

Supplementary Material for

Genetic Risk Factors for CVD in Type 1 Diabetes: the DCCT/EDIC Study

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Supplementary Table S1. Baseline characteristics (mean and standard deviations for quantitative variables, and percentage for categorical variables) of DCCT/EDIC participants included in this study (N=1371) and full cohort (N=1441).

Baseline Characteristic	Genetics Cohort	Full Cohort
	N=1371	N=1441
Intensive Group	49.2%	49.3%
Primary Cohort	50.4%	50.4%
Sex (male)	52.7%	52.7%
Age (years)	26.8 (7.1)	26.8 (7.1)
Duration of T1D (months)	69.7 (49.7)	69.8 (49.7)
Currently Smoking	18.6%	18.4%
Systolic BP (mmHg)	114.6 (11.3)	114.5 (11.3)
Diastolic BP (mmHg)	73.1 (8.5)	73.0 (8.5)
HDL (mg/dl)	50.4 (12.2)	50.6 (12.3)
LDLc (mg/dl)	109.4 (29.1)	109.7 (29.1)
Triglycerides (mg/dl)	81.9 (48.2)	81.3 (47.5)
HbA1c (%)	8.9 (1.6)	8.9 (1.6)
HbA1c (mmol/mol)	73.8 (17.5)	73.8 (17.5)
AER (mg/24 hr)	15.9 (18.8)	15.9 (18.8)
eGFR (mL/min per 1.73 m²)	125.8 (13.9)	126.1 (14.2)

Supplementary Table S2. Number of cardiovascular events observed and proportion of individuals with an event (total and separately by CAD PRS Percentiles).

CAD PRS	CVD	MACE
	N=227	N=112
Tertile		
1	51 (11.2%)	23 (5.0%)
2	72 (15.8%)	35 (7.7%)
3	104 (22.8%)	54 (11.8%)
Quartile		
1	41 (12.0%)	19 (5.6%)
2	40 (11.7%)	17 (5.0%)
3	65 (18.9%)	34 (9.9%)
4	81 (23.7%)	42 (12.3%)

Supplementary Table S3a. Associations between risk factors and the risk of CVD in multivariable Cox proportional hazards models.

Covariate	All Covariates (Akaike IC =2921.67)			Without CAD PRS (Akaike IC =2943.08)			Without LDL (Akaike IC =2922.50)		
	HR	Z-Score	P-Value	HR	Z-Score	P-Value	HR	Z-Score	P-Value
Age (per 1 year)	1.0859 (1.0632, 1.1090)	7.65	2.1E-14	1.0840 (1.0614, 1.1070)	7.51	6.1E-14	1.0882 (1.0656, 1.1112)	7.92	2.4E-15
Time Weighted HbA1c (per 1%)	1.4055 (1.2360, 1.5982)	5.19	2.1e-7	1.3780 (1.2125, 1.5661)	4.91	9.1e-7	1.4301 (1.2604, 1.6227)	5.55	2.8e-8
CAD PRS (per 1SD)	1.3830 (1.2117, 1.5786)	4.81	1.5e-6	-	-	-	1.4090 (1.2369, 1.6051)	5.16	2.5e-7
Log TRG (per 1 mg/dl)	1.6991 (1.3303, 2.1701)	4.25	2.2e-5	1.6948 (1.3264, 2.1657)	4.22	2.5e-5	1.7920 (1.4191, 2.2628)	4.90	9.6e-7
Time weighted SBP (per 1 mmHg)	1.0283 (1.0118, 1.0451)	3.38	7.2e-4	1.0255 (1.0092, 1.0420)	3.08	2.1e-3	1.0296 (1.0131, 1.0463)	3.53	4.1e-4
Time weighted pulse (per 1 bpm)	1.0230 (1.0022, 1.0442)	2.17	3.0e-2	1.0232 (1.0023, 1.0445)	2.18	2.9e-2	1.0250 (1.0043, 1.0460)	2.38	1.7e-2
Family history of MI (Yes vs. No)	1.2975 (0.9935, 1.6945)	1.91	5.6e-2	1.2737 (0.9758, 1.6627)	1.78	7.5e-2	1.3086 (1.0023, 1.7085)	1.98	4.8e-2
Duration of T1D(per 1 month)	1.0025 (0.9999, 1.0051)	1.91	5.6e-2	1.0029 (1.0004, 1.0055)	2.24	2.5e-2	1.0025 (0.9999, 1.0050)	1.86	6.3e-2
ACE inhibitor use (Yes vs. No)	0.7726 (0.5768, 1.0348)	1.73	8.4e-2	0.7936 (0.5925, 1.0628)	1.55	1.2e-1	0.7642 (0.5707, 1.0233)	1.81	7.1e-2
Time weighted LDLc (mg/dl)	1.0052 (0.9989, 1.0116)	1.62	1.1e-1	1.0078 (1.0016, 1.0140)	2.49	1.3e-2	-	-	-

Akaike IC for a fully adjusted model without age is 2982.15, without time weighted HbA1c is 2945.91, without log TRG is 2936.80, and without time weighted SBP is 2931.18. The variables included in the model are the clinical risk factors identified in our previous work (Diabetes, 2016; see footnote for Table 2).

Supplementary Table S3b. Associations between risk factors and the risk of MACE in multivariable Cox proportional hazards models.

Covariate	All Covariates (Akaike IC =1420.55)			Without CAD PRS (Akaike IC =1432.56)			Without LDL (Akaike IC =1423.65)		
	HR	Z-Score	P-Value	HR	Z-Score	P-Value	HR	Z-Score	P-Value
Age (per 1 year)	1.1018 (1.0693, 1.1353)	6.35	2.2E-10	1.1009 (1.0685, 1.1342)	6.31	2.7E-10	1.0997 (1.0674, 1.1329)	6.26	4.0E-10
Time Weighted HbA1c (per 1%)	1.5328 (1.2850, 1.8284)	4.75	2.1e-6	1.5158 (1.2694, 1.8100)	4.60	4.3e-6	1.5574 (1.3083, 1.8538)	4.98	6.3e-7
CAD PRS (per 1 SD)	1.4019 (1.1739, 1.6741)	3.73	1.9e-4	-	-	-	1.4300 (1.1982, 1.7066)	3.96	7.4e-5
Smoking (Yes vs. No)	1.8356 (1.1954, 2.8185)	2.78	5.5e-3	1.9054 (1.2423, 2.9225)	2.95	3.1e-3	1.8547 (1.2084, 2.8468)	2.83	4.7e-3
Log TRG (per 1 mg/dl)	1.6324 (1.1494, 2.3184)	2.74	6.2e-3	1.6246 (1.1438, 2.3077)	2.71	6.7e-3	1.7821 (1.2783, 2.4845)	3.41	6.5e-4
Duration of T1D (per 1 month)	1.0048 (1.0011, 1.0085)	2.56	1.1e-2	1.0049 (1.0013, 1.0086)	2.63	8.6e-3	1.0045 (1.0009, 1.0082)	2.42	1.6e-2
LDLc (per 1 mg/dl)	1.0066 (1.0010, 1.0122)	2.32	2.1e-2	1.0076 (1.0021, 1.0131)	2.70	6.9e-3	-	-	-
Time weighted SBP (per 1 mmHg)	1.0243 (1.0022, 1.0470)	2.16	3.1e-2	1.0247 (1.0025, 1.0475)	2.18	2.9e-2	1.0237 (1.0016, 1.0463)	2.10	3.6e-2
Time weighted pulse (per 1 bpm)	1.0301 (1.0010, 1.0600)	2.03	4.2e-2	1.0291 (1.0000, 1.0592)	1.96	5.0e-2	1.0325 (1.0034, 1.0624)	2.19	2.8e-2
ACE inhibitor use (Yes vs. No)	0.7372 (0.4880, 1.1135)	1.45	1.5e-1	0.7457 (0.4935, 1.1267)	1.39	1.6e-1	0.7181 (0.4762, 1.0829)	1.58	1.1e-1

Akaike IC for a fully adjusted model without age is 1464.44, without time weighted HbA1c is 1445.69, without log TRG is 1432.46, and without time weighted SBP is 1427.46. The variables included in the model are the clinical risk factors identified in our previous work (Diabetes, 2016; see footnote for Table 2).

Supplementary Table S4. Association between CAD PRS and time weighted LDL in longitudinal GEE models with a class variable for visit.

	CAD PRS Estimate*	Z-Score	P-Value
Unadjusted	3.72 (2.48, 4.96)	5.88	4.0e-9
Adjusted for age, time weighted HbA1c	3.66 (2.48, 4.84)	6.08	1.2e-9
Adjusted for age, time weighted HbA1c, duration, lipid lowering medication	3.68 (2.49, 4.87)	6.08	1.2e-9

*per 1 standard deviation increase in CAD PRS.

Supplementary Table S5. Hazard Ratios, z-scores and p-values from Cox proportional hazards models assessing the association between the weighted GRS and the risk of CVD and MACE in unadjusted models, models further adjusted for age and mean updated HbA1c, and in fully adjusted models without and with further adjustment for CAD PRS.

A. Weighted GRS												
	Unadjusted			Adjusted for Age and HbA1c			Fully Adjusted*			Fully Adjusted with CAD PRS and Significant SNPs		
CVD	HR	Z	P	HR	Z	P	HR	Z	P	HR	Z	P
Top 33%	1.60 (1.23, 2.08)	3.50	4.7e-4	1.58 (1.22, 2.06)	3.41	6.5e-4	1.52 (1.17, 1.99)	3.10	1.9e-3	1.09 (0.80, 1.49)	0.54	5.9e-1
Per SD Increase	1.24 (1.09, 1.42)	3.28	1.0e-3	1.25 (1.10, 1.43)	3.33	8.6e-4	1.21 (1.06, 1.38)	2.77	5.6e-3	0.94 (0.79, 1.12)	0.65	5.1e-1
MACE												
Top 33%	1.86 (1.29, 2.70)	3.29	1.0e-3	1.80 (1.24, 2.61)	3.10	2.0e-3	1.77 (1.22, 2.57)	2.99	2.8e-3	1.23 (0.78, 1.93)	0.89	3.7e-1
Per SD Increase	1.34 (1.12, 1.62)	3.12	1.8e-3	1.32 (1.10, 1.58)	2.96	3.1e-3	1.27 (1.06, 1.53)	2.57	1.0e-2	1.03 (0.80, 1.32)	0.19	8.5e-1
B. Unweighted GRS												
CVD	HR	Z	P	HR	Z	P	HR	Z	P	HR	Z	P
Top 33%	1.39 (1.07, 1.82)	2.43	1.5e-2	1.37 (1.05, 1.78)	2.29	2.2e-2	1.28 (0.98, 1.67)	1.79	7.3e-2	0.91 (0.67, 1.24)	0.59	5.6e-1
Per SD Increase	1.15 (1.01, 1.31)	2.13	3.3e-2	1.15 (1.01, 1.31)	2.06	4.0e-2	1.11 (0.98, 1.27)	1.59	1.1e-1	0.90 (0.77, 1.05)	1.33	1.8e-1

MACE												
Top 33%	1.54 (1.06, 2.24)	2.25	2.4e-2	1.48 (1.02, 2.16)	2.05	4.0e-2	1.40 (0.96, 2.04)	1.75	8.1e-2	0.94 (0.61, 1.44)	0.28	7.8e-1
Per SD Increase	1.25 (1.04, 1.51)	2.39	1.7e-2	1.23 (1.02, 1.48)	2.17	3.0e-2	1.19 (0.99, 1.43)	1.82	6.9e-2	0.95 (0.76, 1.20)	0.41	6.8e-1

The fully adjusted models include the clinical risk factors identified in our previous work (Diabetes, 2016).

*The fully adjusted model for CVD was further adjusted for age, time weighted HbA1c, (log) triglycerides, time weighted SBP, time weighted pulse, family history of MI, duration of T1D, ACE inhibitor use, and time weighted LDLc.

*The fully adjusted model for MACE was further adjusted for age, time weighted HbA1c, smoking, (log) triglycerides, time weighted SBP, time weighted pulse, duration of T1D, ACE inhibitor use, and current LDLc.

Supplementary Table S6. Association between SNPs and the risk of CVD and MACE in Cox proportional hazards models, first unadjusted, then adjusted for age and mean updated HbA1c, and in fully adjusted models.

CHR SNP	A. CVD						B. MACE					
	Unadjusted		Adjusted for Age and Mean HbA1c		Fully Adjusted*		Unadjusted		Adjusted for Age and Mean HbA1c		Fully Adjusted**	
	Chi-Square	P-Value	Chi-Square	P-Value	Chi-Square	P-Value	Chi-Square	P-Value	Chi-Square	P-Value	Chi-Square	P-Value
chr1_109817192_A_G [rs7528419]	1.3004	5.2e-1					0.5745	7.5e-1				
chr1_151762308_C_G [rs11810571]	1.5407	4.6e-1					0.0113	9.9e-1				
chr1_154395946_A_G [rs6689306]	2.0300	3.6e-1					5.0757	7.9e-2				
chr1_222823743_T_G [rs67180937]	0.4311	8.1e-1					1.4197	4.9e-1				
chr1_55505647_G_T [rs11591147]	1.8314	4.0e-1					0.0006	9.9e-1				
chr1_57016131_A_C [rs56170783]	2.3415	3.1e-1					2.1370	3.4e-1				
chr10_104604916_T_G [rs11191416]	2.1411	3.4e-1					1.1464	5.6e-1				
chr10_30321598_C_T [rs1887318]	1.1642	5.6e-1					0.0172	9.9e-1				
chr10_44480811_T_G [rs1870634]	2.9738	2.3e-1					1.8192	4.0e-1				
chr10_91004886_A_G [rs2246942]	0.1671	9.2e-1					0.8224	6.6e-1				
chr11_10284499_G_GA [rs201267813]	3.6388	1.6e-1					1.1348	5.7e-1				
chr11_103673294_T_A [rs2839812]	0.1114	9.5e-1					0.1812	9.1e-1				

chr11_116648917_G_C [rs964184]	1.7669	4.1e-1					0.7605	6.8e-1				
chr11_13303071_C_T [rs3993105]	3.4364	1.8e-1					7.6267	2.2e-2	6.8325	3.3e-2	4.3658	1.1e-1
chr11_9751196_G_A [rs10840293]	4.0957	1.3e-1					2.4528	2.9e-1				
chr12_111910219_A_G [rs10774625]	0.5917	7.4e-1					1.6717	4.3e-1				
chr12_118265441_T_G [rs11830157]	7.7118	2.1e-2	9.4756	8.8e-3	8.5497	1.4e-2	3.6511	1.6e-1				
chr12_121416988_A_G [rs2244608]	4.5541	1.0e-1					1.6226	4.4e-1				
chr12_125307053_G_A [rs11057830]	0.4147	8.1e-1					0.2249	8.9e-1				
chr12_57843711_G_A [rs2229357]	1.7456	4.2e-1					1.8292	4.0e-1				
chr12_90008959_A_G [rs2681472]	1.2658	5.3e-1					1.5497	4.6e-1				
chr13_110818102_T_A [rs11617955]	1.1888	5.5e-1					0.1289	9.4e-1				
chr13_29022645_C_T [rs1924981]	3.6530	1.6e-1					0.3786	8.3e-1				
chr14_100145710_C_G [rs10139550]	2.7471	2.5e-1					2.6041	2.7e-1				
chr15_67441750_C_A [rs72743461]	1.4968	4.7e-1					4.6138	1.0e-1				
chr15_79123054_C_T [rs7164479]	0.8912	6.4e-1					0.0746	9.6e-1				
chr15_89574484_T_C [rs2083460]	4.3880	1.1e-1					0.3181	8.5e-1				
chr15_91428197_T_C [rs2071382]	1.0608	5.9e-1					1.3213	5.2e-1				
chr16_56989590_C_T [rs247616]	1.9758	3.7e-1					0.3608	8.3e-1				

chr16_83045790_A_G [rs7500448]	1.6698	4.3e-1					1.1329	5.7e-1				
chr17_17593453_T_C [rs9897596]	0.1005	9.5e-1					3.3523	1.9e-1				
chr17_2088848_CCAGA_C [rs113348108]	0.4108	8.1e-1					1.4093	4.9e-1				
chr17_47123423_T_C [rs4643373]	2.9593	2.3e-1					6.5037	3.9e-2	5.9637	5.1e-2	3.4505	1.8e-1
chr17_59286644_G_C [rs8068952]	1.0088	6.0e-1					1.0090	6.0e-1				
chr18_57832856_A_AC [rs35614134]	0.3752	8.3e-1					7.3692	2.5e-2	10.1231	6.3e-3	8.7251	1.3e-2
chr19_11202306_G_T [rs6511720]	1.8533	4.0e-1					0.7547	6.9e-1				
chr19_33386556_T_C [rs10417115]	9.6482	8.0e-3	9.3675	9.2e-3	12.5451	1.9e-3	7.4353	2.4e-2	6.7060	3.5e-2	8.8370	1.2e-2
chr19_41854534_T_A [rs8108632]	3.0227	2.2e-1					6.0650	4.8e-2	4.8746	8.7e-2	5.3188	7.0e-2
chr19_45412079_C_T [rs7412]	0.3540	8.4e-1					0.2434	8.9e-1				
chr19_46190268_G_A [rs1964272]	3.3894	1.8e-1					0.7122	7.0e-1				
chr19_8429323_G_A [rs116843064]	1.5715	4.6e-1					2.1151	3.5e-1				
chr2_145286559_T_G [rs17678683]	2.7272	2.6e-1					1.4541	4.8e-1				
chr2_19942473_G_A [rs16986953]	4.7958	9.1e-2					4.3710	1.1e-1				
chr2_203831212_T_A [rs114123510]	0.6161	7.3e-1					0.6024	7.4e-1				
chr2_21270554_A_C [rs585967]	3.5144	1.7e-1					0.1227	9.4e-1				
chr2_216304384_T_C [rs1250229]	2.9489	2.3e-1					1.1553	5.6e-1				

chr2_233584109_C_T [rs13003675]	0.7241	7.0e-1					1.9724	3.7e-1				
chr2_44072576_G_T [rs4299376]	1.8694	3.9e-1					3.5372	1.7e-1				
chr2_85788175_T_A [rs7568458]	1.6788	4.3e-1					1.8282	4.0e-1				
chr21_35593827_G_A [rs28451064]	0.5663	7.5e-1					0.5787	7.5e-1				
chr22_24658858_G_T [rs180803]	0.0459	8.3e-1					1.0062	3.2e-1				
chr3_124475201_T_G [rs142695226]	1.8665	3.9e-1					0.9923	6.1e-1				
chr3_138099161_T_TTTC [rs139016349]	2.3784	3.0e-1					0.3272	8.5e-1				
chr3_153839866_G_C [rs12493885]	3.0798	2.1e-1					2.4751	2.9e-1				
chr3_49448566_A_C [rs7623687]	1.9155	3.8e-1					1.4010	5.0e-1				
chr4_120909501_A_C [rs7678555]	1.1541	5.6e-1					1.6646	4.4e-1				
chr4_148401190_G_A [rs6841581]	8.8726	1.2e-2	8.6800	1.3e-2	8.9163	1.2e-2	6.4320	4.0e-2	6.3636	4.2e-2	7.2173	2.7e-2
chr4_156638573_A_G [rs2306556]	2.4852	2.9e-1					3.3057	1.9e-1				
chr4_57839051_C_G [rs72627509]	0.6291	7.3e-1					5.2961	7.1e-2				
chr4_81181072_A_T [rs10857147]	2.0822	3.5e-1					1.1761	5.6e-1				
chr5_131759825_T_C [rs77335401]	0.1908	9.1e-1					0.0013	1.0E+00				
chr6_11327021_C_T [rs742115]	0.0281	9.9e-1					0.2983	8.6e-1				
chr6_12903957_A_G [rs9349379]	0.4086	8.2e-1					0.0467	9.8e-1				

chr6_134173151_A_G [rs12202017]	2.0524	3.6e-1					4.0474	1.3e-1				
chr6_161010118_A_G [rs10455872]	4.1155	1.3e-1					2.4341	3.0e-1				
chr6_22612629_G_A [rs6909752]	3.9677	1.4e-1					0.6924	7.1e-1				
chr6_31888367_C_T [rs3130683]	4.5195	1.0e-1					9.1332	1.0e-2	11.4443	3.3e-3	13.4506	1.2e-3
chr6_34769765_C_T [rs4472337]	3.4491	1.8e-1					1.3312	5.1e-1				
chr6_39152041_C_A [rs56015508]	2.4987	2.9e-1					2.0205	3.6e-1				
chr7_107176780_C_T [rs112370447]	5.2619	7.2e-2					5.2198	7.4e-2				
chr7_129663496_C_T [rs11556924]	5.7487	5.7e-2					4.1729	1.2e-1				
chr7_150690176_C_T [rs3918226]	0.9868	6.1e-1					1.0940	5.8e-1				
chr7_19049388_G_A [rs2107595]	0.6045	7.4e-1					0.9541	6.2e-1				
chr8_126490972_A_T [rs2954029]	0.7966	6.7e-1					0.2333	8.9e-1				
chr8_19865263_T_G [rs2083636]	0.0422	9.8e-1					0.1801	9.1e-1				
chr9_113169775_T_C [rs111245230]	1.1404	5.7e-1					0.0135	9.9e-1				
chr9_136149399_G_A [rs507666]	2.6228	2.7e-1					2.0277	3.6e-1				
chr9_22098619_A_G [rs2891168]	4.7963	9.1e-2					8.0805	1.8e-2	9.4893	8.7e-3	4.9493	8.4e-2

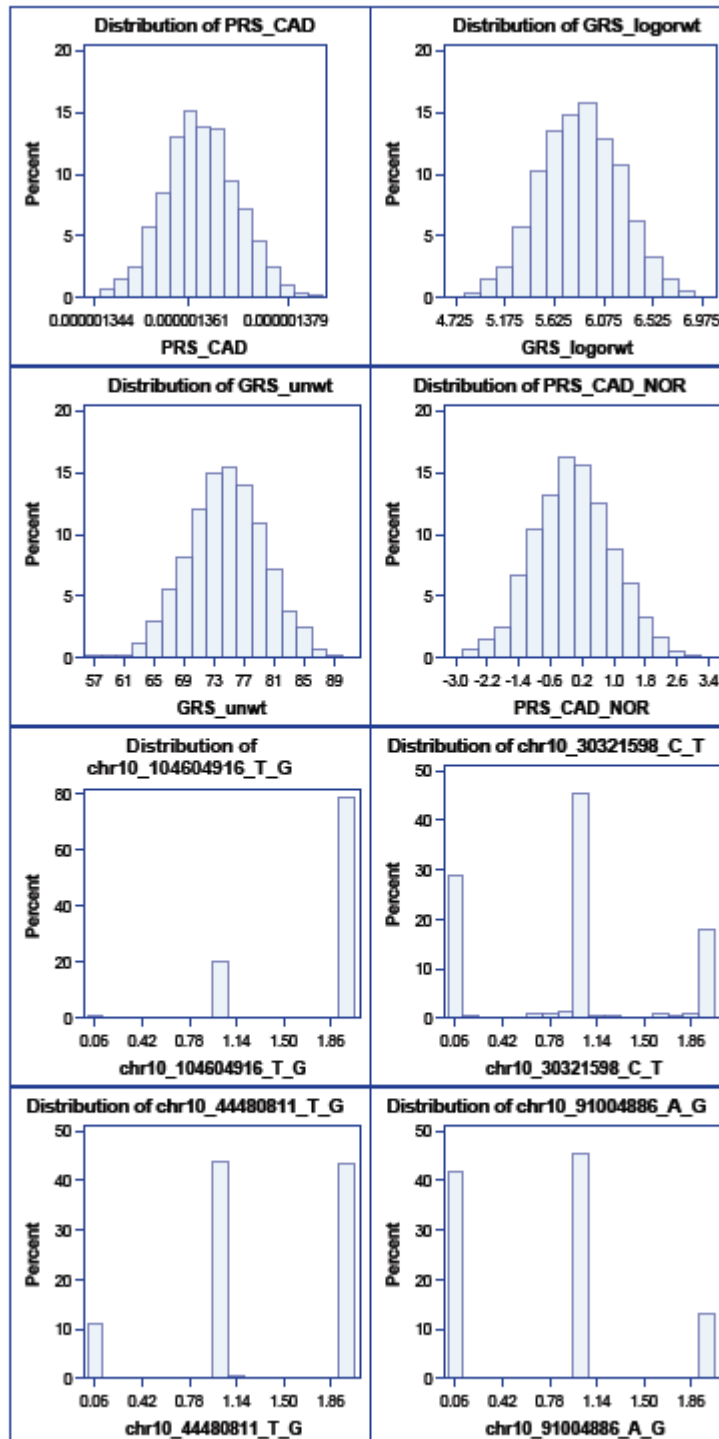
The variables included in the model are the clinical risk factors identified in our previous work (Diabetes, 2016). *Fully adjusted for CAD PRS, age, mean updated HbA1c, family history of MI, mean updated SBP, mean updated pulse, log triglycerides, mean updated LDLc, ACE inhibitor use, and baseline duration. **Fully adjusted for CAD PRS, age, mean updated HbA1c, current smoker, mean updated SBP, mean updated pulse, log triglycerides, current LDLc, ACE inhibitor use, and baseline duration.

Associations significant at level 0.05 in the fully adjusted models are reported in **bold**.

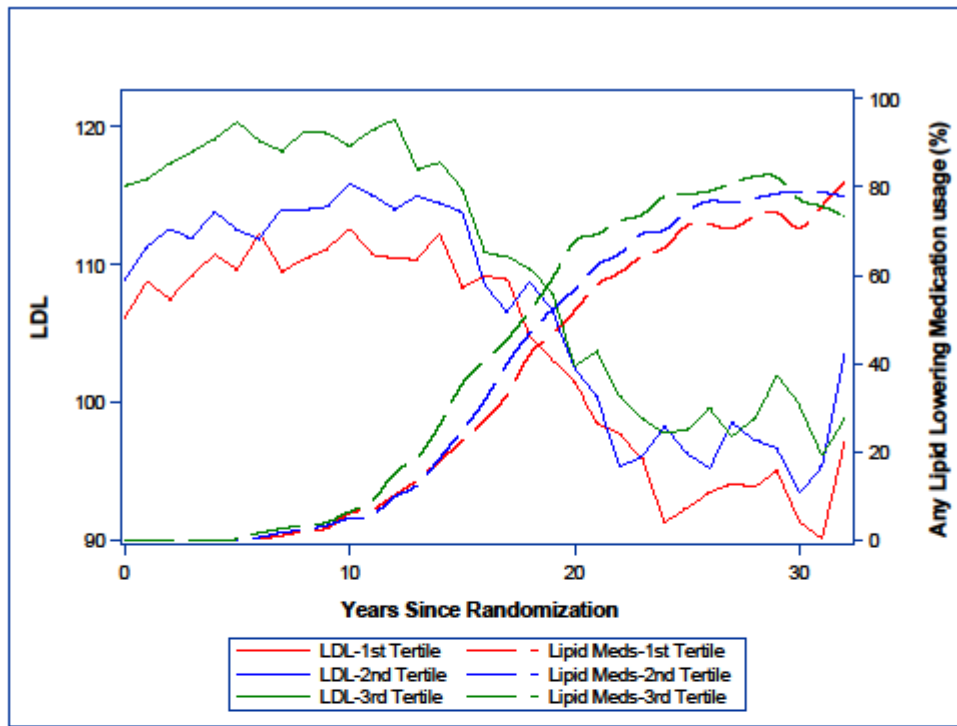
Supplementary Table S7. Hazard Ratios (HR) with 95% Wald confidence intervals, and p-values from Cox proportional hazards models assessing the association between CAD PRS and the risk of CAD (acute/silent MI, and/or PTCA/CABG) in unadjusted models and minimally adjusted models (age and mean updated HbA1c).

	Unadjusted		Minimally Adjusted	
CAD PRS	HR	P-value	HR	P-value
Highest 33%	1.95 (1.45, 2.62)	8.1e-6	1.94 (1.45, 2.60)	9.7e-6
Per SD Increase	1.39 (1.20, 1.61)	1.0e-5	1.39 (1.20, 1.61)	8.1e-6

Supplementary Figure S1. Histograms of polygenic risk scores and individual SNPs.



Supplementary Figure S2. LDLc levels (solid lines) and proportion of participants on lipid-lowering medication (dashed lines) over time separately by CAD PRS tertiles.



Supplementary Figure S3. Flow chart showing the construction of genetic variants in DCCT/EDIC.

