.1 ± 6.7	33.9 ± 6.6	33.9 ± 6.8
Hypertension*	925 (29)	301 (28)	312 (29)	312 (29)
Hyperlipidemia†	2,244 (69)	769 (71)	741 (70)	734 (68)
Fasting glucose (mg/dL)	106.5 ± 8.3	106.7 ± 8.4	106.5 ± 8.5	106.3 ± 8.1
HbA_{1c} (%)	5.9 ± 0.5	5.9 ± 0.5	5.9 ± 0.5	5.9 ± 0.5
HbA_{1c} (mmol/mol)	41.0 ± 5.5	41.0 ± 5.5	41.0 ± 5.5	41.0 ± 5.5

Baseline characteristics are described as means ± SD or *n* (%) as appropriate. *Hypertension is defined as blood pressure of at least 140/90 mmHg or use of antihypertensive medications. †Hyperlipidemia is defined as LDL cholesterol ≥130 mg/dL, triglyceride ≥150 mg/dL, or lipid-lowering medications.

discontinuation and adherence and use of out-of-study metformin due to diabetes development and HbA_{1c}, the estimated risk of all-cause mortality associated with randomized metformin compared with placebo appeared lower, but the conclusion remained unchanged (HR 0.78 [95% CI 0.55, 1.11]).

Table 2—Adjudicated causes of death by DPP randomized groups

Cause of death	Total	Placebo	Metformin	Lifestyle
Cancer	170 (37)	53 (37)	57 (37)	60 (38)
Cardiovascular disease	131 (29)	38 (27)	44 (29)	49 (31)
Neurologic (nonstroke)	36 (8)	12 (8)	12 (8)	12 (8)
Unknown	32 (7)	14 (10)	7 (5)	11 (7)
Infection	25 (5)	8 (6)	11 (7)	6 (4)
Other*	22 (5)	5 (3)	10 (7)	7 (4)
Trauma	20 (4)	8 (6)	6 (4)	6 (4)
Chronic respiratory disease	9 (2)	3 (2)	3 (2)	3 (2)
Renal disease	8 (2)	2 (1)	2 (1)	4 (3)
Total	453	143	152	158

Data are *n* or *n* (%). *Other causes of death include cardiac arrest, multiorgan failure, hepatic failure, suicide, acute pancreatitis, myelofibrosis, upper gastrointestinal bleed, or ventriculitis.

CONCLUSIONS

Among DPP participants at high risk for type 2 diabetes at study entry, all-cause mortality did not differ for those randomized to metformin or lifestyle compared with placebo over a median observation time of 21 years. Although metformin and lifestyle were associated with reductions in several risk factors for cardiovascular disease (29,30), these interventions did not lower cardiovascular mortality compared with placebo. Cancer was the leading cause of death in this study population, but neither metformin nor lifestyle reduced the risk of cancer mortality compared with placebo.

To our knowledge there has been a paucity of epidemiologic data on cause-specific mortality in people with prediabetes in the U.S. Prior reports of cause-

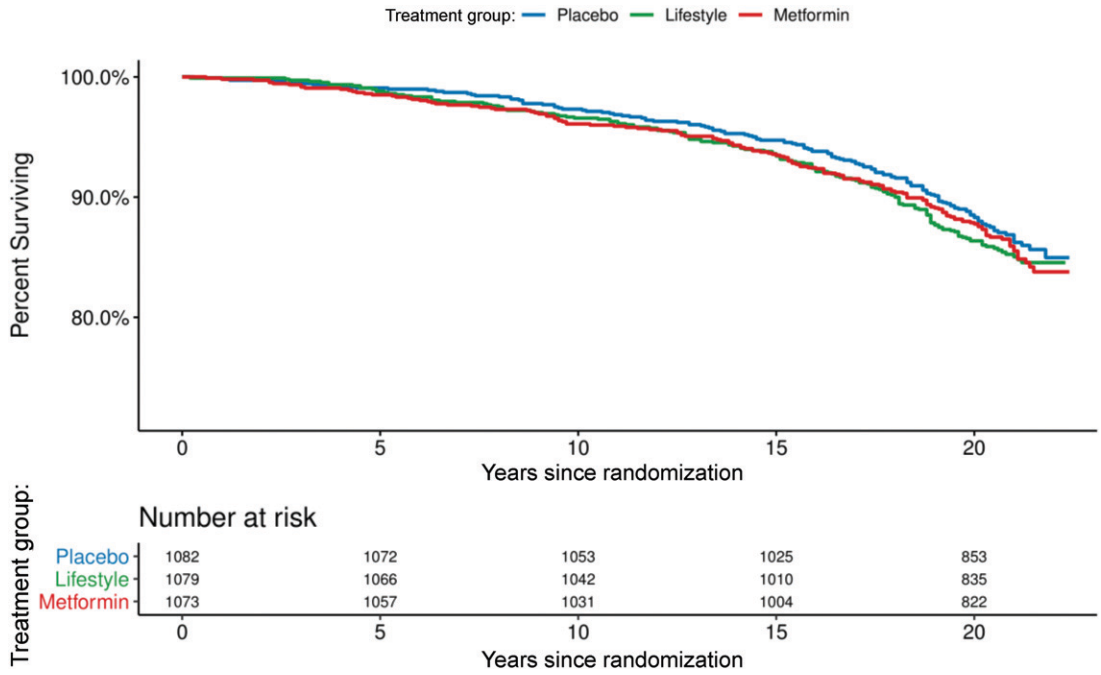

Figure 1—Kaplan-Meier survival curves for metformin, lifestyle, and placebo groups. The figure shows the survival by randomization to metformin, lifestyle, and placebo.

specific mortality among people with diabetes in the U.S. have described cardiovascular disease as the leading cause of death, albeit declining over time (31,32). This may be due to improved cardiovascular risk factor control among people with and without diabetes in the U.S. between 1988 and 2014 (33). A recent publication found that a decline in vascular disease death rates has now resulted in a predominance of deaths due to cancer among individuals with diabetes in England (34). Our finding of cancer being the leading cause of death in this study population of prediabetes is consistent with this and the Centers for Disease Control and Prevention reports of malignant neoplasms being the leading cause of death for U.S. adults age 45–64 years (35).

This trial is unique in its ability to examine the effect of metformin on all-cause and cause-specific mortality in a study population at high risk for type 2 diabetes. While metformin lessened major risk factors for mortality by lowering weight and reducing the risk of diabetes in DPP and longer follow-up in DPPOS (4,36), it did not reduce the risk of all-cause mortality or deaths due to cancer and cardiovascular disease. Throughout DPP and DPPOS, study participants who developed diabetes in all randomized groups were frequently prescribed metformin as first-line therapy for type 2 diabetes by their health care providers. It is possible that the ability to detect an effect of randomization to metformin was hampered by crossover use of metformin in the other groups or by residual confounding due to unmeasured factors introduced during follow-up. Nevertheless, sensitivity analyses to account for out-of-study metformin use, discontinuation of study metformin, and confounding related to metformin treatment and randomization over time did not show any material difference in the risk for all-cause mortality.

Numerous observational studies have suggested that metformin may help lower the risk of all-cause, cardiovascular, and cancer mortality in patients with type 2 diabetes (6–14). Past observational findings may differ from our results due to potential confounding by indication with patients on metformin being healthier than comparison groups treated with other antidiabetes medications for more advanced diabetes or

Table 3—Rates and risk for all-cause and cause-specific mortality associated with metformin and lifestyle compared with placebo

	Number of events			Event rate/1,000 person-years			Metformin versus placebo		Lifestyle versus placebo	
Causes of death	Placebo	Metformin	Lifestyle	Placebo	Metformin	Lifestyle	HR (95% CI)*	*P*	HR (95% CI)*	*P*
All cause	143	152	158	6.59	7.13	7.37	0.99 (0.79, 1.25)	0.95	1.02 (0.81, 1.28)	0.87
Cancer	53	57	60	2.45	2.67	2.80	1.04 (0.72, 1.52)	0.83	1.07 (0.74, 1.55)	0.71
CVD	38	44	49	1.75	2.06	2.28	1.08 (0.70, 1.66)	0.74	1.18 (0.77, 1.81)	0.44
Other	52	51	49	2.40	2.39	2.28	0.94 (0.64, 1.38)	0.74	0.85 (0.58, 1.26)	0.43

*HRs associated with metformin or lifestyle compared with placebo are adjusted for age, race/ethnicity, and sex in Cox proportional hazards models for all-cause mortality and in Fine-Gray models accounting for competing risk of other deaths for cause-specific mortality.

because of a contraindication to metformin, such as severe renal impairment. Although the observational studies attempted to account for confounding by indication and other biases, there still could also be residual confounding by diabetes duration, severity, and complications since patients on metformin may not have progressed further in their disease to require medication change or intensification. Nevertheless, the findings in this study also differ from more definitive evidence from UKPDS showing the lower risk of all-cause mortality with metformin in participants with new-onset type 2 diabetes (18). In both the observational studies and in UKPDS, the ability to detect an effect of metformin on mortality may have been stronger given a higher underlying mortality risk in the population of adults potentially due to preexisting cardiovascular disease or cancer, which were exclusion criterion at DPP enrollment. For example, crude cancer mortality rates reported among adults with prediabetes enrolled in European observational cohorts (4.64 per 1,000 person-years) were much higher than those in the placebo arm of DPPOS (2.40 per 1,000 person-years), though it is difficult to compare, since mortality rates are not age or sex standardized and most of the European cohorts had a higher mean age and greater proportion of males than our study population (3). Albeit not age or sex standardized, mortality rates were certainly higher in metformin-treated participants in UKPDS after 10.7 years (13.5 per 1,000 person-years) than in those in DPPOS after 21 years (7.13 per 1,000 person-years). It is also possible that the greater glycemic difference that was attained with metformin use in the study population of newly diagnosed diabetes enrolled in the UKPDS explains the survival benefit, whereas in DPPOS, baseline dysglycemia was lower and the reduction in HbA_{1c} achieved with metformin was much less (29). Nevertheless, in this study population of adults at risk for developing type 2 diabetes, metformin does not appear to lower mortality rates.

Obesity and diabetes are conditions that confer a higher risk of all-cause, cardiovascular, and cancer mortality (23,24). Although the lifestyle intervention was more efficacious in decreasing the incidence of diabetes and reducing body weight than placebo or metformin in DPP, it did not result in a lower risk of all-cause, cardiovascular, or cancer mortality for adults at high risk of type 2 diabetes. These findings are similar to reports from the Finnish Diabetes Prevention Study despite the longer median follow-up time in DPPOS (21 vs. 10.6 years) and higher total mortality rate in the DPP lifestyle (7.37/1,000 person-years) and placebo (6.59/1,000 person-years) groups compared with the Finnish Diabetes Prevention Study lifestyle (2.2/1,000 person-years) and control (3.8/1,000 person-years) arms (37). However, these findings differ from mortality outcomes published in two other lifestyle intervention trials. The Malmö Preventive Project found a lower risk of all-cause mortality (relative risk 0.45 [95% CI 0.23, 0.85]) for men with impaired glucose tolerance receiving a prevention program of dietary therapy and physical exercise compared with a standard care control group (38). The variance in results between this study and ours may be due to the longer duration of the lifestyle intervention (6 years) and higher-risk study population (males only) in the Malmö Preventive Project, but it may also be due to the fact that the Malmö Preventive Project was not a randomized study, had participants in the control group who were excluded from the intervention group due to contraindications, and could not control for differences in intensity, quality of care, and cardiovascular disease risk factor management between the intervention and control groups during this pragmatic trial. Regardless, the Da Qing Diabetes Prevention Outcome Study was a randomized clinical trial that reported significant reductions in the risk of all-cause and cardiovascular disease mortality in adults with impaired glucose tolerance associated with their lifestyle intervention at 23 and 30 years' follow-up (20,21). While the study population enrolled in the Da Qing Diabetes Prevention Outcome Study was younger at baseline with a lower mean BMI compared with the study population enrolled in DPP, they had other risk factors at baseline that may have contributed to mortality, such as a higher proportion of current smokers and higher mean fasting plasma glucose and systolic and diastolic blood pressure (39). In fact, incident diabetes (for diet and exercise: 96 cases of diabetes per 1,000 person-years at 6-year follow-up) and the mortality rate (intervention group: 14.3 deaths per 1,000 person-years at 23-year follow-up) were much higher in the Da Qing Diabetes Prevention Outcome Study than in DPPOS (lifestyle: 59 cases of diabetes per 1,000 person-years at 10-year follow-up and 7.37 deaths per 1,000 person-years at 20-year follow-up). It is also possible that the underlying pathophysiology contributing to mortality in those with impaired glucose tolerance is different in Asians and that diet and exercise changes are more effective in targeting that defect for Asians. The point estimate from subgroup analysis in our study indicates a 32% lower mortality rate with lifestyle in Asian Americans (Supplementary Table 1), but the very wide CI around this estimate includes the null value and reflects the small sample size and number of deaths in this subgroup.

There are several notable strengths to this study. This current trial has an extended follow-up of participants over a long duration with rigorous adjudication of cause-specific mortality from death certificates, medical records, and NDI cause of death codes. Follow-up for mortality was censored at a fixed closing date (31 December 2018) when ascertainment of vital status was complete, as previously recommended (40). This approach avoids potential biases inherent in other censoring schemes, such as censoring each person's follow-up at last encounter or death date after a fixed closing date.

There are also several limitations to note. While this trial has one of the longest metformin interventions in a population at high risk for type 2 diabetes, the drop-in use of provider-prescribed metformin in all randomized groups when participants developed diabetes may not have been fully controlled for in our sensitivity analyses. Furthermore, there may have been effects of the ethically justified modification of the protocol to offer lifestyle sessions to all participants at the end of DPP. There were also differences in weight, incident diabetes, diabetes duration, and cardiovascular risks over time between the randomized groups, reflecting the positive intervention effects. Multivariable adjustment was performed to account for these differences with no material

changes in the findings. The enrolled DPP study population had to meet strict inclusion and exclusion criteria to ensure safety of the trial interventions, so this was a fairly healthy population at enrollment and results may not generalize to sicker study populations with significant cardiovascular disease, active cancer, or other conditions that would limit their immediate life span. Our healthier study population may account for why this study had much lower mortality rates than other studies of metformin use in populations with type 2 diabetes and lifestyle modification in other populations with impaired glucose tolerance. In addition, secular changes in health care demonstrating improved cardiovascular risk factor control during the majority of our study period may have contributed to the lower total and cardiovascular mortality rates in our study compared with prior studies (33). However, it is difficult to make conclusions from comparisons of crude mortality rates due to potential confounding from differences between our study population and other cohorts like age and sex. The lower mortality rates in DPPOS may have limited the precision of our effect estimates, particularly for smaller subgroup analyses. The all-cause mortality HRs of 0.99 and 1.02 for metformin versus placebo and lifestyle versus placebo, respectively, are the single best estimates of effect of these interventions, but the associated 95% CIs indicate that the true effect for the all-cause mortality may range from 0.79 to 1.25 for metformin versus placebo and 0.81 to 1.28 for lifestyle versus placebo (Table 3), consistent with potential modest beneficial or harmful effects of either intervention. CIs were much wider for specific causes of death (Table 3) and subgroups of participants (Supplementary Fig. 2*A* and *B*).

In summary, while reductions in weight, cardiovascular risk factors, and incident diabetes were achieved with metformin and lifestyle interventions in DPP, these interventions did not lower the risk of all-cause or cause-specific mortality over 20 years' follow-up. Because cancer was found to be the leading cause of death among participants at high risk of type 2 diabetes and others have shown that adults with prediabetes have an increased risk for cancer mortality, dedicated research efforts are needed to better understand how to prevent excess morbidity and mortality from cancer in this population.

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