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Polygenic Risk Scores in Predicting Coronary Artery Disease in Symptomatic Patients. A Validation Study

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Aim: Clinical risk scores for coronary artery disease (CAD) are used in clinical practice to select patients for diagnostic testing and therapy. Several studies have proposed that polygenic risk scores (PRSs) can improve the prediction of CAD, but the scores need to be validated in clinical populations with accurately characterized phenotypes. We assessed the predictive power of the three most promising PRSs for the prediction of coronary atherosclerosis and obstructive CAD.

Methods: This study was conducted on 943 symptomatic patients with suspected CAD for whom the phenotype was accurately characterized using anatomic and functional imaging. Previously published genome-wide polygenic scores were generated to compare a genetic model based on PRSs with a model based on clinical data. The test and PRS cohorts were predominantly Caucasian of northern European ancestry.

Results: All three PRSs predicted coronary atherosclerosis and obstructive CAD statistically significantly. The predictive accuracy of the models combining clinical data and different PRSs varied between 0.778 and 0.805 in terms of the area under the receiver operating characteristic (AUROC), being close to the model including only clinical variables (AUROC 0.769). The difference between the clinical model and combined clinical + PRS model was not significant for PRS1 ($p=0.627$) and PRS3 ($p=0.061$). Only PRS2 slightly improved the predictive power of the model ($p=0.04$). The likelihood ratios showed the very weak diagnostic power of all PRSs.

Conclusion: The addition of PRSs to conventional risk factors did not clinically significantly improve the predictive accuracy for either coronary atherosclerosis or obstructive CAD, showing that current PRSs are not justified for routine clinical use in CAD.

Key words: Coronary artery disease, Coronary atherosclerosis, Risk factors, Polygenic risk score

Introduction

Coronary artery disease (CAD) remains a leading cause of mortality and morbidity worldwide[1)]. Strategies to identify patients with a higher likelihood of CAD are needed to appropriately target diagnostic testing and tailor therapy. Currently, clinical risk scores incorporating clinical risk factors—smoking, hypertension, diabetes, dyslipidemia, age, sex, and family history—are widely used in clinical practice. In addition to these clinical risk factors, genetic risk scores, often referred to as polygenic risk scores (PRSs), have been shown to independently predict the development of CAD[2-6)]. The potential use of genetic data in clinics is based on robust evidence and the importance of family history, with an estimated 40%–60% CAD heritability[6, 7)].

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For common multifactorial diseases, including CAD, polygenic inheritance plays a greater role than rare monogenic mutations. Genome-wide association studies (GWAS) have previously shown that the genetic load for CAD is due to common genetic variants with small effect sizes, in addition to rare variants with stronger effects[7, 8]. Common low-risk to rare high-risk genetic variants most likely act cumulatively to drive the overall risk in an individual[7, 9].

Derived from GWAS, multiple different PRSs have been previously created. PRSs are calculated by summing risk alleles, which are preferably weighted by effect sizes derived from GWAS results[3]. Recent meta-analyses have shown that PRS can be used to evaluate a patient's genetic risk and is an incremental predictor of CAD along with clinical cardiovascular risk factors. In many studies, PRSs have been proposed for clinical work to support the diagnostic process[3]. However, in large population studies, the diagnoses of CAD are based only on general clinical reports of having or not having CAD. The real cardiac phenotype is typically uncertain; thus, the current PRSs have not yet been validated in cohorts with accurate phenotyping of CAD.

Aim

This study aimed to assess the predictive power of the previously published three most promising PRSs in the prediction of CAD in symptomatic patients with suspected CAD in whom the coronary phenotype has been carefully characterized using both anatomic and functional imaging. The applied imaging methods (coronary computed tomography angiography, CTA, and positron emission tomography, PET perfusion imaging) allow accurate detection of anatomic atherosclerotic changes in coronary arteries as well as myocardial ischemia as a sign of functionally obstructive CAD[10, 11]. We hypothesized that the recently documented PRSs would improve the prediction of the development of coronary atherosclerosis and obstructive CAD. Consequently, we assessed the predictive value of three established PRSs in predicting both incident coronary atherosclerosis and obstructive CAD as a stand-alone measure as well as when added to the currently known clinical risk factors.

Materials and Methods

This study complies with the Declaration of Helsinki. The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol, and written informed consent was obtained from all patients. Genetic data were used only for research purposes. Patients or referring physicians did not receive any information regarding the genetic results.

Cohort

The study cohort consisted of 998 symptomatic patients with stable suspected obstructive CAD who had undergone coronary CTA with selective PET perfusion imaging as a diagnostic test at Turku University Hospital from 2006 to 2019. These patients are typically those with an intermediate probability of obstructive CAD and stable symptoms as an indication to undergo diagnostic procedures by clinicians. Patients provided voluntary consent for the collection of blood samples for genetic analyses.

As previously described[12, 13], in our routine practice, patients with suspected CAD first undergo coronary CTA, and immediately thereafter, PET perfusion imaging is performed if coronary CTA alone cannot rule out obstructive CAD. Typically, in all patients in whom CTA shows a suspicious coronary plaque (e.g., stenosis diameter ≥ 50%), the hemodynamic significance of the plaque was evaluated using ^{15}O-water PET perfusion imaging during adenosine stress. The detailed imaging protocol has been described previously[12, 14]. After excluding patients who did not complete the imaging protocol, 943 patients were included in the final analyses.

On the basis of the imaging findings, we classified the patients into three clinical groups. Group 1 had no coronary atherosclerosis. Group 2 had nonobstructive CAD (i.e., nonobstructive atherosclerosis based on CTA alone or atherosclerosis on CTA combined with normal PET perfusion). Group 3 had obstructive CAD (i.e., atherosclerosis on CTA combined with abnormal PET perfusion).

Clinical Data Collection

The patients' clinical characteristics, conventional cardiovascular risk factors, and symptoms were extracted from electronic medical records and saved to a specific cardiac registry database. Age, sex, body mass index, current smoking status, diabetes, hypertension, dyslipidemia, and a family history of premature CAD were considered conventional risk factors. A family history of premature CAD was defined as CAD in a first-degree relative, who is either < 55 years (male) or < 65 years (female). Patients without a family history of premature CAD were pooled together with patients with an unknown family history. For symptoms, the patients were classified into three categories 1) typical angina, 2) atypical/nonanginal pain/dyspnea, or 3) no chest pain

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or dyspnea. The existence and severity of symptoms were derived from electronic medical records. Chest pain was classified according to the Canadian Cardiovascular Society Angina Grade.

Selection of PRSs and Genetic Data Analysis

We selected the following three PRS profiles to be tested: PGS000329 [5], PGS000018 [6], and PGS000013 [2]. These PRSs are among the largest and most recognized in populations genetically close to our study cohort. For clarity, we call them PRS1, PRS2, and PRS3 in this study.

A total of 950 samples were genotyped using Illumina's GSAMD-24v2_0 bead chip. All genotypes were identified using GenomeStudio v. 2.0.3 software. Results were checked using Plink software for sex, identity-by-descent, and Hardy–Weinberg equilibrium. One duplicate sample was found and excluded, and four first-degree relatives were also excluded. Genotyping success rates for the samples were 98.4%–99.6% (GenomeStudio software) after removing the low-quality single-nucleotide polymorphisms (SNPs) and discarded samples. In the quality control, 28904/759993 (3.8%) SNPs were discarded. The plus/forward strand was based on information on "WRayner" (https://www.well.ox.ac.uk/~wrayner/strand/), and map positions were based on the genome build GRCh38.

For imputation, SNPs with a 99% genotyping rate were included. SNPs in linkage disequilibrium were excluded using a window size of 50 kb, a step size of 5, and an r2 threshold of 0.7. Imputation was performed using Minimac4 based on the MIT server (https://imputationserver.sph.umich.edu/) using HRC (HRC-r1.1) as a reference panel 15. Pre-imputation quality control was performed as recommended in the server documentation using the Will Rayner toolbox version 4.2 (https://www.well.ox.ac.uk/~wrayner/tools/index.html#Checking) and using plink. Additionally, the MIT server also employs an extensive pre-imputation quality check on the uploaded datasets and is described at (https://imputationserver.readthedocs.io/en/latest/pipeline/).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 27. All PRSs were standardized to obtain the odds ratio (OR) per SD unit. To evaluate the association between PRS and CAD, a logistic regression model was used $p<5\times10-8$ was considered statistically significant and $P<0.05$ was nominally significant. Models based on the clinical risk factors, PRS alone, and PRS with the clinical risk factors were generated to test whether the inclusion of PRSs improves CAD prediction. The discrimination of the predictive models was evaluated using the area under the receiver operating characteristic (AUROC) values. The Z-test was used to compare AUROC values of the two models. PRS was also stratified into deciles to illustrate its distribution in cases versus controls. To study the diagnostic performance of PRSs, we also calculated the sensitivity, specificity, and positive and negative predictive values, as well as the positive and negative clinical likelihood ratios (LRs) for all decile cutoffs of each PRS. Net reclassification improvement (NRI) values were also calculated for each decile of the PRS cutoff.

Results

Patient Characteristics

The study cohort included 943 patients (59.7% women). The mean age of the patients was 64 years (SD: 8.6 years). A family history of premature CAD was reported by 49.5% (n=467) of participants. Based on the imaging tests, 273 (29.0%) individuals had no coronary atherosclerosis, 465 (49.3%) had nonobstructive CAD, and 205 (21.6%) had obstructive CAD. The characteristics of the study participants are shown in **Table 1**.

To analyze the predictive power of PRS for CAD, we performed two comparisons. The first analysis compared patients with any coronary atherosclerosis (i.e., either nonobstructive or obstructive) (n=670) to those without atherosclerosis (n=273). The second analysis compared patients with obstructive CAD (n=205) to those without (n=738).

The Predictive Power of PRS

All three different PRSs predicted coronary atherosclerosis **(Table 2)** and obstructive CAD **(Table 3)**, and the ORs varied between 1.25 (95% confidence interval (CI) 1.07–1.46) and 1.70 (95% CI 1.44–2.01). The highest OR was found in PRS3 in predicting obstructive CAD. The ORs of clinical data alone were 3.13 (95% CI 2.63–3.72) and 2.53 (95% CI 2.15–2.98) for predicting coronary atherosclerosis or obstructive CAD, respectively. The ORs of models combining clinical data and different PRS varied between 2.59 (95% CI 2.20–3.05) and 3.01 (95% CI 2.53–3.57) in predicting obstructive CAD.

The PRS appeared to perform better in predicting obstructive CAD than coronary atherosclerosis. Therefore, the results for the prediction of obstructive CAD are presented in the main paper, whereas the results for predicting coronary atherosclerosis are presented in the **Supplemental Fig. 1**. **Fig. 1** depicts the receiver operating characteristic

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Table 1. Clinical characteristics and imaging findings for the cohort

	(*n* = 943)
Age (years) [a]	64 ± 8.6
Body mass index (kg/m^2) [a]	27.5 ± 4.9
Male sex	380 (40.3)
Current smoking	95 (10.0)
Diabetes	130 (13.8)
Hypertension	542 (57.5)
Dyslipidemia	611 (64.8)
Family history of premature CAD	
Symptoms	467 (49.5)
Typical angina	250 (26.5)
Atypical/non-anginal pain/dyspnea	594 (63.0)
No chest pain nor dyspnea	99 (10.5)
Imaging findings	
No coronary atherosclerosis	273 (29.0)
Non-obstructive CAD	465 (49.3)
Obstructive CAD	205 (21.7)

[a] mean ± standard deviation (range), CAD=Coronary artery disease

Table 2. The prediction of coronary atherosclerosis by clinical data and three PRS

Model	OR	95% CI	*p*-value
PRS1 (PGS000329)	1.40	1.21-1.62	<0.001
PRS2 (PGS000018)	1.62	1.39-1.89	<0.001
PRS3 (PGS000013)	1.62	1.39-1.88	<0.001
Clinical data [a]	3.13	2.63-3.72	<0.001
Clinical data [a] + PRS1	3.35	2.81-4.00	<0.001
Clinical data [a] + PRS2	3.59	3.00-4.30	<0.001
Clinical data [a] + PRS3	3.59	3.00-4.30	<0.001

Patients with coronary atherosclerosis (*n*=670) are compared against patients without coronary atherosclerosis (*n*=273).
[a]The clinical model includes age, sex, hypertension, diabetes, smoking, dyslipidemia, family history of premature CAD and symptoms. OR=odds ratio, CI=confidence interval.

Table 3. The prediction of obstructive CAD by clinical data and three PRS

Model	OR	95% CI	*p*-value
PRS1 (PGS000329)	1.25	1.07-1.46	0.006
PRS2 (PGS000018)	1.68	1.42-1.97	<0.001
PRS3 (PGS000013)	1.70	1.44-2.01	<0.001
Clinical data [a]	2.53	2.15-2.98	<0.001
Clinical data [a] + PRS1	2.59	2.20-3.05	<0.001
Clinical data [a] + PRS2	2.97	2.50-3.53	<0.001
Clinical data [a] + PRS3	3.01	2.53-3.57	<0.001

Patients with obstructive CAD (*n*=205) are compared against patients without obstructive CAD (*n*=738).
[a]The clinical model includes age, sex, hypertension, diabetes, smoking, dyslipidemia, family history of premature CAD and symptoms. OR=odds ratio, CI=confidence interval.

(ROC) curves of each PRS in predicting obstructive CAD. The areas under the curve of the PRS models vary between 0.561 and 0.640, indicating a rather low predictive power.

ROC curves for models combining clinical data and PRSs for predicting obstructive CAD are shown in **Fig. 2.** The predictive accuracy of the models combining clinical data and different PRS varied

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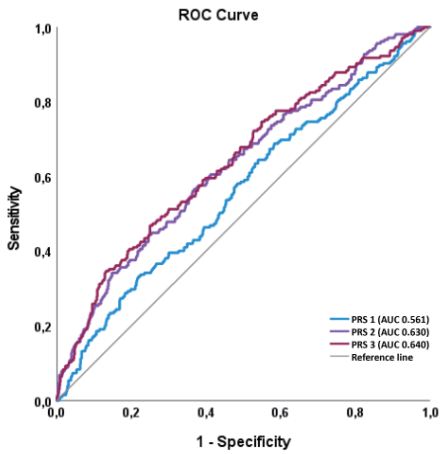

Fig. 1. ROC curves of PRSs

Receiver operating characteristic (ROC) curves of three PRSs in predicting obstructive CAD. AUC = Area under the curve, PRS = Polygenic risk score.

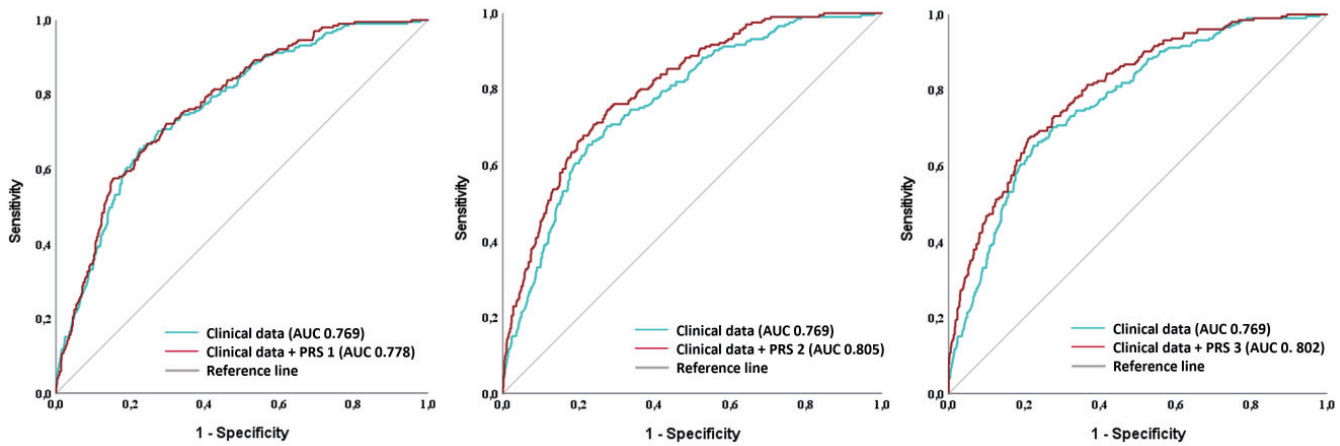

Fig. 2. ROC curves of PRSs with clinical risk factors

Receiver operating characteristic (ROC) curves of clinical data and PRS in predicting obstructive CAD. AUC = Area under the curve, PRS = Polygenic risk score.

between 0.778 and 0.805 (in terms of AUROC), being close to the model including only clinical variables (AUROC: 0.769) and yielding an improvement of only 0.9–3.6 percentage points over clinical data alone. The difference between the clinical model and the combined clinical + PRS model was not significant for PRS1 (p=0.627) and PRS3 (p=0.061). Only PRS2 slightly (AUC change: 0.036) but nominally significantly (without Bonferroni correction for four independent tests) improved the predictive power of the model (p=0.04).

Distribution of the PRS Values

Fig. 3 shows the distribution of the PRS values in patients with and without obstructive CAD. The distribution of the PRS in the two groups completely overlapped with a minor shift toward higher PRS values in patients with obstructive CAD compared with those without obstructive CAD. In Fig. 4, the PRS values are categorized into deciles to visualize the relative risk in each PRS category. The prevalence of obstructive CAD was higher in higher PRS deciles; however, a large proportion of the patients classified as having high risk by PRS did not have obstructive CAD based on imaging tests. Conversely, most patients with obstructive CAD had a PRS lower than the highest deciles. Supplemental Fig. 2 and Supplemental Fig. 3 shows similar distributions for

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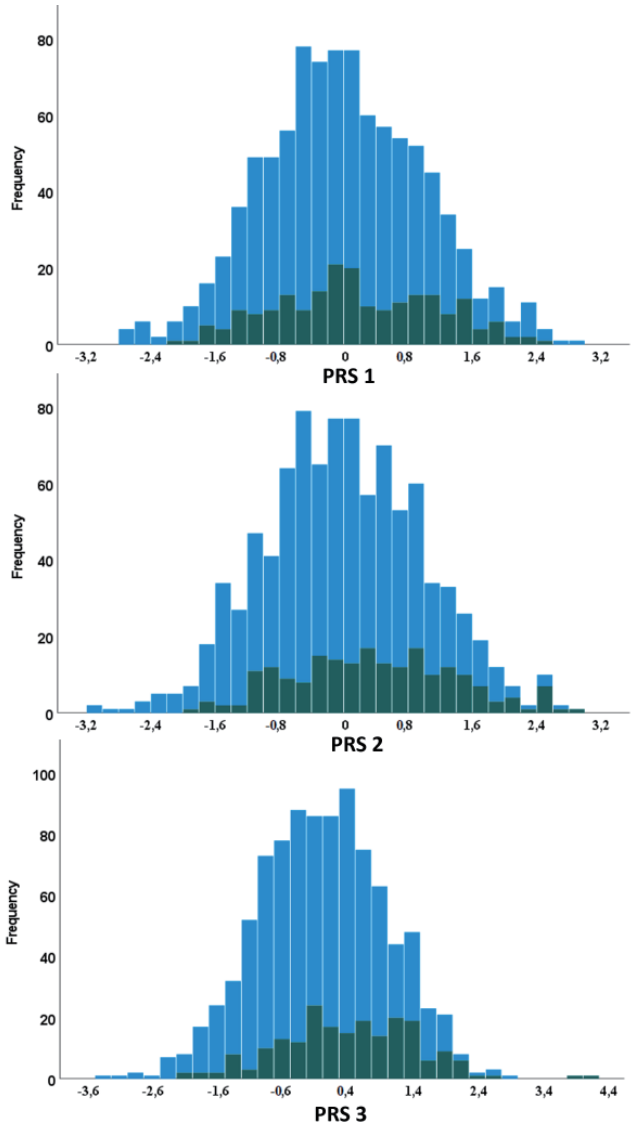

Fig. 3. Distribution charts of PRSs per standard deviation (SD)

Distribution charts demonstrating the distribution of PRSs per SD for each of the three PRSs in patients with (in green) and without (in blue) obstructive CAD.
PRS = Polygenic risk score

the prediction of atherosclerosis.

The calculated sensitivity, specificity, positive and negative predictive values, and the positive and negative LRs for all decile cutoffs of each PRS are shown in the **Supplemental Table 1**. None of the PRS cutoffs provided reasonable sensitivity and specificity at the same time. The positive LR ranged from 1.01 to 1.10 and the negative LR from 0.29 to 0.92. NRI values are shown in the **Supplemental Table 2**.

Discussion

Many studies have reported the use of PRSs to assess the risk of developing diseases, including CAD. Different cohort studies have shown that PRS are independent and incremental predictors of CAD along with clinical cardiovascular risk factors[3-6, 15]. We hypothesized that the previously documented PRSs are useful in predicting the development of coronary atherosclerosis and obstructive CAD along with the traditional risk factors and could be used in clinical workups, as shown by a recent meta-analysis[3]. However, its clinical utility has not been previously

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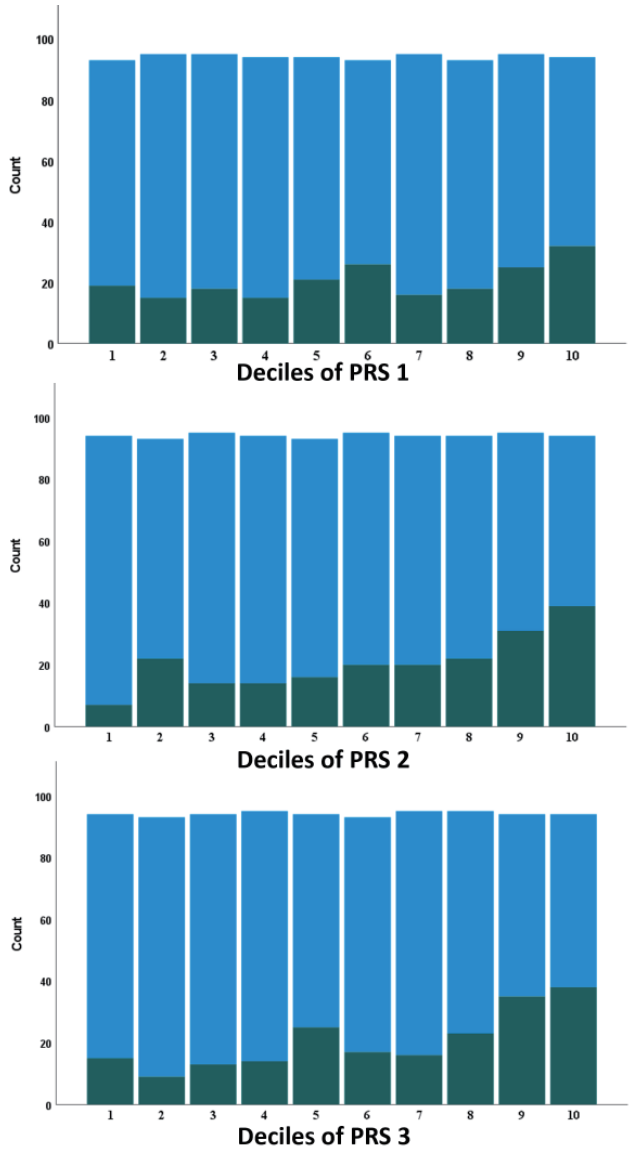

Fig. 4. Distribution of PRSs in deciles

The distribution of PRSs (in deciles) in participants with (in green) and without (in blue) obstructive CAD.
PRS = Polygenic risk score

evaluated at the individual level, and a validation of various PRSs in an independent population with an accurate phenotype is not yet available[3].

In this study, we conducted a validation study in a cohort with a very accurate cardiac imaging phenotype. The results rejected the hypothesis of the high utility of PRSs. Although PRS has some predictive power, it is small and does not appear to provide clinically useful information regarding routine clinical risk factors in the evaluation of incident CAD. Adding PRS, the predictive accuracy improved only by 0.9–3.6 percentage points over the clinical data. Our findings in the symptomatic population with suspected CAD are in agreement with those of a recent review conducted in primary prevention populations[16]. That study used five different PRSs, two of which were the same as those used in our study. In that review, PRSs were also significantly associated with the risk of CAD, but the improvement ranged from negligible to modest when the PRSs were added to traditional risk scores[16].

The strength of the current study is that we included a reasonably large number of patients with very accurate phenotyping of CAD by using anatomical (coronary atherosclerosis and plaques) and functional (ischemia) state-of-the-art imaging.

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Imaging methods have been validated in large populations and are the best for this purpose[17]. As we did not aim to develop new PRSs but to validate existing ones, the cohort we studied was large enough. This is also supported by the expected performance of classic risk factors in the same population.

Another strength is that the patients were symptomatic with suspected CAD. This is the exact group in which PRSs are shown to be used if applied in the diagnostic workup. In addition, we tested three recent, most recognized, and promising PRSs, which were constructed from large sample sizes and huge number of SNPs and complex weighting modalities. The 95% CIs for ORs and AUC values obtained in our study were comparable to those reported in the original studies **(Supplemental Table 3)**. Therefore, we consider the chosen population, PRSs, and the methods as representative. The results demonstrate that despite its clinical use, the genetic characteristics obtained at birth in the form of PRSs have limited clinical value beyond the current risk factors in patients with chest pain and suspected CAD.

Another strength of our analysis is that we used two different phenotype endpoints. The genetic risk for developing atherosclerosis or obstructive CAD may be different because their pathophysiology is different. We found that all PRSs were associated with the development of both atherosclerosis and obstructive CAD[2, 5, 6]. However, it appeared that compared with developing coronary atherosclerosis, obstructive CAD was generally predicted better by PRSs (ORs for atherosclerosis were 0.68 (95% CI 0.59–0.79)–1.62 (95% CI 1.39–1.89) and for obstructive CAD 0.71 (95% CI 0.61–0.83)–1.70 (95% CI 1.44–2.01), although the differences were small.

Typically, PRSs are derived from, and their predictive power is evaluated in large-scale cohorts including hundreds of thousands of healthy individuals and individuals with CAD and a huge number of SNPs. However, in these large studies, the phenotype is typically weakly characterized because the diagnoses of CAD are based only on general clinical reports of having or not having CAD, and no details about the coronary anatomy or myocardial ischemia are available. Therefore, validation of the performance of the PRSs is needed in real-world clinical patients with an accurately characterized phenotype. Our unique setting provided valuable information on the usability of PRS in risk stratification at the individual level and enabled comparison against conventional risk factors.

Our results illustrate the dilemma of the proposed use of PRSs in risk stratification or as a screening test. ORs indicating moderate risk can have significance in population studies in determining the causes of the disease, but they are not applicable in risk prediction on the individual level[18, 19]. ORs or hazard ratios do not directly indicate the discriminatory value of a screening test[18, 19]. Despite these facts, there are big expectations for PRSs in the hope of using them in risk stratification in the future, especially in the publications that introduced PRS.

The challenge of using PRSs in the clinical workup is illustrated in **Fig. 3 and 4**. The range of risk scores by different PRSs overlap in patients who are healthy, atherosclerotic, and have obstructive CAD. This demonstrates that these PRSs do not help to separate patients with and without obstructive CAD in clinical practice. Furthermore, looking at one or two top deciles, it becomes evident that even in the highest deciles, showing a relatively higher likelihood of having obstructive CAD, most patients did not have CAD, rendering low specificity. In addition, most patients with CAD had low PRS, making the sensitivity very low, regardless of the PRS cutoff applied. This is also supported by our LR analysis with all PRS decile cutoffs **(Supplemental Table 2)**. To be clinically useful, any diagnostic test must significantly change the pre-test probability. The power of any test to change probability can be estimated from LRs. In general, LRs above 10 and below 0.1 are considered to provide strong evidence to rule in or rule out diagnoses, respectively, in most circumstances. Positive LRs between 5 and 10 are valuable in individuals with intermediate pre-test probability. In the current analyses, the positive LR ranged from 1.01 to 1.10 and the negative LR ranged from 0.29 to 0.92, suggesting that none of the PRSs in any of their cutoffs provided useful diagnostic information. The findings with NRI also showed the poor incremental diagnostic power of PRSs.

Study Limitations

One of the limitations of this study is that we did not have follow-up data regarding the progression of CAD or the medications used. Second, this study focused on three selected PRSs. We acknowledge that many other PRSs could be considered, but we believe that our selection offers a representative sample that demonstrates and evaluates the topic well. Third, the ethnicity of the study participants may significantly change the discrimination power of the PRS. However, the population tested in our study included participants of Caucasian northern European ancestry from Finland. The tested PRSs were also generated from similar European ancestry (the population in one of the tested PRSs by Mars *et al.*[5] was also Finnish),

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so they should be suitable for our population. Fourth, in our study, one of the clinical risk factors was the family history of premature CAD. This risk factor may include some genetic information, as shown in the study by Mars *et al.*[5] in which PRS did not provide incremental information on the reported family history. In any case, asking for family history is common in clinical work, completely free of cost and with minimal effort, which is not the case with PRSs. In the current analysis, we did not have access to patient clinical outcomes, and further studies are warranted on this topic.

In addition, as PRSs can be constructed in different ways[20], different PRSs can give quite varying risk estimates for an individual with minimal concordance[20, 21]. This needs to be further tested in our cohort and can further hamper the usability of PRSs in a clinical real-world setting in predicting CAD at the individual level.

Conclusions

The current PRSs appear to be statistically significant predictors of coronary atherosclerosis and obstructive CAD. However, the predictive power of scores is limited and does not provide clinically useful information beyond conventional cardiovascular risk factors. The results of this study show that current PRSs are not justified for the clinical routine evaluation of symptomatic patients referred for suspected CAD.

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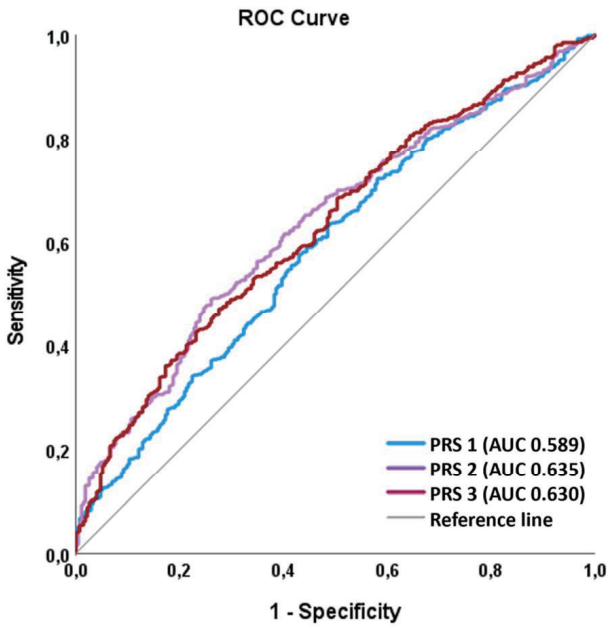
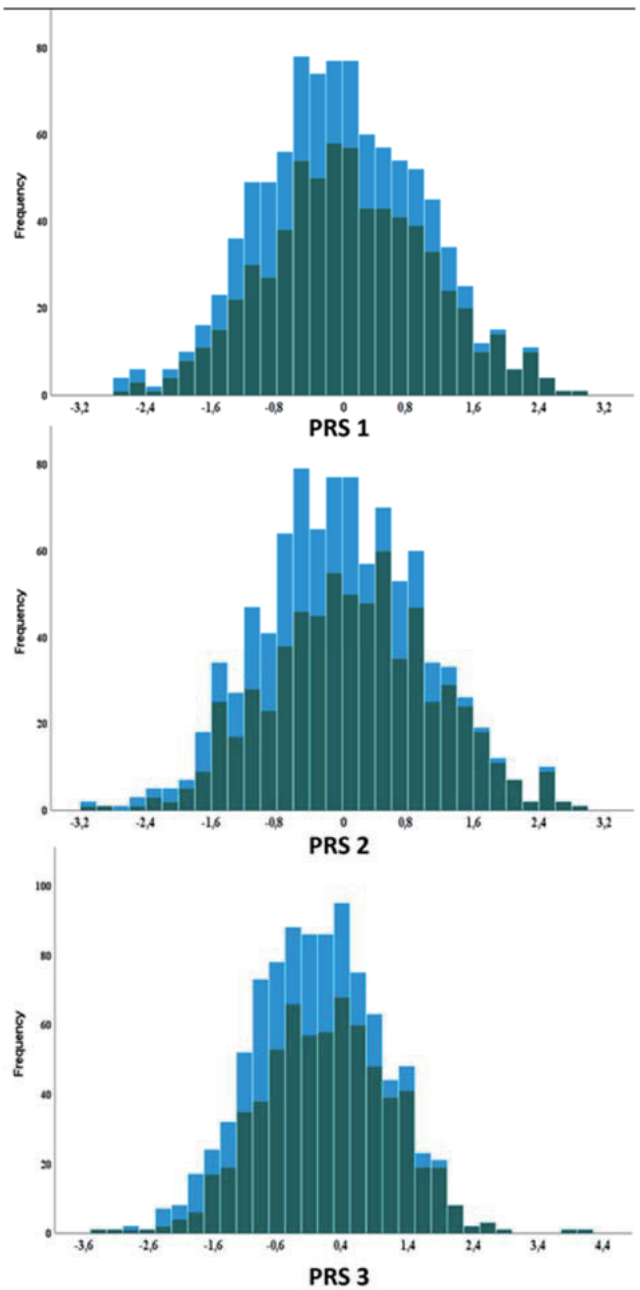


Supplemental Fig. 1. ROC curves

Receiver operating characteristic (ROC) curves of four PRS in predicting atherosclerosis.



Supplemental Fig. 2. Distribution in deciles

Distribution charts per SD. Distribution charts demonstrating distribution of PRS per SD for each four PRS separately in patients with (in green) and without (in blue) atherosclerosis.

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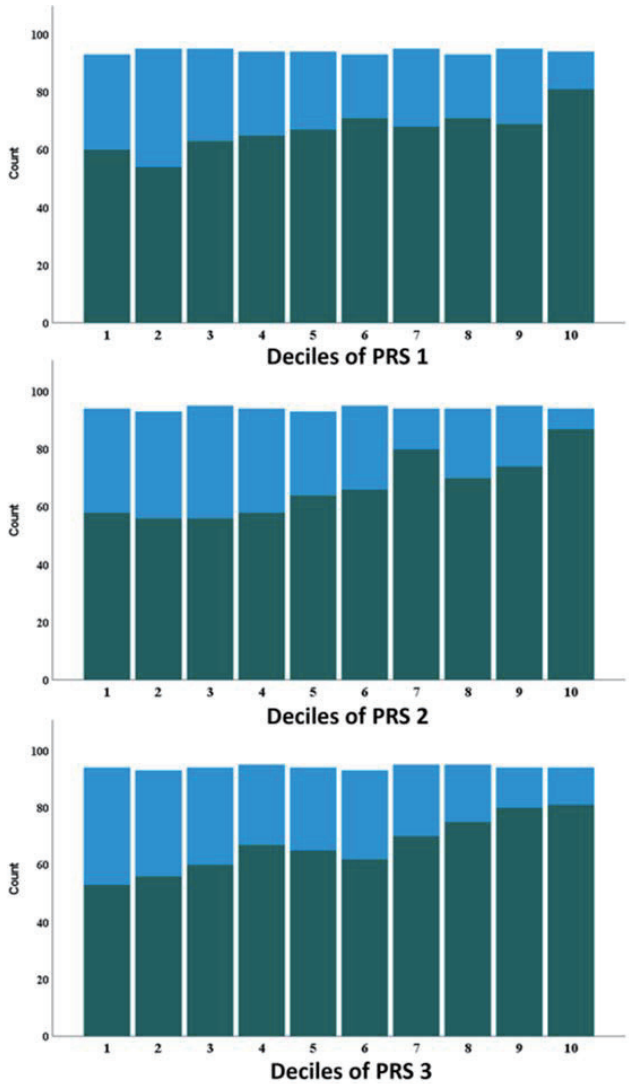

Supplemental Fig. 3. Distribution in deciles.

Distribution of PRS (in deciles) in participants with (in green) and without (in blue) atherosclerosis.

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Supplemental Table 1. Sensitivities, Specificities, LR+, LR-, PPV, NPV, accuracy

	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %
PRS1									
Sensitivity	90.7	83.4	74.6	67.3	57.1	44.4	36.6	27.8	15.6
Specificity	10.1	20.9	31.4	42.1	52.0	61.1	71.9	82.1	91.6
Positive LR	1.01	1.05	1.09	1.16	1.19	1.14	1.30	1.55	1.86
Negative LR	0.92	0.79	0.81	0.78	0.83	0.91	0.88	0.88	0.92
NPV	79.6	81.9	81.6	82.2	81.3	79.8	80.3	80.3	79.6
PPV	21.9	22.7	23.3	24.5	24.9	24.1	26.6	30.2	34.0
Accuracy	27.6	34.5	40.8	47.6	53.1	57.5	64.2	70.2	75.0
PRS2									
Sensitivity	96.6	85.9	79.0	72.2	64.4	54.6	44.9	34.1	19.0
Specificity	11.8	21.5	32.5	43.3	53.8	64.0	74.0	83.8	92.5
Positive LR	1.10	1.09	1.17	1.27	1.39	1.52	1.73	2.10	2.53
Negative LR	0.29	0.66	0.65	0.64	0.66	0.71	0.74	0.79	0.88
NPV	92.6	84.5	84.8	84.8	84.4	83.5	82.8	82.0	80.4
PPV	23.4	23.3	24.6	26.2	28.0	29.7	32.5	37.0	41.5
Accuracy	30.3	35.5	42.6	49.6	56.1	62.0	67.7	73.0	76.5
PRS3									
Sensitivity	92.7	88.3	82.0	75.1	62.9	54.6	46.8	35.6	18.5
Specificity	10.7	22.1	33.2	44.2	53.5	63.9	74.6	84.4	92.4
Positive LR	1.04	1.13	1.23	1.35	1.35	1.51	1.84	2.28	2.43
Negative LR	0.68	0.53	0.54	0.56	0.69	0.71	0.71	0.76	0.88
NPV	84.0	87.2	86.8	86.4	83.8	83.5	83.4	82.5	80.3
PPV	22.4	24.0	25.5	27.3	27.4	29.6	33.9	38.8	40.4
Accuracy	28.6	36.6	43.8	50.9	55.6	61.8	68.5	73.8	76.3

Sensitivities, specificities, positive and negative likelihood ratio, negative predictive value, positive predictive value and accuracy for PRS 1-4, each decile separately. LR = likelihood ratio, NPV=negative predictive value, PPV=positive predictive value, PRS=polygenic risk score.

Supplemental Table 2. NRI values

Deciles	PRS1	PRS2	PRS3
10	-0,0125	-0,0623	-0,0873
9	-0,0298	-0,0111	0,0201
8	0,0534	0,0271	0,0347
7	-0,0222	-0,0146	-0,0098
6	-0,0014	0,0111	0,0000
5	0,0049	0,0173	0,0035
4	-0,0125	-0,0173	-0,0062
3	-0,0014	0,0222	0,0298
2	0,0125	0,0125	0,0125
1	0,0062	0,0125	0,0000

NRI for comparison of clinical moden and clinical model + PRS.
NRI=net reclassification index, PRS=polygenic risk score

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Supplemental Table 3. PRS as predictors by original studies

	Patients' origin	Number of patients	AUC	C-index (95% CI)	NRI (95% CI)	Reference
PRS1, PGS000329	FinnGen	20,165	-	0.820 (0.816–0.824)	1.1 (-0.1,2.2)	Mars N, Koskela JT, Ripatti P, *et al.* Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. Nat. Med., 2020; 26: 549-557. Available at: http://dx.doi.org/10.1038/s41591-020-0800-0
PRS2, PGS000018	UK biobank	482,629	0.79	0.623 (0.615-0.631)	-	Inouye M, Abraham G, Nelson CP, *et al.* Genomic risk prediction of coronary artery disease in 480,000 adults: Implications for primary prevention. J. Am. Coll. Cardiol., 2018; 72: 1883-1893. Available at: http://dx.doi.org/10.1016/j.jacc.2018.07.079
PRS3, PGS000013	UK biobank	184,305	0.81 (0.81–0.81)	-	-	Khera AV, Chaffin M, Aragam KG, *et al.* Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat. Genet., 2018; 50: 1219-1224. Available at: http://dx.doi.org/10.1038/s41588-018-0183

Supplemental table, PRS1-3 patients´ origin, number of patients, AUC, c-index, NRI and reference based on original publifications. PRS=polygenic risk score, AUC=area under the curve, NRI= net reclassification index, CI=confidence interval

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