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Review

Polygenic Risk Scores and Coronary Artery Disease

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Abstract

Background: Polygenic risk scores (PRSs) aggregate the effects of many common genetic variants and are being investigated as tools to refine coronary artery disease (CAD) risk prediction beyond traditional clinical models. Methods and Results: We review the development of PRS from early unweighted scores to contemporary genome-wide models and summarize evidence from major studies. We identified key studies through PubMed searches using the terms "polygenic risk score," "genetic risk prediction," and "coronary artery disease," supplemented by citation chaining of highly cited articles and recent reviews. Large cohorts, such as the UK Biobank, show that individuals in the highest PRS percentiles have a 3–5-fold higher risk of CAD, and may gain the greatest benefit from statin therapy. PRS can also reclassify younger adults at borderline or intermediate risk and may complement coronary artery calcium (CAC) scoring. Conclusions: PRSs hold promise for lifetime risk stratification and targeted prevention in CAD but are limited by ancestry bias in GWAS, underrepresentation of diverse populations, inconsistency in individual estimates, and lack of standardized reporting. Future research should focus on expanding multi-ancestry databases, standardizing methods, prospective validation, and effective communication strategies to support equitable and evidence-based clinical use.

Keywords: polygenic risk scores; coronary artery disease; coronary artery calcification

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1. Introduction

Efforts to identify individuals at risk for coronary artery disease (CAD) have been a topic of considerable interest in the field of preventive cardiology. CAD is one of the leading causes of morbidity and mortality in the United States, contributing to nearly 610,000 deaths and close to six million hospital admissions each year, placing significant strain on the U.S. healthcare system [1,2].

CAD often remains asymptomatic, with no apparent clinical manifestations until the sudden onset of a stroke or acute myocardial infarction [3,4]. This silent progression poses a critical challenge among clinicians and underscores the urgent need for early detection and intervention to prevent serious consequences associated with CAD. The American College of Cardiology and American Heart Association guidelines recommend using pooled cohort equations to estimate 10-year atherosclerotic cardiovascular risk, which is derived from age, systolic blood pressure, total cholesterol, smoking status, hypertension treatment status, diabetes status, and total and high-density lipoprotein HDL cholesterol levels [5,6].

However, the use of current clinical prediction models has limitations, often resulting in the under-treatment of several individuals for cardiovascular disease. Reasons for this include (1) clinical prediction models are less effective for individuals at intermediate risk;

(2) traditional risk factors are less valuable early in life to predict future risk; (3) clinical prediction models do not integrate all risk factors for cardiovascular disease, such as genetic variation [7,8]. Thus, enhancing current guideline-based clinical risk algorithms remains a crucial focus of current cardiovascular research.

There is increasing recognition that integrating genetics with traditional clinical risk factors could significantly enhance clinical prediction models for cardiovascular disease. A landmark study from the Framingham Heart Study demonstrated a 2-fold increased risk of CAD when a parental history of premature coronary artery disease was present [9]. Additionally, CAD has been estimated to have a heritability pattern of around 40–50% [10]. As evidence continues accumulating on the genetic determinants of CAD, and with the growing accessibility of gene sequencing among healthcare and individual consumers, a genetic risk predictor may ultimately emerge as a widely available tool for refining cardiovascular risk stratification [8,11]. The aim of this review is to trace the development of polygenic risk scores (PRS) for coronary artery disease (CAD), summarize evidence for predictive performance across populations, and evaluate potential clinical applications and limitations.

2. Methods for Study Selection

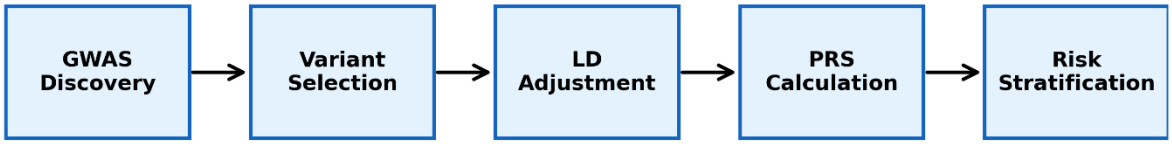
We identified studies through PubMed searches using the terms "polygenic risk score," "genetic risk prediction," and "coronary artery disease." Additional articles were obtained by reviewing the reference lists of highly cited papers (≥200 citations as of 2024) and recent review articles. Priority was given to large cohort studies (Table 1). For each study, we assessed details on cohort size, ancestry representation, PRS construction method (variant selection, weighting, and adjustment for linkage disequilibrium), main performance metrics (odds ratios, hazard ratios, C-statistics, or AUC), and key limitations (Table 1).

Table 1. Key studies of polygenic risk scores for coronary artery disease.

Author (Year)	Cohort/Sample Size	Ancestry	PRS Method	Key Results	Limitations
Tada et al. (2016) [12]	Malmö Diet and Cancer Study, ~24,000	European	50-SNP weighted PRS	Higher PRS associated with increased CAD risk independent of traditional risk factors	Small SNP panel; limited to Europeans
Mega et al. (2015) [13]	JUPITER & ASCOT, ~48,000	European	27-SNP PRS	Statins reduced CAD events most in high-PRS individuals; greatest absolute risk reduction in top PRS group	Small SNP set; European-only
Inouye et al. (2018) [14]	UK Biobank, ~500,000	European	Genome-wide PRS (~1.7 M SNPs)	Top 20% PRS had ~3-fold higher CAD risk vs. bottom 20%; PRS improved reclassification beyond PCE	No non-European validation
Khera et al. (2018) [15]	UK Biobank, ~400,000	Predominantly European; small South Asian & African subsets	Genome-wide PRS (~6.6 M SNPs)	Top 1% PRS ≈ 5-fold higher CAD risk; comparable to monogenic FH	Attenuated prediction in non-Europeans; healthy volunteer bias
Marston et al. (2023) [16]	UK Biobank + external cohorts (~500,000)	European; smaller African ancestry subset	Genome-wide PRS integrated with PCE	Improved prediction in younger adults; weaker discrimination in African ancestry (C-statistic drop 0.78 → 0.62)	Few non-European participants; uncertain clinical translation

3. What Are Polygenic Risk Scores?

Polygenic risk scores (PRS) represent a sum of risk conferred by several DNA variants to estimate the likelihood of disease onset among an individual [17]. Forming a PRS requires using a list of single-nucleotide polymorphisms (SNPs) with their respective effect size, as determined by genome-wide association studies (GWAS) (Figure 1) [18]. Each genetic variant is accompanied by essential information, such as a variant identifier, position within the genome, classification as a risk or protective allele, the effect size of its association with the trait, the confidence level of the effect size estimate, and the statistical significance (*p*-value) [19]. A higher PRS indicates a greater genetic predisposition to disease than a lower PRS [20].



GWAS = Genome-Wide Association Studies | LD = Linkage Disequilibrium | PRS = Polygenic Risk Score

Figure 1. Construction of polygenic risk scores.

PRS can be weighted or unweighted. An unweighted PRS is calculated by summing the total number of risk alleles in an individual's genome across a set of SNPs significantly associated with the disease of interest [19,21]. However, unweighted PRS assumes that each genetic variant included in the score has an equal effect size. This oversimplified assumption limits the predictive capacity of unweighted PRS because most traits include variants with differing levels of impact [22].

In contrast, weighted PRS are preferred over their unweighted counterparts due to increased predictive power [23]. Weighted PRS are calculated by computing the sum of the risk alleles within an individual and then multiplying that by the risk allele effect size estimated by a GWAS on the given phenotype [22].

The next step in calculating the PRS is selecting the optimal *p*-value threshold, which decides the number of SNPs included in the PRS model. Since the optimal *p*-value threshold is unknown beforehand, a range of *p*-value cutoffs is usually tested, and predictions are adjusted accordingly [24]. A more stringent *p*-value threshold results in fewer SNPs being included, leading to a higher trait heritability due to stricter criteria on the number of SNPs included [19]. Conversely, a more lenient *p*-value threshold allows for more SNPs, but this comes at the expense of reduced trait specificity [19]. It is crucial to note that no single *p*-value threshold can optimize PRS capabilities, as variations from GWAS data and the genetic attributes of the given disease are uncontrollable factors that play a significant role [19,25]. Thus, using a range of *p*-value thresholds is essential in creating an optimal range for PRS [25].

Furthermore, an important consideration when calculating PRS is assessing whether or not the variants are in linkage disequilibrium (LD). LD refers to the correlation between two neighboring genetic variants that are more likely to be inherited together due to their physical proximity [26]. As a result, genetic variants with a high LD may be similarly associated with traits in GWAS. This may reduce PRS performance by over-representing the risk for a disease [27]. Therefore, ensuring that the genetic variants used in the PRS are independent is vital to reduce any possible score inflation [27]. Computational tools such as LDpred can help adjust the PRS score LD and, thus, increase PRS accuracy [28].

4. Using PRS to Identify Individuals at Risk for Coronary Artery Disease

An early pioneering study by Kathiresan et al. utilized an unweighted PRS with nine SNPs associated with high-density lipoprotein (HDL) and low-density lipoprotein (LDL) to predict cardiovascular risk [29]. SNPs at nine loci were assessed among individuals from the Malmo Diet and Cancer Study (MDCS), a community-based epidemiological cohort. While the unweighted lipid allele score was found to be associated with incident cardiovascular events, it did not improve the accuracy of clinical cardiovascular risk prediction [29]. The authors suggested that incorporating a more significant number of SNPs could have improved the PRS model's ability to discriminate risk.

Building on this idea, a study by Tada et al. investigated the predictive advantage of using an established CAD PRS of 27 genome-wide significant SNPs vs. an expanded CAD PRS of 50 significant SNPs [12]. Their findings showed that adding th 23 SNPs to an established 27-variant PRS improved risk prediction for coronary heart disease [12]. Furthermore, a study by Abraham et al. generated a PRS of 49,310 SNPs associated with incident coronary heart disease [30]. The authors hypothesized that adding SNPs, including those with less genome-wide significance, could produce clinically relevant predictive power. Indeed, this expanded PRS model was tested among cohorts in the Framingham Heart Study and FINRISK and demonstrated significant improvement in coronary heart disease risk prediction compared to PRS models with only genome-wide significant SNPs [30]. Moreover, combining the expanded PRS model with established risk scores improved 10-year coronary heart disease risk prediction in the FINRISK and Framingham Heart Study cohorts [30].

Recent analytical advancements have made it possible to construct comprehensive PRS models that incorporate millions of genetic variants, significantly improving the prognosis of diseases like CAD. Khera et al. analyzed ~400,000 individuals from the UK Biobank (predominantly European ancestry) using a genome-wide PRS of ~6.6 million variants [15]. People in the top 1% of the score had almost a five-fold higher risk of CAD, similar to the risk seen with familial hypercholesterolemia. Overall, about 8% of the population had at least a three-fold increased risk, making high genetic risk far more common than rare monogenic mutations. The study demonstrated that PRS can identify large groups at very high risk early in life. However, because the work was performed almost entirely in Europeans, the results may not apply equally well to other ancestries [15]. Subsequently, Inouye et al. conducted a large-scale meta-analysis of genetic association data to construct a PRS model with 1.7 million genetic variants associated with CAD [14]. By analyzing data from multiple genetic association studies, they created a PRS score that accounted for nearly 27% heritability for CAD [14]. Their findings also indicated that individuals in the top 20% of the PRS distribution faced a four-fold increased risk of developing CAD compared to those in the bottom 20% [14]. Importantly, this PRS model provided a more reliable prediction risk for CAD than traditional cardiovascular risk factors, such as hypertension, current smoking, diabetes, etc. [14]. Together, the results from Kheera et al. and Inouye et al. suggest the utilization of genetic scores, like PRS, to risk-stratify individuals for adverse cardiovascular events.

5. PRS and Coronary Artery Calcification

Coronary artery calcification (CAC) is a clinical marker for subclinical atherosclerosis [31]. The relationship between PRS and CAC is of particular interest as it can help identify genetically predisposed individuals to atherosclerosis and adverse cardiovascular outcomes.

In a study among Framingham Heart Study patients, a PRS composed of 13 SNPs was significantly associated with increased CAC, suggesting a genetic contribution to the CAC pathophysiology [32]. Further supporting this connection, a more extensive study from

the Multi-Ethnic Study of Atherosclerosis (MESA) involving 6600 individuals calculated a PRS score with 157 genome-wide significant SNPs associated with non-zero CAC [33]. Such findings are crucial because a CAC-associated PRS may influence clinicians in early screening for CAD with computer tomography and initiation of statin therapy.

Additionally, a large observational study by Khan et al., using data from the Multi-Ethnic Study of Atherosclerosis and the Rotterdam study, evaluated CAC and PRS in predicting risk for coronary heart disease [34]. Khan et al. found that while CAC significantly improved coronary heart disease risk discrimination when added to traditional risk models, the addition of PRS alone did not yield the same benefit [34]. Furthermore, the combined use of CAC and PRS did not provide additional predictive value beyond CAC alone, suggesting that CAC may be a more robust cardiovascular clinical risk predictor.

6. PRS Risk Stratification Among Young Patients

As genetic testing becomes increasingly popular and accessible, it is important to identify which individuals may benefit most, particularly in cardiovascular risk management. Marston and colleagues evaluated more than 330,000 UK Biobank participants without prior CAD and replicated their findings in Biobank Japan [16]. They tested a PRS derived from 241 genome-wide significant variants and found it was associated with myocardial infarction risk across all ages, with the strongest effect observed in adults younger than 50 years. In this group, each 1-SD increase in PRS conferred a hazard ratio of 1.72, and those in the top 20% of the distribution had a 3–4-fold higher risk of MI compared with those in the lowest 20%. Adding PRS to the pooled cohort equations (PCE) reclassified about 20% of borderline-risk younger adults into the statin-eligible intermediate-risk category, while down-classifying another 20% to low risk [16]. The authors reasoned that genetics plays a larger role in early adulthood, when traditional risk factors have not yet accumulated, whereas lifestyle and clinical factors dominate risk later in life. These findings suggest that targeted use of PRS could help refine statin decisions in younger adults, although further studies across diverse populations are needed before routine clinical implementation.

7. PRS and Risk Mitigation

The clinical utility of PRS depends on the corresponding treatment and interventions available [35]. Among four independent studies with 55,685 participants, a PRS of 50 genome-wide significant SNPs was significantly associated with clinical and subclinical CAD [36]. However, among individuals with a high genetic burden, lifestyle interventions were highly favorable in influencing prognosis [36]. A favorable lifestyle was described as engaging in at least three healthy behaviors: having a healthy diet, regular physical activity, no smoking, and no obesity. Individuals in the top PRS risk quartile who adhered to this healthy lifestyle attained a nearly 50% reduction in CAD compared to those high genetic risk individuals who did not adhere to a favorable lifestyle [36].

Further supporting the clinical utility of PRS, Mega et al. analyzed data from a large community cohort (the Malmö Diet and Cancer Study) and four randomized statin trials (JUPITER, ASCOT, CARE, and PROVE IT–TIMI 22), encompassing 48,421 individuals [13]. They used a 27-SNP genetic risk score and observed a clear gradient of statin benefit across genetic risk categories. Compared with the lowest-risk group, individuals at intermediate genetic risk had a hazard ratio of 1.34 for coronary events, and those at high genetic risk had a hazard ratio of 1.72 [13,19]. Importantly, statin therapy conferred the greatest benefit in the high-risk genetic group, with relative risk reductions of 13% in low, 29% in intermediate, and 48% in high genetic risk groups. This translated into a threefold difference in the number needed to treat: for example, in JUPITER, 66 individuals at low genetic risk needed

treatment to prevent one event over 10 years, compared with only 25 in the high-risk group [13].

These findings highlight how PRS can complement traditional risk factors by identifying individuals most likely to benefit from preventive interventions, whether through intensive lifestyle modification or pharmacological therapy such as statins.

8. PRS Across Diverse Populations

Most landmark PRS studies discussed so far have relied on large European and North American cohorts, which have limited their generalizability across diverse populations. This Eurocentric bias has been repeatedly demonstrated to reduce predictive accuracy in underrepresented groups, contributing to concerns about equity and clinical utility. For instance, in the U.S.-based electronic Medical Records and Genomics (eMERGE) system, a genome-wide PRS for CAD derived from the UK biobank was associated with a relative risk of 1.53 in European individuals, but only 1.27 in those of African ancestry ($p = 0.003$) [3,7–38]. Thereby, emphasizing how scores within European datasets may not be applicable to other populations, particularly African ancestry groups, where differences in haplotype and linkage disequilibrium patterns reduce predictive accuracy [38]. Nevertheless, recent multi-ancestry efforts highlight important progress.

A recent study by Ratman et al. further demonstrated how multi-ancestry approaches can refine CAD risk prediction among diverse populations [39]. The investigators developed a cross-ancestry PRS (caPRS) and an integrated risk score (caIRS) that combined the caPRS with the Pooled Cohort Equations (PCE). Validated across four independent cohorts, including the Penn Medicine Biobank, ARIC, MESA, and UK Biobank, the caPRS was significantly associated with incident CAD in all ancestry groups, with hazard ratios per standard deviation ranging from 1.35 in African American individuals to 1.82 in South Asian participants. Importantly, among individuals at borderline or intermediate clinical risk by PCE (5–20%), the caIRS reclassified 7–11% into a high-risk group with markedly higher CAD incidence (HRs 3.20–3.84). The greatest improvements in net reclassification were observed among Hispanic and South Asian individuals, with net reclassification improvements (NRIs) exceeding 15%. Although performance remained attenuated in African American participants, this study underscores the promise of multi-ancestry ensemble PRS in refining CAD risk prediction across diverse populations.

Similarly, Smith et al. developed and validated multi-ancestry PRS for CHD using summary statistics from a GWAS of 1.1 million individuals across five ancestry groups [40]. In validation cohorts, the best-performing PRS demonstrated strong associations with CHD in South Asian and European ancestry individuals (OR per 1 SD~2.75 and 1.65, respectively), with more modest associations in East Asian, Hispanic/Latino, and African ancestry groups (ORs 1.56, 1.38, and 1.2, respectively). Individuals in the top 5% of the PRS distribution had a 2- to 5-fold higher CHD risk compared with the rest of their ancestry group. While performance was consistently better than single-ancestry models, predictive gains were most limited in African ancestry participants, emphasizing the need for larger and more diverse GWAS to reduce disparities.

Together, these findings highlight both the challenges of PRS portability and the potential of multi-ancestry and ancestry-specific models to improve equity in risk prediction. Ongoing global initiatives, such as Biobank Japan and the Million Veteran Program, will be critical for building more representative datasets and ensuring that the clinical application of PRS does not worsen pre-existing health disparities.

9. PRS Limitations

The predictive capabilities of PRS are dependent on the GWAS population model and SNPs that have been tested [41]. While much progress has been made in identifying genetic variants associated with CAD and other diseases, the current genetic associations still need to be completed [41]. In addition, numerous genetic factors that influence disease risk likely remain undiscovered, limiting the ability of PRS to accurately assess an individual's genetic predisposition to the development of diseases like CAD.

The most concerning limitation associated with PRS is its poor generalizability across different ancestries. The majority of GWAS models have been conducted almost exclusively in European ancestry participants [42]. Among polygenic scoring studies from 2008 to 2017, only 3.8% included cohorts of African, Hispanic, or Indigenous populations [43]. As a result, most groups remain underrepresented, and PRS models may inaccurately estimate risk in these populations, potentially exacerbating health disparities [44]. In addition, a recent study by Abramowitz et al. demonstrated that coronary heart disease polygenic risk scores with similar population-level discrimination did not provide consistent individual-level risk estimates [45]. This finding underscores that while PRS can stratify groups effectively, their reliability for predicting risk in individual patients remains uncertain. Therefore, both more inclusive genetic research and further evaluation of individual-level performance are needed to ensure the accurate and equitable use of PRS across diverse populations.

Finally, there are currently no universally adopted guidelines on how PRS should be reported in a clinical setting. This absence of clear standards presents a significant challenge, as how genetic risk information is communicated can greatly influence a patient's understanding of risk. Although no global consensus exists, the European Society of Cardiology (ESC) recently released a clinical consensus statement proposing a preliminary workflow for the potential use of PRS in cardiovascular disease prevention [46]. This statement suggests that PRS may be most meaningful when applied as an adjunct to existing risk calculators in patients near clinical decision thresholds, while underscoring the need for standardized methods, validation across ancestries, and prospective outcome trials before broad adoption [42]. A study by Lewis et al. involving semi-structured interviews of patients and primary care providers examined mock clinical PRS report scenarios [47]. The findings revealed that most patients struggled to interpret PRS information accurately. Additionally, the majority of patients expressed the belief that there was nothing they could do to lower their risk, using deterministic language such as "definitely going to get the disease" [47]. These results underscore the need to carefully consider how PRS results are communicated to avoid misconceptions. Questions remain on how to convey PRS information in a way that ensures patients can make informed decisions.

10. Conclusions

Given the growing accessibility of genetic testing, polygenic risk scores (PRS) represent a promising tool for risk stratification in coronary artery disease. Current evidence shows that PRS can identify individuals at substantially elevated lifetime risk and, in some studies, those who derive the greatest benefit from preventive therapies such as statins. However, the clinical utility of PRS remains limited by several factors: the Eurocentric focus of most genome-wide association studies, variability in study design and reporting, and the difficulty of effectively communicating genetic risk to patients. To realize the full potential of PRS in cardiovascular prevention, future efforts must emphasize more diverse GWAS, standardized methods for score construction and reporting, and prospective implementation studies that test how PRS can be integrated alongside established clinical and imaging-based risk tools. Until such evidence is available, PRS should be viewed primarily as a complementary research instrument rather than a routine clinical test.

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