P333: Polygenic risk scores improve 10-year risk prediction of coronary artery disease in individuals at borderline and intermediate clinical risk

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BACKGROUND

- Coronary Artery Disease (CAD) is the leading cause of death worldwide.
- CAD often develops over decades; symptoms may go unnoticed until a significant blockage causes problems or a heart attack occurs.
- The Atherosclerotic Cardiovascular Disease (ASCVD) risk estimator or Pooled Cohort Equation (PCE) is widely used to predict 10-year risk of CAD; it is also used as a tool to guide decision for statin treatment initiation. It includes age, race, sex, systolic blood pressure, total cholesterol level, HDL-C level, diabetes status, and smoking status.
- Genome-wide association studies (GWAS) for CAD have identified many common genetic variants with modest effect size.
- Polygenic risk scores (PRS) weight these variants and aggregate them into a single measure explaining a significant proportion of genetic CAD predisposition.
- Most PRS for CAD are derived from mainly European cohorts; their validity in individuals of other ancestries is unclear.

OBJECTIVE

To develop and validate:

- a PRS for prediction of CAD in individuals of diverse ancestries (CAD caPRS).
- a screening tool that combines the CAD caPRS with ASCVD-PCE to identify high risk individuals who are invisible to traditional risk assessments for CAD.
- Identify individuals who may benefit from early intervention such as statin.

METHODS

Cross-ancestry Polygenic Risk Score (caPRS)

- We constructed internal PRS models using multi ancestry GWAS summary statistics from Cardiogram (European cohort), Biobank Japan (2 Japanese cohorts) and Million Veterans Program (Hispanic, European and African cohorts).
- Internal PRS models were combined with publicly available CAD models (polygenic score catalog) into ancestry-specific ensembles trained via elastic net regression.
- The caPRS was calculated as a linear combination of the best performing ensemble score weighted by the product of the ancestry-specific effect size and fractional ancestry estimate:

$$caPRS = \sum_{i=1}^{5} f_i * \beta_i * ensemblePRS_i$$

where i corresponds to one of the 5 continental ancestry groups.

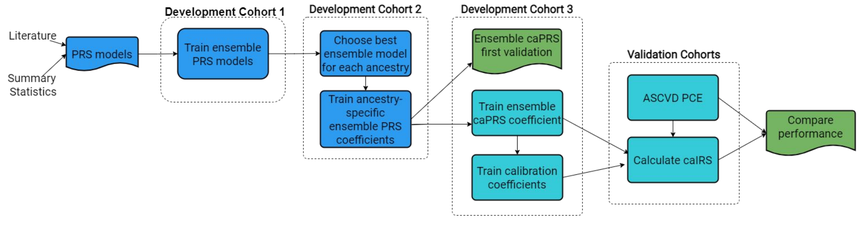
Integrated risk score (IRS)

- The IRS combines genetic and clinical information and is defined as follows:

$$IRS = 1 - (1 - \text{ASCVD-PCE})^{exp(\beta * caPRS + C_k)}$$

where ASCVD-PCE is the 10-year risk calculated using the ASCVD-PCE algorithm, β is the effect size associated with caPRS and Ck depends on sex and age.

Figure 1. Schematic development and validation workflow.



PRS combined with a clinical risk score can more accurately identify people at high risk of developing coronary artery disease across diverse populations.

RESULTS

- The caPRS was significantly associated with 10-year CAD risk across all 3 validation cohorts: UK biobank (UKB), Atherosclerosis Risk in Communities (ARIC) and Multi-Ethnic Study of Atherosclerosis (MESA); and ancestry groups (Figure 2).
- The IRS model outperformed the baseline ASCVD-PCE model across all population groups with largest improvements in South Asian and European ancestry groups (Figure 3).
- The IRS model identified additional individuals at high risk of CAD among those classified as borderline/intermediate risk by the ASCVD-PCE model (Figure 4 and Table 1).

Figure 2. Cox PH Model results for the association between caPRS and 10-year CAD incidence across validation cohorts and self-reported ancestry groups.

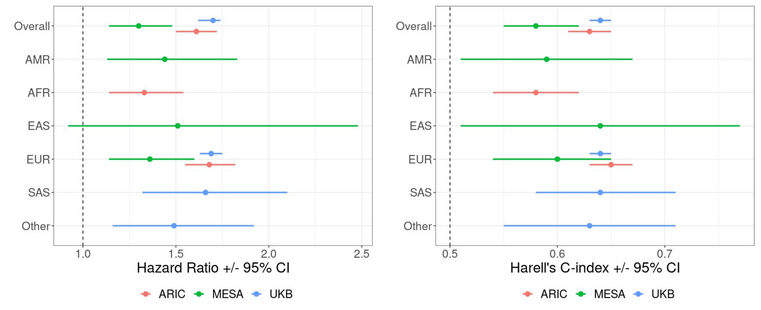


Figure 3. Performance of the ASCVD-PCE and IRS across validation cohorts and self-reported ancestry groups.

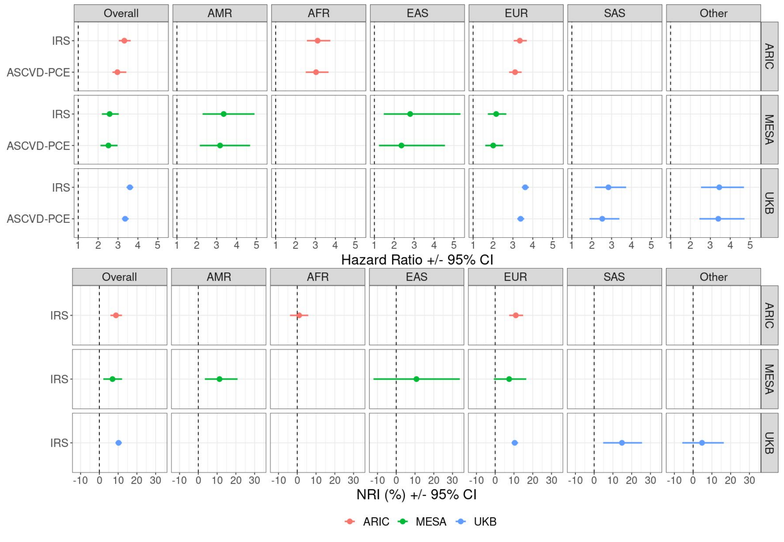


Figure 4. 10-year cumulative incidence of CAD among individuals identified as borderline or intermediate risk using ASCVD-PCE and those reclassified into high and low risk group by IRS (see also the corresponding Table 1 below).

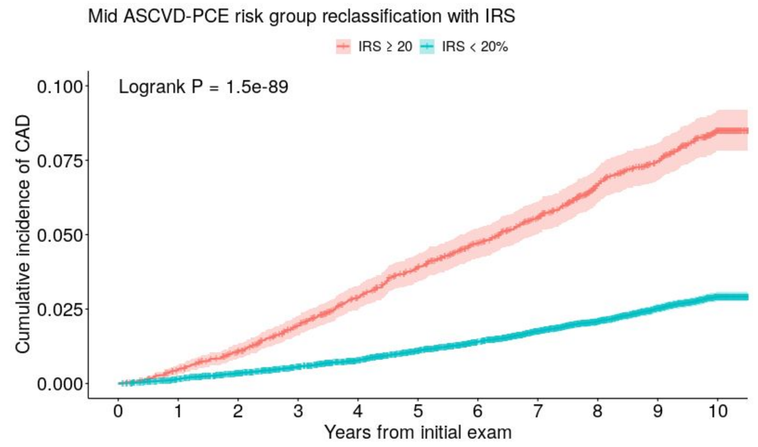


Table 1. 10-year CAD incidence rates among individuals identified as borderline or intermediate risk using ASCVD-PCE and those reclassified into high and low risk group by IRS.

ASCVD-PCE	IRS	N (%)	CAD incidence	Cohort
5 - 20%	-	53161 (100%)	3.54 (3.38 - 3.70)	UKB
5 - 20%	< 20%	46371 (87%)	2.85 (2.70 - 3.00)	UKB
5 - 20%	≥ 20%	6790 (13%)	8.26 (7.62 - 8.94)	UKB
5 - 20%	-	5752 (100%)	8.62 (7.91 - 9.38)	ARIC
5 - 20%	< 20%	5158 (90%)	7.25 (6.56 - 7.99)	ARIC
5 - 20%	≥20%	594 (10%)	22.68 (17.36 - 24.01)	ARIC
5 - 20%	-	1863 (100%)	6.44 (5.37 - 7.65)	MESA
5 - 20%	< 20%	1698 (91%)	5.65 (4.60 - 6.86)	MESA
5 - 20%	≥20%	165 (9%)	14.55 (9.55 - 20.87)	MESA

CONCLUSIONS AND FUTURE DIRECTIONS

- **Adding the CAD caPRS to the ASCVD-PCE algorithm improved 10-year CAD risk stratification for individuals across diverse populations.**
- Validate the CAD caPRS and IRS in larger non-European cohorts.
- Assess the utility and effectiveness of the IRS in a prospective, observational study of participants at risk of CAD.

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