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Diabetes Status and the Association Between a Coronary Artery Disease Polygenic Risk Score and Incident Coronary Artery Disease in an Iranian Prospective Cohort

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Abstract

Background: Polygenic risk scores (PRSs) for coronary artery disease (CAD) may provide a quantitative assessment of inherited susceptibility that extends beyond conventional clinical risk factors. However, the relationship between CAD PRS and the incidence of CAD may differ across various cardiometabolic risk groups. This study aimed to evaluate whether baseline diabetes status influences the association between CAD PRS and the incidence of CAD.

Methods: This cohort comprised 5,139 adults from the Tehran Cardiometabolic Genetic Study (TCGS) who were free of CAD at baseline. The CAD PRS was constructed using a maximum clumping-and-thresholding approach based on external CAD genome-wide association summary statistics. Associations between the PRS and cumulative incident CAD were assessed according to diabetes status using logistic regression. Model discrimination and prediction error were evaluated using the area under the curve (AUC) and the Brier score.

Results: Among 5,139 participants, 1,171 had diabetes while 3,968 did not; incident CAD occurred in 334 diabetic and 427 non-diabetic participants. After adjusting for traditional risk factors, each 1-SD increase in the PRS was associated with higher odds of incident CAD in diabetic participants (OR, 1.36; 95% CI, 1.20–1.55) and non-diabetic participants (OR, 1.27; 95% CI, 1.14–1.41). A significant interaction between PRS quintiles and diabetes status was observed ($P = 0.017$). The model incorporating the PRS alongside traditional risk factors demonstrated greater discrimination in non-diabetic compared to diabetic participants (AUC, 0.776 vs 0.600).

Conclusion: CAD PRS was associated with incident CAD across diabetes-defined strata; however, its predictive relevance varied according to baseline diabetes status. These findings support the use of PRS as a marker of inherited susceptibility rather than as evidence for clinical risk reclassification or as a stand-alone predictive tool.

Keywords: Coronary artery disease, Diabetes mellitus, Polygenic risk score, TLGS, Iran

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Introduction

The burden of ischemic heart disease is substantial in Middle Eastern populations (1). Risk assessment for coronary artery disease (CAD) is an important component of primary prevention, as the intensity of preventive interventions is frequently guided by estimated risk (2). Standard prediction models rely on clinical and biochemical variables measured in adulthood, including age, sex, cholesterol levels, blood pressure, smoking status, and diabetes (3). Although these predictors are clinically valuable, they do not fully capture inherited susceptibility to CAD (4). Polygenic risk scores (PRSs) may enhance risk assessment by aggregating the effects of numerous common genetic variants into a quantitative measure of inherited predisposition (5).

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Key Messages:

↑What is "already known" in this topic:

CAD polygenic risk scores are associated with the incidence of coronary artery disease; however, their interpretation may vary across populations and clinical subgroups.

→What this article adds:

In this Iranian cohort, the CAD PRS was associated with the incidence of CAD in both diabetic and non-diabetic participants, and diabetes status modified the association between PRS and CAD.

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Large genome-wide association studies have facilitated the development of CAD PRSs by identifying common variants associated with CAD (6, 7). Prospective studies have demonstrated that CAD PRSs correlate with incident CAD and may improve risk stratification beyond conventional clinical factors (5, 8, 9). However, the additional predictive value of CAD PRSs beyond established clinical models has varied across studies, underscoring the need for evaluation within specific clinical contexts (10).

Diabetes is clinically significant for PRS evaluation due to its strong association with CAD and vascular outcomes, while the CAD risk among diabetic individuals remains heterogeneous (11, 12). Previous studies have established a link between CAD/CHD PRS and angiographic atherosclerotic burden, as well as coronary risk assessment in individuals with type 2 diabetes, thereby supporting the relevance of inherited susceptibility within this clinical group (12, 13). An earlier onset of type 2 diabetes has also been associated with an increased cardiovascular and genetic CAD risk (14, 15).

These findings suggest that the evaluation of CAD polygenic risk should consider diabetes status as a clinically relevant context, rather than relying solely on overall population estimates (12, 15). Given that diabetes substantially alters baseline coronary risk, the same level of inherited susceptibility may not yield identical clinical implications for diabetic and non-diabetic individuals (11, 12). Therefore, it is essential to determine whether CAD PRS is associated with incident CAD within each diabetes-defined stratum and whether diabetes status modifies this association. However, limited evidence exists regarding the modification of the association between CAD PRS and incident CAD by diabetes status. In the present study, we assessed whether the association between CAD PRS and incident CAD varied according to baseline diabetes status.

Methods

Study Design and Analytic Sample

This study was conducted as a secondary analysis of existing data within the Tehran Cardiometabolic Genetic Study (TCGS) cohort, which represents the genomic component of the Tehran Lipid and Glucose Study (TLGS). The TLGS is a prospective community-based cohort initiated in Tehran in 1999, with follow-up examinations occurring approximately every 3 years. Incident CAD events, hospitalizations, and deaths were identified during the cohort follow-up and adjudicated according to predefined study criteria (16, 17). Participants with available genotype data, phenotype measurements, baseline diabetes status, and CAD outcome data were eligible for inclusion. Individuals with baseline cardiovascular disease, missing CAD outcome data, or incomplete follow-up were excluded.

The present secondary analysis was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNS.REC.1403.051). Written informed consent was obtained from all participants in the original TLGS/TCGS, and the requirement for additional informed consent for this secondary analysis was waived by the ethics committee.

Ascertainment of CAD and Diabetes

CAD was defined according to the established TCGS outcome adjudication framework, which included myocardial infarction, unstable angina, angiography-confirmed coronary disease, coronary revascularization, or CAD-related death. Angiography-confirmed CAD was defined as at least 50% stenosis in a major coronary artery or a history of angioplasty or bypass surgery (17). Diabetes was defined using TLGS criteria as the use of glucose-lowering medication, fasting plasma glucose ≥126 mg/dL, or 2-hour post-load plasma glucose ≥200 mg/dL (16, 18). Participants with type 1 diabetes, congenital diabetes, monogenic diabetes, or maturity-onset diabetes of the young were excluded from diabetes-stratified analyses (16).

Genotyping and Genetic Quality Control

Genomic DNA extraction, genotyping, whole-genome sequencing, and genotype imputation in the TCGS have been previously described (16, 17). In the present study, variant-level quality control excluded variants with an imputation INFO score ≤0.70, missingness >2%, Hardy-Weinberg equilibrium $P < 1 \times 10^{-6}$, or minor allele frequency <0.01. Sample-level quality control excluded participants with discordance between reported and genetically inferred sex, a genotype call rate <98%, excess heterozygosity beyond ±3 SD, or cryptic relatedness defined as pi-hat >0.125. After applying these filters, 5,139 unrelated participants and 10,390,718 variants remained for genetic analyses.

Polygenic Risk Score

Coronary artery disease polygenic risk scores were constructed using a maximum clumping-and-thresholding (maxCT) approach. Published CAD GWAS summary statistics from Aragam et al., which included 181,522 CAD cases among 1,165,690 participants, along with additional cross-ancestry data from Biobank Japan, served as the base dataset (7). Quality-controlled and imputed TCGS genotype data were used as both the target dataset and linkage disequilibrium (LD) reference. After matching the base and target datasets by SNP identifiers, LD clumping and threshold-specific scoring were performed across seven prespecified GWAS P-value thresholds: 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5, following the standard clumping-and-thresholding framework (19, 20). For each participant, PRS was calculated as the weighted sum of CAD risk alleles, $PRS_i = \Sigma_j G_{ij}\beta_j$, where G_{ij} denotes the number of effect alleles and β_j represents the GWAS-derived effect estimate (21). The distribution of scoring variants and threshold-specific model performance across candidate C+T thresholds are summarized in Appendix Table 1, Appendix Table 2, and Appendix Figure 1.

Statistical Analysis

Baseline characteristics were summarized according to CAD status in the overall cohort as mean (SD) for continuous variables and number (%) for categorical variables. Group differences were assessed using the Wilcoxon rank-sum test for continuous variables and the Pearson χ^2 test for categorical variables. Associations between PRS and

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cumulative incident CAD were estimated using logistic regression. Multivariable models included principal components, demographic variables, and traditional cardiovascular risk factors (including age, sex, smoking status, hypertension, low HDL-C, and BMI category); diabetes status was omitted from diabetes-stratified models. Cox proportional hazards regression was performed as a sensitivity analysis to account for person-time, censoring, and time to CAD, using the same covariate structure as the fully adjusted models. Additionally, log-binomial regression was conducted as a sensitivity analysis to estimate risk ratios for incident CAD. The PRS × diabetes interaction was assessed by incorporating interaction terms into the multivariable model and comparing nested models using likelihood ratio tests. Discrimination and prediction error were evaluated through repeated five-times 5-fold cross-validation, using the AUC and the Brier score. For each of the seven prespecified P-value thresholds, the PRS+PC model was fit on the training folds and predictions were generated for the held-out validation fold, repeated across five iterations of 5-fold cross-validation; the resulting cross-validated AUCs were then compared across thresholds to select the final PRS.

Results

Study Population and Baseline Characteristics

Among the 761 participants who developed incident CAD, 427 cases occurred in non-diabetic participants and 334 in diabetic participants, corresponding to cumulative incidences of 10.8% and 28.5%, respectively. The median follow-up duration was 15.02 years (IQR, 11.24–16.35). Compared with non-CAD participants, those with CAD were older, more frequently male, and exhibited a higher prevalence of diabetes, current smoking, and hypertension. Additionally, CAD cases had lower HDL-C levels and a less favorable BMI distribution, with a greater proportion classified as overweight or obese. The distribution of PRS quintiles differed significantly by CAD status; participants with CAD were less frequently found in the lowest PRS quintile and more frequently in the highest PRS quintile compared to non-CAD participants (Table 1).

Association of PRS Quintiles and Clinical Risk Factors with CAD

In the overall cohort, higher PRS quintiles were associated with increased odds of CAD. In the fully adjusted model, participants in Q4 and Q5 exhibited higher odds of CAD compared to those in Q1 (Q4: OR, 1.36; 95% CI, 1.06–1.75; Q5: OR, 1.45; 95% CI, 1.13–1.87). Additionally, age, male sex, diabetes, hypertension, and lower HDL-C were also associated with CAD (Table 2). The global multiplicative interaction between PRS quintiles and diabetes status was statistically significant (P=0.017). Detailed interaction estimates, including quintile-specific interaction terms and likelihood ratio tests, are provided in Appendix Table 3, Appendix Table 4a, and Appendix Table 4b.

PRS Associations According to Diabetes Status

Among diabetic participants, higher quintiles of the PRS demonstrated a stronger association with CAD. In the fully adjusted model, the fifth quintile (Q5) was associated with increased odds of CAD compared to the first quintile (Q1) (Q5: odds ratio [OR], 2.15; 95% confidence interval [CI], 1.56–2.96). Among non-diabetic participants, the fourth (Q4) and Q5 were also associated with higher odds of CAD compared to Q1 (Q4: OR, 1.66; 95% CI, 1.20–2.31; Q5: OR, 1.53; 95% CI, 1.09–2.15) (Appendix Table 5). In the PRS-only and PCs, each 1-standard deviation (SD) increase in PRS was associated with CAD in both diabetic (OR, 1.314; 95% CI, 1.164–1.484) and non-diabetic participants (OR, 1.198; 95% CI, 1.091–1.317) (Table 3). Cox and log-binomial sensitivity analyses corroborated the main findings (Appendix Table 6; Appendix Table 7).

Table 1. Baseline characteristics of study participants according to coronary artery disease

Characteristic	Non-CAD N = 4,378[1]	CAD N = 761[1]	Standardized difference	*P*-value[2]
Age, years	39.4 (14.5)	53.2 (11.8)	1.04	<0.001
Sex			0.30	<0.001
Male	1,805 (41.2%)	425 (55.8%)		
Female	2,573 (58.8%)	336 (44.2%)		
Diabetes status, yes	837 (19.1%)	334 (43.9%)	0.55	<0.001
PRS quintile			0.21	<0.001
Q1	920 (21.0%)	108 (14.2%)		
Q2	876 (20.0%)	152 (20.0%)		
Q3	876 (20.0%)	152 (20.0%)		
Q4	867 (19.8%)	160 (21.0%)		
Q5	838 (19.1%)	189 (24.8%)		
Smoking status			0.15	<0.001
Non-Smoker	3,772 (89.8%)	629 (85.0%)		
Current Smoker	428 (10.2%)	111 (15.0%)		
Hypertension	733 (18.3%)	301 (40.3%)	0.50	<0.001
HDL-C, mg/dL	42 (11.1)	40.2 (10.6)	0.17	<0.001
BMI category			0.19	<0.001
Normal	1,460 (33.3%)	191 (25.1%)		
Overweight	1,609 (36.8%)	333 (43.8%)		
Obese	1,309 (29.9%)	237 (31.1%)		

[1]Mean (SD); n (%).
[2]Wilcoxon rank sum test; Pearson's Chi-squared test

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Table 2. Associations of polygenic risk score quintiles and clinical risk factors with coronary artery disease in the overall cohort

Characteristic	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Age, per 10 years increase		1.43 (1.35 - 1.51)	1.44 (1.36 - 1.53)
Sex (male vs. female)		1.57 (1.31 - 1.87)	1.56 (1.31 - 1.87)
Diabetes status (yes vs. no)		2.31 (1.96 - 2.73)	2.29 (1.94 - 2.71)
PRS quintile (Q1 as reference)			
Q2	1.11 (0.88 - 1.4)		1.13 (0.87 - 1.47)
Q3	1.16 (0.92 - 1.47)		1.27 (0.98 - 1.64)
Q4	1.28 (1.02 - 1.61)		1.36 (1.06 - 1.75)
Q5	1.37 (1.09 - 1.72)		1.45 (1.13 - 1.87)
Smoking status (current vs. non-current)		0.93 (0.7 - 1.2)	0.93 (0.71 - 1.21)
Hypertension (yes vs. no)		1.62 (1.36 - 1.92)	1.61 (1.35 - 1.91)
HDL-C, mg/dL		0.98 (0.97 - 0.99)	0.98 (0.97 - 0.99)
BMI category (<25 as reference)			
25-29.9		1.25 (1.01 - 1.55)	1.24 (1 - 1.55)
≥ 30		1.2 (0.95 - 1.53)	1.19 (0.94 - 1.51)

Odds ratios (ORs) and 95% confidence intervals (CIs).
Model 1 included PRS quintiles and PCs.
Model 2 included age, sex, smoking status, BMI category, hypertension, diabetes status and HDL-C.
Model 3 additionally included PCs and PRS (full multivariable model)

Table 3. Associations of a 1-s.d. increase in polygenic risk score with coronary artery disease according to diabetes status

Model	Overall OR (95% CI)	Diabetic OR (95% CI)	Non-Diabetic OR (95% CI)
Model 1: PRS	1.254 (1.167 - 1.347)	1.314 (1.164 - 1.484)	1.198 (1.091 - 1.317)
Model 2: PRS + age + sex	1.362 (1.262 - 1.47)	1.368 (1.209 - 1.55)	1.305 (1.181 - 1.442)
Model 3: PRS + TRF	1.313 (1.213 - 1.423)	1.361 (1.198 - 1.549)	1.268 (1.144 - 1.407)

Odds ratios represent the association of a 1-SD increase in PRS

Model Performance

The PRS alone demonstrated limited discrimination in both diabetes strata, whereas models incorporating age, sex, or traditional risk factors exhibited improved performance. Discrimination was higher in non-diabetic participants compared to diabetic participants; the PRS combined with the traditional risk factor model achieved an AUC of 0.776 in non-diabetic participants and 0.600 in diabetic participants (Figure 1). Prediction error showed a similar trend, with lower Brier scores observed in non-diabetic participants; the PRS plus traditional risk factor model recorded Brier scores of 0.088 and 0.205 in non-diabetic and diabetic participants, respectively (Table 4).

Discussion

This study showed that the CAD polygenic risk was associated with incident CAD in both diabetic and non-diabetic adults, and this association persisted after adjusting

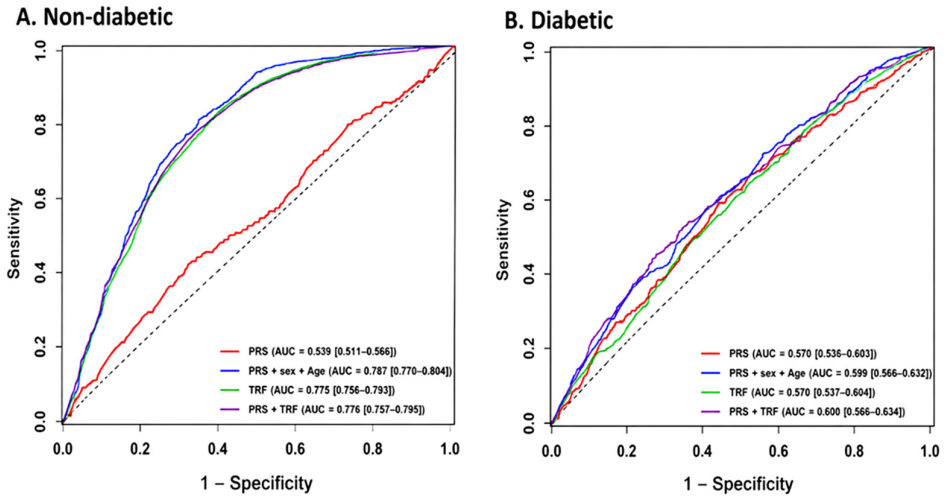

Figure 1. Comparative ROC curves and AUCs for PRS-based model combinations according to baseline diabetes status

Table 4. Model performance by diabetes status

Model	Overall Brier score (95% CI)	Diabetic Brier score (95% CI)	Non-diabetic Brier score (95% CI)
PRS	0.127 (0.122–0.134)	0.214 (0.204–0.224)	0.095 (0.088–0.101)
PRS + sex + Age	0.118 (0.112–0.124)	0.211 (0.201–0.221)	0.088 (0.082–0.095)
TRF	0.115 (0.109–0.121)	0.208 (0.198–0.218)	0.088 (0.082–0.095)
PRS + TRF	0.114 (0.109–0.119)	0.205 (0.195–0.216)	0.088 (0.082–0.094)

Brier score values were calculated using repeated 5-fold cross-validation

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for traditional cardiovascular risk factors. The findings indicate that inherited susceptibility is linked to incident CAD across diabetes-defined clinical strata; however, the pattern of association varies by diabetes status. A higher CAD risk was more evident in the upper PRS categories among non-diabetic participants, whereas in diabetic participants, the association was more evident when the PRS was analysed as a continuous standardized score. These results suggest that diabetes may influence the clinical manifestation of inherited coronary susceptibility rather than diminish the significance of polygenic risk.

The findings of this study are consistent with previous studies showing that CAD PRS is associated with incident CAD events and long-term CAD risk. Hindy et al. reported that genome-wide CAD polygenic risk stratified individuals into distinct trajectories of CAD risk over time (8). Khera et al. demonstrated that genome-wide polygenic scores can identify individuals with significantly increased inherited risk for common diseases, including CAD (5). Additionally, Elliott et al. and Mosley et al. reported significant associations between CAD PRS and incident coronary outcomes; however, the clinical prediction gain beyond established risk models was modest (10, 22). This study extends the existing evidence by evaluating CAD PRS in relation to baseline diabetes status, a clinically relevant context in which CAD risk is both high and heterogeneous.

The diabetes-stratified findings are biologically plausible, as diabetes promotes endothelial dysfunction, oxidative stress, inflammation, platelet hyperactivity, and accelerated atherosclerosis (23, 24). Previous studies in type 2 diabetes have shown that the CHD/CAD PRS is associated with coronary outcomes and angiographic atherosclerotic burden, capturing risk that is not fully reflected by traditional clinical markers (12, 25). These findings support the interpretation that the PRS may represent inherited atherosclerotic liability; however, genomic information alone remains insufficient for accurate prediction.

The evidence for heterogeneity based on diabetes status should be interpreted with caution. The findings align more closely with context-dependent expression of polygenic risk rather than a straightforward dose-response interaction across all PRS categories. Truong et al. reported that CAD PRS can modify the association between various clinical risk factors and incident CAD, including type 2 diabetes, BMI, C-reactive protein, LDL-C, and total cholesterol (26). Genetic studies also indicate that type 2 diabetes and CAD share both common and distinct biological pathways, including insulin resistance, lipid metabolism, inflammation, and vascular injury (27). Previous reports linking poor glycemic control to an enhanced 9p21-associated CAD risk, along with the identification of a diabetes-specific CHD signal near GLUL, further suggest that the diabetic vascular environment may influence the expression of inherited coronary risk (28, 29). Consequently, the interaction findings in the present study should be regarded as hypothesis-generating and require validation in larger diabetes-stratified cohorts.

PRS alone showed limited discrimination, while models including TRF exhibited improved performance. Although the combined clinical–genetic model resulted in a lower prediction error compared to PRS alone, this does not advocate for the replacement of established risk assessment methods with PRS. Rather, CAD PRS should be regarded as a complementary marker of inherited susceptibility in conjunction with conventional risk factors. Any clinical application of PRS necessitates further evaluation of external validity, ancestry portability, calibration, and clinical utility (30). Furthermore, high genetic risk is not deterministic, as favorable lifestyle choices and lipid-lowering therapy may mitigate CAD risk among genetically susceptible individuals (31, 32).

This study possesses several strengths, including its community-based design, incident CAD outcomes, diabetes-stratified analyses, adjustment for genetic principal components, and evaluation of PRS both continuously and by quintiles. These features facilitated the assessment of inherited CAD susceptibility across diabetes-defined strata. Key limitations include the reliance on external GWAS summary statistics predominantly derived from European-ancestry populations, which may restrict the portability of PRS to the Iranian Middle Eastern TCGS cohort due to ancestry-related differences in allele frequencies, linkage disequilibrium, imputation quality, and effect-size transferability. Additionally, the analyses lacked information on diabetes duration, longitudinal glycemic control, kidney function, medication use, inflammatory biomarkers, and imaging markers of subclinical atherosclerosis. Selection bias stemming from the restriction to participants with genetic data, unexamined gene–environment interactions, and unassessed sex-specific PRS effects should also be considered. Finally, although the base GWAS and TCGS target cohort were independent, PRS threshold selection was conducted within the target cohort; thus, some optimism from threshold tuning cannot be excluded without external validation in independent cohorts with similar ancestry and adjudicated CAD outcomes.

Conclusion

CAD PRS was associated with incident coronary disease in both diabetic and non-diabetic participants, with diabetes status appearing to influence the pattern of this association. These findings support CAD PRS as a marker of inherited coronary susceptibility across diabetes-defined clinical strata. The limited discrimination of PRS alone suggests that it should be interpreted as a complementary marker of inherited susceptibility rather than a stand-alone clinical prediction tool. Future studies should validate these findings externally and assess whether PRS-informed approaches enhance clinical decision-making or improve cardiovascular outcomes.

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Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

FM contributed to the study design, methodology, software development, formal analysis, investigation, visualization, and drafting of the manuscript. MA contributed to the methodology, software validation, and manuscript revision. SS, LNH-B, HL, and AD were involved in the conceptualization, validation, and review of the manuscript, with AD also supervising the study. MSD contributed to the conceptualization, methodology, software development, formal analysis, investigation, validation, manuscript revision, supervision, and project administration.

Ethical Considerations

The present secondary analysis was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNS.REC.1403.051). Written informed consent was obtained from all participants in the original TLGS/TCGS, and the ethics committee waived the requirement for additional informed consent for this secondary analysis.

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Data Availability

The data are available from the corresponding author upon reasonable request.

AI Use Statement

During the preparation of this work, the authors used ChatGPT solely for language editing and improving the readability of the manuscript. No AI tools were used for data collection, statistical analysis, interpretation of results, or drawing conclusions. All scientific content remains the responsibility of the authors.

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Appendix Table 1. Summary of clumping-and-thresholding PRS profiles across score thresholds and diabetes subgroups.

Threshold	Subgroup	Approx. scoring SNPs	Mean scored alleles
0.001	Overall	3,757	5.682
0.05	Overall	53,173	87.666
0.1	Overall	90,550	151.591
0.2	Overall	144,886	245.921
0.3	Overall	189,164	323.767
0.4	Overall	227,049	390.842
0.5	Overall	259,554	448.813
0.001	Diabetic	3,755	5.680
0.05	Diabetic	53,170	87.651
0.1	Diabetic	90,539	151.567
0.2	Diabetic	144,863	245.885
0.3	Diabetic	189,147	323.716
0.4	Diabetic	227,030	390.781
0.5	Diabetic	259,531	448.743
0.001	Non-diabetic	3,757	5.682
0.05	Non-diabetic	53,174	87.670
0.1	Non-diabetic	90,554	151.598
0.2	Non-diabetic	144,889	245.932
0.3	Non-diabetic	189,167	323.781
0.4	Non-diabetic	227,054	390.859
0.5	Non-diabetic	259,564	448.833

Rows are shown for the overall cohort and for diabetes-stratified subgroups. The P<0.05 threshold is shaded because it was selected as the primary threshold for downstream analyses. Approximate scoring SNPs were calculated as median CNT divided by 2. Missing PRS values were zero for all thresholds.

Appendix Table 2. Performance of the polygenic risk score model with genetic principal components across different C+T thresholds

Subgroup	Threshold	AUC (95% CI)	Cutoff	Sensitivity	Specificity	PPV	NPV	Youden Index
Diabetes sub-group	0.001	0.565 (0.528–0.602)	0.316	0.539	0.590	0.345	0.763	0.130
	0.05	0.570 (0.533–0.607)	0.314	0.555	0.585	0.348	0.767	0.140
	0.1	0.564 (0.527–0.601)	0.318	0.404	0.724	0.369	0.753	0.128
	0.2	0.568 (0.531–0.605)	0.312	0.471	0.664	0.359	0.759	0.136
	0.3	0.571 (0.534–0.608)	0.311	0.588	0.551	0.345	0.771	0.140
	0.4	0.565 (0.528–0.602)	0.313	0.546	0.583	0.344	0.763	0.130
	0.5	0.566 (0.529–0.603)	0.301	0.680	0.451	0.331	0.780	0.132
Non-diabetes sub-group	0.001	0.540 (0.511–0.569)	0.107	0.453	0.625	0.128	0.905	0.077
	0.05	0.539 (0.510–0.568)	0.109	0.340	0.738	0.135	0.903	0.078
	0.1	0.538 (0.509–0.567)	0.111	0.176	0.900	0.175	0.901	0.076
	0.2	0.536 (0.507–0.565)	0.108	0.372	0.700	0.130	0.902	0.072
	0.3	0.536 (0.507–0.565)	0.108	0.346	0.727	0.132	0.902	0.072
	0.4	0.536 (0.507–0.565)	0.108	0.347	0.726	0.132	0.902	0.072
	0.5	0.535 (0.506–0.564)	0.112	0.150	0.921	0.185	0.900	0.070
Overall cohort	0.001	0.557 (0.534–0.580)	0.153	0.431	0.684	0.191	0.873	0.114
	0.05	0.560 (0.537–0.583)	0.153	0.467	0.654	0.190	0.876	0.120
	0.1	0.559 (0.536–0.582)	0.153	0.476	0.642	0.188	0.876	0.118
	0.2	0.561 (0.538–0.584)	0.154	0.431	0.690	0.195	0.875	0.120
	0.3	0.557 (0.534–0.580)	0.153	0.454	0.660	0.188	0.874	0.114
	0.4	0.559 (0.536–0.582)	0.152	0.487	0.632	0.187	0.876	0.118
	0.5	0.555 (0.532–0.578)	0.150	0.560	0.549	0.178	0.878	0.110

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; C+T, clumping-and-thresholding; NPV, negative predictive value; PPV, positive predictive value; PRS, polygenic risk score.

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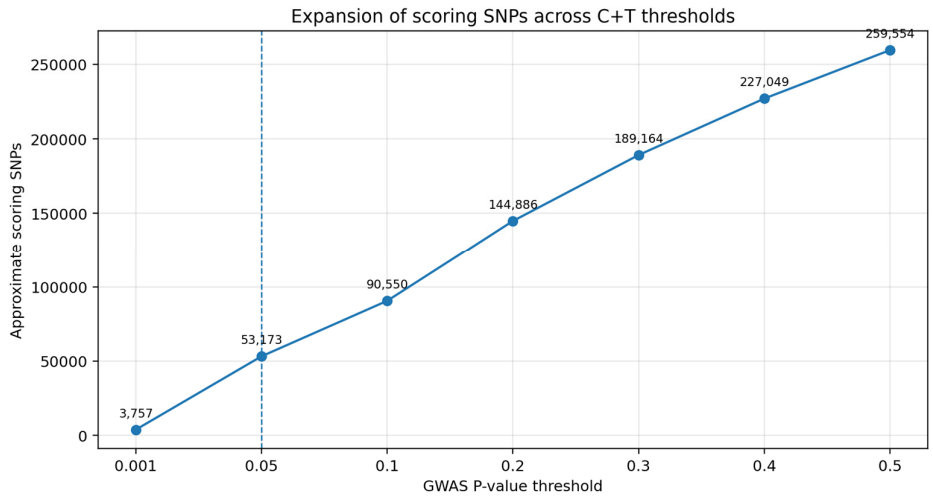

Appendix Figure 1. Approximate number of scoring SNPs in the overall cohort across C+T thresholds. The vertical dashed line marks the selected P<0.05 threshold. The figure demonstrates the rapid increase in the number of retained variants as GWAS P-value thresholds become more inclusive.

Appendix Table 3. Interaction analysis between PRS quintiles and diabetes status for CAD risk.

Interaction	Term	OR (95% CI)	*P* value
PRS quintile x diabetes	Q2 x diabetes	1.00 (0.57-1.74)	0.9860
PRS quintile x diabetes	Q3 x diabetes	1.75 (1.01-3.07)	0.0484
PRS quintile x diabetes	Q4 x diabetes	1.45 (1.13-1.87)	0.0040
PRS quintile x diabetes	Q5 x diabetes	1.34 (0.78-2.30)	0.2850

Interaction terms were estimated in the fully adjusted model with Q1 as the reference PRS category. OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; PRS, polygenic risk score.

Appendix Table 4a. Global likelihood ratio test for interaction between PRS and diabetes status.

Model	Interaction	Df	Deviance	P interaction
Model 3	PRS x diabetes	4	12.03048	0.01712607

The global likelihood ratio test compared nested models with and without PRS x diabetes interaction terms. The result supports heterogeneity of the PRS-CAD association by baseline diabetes status.

Appendix Table 4b. Standardized Continuous PRS × T2D Interaction Model - Overall Population

Characteristic	Interaction Term	OR (95% CI)	Wald P value	LRT P value
Continuous PRS × Diabetes interaction	Standardized continuous PRS × Diabetes	1.13 (0.96 - 1.33)	0.139	0.138

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Appendix Table 5. Associations of PRS quintiles with CAD according to diabetes status.

Characteristic	Diabetic Model 1	Diabetic Model 2	Diabetic Model 3	Non-diabetic Model 1	Non-diabetic Model 2	Non-diabetic Model 3
Age, per 10 years increase		1.11 (1.01-1.23)	1.12 (1.02-1.24)		1.57 (1.46-1.69)	1.58 (1.47-1.71)
Sex, male vs. female		1.43 (1.09-1.88)	1.44 (1.10-1.90)		1.62 (1.28-2.05)	1.63 (1.28-2.07)
PRS quintile, Q1 reference						
Q2	1.01 (0.72-1.41)		0.94 (0.66-1.33)	1.25 (0.92-1.71)		1.30 (0.93-1.84)
Q3	1.08 (0.77-1.52)		1.00 (0.70-1.42)	1.19 (0.87-1.63)		1.35 (0.96-1.90)
Q4	1.26 (0.87-1.83)		1.27 (0.97-1.66)	1.57 (1.17-2.12)		1.66 (1.20-2.31)
Q5	2.40 (1.77-3.28)		2.15 (1.56-2.96)	1.38 (1.01-1.88)		1.53 (1.09-2.15)
Smoking, current vs. non-current		0.75 (0.46-1.19)	0.74 (0.45-1.19)		1.01 (0.71-1.37)	0.99 (0.71-1.36)
Hypertension, yes vs. no		1.34 (1.03-1.75)	1.33 (1.01-1.74)		1.81 (1.45-2.26)	1.78 (1.43-2.23)
HDL-C, mg/dL		0.99 (0.98-1.00)	0.99 (0.98-1.00)		0.98 (0.97-0.99)	0.98 (0.97-0.99)
BMI category, <25 reference						
25-29.9		1.26 (0.87-1.86)	1.29 (0.88-1.90)		1.22 (0.94-1.61)	1.22 (0.94-1.61)
>=30		1.05 (0.70-1.58)	1.07 (0.72-1.62)		1.25 (0.93-1.69)	1.24 (0.92-1.67)

Values are odds ratios with 95% confidence intervals from logistic regression models. Model 1 included PRS quintile and PC1-PC6. Model 2 included age at entry, sex, smoking status, BMI category, hypertension, and HDL-C. Model 3 included Model 2 plus PRS quintile and PC1-PC6. Diabetes status was not included in the stratified models. Q1 was the reference category for PRS quintiles. Empty cells indicate covariates not included in that model. BMI, body mass index; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; PC, principal component; PRS, polygenic risk score.

Appendix Table 6. Cox proportional hazards analysis stratified by baseline diabetes status

Characteristic	Without diabetes HR (95% CI)	With diabetes HR (95% CI)
PRS quintile (Q1 as reference)		
Q2	1.42 (1.06, 1.91)	1.37 (0.94, 2.00)
Q3	1.31 (0.96, 1.79)	1.55 (1.06, 2.27)
Q4	1.42 (1.04, 1.94)	1.81 (1.25, 2.62)
Q5	1.74 (1.30, 2.33)	2.15 (1.48, 3.12)
Age (per 10-year increase)	1.45 (1.35, 1.56)	1.39 (1.27, 1.52)
Sex (male vs. female)	1.68 (1.36, 2.08)	1.48 (1.18, 1.86)
Current smoking (yes vs. no)	1.44 (1.09, 1.91)	1.20 (0.81, 1.77)
Low HDL-C (<40 vs. ≥40 mg/dL)	1.16 (0.95, 1.42)	1.03 (0.81, 1.30)
High triglycerides (yes vs. no)	1.09 (0.89, 1.35)	1.00 (0.78, 1.28)
BMI category (<25 kg/m² as reference)		
Overweight (25–29.9 kg/m²)	1.24 (0.97, 1.57)	1.16 (0.85, 1.59)
Obesity (≥30 kg/m²)	1.34 (1.02, 1.76)	1.12 (0.81, 1.56)
Hypercholesterolemia (yes vs. no)	1.61 (1.28, 2.03)	1.62 (1.29, 2.02)
Hypertension (yes vs. no)	1.93 (1.57, 2.38)	1.15 (0.93, 1.44)

Values are hazard ratios (HRs) with 95% confidence intervals (CIs) from Cox proportional hazards models stratified by baseline diabetes status. Follow-up time was defined from baseline to incident CAD, censoring, death, loss to follow-up, or the end of follow-up, whichever occurred first. Models included PRS quintiles, age, sex, current smoking, low HDL-C, high triglycerides, BMI category, hypercholesterolemia, hypertension, and ancestry principal components (PC1–PC6).

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; PC, principal component; PRS, polygenic risk score.

Appendix Table 7. Log-binomial regression analysis stratified by baseline diabetes status

Characteristic	Without diabetes RR (95% CI)	With diabetes RR (95% CI)
PRS quintile (Q1 as reference)		
Q2	1.42 (1.07, 1.89)	1.36 (0.98, 1.90)
Q3	1.24 (0.92, 1.66)	1.69 (1.23, 2.31)
Q4	1.55 (1.17, 2.06)	1.83 (1.35, 2.48)
Q5	1.74 (1.33, 2.28)	1.89 (1.39, 2.57)
Age (per 10-year increase)	1.37 (1.30, 1.45)	1.09 (1.01, 1.17)
Sex (male vs. female)	1.55 (1.28, 1.88)	1.27 (1.06, 1.52)
Current smoking (yes vs. no)	1.07 (0.82, 1.40)	0.83 (0.59, 1.16)
Low HDL-C (<40 vs. ≥40 mg/dL)	1.31 (1.09, 1.57)	1.27 (1.07, 1.51)
BMI category (<25 kg/m² as reference)		
Overweight (25–29.9 kg/m²)	1.23 (0.99, 1.53)	1.21 (0.94, 1.57)
Obesity (≥30 kg/m²)	1.21 (0.95, 1.54)	1.03 (0.78, 1.36)
Hypertension (yes vs. no)	1.57 (1.30, 1.90)	1.17 (0.98, 1.40)

Values are risk ratios (RRs) with 95% confidence intervals (CIs) from log-binomial regression models stratified by baseline diabetes status. The adjusted model included PRS quintiles, age, sex, current smoking, low HDL-C, BMI category, hypertension, and ancestry principal components (PC1–PC6). Abbreviations: BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; PC, principal component; PRS, polygenic risk score; RR, risk ratio.

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