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Associations of a polygenic risk score with coronary artery disease phenotypes in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial

Jonathan D. Newman, MD, MPH, Pamela S. Douglas, MD, Ilya Zhbannikov, PhD, Maros Ferencik, MD, PhD, MCR, Borek Foldyna, MD, Udo Hoffmann, MD, MPH, Svati H. Shah, MD, MHS, Geoffrey S. Ginsburg, MD, PhD, Michael T. Lu, MD, MPH, and Deepak Voora, MD

A polygenic risk score (PGS) is associated with obstructive coronary artery disease (CAD) independent of traditional risk factors. Coronary computed tomography angiography (CTA) can characterize coronary plaques, including features of high-risk CAD. However, it is unknown if a PGS is associated with obstructive CAD and high-risk CAD phenotypes in patients with symptoms suggestive of CAD. (Am Heart J 2022;252:12–15.)

Background

Genome-wide association studies show that the genetic underpinning of CAD is due - in part - to common genetic variants with small effect sizes in addition to rare variants with larger effects. The common genetic variants contributing to CAD risk can be represented by a polygenic risk score (PGS), a quantitative factor that captures the aggregate genetic influence of many common genetic variants. Previous studies have shown that a polygenic risk score (PGS) can summarize genetic risk for coronary artery disease (CAD), is independent of clinical characteristics, and may have clinical utility. However, validation in a North American chest pain population using standardized core-lab assessment of coronary computed tomography angiography (CTA) to define obstructive CAD (oCAD) is needed to more precisely classify the extent of CAD in order to characterize use of PGSs as a risk stratification tool. To address this need, we tested whether an existing PGS is associated with obstructive CAD and high-risk CAD phenotypes by core-lab assessed coronary CTA among well-characterized outpatients with stable symptoms suggestive of CAD randomized to standard of care vs. coronary CTA for evaluation as participants in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. We tested the hypothesis that a PGS would be associated with oCAD and high-risk CAD phenotypes independent of traditional cardiovascular risk factors.

Methods

Of the 10,003 randomized PROMISE participants, 4,996 were randomized to the CTA arm, and 4,725 had CTA core lab data available. Of those, 4,070 participated in the PROMISE biorepository. Biorepository participants had similar characteristics at baseline to the overall PROMISE cohort. From the 4,017 participants with blood for DNA extraction, 605 patients [(n = 488 no CAD; n = 95 oCAD (≥50% stenosis); n = 22 (high-risk CAD)] with active consent, high quality DNA and complete CTA data were identified for this nested case-control study. We compared genotyped PROMISE participants with no CAD, oCAD or high-risk CAD on CTA. Genotyping was performed using the Illumina Global Screening Array (Illumina, Inc. San Diego, CA). We calculated a genome-wide PGS for CAD comprising a weighted sum of over 6.6 million common (minor allele frequency >1%) genetic variants using genetic data from a published genome-wide association studies of CAD. The LDpred computational algorithm was used to calculate an ancestry-adjusted PGS, as previously described. The resulting PGS score is a normally distributed, quantitative trait with higher scores associated with CAD. Core-lab characterization of oCAD using a 50% stenosis threshold in PROMISE are described elsewhere. High-risk CAD was defined as either oCAD ≥70% stenosis, coronary
**Figure 1**

### A.

| Characteristics | All (n=803) | Q1 (n=126) | Q2 (n=123) | Q3 (n=119) | Q4 (n=118) | Q5 (n=119) |
|-----------------|-------------|------------|------------|------------|------------|------------|
| Mean age, years (S.D.) | 58.64 (7.3) | 56.97 (7.1) | 58.59 (7.3) | 57.69 (7.0) | 58.87 (7.1) | 59.16 (7.7) |
| Female sex (%) | 349 (57.7) | 80 (63.5) | 72 (58.5) | 63 (52.9) | 70 (59.3) | 64 (53.8) |
| Race/ethnicity | | | | | | |
| Non-Hispanic white (%) | 481 (79.5) | 102 (81.0) | 97 (78.9) | 95 (79.8) | 86 (74.6) | 99 (83.2) |
| Asian (%) | 10 (1.7) | 1 (0.8) | 3 (2.4) | 2 (1.7) | 3 (2.5) | 1 (0.8) |
| Non-Hispanic black (%) | 50 (8.5) | 12 (9.5) | 9 (7.3) | 12 (10.1) | 10 (8.5) | 7 (5.9) |
| Hispanic (%) | 56 (9.3) | 11 (8.7) | 13 (10.6) | 8 (6.7) | 13 (11.0) | 11 (9.2) |
| Hypertension (%) | 382 (63.1) | 73 (57.9) | 82 (66.7) | 76 (63.9) | 72 (61.0) | 79 (66.4) |
| Diabetes (%) | 104 (17.2) | 23 (18.3) | 16 (13.0) | 19 (16.0) | 18 (15.3) | 28 (23.5) |
| Dyslipidemia (%) | 385 (63.6) | 73 (57.9) | 85 (69.1) | 73 (61.3) | 74 (62.7) | 80 (67.2) |
| Family history of premature CAD (%) | 186 (31.1) | 38 (30.2) | 41 (33.3) | 35 (29.4) | 34 (29.8) | 40 (33.6) |
| PAD/cerebrovascular disease (%) | 27 (4.5) | 9 (7.1) | 3 (2.4) | 6 (5.0) | 2 (1.7) | 7 (5.9) |
| Current/prior tobacco (%) | 290 (47.9) | 63 (50.0) | 50 (40.7) | 60 (50.4) | 53 (44.9) | 64 (53.9) |
| Sedentary (%) | 326 (53.3) | 69 (54.8) | 68 (55.3) | 58 (48.7) | 64 (54.2) | 67 (56.3) |
| ESC PTP Score, N (%) | | | | | | |
| <5 | 22 (3.6) | 4 (3.2) | 3 (2.4) | 7 (5.9) | 2 (1.7) | 6 (5.0) |
| 5 ≤ PTP <15 | 364 (58.5) | 82 (65.1) | 72 (58.5) | 71 (59.7) | 68 (57.6) | 61 (51.3) |
| ≥15 | 229 (37.9) | 40 (31.8) | 48 (39.0) | 41 (34.5) | 48 (40.7) | 52 (43.7) |
| Baseline medication (%) | | | | | | |
| Beta-blocker | 140 (23.1) | 32 (25.4) | 22 (18.0) | 31 (26.1) | 31 (26.3) | 24 (20.2) |
| ACE inhibitor or ARB | 239 (39.5) | 51 (40.5) | 51 (41.5) | 47 (39.5) | 42 (35.6) | 48 (40.3) |
| Statin | 246 (40.7) | 49 (38.9) | 58 (47.2) | 41 (34.5) | 49 (41.5) | 49 (41.2) |
| Aspirin | 580 (95.9) | 120 (95.2) | 118 (95.9) | 116 (97.5) | 110 (93.2) | 116 (97.5) |
| Categories of CAD by coronary CTA | | | | | | |
| No CAD (%) | 488 (81) | 112 (88.9) | 105 (86.4) | 100 (84.0) | 95 (80.5) | 76 (63.9) |
| oCAD ≥50% (%) | 95 (15.7) | 12 (9.5) | 13 (10.6) | 14 (11.8) | 16 (13.6) | 40 (33.6) |
| High risk CAD (%) | 117 (19.3) | 14 (11.1) | 18 (14.6) | 19 (16.0) | 23 (19.5) | 43 (36.1) |

### B.

#### Subgroup

| Subgroup | No. of cases/total no. (%) | aOR* (95%CI) |
|----------|---------------------------|--------------|
| CAD stenosis ≥ 50% | | |
| Q2 | 13/123 (10.6) | 1.19 (0.48, 2.98) |
| Q3 | 14/119 (11.8) | 1.55 (0.63, 3.82) |
| Q4 | 16/118 (13.6) | 1.43 (0.58, 3.51) |
| Q5 | 40/119 (33.6) | 5.51 (2.45, 12.37) |
| High-risk CAD composite | | |
| Q2 | 18/107 (16.8) | 1.59 (0.67, 3.76) |
| Q3 | 19/109 (17.4) | 1.74 (0.74, 4.05) |
| Q4 | 23/99 (23.2) | 2.27 (0.98, 5.24) |
| Q5 | 43/104 (41.3) | 5.43 (2.45, 12.05) |

*Q1 was used as reference
**Natural logarithmic scale

A. Baseline characteristics of study cohort by polygenic risk score quintiles. S.D., standard deviation; CAD, coronary artery disease; PAD, peripheral artery disease; ESC PTP, European Society of Cardiology Pre-test Probability; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; oCAD, obstructive CAD; Q1-Q5, quintile 1 through quintile 5. B. Multivariate adjusted odds ratios of between no CAD, CAD ≥50% stenosis and high-risk CAD with polygenic risk score quintiles. The square size (point estimate) reflects an effect size. CAD, coronary artery disease; Q1-Q5, quintile 1 through quintile 5; aOR, adjusted odds ratio.
artery calcium (CAC) >400, Leaman Score >5 (measure of extent of stenosis and plaque burden), or high-risk plaque features (positive remodeling, low attenuation, or napkin ring sign) on CTA.

We calculated the mean (± standard deviation, S.D.) PGS score and adjusted odds ratios (aORs) and 95% confidence intervals (C.I.) of oCAD and high-risk CAD for PGS quintiles 2-5 with quintile 1 as the referent using logistic regression models adjusted for European Society of Cardiology (ESC) pre-test probability (PTP) risk score categories, as the ESC PTP risk score may be preferred to estimate risk of oCAD among patients with chest pain. We conducted a sensitivity analysis using the American Heart Association/American College of Cardiology atherosclerotic cardiovascular disease (ASCVD) risk score instead of the ESC PTP score and performed an exploratory comparison of the PGS of patients with oCAD with that of patients with high-risk CAD, but without oCAD (excluding the overlap between oCAD and high-risk CAD).

Results

Among the 605 participants in this analysis, baseline characteristics, cardiovascular risk factors, ESC PTP risk score categories and cardiovascular medications were similar across PGS quintiles (all \( P > .2 \)), Panel A. At baseline 488 (81%) of participants had no CAD, 95 (16%) had oCAD, and 117 (19%) had high-risk CAD (overlap of oCAD and high-risk CAD = 95). The proportion of oCAD and high-risk CAD was greatest in the highest PGS quintile, Panel A. The mean (± S.D.) PGS of patients with oCAD ≥50% (0.50 ± 1.08) or high-risk CAD (0.45 ± 1.03) was greater than the mean PGS of patients with no CAD (0.12 ± 0.98), \( P < .001 \) for both comparisons. After multivariable adjustment with the ESC PTP score, PGS quintile 5 was associated with significantly increased odds of oCAD ≥50% (aOR 5.51, 95% C.I. 2.45, 12.37) and high-risk CAD (aOR 5.43, 95% C.I. 2.45, 12.05) as compared with quintile 1. Panel B. Similar findings were observed after adjustment for ASCVD risk categories instead of the ESC PTP risk score (data not shown). After exclusion of the 95 patients with overlap between oCAD and high-risk CAD, there was no evidence of a difference in the PGS score between the 22 patients with high-risk CAD without oCAD ≥50% (0.11 ± 0.71) vs the PGS of patients with oCAD (0.50 ± 1.08), \( P = .08 \) or no CAD (0.12 ± 0.98), \( P = .23 \).

Discussion

In a population of stable symptomatic outpatients, a higher PGS was associated with oCAD on CTA even after adjustment for pretest probability of CAD. In this nested case-control analysis, all patients with oCAD ≥50 had high-risk features, but not all patients with high-risk features had oCAD ≥50%. Consistent with other analyses, we observed that the polygenic risk for oCAD is independent of clinical risk factors. In contrast to prior studies, \(^2\) we did not observe an association between the PGS and high-risk CAD features. This may be because prior studies did not test the association between a PGS and high-risk CAD features after excluding the overlap with oCAD, or because studies lacked standardized core-lab interpretation of oCAD for all participants. Strengths of this analysis include detailed clinical phenotyping and blinded independent core-lab characterized oCAD ≥50% and high-risk CAD by coronary CTA, reducing potential misclassification bias, \(^1\),\(^10\) and a representative North American population with more than 50% female participants. \(^3\) Limitations of this study include the case-control study cohort design and a predominantly white study population. While our findings suggest current PGSs may not be optimized for high-risk features, this analysis is likely underpowered to examine associations between a PGS and high-risk CAD independent of oCAD. Our findings from a subset of participants in the PROMISE trial provide evidence supporting the use of a PGS to risk stratify outpatients with symptoms suggestive of cardiac chest pain and obstructive CAD. \(\text{Figure 1}\)

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Conflict of interest

The funding source had no role in the design and conduct of this study, study analyses and interpretation of the data, the drafting and editing of the manuscript and its final contents, approval of the manuscript, and the decision to submit the manuscript for publication. The views expressed in this article do not necessarily represent the official views of the NHLBI.

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