PB4223: Integration of Polygenic Risk Scores with Clinical Factors Improves 10-year Risk Prediction of Coronary Artery Disease

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BACKGROUND

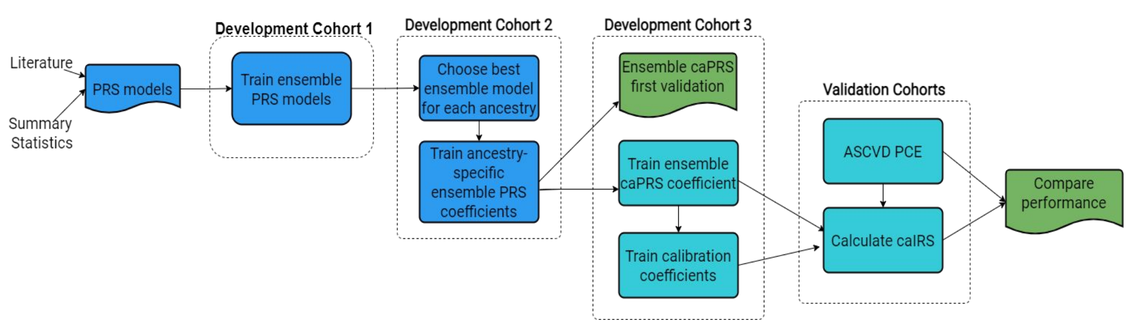
- Coronary Artery Disease (CAD) is the leading cause of death worldwide.
- The Atherosclerotic Cardiovascular Disease (ASCVD) Pooled Cohort Equation (PCE) is a common risk tool used to predict 10-year risk of CAD; it is also used as a tool to guide decision for statin treatment initiation. It includes age, race, sex, systolic blood pressure, total cholesterol level, HDL-C level, diabetes status, and smoking status.
- Polygenic risk scores (PRS) have the potential to improve the accuracy of clinical risk tools and identify additional individuals at elevated risk of CAD.
- The generalizability of a risk model that includes PRS across populations and its utility in individuals with unclear clinical risk is uncertain.

OBJECTIVE

- To validate a PRS for prediction of 10-year CAD in individuals of diverse ancestries (CAD caPRS).
- To test a screening tool that combines the CAD caPRS with the PCE to identify high risk individuals who may benefit from early intervention such as statin.

METHODS

Figure 1. Schematic Development and Validation Workflow



<u>Cross-ancestry Polygenic Risk Score (caPRS)</u>

- 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 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.

<u>Integrated risk score (calRS)</u>

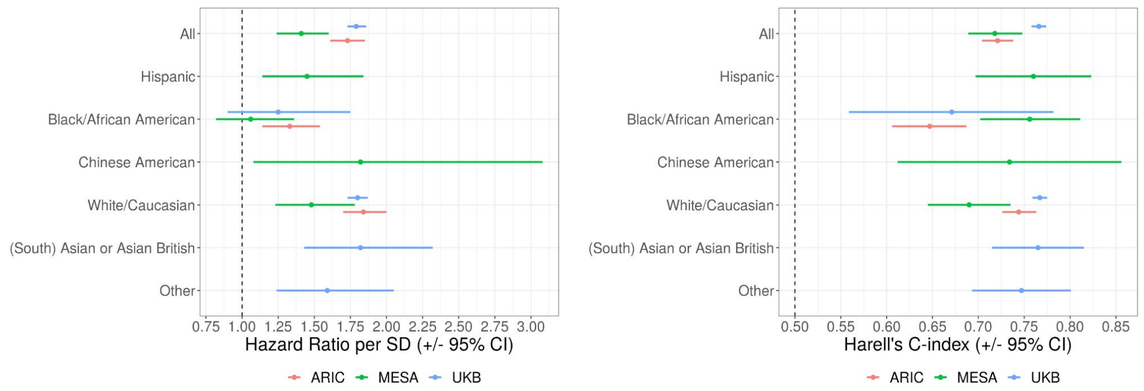
- The calRS combines genetic and clinical information and is defined as follows:

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

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

Combining PRS and clinical risk factors improves the identification of individuals at an elevated risk of developing CAD, particularly among those in the borderline or intermediate clinical risk categories

Figure 2. Association between caPRS and 10-year CAD Incidence



RESULTS

- The caPRS was significantly associated with 10-year CAD incidence across all validation cohorts (Figure 2) including UK Biobank (UKB), Multi-Ethnic Study of Atherosclerosis (MESA) and Atherosclerosis Risk in Communities (ARIC).
- The calRS improved discrimination compared to the PCE in all validation cohorts and ancestries tested (Figure 3).
- South Asian individuals had the largest gain in discrimination, a 6% increase in C-index, and net reclassification improvement (NRI) (15.33 ; 95% CI: 6.23 - 24.07).
- The calRS Identified up to 27 additional CAD cases per 1,000 individuals in the borderline/intermediate PCE group (Figure 4).

Figure 3. Performance of the ASCVD-PCE and calRS across Validation Cohorts

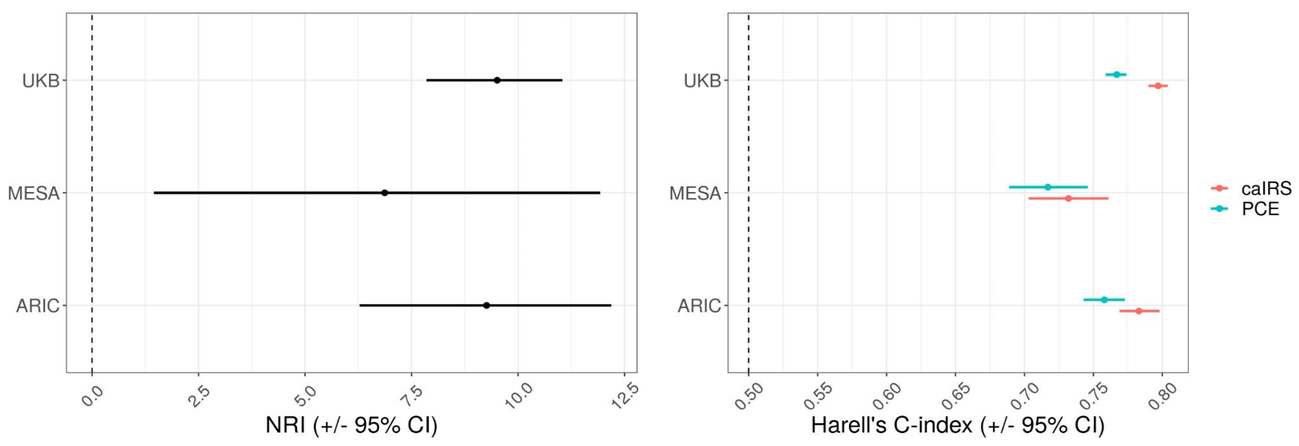
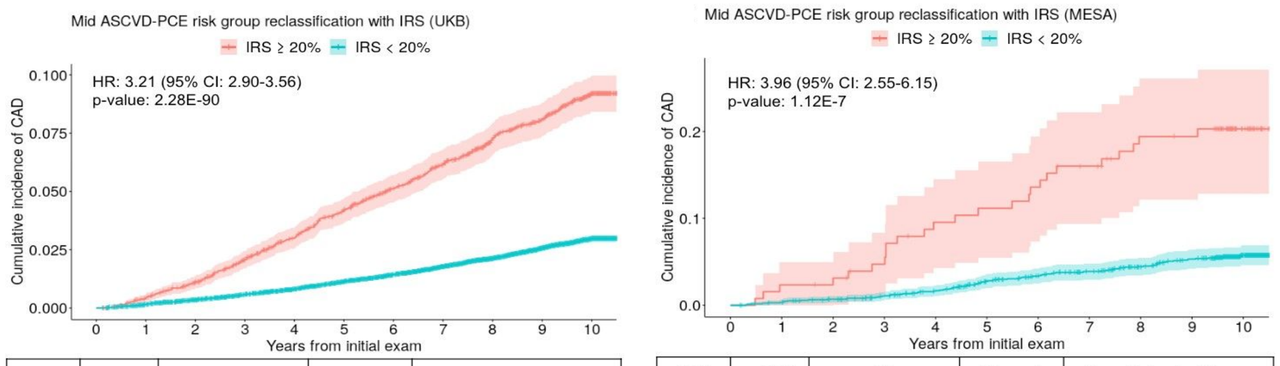


Figure 4. 10-year Cumulative Incidence of CAD among Individuals Identified as Borderline or Intermediate Risk using PCE and those Reclassified into High and Low Risk Groups by calRS



PCE	calRS	N	N event	Cumulative incidence
5-20%	-	53019 (100%)	1877	3.63 (3.47 - 3.79)
5-20%	<20%	47419 (89.4%)	1377	2.98 (2.82 - 3.13)
5-20%	≥20%	5600 (10.6%)	500	9.2 (8.43 - 9.97)

PCE	calRS	N	N event	Cumulative incidence
5-20%	-	1863 (100%)	120	6.74 (5.57 - 7.91)
5-20%	<20%	1735 (93.1%)	95	5.75 (4.62 - 6.87)
5-20%	≥20%	128 (6.9%)	25	20.28 (12.84 - 27.08)

CONCLUSIONS

- **The calRS, which combines genetics with traditional clinical risk factors, improved the identification of individuals at high risk of CAD across diverse populations.**
- **Using the calRS to refine the risk of individuals at borderline/intermediate clinical risk has the potential to influence treatment guidance in a primary prevention setting.**

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