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Genetic Risk of Coronary Artery Disease, Features of Atherosclerosis, and Coronary Plaque Burden

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***Background*—**Polygenic risk scores (PRSs) based on risk variants from genome-wide association studies predict coronary artery disease (CAD) risk. However, it is unknown whether the PRS is associated with specific CAD characteristics.

***Methods and Results*—**We consecutively included 1645 patients with suspected stable CAD undergoing coronary computed tomography angiography. A multilocus PRS was calculated as the weighted sum of CAD risk variants. Plaques were evaluated using an 18-segment model and characterized by stenosis severity and composition (soft [0%-19% calcified], mixed-soft [20%-49% calcified], mixed-calcified [50%-79% calcified], or calcified [≥80% calcified]). Coronary artery calcium score and segment stenosis score were used to characterize plaque burden. For each standard deviation increase in the PRS, coronary artery calcium score increased by 78% (P=4.1e-26) and segment stenosis score increased by 16% (P=2.4e-29) in the fully adjusted model. The PRS was associated with a higher prevalence of obstructive plaques (odds ratio [OR]: 1.78, P=5.6e-16), calcified (OR: 1.69, P=6.5e-17), mixed-calcified (OR: 1.67, P=7.3e-9), mixed-soft (OR: 1.45, P=1.6e-6), and soft plaques (OR: 1.49, P=2.5e-6), and a higher prevalence of plaque in each coronary vessel (all P<1.0e-4). However, when analyzing data on a plaque level (3007 segments with plaque in 849 patients) the PRS was not associated with stenosis severity, plaque composition, or localization (all P>0.05).

***Conclusions*—**Our results suggest that polygenic risk based on large genome-wide association studies increases CAD risk through an increased burden of coronary atherosclerosis rather than promoting specific plaque features.

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Coronary artery disease (CAD) is characterized by a substantial and complex polygenic contribution to disease risk.[1] Studies consistently show that ≈50% of the

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phenotypic variance in CAD may be explained by genetics (ie, heritability).[2,3] Since 2007, genome-wide association studies (GWASs) have identified a large number of common genetic variants associated with CAD.[4] Independently, the effect of each risk variant is modest. However, assessing the polygenic risk by summing the effect of all risk variants into a polygenic risk score (PRS) predicts incident and recurrent CAD events on top of traditional risk factors[5–7] and may identify individuals who obtain increased benefit from adherence to a healthy lifestyle or preventive medical treatment.[8,9] Since the PRS is calculated based on common inherited variants, it may allow translation into future clinical practice for estimation of CAD risk and tailoring medical treatment at any time in life and even from birth before any traditional risk factors develop.

Coronary computed tomography angiography (CTA) is a well-established method to visualize coronary atherosclerosis and the preferred diagnostic modality for patients at suspected low-to-intermediate risk of stable CAD.[10] Using coronary CTA, coronary plaque burden and composition may directly be quantified, including high-risk plaque features

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Clinical Perspective

What Is New?

- A polygenic risk score, as a measure of genetically determined risk of coronary artery disease, strongly associates with an increased coronary plaque burden.
- The association is driven by an increased burden of all types of coronary plaques and a higher prevalence of plaque in all coronary vessels.
- The polygenic risk score does not associate with any specific plaque characteristics over others.

What Are the Clinical Implications?

- Our findings provide a better understanding of the inheritance of coronary artery disease by suggesting that genetically determined risk increases coronary artery disease risk through the development of atherosclerosis in general rather than promoting specific plaque features.

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responsible for myocardial ischemia or subsequent plaque rupture.[11,12] We have previously demonstrated that genetically predisposed individuals carry an elevated coronary plaque burden as measured by coronary CTA, including an increased burden of high-risk plaque features.[13] In prior studies, PRSs based on CAD-GWASs have been associated with increased coronary artery calcium scores (CACS).[8,14] However, the impact of PRSs on coronary plaque burden or detailed coronary plaque characteristics beyond CACS remains unknown.

Therefore, we aimed to investigate whether a PRS based on CAD-GWASs is associated with coronary plaque burden and specific plaque characteristics, in patients with suspected CAD referred for coronary CTA.

Methods

Study Design and Patients

The study comprised consecutive patients without known CAD referred for coronary CTA because of symptoms suggestive of stable CAD, who had been included in the Dan-NICAD trial (Danish Multicenter Study of Non-Invasive Testing in Coronary Artery Disease). The data that support the findings of the study are available from the corresponding author upon reasonable request. The study protocol including enrollment criteria has previously been described in detail.[15] Briefly, the Dan-NICAD trial was designed to assess the diagnostic accuracy of second-line tests in a population with suspected obstructive CAD based on coronary CTA. In total, 1675 consecutive patients underwent blood sampling and a clinical interview to assess symptoms and CAD risk factors

before coronary CTA.[15,16] A family history of CAD was defined as self-reported CAD <60 years among first-degree relatives.

The Committee on Health Research Ethics in the Region of Central Denmark and the Danish Data Protection Agency approved the study. All patients provided written informed consent.

Genotyping, Quality Control, Imputing, and PRS Calculation

Out of 1675 enrolled patients, 1665 patients provided a 4-mL EDTA whole blood sample for DNA isolation. After DNA extraction, high-quality DNA was available for 1653 patients for genotyping. Genotyping was performed using the Illumina Global Screening Array (Illumina, Inc., San Diego, CA) at deCODE Genetics. Imputing was carried out using a reference panel consisting of 1KG phase 3 and HapMap to predict nongenotyped single-nucleotide polymorphisms with minor allele frequency >1%. Principal components were calculated using FlashPCA.[17] After quality control, 1645 patients remained.

Calculation of the PRS was performed using LDpred[18] in the pipeline at deCODE Genetics as previously described.[19] Briefly, the calculation was based on P values and $\log_{10}$ odds ratios from the CARDIoGRAMplusC4D meta-analysis of CAD.[20] The fraction of causal markers was set to 0.001, because this has previously been shown to generate the best discrimination of CAD patients from healthy controls.[21]

CACS, Coronary CTA, and Image Analysis

Coronary CTA was performed on a 320-slice-volume computed tomography scanner (Aquillion One; Toshiba Medical Systems, Japan) as previously described.[15,16] Scans were performed with and without iodine-containing contrast according to clinical guidelines, and plaque analyses were performed on a Vitrea Advanced Workstation (Vital Images, USA) by an experienced cardiologist blinded to the PRS. CACS was calculated using the Agatston method,[22] and coronary CTA analysis was performed on segments with a diameter ≥2 mm using an 18-segment model.[23] Proximal CAD was defined as plaque in the left main artery or any of the proximal segments of the left anterior descending, circumflexus, or right coronary artery (segment 1, 5, 6, or 11). All segments with plaque were visually categorized according to plaque composition as soft (0%-19% calcified), mixed-soft (20%-49% calcified), mixed-calcified (50%-79% calcified), or calcified (≥80% calcified). Similarly, segments with plaque were classified based on the visual luminal diameter reduction and categorized as no stenosis (0% diameter reduction; ≈0% area reduction), mild stenosis (1%-29% diameter reduction; ≈1%-49% area reduction), moderate stenosis (30-49%

diameter reduction; ≈50-69% area reduction); and severe stenosis (50%-100% diameter reduction; ≈70%-100% area reduction). Obstructive CAD was defined as the presence of any severe stenosis. The segment stenosis score (SSS) was calculated by grading each coronary segment based on plaque stenosis severity (ie, grades 0–3) and summing the grades from all segments.[24] CACS and SSS were used as overall measures of coronary plaque burden.

Statistical Analysis

Data are presented as number (proportion) or median (interquartile range [IQR]). Differences in patient characteristics between the PRS groups were compared using the χ^2 test or Kruskal-Wallis test as appropriate. Patients were categorized as having a low- (<20th percentile), average- (20th–80th percentile), or high PRS (>80th percentile) for reporting of plaque prevalence. Although the PRS is a continuous risk variable, these cutoffs have previously been adopted to define PRS risk categories[8]; thus, plaque prevalence was also reported for each of these groups for comparability.

Multivariable regression models were used to assess the relationship between the PRS and plaque measures. Since the PRS approximated a normal distribution, the PRS was standardized (ie, mean=0, SD=1) in order to obtain a more meaningful interpretation of the effect size. In model 1 the association of the PRS was adjusted for age, sex, the first 4 principal components of ancestry, as well as an interaction term between age and sex, since these variables had a statistically significant interaction in the analyses on CACS and SSS. Model 2 comprised the same covariables as model 1 but also included adjustment for traditional risk factors including antihypertensive treatment, lipid-lowering treatment, body mass index, angina symptoms, and active smoking. Linear regression models were used to analyze the relationship between the PRS and CACS and SSS, respectively. Diabetes mellitus and cholesterol levels were not added as covariables because they may act as intermediate steps between genetic predisposition to CAD and atherosclerosis development rather than being confounders.[7] Because of the skewed distribution, linear regression was performed with both variables log-transformed as $\log_e$ (value + 1). Linear effect of the PRS was confirmed by a spline representation (Figure S1). Beta-coefficients were back-transformed for reporting. Hence, the reported effect size corresponds to the percentage change in the geometric mean, after adjustment, per SD increase in the PRS. The models were validated by inspecting QQ-plots of residuals and by plotting residuals against fitted values and explanatory variables. For dichotomous plaque measures, logistic regression models were used and effect sizes reported as odds ratios.

To evaluate whether the PRS had a larger effect on any specific plaque characteristics over others, we analyzed the data on a plaque-level (coronary segment-level) comparing the relationship between the PRS and plaque characteristics among 3007 plaques (from 849 patients with plaque). Logistic and ordinal logistic regression models were used to analyze dichotomous and categorical plaque characteristics taking within-individual correlation into account using the Huber-White clustered sandwich variance estimator. The models were adjusted for the same covariables as in the patient-level analyses. However, since we wanted to evaluate the effect on a plaque level independent of overall plaque burden, a spline representation of the SSS was also added in both models. Effect sizes were reported as odds ratios.

Statistical analyses were performed using Stata version 13.1 (StataCorp, 4905 Lakeway Dr, College Station, TX). Violin plots were generated using R version 3.2.2 (http://www.r-project.org/).

Results

We included 1645 patients in the study. Patient characteristics are displayed in Table 1. Median age was 57 (IQR 50-64) years and 799 (49%) were males. Patients in higher PRS categories were more likely to have a self-reported family history of CAD and more frequently received lipid-lowering treatment (Table 1). Anginal symptoms, age, and triglycerides also differed slightly among PRS categories. No significant difference in body mass index, cholesterol levels, diabetes mellitus status, and smoking was found between the groups.

Patient-Level Analyses

The PRS was strongly associated with overall plaque burden as measured by CACS and SSS (Figure 1 and Table 2). Across the PRS deciles, CACS and SSS showed a steady upward increase in distribution (Figure 2). Going from low to average and high genetic risk patients the median CACS increased from 0 (IQR 0-21) to 0 (IQR 0-85) and 18 (IQR 0-178), and SSS increased from 0 (IQR 0-1) to 1 (IQR 0-4) and 2 (IQR 0-7). This association was seen for both males and females and for different age spans (Figure 3). Correspondingly, in the fully adjusted model the geometric mean CACS increased by +78% (95% CI +60% to +98%, P=4.1e-26) and SSS increased by +16% (95% CI +11% to +21%, P=2.4e-29) per SD increase in the PRS. The upward shift in PRS distribution with increasing coronary plaque burden can be seen in Figure S2. A higher PRS was associated with a higher prevalence of calcified, mixed-calcified, mixed-soft, and soft plaques and an increased prevalence of plaque in proximal- and non-proximal segments as well as in all coronary vessels (Table 3). Moreover, the PRS

Table 1. Patient Characteristics (n=1645)

	Total (n=1645)	Low PRS (n=329)	Average PRS (n=987)	High PRS (n=329)	P Value
Age, y	57 (50–64)	58 (51–64)	57 (51–64)	56 (49–63)	0.022
Male sex	799 (49%)	170 (52%)	518 (52%)	158 (48%)	0.37
Family history of CAD <60 y in first-degree relative	601 (37%)	93 (28%)	358 (36%)	150 (46%)	<0.001
Antihypertensive treatment	411 (25%)	83 (25%)	249 (25%)	79 (24%)	0.90
Lipid-lowering treatment	384 (24%)	59 (18%)	236 (24%)	89 (28%)	0.015
Diabetes mellitus	94 (6%)	15 (5%)	59 (6%)	20 (6%)	0.60
Active smoking	266 (16%)	57 (17%)	156 (16%)	53 (16%)	0.82
Symptoms					
Typical chest pain	89 (27%)	72 (22%)	291 (30%)	89 (27%)	0.005
Atypical chest pain	550 (34%)	115 (35%)	306 (31%)	129 (39%)	
Nonanginal chest pain	293 (18%)	63 (19%)	189 (19%)	41 (13%)	
Dyspnea	340 (21%)	76 (23%)	195 (20%)	69 (21%)	
BMI, kg/m^2	26.3 (23.8–29.4)	26.9 (24.3–29.6)	26.2 (23.7–29.3)	26.5 (23.7–29.5)	0.21
Total cholesterol, mmol/L	5.3 (4.7-6.0)	5.2 (4.6–5.9)	5.3 (4.7–6.1)	5.3 (4.6–6.2)	0.17
HDL cholesterol, mmol/L	1.4 (1.1–1.7)	1.4 (1.2–1.7)	1.4 (1.1–1.7)	1.4 (1.1–1.7)	0.14
LDL cholesterol, mmol/L	3.3 (2.6–3.9)	3.1 (2.6–3.8)	3.3 (2.7–3.9)	3.4 (2.6–4.0)	0.055
Triglycerides, mmol/L	1.3 (1.0–2.0)	1.3 (0.9–1.9)	1.3 (1.0–2.0)	1.4 (1.0–2.2)	0.049
Creatinine, μmol/L	74 (65–85)	75 (65–85)	74 (65–85)	75 (66–85)	0.67

Data are presented as number (percentage) or median (interquartile range). Family history was missing in 6 patients, lipid-lowering treatment was missing in 28 patients, diabetes mellitus was missing in 6 patients, smoking was missing in 7 patients, symptoms was missing in 10 patients, BMI was missing in 9 patients, total cholesterol was missing in 100 patients, HDL cholesterol was missing in 97 patients, LDL cholesterol was missing in 105 patients, triglycerides was missing in 109 patients, and creatinine was missing in 14 patients. BMI indicates body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRS, polygenic risk score.

was associated with the presence of obstructive plaques 1.78 (95% CI 1.55–2.05, P=5.6e-16) per SD increase in the PRS) with the mean PRS being 0.40 SD higher among patients with obstructive CAD compared with patients without obstructive CAD (P=0.022).

In a sensitivity analysis, we tested whether the association of the PRS with plaque burden differed in patients with and without a family history of CAD. The PRS displayed a positive association with plaque burden both in patients with and without a family history of CAD (Figure S3). Accordingly, adding adjustment for family history of CAD did not alter any of the observed associations between the PRS and plaque burden (Table S1).

Segment-Level Analyses

Subsequently, we extracted all segments with plaque and analyzed these separately in order to evaluate whether the PRS had a larger effect on any specific plaque characteristics over others. For this analysis we had a total 3007 segments with plaque from 849 patients. Among segments with plaque, the PRS was not associated with plaque stenosis, composition, or location in any specific coronary vessel in any of the

adjusted models with SSS included (Table 4). In line with this, a visual representation of the PRS distribution for segments grouped according to plaques characteristics or plaque location showed almost identical curves in all comparisons (Figure S4).

Discussion

In the present study we investigated the association between polygenic risk of CAD quantified by a PRS and characteristics of coronary atherosclerosis as assessed by coronary CTA. The main finding was a strong association of the PRS with overall coronary plaque burden. The association was driven by an increased burden of all types of plaque and a higher prevalence of plaque in all coronary vessels. However, the PRS did not associate with any specific plaque characteristics over others.

The risk of CAD observed in patients with a high polygenic risk was notable. These patients were twice as likely to have any CAD and 3 times as likely to have obstructive CAD compared with patients at low polygenic risk. The any CAD and obstructive CAD prevalence of 64% and 35% in high PRS patients may be comparable to the risk observed among other
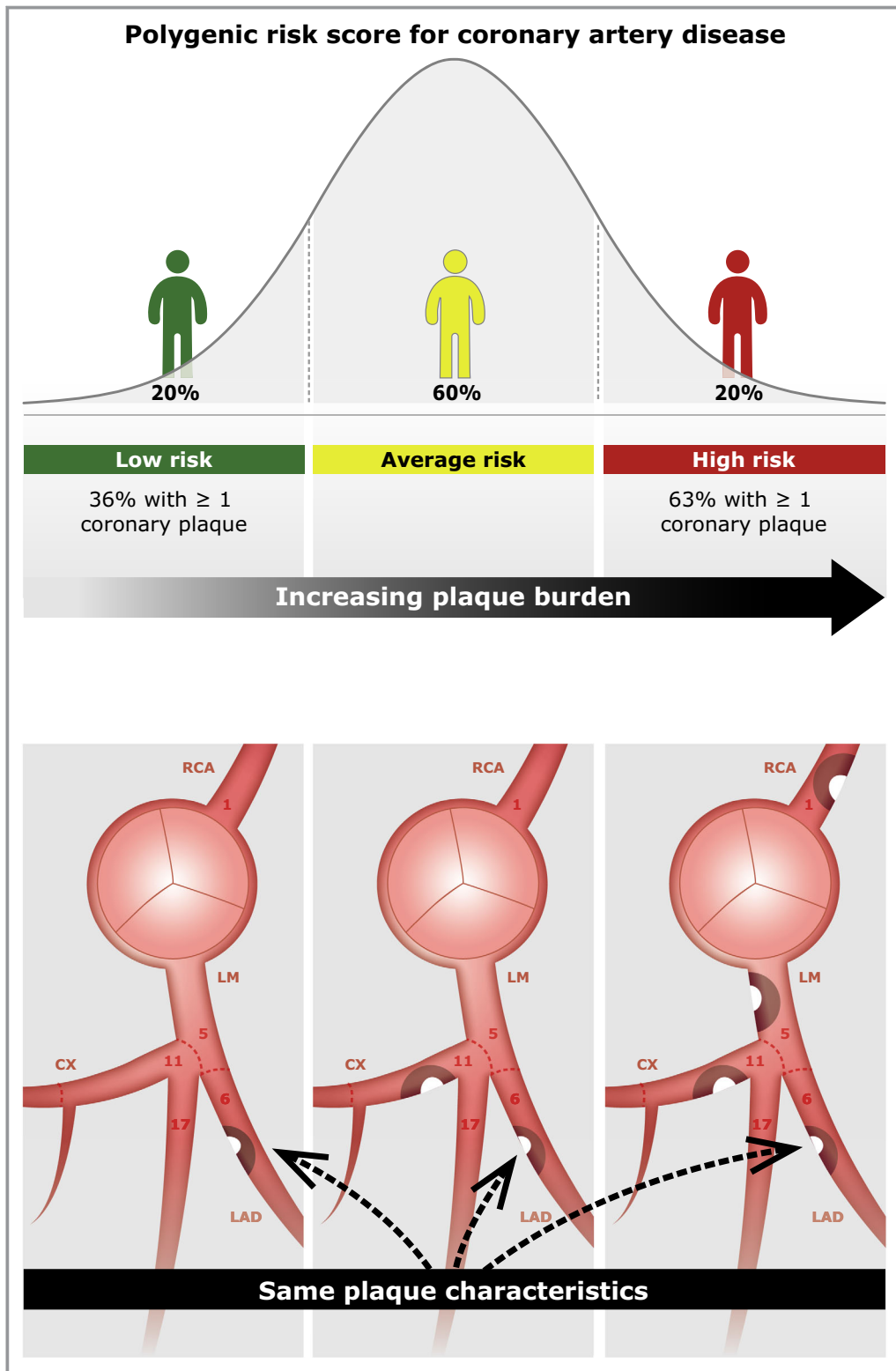
Figure 1. Visual overview. CX indicates circumflex ramus; LAD, left anterior descending; LM, left main; RCA, right coronary artery.

patients at increased cardiovascular risk. In the CONFIRM (Coronary Angiography Evaluation For Clinical Outcomes: An International Multicenter) Registry, the prevalence of any CAD

and obstructive CAD was 76% and 52% in 5-year-older diabetes mellitus patients,[25] and 56% and 19% in hypertensive patients at a similar age.[26] In a study of asymptomatic statin-

Table 2. Association of the PRS With Plaque Burden (n=1645 patients)

	Coronary Plaque Burden Median (25–75th Percentile) [1–99th Percentile]			Model 1 Effect Size (95% CI, P Value)	Model 2 Effect Size (95% CI, P Value)
	Low PRS (n=329)	Average PRS (n=987)	High PRS (n=329)		
CACS	0 (0–21) [0–841]	0 (0–85) [0–2565]	18 (0–178) [0–2122]	+81% (+63% to +101%, P=2.0e-27)	+78% (+60% to +98%, P=4.1e-26)
Segment stenosis score	0 (0 to 1) [0 to 19]	1 (0 to 4) [0 to 25]	2 (0–7) [0–26]	+29% (+23% to +34%, P=1.5e-30)	+16% (+11% to +21%, P=2.4e-29)

The effect size corresponds to the change in % in the geometric mean of the variable per SD increase in the PRS. Model 1 was adjusted for age, sex, the first 4 principal components of ancestry, as well as an interaction term between age and sex. Model 2 was further adjusted for antihypertensive treatment, lipid-lowering treatment, body mass index, symptoms, and active smoking. CACS indicates coronary artery calcium score; PRS, polygenic risk score.

treated patients with familial hypercholesterolemia, the presence of any CAD and obstructive CAD was 85% and 26%, respectively.[27] Thus, a high PRS may confer a risk of CAD presence and severity to an extent similar to that obtained from traditional risk factors. This is also in accordance with an observation from the UK biobank, in which high PRS patients had a 2.5-fold higher CAD risk compared with the remaining 80% of the population, an effect similar to or stronger than any single traditional risk factor.[21]

A few prior studies have investigated the relationship between a CAD-PRS and measures of plaque burden. In a coronary angiography study of early-onset acute coronary syndrome patients, a 30-variant PRS and a family history of CAD were independently associated with the presence of multivessel disease.[28] A study consisting of asymptomatic individuals without evident CAD from the BioImage cohort demonstrated a dose-responsive relationship between a 50-variant PRS and CACS, which was independent of lifestyle risk factors.[8] Another analysis on the same cohort demonstrated that the same CAD-based PRS was associated with carotid artery plaque burden determined by ultrasonography with a 9.7% (95% CI 2.2–17.8%) increase in plaque area per SD increase in the PRS.[14] Similarly, a Swedish general population study demonstrated a CAD-based 13-variant PRS to be associated with carotid bulb intima-media thickness and carotid plaques,[29] which underscores the common polygenic background of atherosclerosis. To our knowledge the present study is the first to dissect the relationship between polygenic risk of CAD and the complex phenotypes of coronary atherosclerosis. Extending prior findings, our
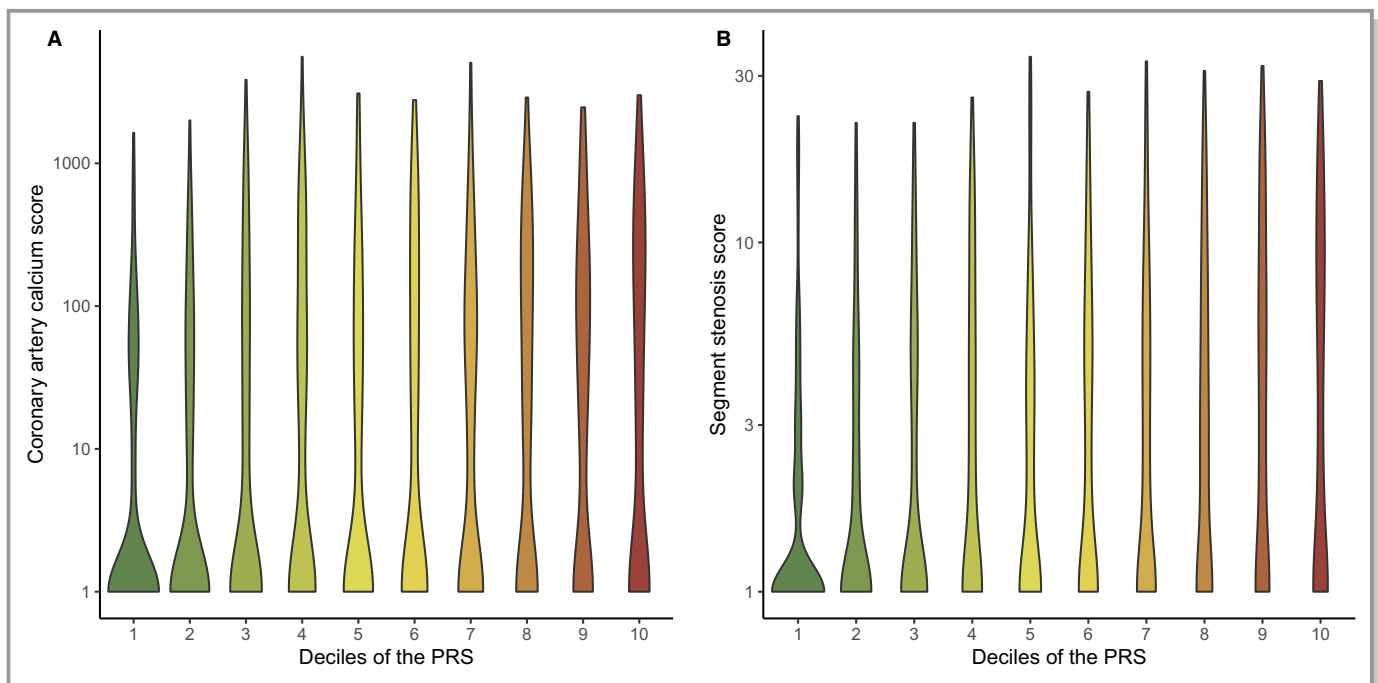

Figure 2. Violin plots displaying the distribution of coronary artery calcium score (**A**) and segment stenosis score (**B**) across the deciles of the PRS (n=1645 patients). A log scale was used for the *y*-axis for display purposes. All values were transformed as log$_e$ (value + 1). PRS indicates polygenic risk score.
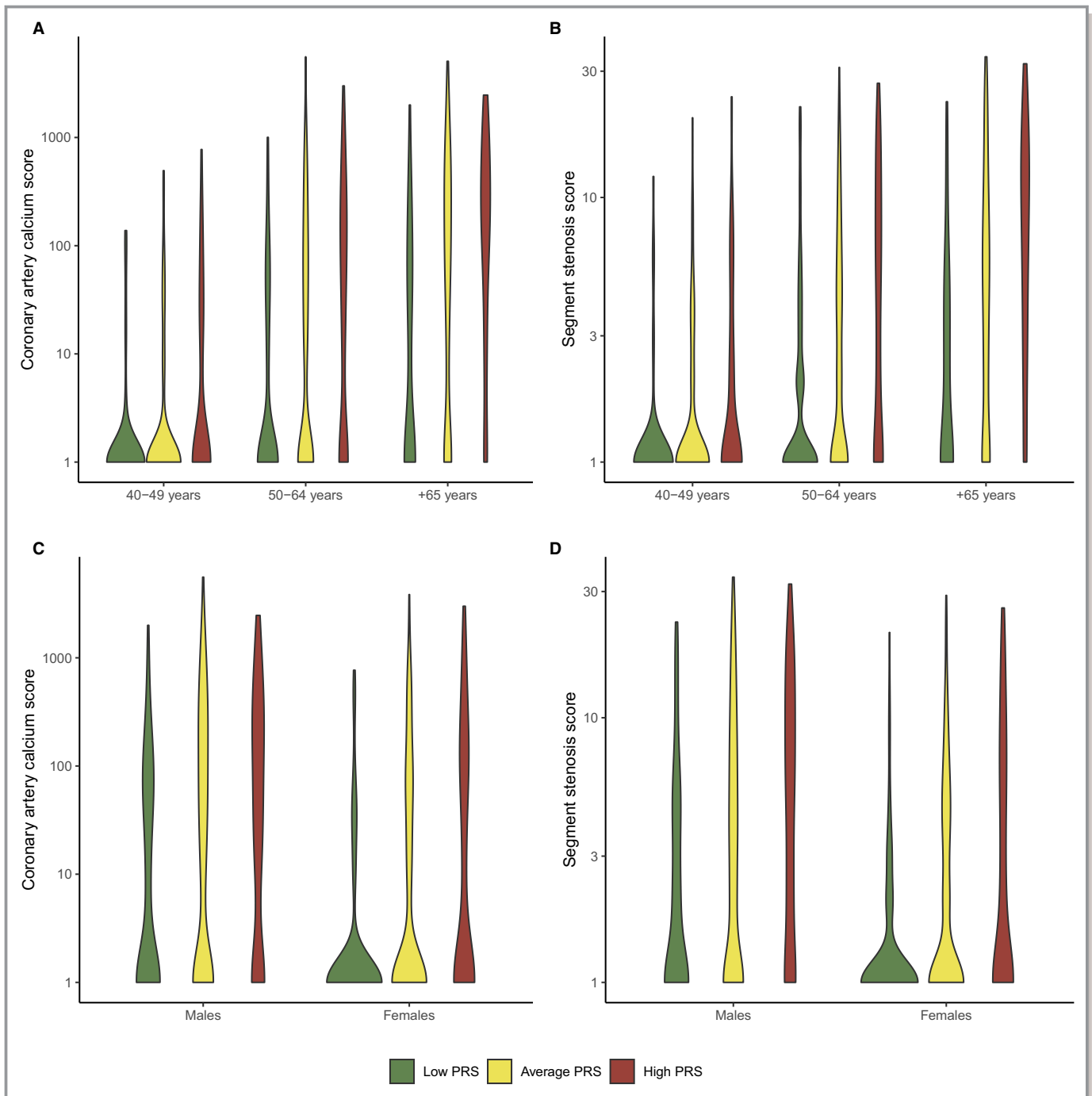
Figure 3. Violin plots displaying the distribution of coronary artery calcium score (**A** and **C**) and segment stenosis score (**B** and **D**) according to the PRS stratified by age and sex (n=1645 patients). Patients were categorized as low- (<20th percentile), average- (20th to 80th percentile), or high PRS (>80th percentile). A log scale was used for the *y*-axis for display purposes. All values were transformed as $\log_e$ (value + 1). PRS indicates polygenic risk score.

study suggests that polygenic risk increases CAD risk through an increased burden of all coronary atherosclerosis components rather than promoting any specific adverse plaque characteristics. This is plausible since coronary plaque burden as quantified by CACS and SSS are well-established and strong predictors of an adverse

outcome.[24,30] However, the hypothesis needs to be supported by longitudinal studies.

Sibling studies among patients undergoing coronary angiography have suggested that heritability of stenoses in the left main artery (h^2=47% [95% CI 29–64%]), coronary calcifications (h^2=51% [95% CI 37–65%]), and plaques with

Table 3. Association of the PRS With Presence of Plaque (n=1645 Patients)

	Number of Patients (Proportion)			Model 1 OR (95% CI, P Value)	Model 2 OR (95% CI, P Value)
	Low PRS (n=329)	Average PRS (n=987)	High PRS (n=329)		
CAD severity					
Any plaque	119 (36%)	522 (53%)	208 (63%)	1.76 (1.56–1.98, P=1.3e-20)	1.79 (1.58–2.03, P=6.3e-20)
Any obstructive plaque	40 (12%)	229 (23%)	116 (36%)	1.75 (1.53–2.00, P=3.4e-16)	1.78 (1.55–2.05, P=5.6e-16)
Plaque composition					
Any soft plaque	37 (11%)	172 (17%)	76 (23%)	1.39 (1.21–1.60, P=2.2e-6)	1.40 (1.22–1.62, P=2.5e-6)
Any mixed-soft plaque	32 (10%)	154 (16%)	68 (21%)	1.45 (1.25–1.68, P=9.3e-7)	1.45 (1.24–1.68, P=1.6e-6)
Any mixed-calcified plaque	18 (5%)	117 (12%)	57 (17%)	1.68 (1.42–1.99, P=1.7e-9)	1.67 (1.40–1.98, P=7.3e-9)
Any calcified plaque	91 (28%)	414 (42%)	174 (53%)	1.67 (1.48–1.88, P=1.9e-17)	1.69 (1.49–1.91, P=6.5e-17)
Plaque localization					
Any LM plaque	24 (7%)	115 (12%)	57 (17%)	1.48 (1.25–1.75, P=4.6e-6)	1.46 (1.23–1.73, P=1.5e-5)
Any LAD plaque	98 (30%)	476 (48%)	186 (57%)	1.75 (1.56–1.97, P=1.6e-20)	1.79 (1.58–2.03, P=3.9e-20)
Any CX plaque	34 (10%)	202 (20%)	100 (30%)	1.74 (1.51–2.00, P=1.4e-14)	1.75 (1.51–2.03, P=5.1e-14)
Any RCA plaque	55 (17%)	271 (27%)	133 (40%)	1.72 (1.51–1.95, P=1.0e-16)	1.72 (1.51–1.97, P=7.3e-16)
Any proximal plaque	103 (31%)	455 (46%)	182 (55%)	1.66 (1.47–1.86, P=5.0e-17)	1.67 (1.48–1.89, P=1.9e-16)
Any nonproximal plaque	79 (24%)	398 (40%)	177 (54%)	1.82 (1.62–2.06, P=1.3e-22)	1.85 (1.63–2.10, P=6.4e-22)

ORs are reported per SD increase in the PRS. Model 1 was adjusted for age, sex, the first 4 principal components of ancestry, as well as an interaction term between age and sex. Model 2 was further adjusted for antihypertensive treatment, lipid-lowering treatment, body mass index, symptoms, and active smoking. CAD indicates coronary artery disease; CX, circumflex ramus; LAD, left anterior descending; LM, left main artery; OR, odds ratio; PRS, polygenic risk score; RCA, right coronary artery.

expansive vessel remodeling (h^2=54% [95% CI 38–70%]) is high, whereas extent of CAD and plaques in the nonproximal segments appeared only modestly heritable or nonheritable (h^2 estimates <10%, nonsignificant).[3,31] These findings appear to be in contrast to our findings, where the PRS was similarly associated with all plaque characteristics including atherosclerosis in nonproximal segments. Although the explanation for the discrepancy is not obvious, we did not demonstrate any association between the PRS and specific plaque locations or characteristics per se. One possible explanation for this may be that PRSs are built on risk variants identified from CAD-GWASs, in which cases of CAD patients comprise a heterogeneous group in terms of atherosclerosis subphenotypes. Consequently, the PRSs also represent the sum of a heterogeneous set of variants predisposing to CAD development through a number of different pathways that may each drive the formation of different atherosclerosis subtypes. For example, studies have shown that the lead variant at the *ABO* locus, identified in CAD-GWASs, is specifically associated with myocardial infarction in contrast to the majority of other CAD risk variants;[20,32] an effect possibly driven by an influence on platelet aggregation.[33] It is possible that future GWASs based on patients with detailed phenotyping by coronary CTA will help identify variants with specific effects on atherosclerosis and thereby further aid explaining the underlying mechanisms behind the development of different CAD phenotypes.

Another possible explanation for the lack of association between the PRS and specific plaque locations and characteristics may be that polygenic CAD risk only acts as a driver of coronary atherosclerosis development, whereas specific locations and characteristics are governed by a number of nongenetic factors including dietary and lifestyle habits. Lastly, different plaque locations and characteristics may in part simply be explained by different disease stages, a possibility that may not be elucidated in the present study because of the cross-sectional design.

Besides the pathophysiological insights into polygenic CAD risk and its effects on plaque burden and atherosclerosis characteristics, our study may also have some clinical implications and set the direction for future research. The knowledge of a high PRS may alert clinicians of patients at high risk of accelerated atherosclerosis development, who may benefit from recommendations on a healthy lifestyle or preventive medical treatment before atherosclerosis develops or progresses into a clinically significant disease state. In the setting of patients with chest symptoms, the PRS may aid discriminating between patients with and without obstructive CAD requiring coronary CTA and potentially downstream coronary revascularization. Particularly, since the vast majority of patients undergoing coronary CTA do not have obstructive CAD, it may be speculated that a low PRS could be used for risk assessment to down-classify the estimated

Table 4. Segment-Level Analyses of the Association Between the PRS and Plaque Characteristics (n=3007 Segments With Plaque Among 849 Patients)

	Number of Segments With Plaque (proportion)			Model 1 OR (95% CI, *P* Value)	Model 2 OR (95% CI, *P* Value)
	Low PRS (n=330)	Average PRS (n=1818)	High PRS (n=859)		
Severity					
No stenosis	18 (5%)	67 (4%)	34 (4%)		
Mild stenosis	180 (55%)	948 (52%)	369 (43%)		
Moderate stenosis	52 (16%)	250 (14%)	140 (16%)		
Severe stenosis	80 (24%)	553 (30%)	316 (37%)		
More severe stenosis category*				0.98 (0.90–1.07, *P*=0.72)	1.00 (0.92–1.09, *P*=0.94)
Plaque composition					
Calcified	205 (62%)	1166 (64%)	531 (62%)		
Mixed-calcified	26 (8%)	172 (9%)	79 (9%)		
Mixed-soft	47 (14%)	224 (12%)	121 (14%)		
Soft	52 (16%)	256 (14%)	128 (15%)		
More noncalcified composition category*				0.99 (0.88–1.12, *P*=0.90)	1.01 (0.90–1.14, *P*=0.82)
Plaque location					
LM	24 (7%)	115 (6%)	57 (7%)	0.95 (0.83–1.09, *P*=0.50)	0.95 (0.82–1.08, *P*=0.43)
LAD	164 (50%)	873 (48%)	399 (46%)	1.05 (0.98–1.13, *P*=0.16)	1.05 (0.98–1.13, *P*=0.16)
CX	51 (15%)	325 (18%)	167 (19%)	1.00 (0.91–1.09, *P*=0.99)	1.01 (0.92–1.10, *P*=0.86)
RCA	91 (28%)	505 (28%)	236 27%)	0.96 (0.88–1.03, *P*=0.26)	0.95 (0.88–1.03, *P*=0.22)
Proximal	157 (48%)	835 (46%)	375 (44%)	1.01 (0.95–1.07, *P*=0.86)	1.01 (0.95–1.07, *P*=0.85)

Each segment with plaque contributes with an observation (ie, the PRS from 1 individual with >1 plaque contributes with the PRS for each plaque). ORs are reported per SD increase in the PRS. Model 1 was adjusted for age, sex, a spline representation of the segment stenosis score, the first 4 principal components of ancestry, as well as an interaction term between age and sex. Model 2 was further adjusted for antihypertensive treatment, lipid-lowering treatment, body mass index, symptoms, and active smoking. All analyses were performed accounting for within-individual correlation using the clustered sandwich estimator. CX indicates circumflex ramus; LAD, left anterior descending; LM, left main artery; OR, odds ratio; RCA, right coronary artery; PRS, polygenic risk score.
*Analyses were performed using ordered logistic regression.

pretest probability of obstructive CAD and avoid the need for coronary CTA. However, further studies are required in order to delineate the clinical utilities of the PRS.

Strengths and Limitations

The main strengths of the study include the well-validated multilocus PRS and the inclusion of consecutive patients referred for coronary CTA in a standardized protocol. However, a number of limitations deserve attention. The patient population comprised patients without prior CAD but with symptoms suggestive of stable CAD. This may have introduced selection bias since patients carrying the most vulnerable plaques are more likely to develop myocardial infarction as a first manifestation of CAD, which would render them ineligible for study inclusion. Consequently, patients with the highest PRSs may have been excluded from the study. Also, compared with a general population cohort, a selection based on symptoms may have caused index event

bias (ie, the distortion of risk factor distribution among included patients).[34] This could arise because symptomatic patients with obstructive CAD developed from a high polygenic risk do not require the same burden of traditional risk factors as patients with a low polygenic risk for disease to develop. In such case the observed association between the PRS and plaque burden may likely be driven towards the null (ie, no difference), suggesting that the associations between PRS and plaque burden in this study is a conservative estimate. A second limitation is the fact that the PRS is built on CAD-GWASs in which some control individuals may have subclinical CAD. It may be speculated that control individuals with subclinical CAD carry a certain phenotype of atherosclerosis, which in such case might affect the association between the PRS and CAD characteristics. A third limitation was that CACS and SSS were used as surrogates of coronary plaque burden, although neither CACS nor SSS directly measure plaque volume. In particular, CACS does not quantify noncalcified plaque material and SSS does not capture

plaques with extrinsic plaque remodeling nor grade plaque length. Therefore, these measures might deviate from the true volume of coronary atherosclerosis. Finally, a limitation is the sample size. Although the sample is substantial for a study with this amount of phenotypic details, polygenic traits may require hundreds of thousands of samples to detect small effects. Therefore, although we did not detect any association of the PRS with specific plaque characteristics per se, it does not preclude the existence of minor effects, which we cannot detect with the current sample size.

Conclusions

A PRS based on CAD-GWASs was strongly associated with coronary plaque burden as assessed by coronary CTA. The association was driven by an increased prevalence of all plaque subtypes throughout the coronary artery tree. However, in the segment-level analyses adjusted for total plaque burden, the PRS was not associated with stenosis severity, plaque composition, or localization. Therefore, our findings suggest that the polygenic risk captured by PRSs increases CAD risk through the overall formation of coronary atherosclerosis rather than promoting specific plaque char-acteristics.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Association of the PRS with coronary plaque burden and presence of plaque characteristics including adjustment for family history (n=1645 patients).

	Model 2 (excluding FHx) Effect (95% CI)	Model 2 (including FHx) (95% CI)
Plaque burden		
CACS	+78% (+60% - +98%, p=4.1e-26)	+75% (+57% - +94%, p=1.5e-24)
Segment stenosis score	+16% (+11% - +21%, p=2.4e-29)	+27% (+22% - +33%, p=1.4e-27)
Plaque severity		
Any plaque	1.79 (1.58 - 2.03, p=6.3e-20)	1.76 (1.55 - 2.00, p=9.2e-19)
Any obstructive plaque	1.78 (1.55 - 2.05, p=5.6e-16)	1.75 (1.52 - 2.01, p=3.8e-15)
Plaque composition		
Any soft plaque	1.40 (1.22 - 1.62, p=2.5e-6)	1.39 (1.20 - 1.60, p=6.2e-6)
Any mixed-soft plaque	1.45 (1.24 - 1.68, p=1.6e-6)	1.43 (1.23 - 1.66, p=3.7e-6)
Any mixed-calcified plaque	1.67 (1.40 - 1.98, p=7.3e-9)	1.64 (1.38 - 1.96, p=2.1e-8)
Any calcified plaque	1.69 (1.49 - 1.91, p=6.5e-17)	1.66 (1.47 - 1.88, p=5.7e-16)
Plaque localization		
Any LM plaque	1.46 (1.23 - 1.73, p=1.5e-5)	1.44 (1.21 - 1.70, p=3.2e-5)
Any LAD plaque	1.79 (1.58 - 2.03, p=3.9e-20)	1.76 (1.56 - 2.00, p=4.6e-19)
Any CX plaque	1.75 (1.51 - 2.03, p=5.1e-14)	1.71 (1.48 - 1.98, p=6.1e-13)
Any RCA plaque	1.72 (1.51 - 1.97, p=7.3e-16)	1.70 (1.49 - 1.94, p=5.9e-15)
Any proximal plaque	1.67 (1.48 - 1.89, p=1.9e-16)	1.65 (1.46 - 1.87, p=1.5e-15)
Any non-proximal plaque	1.85 (1.63 - 2.10, p=6.4e-22)	1.82 (1.60 - 2.06, p=1.8e-20)

*The effect size for continuous variables corresponds to the change in % in the geometric mean of the variable per SD increase in the PRS. Effect sizes for binary variables are reported as the OR per SD increase in the PRS. Effect sizes were adjusted for age, sex, antihypertensive treatment, lipid-lowering treatment, body mass index, symptoms, active smoking, the first four principal components of ancestry, and +/- family history of CAD in 1st degree relative <60 years. PRS: Polygenic risk score.

Figure S1. Spline representation of the effect of the standardized PRS on plaque burden.
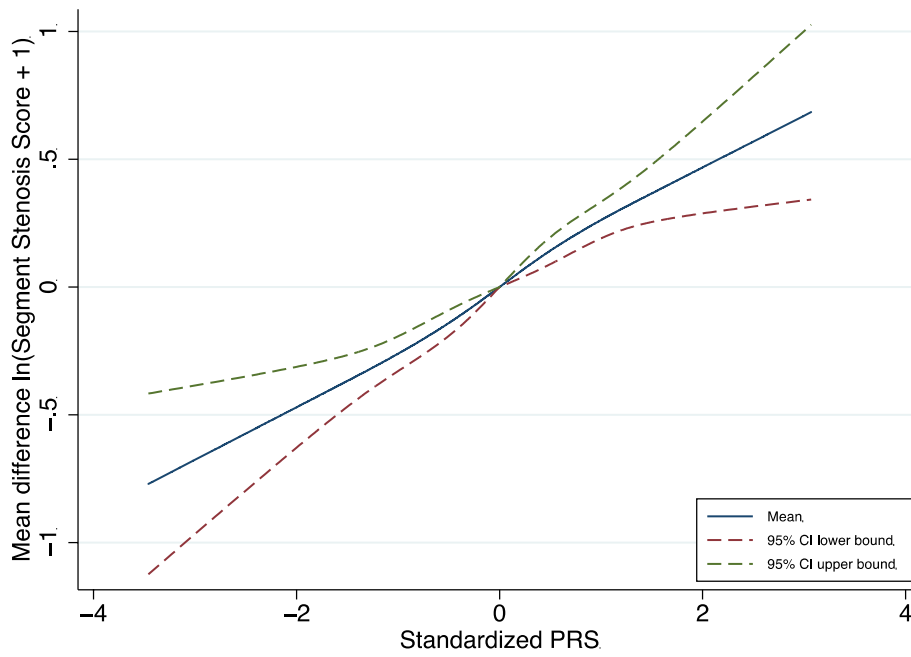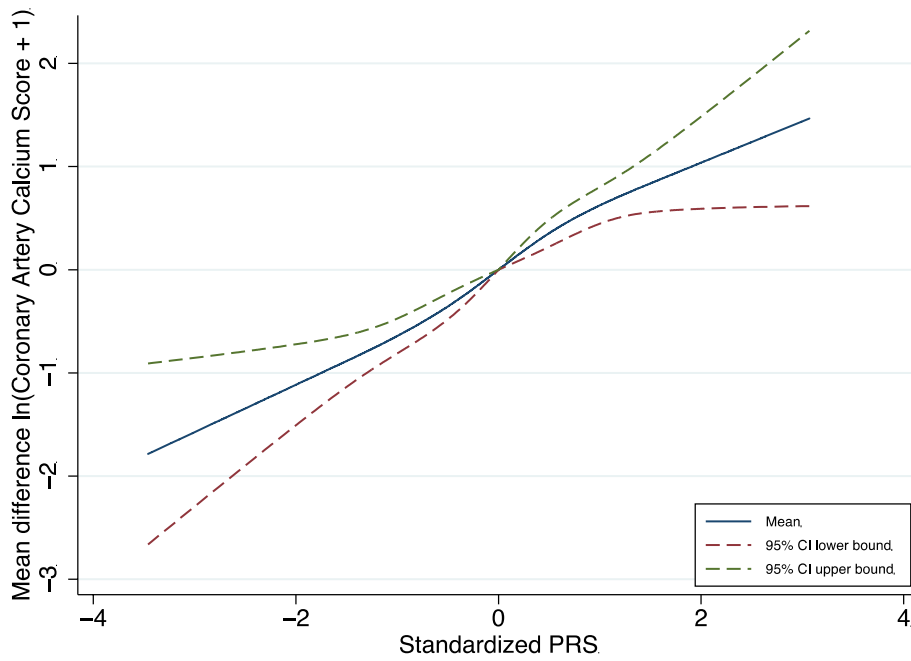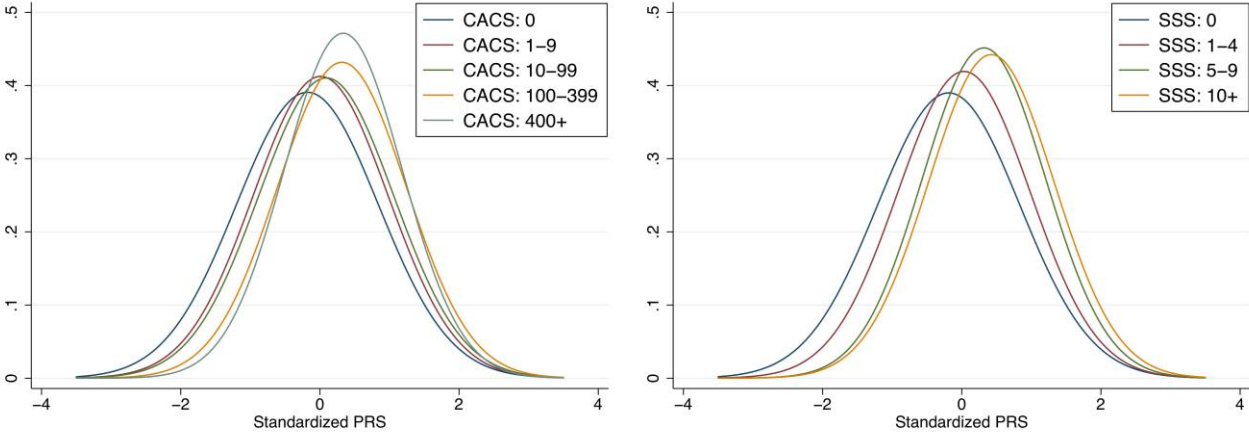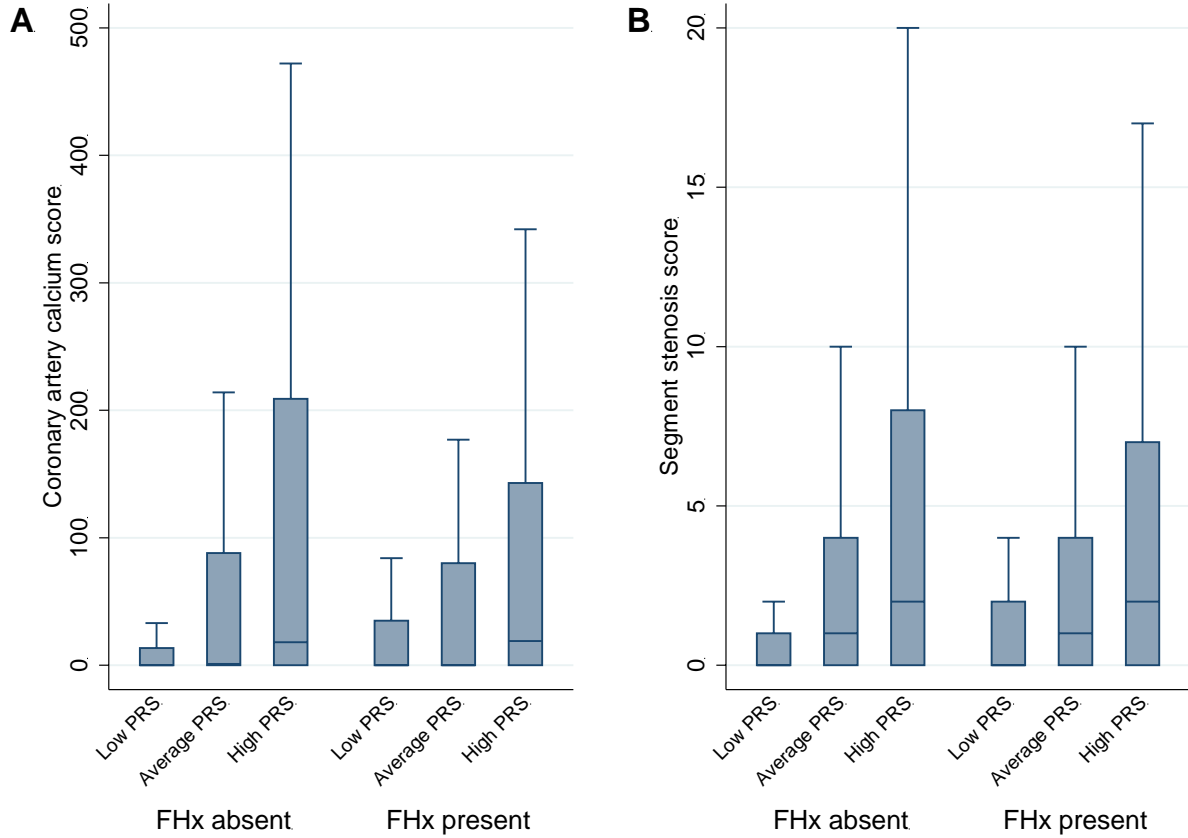
Figure S2. Distribution of the smoothed and standardized PRS according to plaque burden.


CACS: Coronary artery calcium score. PRS: Polygenic risk score. SSS: Segment stenosis score.

Figure S3. Distribution of coronary plaque burden according to the PRS stratified by FHx (n=1645 patients).

Boxes and whiskers represent the median, interquartile range, and adjacent values. Outliers were omitted from the graph for display purposes. FHx: Family history of coronary artery disease <60 years among 1st degree relatives. PRS: Polygenic risk score.

Figure S4. Distribution of the smoothed and standardized PRS according to plaque characteristics (n=3007 segments with plaque among 849 patients).
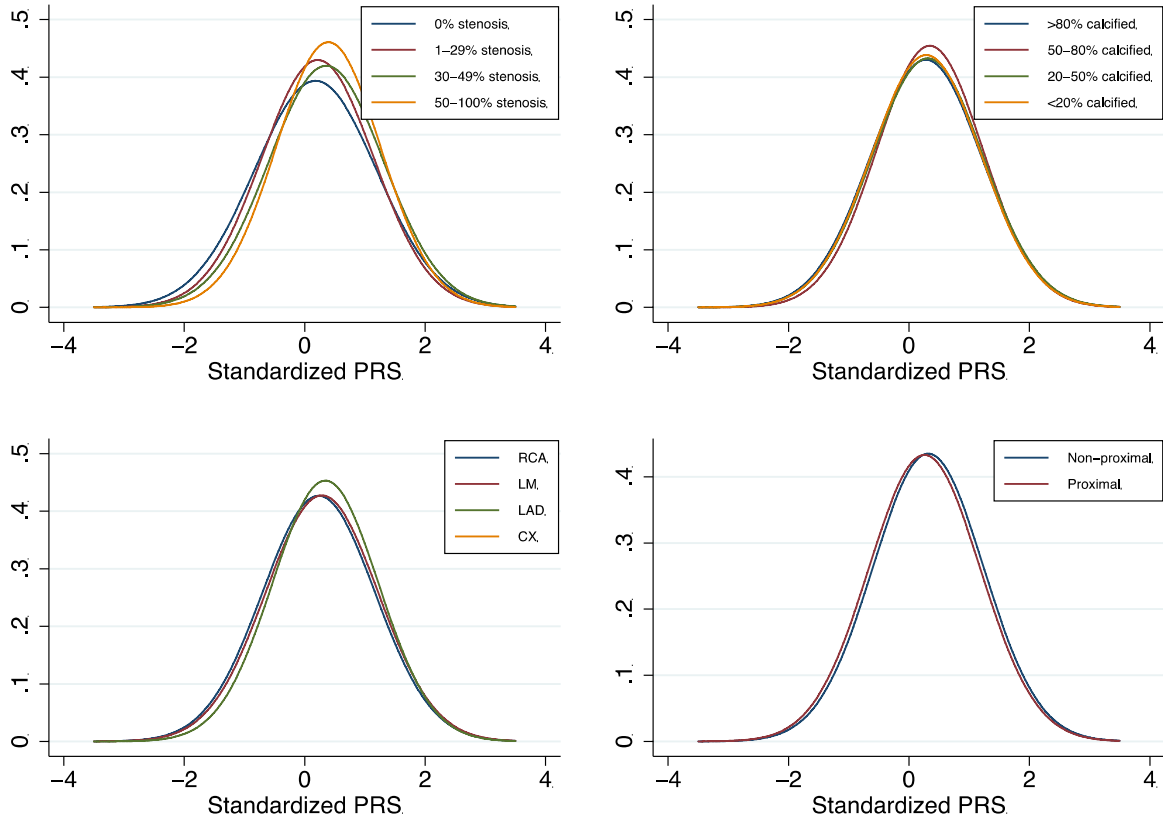
Each segment with plaque contributes to the distribution (i.e. the PRS from one individual with more than one segment with plaque contributes with the PRS for each segment with plaque). CX: Circumflexus. LAD: Left anterior descending. LM: Left main. PRS: Polygenic risk score. RCA: Right coronary artery.