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Use of a polygenic risk score to enhance early detection of coronary atherosclerosis

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HIGHLIGHTS

- CAD-PRS associates with CCTA-detected plaque presence, extent, and severity, with the strongest impact of genetic risk on plaque presence seen among younger adults.
- On average, individuals at high genetic risk appear to develop plaque nearly two decades earlier than their low genetic risk counterparts, underscoring that CAD-PRS can be used to improve the yield of identifying premature atherosclerosis.
- Incorporating CAD-PRS improved discrimination for plaque presence, extent, and severity beyond age, sex, and traditional risk factors.
- Genetic risk stratification may help identify younger individuals who could benefit from coronary imaging to detect premature atherosclerosis and enhance preventive therapies.

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ABSTRACT

Background: Coronary CT angiography (CCTA) enables early noninvasive detection of coronary atherosclerosis, but its use in younger adults is limited by low pretest probability. Coronary artery disease polygenic risk score (CAD-PRS) may help identify individuals with increased likelihood of coronary plaque.
Methods: We conducted a retrospective cohort study of patients without prior coronary artery disease who underwent CCTA between 2004 and 2021 and were genotyped through the Mass General Brigham Biobank (n = 1991), with follow-up through 2024. CAD-PRS was analyzed continuously and by risk categories (high [top decile], intermediate, low [bottom decile]). Plaque was classified as absent (CAD-RADS 0), non-obstructive (CAD-RADS 1–2), or obstructive (CAD-RADS 3–5). Extensive plaque was defined as ≥3-vessel involvement. Relative risk regression evaluated associations with plaque stratified by age. Kaplan–Meier and Cox proportional hazards models evaluated associations with adverse cardiovascular outcomes.
Results: Plaque was present in 65.6% of participants, extensive plaque in 32.2%, and obstructive disease in 24.6%. Compared with the low-PRS group, high CAD-PRS was associated with greater risk of any plaque (RR 1.68, 95% CI 1.48–1.92), extensive plaque (RR 2.62, 95% CI 1.94–3.54), and obstructive disease (RR 2.82, 95% CI 1.87–4.27) (all $P < .001$). Associations were strongest among younger individuals (PRS–age interaction P =

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.017). CAD-PRS improved discrimination beyond age, sex, and traditional risk factors (C-statistic 0.832 [95% CI, 0.814–0.851] vs 0.803 [0.782–0.823]). High CAD-PRS was independently associated with increased cardiovascular events (aHR 2.76, 95% CI 1.55-4.92, $P < .001$).
Conclusions: High CAD-PRS was independently associated with greater presence, extent, and severity of CAD on CCTA. The impact of genetic risk was strongest in younger adults—a group for whom identifying early atherosclerotic plaque may have the greatest impact.

1. Introduction

The ability of coronary computed tomography angiography (CCTA) to non-invasively identify and characterize coronary plaque at earlier stages makes it an increasingly used tool in preventive cardiology. The Swedish CArdioPulmonary bioImage Study (SCAPIS) enrolled asymptomatic individuals between the age of 50 to 64 years and showed that coronary atherosclerosis was found among 42% of the population evaluated [1]. More recently, the 2024 Lancet Commission suggested that direct visualization of plaque may provide a more personalized approach to guide preventive strategies [2]. Importantly, the detection of any coronary plaque—even in young or asymptomatic individuals—is associated with significantly higher lifetime cardiovascular risk, offering an opportunity for earlier and more targeted prevention [3]. Despite these benefits, routine use of CCTA in younger individuals is not broadly recommended, primarily due to the low prevalence of coronary artery disease (CAD) in this population and the need to balance diagnostic yield with cost and radiation exposure. As a result, there is a need for novel methods to enrich likelihood of identifying plaque in the population of young individuals who may be eligible for CCTA.

One promising approach lies in genetic risk stratification. CAD has a high degree of heritability, estimated at 40% to 60% [4–6]. Large genome-wide association studies (GWAS) have identified numerous common genetic variants associated with CAD and the aggregate effects of these common DNA variants can be captured into a single quantitative predictor or polygenic risk score (PRS). The polygenic risk score for coronary artery disease (CAD-PRS) is one of the most widely studied and has been shown to improve risk prediction for incident CAD, particularly among younger individuals, and to refine long-term risk estimates beyond traditional clinical factors [7–10]. While it is known that CAD-PRS performs better in younger individuals based on outcome predictions, it remains unknown whether the same is true for imaging-based atherosclerosis, which may be especially relevant for primary prevention in this group.

The current study examines whether genetic risk – as defined through CAD-PRS – could help in improving the yield of imaging by predicting the presence, extent, and severity of coronary plaque on CCTA.

2. Methods

2.1. Study design and patient population

All patients at Mass General Brigham who underwent CCTA between 2004–2021 without a prior known history of CAD and who had genomic data available in the Mass General Brigham Biobank (MGBB) [11,12] were included (eFig. 1 in Supplement). The institutional review board approved the study with waiver of informed consent.

2.2. Genetic risk score

Genotyping and imputation followed established methods [13]. The CAD-PRS was computed using a validated score (PGS003725) obtained from the Polygenic Score Catalog [14]. This score was derived from a multi-ancestry genome-wide association study (GWAS) meta-analysis of

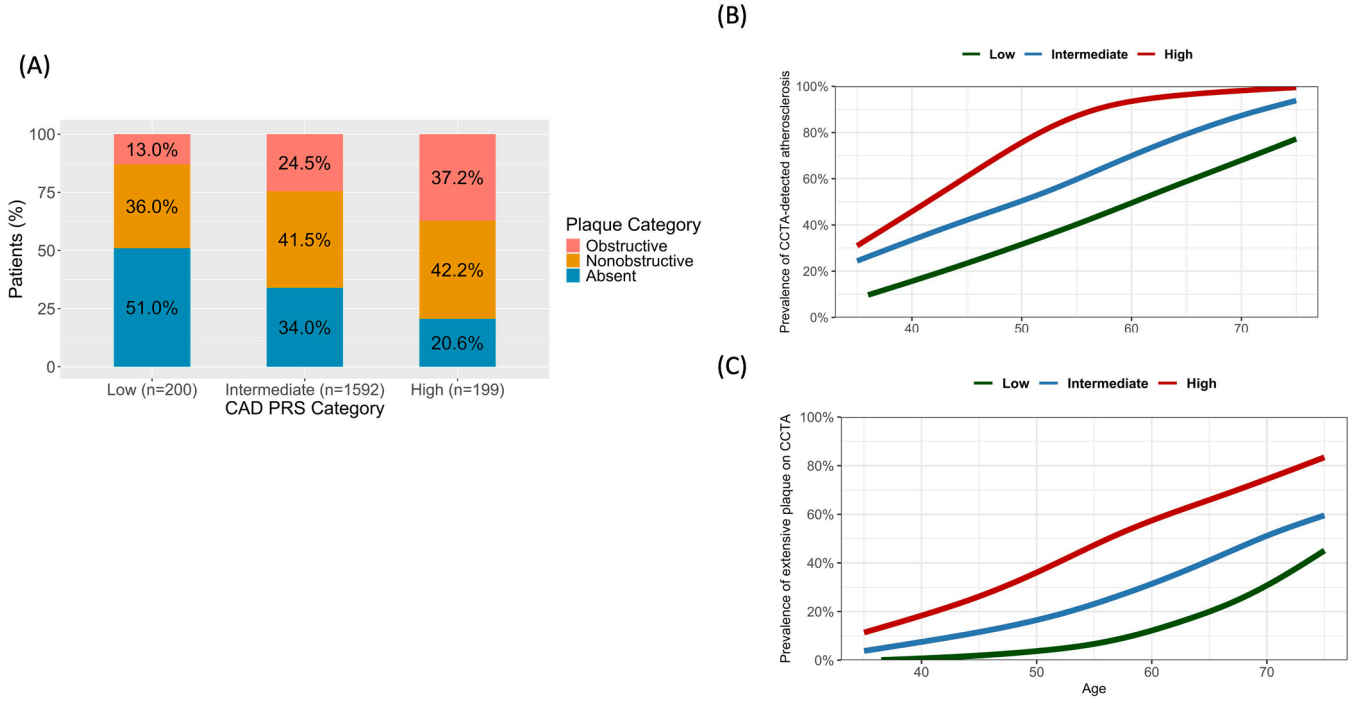

Fig. 1. Presence, extent and severity of coronary plaque by genetic risk category. (A) Bar graph highlights the stepwise increase in CCTA-detected atherosclerosis and plaque severity across the genetic risk categories. Across the adult age spectrum, the prevalence of CCTA-detected atherosclerosis (B) and prevalence of extensive plaque (C) both increase by genetic risk category (P-trend $< .001$ for graded increase in presence, extent, and severity).

over one million participants (1,443,386) [15]. The score comprises 1, 296,172 variants and was computed using PLINK 2.0 [16]. Individual CAD-PRS values were standardized, adjusted for the first 5 principal components of genetic ancestry, and categorized into risk groups: low (bottom decile), intermediate (middle 80%) and high (top decile).

2.3. Coronary CT angiography

CCTA was performed on >64-slice scanners, following institutional protocols and Society of Cardiovascular Computed Tomography (SCCT) guidelines. Image interpretation was conducted by level III-trained cardiologists or radiologists. Information regarding plaque presence and luminal stenosis was extracted from reports on a per-vessel basis using a validated natural language processing (NLP) approach (Canary platform; accuracy>95% versus manual cardiologist adjudication) [17,18]. For participants with multiple CCTAs, the earliest was analyzed. The presence and severity of CAD was categorized using the Coronary Artery Disease Reporting and Data System (CAD-RADS) [19–22] classification, which categorized the severity of stenosis in the worst segment as follows: [1] no CAD (CAD-RADS 0), [2] non-obstructive CAD (<50% stenosis; CAD-RADS 1–2), and [3] obstructive CAD (≥50% stenosis; CAD-RADS 3–5). Vessel involvement was broken down into four broad vessel categories defined as [1] left main, [2] LAD/diag/ramus [3] LCX/OM [4] and RCA. Extensive plaque was defined as involving ≥3 vessels.

2.4. Cardiovascular outcomes

Participants were followed through December 2024 for adverse outcomes. The primary composite outcome included cardiovascular (CV) death, myocardial infarction (MI) or coronary revascularization. Definitions and International Classification of Disease (ICD)/ Current Procedural Terminology (CPT) codes appear in Table S1 in the Supplement. Acute MI was defined by a primary discharge ICD 9/10 code. Revascularization was defined as the composite of coronary artery bypass grafting and percutaneous coronary intervention, identified by procedural ICD or CPT codes. Cause of death was determined by linkage to the National Death Index and the Massachusetts Office of Vital Statistics for patients recorded as deceased by the Social Security Administration Death Master File and CV mortality was determined based on the ICD-coded underlying causes of death [23–26]. Individuals who died from non-CV or undetermined causes were conservatively labeled as not experiencing CV mortality and censored at the date of death.

3. Statistical analysis

Baseline characteristics of participants are summarized as mean (SD) or number (percent). CCTA findings of plaque presence, extent, and severity were compared across CAD-PRS categories in the overall cohort, and further stratified by age (men <50 years/ women <60 years vs. older) and sex. Relative risk (RR) estimates were obtained using the *cumincglm* function from the *eventglm* R package, which fits generalized linear models to pseudo-observations of the cumulative incidence for time-to-event or binary outcomes. Models included a restricted cubic spline for age, PRS categories, their interaction with age, and the following covariates: sex, history of hypertension, antihypertensive treatment, history of dyslipidemia, statin use, type 2 diabetes, chronic kidney disease, smoking, and the first five principal components of ancestry. A log link function estimated RRs on the log scale. The significance of the PRS-age interaction was evaluated using *linearHypothesis* function from the *car* package, providing a Wald test.

Discrimination of the logistic regression models was assessed using the C-statistic (area under the receiver operating characteristic curve [AUC]), with 95% confidence intervals.

Kaplan-Meier (KM) curves were generated for the composite outcome of cardiovascular death, acute myocardial infarction (MI), and revascularization. Event rates were estimated from KM survival models at the median follow-up time, stratified by categorical PRS risk group and plaque severity. Cox proportional hazards models, adjusted for the same covariates, were used to estimate hazard ratios for outcomes. Sensitivity analyses used alternative PRS thresholds. All analyses were conducted in R version 4.4.0 and Python (version 3.11.8). A two-sided *P*-value < .05 was considered statistically significant.

4. Results

4.1. Study population

The study included 1991 participants without a prior known history of CAD, of whom 48.7% were female and 84.5% were of European ancestry with mean age of 58.3 (SD 12.4) years and mean BMI of 29.6 (SD 6.8) kg/m^2. Baseline characteristics for the overall cohort and by genetic risk category are shown in Table 1. Hypertension was present in

Table 1
Baseline Characteristics by Genetic Risk Category.

Variable	Total (N = 1991)	Low Bottom 10% (N = 200)	Intermediate Middle 80% (N = 1592)	High Top 10% (N = 199)
Age at CCTA, mean (SD), y				
Mean (SD)	58.3 (12.4)	59.9 (12.9)	58.4 (12.4)	56.0 (11.6)
Sex, No. (%)				
Female	969 (48.7)	82 (41.0)	771 (48.4)	116 (58.3)
BMI at CCTA, mean (SD)	29.6 (6.8)	28.4 (6.3)	29.6 (6.8)	30.9 (7.5)
Genetic Ancestry, n (%)[a]				
European (EUR)	1682 (84.5)	172 (86.0)	1342 (84.3)	168 (84.4)
African (AFR)	114 (5.7)	9 (4.5)	93 (5.8)	12 (6.0)
Admixed American (AMR)	165 (8.3)	14 (7.0)	136 (8.5)	15 (7.5)
Asian (EAS+SAS)	30 (1.5)	5 (2.5)	21 (1.3)	4 (2.0)
Comorbidities, No. (%)				
Hypertension	1416 (71.1)	125 (62.5)	1129 (70.9)	162 (81.4)
Diabetes mellitus type 2	437 (21.9)	26 (13.0)	341 (21.4)	70 (35.2)
Dyslipidemia	1349 (67.8)	111 (55.5)	1084 (68.1)	154 (77.4)
Chronic kidney disease	185 (9.3)	19 (9.5)	154 (9.7)	12 (6.0)
Ever Smoker	726 (36.5)	61 (30.5)	583 (36.6)	82 (41.2)
Medication use, No. (%)				
Statin	930 (46.7)	70 (35.0)	754 (47.4)	106 (53.3)
Anti-hypertensive	1100 (55.2)	96 (48.0)	884 (55.5)	120 (60.3)

[a] Population labels are based on genetic ancestry derived from principal components or imputed ancestry reference panels (e.g., 1000 Genomes Project classifications). East Asian (EAS) and South Asian (SAS) groups were combined as Asian (EAS+SAS) due to small sample sizes.

71.1% of participants, dyslipidemia in 67.8%, and type II diabetes in 21.9% – all of which were more prevalent in the high genetic risk group. Prior statin use was noted in 46.7% of the cohort. Age-stratified characteristics are presented in Table S2 in the Supplement with mean age 46.3 (SD 9.0) in the younger and 65.3 (SD 8.0) in the older cohort.

4.2. Association of CAD-PRS with CCTA findings

Coronary plaque was present in 1306 (65.6%) participants (41.0% non-obstructive, 24.6% obstructive). Prevalence increased stepwise across PRS categories—49.0% in the low-risk group, 66.0% in the intermediate-risk group, and 79.4% in the high-risk group (*P*-trend < .001; Fig. 1A). Similarly, the proportion with obstructive plaque rose from 13.0% in the low-risk group to 37.2% in the high-risk group (*P*-trend < .001). The genetic risk category differences were observed across the age spectrum for both the prevalence of CCTA detected atherosclerosis and for the prevalence of extensive plaque (*P*-trend for both < .001, Fig. 1B-C)

Adjusted relative risks (RR) for any plaque, extensive plaque, and obstructive plaque are shown in Fig. 2 according to CAD-PRS category, with models adjusted for conventional cardiovascular risk factors. After multivariable adjustment, high CAD-PRS was associated with 1.7-fold higher risk of any plaque, a 2.6-fold higher risk of extensive plaque and a 2.8-fold higher risk of obstructive plaque compared with the low-risk group (all $P < .001$). Each 1-SD increase in the CAD-PRS corresponded to a 13% higher risk of any plaque (95% CI: 1.10–1.16), 33% higher risk of extensive plaque (95% CI: 1.25–1.42), and 38% higher risk of obstructive plaque (95% CI: 1.27–1.49, all $P < .001$). Notably, individuals with high CAD-PRS reached a 50% probability of having coronary plaque nearly two decades earlier than those with low genetic risk (estimated age 42.3 vs. 61.7).

The association between genetic risk and earlier plaque development was observed in both sexes, though the onset of atherosclerosis occurred later in females (Figure S2 in the Supplement). In males, the high-risk group reached a 50% probability of coronary plaque at age 42.1 compared with age 53.9 in the low-risk group; in females, at 44.7 and 68.2 years.

4.3. Age-Stratified associations between CAD-PRS and CCTA findings

We observed a significant interaction between age and PRS group for coronary plaque presence (Wald test for interaction $P = .017$). As shown in Fig. 3, individuals with high PRS had markedly elevated relative risk of plaque at younger ages, with a gradual attenuation of risk with advancing age. For instance, at age 40, the RR for plaque in the high- versus low-PRS group was nearly 3-fold (2.99), decreasing to 1.3x by age 75.

Among younger individuals (mean age 46.3 years), plaque was present in 63.2% of those with high CAD-PRS versus 22.4% with low CAD-PRS, representing nearly a threefold higher diagnostic yield. Patterns for both obstructive and nonobstructive CAD followed a similar stepwise pattern (Figure S3A in the Supplement). Age-stratified relative risk estimates for plaque presence, extent, and severity are shown in Figure S3B and Figure S4 in the Supplement.

4.4. Integration of CAD-PRS with clinical risk factors

Compared with models including traditional risk factors, addition of CAD-PRS to age and sex yielded numerically higher model discrimination for the presence of plaque (C-statistic [95% CI] 0.821 [0.802–0.840] vs. 0.803 [0.782–0.823]), extent of plaque (0.810 [0.791–0.829] vs. 0.795 [0.775–0.816]), and severity of plaque (0.773 [0.749–0.798] vs. 0.755 [0.731–0.779]). Across all three CCTA plaque measures, inclusion of CAD-PRS also improved discrimination beyond models incorporating age, sex, and traditional cardiovascular risk factors (Fig. 4). For plaque presence, the C-statistic increased from 0.803 (0.782–0.823) for the model including age, sex, and risk factors to 0.832 (0.814–0.851) after addition of CAD-PRS. Similar improvements were

Variable		N	Estimate	p
1. Presence of plaque (any atherosclerosis; CAD-RADS 1-5 vs. 0)				
PRS_decile	Low	188	Reference	
	Intermediate	1493	1.35 (1.20, 1.52)	<0.001
	High	184	1.68 (1.48, 1.92)	<0.001
2. Extent of plaque (high risk vs. low or no risk; N of vessels 3-4 vs. 0-2)				
PRS_decile	Low	188	Reference	
	Intermediate	1493	1.63 (1.24, 2.16)	<0.001
	High	184	2.62 (1.94, 3.54)	<0.001
3. Severity of plaque (obstructive vs. nonobstructive/absent; CAD-RADS 3-5 vs. 0-2)				
PRS_decile	Low	188	Reference	
	Intermediate	1493	1.74 (1.18, 2.54)	0.005
	High	184	2.82 (1.87, 4.27)	<0.001

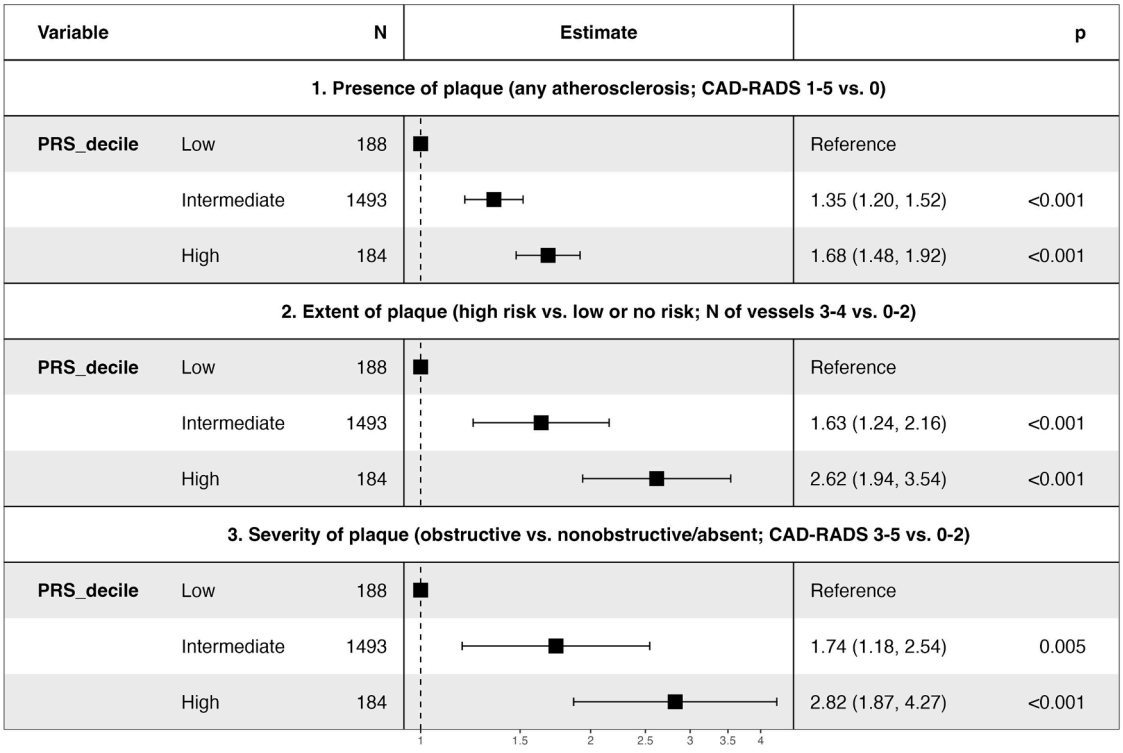

Fig. 2. Association between CAD-PRS categories and presence, extent, and severity of plaque. Relative risk regression models for presence, extent, and severity of plaque on CCTA were adjusted for age, sex, smoking status, history of dyslipidemia, history of hypertension, history of chronic kidney disease, history of diabetes, statin treatment, antihypertensive treatment, and principal components 1–5.

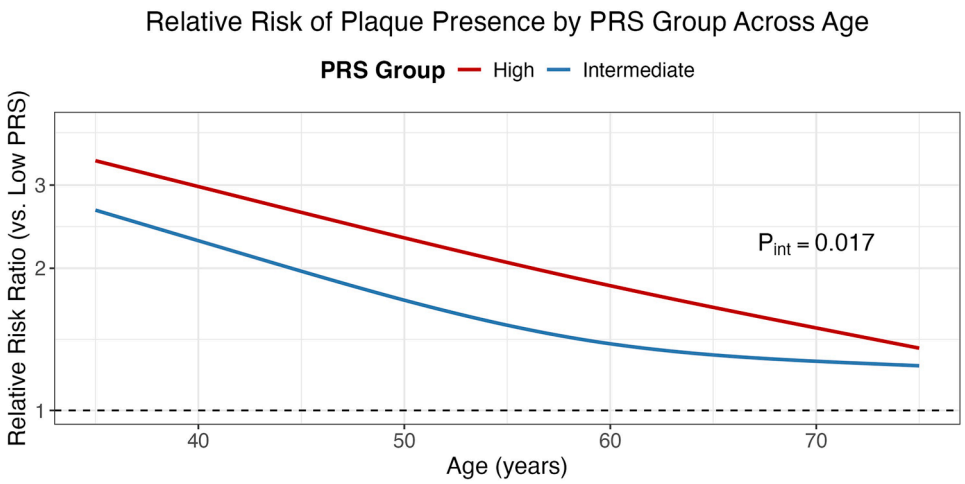

Fig. 3. Age-stratified analysis. Continuous modeling of relative risk using a spline function demonstrates a stronger effect of high CAD-PRS at younger ages, with attenuation of genetic risk with increasing age. A significant interaction between age and PRS group was observed (Wald test $P = 0.017$).

observed for plaque extent and plaque severity (Fig. 4).

4.5. CAD-PRS and CV events

Over a median 5.9-year follow up (IQR: 3.5, 9.0), 271 participants experienced an adverse CV event (50 acute MI, 208 coronary revascularization, and 52 cardiovascular deaths). In KM analyses, participants with high PRS had significantly higher cumulative incidence of CV events compared with those in the intermediate and low PRS (log-rank $P < .0001$, Figure S5 in the Supplement). In adjusted Cox models, individuals in the high CAD-PRS group had a 2.76-fold higher risk of the composite outcome (95% CI, 1.55–4.92; $P < .001$) compared with those in the low PRS group, while those in the intermediate PRS group had a 1.43-fold higher risk (95% CI, 0.88–2.35; $P = .15$).

Event rates for adverse CV outcomes varied by both plaque severity and PRS category and were largely driven by plaque severity on CCTA (Fig. 5). The highest event rate was observed among individuals with obstructive CAD, with risk ranging from 13.2% in the low PRS group to 28.2% in the high PRS group. With no detectable plaque on CCTA, event rates were low across genetic strata (2.4%, 1.6%, and 3.6% for high, intermediate, and low PRS groups, respectively).

5. Discussion

In this study of nearly 2000 individuals with no known CAD undergoing CCTA, we found that CAD-PRS was significantly associated with the presence, extent, and severity of atherosclerosis across the adult lifespan, independent of traditional CV risk factors. Notably, CAD-PRS was a stronger predictor of CCTA-detected plaque among younger individuals, underscoring its potential for improving the yield of CCTA and enabling early risk stratification. Our results also demonstrated that CAD-PRS improved the discrimination of predictive models to identify CCTA findings beyond age, sex, and conventional risk factors, and was associated with future cardiovascular events independently of traditional CV risk factors.

Across the cohort, high genetic risk conferred 1.7-fold higher risk of any plaque, 2.6-fold higher risk of extensive plaque and a 2.8-fold higher risk of obstructive plaque, consistent with prior smaller studies. In DanNICAD ($n = 1645$, median age of 57), each SD increase in CAD-PRS corresponded to 78% higher odds of obstructive plaque on CCTA [27]. Similarly, in the PROMISE trial subset ($n = 518$, mean age 58), and a Finnish cohort ($n = 943$, mean age 64), high PRS associated with approximately 6-fold higher odds of obstructive CAD [28,29].

In our study, we found that CAD-PRS was not only associated with obstructive disease, but also with the presence and extent of plaque, including non-obstructive plaque in younger adulthood, suggesting potential utility in identifying patients with early subclinical atherosclerosis. In fact, individuals in the high CAD-PRS group reached a 50% probability of having coronary plaque nearly two decades earlier than those in the low-risk group (estimated age 42.3 vs. 61.7). Identifying this premature onset of atherosclerosis can lead to earlier initiation or intensification of preventive therapies thereby altering an individual's

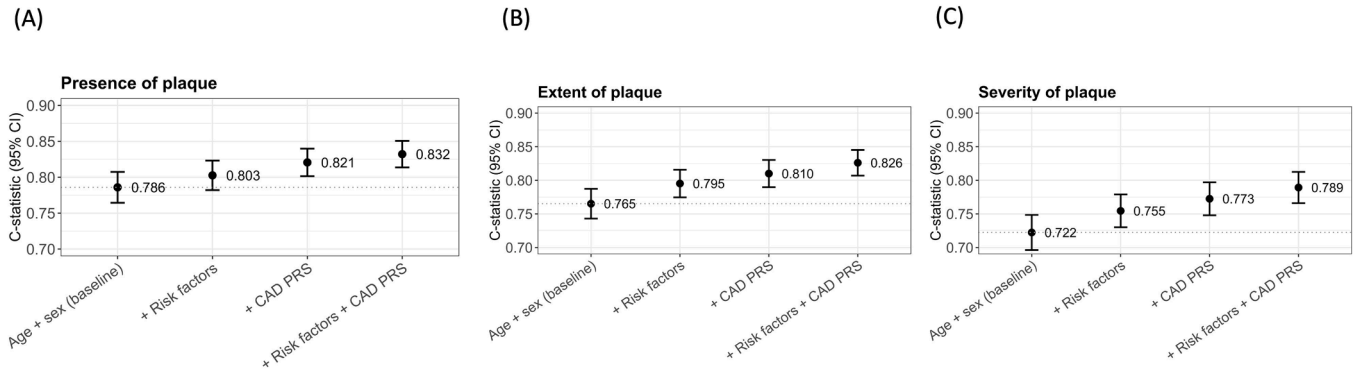

Fig. 4. Discrimination performance of sequential prediction models for coronary plaque. C-statistics are shown for sequentially adjusted models predicting (A) presence of plaque, (B) extent of plaque, and (C) severity of plaque. Models were evaluated with stepwise inclusion of covariates: age and sex (baseline model), addition of traditional cardiovascular risk factors, addition of the coronary artery disease polygenic risk score (CAD PRS), and the fully adjusted model including both risk factors and CAD PRS. Points represent C-statistics and error bars denote 95% confidence intervals; dotted lines indicate performance of the baseline model.

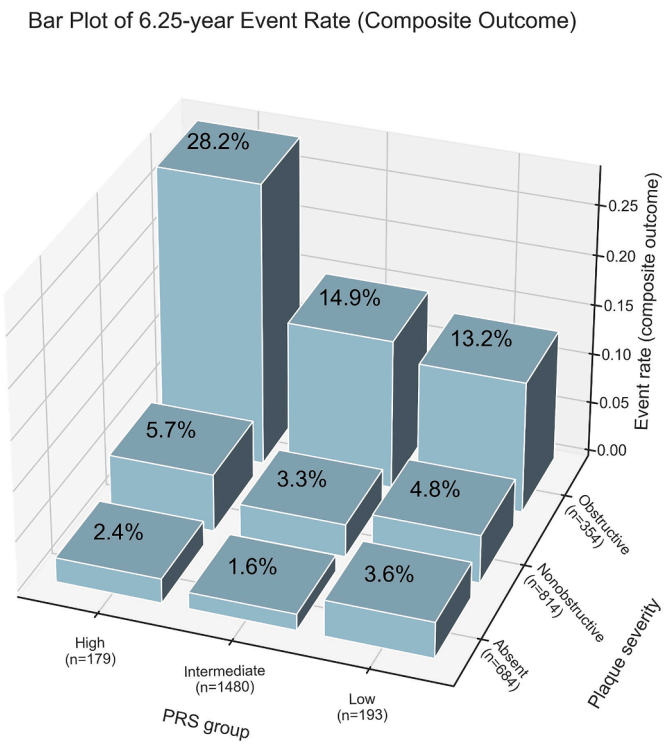

Fig. 5. Bar plot of cardiovascular event rates (composite of CV death, MI, and late coronary revascularization >90 days after CCTA) stratified by CCTA plaque severity (none, nonobstructive, obstructive) and CAD-PRS (low, intermediate, high) over a median follow-up of 6.3 years ($P < .001$ for global comparison). Event rates include only revascularizations occurring >90 days after CCTA to minimize inclusion of procedures related to the index study, differing from time-to-event analyses that include all revascularizations.

disease trajectory. However, even among individuals with low CAD-PRS, plaque was not universally absent at younger ages. Among participants younger than 40 years, plaque prevalence was ~9% in females with low CAD-PRS and ~17% in males. If CCTA was to be used more commonly for screening selected subgroups, health care systems would need to decide what is the appropriate yield (e.g. number needed to scan to detect one individual with plaque) of testing and whether CAD-PRS could improve it.

Our study adds to existing literature [27–30] by demonstrating that genetic risk had the strongest impact on CCTA-detected plaque in younger adults, with relative risks declining with age. The age-PRS interaction was statistically significant, supporting age-specific relevance of genetic screening for atherosclerosis. In the younger cohort, high CAD-PRS conferred a greater than threefold increase in plaque prevalence (aRR 3.2), double that seen in the older cohort (aRR 1.5). The relative risk attenuation in older individuals may reflect the increased background prevalence of other comorbidities and the role of aging in driving atherosclerosis. In REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV), CAD-PRS was associated with increased plaque presence and severity, but effects were similar across age subgroups [31]. Differences between our findings and REPRIEVE subset may relate to differences in study populations, as REPRIEVE focused exclusively on individuals with HIV, or to differences in underlying disease prevalence. Nonetheless, our results align with studies showing stronger event prediction by CAD-PRS in younger individuals [7,8,32], and extend these findings by providing direct anatomical validation using coronary imaging.

In all three domains—presence, extent, and severity of plaque—models that included CAD-PRS outperformed those using traditional risk factors alone. Models with age, sex, and CAD-PRS achieved slightly higher C-statistic than those with age, sex, and traditional cardiovascular risk factors, highlighting independent utility of genetic risk in prediction. Full models combining clinical risk factors and CAD-PRS achieved the best discrimination. While the utility of CCTA in asymptomatic populations remains debated, our findings suggest that CAD-PRS could help refine selection criteria by identifying individuals with higher pretest probability of subclinical disease–particularly important in younger individuals given that many of them do not manifest traditional risk factors, are classified as low risk, and are undertreated [33,34].

Our findings extend prior work by integrating genetic risk with CCTA-defined plaque severity to predict adverse cardiovascular outcomes. Imaging-defined CAD severity was the dominant determinant of risk, with obstructive disease conferring the highest event rate irrespective of genetic predisposition. However, within the obstructive CAD group, those with high CAD-PRS had the highest rates, suggesting persistent genetic influence even with obstructive disease. Beyond identifying patients at higher risk of plaque on CCTA, prior work has shown polygenic risk scores may also help identify individuals who derive a greater relative benefit from LDL-lowering therapies[36,37], suggesting that genetic risk may help flag atherosclerotic disease that is both higher-risk and more amenable to modification.

One limitation of our study is that indications for CCTA were not systematically captured, as all scans were performed as part of clinical care. This may limit generalizability to asymptomatic or population-based cohorts. However, the majority of participants did not have obstructive CAD, suggesting that symptoms that led to CCTA were often non-cardiac and that the detected plaque findings largely reflect subclinical atherosclerosis. Plaque prevalence observed in our younger cohort (46% in men and 39% in women) was similar to that reported in large asymptomatic cohorts, including MiHEART (age 40–65 years; any plaque 49%) [35] and SCAPIS (age 50–64 years; any plaque ~42.1%) [36], supporting the representativeness of our findings for this age group. An additional limitation is that our cohort was predominantly of European ancestry, limiting applicability to other populations. We sought to mitigate this limitation by applying a multi-ancestry CAD polygenic risk score developed to enhance transferability across ancestries, although validation in ancestrally diverse populations is still warranted. While CAD-RADS provided standardized plaque assessment, it does not offer quantitative metrics of plaque volume or composition. Nevertheless, plaque analysis is only considered in cases where there is visual identification of plaque, and thus our findings regarding the presence and severity of CAD would still apply. Certainly, the ability to quantify plaque may reveal further granularity regarding the association of CAD-PRS with plaque burden and plaque composition. Prospective studies, incorporating CAD-PRS enrichment into imaging strategies for younger and asymptomatic patients, are warranted to validate these findings in broader populations.

In conclusion, CAD-PRS was found to be independently associated with the presence, extent, and severity of coronary atherosclerosis across the adult lifespan, with stronger impact of genetic risk seen among younger individuals. Our findings show the potential for integration of CAD-PRS into imaging-based risk assessment strategies to possibly inform earlier and more personalized prevention of coronary artery disease.

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Ethical approval

This study was approved by the Mass General Brigham Institutional Review Board with waiver of informed consent.

CRediT authorship contribution statement

Milena Petranović: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Investigation. **Yi-Pin Lai:** Formal analysis, Methodology, Visualization, Writing – review & editing. **Daniel Huck:** Data curation, Investigation, Methodology, Writing – review & editing. **Arthur Shiyovich:** Data curation, Investigation, Writing – review & editing. **Stephanie A. Besser:** Data curation, Writing – review & editing. **Camila V. Blair:** Investigation, Writing – review & editing. **Adam N. Berman:** Data curation, Investigation, Writing – review & editing. **Avinainder Singh:** Investigation, Writing – review & editing. **Brittany Weber:** Investigation, Writing – review & editing. **Akl C. Fahed:** Investigation, Writing – review & editing. **Joanne Miao:** Data curation, Writing – review & editing. **Jon Hainer:** Data curation, Writing – review & editing. **Frederick K. Kamanu:** Data curation, Methodology, Writing – review & editing. **Giorgio E.M. Melloni:** Data curation, Methodology, Writing – review & editing. **Rhanderson Cardoso:** Investigation, Writing – review & editing. **Sandeep Hedgire:** Investigation, Writing – review & editing. **Brian Ghoshhajra:** Investigation, Writing – review & editing. **Marcelo Di Carli:** Investigation, Writing – review & editing. **Marc S. Sabatine:** Methodology, Writing – review & editing, Investigation. **Rajat M. Gupta:** Writing – review & editing, Investigation. **Christian T. Ruff:** Investigation, Writing – review & editing, Methodology. **Ron Blankstein:** Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing. **Nicholas A. Marston:** Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2026.101578.

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