## Title

Effects of Long-term Metformin and Lifestyle Interventions on Cardiovascular Events in the Diabetes Prevention Program and Its Outcome Study



## Journal

Circulation, 145(22)

## ISSN

0009-7322

## Authors

Goldberg, Ronald B
Orchard, Trevor J
Crandall, Jill P
et al.

## Publication Date

2022-05-31

## DOI

10.1161/circulationaha.121.056756

Peer reviewed

Published in final edited form as:

*Circulation*. 2022 May 31; 145(22): 1632–1641. doi:10.1161/CIRCULATIONAHA.121.056756.

# Effects of Long-term Metformin and Lifestyle Interventions on Cardiovascular Events in the Diabetes Prevention Program and its Outcome Study

**Ronald B. Goldberg, MD**[1], **Trevor J. Orchard, MD**[2], **Jill P. Crandall, MD**[3], **Edward J. Boyko, MD, MPH**[4], **Matthew Budoff, MD**[5], **Dana Dabelea, MD, PHD**[6], **Kishore M. Gadde, MD**[7], **William C. Knowler, MD, DrPH**[8], **Christine G. Lee, MD, MS**[9], **David M. Nathan, MD**[10], **Karol Watson, MD**[11], **Marinella Temprosa, PhD**[12], **Diabetes Prevention Program Research Group***

[1]University of Miami Miller School of Medicine, Miami, FL

[2]University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

[3]Albert Einstein College of Medicine, Bronx, NY

[4]VA Puget Sound Health Care System, Seattle, WA

[5]Los Angeles Biomedical Research Institute, Torrance CA

[6]University of Colorado Anschutz Medical Campus, Aurora, CO

[7]Pennington Biomedical Research Center, Baton Rouge, LA

[8]National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ

[9]National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD

[10]Massachusetts General Hospital, Harvard Medical School, Boston, MA

[11]David Geffen School of Medicine at UCLA, Los Angeles, CA

[12]Biostatistics Center and Milken Institute School of Public Health, George Washington University, Rockville, MD

## Abstract

**Background:** Lifestyle intervention and metformin have been shown to prevent diabetes; however, their efficacy in preventing cardiovascular disease associated with diabetes development is unclear. We examined whether these interventions reduced the incidence of major cardiovascular events over 21-years median follow-up of participants in the Diabetes Prevention Program (DPP) and its Outcomes Study (DPPOS).

*Members listed in the appendix

Please address all correspondence regarding this paper to: DPP Research Group, Diabetes Prevention Program Coordinating Center, George Washington University Biostatistics Center, 6110 Executive Blvd, Rockville, MD 20852, Tele: (301)-881-9260, dppmail@bsc.gwu.edu.

Disclosures

Kishore M. Gadde received grant support from AstraZeneca and BioKer.

**Methods:** During DPP 3,234 participants with impaired glucose tolerance were randomized to metformin 850 mg twice daily, intensive lifestyle or placebo and followed for 3 years. During the next 18-year average follow-up in DPPOS, all participants were offered a less intensive group lifestyle intervention, and unmasked metformin was continued in the metformin group. The primary outcome was the first occurrence of nonfatal myocardial infarction, stroke, or cardiovascular death adjudicated by standard criteria. An extended cardiovascular outcome included the primary outcome or hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, coronary heart disease diagnosed by angiography, or "silent" myocardial infarction by electrocardiogram. Electrocardiograms and cardiovascular risk factors were measured annually.

**Results:** Neither metformin nor lifestyle reduced the primary outcome: metformin versus placebo hazard ratio 1.03 (95% CI 0.78, 1.37, p=0.81), lifestyle versus placebo hazard ratio 1.14 (95% CI 0.87, 1.50, p=0.34). Risk factor adjustment did not change these results. No effect of either intervention was seen on the extended cardiovascular outcome.

**Conclusion:** Neither metformin nor lifestyle reduced major cardiovascular events in DPPOS over 21 years despite long-term prevention of diabetes. Provision of group lifestyle intervention to all, extensive out-of-study use of statin and antihypertensive agents and reduction in use of study metformin together with out-of-study metformin use over time may have diluted the effects of the interventions.

**Clinical Trial Registration:** URL: https://www.clinicaltrials.gov. Trial registration No. DPP (NCT00004992) and DPPOS (NCT00038727)

### Keywords

metformin; diabetes; cardiovascular disease

## Introduction

Type 2 diabetes is associated with a 2-3 fold increased risk for cardiovascular disease [1, 2]. While glycemia-related mechanisms are a likely contributor[2], attempts to reduce risk with intensive management of glycemia have had variable results[3-6] with several long-term follow-up studies of initially negative clinical trials suggesting a benefit[7,8], albeit potentially short-lived[9] and one positive trial demonstrating long-term beneficial effects in myocardial infarction survivors[10]. Metformin has been shown to have a beneficial effect in reducing myocardial infarctions and total cardiovascular events in a single study[11].

This mixed picture of hyperglycemia predicting cardiovascular events, while glycemia reduction does not consistently lower their incidence, supports a multifactorial pathogenesis of cardiovascular disease in diabetes wherein some of the diabetes associated cardiovascular risk is mediated by non-glycemic pathways. The diabetes-atherogenesis link may thus have its roots with earlier metabolic disturbances, like insulin resistance[12] and prediabetes[13]. This concept suggests that intervention in an earlier, prediabetic phase may be of greater benefit with regard to cardiovascular disease (CVD) reduction.

Successful diabetes prevention studies[14-17] have thus examined the impact of their interventions on cardiovascular disease risk with no clear benefit emerging except for acarbose[17] which was not confirmed subsequently[18]. However, extended follow-up of the Da Qing lifestyle intervention study showed benefit for cardiovascular mortality after 23 years[19] and for cardiovascular events after 30 years follow-up[20].

The randomized interventions in the Diabetes Prevention Program (DPP) were highly successful after an average of 2.8 years in reducing cumulative diabetes incidence by 58% with intensive lifestyle and by 31% with metformin compared with placebo[16]. The benefits on diabetes prevention have continued for as long as 15 years after randomization during continued follow-up in the DPP Outcomes Study (DPPOS)[21]. DPPOS has recently focused on the cardiovascular impact of metformin given its suggestive benefit in the United Kingdom Prospective Diabetes Study (UKPDS)[11], and beneficial effects on cardiovascular risk factors[22, 23], the arterial wall[24] and on coronary calcification[25]. The current report's primary objective is to assess the effect of the original DPP randomization to metformin or lifestyle interventions on major adverse cardiovascular events compared to placebo.

## Methods

### DPP/DPPOS Design

The DPP randomized clinical trial (1996-2002, with a mean of 3 years of study) compared metformin or lifestyle with placebo to prevent or delay diabetes in 3,234 participants with impaired glucose tolerance (IGT), fasting plasma glucose 5.27-6.94 mmol/L (95 to 125 mg/dl), and body mass index ≥24 kg/m$^2$, hereafter referred to as "prediabetes"[16]. Individuals who had experienced a cardiovascular event within 6 months of screening were excluded. The methods have been described in detail[26]. 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 all of which approved the trial. Eligible persons were randomly assigned to metformin 850 mg twice daily, placebo twice daily, or lifestyle intervention aimed at weight reduction of ≥7% of initial body weight and at least 150 minutes per week of moderate intensity physical activity (CONSORT diagram-Supplemental Fig S1). Treatment assignments were stratified according to clinical center and double-blinded for metformin and placebo. Standardized questionnaires, assessment of systolic and diastolic blood pressure, height and weight and measurement of glycated hemoglobin, insulin, lipid profile, urine albumin/creatinine ratio and estimation of glomerular filtration rate were performed annually as previously described[16, 21, 26]. Diabetes was diagnosed by an annual oral glucose tolerance test or a semi-annual fasting glucose[21] and required confirmation by a second test. If confirmed, diabetes management was transferred to the participant's health care provider. Metformin or placebo were still provided until the fasting plasma glucose level was ≥7.7 mmol/L (≥140 mg/dl) during DPP.

At the end of DPP, all surviving members regardless of diabetes status were invited to participate in the DPPOS (2002 to 2019). In view of the clear evidence of benefit of the lifestyle intervention all participants were offered the lifestyle intervention in a group format during a 1-year bridge period between DPP and DPPOS. During DPPOS, randomized

metformin therapy, now unmasked, was continued until the glycated hemoglobin was >7% at which time study drug was discontinued. After diabetes diagnosis and cessation of study-supplied metformin, 28% of participants were treated with metformin by their own health care providers. Such use was tracked and called “out-of-study” metformin in this report. At the end of DPP, all participants were offered lifestyle in a supplementary semiannual group lifestyle program[21]. During DPP and DPPOS, treatment of cardiovascular risk factors was left to the participants’ own health care providers.

## Cardiovascular disease outcomes

All fatal and non-fatal cardiovascular events were adjudicated by an Outcomes Classification Committee of physicians masked to treatment assignment. using medical records, death certificates, autopsy reports and research records. The committee membership was largely unchanged over the duration of the study, The primary outcome was the first occurrence of a major cardiovascular event defined as non-fatal myocardial infarction (excluding silent myocardial infarction), non-fatal stroke or fatal cardiovascular disease. An extended cardiovascular event outcome comprised the first occurrence of a major event as above, or hospitalization for congestive heart failure or unstable angina, coronary or peripheral revascularization, coronary heart disease diagnosed by angiography, or silent myocardial infarction. The definitions of the cardiovascular outcomes are tabulated in Supplementary Table 1.

From DPP inception in 1996 through DPPOS, participants were screened for CVD events at every contact to obtain medical records for adjudication of myocardial infarction and other cardiovascular outcomes based on criteria used in the Women’s Health Initiative[27] and in the randomized clinical trial of the Prevention of Events with ACE Inhibition (PEACE)[28, 29]. Due to advances in laboratory methodology related to troponin levels, as well as other changes, new criteria for adjudication of myocardial infarction in clinical trials were established by the American Heart Association/American College of Cardiology task force and published in 2015[30]. These new criteria were adopted by the DPPOS for adjudication of new cases beginning in November 2016. Electrocardiograms were recorded at baseline and annually until DPPOS Year 14 and biennially thereafter in all participants using standardized procedures on identical electrocardiographs (MAC 1200, Marquette Electronics Inc., Milwaukee, WI) at all clinic sites. Electrocardiograms were processed centrally at the Epidemiological Cardiology Research Center (EPICARE) of Wake Forest School of Medicine (Winston-Salem, NC), where all were visually inspected for technical errors and overall quality. Electrocardiograms from hospital records were read by EPICARE using Minnesota Code criteria[31] and used in the adjudication process. For participants lost to follow-up, a search was conducted of the National Death Index with deaths reported as of 12/31/2018 as well as a commercial investigation firm (ASG) to determine more updated vital status as of 12/31/2019. The causes of death indicated on National Death Index reports were reviewed and classified similarly as other deaths. The total follow-up described in this report covers the average 3-year follow-up in DPP plus up to 18 years during DPPOS for a total median follow-up of 21 years.

## Statistical Methods

A primary goal of DPPOS was to assess the long-term effects of metformin, in comparison to placebo, on the incidence of major adverse cardiovascular events among participants who had prediabetes at the study entry. To detect a 30% risk reduction in the metformin versus placebo comparison with 85% power and a 2-sided significance level of 0.05 using a log-rank test, it was estimated that 145 events would be required in the placebo group. While it was projected that we needed to follow the participants until approximately 2025, a pre-specified interim analysis of this outcome for the metformin versus placebo group was conducted to assess futility of the major adverse cardiovascular event outcome for the metformin vs placebo comparison. A non-binding guideline based on a conditional power criterion of <15% and an efficacy interim look using an O'Brien-Fleming alpha spending function to control the Type 1 error rate at 0.05 was used. The interim analysis occurred in March 2019 when the Data Safety Monitoring Board declared futility for the metformin vs placebo comparison of the major adverse cardiovascular event outcome leading to this early report. With 57% of the information, the pre-specified futility analysis showed a HR (95% CI) of 0.91 (0.68, 1.23) for the metformin vs placebo comparison with $p = 0.54$ and conditional power (95% CI) of 4.1% (0.1%, 32.6%) under the current trend. The data used for this report included results for an additional year to maximize adjudicated data for the analysis. The lifestyle and placebo comparison is considered a secondary analysis.

Primary analyses used the "intention-to-treat" paradigm including all participants with data at the data lock which was February 23, 2020. Generalized Estimating Equations (with identity link for continuous and logit link for binary measures) were used to assess time-weighted differences in longitudinal measures to account for within-person correlation and assumed that data are missing at random. Risk factor data before the development of a major cardiovascular event were included in these analyses. The time to first cardiovascular event analysis was based on the first occurrence as adjudicated by the Outcomes Classification Committee. Each participant had two censor dates to reflect differences in ascertainment of events namely, the last contact or visit in DPP or DPPOS for non-fatal events prior to the datalock in February 2020 and the last survey for deaths in December 2019. Cumulative incidence rates accounted for competing risk due to non-cardiovascular deaths using Fine-Gray's estimates[32] in marginal Cox proportional hazards models to assess treatment and covariate effects[33] and to accommodate separate ascertainment times for fatal and non-fatal events. Treatment effects are tested and expressed as hazard ratios and 95% confidence limits. Secondary analyses for assessing the effects of metformin and lifestyle compared to placebo according to pre-specified subgroups were conducted without adjustment for multiplicity. Extended follow-up increased the likelihood that time-varying confounders due to intercurrent events may attenuate the hypothesized effect of randomized metformin compared to placebo[34]. Therefore, additional Cox models assessed the effect of lifestyle and metformin compared to placebo after adjustment for cardiovascular risk factors and out-of-study metformin use to explore these potential sources of confounding.

## Results

The characteristics of the overall study population at baseline and by treatment group, time-weighted during follow-up, are shown in Table 1. At baseline, the population was middle aged (mean age 51years) with more women (68%) than men and was racially diverse with 54.7% being White, 19.9 % Black, 15.7% Hispanic, 5.3%, American Indian and 4.4% Asian. All baseline characteristics were similar among the three treatment groups except for significantly lower high-density lipoprotein cholesterol and higher triglyceride concentrations in the placebo compared to the metformin or lifestyle groups. During follow-up, cardiovascular risk factors were generally more favorable in the active intervention compared to the placebo groups, except for low-density lipoprotein cholesterol (LDL-C), urine albumin and glomerular filtration rate which did not differ over time by treatment group. Overall antihypertensive medication and statin use were common at 68 to 74% and 56 to 62%, respectively; however, use of statins was modestly albeit significantly lower in the lifestyle, but not the metformin group, compared to the placebo group (Table 1). Smoking rates were generally low at 7% and fell over time in all groups although to a greater extent in the lifestyle group. Importantly, diabetes development was significantly lower in both the metformin and lifestyle than in the placebo groups. Figure 1 shows the overall improvement in cardiovascular risk factors over time, except for glycated hemoglobin and systolic blood pressure which increased in later years.

During 21 years of median follow-up, 310 individuals experienced a first major cardiovascular event (Table 2, Figure 2). The incidence did not differ by treatment group; metformin versus placebo hazard ratio was 1.03 (95% CI 0.78, 1.37; p=0.81) and lifestyle versus placebo hazard ratio was 1.14 (95% CI 0.87, 1.50; p=0.34). Among the major cardiovascular event components, there were fewer non-fatal strokes in the metformin than the placebo group. with no significant difference in rates, hazard ratio 0.57 (95% CI 0.31, 1.06; p=0.07), while lifestyle showed an opposite trend; hazard ratio 1.42 (95% CI 0.87, 2.30; p=0.16). Compared to placebo, risk for cardiovascular death in both metformin and lifestyle groups trended higher but were not different from the placebo group, hazard ratios 1.46 (95% CI 0.90, 2.39; p= 0.13) and 1.40 (95% CI 0.85, 2.29; p=0.19) respectively. There were no significant associations between interventions and the incidence of the extended cardiovascular event outcome (Table 2, Figure 3, Supplementary Appendix Table S2),

Pre-specified subgroup analyses for intervention effects on major cardiovascular events (Figure 4, Supplementary Appendix Table S3) showed no significant heterogeneity by age, sex, race/ethnicity or diabetes development for either metformin or lifestyle.

Study metformin use gradually fell, from 77% at the end of DPP to 41% at the most recent assessment while out-of-study metformin use increased in all three original treatment groups (Table 1), primarily after diabetes diagnosis. We thus constructed adjusted models (Supplemental Table S4) with time-dependent cardiovascular risk factors, diabetes status and out-of-study metformin use which confirmed that assignment to metformin did not result in any benefit or harm in terms of major cardiovascular events.

## Discussion

In this 21 year-long follow up study of the effects of metformin and lifestyle interventions, each of which reduced development of diabetes compared to placebo on cardiovascular events in an ethnically diverse cohort with prediabetes, we found no overall beneficial or unfavorable effects associated with either intervention on time to first major cardiovascular event, or to the extended cardiovascular outcome. These metformin findings are consistent with a meta-analysis of clinical trials of metformin in type 2 diabetes[35] which found no significant benefit for metformin on cardiovascular disease although there were favorable, non-significant, trends. However, the original UKPDS study performed in the pre-statin era and which was not included in the meta-analysis, found that metformin significantly reduced myocardial infarction by 39% and stroke by 41% in overweight subjects with newly diagnosed diabetes[11]. In addition, metformin treatment was associated with a 53% reduction in stroke over a 4-year period in an observational Taiwanese database study[36]. We found no significant difference in stroke events between the metformin and placebo groups.

Our earlier observation that coronary calcification, measured after 14 years of follow-up, was lower in men in the metformin than in the placebo group[25], raised the possibility that metformin would have beneficial effects on cardiovascular events. The absence of such an effect may be related to the fact that coronary calcification is a subclinical precursor of cardiovascular events and more time may be needed to determine whether this beneficial effect of metformin on coronary calcification translates into a reduced number of events.

Overall rates for major cardiovascular events were slightly lower than national cross-sectional estimates for prediabetes and considerably lower than those for diagnosed diabetes[37]. Our cohort with prediabetes is unique because of the selection criteria used for inclusion in the study and the semiannual fasting glucose and annual oral glucose tolerance testing protocol used to diagnose diabetes at the earliest timepoint. Furthermore, even after 21 years of follow-up, the degree of hyperglycemia in the cohort was mild, with mean glycated hemoglobin values 6.0-6.1% despite the fact that 53-60% of participants had developed diabetes based on fasting glucose and oral glucose tolerance testing in the three treatment groups. Furthermore, while only 16% and 4% of participants were taking antihypertensive and statin agents at randomization, between 68-74% and 53-62% respectively were receiving these medications from their physicians and the mean blood pressure was 122/73 and LDL-C 2.8 mmol/l (108 mg/dl) in the three groups at 21 years of follow-up. Effective control of major cardiovascular risk factors in cohorts with diabetes has been shown to reduce risk of cardiovascular disease[38, 39]. This was therefore a relatively low risk cohort from the standpoint of prevention of cardiovascular disease. It is thus possible that the accelerating effect of duration of clinically diagnosed diabetes on cardiovascular risk[40, 41] has still not had enough time to manifest, making it more difficult to identify a beneficial effect of metformin.

The finding that lifestyle intervention had no beneficial effect on cardiovascular events, despite favorable influences on cardiovascular risk factors, may in part be due to the fact that the lifestyle intervention was intensive only during DPP, after which group-lifestyle was offered to all participants. Nevertheless, our findings are consistent with the lack of effect

on cardiovascular events in two other studies of lifestyle change on diabetes prevention, namely the 10-year Finnish Diabetes Prevention Study[14] and the 20-year follow-up of the Da Qing study[15]. Lifestyle intervention also failed to show benefit despite favorable risk factor changes in the Look AHEAD (Action for Health in Diabetes) cohort with type 2 diabetes[42]. However, a longer, 30-year follow-up of the Da Qing study did demonstrate a benefit with lifestyle for major cardiovascular events (hazard ratio 0.74 95% CI 0.59, 0.92)[20]. It should also be noted that the Da Qing cohort was a higher risk population with a greater proportion of smokers, a higher prevalence of hypertension and diabetes with more severe hyperglycemia and a higher overall CVD event rate[19]. Thus, further follow-up of DPPOS may clarify our findings in terms of lifestyle intervention.

Unlike the studies referred to above, the current report raises the possibility of a sex difference in the effect of lifestyle on major cardiovascular events where there was borderline heterogeneity (p=0.053), with lifestyle being potentially harmful in women yet somewhat protective in men. We have also previously reported a less favorable effect of metformin in DPP on the development of the metabolic syndrome in women compared to men[23]. These sex differences merit further investigation. Similarly the finding of a reduced number of events in men aged <45 years compared to placebo that was not significant, given our earlier findings of a beneficial effect of metformin on coronary calcification in this group[25], should be further investigated to determine whether it too is simply the result of a play of chance.

A further limitation of these analyses is the possibility that the impact of our interventions was lessened by the reduced intensity of the lifestyle intervention after the DPP phase of the study as mentioned above, and by the gradual reduction in adherence to study metformin over time. Another limitation is the expanded use of out-of-study metformin which may have diluted differences between study groups, especially in those with diabetes, although sensitivity analysis failed to show such an effect. Increased use of statin and antihypertensive treatment prescribed by participants' primary care providers overall and significantly lower use of statins and nominally lower use of antihypertensive medications in the lifestyle group, may also have influenced results although adjustment for medication use did not alter the results. It should also be recognized that these results cannot be generalized to all people with prediabetes since we selected a subgroup with both IGT and an elevated fasting glucose >5.3 mmol/L (95 mg/dl) who were at particularly high risk for diabetes development. Lastly there may also have been some under-estimation of non-fatal events resulting from loss to follow-up.

Ultimately, these findings need to be evaluated in the context of the role of metformin and lifestyle intervention in diabetes prevention. Both interventions have demonstrated long-term reduction in diabetes development in DPP/DPPOS. Although it is reassuring that metformin was not associated with any overall unfavorable effects on cardiovascular disease, it is surprising that neither intervention yielded benefit for cardiovascular disease through their effect on diabetes prevention. It may be that a beneficial effect related to diabetes prevention was not apparent in our study because the development of diabetes in its very early stages may not, *per se*, have increased cardiovascular risk above the effect of known risk factors.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

The DPP Research Group gratefully acknowledges the commitment and dedication of the participants of the DPP and DPPOS as well as the Outcomes Committee Members (Jill Crandall [Chairperson], Robert Ratner [prior Chair], Angela Brown, Richard Arakaki, Anna Bowers, Enrico Cagliero, Sharon Edelstein, David Ehrmann, Ronald Goldberg, Kieren Mather, Trevor Orchard, Hanna Sherif, Preethi Srikanthan, Marinella Temprosa, and Karol Watson), and the Data Safety Monitoring Board (Jeffrey Halter [chair]) Aaron Folsom, Kathleen Dunegan, George Grunberger, Dennis Han, Todd MacKenzie, and Jazon Zell]. The sponsor of this study was represented on the Steering Committee and played a part in study design, how the study was done, and publication. All authors in the writing group had access to all data. The opinions expressed are those of the study group and do not necessarily reflect the views of the funding agencies. A complete list of Centers, investigators, and staff can be found in the Appendix.

### Sources of Funding

The DPP Research Group gratefully acknowledges the commitment and dedication of the participants of the DPP and DPPOS. Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) under award numbers U01 DK048489, U01 DK048339, U01 DK048377, U01 DK048349, U01 DK048381, U01 DK048468, U01 DK048434, U01 DK048485, U01 DK048375, U01 DK048514, U01 DK048437, U01 DK048413, U01 DK048411, U01 DK048406, U01 DK048380, U01 DK048397, U01 DK048412, U01 DK048404, U01 DK048387, U01 DK048407, U01 DK048443, and U01 DK048400, by providing funding during DPP and DPPOS to the clinical centers and the Coordinating Center for the design and conduct of the study, and collection, management, analysis, and interpretation of the data. Funding was also provided by the National Institute of Child Health and Human Development, the National Institute on Aging, the National Eye Institute, the National Heart Lung and Blood Institute, the National Cancer Institute, the Office of Research on Women's Health, the National Institute on Minority Health and Health Disparities, the Centers for Disease Control and Prevention, and the American Diabetes Association. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The Southwestern American Indian Centers were supported directly by the NIDDK, including its Intramural Research Program, and the Indian Health Service. The General Clinical Research Center Program, National Center for Research Resources, and the Department of Veterans Affairs supported data collection at many of the clinical centers. Merck KGaA provided medication for DPPOS. DPP/DPPOS have also received donated materials, equipment, or medicines for concomitant conditions from Bristol-Myers Squibb, Parke-Davis, and LifeScan Inc., Health O Meter, Hoechst Marion Roussel, Inc., Merck-Medco Managed Care, Inc., Merck and Co., Nike Sports Marketing, Slim Fast Foods Co., and Quaker Oats Co. McKesson BioServices Corp., Matthews Media Group, Inc., and the Henry M. Jackson Foundation provided support services under subcontract with the Coordinating Center. The sponsor of this study was represented on the Steering Committee and played a part in study design, how the study was done, and publication. All authors in the writing group had access to all data. The opinions expressed are those of the study group and do not necessarily reflect the views of the funding agencies. A complete list of Centers, investigators, and staff can be found in the Appendix.

## Appendix

Pennington Biomedical Research Center

(Baton Rouge, LA)

George A. Bray, MD*

Kishore M. Gadde, MD*

Iris W. Culbert, BSN, RN, CCRC**

Jennifer Arceneaux RN, BSN**

Annie Chatellier, RN, CCRC**

Amber Dragg RD, LDN**

Catherine M. Champagne, PhD, RD

Crystal Duncan, LPN

Barbara Eberhardt, RD, LDN

Frank Greenway, MD

Fonda G. Guillory, LPN

April A. Herbert, RD

Michael L. Jeffirs, LPN

Betty M. Kennedy, MPA

Erma Levy, RD

Monica Lockett, LPN

Jennifer C. Lovejoy, PhD

Laura H. Morris, BS

Lee E. Melancon, BA, BS

Donna H. Ryan, MD

Deborah A. Sanford, LPN

Kenneth G. Smith, BS, MT

Lisa L. Smith, BS

Julia A. St.Amant, RTR

Richard T. Tulley, PhD

Paula C. Vicknair, MS, RD

Donald Williamson, PhD

Jeffery J. Zachwieja, PhD

University of Chicago (Chicago, IL)

Kenneth S. Polonsky, MD*

Janet Tobian, MD, PhD*

David A. Ehrmann, MD*

Margaret J. Matulik, RN, BSN**

Karla A. Temple, PhD, RDN, LDN**

Bart Clark, MD

Kirsten Czech, MS

Catherine DeSandre, BA

Brittnie Dotson, MS

Ruthanne Hilbrich, RD

Wylie McNabb, EdD

Ann R. Semenske, MS, RD

Jefferson Medical College (Philadelphia, PA)

Jose F. Caro, MD*

Kevin Furlong, DO*

Barry J. Goldstein, MD, PhD*

Pamela G. Watson, RN, ScD*

Kellie A. Smith, RN, MSN**

Jewel Mendoza, RN, BSN**

Marsha Simmons, CCRP**

Wendi Wildman, RN**

Renee Liberoni, MPH

John Spandorfer, MD

Constance Pepe, MS, RD

University of Miami (Miami, FL)

Richard P. Donahue, PhD*

Ronald B. Goldberg, MD*

Ronald Prineas, MD, PhD*

Jeanette Calles, MSEd**

Anna Giannella, RD, MS**

Patricia Rowe, MPA**

Juliet Sanguily, RN**

Paul Cassanova-Romero, MD

Sumaya Castillo-Florez, MPH

Hermes J. Florez, MD

Rajesh Garg, MD

Lascelles Kirby, MS

Olga Lara

Carmen Larreal

Valerie McLymont, RN

Jadell Mendez

Arlette Perry, PhD

Patrice Saab, PhD

Bertha Veciana

The University of Texas Health Science Center

(San Antonio, TX)

Steven M. Haffner, MD, MPH*

Helen P. Hazuda, PhD*

Maria G. Montez, RN, MSHP, CDE**

Kathy Hattaway, RD, MS

Juan Isaac, RN, BSN

Carlos Lorenzo, MD, PhD

Arlene Martinez, RN, BSN, CDE

Monica Salazar

Tatiana Walker, RD, MS, CDE

University of Colorado (Denver, CO)

Dana Dabelea, MD, PhD*

Richard F. Hamman, MD, DrPH*

Patricia V. Nash, MS**

Sheila C. Steinke, MS**

Lisa Testaverde, MS**

Jennifer Truong, MPH**

Denise R. Anderson, RN, BSN

Larry B. Ballonoff, MD

Alexis Bouffard, MA, RN, BSN

Brian Bucca OD, FAOO

B. Ned Calonge, MD, MPH

Lynne Delve

Martha Farago, RN

James O. Hill, PhD

Shelley R. Hoyer, BS

Tonya Jenkins, RD, CDE

Bonnie T. Jortberg, MS, RD, CDE

Dione Lenz, RN, BSN, CDE

Marsha Miller, MS, RD

Thomas Nilan, BS

Leigh Perreault, MD

David W. Price, MD

Judith G. Regensteiner, PhD

Emily B. Schroeder, MD

Helen Seagle, MS, RD

Carissa M. Smith, BS

Brent VanDorsten, PhD

Joslin Diabetes Center (Boston, MA)

Edward S. Horton, MD*

Medha Munshi, MD*

Kathleen E. Lawton, RN**

Sharon D. Jackson,CCRC,MS, RD, CDE**

Catherine S. Poirier, RN, BSN**

Kati Swift, RN, BSN**

Ronald A. Arky, MD

Marybeth Bryant

Jacqueline P. Burke, BSN

Enrique Caballero, MD

Karen M. Callaphan, BA

Barbara Fargnoli, RD

Therese Franklin

Om P. Ganda, MD

Ashley Guidi, BS

Mathew Guido, BA

Alan M. Jacobsen, MD

Lyn M. Kula, RD

Margaret Kocal, RN, CDE

Lori Lambert, MS, RD, LD

Kathleen E. Lawton, RN

Sarah Ledbury, Med, RD

Maureen A. Malloy, BS

Roeland J.W. Middelbeek, MD

Maryanne Nicosia, MS, RD

Cathryn F. Oldmixon, RN

Jocelyn Pan, BS, MPH

Marizel Quitingon

Riley Rainville, BS

Stacy Rubtchinsky, BS

Ellen W. Seely, MD

Jessica Sansoucy, BS

Dana Schweizer, BSN

Donald Simonson, MD

Fannie Smith, MD

Caren G. Solomon, MD, MPH

Jeanne Spellman, RD

James Warram, MD

VA Puget Sound Health Care System and University of Washington (Seattle, WA)

Steven E. Kahn, MB, ChB*

Basma Fattaleh, BA **

Brenda K. Montgomery, RN, BSN, CDE**

Celeste Colegrove, BS

Wilfred Fujimoto, MD

Robert H. Knopp, MD

Edward W. Lipkin, MD

Michelle Marr, BA

Ivy Morgan-Taggart

Anne Murillo, BS

Kayla O'Neal, BS

Dace Trence, MD

Lonnese Taylor, RN, BS

April Thomas, RD, MPH, CDE

Elaine C. Tsai, MD, MPH

University of Tennessee (Memphis, TN)

Samuel Dagogo-Jack, MD, MSc, FRCP, FACP*

Abbas E. Kitabchi, PhD, MD, FACP*

Mary E. Murphy, RN, MS, CDE, MBA**

Laura Taylor, RN, BSN, CDE**

Jennifer Dolgoff, RN, BSN**

William B. Applegate, MD, MPH

Michael Bryer-Ash, MD

Debra Clark, LPN

Sandra L. Frieson, RN

Uzoma Ibebuogu, MD

Raed Imseis, MD

Helen Lambeth, RN, BSN

Lynne C. Lichtermann, RN, BSN

Hooman Oktaei, MD

Harriet Ricks

Lily M.K. Rutledge, RN, BSN

Amy R. Sherman, RD, LD

Clara M. Smith, RD, MHP, LDN

Judith E. Soberman, MD

Beverly Williams-Cleaves, MD

Avnisha Patel, MLT

Ebenezer A. Nyenwe, MD, FACP

Ethel Faye Hampton, R.N.

Northwestern University's Feinberg School of Medicine (Chicago, IL)

Boyd E. Metzger, MD*

Mark E. Molitch, MD*

Mariana K. Johnson, MS, RN**

Daphne T. Adelman, MBA, RN

Catherine Behrends

Michelle Cook, MS

Marian Fitzgibbon, PhD

Mimi M. Giles, MS, RD

Deloris Heard, MA

Cheryl K.H. Johnson, MS, RN

Diane Larsen, BS

Anne Lowe, BS

Megan Lyman, BS

David McPherson, MD

Samsam C. Penn, BA

Thomas Pitts, MD

Renee Reinhart, RN, MS

Susan Roston, RN, RD

Pamela A. Schinleber, RN, MS

Amisha Wallia, MD

Massachusetts General Hospital (Boston, MA)

David M. Nathan, MD*

Charles McKitrick, BSN**

Heather Turgeon, BSN**

Mary Larkin, MSN**

Marielle Mugford, BA**

Kathy Abbott

Ellen Anderson, MS, RD

Laurie Bissett, MS, RD

Kristy Bondi, BS

Enrico Cagliero, MD

Jose C. Florez, MD, PhD+

Linda Delahanty, MS, RD

Valerie Goldman, MS, RD

Elaine Grassa

Lindsery Gurry BSN, RN, CDE

Kali D'Anna

Fernelle Leandre BS

Peter Lou, MD

Alexandra Poulos

Elyse Raymond, BS

Valerie Ripley, BS

Christine Stevens, RN

Beverly Tseng

University of California-San Diego (La Jolla, CA)

Jerrold M. Olefsky, MD*

Elizabeth Barrett-Connor, MD*

Sunder Mudaliar, MD*

Maria Rosario Araneta, PhD*

Mary Lou Carrion-Petersen, RN, BSN**

Karen Vejvoda, RN, BSN, CDE, CCRC**

Sarah Bassiouni, MPH

Madeline Beltran, RN, BSN, CDE

Lauren N. Claravall, BS

Jonalle M. Dowden, BS

Steven V. Edelman, MD

Pranav Garimella, MBBS

Robert R. Henry, MD

Javiva Horne, RD

Marycie Lamkin, RN

Simona Szerdi Janesch, BA

Diana Leos

William Polonsky, PhD

Rosa Ruiz

Jean Smith, RN

Jennifer Torio-Hurley

Columbia University (New York, NY)

F. Xavier Pi-Sunyer, MD*

Jane E. Lee, MS**

Susan Hagamen, MS, RN, CDE**

David B. Allison, PhD

Nnenna Agharanya

Nancy J. Aronoff, MS, RD

Maria Baldo

Jill P. Crandall, MD

Sandra T. Foo, MD

Jose A. Luchsinger, MD, MPH

Carmen Pal, MD

Kathy Parkes, RN

Mary Beth Pena, RN

Ellen S. Rooney, BA

Gretchen E.H. Van Wye, MA

Kristine A. Viscovich, ANP

Indiana University (Indianapolis, IN)

Mary de Groot, PhD*

David G. Marrero, PhD*

Kieren J. Mather, MD*

Melvin J. Prince, MD*

Susie M. Kelly, RN, CDE**

Marcia A. Jackson**

Gina McAtee**

Paula Putenney, RN**

Ronald T. Ackermann, MD

Carolyn M. Cantrell

Yolanda F. Dotson, BS

Edwin S. Fineberg, MD

Megan Fultz

John C. Guare, PhD

Angela Hadden

James M. Ignaut, MA

Marion S. Kirkman, MD

Erin O'Kelly Phillips

Kisha L Pinner

Beverly D. Porter, MSN

Paris J. Roach, MD

Nancy D. Rowland, BS, MS

Madelyn L. Wheeler, RD

Medstar Research Institute (Washington, DC)

Vanita Aroda, MD*

Michelle Magee, MD*

Robert E. Ratner, MD*

Gretchen Youssef, RD, CDE**

Sue Shapiro, RN, BSN, CCRC**

Natalie Andon, RN

Catherine Bavido-Arrage, MS, RD, LD

Geraldine Boggs, MSN, RN

Marjorie Bronsord, MS, RD, CDE

Ernestine Brown

Holly Love Burkott, RN

Wayman W. Cheatham, MD

Susan Cola

Cindy Evans

Peggy Gibbs

Tracy Kellum, MS, RD, CDE

Lilia Leon

Milvia Lagarda

Claresa Levatan, MD

Milajurine Lindsay

Asha K. Nair, BS

Jean Park, MD

Maureen Passaro, MD

Angela Silverman

Gabriel Uwaifo, MD

Debra Wells-Thayer, NP, CDE

Renee Wiggins, RD

University of Southern California/UCLA Research Center (Alhambra, CA)

Mohammed F. Saad, MD*

Karol Watson, MD*

Maria Budget**

Sujata Jinagouda, MD**

Medhat Botrous, MD**

Anthony Sosa**

Sameh Tadros**

Khan Akbar, MD

Claudia Conzues

Perpetua Magpuri

Kathy Ngo

Amer Rassam, MD

Debra Waters

Kathy Xapthalamous

Washington University (St. Louis, MO)

Julio V. Santiago, MD*

Samuel Dagogo-Jack, MD, MSc, FRCP, FACP*

Neil H. White, MD, CDE*

Angela L. Brown, MD*

Samia Das, MS, MBA, RD, LD**

Prajakta Khare-Ranade, MSc, RDN, LD**

Tamara Stich, RN, MSN, CDE**

Ana Santiago, RN

Edwin Fisher, PhD

Emma Hurt, RN

Tracy Jones, RN

Michelle Kerr, RD

Lucy Ryder, RN

Cormarie Wernimont, RD, LD

Johns Hopkins School of Medicine

(Baltimore, MD)

Sherita Hill Golden, MD, MHS, FAHA*

Christopher D. Saudek, MD*

Vanessa Bradley, BA**

Emily Sullivan, MEd, RN**

Tracy Whittington, BS**

Caroline Abbas

Adrienne Allen

Frederick L. Brancati, MD, MHS

Sharon Cappelli

Jeanne M. Clark, MD

Jeanne B. Charleston, RN, MSN

Janice Freel

Katherine Horak, RD

Alicia Greene

Dawn Jiggetts

Deloris Johnson

Hope Joseph

Kimberly Loman

Nestoras Mathioudakis, MD, MHS

Henry Mosley

John Reusing

Richard R. Rubin, PhD

Alafia Samuels, MD

Thomas Shields

Shawne Stephens

Kerry J. Stewart, EdD

LeeLana Thomas

Evonne Utsey

Paula Williamson

University of New Mexico (Albuquerque, NM)

David S. Schade, MD*

Karwyn S. Adams, RN, MSN**

Janene L. Canady, RN, CDE**

Carolyn Johannes, RN, CDE**

Claire Hemphill, RN, BSN**

Penny Hyde, RN, BSN**

Leslie F. Atler, PhD

Patrick J. Boyle, MD

Mark R. Burge, MD

Lisa Chai, RN

Kathleen Colleran, MD

Ateka Fondino

Ysela Gonzales

Doris A. Hernandez-McGinnis

Patricia Katz, LPN

Carolyn King, Med

Julia Middendorf, RN

Amer Rassam, MD

Sofya Rubinchik, MD

Willette Senter, RD

Debra Waters, PhD

Albert Einstein College of Medicine (Bronx, NY)

Jill Crandall, MD*

Harry Shamoon, MD*

Janet O. Brown, RN, MPH, MSN**

Gilda Trandafirescu, MD**

Danielle Powell, MPH

Elsie Adorno, BS

Liane Cox, MS, RD

Helena Duffy, MS, C-ANP

Samuel Engel, MD

Allison Friedler, BS

Angela Goldstein, FNP-C, NPP, CSW

Crystal J. Howard-Century, MA

Jennifer Lukin, BA

Stacey Kloiber, RN

Nadege Longchamp, LPN

Helen Martinez, RN, MSN, FNP-C

Dorothy Pompi, BA

Jonathan Scheindlin, MD

Elissa Violino, RD, MS

Elizabeth A. Walker PhD, RN

Judith Wylie-Rosett, EdD, RD

Elise Zimmerman, RD, MS

Joel Zonszein, MD

University of Pittsburgh (Pittsburgh, PA)

Trevor Orchard, MD*

Elizabeth Venditti, PhD*

Rena R. Wing, PhD*

Susan Jeffries, RN, MSN**

Gaye Koenning, MS, RD**

M. Kaye Kramer, BSN, MPH**

Marie Smith, RN, BSN**

Susan Barr, BS

Catherine Benchoff

Miriam Boraz, PhD

Lisa Clifford, BS

Rebecca Culyba, BS

Marlene Frazier

Ryan Gilligan, BS

Stephanie Guimond, BS

Susan Harrier, MLT

Louann Harris, RN

Andrea Kriska, PhD

Qurashia Manjoo, MD

Monica Mullen, MHP, RD

Alicia Noel, BS

Amy Otto, PhD

Jessica Pettigrew, CMA

Bonny Rockette-Wagner, PhD

Debra Rubinstein, MD

Linda Semler, MS, RD

Cheryl F. Smith, PhD

Valarie Weinzierl, MPH

Katherine V. Williams, MD, MPH

Tara Wilson, BA

University of Hawaii (Honolulu, HI)

Marjorie K. Mau, MD*

Narleen K. Baker-Ladao, BS**

John S. Melish, MD

Richard F. Arakaki, MD*

Renee W. Latimer, BSN, MPH**

Mae K. Isonaga, RD, MPH**

Ralph Beddow, MD

Nina E. Bermudez, MS

Lorna Dias, AA

Jillian Inouye, RN, PhD

Kathy Mikami, BS, RD

Pharis Mohideen, MD

Sharon K. Odom, RD, MPH

Raynette U. Perry, AA

Robin E. Yamamoto, CDE, RD

Southwest American Indian Centers

(Phoenix, AZ; Shiprock, NM; Zuni, NM)

William C. Knowler, MD, DrPH*+

Harelda Anderson, LMSW**

Norman Cooeyate**

Charlotte Dodge**

Mary A. Hoskin, RD, MS**

Carol A. Percy, RN, MS**

Alvera Enote**

Camille Natewa**

Kelly J. Acton, MD, MPH

Vickie L. Andre, RN, FNP

Rosalyn Barber

Shandiin Begay, MPH

Peter H. Bennett, MB, FRCP

Mary Beth Benson, RN, BSN

Evelyn C. Bird, RD, MPH

Brenda A. Broussard, RD, MPH, MBA, CDE

Brian C. Bucca, OD, FAAO

Marcella Chavez, RN, AS

Sherron Cook

Jeff Curtis, MD

Tara Dacawyma

Matthew S. Doughty, MD

Roberta Duncan, RD

Cyndy Edgerton, RD

Jacqueline M. Ghahate

Justin Glass, MD

Martia Glass, MD

Dorothy Gohdes, MD

Wendy Grant, MD

Robert L. Hanson, MD, MPH

Ellie Horse

Louise E. Ingraham, MS, RD, LN

Merry Jackson

Priscilla Jay

Roylen S. Kaskalla

Karen Kavena, ANP

David Kessler, MD

Kathleen M. Kobus, RNC-ANP

Jonathan Krakoff, MD

Jason Kurland, MD

Catherine Manus, LPN

Cherie McCabe

Sara Michaels, MD

Tina Morgan

Yolanda Nashboo

Julie A. Nelson, RD

Steven Poirier, MD

Evette Polczynski, MD

Christopher Piromalli, DO

Mike Reidy, MD

Jeanine Roumain, MD, MPH

Debra Rowse, MD

Robert J. Roy

Sandra Sangster, RD

Janet Sewenemewa

Miranda Smart

Chelsea Spencer

Darryl Tonemah, PhD

Rachel Williams, FNP

Charlton Wilson, MD

Michelle Yazzie

George Washington University Biostatistics Center (DPP Coordinating Center Rockville, MD)

Raymond Bain, PhD*

Sarah Fowler, PhD*

Marinella Temprosa, PhD*

Michael D. Larsen, PhD*

Tina Brenneman**

Sharon L. Edelstein, ScM**

Solome Abebe, MS

Julie Bamdad, MS

Melanie Barkalow

Joel Bethepu

Tsedenia Bezabeh

Anna Bowers

Nicole Butler

Jackie Callaghan

Caitlin E. Carter

Costas Christophi, PhD

Gregory M. Dwyer, MPH

Mary Foulkes, PhD

Yuping Gao

Robert Gooding

Adrienne Gottlieb

Kristina L. Grimes

Nisha Grover-Fairchild, MPH

Lori Haffner, MS

Heather Hoffman, PhD

Kathleen Jablonski, PhD

Steve Jones

Tara L. Jones

Richard Katz, MD

Preethy Kolinjivadi, MS

John M. Lachin, ScD

Yong Ma, PhD

Pamela Mucik

Robert Orlosky

Qing Pan, PhD

Susan Reamer

James Rochon, PhD

Alla Sapozhnikova

Hanna Sherif, MS

Charlotte Stimpson

Ashley Hogan Tjaden, MPH

Fredricka Walker-Murray

Lifestyle Resource Core

Elizabeth M. Venditti, PhD*

Andrea M. Kriska, PhD

Linda Semler, MS, RD, LDN

Valerie Weinzierl, MPH

Central Biochemistry Laboratory (Seattle, WA)

Santica Marcovina, PhD, ScD*

F. Alan Aldrich**

Jessica Harting**

John Albers, PhD

Greg Strylewicz, PhD

NIH/NIDDK (Bethesda, MD)

R. Eastman, MD

Judith Fradkin, MD

Sanford Garfield, PhD

Christine Lee, MD, MS

Centers for Disease Control & Prevention

(Atlanta, GA)

Edward Gregg, PhD

Ping Zhang, PhD

Carotid Ultrasound

Dan O'Leary, MD*

Gregory Evans

Coronary Artery Calcification Reading Center

Matthew Budoff, MD

Chris Dailing

CT Scan Reading Center

Elizabeth Stamm, MD*

Dual Energy X-ray Absorptiometry Reading Center (San Francisco, CA)

Ann Schwartz, PhD

Caroline Navy

Lisa Palermo, MS

Epidemiological Cardiology Research Center-Epicare (Winston-Salem, NC)

Pentti Rautaharju, MD, PhD*

Ronald J. Prineas, MD, PhD**

Teresa Alexander

Charles Campbell, MS

Sharon Hall

Yabing Li, MD

Margaret Mills

Nancy Pemberton, MS

Farida Rautaharju, PhD

Zhuming Zhang, MD

Elsayed Z. Soliman, MD*

Julie Hu, MSc

Susan Hensley, BS

Lisa Keasler

Tonya Taylor

Fundus Photo Reading Center (Madison, WI)

Barbara Blodi, MD*

Ronald Danis, MD*

Matthew Davis, MD*

Larry Hubbard*

Ryan Endres**

Deborah Elsas**

Samantha Johnson**

Dawn Myers**

Nancy Barrett

Heather Baumhauer

Wendy Benz

Holly Cohn

Ellie Corkery

Kristi Dohm

Amitha Domalpally, MD, PhD

Vonnie Gama

Anne Goulding

Andy Ewen

Cynthia Hurtenbach

Daniel Lawrence

Kyle McDaniel

Jeong Pak

James Reimers

Ruth Shaw

Maria Swift

Pamela Vargo, CRA

Sheila Watson

Neurocognitive Assessment Group

Jose A. Luchsinger, MD, MPH

Jennifer Manly, PhD

Nutrition Coding Center (Columbia, SC)

Elizabeth Mayer-Davis, PhD*

Robert R. Moran, PhD**

Quality of Well-Being Center (La Jolla, CA)

Ted Ganiats, MD*

Kristin David, MHP*

Andrew J. Sarkin, PhD*

Erik Groessl, PhD

Naomi Katzir

Helen Chong, MA

University of Michigan (Ann Arbor, MI)

William H. Herman, MD, MPH

Michael Brändle, MD, MS

Morton B. Brown, PhD

+Genetics Working Group

Jose C. Florez, MD, PhD[1, 2]

David Altshuler, MD, PhD[1, 2]

Liana K. Billings, MD[1]

Ling Chen, MS[1]

Maegan Harden, BS[2]

Robert L. Hanson, MD, MPH[3]

William C. Knowler, MD, DrPH[3]

Toni I. Pollin, PhD[4]

Alan R. Shuldiner, MD[4]

Kathleen Jablonski, PhD[5]

Paul W. Franks, PhD, MPhil, MS[6, 7, 8]

Marie-France Hivert, MD[9]

1=Massachusetts General Hospital

2=Broad Institute

3=NIDDK

4=University of Maryland

5=Coordinating Center

6=Lund University, Sweden

7=Umeå University, Sweden

8=Harvard School of Public Health

9=Université de Sherbrok

* denotes Principal Investigator

** denotes Program Coordinator

## Non-standard Abbreviations and Acronyms

| | |
|---|---|
| **DPP** | Diabetes Prevention Program |
| **DPPOS** | Diabetes Prevention Program Outcome Study |

| | |
|---|---|
| **CVD** | Cardiovascular disease |
| **UKPDS** | United Kingdome Prospective Diabetes Study |
| **IGT** | Impaired glucose tolerance |
| **LDL-C** | low density lipoprotein cholesterol |

## References


1). Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16:434–444. Doi: 10.2337/diacare.16.2.434. [PubMed: 8432214]

2). Barrett-Connor E, Wingard D, Wong N, Goldberg R. Diabetes and Heart Disease. In: Cowie CC, Casagrande SS, Menke A, Cissell MA, Eberhardt MS, Meigs JB, Gregg EW, Knowler WC, Barrett-Connor E, Becker DJ, et al., editors. Diabetes in America, 3rd ed. Bethesda, (MD), National Institutes of Health (US); 2018 Aug. CHAPTER 18.

3). UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837–853. [PubMed: 9742976]

4). The Action to Control Cardiovascular Risk in Diabetes Study Group. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–2559. Doi: 10.1056/NEJMoa0802743. [PubMed: 18539917]

5). Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129–139. Doi: 10.1056/NEJMoa0808431. [PubMed: 19092145]

6). The ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–2572. Doi: 10.1056/NEJMoa0802987. [PubMed: 18539916]

7). Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–1589. Doi: 10.1056/NEJMoa0806470. [PubMed: 18784090]

8). Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, McCarren M, Duckworth WC, Emanuele NV; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;372:2197–2206. Doi: 10.1056/NEJMoa1414266. [PubMed: 26039600]

9). Reaven PD, Emanuele NV, Wiitala WL, Bahn GD, Reda DJ, McCarren M, Duckworth WC, Hayward RA; VADT Investigators. Intensive Glucose Control in Patients with Type 2 Diabetes — 15-Year Follow-up. N Engl J Med. 2019;380: 2215–2224. Doi: 10.1056/NEJMoa1806802. [PubMed: 31167051]

10). Ritsinger V, Malmberg K, Mårtensson A, Rydén L, Wedel H, Norhammar A. Intensified insulin-based glycaemic control after myocardial infarction: mortality during 20 year follow-up of the randomised Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) trial. Lancet Diabetes Endocrinol. 2014 Aug;2(8):627–633. [PubMed: 24831989]

11). UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854–865. [PubMed: 9742977]

12). Rewers M, Zaccaro D, D'Agostino R, Haffner S, Saad MF, Selby JV, Bergman R, Savage P. Insulin sensitivity, insulinemia, and coronary artery disease: the Insulin Resistance Atherosclerosis Study. Diabetes Care. 2004;27:781–787. Doi: 10.2337/diacare.27.3.781. [PubMed: 14988302]

13). Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999;22:233–240. Doi: 10.2337/diacare.22.2.233. [PubMed: 10333939]

14). Uusitupa M, Peltonen M, Lindström J, Aunola S, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Valle TT, Eriksson JG, Tuomilehto J. Finnish Diabetes Prevention Study Group. Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study—secondary analysis of the randomized trial. PloS One. 2009;4:e5656. Doi: 10.1371/journal.pone.0005656. [PubMed: 19479072]

15). Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, et al. The long-term effect of lifestyle interventions to prevent diabetes in the Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet. 2008;371:1783–1789. Doi: 10.1016/S0140-6736(08)60766-7. [PubMed: 18502303]

16). Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403. Doi: 10.1056/NEJMoa012512. [PubMed: 11832527]

17). Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. The STOP-NIDDM Trial. JAMA. 2003;290:486–494. Doi: 10.1001/jama.290.4.486. [PubMed: 12876091]

18). Holman RR, Coleman RL, Chan JCN, Chiasson JL, Feng H, Ge J, Gerstein HC, Gray R, Huo Y, Lang Z. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomized, double-blind, placebo controlled trial. Lancet Diabetes Endocrinol. 2017;5:877–886. Doi: 10.1016/S2213-8587(17)30309-1. [PubMed: 28917545]

19). An Y, Zhang P, Wang J, Gong Q, Gregg EW, Yang W, Li H, Zhang B, Shuai Y, Chen Y. Cardiovascular and All-Cause Mortality Over a 23-Year Period Among Chinese With Newly Diagnosed Diabetes in the Da Qing IGT and Diabetes Study. Diabetes Care. 2015;38:1365–1371. Doi: 10.2337/dc14-2498. [PubMed: 25887356]

20). Gong Q, Zhang P, Wang J, Ma J, An Y, Chen Y, Zhang B, Feng X, Li H, Chen X. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30 year results of the Da Qing Diabetes Prevention Outcome Study. Lancet Diabetes Endocrinol. 2019;7:452–446. Doi: 10.1016/S2213-8587(19)30093-2. [PubMed: 31036503]

21). Diabetes Prevention Program Research Group. 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. Lancet Diabetes Endocrinol. 2015;3:866–875. Doi: 10.1016/S2213-8587(15)00291-0. [PubMed: 26377054]

22). Goldberg RB, Temprosa MG, Mather KJ, Orchard TJ, Kitabchi AE, Watson KE. Lifestyle and Metformin Interventions Have a Durable Effect to Lower CRP and tPA Levels in the Diabetes Prevention Program Except in Those Who Develop Diabetes. Diabetes Care. 2014;37:2253–2260. Doi: 10.2337/dc13-2471. [PubMed: 24824548]

23). 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;142:611–619. Doi: 10.7326/0003-4819-142-8-200504190-00009. [PubMed: 15838067]

24). Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol. 2001;37:1344–1350. Doi: 10.1016/s0735-1097(01)01129-9. [PubMed: 11300445]

25). Goldberg RB, Aroda VR, Bluemke DA, Barrett-Connor E, Budoff M, Crandall JP, Dabelea D, Horton ES, Mather KJ, Orchard TJ. Effect of Long-Term Metformin and Lifestyle in the Diabetes Prevention Program and Its Outcome Study on Coronary Artery Calcium. Circulation. 2017;136:52–64. Doi: 10.1161/CIRCULATIONAHA.116.025483. [PubMed: 28476766]

26). The Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. Diabetes Care. 1999;22:623–634. Doi: 10.2337/diacare.22.4.623. [PubMed: 10189543]

27). Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Ann Epidemiol. 2003;13(9 Suppl):122–128. Doi: 10.1016/s1047-2797(03)00048-6.

28). Pfeffer MA, Domanski M, Rosenberg Y, Verter J, Geller N, Albert P, Hsia J, Braunwald E. Prevention of events with angiotensin-converting enzyme inhibition (the PEACE study design). Prevention of events with angiotensin-converting enzyme inhibition. American Journal of Cardiology. 1998;82(3A):25H–30H. doi: 10.1016/s0002-9149(98)00488-3.

29). Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, Pfeffer MA, Rice MM, Rosenberg YD, Rouleau JL. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004;351:2058–2068. Doi: 10.1056/NEJMoa042739. [PubMed: 15531767]

30). Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH. ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: A Report of the American College of Cardiology/American Heart Association task force on clinical data standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Am Coll Cardiol. 2015;66:403–469. Doi: 10.1016/j.jacc.2014.12.018. [PubMed: 25553722]

31). Prineas RJ, Crow RS, Zhang Z. The Minnesota code manual of electrocardiographic findings. Springer Science & Business Media; 2nd ed 2010.

32). Fine Jason P; Gray Robert J. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 1999;94:496–509.

33). Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. The Annals of Statistics. 1988;16:1141–1154.

34). Toh S, Hernán MA. Causal inference from longitudinal studies with baseline randomization. Int J Biostat. 2008;4:22. Doi: 10.2202/1557-4679.1117.

35). Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of 17 randomized trials among people with type 2 diabetes. Diabetologia. 2017;60:1620–1629. Doi: 10.1007/s00125-017-4337-9. [PubMed: 28770324]

36). Cheng YY, Leu HB, Chen TJ, Chen CL, Kuo CH, Lee SD, Kao CL. Metformin-inclusive therapy reduces the risk of stroke in patients with diabetes: a 4-year follow-up study. J Stroke Cerebrovasc Dis. 2014;23:e99–e105. Doi: 10.1016/j.jstrokecerebrovasdis.2013.09.001. [PubMed: 24119365]

37). Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988-2014. Lancet Diabetes Endocrinol. 2018;6:392–403. Doi: 10.1016/S2213-8587(18)30027-5. [PubMed: 29500121]

38). Gæde P, Oellgaard J, Carstensen B, Rossing P, Lund-Andersen H, Parving HH, Pedersen O. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia. 2016;59:2298–2307. doi: 10.1007/s00125-016-4065-6. Epub 2016 Aug 16. PMID: 27531506; PMCID: PMC5506099. [PubMed: 27531506]

39). Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2018 Aug 16;379(7):633–644. doi: 10.1056/NEJMoa1800256. PMID: 30110583. [PubMed: 30110583]

40). Kim NH, Pavkov ME, Looker HC, Nelson RG, Bennett PH, Hanson RL, Curtis JM, Sievers ML, Knowler WC. Plasma glucose regulation and mortality in Pima Indians. Diabetes Care. 2008;31:488–492. Doi: 10.2337/dc07-1850. [PubMed: 18071000]

41). Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. J Gen Intern Med. 2016;31:387–393. Doi: 10.1007/s11606-015-3556-3. [PubMed: 26666660]

42). The Look AHEAD Research Group. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. New Eng J Med. 2013;369:145–154. Doi: 10.1056/NEJMoa1212914. [PubMed: 23796131]

## Clinical Perspective

**What Is New?**

- During 21-years follow-up of the 3234 Diabetes Prevention Program (DPP) participants who began with impaired glucose tolerance and were followed in the DPP Outcomes Study (DPPOS), neither metformin nor the lifestyle interventions reduced major adverse cardiovascular events compared to placebo, despite decreasing diabetes development.
- Results should be viewed in the context of modest progression of hyperglycemia, extensive out-of-study use of lipid-lowering and antihypertensive medications, provision of less intensive lifestyle intervention to all DPPOS participants, and increased out-of-study metformin use over time, which may both have limited the apparent effects of the interventions and have been valuable preventive strategies.

**What Are the Clinical Implications?**

- Despite significant long-term reduction in diabetes development, metformin and lifestyle interventions may not have additional effects on cardiovascular disease prevention in the setting of impaired glucose tolerance or early type 2 diabetes with minimal cardiovascular disease and modern glucose-lowering, lipid-lowering and antihypertensive treatment strategies.
- Metformin and lifestyle intervention reduce the risk of type 2 diabetes, but may not provide additional protection against cardiovascular disease when glycemia, lipids and blood pressure are well controlled.

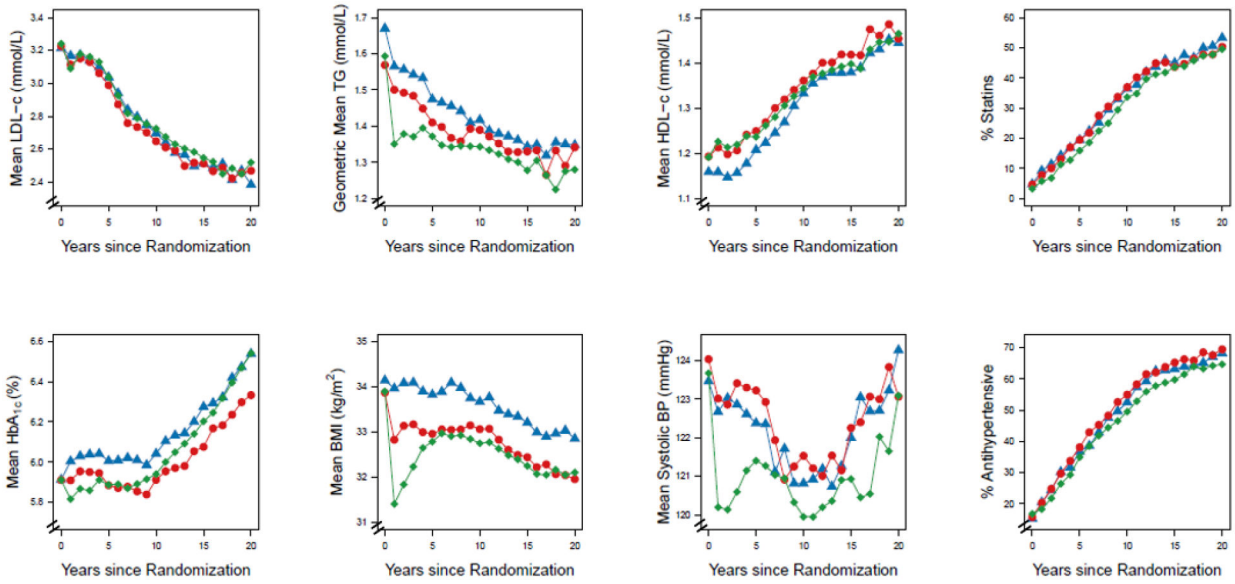



**Figure 1: Cardiovascular risk factors during follow-up**

The figure shows the trajectories of mean low density lipoprotein cholesterol (LDL-C), triglyceride (TG), systolic blood pressure (SBP), body mass index (BMI), high density lipoprotein cholesterol (HDL-C), glycosylated hemoglobin (HbA1c), and percent receiving statin and antihypertensive medications by intervention groups from randomization until the most recent datalock. Metformin is shown in red circles, lifestyle in green diamonds and placebo in blue triangles. (See also Table 1). All participants with data were used in the analyses for all time points either until they developed an event or in the absence of an event until the datalock. The number of participants at each timepoint (n) is as follows: baseline; n=3234, year 5; n=2573, year 10; n=2356, year 15; n=2144, year 20; n=1884.

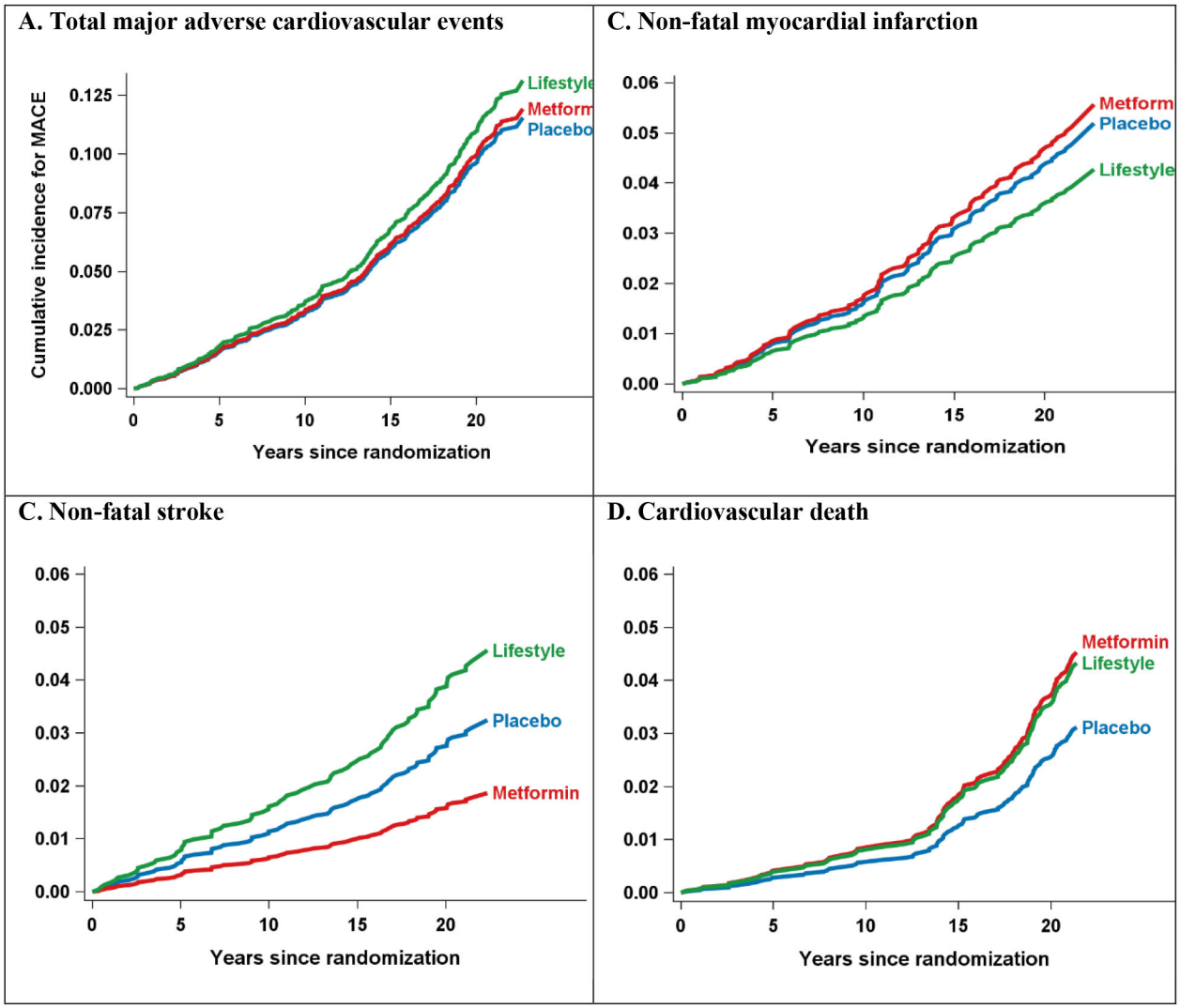



**Figure 2: Cumulative incidence of total major adverse cardiovascular (MACE) events and individual cardiovascular event components by intervention groups**

The figure shows the effects of the interventions on the cumulative incidence (%) of first major adverse cardiovascular events in Panel A. First occurrence of individual major cardiovascular component events shown are: Non-fatal myocardial infarction (Panel B), Non-fatal stroke (Panel C) and Cardiovascular death (Panel D). The metformin group is shown in red circles, the lifestyle group in green diamonds and the placebo group in blue triangles.

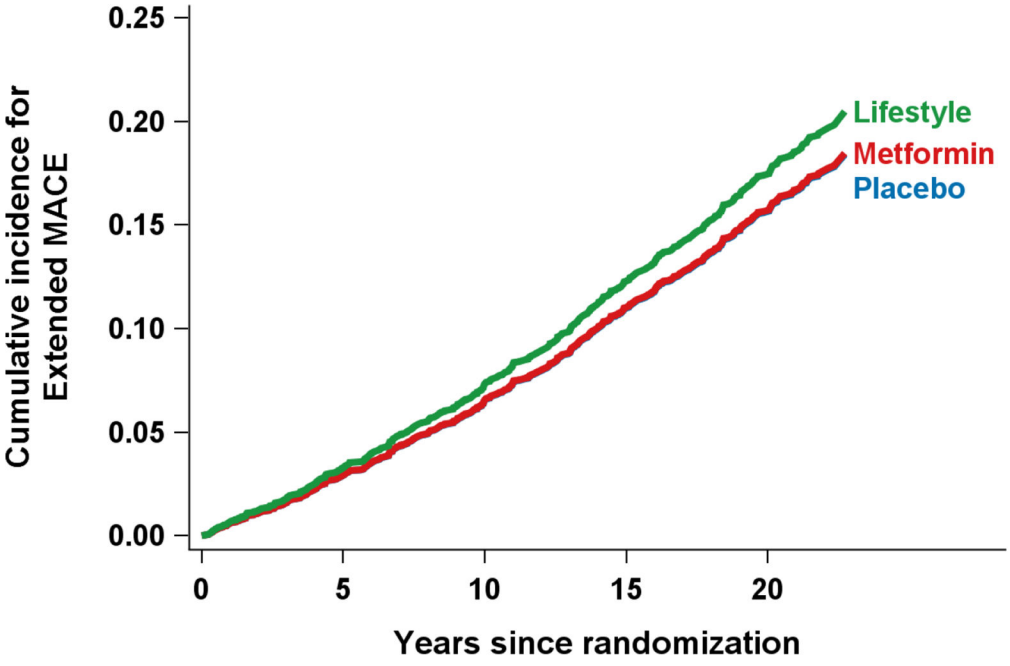
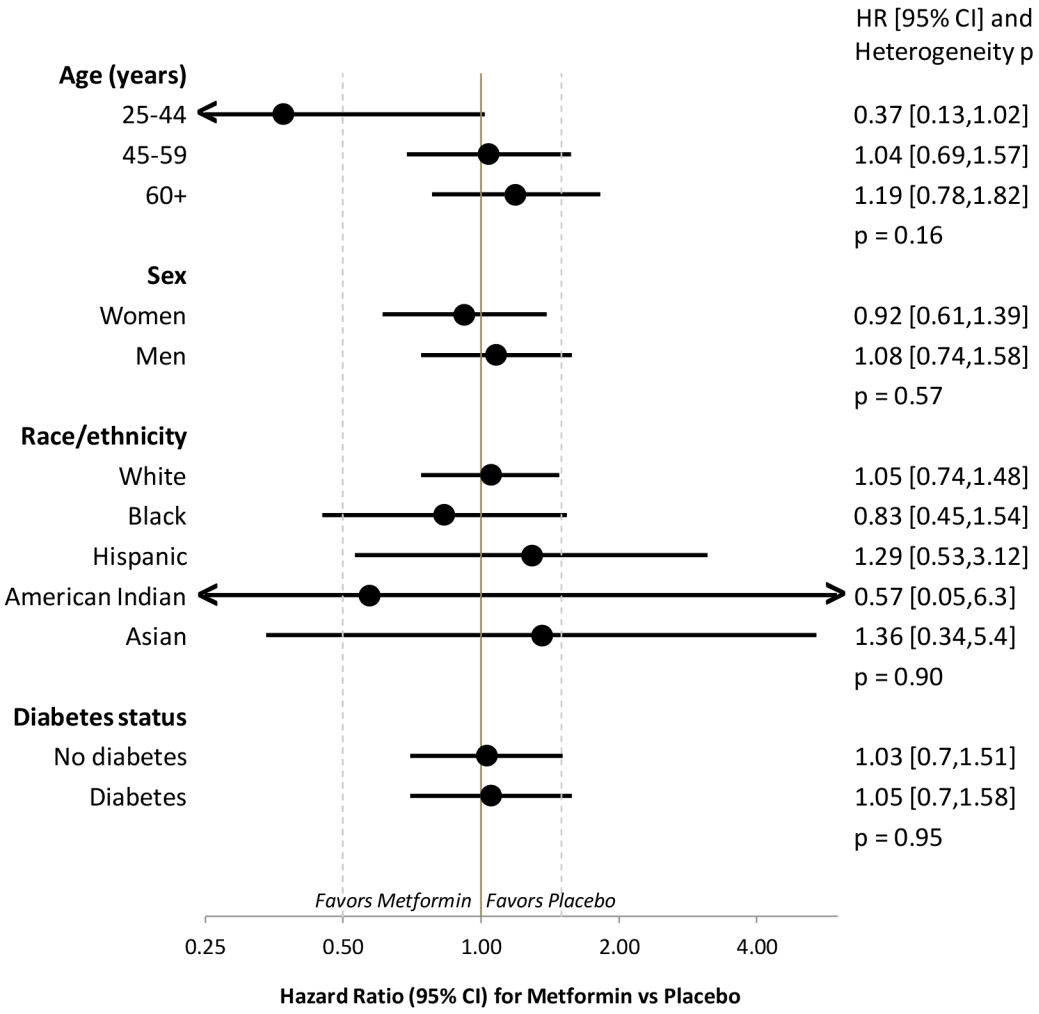



**Figure 3. Effect of metformin and lifestyle interventions versus placebo on cumulative incidence of the extended major adverse cardiovascular event (Extended MACE) outcome**

The figure shows the effects of the interventions on the cumulative incidence (%) of first occurrence of the extended cardiovascular event outcome. The metformin group is shown in red circles, the lifestyle group in green diamonds and the placebo group in blue triangles.

**A. Metformin vs Placebo**



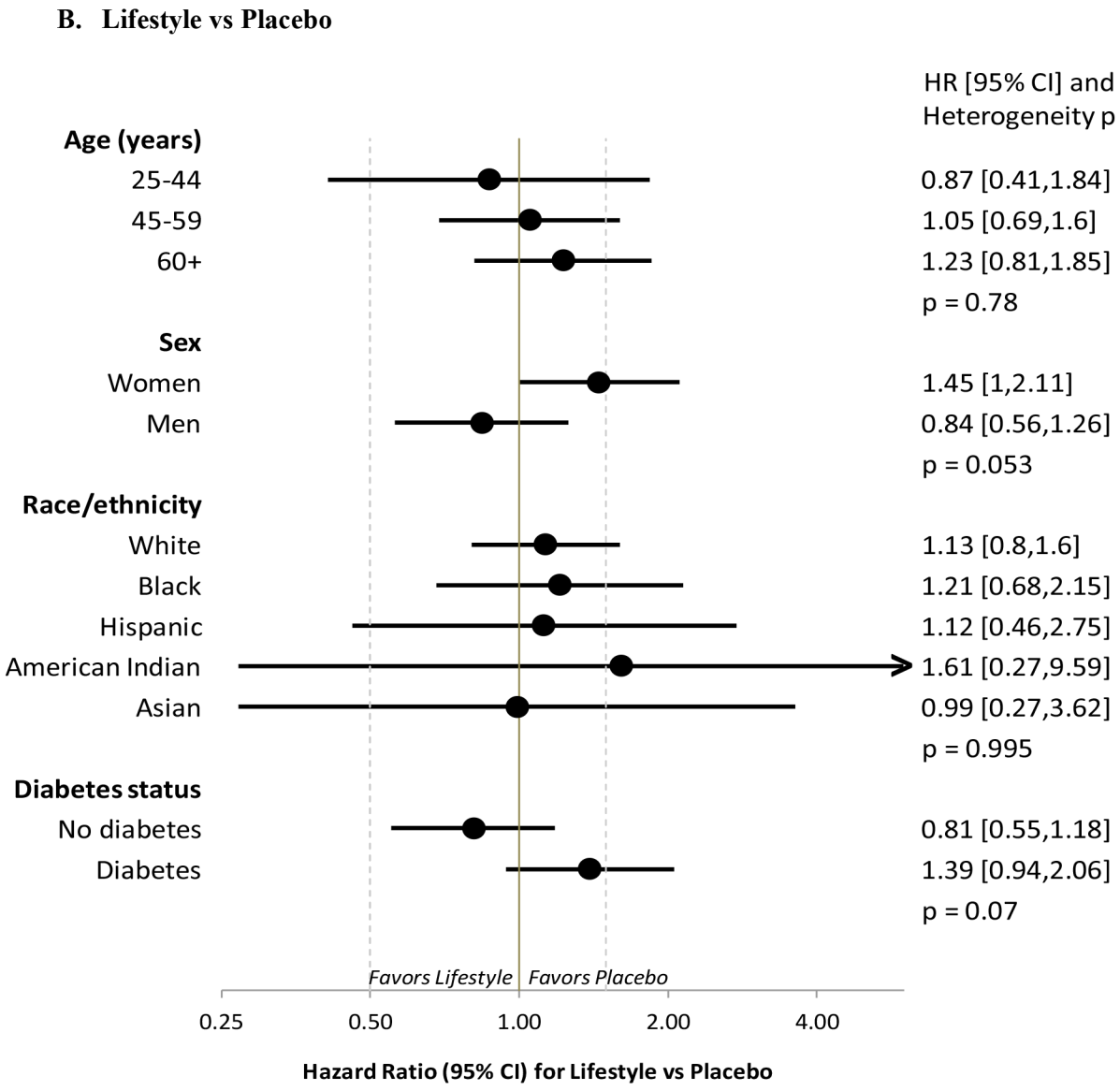



**Figure 4. Effect of metformin and lifestyle interventions versus placebo on the incidence of major adverse cardiovascular events by age, sex, race/ethnicity and diabetes status subgroups**

Panel A shows the effect of metformin versus placebo groups and Panel B the effect of lifestyle versus placebo groups on major cardiovascular events in prespecified age, sex, race/ethnicity and diabetes status subgroups showing hazard ratio (95% CI). The heterogeneity p values reflect the interaction of subgroup x treatment group to assess differences in treatment effect among subgroups. Absence of diabetes is defined as never having diabetes or not yet having developed diabetes. Arrows on the confidence interval indicate lower or upper bounds that extend beyond the axis.

**Table 1.**

Participant characteristics at baseline, and time-weighted mean during 21 years post-randomization follow-up, by original DPP randomized groups

| | Baseline (n=3234) | Characteristics During Follow-up | | | | |
|---|---|---|---|---|---|---|
| **Interventions** | | **Placebo (n=1073)** | **Metformin (n=1082)** | **Lifestyle (n=1079)** | **MET vs PLB p-value†** | **ILS vs PLB p-value†** |
| | | **Time-weighted mean during follow-up *** | | | | |
| BMI (kg/m2) | 34.0 (33.7, 34.2) | 33.6 (33.2–34.1) | 32.8 (32.4–33.3) | 32.5 (32.1–32.9) | 0.017 | <0.001 |
| Waist | 105 (105-106) | 106 (105–107) | 105 (104–106) | 104 (103–105) | 0.071 | 0.001 |
| Fasting glucose (mmol/L) | 5.9 (5.9-5.9) | 6.5 (6.4–6.6) | 6.2 (6.1–6.3) | 6.3 (6.2–6.4) | <0.001 | <0.001 |
| HbA1c (%) | 5.9 (5.9-5.9) | 6.1 (6.1–6.2) | 6.0 (6.0–6.0) | 6.0 (6.0–6.0) | <0.001 | 0.005 |
| HbA1c (IFCC) | 41.1 (40.9-41.3) | 43.4 (42.9–43.9) | 42.0 (41.5–42.5) | 42.4 (41.9–42.9) | <0.001 | 0.006 |
| Fasting insulin (pmol/l) | 160 [158-164] | 178 [174-184] | 165 [160–169] | 161 [156–166] | <0.001 | <0.001 |
| LDL-C (mmol/l) | 3.23 (3.20-3.26) | 2.83 (2.79–2.88) | 2.81 (2.77–2.8) | 2.85 (2.81–2.89) | 0.24 | 0.96 |
| HDL-C (mmol/l)# | 1.18 (1.17-1.19) | 1.27 (1.25–1.29) | 1.32 (1.3–1.34) | 1.30 (1.28–1.33) | 0.003 | 0.007 |
| Triglyceride (mmol/l) # | 1.61 [1.58-1.64] | 1.45 [1.42-1.49] | 1.40 [1.37-1.44] | 1.35 [1.32-1.39] | 0.052 | <0.001 |
| Systolic BP | 124 (123-124) | 122 (122–123) | 122 (122–123) | 121 (120–122) | 0.57 | 0.006 |
| Diastolic BP | 78 (78-79) | 73 (73–74) | 73 (73–74) | 73 (738–74) | 0.77 | 0.047 |
| Urine ACR (mg/mmol) | 0.67 [0.65-0.69] | 0.93 [0.88–0.98] | 0.90 [0.85–0.95] | 0.91 [0.86-0.96] | 0.41 | 0.61 |
| eGFR (ml/min/1.73 $m^2$) | 98.4 (97.8-99.0) | 89.6 (88.7–90.5) | 88.7 (87.8–89.7) | 88.7 (87.7–89.7) | 0.36 | 0.63 |
| **Percent with condition at baseline and during follow-up** | | | | | | |
| Smoking | | | | | 0.059 | 0.012 |
| Never | 59% | 60% | 63% | 61% | | |
| Past | 34% | 32% | 33% | 35% | | |
| Current | 7% | 8% | 5% | 4% | | |
| Hypertension % | 29% | 80% | 82% | 79% | 0.28 | 0.32 |
| Hyperlipidemia % | 69% | 94% | 92% | 91% | 0.09 | 0.03 |
| Diabetes % | n/a | 60% | 55% | 53% | 0.01 | 0.001 |
| Out-of-study metformin % | n/a | 43% | 28% | 37% | <.0001 | 0.002 |
| Antihypertensive medications % | 16% | 74% | 73% | 68% | 0.48 | 0.13 |
| Statin therapy % | 4% | 62% | 59% | 56% | 0.15 | 0.004 |

Baseline data are presented as mean (95% CI), or geometric mean [95% CI] for continuous measures and n (%) for categorical measures.

# Baseline levels of high density lipoprotein cholesterol lower and triglyceride were higher in placebo than in metformin and lifestyle groups.

* Characteristics over a median duration follow-up of 21 years were censored at the time of development of a major cardiovascular event and represent the marginal mean estimated from general estimating equation models as mean (95% CI), geometric mean [95% CI] or percent of the cohort with condition at any time during baseline or follow-up.

† p-value represents differences between groups throughout follow-up. Hypertension was defined as a BP140/90 or greater or taking antihypertensive medications; hyperlipidemia was defined as a triglyceride value≥150 mg/dl or an LDL-C≥130mg/dl or taking lipid lowering medications.

Conversion factors from conventional to SI units used are fasting insulin (uU/ml =6.945 pmol/L), glucose (mg/dl =0.0555 mmol/l), LDL-C and HDL-C (mg/dl =0.0259 mmol/l), triglyceride (mg/dl =0.0113 mmol/l), and urine ACR (mg/g =0.113 mg/mmol).

Abbreviations: MET=Metformin, PLB=Placebo, ILS=Intensive Lifestyle, BMI=Body Mass Index, HbA1c=glycated hemoglobin, IFCC=International Federation of Clinical Chemists, LDL-C=low density lipoprotein cholesterol=HDL-C, BP=Blood pressure, ACR=Albumin/creatinine ratio, eGFR=estimated glomerular filtration rate

**Table 2.**

Effect of metformin and lifestyle on first major adverse cardiovascular events and the first occurrence of individual major cardiovascular components and extended cardiovascular outcome events.

| Cardiovascular events | Number of Events | | | Event Rate/1000 person-year | | | Metformin versus Placebo | | Lifestyle versus Placebo | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo | Metformin | Lifestyle | Placebo | Metformin | Lifestyle | Hazard Ratio (95% CI) | p | Hazard Ratio (95% CI) | p |
| Total major adverse cardiovascular events | 98 | 101 | 111 | 5.28 | 5.51 | 6.10 | 1.03 (0.78, 1.37) | 0.81 | 1.14 (0.87, 1.50) | 0.34 |
| Non-fatal myocardial infarction | 43 | 46 | 35 | 2.30 | 2.49 | 1.90 | 1.07 (0.71, 1.63) | 0.73 | 0.82 (0.52, 1.28) | 0.38 |
| Non-fatal stroke | 28 | 16 | 39 | 1.48 | 0.86 | 2.12 | 0.57 (0.31, 1.06) | 0.07 | 1.42 (0.87, 2.30) | 0.16 |
| Cardiovascular death | 27 | 39 | 37 | 1.42 | 2.07 | 1.99 | 1.46 (0.90, 2.39) | 0.13 | 1.40 (0.85, 2.29) | 0.19 |
| Extended cardiovascular events outcome | 157 | 157 | 174 | 8.73 | 8.86 | 9.93 | 1.00 (0.80, 1.25) | 0.99 | 1.12 (0.90, 1.39) | 0.29 |