

## SUPPLEMENTARY DATA

### **Supplement to: Interaction between type 2 diabetes prevention strategies and genetic determinants of coronary artery disease on cardiometabolic risk factors.**

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## SUPPLEMENTARY DATA

**Supplementary Table 1.** Characteristics of genetic variants used to build the coronary artery disease polygenic risk score.

## SUPPLEMENTARY DATA

**Supplementary Table 2.** Differences in baseline characteristics between the sample of participants included in this study and all Diabetes Prevention Program participants.

	DPP Study Sample (n=2,658)	All DPP (n=3,234)	P value*
<b>Demographics</b>			
Age, y	50.7 ± 10.7	50.6 ± 10.7	0.444
Sex, Female n (%)	1,789 (67.3)	2,191 (67.7)	0.242
Race/Ethnicity, n (%)			
White	1,476 (55.5)	1,768 (54.7)	<0.001
African American	537 (20.2)	645 (19.9)	
Hispanic	451 (17.0)	508 (15.7)	
Other	194 (7.3)	313 (9.6)	
Current Smoker, n (%)	192 (7.2)	226 (7.0)	0.306
Hyperlipidemia n (%)	136 (5.1)	169 (5.2)	0.824
On lipid lowering med, n (%)	126 (4.7)	157 (4.9)	0.567
Hypertension, n (%)	427 (16.1)	520 (16.1)	0.962
Systolic blood pressure, mm Hg	124 ± 15	124 ± 15	0.893
Diastolic blood pressure, mm Hg	78.3 ± 9.3	78 ± 9	0.625
<b>Anthropometrics &amp; Lifestyle</b>			
BMI, kg/m <sup>2</sup>	34.1 ± 6.6	34.0 ± 6.7	0.039
Waist circumference, cm	105 ± 15	105 ± 15	0.047
AHEI-2010, units	46.4 ± 10.1	44.2 ± 10.4 <sup>^</sup>	0.001
MET-hours/week <sup>#</sup>	9.5 (3.8, 20.2)	9.8 (3.9, 20.6)	0.286
<b>Biochemical</b>			
Fasting glucose, mmol/L	5.93 ± 0.45	5.91 ± 0.46	<0.001
HOMA-IR, units <sup>#</sup>	6.18 (4.25, 8.95)	6.16 (4.22, 8.85)	0.252
Total cholesterol, mmol/L	5.27 ± 0.94	5.26 ± 0.94	0.437
LDL-cholesterol, mmol/L	3.23 ± 0.85	3.23 ± 0.85	0.734
HDL-cholesterol, <sup>#</sup>	1.18 (0.96, 1.35)	1.10 (0.98, 1.30)	0.380

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Triglycerides, mmol/L <sup>#</sup>	1.61 (1.19, 2.31)	1.59 (1.12, 2.27)	0.236
CRP, mg/dl <sup>#</sup>	0.38 (0.17, 0.77)	0.37 (0.17, 0.76)	0.010
tPA, ng/ml <sup>#</sup>	11.0 (8.8, 13.4)	10.9 (8.7, 13.4)	0.078
Fibrinogen, umol/L	11.3 ± 2.5	11.5 ± 2.6	0.305

Values are given as the mean ± SD or median (25th, 75th percentile)<sup>#</sup> except for qualitative variables expressed as n (%). BMI; Body mass index, HOMA-IR; homeostasis model assessment of insulin resistance, CRP; C-reactive protein, tPA, tissue plasminogen activator.

\**P* values are generated from a general estimating equation models. ^ n=3,175

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**Supplementary Table 3.** One-year change in lifestyle components.

	PBO (n=865)	MET (n=852)	ILS (n=869)	P Met vs PBO	P ILS vs PBO
<b>Diet</b>					
1-y change AHEI-2010, units	1.49 ± 0.27	0.84 ± 0.27	4.22 ± 0.27	0.661	<0.001
<b>Physical activity</b>					
1-y change MET-hours/week	1.28 ± 1.05	1.46 ± 1.06	6.96 ± 1.05	0.588	<0.001
<b>Body weight loss, kg</b>	-0.53 ± 0.19	-2.55 ± 0.19	-6.9 ± 0.19	<0.001	<0.001

**Table Legend:** Values represents adjusted means ± SE. The change in physical activity is not normally distributed and has been ln transformed.

*P*-value extracted from general linear model adjusted for baseline lifestyle component, age at randomization, sex and ancestry markers.

Eating Index 2010 (AHEI-2010). MET-hours/week (Metabolic equivalents\*hours/week).

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**Supplementary Table 4.** Association between one-year change in body weight and one-year change in risk factors by study intervention.

Cardiometabolic risk factor	PBO (n=888)		MET (n=880)		ILS (n=890)	
	$\beta$ (95% CI)	P value*	$\beta$ (95% CI)	P value*	$\beta$ (95% CI)	P value*
BMI, kg/m <sup>2</sup>	-0.11 (-0.012, -0.010)	<0.001	-0.011 (-0.012, -0.010)	<0.001	-0.011 (-0.012, -0.010)	<0.001
Waist circumference, cm	-0.681 (-0.743, -0.619)	<0.001	-0.626 (-0.703, -0.549)	<0.001	-0.756 (-0.806, -0.706)	<0.001
Fasting glucose <sup>#</sup>	0.994 (0.993, 0.996)	<0.001	0.995 (0.994, 0.996)	<0.001	0.995 (0.994, 0.996)	<0.001
LDLc, mmol/L	-0.006 (-0.014, 0.002)	0.143	-0.011 (-0.019, -0.003)	0.008	-0.016 (-0.021, -0.010)	<0.001
HDLc, mmol/L	0.003 (0.005, 0.007)	0.002	0.008 (0.006, 0.010)	<0.001	0.004 (0.002, 0.006)	<0.001
Triglycerides <sup>#</sup>	0.981 (0.975, 0.990)	<0.001	0.978 (0.974, 0.984)	<0.001	0.981 (0.976, 0.989)	<0.001
Systolic BP, mmHg	-0.456 (-0.612, -0.285)	<0.001	-0.368 (-0.536, -0.199)	<0.001	-0.374 (-0.494, -0.254)	<0.001
Diastolic BP, mmHg	-0.220 (-0.329, -0.111)	<0.001	-0.197 (-0.309, -0.085)	<0.001	-0.245 (-0.321, -0.169)	<0.001
CRP <sup>#</sup>	0.966 (0.957, 0.975)	<0.001	0.974 (0.964, 0.983)	<0.001	0.964 (0.957, 0.971)	<0.001
tPA, ng/mL	-0.130 (-0.167, -0.093)	<0.001	-0.175 (-0.214, -0.136)	<0.001	-0.163 (-0.188, -0.137)	<0.001
Fibrinogen, umol/L	0.010 (-0.017, 0.037)	0.412	-0.004 (-0.020, 0.029)	0.784	-0.013 (-0.048, 0.005)	0.151

**Table Legend;** Each cardiometabolic risk factor represents a separate linear regression model on the association between in cardiometabolic risk factor levels and body weight loss (1kg). Regression coefficients for natural log transformed CRFs<sup>#</sup> are expressed as exp( $\beta$ ) ratio of one-year change in coronary artery disease risk factors according to intervention group.

BMI; Body mass index, CRP; C-reactive protein, tPA, tissue plasminogen activator.

\*P-value derived by general linear model adjusted for baseline risk factor, age at randomization, sex, and PCs ancestry markers.

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**Supplementary Table 5.** Association between one-year change in physical activity and one-year change in risk factors by study intervention.

Cardiometabolic risk factor	PBO (n=888)		MET (n=880)		ILS (n=890)	
	$\beta$ (95% CI)	P value*	$\beta$ (95% CI)	P value*	$\beta$ (95% CI)	P value*
BMI, kg/m <sup>2</sup>	-0.024 (-0.051, 0.016)	0.108	-0.015 (-0.022, 0.015)	0.458	-0.030 (-0.053, -0.011)	0.008
Waist circumference, cm	-0.084 (-0.195, 0.027)	0.136	-0.032 (-0.160, 0.097)	0.629	-0.227 (-0.439, -0.016)	0.035
Fasting glucose <sup>#</sup>	0.097 (0.991, 1.003)	0.416	0.999 (0.997, 1.001)	0.837	-0.998 (0.995, 1.001)	0.087
LDLc, mmol/L	0.003 (-0.008, 0.015)	0.554	-0.011 (-0.023, 0.001)	0.081	-0.005 (-0.021, 0.011)	0.563
HDLc, mmol/L	0.001 (-0.003, 0.003)	0.907	-0.002 (-0.006, 0.001)	0.249	0.001 (-0.004, 0.006)	0.693
Triglycerides <sup>#</sup>	0.996 (-0.980, 1.003)	0.235	0.997 (0.990, 1.005)	0.439	1.002 (0.991, 1.012)	0.759
Systolic BP, mmHg	-0.158 (-0.398, 0.081)	0.196	-0.150 (-0.399, 0.099)	0.238	-0.448 (-0.810, -0.087)	0.015
Diastolic BP, mmHg	-0.021 (-0.178, 0.137)	0.798	-0.101 (-0.265, 0.063)	0.226	-0.314 (-0.545, -0.084)	0.008
CRP <sup>#</sup>	1.009 (0.995, 1.023)	0.187	1.004 (0.989, 1.013)	0.613	0.990 (0.967, 1.012)	0.368
tPA, ng/mL	0.006 (-0.054, 0.067)	0.837	-0.027 (-0.091, 0.038)	0.420	-0.037 (-0.119, 0.046)	0.388
Fibrinogen, umol/L	0.035 (-0.004, 0.073)	0.076	0.001 (-0.024, 0.051)	0.482	0.001 (-0.005, 0.005)	0.959

**Table Legend:** Each cardiometabolic risk factor represents a separate linear regression model on the association between in cardiometabolic risk factor levels and increment of 10 MET-hours/week. Regression coefficients for natural log transformed CRFs<sup>#</sup> are expressed as exp( $\beta$ ) ratio of one-year change in coronary artery disease risk factors according to intervention group.

BMI; Body mass index, CRP; C-reactive protein, tPA, tissue plasminogen activator.

\*P-value derived by general linear model adjusted for baseline risk factor, age at randomization, sex, and PCs ancestry markers.

## SUPPLEMENTARY DATA

**Supplementary Table 6.** Association between one-year change in dietary score and one-year change in risk factors by study intervention.

Cardiometabolic risk factor	PBO (n=888)		MET (n=880)		ILS (n=890)	
	$\beta$ (95% CI)	P value*	$\beta$ (95% CI)	P value*	$\beta$ (95% CI)	P value*
BMI, kg/m <sup>2</sup>	-0.060 (-0.108, -0.013)	0.011	-0.071 (-0.150, -0.006)	0.005	-0.094 (-0.158, -0.026)	<0.001
Waist circumference, cm	-0.314 (-0.774, 0.146)	0.181	-0.703 (-1.241, -0.192)	0.007	-1.294 (-1.852, -0.192)	<0.001
Fasting glucose <sup>#</sup>	0.994 (0.983, 1.005)	0.231	0.997 (0.982, 1.010)	0.712	0.995 (0.988, 1.004)	0.253
LDLc, mmol/L	-0.011 (-0.058, -0.035)	0.648	0.030 (-0.016, 0.076)	0.206	-0.041 (-0.084, 0.001)	0.056
HDLc, mmol/L	0.003 (-0.001, 0.015)	0.662	0.013 (-0.001, 0.027)	0.056	0.022 (0.008, 0.036)	0.002
Triglycerides <sup>#</sup>	0.990 (0.961, 1.002)	0.539	0.966 (0.938, 0.996)	0.018	0.951 (0.928, 0.989)	0.008
Systolic BP, mmHg	-0.222 (-1.127, 0.762)	0.658	-0.811 (-1.794, -0.173)	0.106	-0.798 (-1.765, -0.170)	0.106
Diastolic BP, mmHg	-0.018 (-0.665, 0.629)	0.957	-0.783 (-1.429, -0.136)	0.018	-0.256 (-0.877, -0.365)	0.419
CRP <sup>#</sup>	0.933 (0.886, 0.990)	0.019	0.996 (0.943, 1.064)	0.914	0.938 (0.863, 0.980)	0.011
tPA, ng/mL	-0.126 (-0.375, 0.123)	0.320	-0.103 (-0.338, 0.132)	0.388	-0.165 (-0.388, 0.057)	0.145
Fibrinogen, umol/L	-0.017 (-0.174, 0.139)	0.829	-0.172 (-0.320, -0.024)	0.023	-0.133 (-0.276, 0.010)	0.067

**Table Legend:** Each cardiometabolic risk factor represents a separate linear regression model on the association between in cardiometabolic risk factor levels and increment of 10 units in the dietary score. Regression coefficients for natural log transformed CRFs<sup>#</sup> are expressed as exp( $\beta$ ) ratio of one-year change in coronary artery disease risk factors according to intervention group.

BMI; Body mass index, CRP; C-reactive protein, tPA, tissue plasminogen activator.

\*P-value derived by general linear model adjusted for baseline risk factor, age at randomization, sex, and PCs ancestry markers.

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**Supplementary Table 7.** Modification of coronary artery disease genetic risk effect on one-year change in intermediate risk factors by lifestyle components.

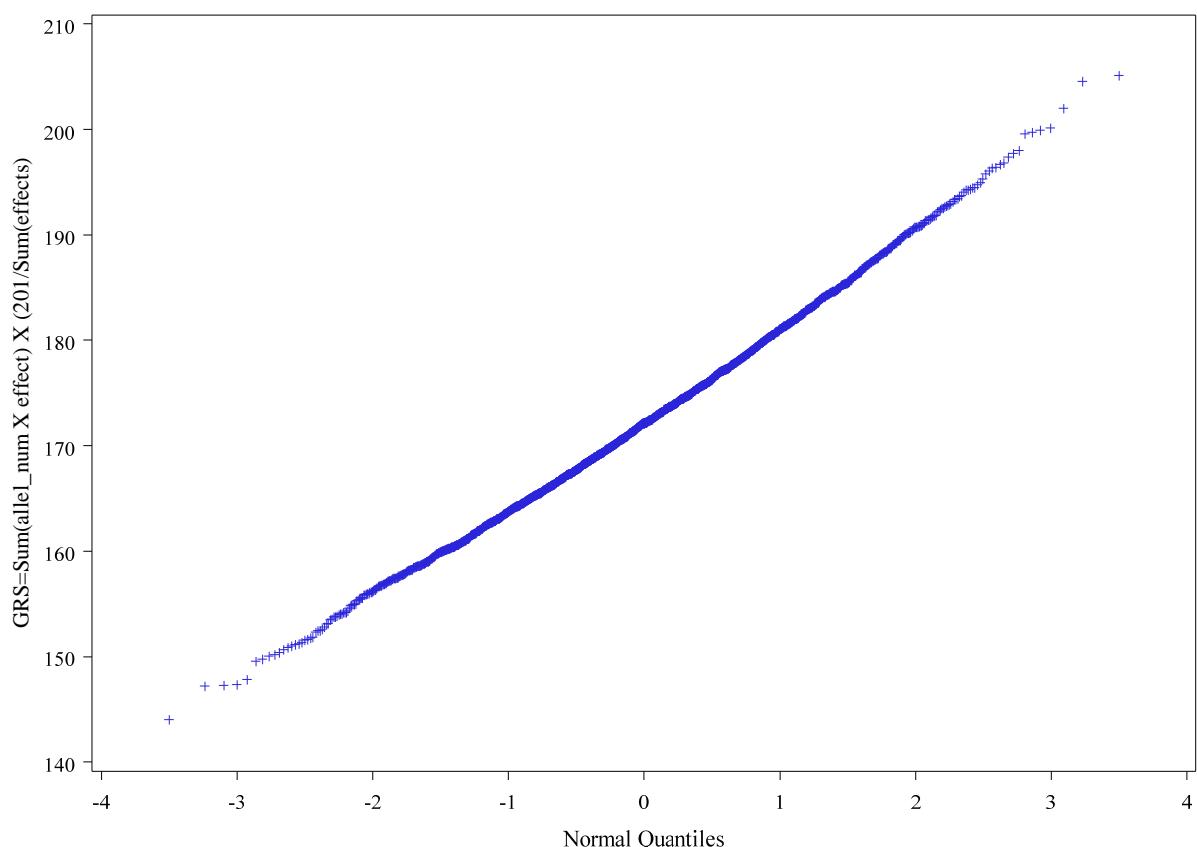
One-year change in risk factor	One-year change in LS component	Treatment arm	Low genetic risk	Intermediate genetic risk	High genetic risk	<i>P</i> <sub>interaction</sub>
			$\beta$ (SE)	$\beta$ (SE)	$\beta$ (SE)	
BMI, kg/m <sup>2</sup>	Diet	MET	-0.191 (0.095)	-0.288 (0.103)	-0.515 (0.114)	0.012
BMI, kg/m <sup>2</sup>	PA	MET	-0.003 (0.018)	-0.261 (0.098)	-0.323 (0.123)	0.014
Triglycerides <sup>#</sup>	Diet	MET	0.996 (0.960, 1.031)	0.969 (0.925, 1.016)	0.934 (0.892, 0.977)	0.024
Fasting glucose <sup>#</sup>	PA	PBO	1.005 (0.991, 1.021)	0.993 (0.983, 1.002)	0.989 (0.977, 1.000)	0.012
HDLc, mmol/L	PA	PBO	0.022 (0.009)	-0.011 (0.009)	-0.012 (0.008)	0.033

**Table Legend:** Predicted one-year changes on cardiometabolic risk factors by 1SD increase in lifestyle behaviors among individuals at low, intermediate, and high genetic risk. *P*<sub>interaction</sub> values were derived by general linear models with interaction terms for CAD PRS and lifestyle behaviors (dietary quality score or physical activity), after adjustment for age at randomization, sex, the top 10 principal components for ancestry, and the respective baseline cardiac risk factors. For non-normally distributed variables<sup>#</sup>, we calculated the natural log year 1 value minus natural log baseline value. incidence. Displayed only nominal significant interactions.

BMI, body mass index; MET, metformin; PBO, placebo.

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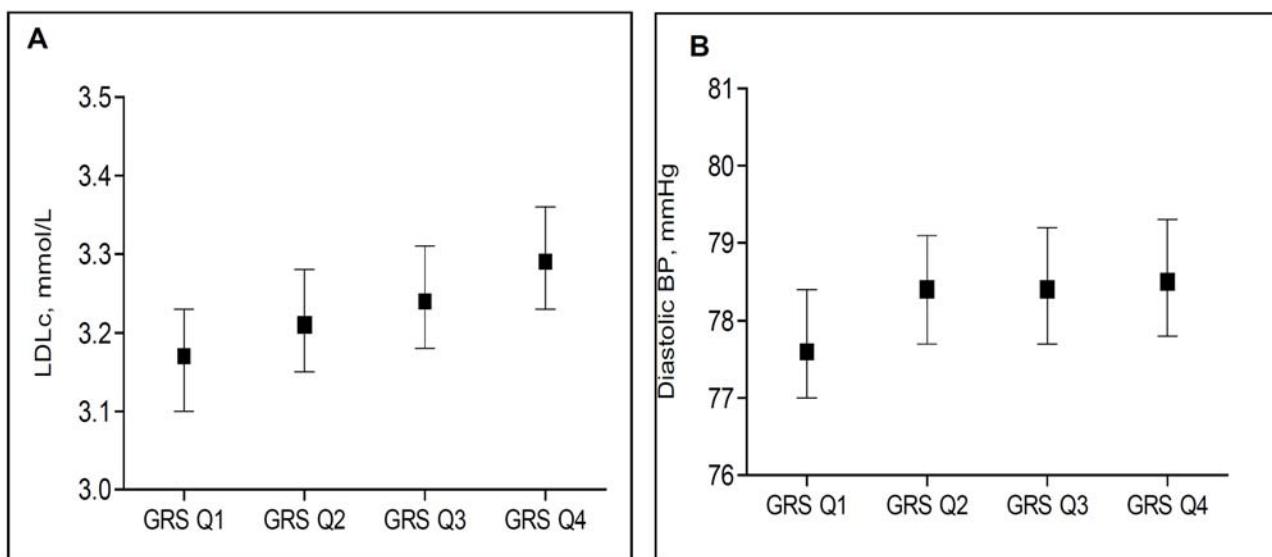
**Supplementary Figure 1.** Coronary artery disease polygenic risk score distribution.



**Figure legend;** Q-Q plot for the distribution of the CAD polygenic risk score. The y axis displays CAD polygenic risks core values. The x axes represent quartiles of the distribution in the CAD polygenic risk score.

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**Supplementary Figure 2.** Adjusted-mean values of baseline lipid and diastolic blood pressure levels according quartiles of the genetic risk score.



**Figure legend;** Baseline mean concentrations of intermediate risk factors according to the number of risk alleles at identified CAD loci, weighted by effect size in an aggregate genotype score. The right y axis displays adjusted mean and 95% confidence interval values of LDLc (A) and DBP (B) according to PRS quartiles. P-value was obtained from general linear models after adjustment for age at randomization, sex, and ancestry markers.  $P < 0.001$  for LDLc and 0.027 for DBP.

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