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Authors

Merino, Jordi
Jablonski, Kathleen A
Mercader, Josep M
et al.

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Interaction Between Type 2 Diabetes Prevention Strategies and Genetic Determinants of Coronary Artery Disease on Cardiometabolic Risk Factors

Jordi Merino,[1,2,3,4,5] Kathleen A. Jablonski,[6] Josep M. Mercader,[1,2,3] Steven E. Kahn,[7] Ling Chen,[1,2,3] Maegan Harden,[8] Linda M. Delahanty,[2,4] Maria Rosario G. Araneta,[9] Geoffrey A. Walford,[1,2] Suzanne B.R. Jacobs,[1,2,3] Uzoma N. Ibebuogu,[10] Paul W. Franks,[11,12,13] William C. Knowler,[14] and Jose C. Florez,[1,2,3,4] for the Diabetes Prevention Program Research Group*

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Coronary artery disease (CAD) is more frequent among individuals with dysglycemia. Preventive interventions for diabetes can improve cardiometabolic risk factors (CRFs), but it is unclear whether the benefits on CRFs are similar for individuals at different genetic risk for CAD. We built a 201-variant polygenic risk score (PRS) for CAD and tested for interaction with diabetes prevention strategies on 1-year changes in CRFs in 2,658 Diabetes Prevention Program (DPP) participants. We also examined whether separate lifestyle behaviors interact with PRS and affect changes in CRFs in each intervention group. Participants in both the lifestyle and metformin interventions had greater improvement in the majority of recognized CRFs compared with placebo ($P < 0.001$) irrespective of CAD genetic risk ($P_{interaction} > 0.05$). We detected nominal significant interactions between PRS and dietary quality and physical activity on 1-year change in BMI, fasting glucose, triglycerides, and HDL cholesterol in individuals randomized to metformin or placebo, but none of them achieved the multiple-testing correction for significance. This study confirms that diabetes preventive interventions improve CRFs regardless of CAD genetic risk and delivers hypothesis-generating data on the varying benefit of increasing physical activity and improving diet on intermediate cardiovascular risk factors depending on individual CAD genetic risk profile.

The risk of coronary artery disease (CAD), the leading cause of disability and mortality worldwide (1), is increased by known cardiometabolic risk factors (CFRs), such as obesity, high blood pressure, impaired lipid and glucose metabolism, and systemic inflammation (2,3). These metabolic features are also present in many individuals with type 2 diabetes, which may contribute to the approximate doubling of CAD risk in persons with diabetes (4,5). A number of studies have demonstrated the

[1]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA
[2]Diabetes Unit, Massachusetts General Hospital, Boston, MA
[3]Programs in Metabolism and Medical and Population Genetics, Eli and Edythe L. Broad Institute of MIT and Harvard, Cambridge, MA
[4]Department of Medicine, Harvard Medical School, Boston, MA
[5]Research Unit on Lipids and Atherosclerosis, CIBERDEM, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Reus, Spain
[6]The Biostatistics Center, Department of Epidemiology and Biostatistics, Milken Institute School of Public Health, The George Washington University, Rockville, MD
[7]Division of Metabolism, Endocrinology and Nutrition, VA Puget Sound Health Care System and University of Washington, Seattle, WA
[8]Genomics Platform, Eli and Edythe L. Broad Institute of MIT and Harvard, Cambridge, MA
[9]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA
[10]Division of Cardiovascular Diseases, Department of Medicine, The University of Tennessee Health Science Center, Memphis, TN
[11]Genetic & Molecular Epidemiology Unit, Lund University Diabetes Centre, Malmo, Sweden
[12]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[13]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA
[14]Diabetes Epidemiology and Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ

Corresponding author: Jose C. Florez, jcflorez@partners.org

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*A complete list of the Diabetes Prevention Program Research Group members can be found in the Supplementary Data.

effectiveness of control of CRFs in reducing the risk of cardiovascular outcomes among patients with type 2 diabetes (6–10).

Individual risk of CAD and type 2 diabetes reflects the interplay between lifestyle behaviors acting on a backdrop of genetic predisposition (11,12). Previous studies have shown that preventive interventions for type 2 diabetes—including lifestyle intervention programs, increasing physical activity, dietary modifications, and the administration of metformin—can improve CRFs among individuals with dysglycemia (13–15). However, it is unclear whether the benefits of type 2 diabetes preventive interventions on CRFs are similar for individuals at lower or higher genetic risk for CAD.

In the current study, we leveraged data from the Diabetes Prevention Program (DPP) to examine whether type 2 diabetes prevention strategies, either an intensive lifestyle intervention (ILS) or metformin treatment (MET), modify the association between CAD genetic risk and CRFs in participants at high risk of type 2 diabetes. In addition, we investigated the extent to which separate lifestyle behaviors including physical activity, dietary quality, and body weight loss interact with CAD genetic risk to differently affect CRFs in each DPP intervention group.

RESEARCH DESIGN AND METHODS

DPP

The Diabetes Prevention Program Research Group conducted a multicenter randomized controlled trial in the U.S. that tested the effects of ILS and MET interventions on the incidence of diabetes in glucose-intolerant individuals as previously described in detail (16,17). In brief, a total of 3,234 participants with fasting plasma glucose levels between 5.3 and 6.9 mmol/L, and 2-h plasma glucose levels between 7.8 and 11.0 mmol/L during a standard 75-g oral glucose tolerance test, were randomized to ILS ($n = 1,079$), MET (850 mg twice daily [$n = 1,073$]), or placebo (PBO [$n = 1,082$]). The ILS arm included individual counseling sessions through which participants were encouraged to achieve and maintain a weight reduction of at least 7% of initial body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 min per week. A total of 2,658 participants with available DNA, detailed lifestyle information, and CRF measurements had paired information at both baseline and 1-year follow-up. Each clinical center and the coordinating center obtained institutional review board approval. The 2,658 included in this report provided written informed consent for the main study and subsequent genetic investigations.

Lifestyle Behaviors

Specific lifestyle behaviors including changes in physical activity, dietary quality, and weight loss were assessed at baseline and 1 year. Self-reported levels of leisure-time physical activity were assessed at baseline and after 1 year of follow-up with the Modifiable Activity Questionnaire (18). The physical activity level was calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the MET of the activity and summed for all activities performed. Usual daily caloric intake during the previous year, including calories from fat, carbohydrate, protein, and other nutrients, was assessed with a modified version of the Block Food Frequency Questionnaire (19). We further characterized overall dietary quality at baseline and after 1 year of follow up using the Alternate Healthy Eating Index-2010 (AHEI-2010) (20). The AHEI-2010 score is based on 11 foods and nutrients emphasizing higher intake of vegetables (excluding potatoes), fruits, whole grains, nuts and legumes, long-chain n-3 fats, and polyunsaturated fatty acids; moderate intake of alcohol; and lower intake of sugar-sweetened drinks and fruit juice, red and processed meats, *trans* fat, and sodium. Each component is scored from 0 (unhealthiest) to 10 (healthiest) points, with intermediate values scored proportionally. All component scores were summed to obtain a total score ranging from 0 (nonadherence) to 110 (best adherence) points. Body weight change was defined by the difference between baseline and 1-year follow-up.

Baseline and 1-Year CRF Measurements

We considered the following well-established risk factors for CAD at baseline and 1-year follow-up: BMI, waist circumference (WC), fasting glucose, LDL cholesterol (LDLc), HDL cholesterol (HDLc), triglycerides (TG), systolic (SBP) and diastolic (DBP) blood pressure, C-reactive protein (CRP), fibrinogen, and tissue plasminogen activator (tPA). Measurements were performed at baseline and at 1-year follow-up (95% of participants completed the 1-year follow-up). We also included diabetes incidence as an intermediate CAD risk factor. Diabetes incidence was ascertained at the end of study follow-up. Anthropometric measures included height, weight, waist circumference, and SBP and DBP using standardized methods. Participants fasted for 12 h the night before blood was drawn from an antecubital vein. Standard blood glucose and lipid measurements (TG, HDLc, calculated LDLc) were performed at the DPP central biochemistry laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, WA) using enzymatic methods standardized to the Centers for Disease Control and Prevention reference methods (21). Measurements of inflammatory markers, including CRP, fibrinogen, and tPA, were also performed at the DPP central biochemistry laboratory as previously reported (13,22).

Genotyping and CAD Polygenic Risk Score

We extracted DNA from peripheral blood leukocytes. Genotyping was done with the HumanCoreExome genotyping array from Illumina at the Genomics Platform. Genotypes were called using Birdsuite (https://www.broadinstitute.org/birdsuite/birdsuite-analysis). A two-stage imputation procedure consisting of prephasing the genotypes into whole chromosome haplotypes followed by imputation itself was conducted. The prephasing was

performed using SHAPEIT2 (23). We used 1000 Genomes phase 3 haplotypes as the reference panel (24), and the genotype imputation was done using IMPUTE2 (25). We derived a polygenic risk score (PRS) of 204 variants representative of all the 160 CAD loci that had achieved genome-wide significance for association with CAD in previous association studies published as of December 2017 (26) and used recently to predict the risk of major CAD events among participants with type 2 diabetes at high cardiovascular risk (27) (Supplementary Table 1). For loci with multiple independent variants, the variant with the highest significant association with CAD reported in literature (lead variant) was selected first, followed by any other variant at that locus (independent variant) that was not in linkage disequilibrium ($r^2 < 0.2$) with the lead variant. Three of the 204 CAD risk-increasing variants (rs7797644, rs9365196, and rs9457995) were not available in the DPP genome-wide association study data set (neither were proxies in linkage disequilibrium [$r^2 > 0.8$]). A total of 138 of the 201 CAD risk–increasing variants considered in the study were genotypes and the remaining 63 imputed at high quality (median info score 0.99 [interquartile range 0.97–1.00]).

For calculation of the CAD PRS, each variant was recoded as 0, 1, or 2 according to the number of risk alleles (CAD increasing alleles) and weighted by its relative effect size (β-coefficient) on CAD obtained by the literature-based estimates. We calculated the CAD PRS by using the following equation: $\text{PRS} = (\beta_1 \times \text{SNP}_1 + \beta_2 \times \text{SNP}_2 + \ldots + \beta_{201} \times \text{SNP}_{201}) \times (201/\text{sum of the } \beta\text{-coefficients})$, where SNP_i is the risk allele number of each single nucleotide polymorphism. The CAD PRS ranges from 0 to 402, with each unit corresponding to one average risk allele and higher scores indicating a higher genetic predisposition to CAD. For participants with missing genetic variants, we adjusted the CAD PRS by the number of missing values. Distribution of the weighted CAD PRS falls into the normal distribution curve (Supplementary Fig. 1).

Statistical Analysis

Baseline characteristics that are continuous variables are reported as mean ± SD if normally distributed or as median (25th, 75th percentiles) if not. Categorical variables are presented as frequency. We used generalized linear models to estimate the association of the CAD PRS with CRFs at baseline after adjustment for age at randomization, sex, and the top 10 principal components (PCs) for ancestry. Nonnormally distributed outcomes were log transformed and presented on the ratio scale, exp(β), as the estimated value of CRFs per each 10-unit increase in CAD PRS. In this case, the estimated effect size corresponds with a fractional difference in CRFs. For example, a ratio of 0.9 indicates that the outcome variable changes by a ratio of 0.9 (i.e., 10% lower) per 10-unit higher PRS. Associations were also tested for changes from baseline to 1 year with interaction terms for intervention arms (ILS or MET vs. PBO) after adjustment for age at randomization, sex, PCs, and the respective baseline CRFs. We used Cox proportional hazards models adjusted for the same confounders to investigate the association between CAD PRS and diabetes incidence and the extent to which type 2 diabetes–preventive interventions modified the association between CAD PRS and diabetes incidence. We also tested associations of changes in physical activity, dietary quality, and body weight with 1-year change in CRFs in each treatment group separately. We investigated potential interactions between lifestyle behaviors and PRS on 1-year change in CRFs in each treatment group separately. For statistically significant interactions ($P < 0.05$), we tested the associations between each 1-SD increase in lifestyle variables and 1-year change in CRFs among individuals classified as at low, intermediate, and high genetic risk on the basis of thirds of the CAD PRS. For each category, we used general linear models after adjustment for age at randomization, sex, the top 10 PCs for ancestry, and the respective baseline CRFs. For rejection of the null hypothesis that type 2 diabetes prevention strategies did not modify the association between CAD genetic risk and CRFs, a two-sided α-level of 0.05 was used to determine statistical significance. SAS, version 9.3, was used for all analyses (SAS Institute, Cary, NC).

Data and Resource Availability

Data used in this study are available on request at dppmail@bsc.gwu.edu or by accessing the NIDDK Central Repository.

RESULTS

To investigate whether type 2 diabetes prevention strategies modify the association between CAD genetic risk and CRFs, we used genetic and clinical data collected from 2,658 participants in the DPP. Participants randomly assigned to PBO, ILS, or MET groups displayed no significant differences in baseline characteristics—exception for a lower HDLc and higher TG in the PBO individuals compared with individuals assigned to MET or ILS (Table 1). There were also no major clinical differences between participants included in this study and all DPP participants (Supplementary Table 2).

We first assessed the association between CAD PRS and CRFs before intervention in all three treatment groups combined. At baseline, each 10–risk allele increase in the CAD PRS was associated with higher LDLc (mmol/L) (β = 0.09 [95% CI 0.06, 0.13], $P < 0.01$) and higher DBP (mmHg) (β = 0.52 [95% CI 0.09, 0.95], $P = 0.02$) after adjustment for age at randomization, sex, and PCs ancestry markers (Table 2). Adjusted mean values of baseline lipid levels and DBP across CAD PRS quartiles are provided in Supplementary Fig. 2. No additional associations were found between CAD PRS and other baseline CRFs, including glycemic traits, anthropometric measures, and inflammation markers (Table 2).

We next investigated the effect of type 2 diabetes–preventive strategies, CAD PRS, and the interaction between them on 1-year change in CRFs. Participants

Table 1—Baseline characteristics of DPP participants according to randomization group among those included in the present analysis

	Total (n = 2,658)	PBO (n = 888)	MET (n = 880)	ILS (n = 890)	P*
Demographics					
Age, years	50.7 ± 10.7	50.6 ± 10.4	50.9 ± 10.3	50.6 ± 11.4	0.93
Female sex	1,789 (67.3)	607 (68.4)	583 (66.3)	599 (67.3)	0.641
Race/ethnicity					
White	1,476 (55.5)	490 (55.2)	507 (57.6)	479 (53.8)	0.298
African American	537 (20.2)	186 (20.9)	178 (20.2)	173 (19.4)	
Hispanic	451 (17.0)	147 (16.6)	143 (16.3)	161 (18.1)	
Other	194 (7.3)	65 (7.3)	52 (5.9)	77 (8.7)	
Current smoker	192 (7.2)	69 (7.8)	60 (6.8)	63 (7.1)	0.726
Hyperlipidemia	136 (5.1)	50 (5.6)	47 (5.3)	39 (4.4)	0.486
On lipid-lowering medication	126 (4.7)	45 (5.1)	45 (5.1)	36 (4.0)	0.455
Hypertension	427 (16.1)	139 (15.7)	140 (15.9)	148 (16.6)	0.845
SBP, mmHg	123.7 ± 14.7	123.5 ± 14.4	124.2 ± 15.0	123.5 ± 14.6	0.961
DBP, mmHg	78.3 ± 9.3	78.0 ± 9.2	78.3 ± 9.5	78.5 ± 9.1	0.227
Anthropometrics and lifestyle					
BMI, kg/m^2	34.1 ± 6.6	34.3 ± 6.7	34.0 ± 6.6	34.0 ± 6.6	0.312
Waist circumference, cm	105.3 ± 14.5	105.5 ± 14.3	105.0 ± 14.4	105.4 ± 14.8	0.823
AHEI-2010, units	46.4 ± 10.1	45.9 ± 10.2	44.9 ± 9.9	48.6 ± 9.9	0.001
MET h/week#	9.5 (3.8, 20.3)	9.8 (4.0, 21.1)	9.9 (3.8, 21.2)	9.1 (3.8, 18.1)	0.180
Biochemical					
Fasting glucose, mmol/L	5.93 ± 0.45	5.95 ± 0.47	5.92 ± 0.46	5.92 ± 0.44	0.117
HOMA-IR, units#	6.2 (4.3, 9.0)	6.2 (4.2, 8.8)	6.2 (4.3, 9.1)	6.2 (4.3, 9.1)	0.938
Total cholesterol, mmol/L	5.27 ± 0.94	5.26 ± 0.94	5.26 ± 0.93	5.28 ± 0.95	0.638
LDLc, mmol/L	3.23 ± 0.85	3.22 ± 0.86	3.23 ± 0.84	3.24 ± 0.85	0.692
HDLc, mmol/L#	1.14 (0.96, 1.35)	1.11 (0.96, 1.32)	1.14 (0.98,1.32)	1.14 (0.96, 1.35)	0.022
TG, mmol/L#	1.61 (1.12, 2.31)	1.67 (1.18, 2.37)	1.58 (1.11, 2.25)	1.57 (1.09, 2.27)	0.005
CRP, mg/dL#	0.38 (0.17, 0.77)	0.38 (0.17, 0.80)	0.36 (0.17, 0.74)	0.39 (0.18, 0.76)	0.472
tPA, ng/mL#	11.0 (8.8, 13.4)	10.9 (8.8, 13.5)	10.9 (8.7, 13.2)	11.2 (8.7, 13.5)	0.902
Fibrinogen, μmol/L	11.3 ± 2.5	11.4 ± 2.6	11.2 ± 2.5	11.3 ± 2.5	0.840
Genetics: genetic risk score, units	172 ± 9	172 ± 9	172 ± 9	173 ± 9	0.222

Values are given as the mean ± SD or median (25th, 75th percentile) except for qualitative variables expressed as n (%). HOMA-IR, HOMA of insulin resistance. *P values obtained by #Kruskall-Wallis, ANOVA, and χ^2 tests with 2 df as appropriate.

randomized to ILS had greater improvement in all studied CRFs compared with those in the PBO group ($P < 0.01$ for all) (Table 3). Individuals randomized to MET displayed a significant improvement in glycemia, anthropometric measures, LDLc, HDLc, CRP, and tPA compared with PBO (Table 3). The PRS did not significantly predict 1-year changes in CRFs when we analyzed the entire study population together or in any of the study arms ($P > 0.05$ for all) (Table 4). The effect of the interaction between CAD PRS and type 2 diabetes–preventive strategies on CRFs outcomes was not significant ($P_{\text{interaction}} > 0.05$ for all) (Table 5).

We further evaluated associations between changes in physical activity, diet, and body weight and 1-year change in CRFs in each treatment group and the extent to which lifestyle behaviors interacted with CAD PRS to differently affect 1-year change in CRFs. The greatest changes in physical activity, diet, and body weight were observed in ILS compared with PBO ($P < 0.01$ for all) (Supplementary Table 3). We showed that changes in body weight improved the majority of CRF parameters irrespectively of the intervention arm ($P < 0.01$ for all except fibrinogen [Supplementary Table 4]) and that changes in physical activity and dietary score associated with improved anthropometrics, blood lipids, and blood pressure measures among participants in the lifestyle intervention arm (Supplementary Tables 5 and 6). We detected nominal significant interactions between PRS and healthy diet and physical activity on 1-year change in BMI, fasting glucose, TG, and HDLc in individuals randomized to MET or PBO, but none of them achieved the multiple-testing correction for significance (Supplementary Table 7). Among these hypothesis-generating interactions, we highlight the association between increasing dietary quality and 1-year changes in BMI among individuals randomized to MET, which was more prominent in participants at high genetic risk ($P_{\text{interaction}} = 0.01$). Mean ± SE changes in BMI per 1-SD increase in diet quality score were −0.19 ± 0.10, −0.29 ± 0.10, and −0.52 ± 0.11 kg/m^2 among participants at low, intermediate, and high genetic risk, respectively (Supplementary Table 7).

DISCUSSION

Our findings in the DPP provide evidence on the interplay between genetic factors and type 2 diabetes–preventive strategies on intermediate CRFs. We show that either an ILS or MET has a beneficial effect on 1-year change in different CRFs. While a genetic risk score (comprised of 201 variants associated with CAD) does not appear to

Table 2—Baseline association between the genetic risk score and CAD risk factors

	PRS		
CRF	β	95% CI	*P*
BMI, kg/m^2	−0.029	−0.319, 0.261	0.845
Waist circumference, cm	0.071	−0.583, 0.724	0.832
Fasting glucose, mmol/L	0.007	0.014, 0.028	0.507
LDLc, mmol/L	0.094	0.055, 0.133	<0.001
HDLc, mmol/L#	0.991	0.980, 1.001	0.090
TG, mmol/L#	1.017	0.994, 1.041	0.157
SBP, mmHg	0.544	−0.107, 1.197	0.102
DBP, mmHg	0.524	0.094, 0.953	0.017
CRP, mg/dL#	1.029	0.982, 1.077	0.230
tPA, ng/mL#	0.996	0.980, 1.014	0.694
Fibrinogen, μmol/L	0.039	−0.077, 0.154	0.511

Each CRF represents a separate general linear model on the association between baseline risk factor levels and the increment of 10 risk alleles in the PRS. *P* value derived by general linear model adjusted for age at randomization, sex, and PCs ancestry markers. #Regression coefficients for natural log–transformed CRFs are expressed as exp(β) differences in baseline risk factor levels.

alter the effectiveness of either intervention, we show preliminary evidence that increasing physical activity and adhering to a healthy dietary pattern may have a more prominent effect on BMI, fasting glucose, and TG in people at high genetic risk who were not assigned to an ILS. However, these findings warrant further replication in appropriate randomized clinical studies specially designed to investigate such effects. Taken together, our data suggest that independent of genetic risk, interventions designed to prevent the development of type 2 diabetes in individuals with elevated fasting glucose, impaired glucose tolerance, and overweight/obesity can improve the majority of recognized cardiovascular risk factors and that among individuals not randomized to an ILS, the benefit of increasing physical activity and improving diet may vary depending on individual CAD genetic risk profile.

There are three important findings. First, a PRS for CAD is associated with baseline lipid levels and DBP but was not associated with other CAD risk factors such as glycemia or inflammatory markers and did not predict 1-year change in these CRFs during preventive interventions for type 2 diabetes. Our findings that CAD PRS has a strong association with lipid levels is well aligned with findings of previous studies (28–31), but the positive association with other intermediate risk factors such as DBP or the lack of association with inflammation parameters has not previously been reported as far as we know. While our results need to be interpreted with caution in the context of multiple hypothesis testing, the most recent data on the genetic overlap between CAD and CRFs suggested that 5–10% of CAD loci relate to blood pressure (32). The potential mechanism linking overlapping loci is likely to be via vascular tone regulation and platelet aggregation (28,33), features that have been predominantly linked with SBP rather than DBP and have inflammation as a common underlying factor (2). Our findings, in individuals at high risk of developing type 2 diabetes, where hypertension is a key feature of the metabolic abnormalities present in individuals with type 2 diabetes, highlight the role of DBP in the complex overlap between CRFs and the polygenic architecture of CAD.

Second, the type 2 diabetes–preventive intervention strategies that we evaluated, MET and ILS, did not interact with CAD genetic risk to differently affect 1-year change in

Table 3—Effect of type 2 diabetes–preventive strategies on 1-year change in CAD risk factors by study intervention

CRF	PBO (*n* = 888)	MET (*n* = 880)	ILS (*n* = 890)	$P_{ILS\ vs.\ PBO}$	$P_{MET\ vs.\ PBO}$
BMI, kg/m^2	−0.192 (−0.326, −0.057)	−0.911 (−1.047, −0.774)	−2.465 (−2.601, −2.330)	<0.001	<0.001
Waist circumference, cm	−0.843 (−1.268, −0.417)	−2.153 (−2.582, −1.725)	−6.479 (−6.905, −6.053)	<0.001	<0.001
Fasting glucose, mmol/L#	0.001 (−0.006, 0.007)	−0.039 (−0.045, −0.032)	−0.052 (−0.058, −0.045)	<0.001	<0.001
LDLc, mmol/L	−0.060 (−0.097, −0.023)	−0.116 (−0.154, −0.078)	−0.161 (−0.199, −0.124)	<0.001	0.038
HDL, mmol/L	−0.006 (−0.017, 0.005)	0.021 (0.010, 0.032)	0.038 (0.027, 0.049)	<0.001	<0.001
TG, mmol/L#	−0.060 (−0.084, −0.036)	−0.047 (−0.071, −0.023)	−0.169 (−0.193, −0.145)	<0.001	0.452
SBP, mmHg	−0.728 (−1.538, 0.081)	−0.856 (−1.672, −0.040)	−3.003 (−3.814, −2.192)	<0.001	0.828
DBP, mmHg	−0.955 (−1.483, −0.428)	−1.259 (−1.791, −0.728)	−3.550 (−4.078, −3.022)	<0.001	0.427
CRP, mg/dL#	−0.020 (−0.069, 0.029)	−0.146 (−0.196, −0.097)	−0.396 (−0.445, −0.347)	<0.001	<0.001
tPA, ng/mL	−0.712 (−0.910, −0.515)	−2.049 (−2.249, −1.849)	−2.564 (−2.762, −2.367)	<0.001	<0.001
Fibrinogen, μmol/L	0.084 (−0.039, 0.208)	−0.063 (−0.188, 0.061)	−0.298 (−0.421, −0.174)	<0.001	0.100

Values in this table represent adjusted mean (95% CI) change in CRF levels. *P* values from *t* tests comparing mean change in ILS or MET with PBO derived by general linear model adjusted for baseline risk factor, age at randomization, sex, and PCs ancestry markers. #For nonnormally distributed variables, we calculated the natural log year 1 value minus natural log baseline value and show mean (95% CI) change in CRF levels.

Table 4—Association between CAD PRS and 1-year change in risk factors by study intervention

	All study participants (n = 2,658)		PBO (n = 888)		MET (n = 880)		ILS (n = 890)	
CRF	β (95% CI)	*P**	β (95% CI)	*P**	β (95% CI)	*P**	β (95% CI)	*P**
BMI, kg/m^2	0.013 (−0.084, 0.109)	0.799	0.015 (−0.134, 0.164)	0.841	0.021 (−0.121, 0.163)	0.770	0.001 (−0.204, −0.201)	0.994
Waist circumference, cm	−0.027 (−0.330, 0.277)	0.863	−0.008 (−0.474, 0.457)	0.972	−0.212 (−0.724, 0.288)	0.398	0.168 (−0.433, 0.769)	0.584
Fasting glucose, mmol/L#	0.998 (0.994, 1.004)	0.728	0.999 (0.988, 1.005)	0.414	0.998 (0.991, 1.005)	0.526	1.002 (0.995, 1.011)	0.502
Diabetes risk	1.021 (0.919, 1.136)	0.696	0.952 (0.809, 1.120)	0.552	1.088 (0.904, 1.309)	0.371	1.068 (0.851, 1.341)	0.571
LDLc, mmol/L	0.010 (−0.017, 0.036)	0.481	0.012 (−0.036, 0.059)	0.632	−0.019 (−0.065, 0.028)	0.424	0.034 (−0.012, 0.080)	0.152
HDLc, mmol/L	−0.007 (−0.015, 0.001)	0.075	−0.009 (−0.022, 0.003)	0.147	−0.002 (−0.016, 0.012)	0.822	−0.013 (−0.028, 0.002)	0.094
TG, mmol/L#	1.016 (0.999, 1.033)	0.059	1.009 (0.998, 1.038)	0.562	1.011 (0.993, 1.040)	0.427	1.028 (0.999, 1.058)	0.063
SBP, mmHg	0.489 (−0.088, 1.067)	0.097	0.685 (−0.314, 1.683)	0.179	−0.288 (−1.267, 0.692)	0.565	0.951 (−0.073, 1.974)	0.069
DBP, mmHg	0.085 (−0.291, 0.462)	0.657	0.052 (−0.606, 0.711)	0.876	−0.150 (−0.797, 0.497)	0.649	0.256 (−0.398, 0.911)	0.442
CRP, mg/dL#	0.981 (0.947, 1.015)	0.272	0.967 (0.913, 1.024)	0.252	1.007 (0.946, 1.067)	0.811	0.971 (0.927, 1.033)	0.354
tPA, ng/mL	0.056 (−0.085, 0.197)	0.440	0.090 (−0.162, 0.024)	0.484	0.081 (−0.155, 0.318)	0.501	0.229 (−0.214, 0.259)	0.850
Fibrinogen, μmol/L	−0.019 (−0.106, 0.069)	0.679	−0.028 (−0.188, 0.131)	0.728	0.006 (−0.142, 0.154)	0.935	−0.037 (−0.188, 0.115)	0.634

Each CRF represents a separate linear regression model on the association between 1-year change in CRF levels and the increment of 10 risk alleles in the PRS. Cox models were used to investigate the association between CAD PRS and diabetes incidence; estimates are reported as hazard ratios (95% CI). #Regression coefficients for natural log–transformed CRFs are expressed as exp(β) ratio of 1-year change in CAD risk factors in the entire study population and according to intervention group. **P* value derived by general linear model adjusted for baseline risk factor, age at randomization, sex, and PCs ancestry markers.

Table 5—Interaction between CAD PRS and intervention group on 1-year change in CAD risk factors

CRF	ILS vs. PBO $P_{interaction}$	MET vs. PBO $P_{interaction}$
BMI, kg/m^2	0.617	0.807
Waist circumference, cm	0.670	0.787
Fasting glucose, mmol/L#	0.181	0.394
Diabetes risk	0.166	0.198
LDLc, mmol/L	0.905	0.395
HDLc, mmol/L	0.486	0.586
TG, mmol/L#	0.649	0.838
SBP, mmHg	0.952	0.157
DBP, mmHg	0.348	0.818
CRP, mg/dL#	0.745	0.285
tPA, ng/mL	0.470	0.800
Fibrinogen, μmol/L	0.687	0.982

Values in this table represents adjusted interaction *P* values. $P_{interaction}$ values were derived by general linear models with interaction terms for intervention arms (ILS or MET vs. PBO), after adjustment for age at randomization, sex, the top 10 PCs for ancestry, and the respective baseline CRFs. Cox models were used to investigate interactions between type 2 diabetes prevention strategies and CAD PRS on diabetes incidence. #For nonnormally distributed variables, we calculated the natural log year 1 value minus natural log baseline value.

CRFs. In other words, participants were likely to benefit similarly from these interventions despite their genetic susceptibility for CAD. These findings need to be interpreted with caution, since it is possible that highly penetrant single genetic variants could interact with type 2 diabetes prevention strategies with strong effects on specific CRFs. The rationale to use a combined PRS in this study relies on the observation that, similar to type 2 diabetes, for the vast majority of individuals with CAD, genetic susceptibility results from the cumulative effects of numerous variants with modest effects disrupting multiple pathways at the same time (34). Our results are consistent with recent prospective observational studies that have reported that both lifestyle behaviors and genetic predisposition drive CAD risk without evidence of significant interactions (35). In addition, the DPP showed that an intenive lifestyle modification is effective for the prevention of type 2 diabetes regardless of genetic risk based on 34 type 2 diabetes–associated loci (36). Data from Look AHEAD (Action for Health in Diabetes), a long-term randomized clinical trial investigating whether an ILS for weight loss would decrease cardiovascular morbidity and mortality among individuals with type 2 diabetes, showed that a behavioral weight loss treatment did not alter the association between a CAD genetic risk and CAD (37). Findings from the current study in individuals at high risk of type 2 diabetes support the beneficial effect of early type 2 diabetes prevention strategies regardless of CAD genetic susceptibility.

Third, while our results need to be interpreted in the context of multiple hypothesis testing and lack of replication in independent randomized clinical studies (mainly due to the unavailability of similar resources), we found suggestive evidence that improving dietary quality and increasing physical activity may have a more favorable effect on 1-year changes in BMI, fasting glucose, and TG in people at high genetic risk for CAD than in those at low genetic risk. Thus, while an ILS aimed to achieve and maintain a weight reduction of at least 7% of initial body weight through diet and physical activity can effectively reduce intermediate CRFs regardless of genetic risk, the detection of an interaction of CAD genetic risk with dietary quality and physical activity in participants not assigned to the lifestyle intervention suggests a potential additional benefit in those who are at increased genetic risk for CAD. In these individuals not assigned to the lifestyle intervention, the adoption of at least specific lifestyle behaviors such as improving diet or increasing physical activity may be particularly beneficial. In other words, a comprehensive lifestyle intervention that achieves 7% weight loss is effective across the entire gradient of CAD genetic risk, whereas other combinations (such as MET with healthy lifestyles that have a less dramatic effect on weight loss) benefit most those at highest CAD risk. This hypothesis is supported by the observation that we did not see effects of significant interactions between changes in body weight, as a measure of the overall lifestyle modification, and genetic risk for CAD on specific CRFs. However, further studies are needed to confirm these initial findings.

Several limitations of our study are worth noting. First, the findings are based on a single randomized clinical trial. We were not able to conduct a replication study due to the lack of available genetic information in other similar clinical intervention studies that included individuals at high risk of developing type 2 diabetes (38,39). Second, we did not directly investigate the association between the CAD PRS and CAD events due to the unavailability of data in the current study; instead, we used CRFs, which provide early insights into the atherosclerosis disease process, as a proxy for CAD events. Third, the significant interactions we observed may be chance observations due to multiple testing or be affected by risk magnification (i.e., because participants at low risk of a clinical outcome cannot have large absolute risk reduction, the risk difference is magnified by having a higher baseline risk). Finally, while the CAD genetic variants included in our PRS were selected on the basis of the most novel discoveries of genetic variants for CAD risk, we cannot rule out the possibility that a PRS constructed from a different set of as-yet-undiscovered CAD risk variants will influence response to type 2 diabetes–preventive interventions.

In conclusion, our findings in individuals at high risk of type 2 diabetes provide evidence for the beneficial effects of type 2 diabetes–preventive strategies on CRFs regardless of CAD genetic risk profile. Additionally, the effect modification by improving dietary quality and increasing physical activity and diet on the association of CAD genetic risk with cardiovascular risk factors among individuals

randomized to MET or PBO illustrates how early CAD-preventive strategies may achieve slightly variable success in individuals with different genetic susceptibility.

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