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Original Article

Clinical Utility and Practical Considerations of a Coronary Artery Disease Genetic Risk Score

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ABSTRACT

Background: Coronary artery disease (CAD) risk traditionally has been assessed using clinical risk factors. We evaluated whether molecular genetic markers for CAD risk could add information to traditional variables.

Methods: We developed a false discovery rate 267-marker genetic risk score (FDR_{267}) from markers that were significantly associated with CAD in the UK Biobank cohort meta-analysis. FDR_{267} was tested in the Atherosclerosis Risk in Communities cohort using logistic regression and Cox proportional hazards analyses in the European and African American groups.

Results: Our genetic risk score (FDR_{267}) was associated with a 1.45 (95% confidence interval, 1.39-1.51) increase in odds ratio and a 1.32 (95% confidence interval, 1.26-1.38) increase in hazard ratio per standard deviation of the score. The score modestly improved the area

RÉSUMÉ

Introduction : L'évaluation du risque de maladie coronarienne (MC) a traditionnellement reposé sur les facteurs de risque cliniques. Nous avons évalué si les marqueurs génétiques moléculaires de risque de MC pourraient servir de complément aux variables traditionnelles.

Méthodes : Nous avons élaboré un taux de fausses découvertes (FDR pour *false discovery rate*) du score de risque génétique du marqueur 267 (FDR_{267}) provenant des marqueurs qui étaient associés de manière significative à la MC dans la méta-analyse de cohortes de la UK Biobank. Le FDR_{267} a été testé dans la cohorte du Atherosclerosis Risk in Communities à l'aide de la régression logistique et des analyses selon le modèle à risques proportionnels de Cox dans des groupes européens et afro-américains.

Résultats : Notre score de risque génétique (FDR_{267}) a été associé à une augmentation de 1,45 (intervalle de confiance [IC] à 95 %,

Coronary artery disease (CAD) is common and involves both genetic susceptibility and environmental exposures.[1] Traditionally, clinical risk factors are used by physicians to stratify an individual's risk for CAD and can guide management.[2,3] In recent years, however, powerful genetic technologies have enabled dissection of the genetic architecture of CAD.[4,5] Using large-scale genome-wide association studies (GWASs), researchers now hope to leverage individuals' genomic data to help make personalized clinical decisions.

One strategy to quantify the complex genetic contribution is to build a genetic risk score (GRS) that considers the additive effects of single nucleotide polymorphisms (SNPs). The SNP set is selected from those found to be significantly and independently associated with the disease of interest in a large-scale GWAS study. This approach has been shown to identify individuals at a higher burden of "polygenic risk" and is being considered for clinical use in guiding discussions with patients about their risk, intensifying primary prevention and screening populations.[6-8] Polygenic factors are also important determinants of CAD risk factors, such as plasma lipids.[9-11] However, before it can be translated into clinical practice, we need evidence that a GRS test adds clinical utility beyond traditional risk factors. Moreover, because much of the existing GWAS data are generated from cohorts of predominantly European patients, the approach has been shown to inconsistently assess risk across ethnicities.[12,13]

Our study investigated the performance of a false discovery rate 267-marker genetic risk score (FDR_{267}) in the

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Ethics Statement: The project was approved by the Western University Research Ethics Board (number 07920E).

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See page 74 for disclosure information.

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under the curve (AUC) statistic when added to a clinical model (ΔAUC = 0.0112, P = 0.0002). FDR_{267} predicted incident CAD (C-index = 0.60), although it did not improve on clinical risk factors (ΔAUC = 0.0159, P = 0.0965). Individuals in the top quintile of FDR_{267} genetic risk were at approximately 2-fold increased risk compared with the bottom quintile, which is comparable to risk associated with self-reported family history. The performance of FDR_{267} was less robust in the African American sample.

Conclusions: FDR_{267} is significantly associated with CAD in the European sample, with an effect size comparable to self-reported family history. FDR_{267} discriminated between individuals with and without CAD, but did not improve CAD risk prediction over clinical variables. FDR_{267} was less predictive of CAD risk in African Americans.

1,39-1,51) du rapport des cotes et d'une augmentation de 1,32 (IC à 95 %, 1,26-1,38) du risque relatif par l'écart-type des scores. Le score a modestement amélioré l'aire sous la courbe (ASC) lorsqu'il a été ajouté à un modèle clinique (ΔASC = 0,0112, P = 0,0002). Le FDR_{267} a prédit les nouveaux cas de MC (C-index [indice de concordance] = 0,60), mais il n'a pas amélioré les facteurs de risque cliniques (ΔASC = 0,0159, P = 0,0965). Les individus dans le quintile supérieur du risque génétique du FDR_{267} ont montré un risque accru d'environ 2 fois par rapport au quintile inférieur, soit un risque comparable au risque associé aux antécédents familiaux auto-rapportés. La performance du FDR_{267} s'est révélée moins robuste chez les Afro-Américains.

Conclusions : Le FDR_{267} est associé de manière significative à la MC dans l'échantillon d'Européens et a une taille de l'effet comparable aux antécédents familiaux auto-rapportés. Le FDR_{267} a fait la discrimination entre les individus atteints ou non atteints de MC, mais n'a pas amélioré la prédiction du risque de MC par rapport aux variables cliniques. Le FDR_{267} a moins bien prédit le risque de MC chez les Afro-Américains.

Atherosclerosis Risk in Communities (ARIC) cohort. We stratified the ARIC cohort by ethnicity (European Americans and African Americans) and tested the association between genetic risk and CAD in each sample. Next, we asked whether FDR_{267} could add predictive value to a model that considers only traditional Framingham risk factors. Finally, we compared the predictive value of FDR_{267} against a positive self-reported family history.

Materials and Methods

Study population

ARIC is a prospective cohort population of 15,792 European and African Americans aged 45 to 64 years recruited at 4 separate field centres in the United States between 1987 and 1989. These individuals were extensively examined at recruitment; baseline sociodemographic and medical data were gathered. A total of 3 follow-up examinations occurred every 3 years; the time ranges were 1990-1992, 1993-1995, and 1996-1998. One final visit occurred between 2011 and 2013. Yearly follow-up assessments by telephone were also conducted to maintain contact with patients. The event definition for CAD was fatal or nonfatal myocardial infarction (MI), revascularization procedure, and silent MI detected by electrocardiogram. Detailed methodology has been previously published.[14] Of these 15,792 individuals, 12,771 were genotyped with the Affymetrix version 6.0 SNP array to evaluate the genetic landscape of 934,940 SNPs as part of the Gene Environment Association Studies (GENEVA) initiative. Data were accessed through the database of Genotypes and Phenotypes, available with controlled access from the National Institutes of Health.

Quality control

Variants from the Affymetrix 6.0 genotyping platform were filtered for missingness > 2%, Hardy–Weinberg disequilibrium ($< 10^{-6}$), nonautosomal variants, and minor allele frequency (< 1%). Individuals were removed for missing genetic data (> 2%), sex inconsistency, and cryptic relatedness (pi-hat < 0.1875). All quality-control steps were performed on PLINK 1.9 with additional scripts for cryptic relatedness written with Python 3.6.5. Imputation was performed with the Michigan Imputation Server using the unphased ShapeIT v2.r790 algorithm; the mixed Haplotype Reference Consortium (r1.1 2016) was the reference panel.[15]

Genetic risk score

SNPs used in the GRS were selected on the basis of the 304 independent variants discovered to be associated with CAD (revascularization procedure, self-reported angina, or MI) at a false discovery rate (FDR) < 5% in the 2017 UK Biobank GWAS meta-analysis.[4] We only included variants that were directly genotyped by the Affymetrix 6.0 chip after quality control or that could be reliably imputed on the basis of an INFO score of > 0.3. For the remaining SNPs that did not meet these criteria, we sought reliable proxies by linkage disequilibrium ($r^2 > 0.8$) using PLINK 1.9 and the 1000 Genome phase 3 version 5 dataset.

The weighted GRS was calculated with PLINK 1.9 using regression coefficients from the UK Biobank study obtained from the CARDIoGRAMplusC4D website (http://www.cardiogramplusc4d.org/) using the following equation:

$$\text{Genetic risk score} = \sum_{i \in GRS}^{x} w_i D_i$$

$$x = \text{total set of SNPs},\ w_i = \text{beta},\ D_i = \text{dosage of risk allele}$$

Statistical analyses

The computed GRSs were standardised by subtracting the mean and dividing by the standard deviation to obtain odds ratio or hazard ratio (HR) changes per standard deviation of the score. Correlations between continuous variables were tested using the Pearson product-moment correlation. Association with binary outcome variables was tested by fitting data to a logistic regression model and testing for model significance using the analysis of variance chi-square test. Density

Table 1. Baseline demographic and clinical characteristics of the ARIC population

Phenotype	European*	African
Total number	8267	2311
Male	4026 (48.7%)	890 (38.5%)
Age (y)	54.4 ± 5.7	53.5 ± 5.8
Total cholesterol (mg/dL)	214.6 ± 40.6	215.8 ± 44.8
mmol/L	5.55 ± 1.05	5.58 ± 1.16
HDL cholesterol (mg/dL)	50.5 ± 16.7	54.8 ± 17.4
mmol/L	1.31 ± 0.43	1.42 ± 0.45
Systolic blood pressure (mm Hg)	118.5 ± 16.8	128.3 ± 20.6
Antihypertensive treatment	1612 (19.5%)	965 (41.7%)
Current smoker	1975 (23.9%)	669 (28.9%)
Type 2 diabetes	710 (8.59%)	462 (20.0%)
CAD at baseline	338 (4.09%)	93 (4.02%)
CAD during follow-up	652 (7.89%)	184 (7.95%)

ARIC, Atherosclerosis Risk in Communities; CAD, coronary artery disease; HDL, high-density lipoprotein.

*Numerical entries are means + standard deviations for continuous traits and total number (with percentage in parentheses) for discrete traits.

distribution differences were tested for difference using the Kolmogorov–Smirnov test. A Cox proportional hazards model was fitted for incidence analysis and tested for goodness-of-fit using the likelihood ratio test. Uno's concordance index was estimated for the Cox proportional hazard models.[16] Receiver-operator curves (ROCs) were constructed, and the area under the curve (AUC) was calculated to assess the discrimination ability of different models. Differences in AUC between models were evaluated using DeLong's test.[17] All statistical analyses were performed on Rv3.5.1 and SAS v9.4 (SAS Institute, Inc, Cary, NC). R packages obtained from the CRAN mirror and used include "survival," "survminer," "ggplot2," "PredictABEL," "ggpubr," "pROC," "rms," and "qwraps2."

Results

Baseline demographic and modifiable risk factors

After quality-control analysis of the ARIC population, 10,578 individuals had all data available for analysis. The baseline demographic and Framingham risk factor characteristics by ethnic group are found in Table 1. A total of 836 events occurred during the follow-up period, with 1138 cases of CAD when considering both individuals with CAD at baseline and those who had an event during follow-up.

Associations among GRS, clinical risk factors, and CAD

After quality control, 265 of the 301 SNPs identified in the UK Biobank study were found to have been directly genotyped or reliably imputed with an imputation quality score > 0.3 in the ARIC population. Two additional SNPs were included in the GRS build as proxies with an $r^2 > 0.8$ to the reported SNPs. The list of SNPs included in the final GRS build (FDR_{267}) can be found in Supplementary Table S1.

When tested against traditional Framingham risk factors, FDR_{267} was significantly associated with total and high-density lipoprotein (HDL) cholesterol, systolic blood pressure, antihypertensive treatment, and type 2 diabetes in the European sample and systolic blood pressure in the African American sample (Supplementary Table S2). FDR_{267} was normally distributed in both samples and was significantly right shifted in cases compared with controls (Fig. 1). The odds ratio of CAD per standard deviation of FDR_{267} was 1.45 (95% confidence interval [CI], 1.39-1.51; $P < 0.001$) and 1.05 (95% CI, 0.99-1.11; $P = 0.411$), respectively, for the European and African American samples when corrected for age and sex.

Prediction of incident CAD by FDR_{267}

The 431 individuals with CAD at baseline were excluded from survival-to-event analyses. The HR per standard deviation of FDR_{267} when corrected for age and sex was 1.32 (95% CI, 1.26-1.38, $P < 0.001$) and 1.11 (95% CI, 1.04-1.19, $P = 0.0985$) for the European and African American samples, respectively. Concordance indices (C) for FDR_{267} were 0.60 (95% CI, 0.56-0.64) and 0.54 (95% CI, 0.48-0.60) for the European and African American samples, respectively.

Quintile analysis was performed in the European sample. There was an increase in HR across quintiles (Table 2).

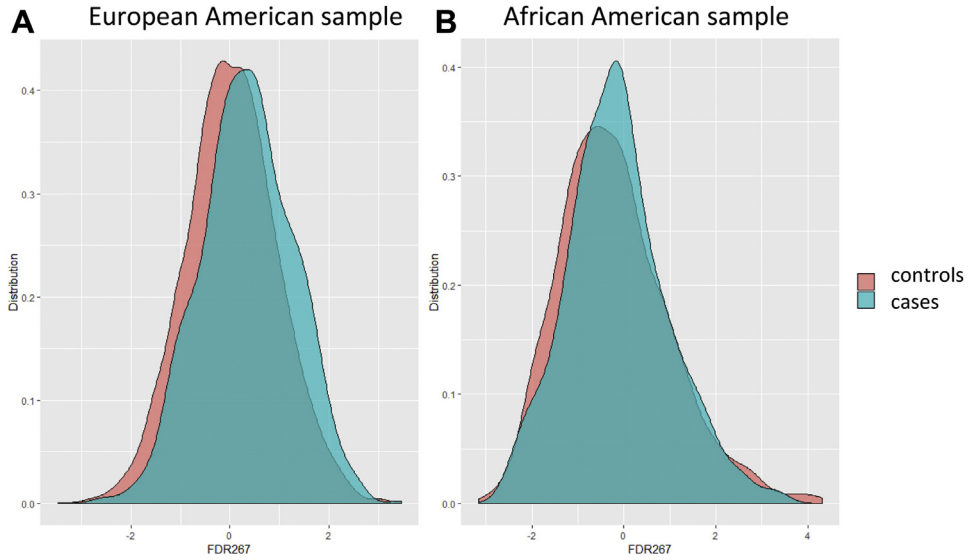

Figure 1. Density distribution plots of false discovery rate 267-marker genetic risk score (FDR_{267}) score for the (**A**) European American sample and (**B**) African American sample. Corresponding Kolmogorov–Smirnov test *P* values were 3.475×10^{-14} and 0.0972, respectively.

Table 2. Hazard ratios at increasing quintiles of FDR_{267} in the European sample

Quintile	Hazard ratio (95% CI)	*P* value
1	Reference	-
2	1.03 (0.87-1.18)	0.8693
3	1.45 (1.31-1.60)	0.0097
4	1.52 (1.38-1.66)	0.00334
5	1.89 (1.42-2.44)	0.0000039

CI, confidence interval; FDR_{267}, false discovery rate 267-marker genetic risk score.

Individuals in the fifth quintile of FDR_{267} had an HR of 1.89 (95% CI, 1.42-2.44) for CAD when compared with the lowest quintile. Survival curves built for individuals at increasing degrees of genetic risk (low = first quintile, moderate = 2-4 quintiles, and high = fifth quintile) are shown in Supplementary Figure S1.

FDR_{267} and clinical risk

Incremental discriminatory value of FDR_{267} was assessed by ROC analysis (Fig. 2). In the European sample, the AUC for a model based on clinical factors (systolic blood pressure, total and HDL cholesterol, smoking status, type 2 diabetes, age, and sex) was 0.74 (95% CI, 0.72-0.76). Including FDR_{267} to the model resulted in a modest and significant increase in the AUC (ΔAUC = 0.0112, $P = 0.0002$) (Table 3 and Supplementary Fig. S2). Likewise, when we investigated CAD incidence, adding genetic risk to a model with Framingham risk factors alone did not significantly change the C-index (Table 4 and Supplementary Fig. S3), giving similar results to those seen with the AUC analysis in Table 3.

Comparison of FDR_{267} with self-reported family history

The ROCs for the European and African American samples are shown in Figure 3. When tested against self-reported family history of CAD in at least 1 first-degree relative, the ORs for FDR_{267} were 2.00 (95% CI, 1.70-2.35; $P < 0.001$) and 1.61 (95% CI, 1.17-2.22, $P = 0.00379$) for the European and African American samples, correcting for sex and age, respectively. The respective HRs associated with a positive self-reported family history were 1.72 (95% CI, 1.56-1.90; $P < 0.001$) and 1.51 (95% CI, 1.25-1.83; $P = 0.0319$), when correcting for age and sex. The corresponding C-indices for FDR_{267} were 0.53 (95% CI, 0.51-0.56) and 0.55 (95% CI, 0.49-0.61), respectively. There was no significant difference in the C-index when comparing the FDR_{267} and family history models in the European sample ($\Delta C = -0.0292$, $P = 0.2325$) or the African sample, after adjusting for age and sex.

Discussion

In European individuals, FDR_{267} was associated with a 1.45 (95% CI, 1.39-1.51; $P < 0.001$) and a 1.32 (95% CI, 1.26-1.38; $P < 0.001$) increase in CAD odds ratio and HR, respectively, per standard deviation of the score. The score modestly improved the AUC statistic when added to a clinical model. It predicted incident CAD (C-index = 0.60), although it did not improve on clinical risk factors ($\Delta C = 0.0159$, $P = 0.0965$). Individuals in the top quintile of FDR_{267} genetic risk are at an approximately 2-fold increased risk compared with the bottom quintile, which is comparable to risk associated with self-reported family history of CAD. The performance of FDR_{267} in the African American sample was notably weaker.

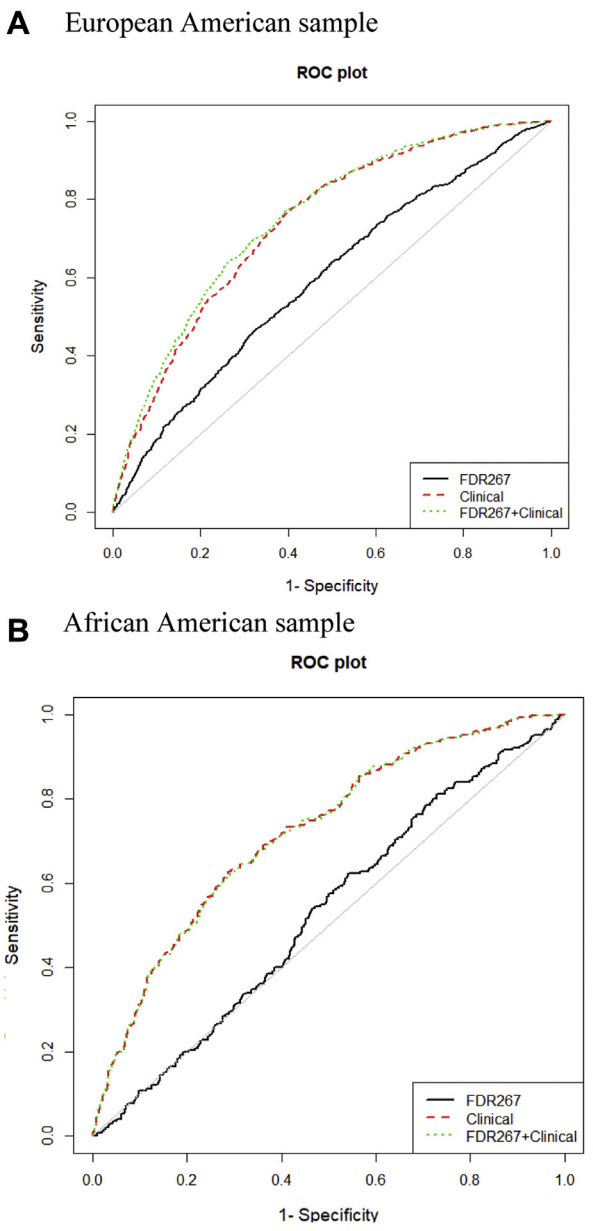

Figure 2. Receiver-operator curve (ROC) plots of 3 models (genetic FDR_{267} risk only, clinical risk only, and combined genetic FDR_{267} risk + clinical risk model) in the (**A**) European American sample and (**B**) African American sample. FDR_{267}, false discovery rate 267-marker genetic risk score.

FDR_{267} was built from variants evaluated by the 2017 UK Biobank GWAS meta-analysis for CAD. There are multiple strategies to filter out nonrelevant SNPs when building a GRS. These include, but are not limited to thresholding by significance, linkage disequilibrium, effect size, and biological significance.[8,18,19] Traditionally, only independent SNPs that have reached a significance threshold of $P < 5 \times 10^{-8}$ are considered to be statistically significant for the model after Bonferroni correction. However, the stringency of this threshold risks

Table 3. Areas under the curve of ROCs for 3 models in the European and African American samples

Model	European AUC (95% CI)	African AUC (95% CI)
FDR_{267} genetic risk only	0.60 (0.58-0.62)	0.53 (0.49-0.56)
Clinical risk only	0.74 (0.72-0.76)	0.72 (0.69-0.75)
Clinical risk plus FDR_{267}	0.75 (0.74-0.77)	0.72 (0.69-0.75)

AUC, area under the curve; CI, confidence interval; FDR_{267}, false discovery rate 267-marker genetic risk score; ROC, receiver-operator curve.

excluding SNPs with smaller, but real, effects on disease risk. Indeed, when GRSs are built solely from SNPs that reach this level of significance, they are only able to explain 10% of CAD heritability.[19] Therefore, we sought to expand the SNP selection by filtering SNPs by an FDR (< 5%) approach. The 304 independent SNPs that reach an FDR < 5% have been shown in the UK Biobank cohort to explain 21.2% of CAD heritability.[5]

When tested in the ARIC European sample, a higher burden of genetic risk measured by FDR_{267} was indeed associated with CAD and could predict incident CAD. Individuals in the top quintile of genetic risk had an approximately 2-fold increase in CAD risk compared with those in the lowest quintile (HR, 1.89), an effect comparable to that conferred by a positive family history (HR, 1.72). Of note, there was no significant difference in risk discrimination between genetic risk assessed by FDR_{267} and that by family history. Although FDR_{267} is associated with self-reported family history, its effect on CAD risk was not significantly attenuated when adjusting for family history (HR, 1.29; 95% CI, 1.20-1.38). Therefore, FDR_{267} may capture components of an individual's genetic risk for CAD that cannot be explained through family history.[20]

Compared with a model with Framingham risk factors alone, inclusion of FDR_{267} improved discrimination of CAD cases from controls in Europeans ($\Delta AUC = 0.0112$, $P = 0.0002$). Yet it did not add predictive value to the model. The modest increase in the C-index ($\Delta C = 0.0159$) did not reach statistical significance. This is possibly because a large proportion of the genetic risk measured by FDR_{267} is already, indirectly, being captured by baseline clinical variables. Indeed, FDR_{267} is significantly associated with multiple Framingham risk factors (ie, total and HDL cholesterol, systolic blood pressure, and type 2 diabetes). Moreover, many of the SNPs in FDR_{267} are also implicated in GRSs for the clinical risk factors.[21-23] Nonetheless, the HR associated with FDR_{267} is not significantly attenuated when correcting for clinical risk factors: HR, 1.27 (95% CI, 1.18-1.36) vs 1.32 (95% CI, 1.26-1.38). It is also likely that our sample size limits further clarification of this issue.

These results suggest modest utility of GRS testing in the 45- to 64-year-old population, for whom there are already well-validated clinical risk models.[2] There is overlap between information provided by assessing pertinent risk phenotypes prevalent in this age group (ie, type 2 diabetes, dyslipidemia, and hypertension) and that measured by FDR_{267}. However, there may be greater value of GRS testing in early screening for high-risk individuals. The low prevalence of risk phenotypes in a young population makes CAD risk assessment difficult.[24] However, this is not to say that certain individuals do not possess high baseline genetic risk for CAD. In fact, our score was able to identify individuals at 2-fold increased risk

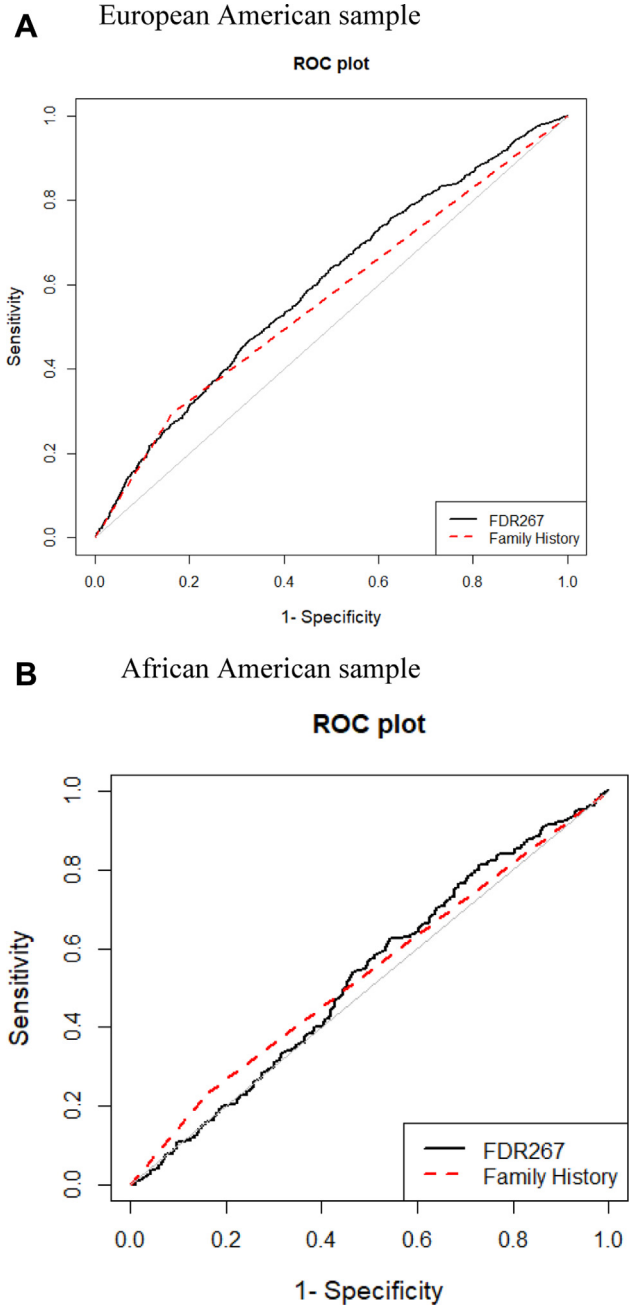

Figure 3. ROC plots of genetic FDR_{267} risk and family history model in the (**A**) European American sample and (**B**) African American sample. FDR_{267}, false discovery rate 267-marker genetic risk score; ROC, receiver-operator curve.

Table 4. C-indices for 3 models in the European and African American participants

Model	European C-index (95% CI)	African C-index (95 % CI)
FDR_{267} genetic risk only	0.60 (0.56-0.64)	0.54 (0.48-0.60)
Clinical risk only	0.72 (0.70-0.75)	0.75 (0.70-0.80)
Clinical risk plus FDR_{267}	0.74 (0.72-0.77)	0.75 (0.70-0.80)

CI, confidence interval; FDR_{267}, false discovery rate 267 marker genetic risk score.

without considering any clinical risk factors. Early identification of such individuals and targeting lifestyle or medical interventions might prove useful in mitigating CAD risk.[7,8]

Our results also show that compared with European subjects, FDR_{267} is weakly associated with CAD and has less predictive value for incident CAD in African Americans. Although the lack of statistical significance could be explained by an underpowered sample, there is nonetheless a consistent pattern of less robust evaluation metrics for CAD risk in the African American sample. Among Framingham risk factors, FDR_{267} was significantly associated only with systolic blood pressure in the African American sample. The strong association of FDR_{267} with lipid phenotypes in the European sample was not observed in the African American sample.

Haplotype variability, Eurocentric content of SNP genotyping arrays, and SNP ascertainment bias have all been suggested as reasons why GRSs are misestimated for individuals of African descent.[25-27] Indeed, effect allele frequencies and thus effect estimates for lipid phenotypes were shown to be imperfectly correlated between white and African groups in the Million Veteran Program study.[22] The UK Biobank population consists predominantly of Europeans (94.6%), with only 1.6% of the cohort being black or black British.[28,29] With such a discrepancy between the recruitment of the 2 ethnicities, it would follow that our GRS is biased toward the most represented ethnicity. Our results highlight the importance in considering ethnic diversity when developing risk modelling tools.

Study limitations

The main limitations of this study include our inability to assess FDR_{267} in other ethnic groups and the likelihood that polygenic risk scores comprising a larger number of variants would show better clinical performance. A previous 25-SNP GRS was shown in a multi-ethnic sample of 8556 participants to have a consistent association with CAD across Europeans, South Asians, Southeast Asians, and Arabs, but similar to our study, it was not significant in Africans.[30] As with FDR_{267}, addition of the 25-SNP GRS to clinical risk factors did not markedly improve CAD risk prediction.[30] Very recently, extremely large GRSs have been constructed using millions of SNPs, almost all of which are not individually significantly associated with CAD risk.[18] These enormous and complex polygenic scores seem to better predict CAD status, with significant ORs between high- and low-risk scores in the range of 3 to 4.[18] These "mega" or "meta" GRSs also appear to substantially improve discrimination over family history and clinical variables.[18] If an inexpensive laboratory test of such mega-GRSs can be developed, they might have potential clinical utility.

Conclusions

Our GRS was significantly associated with CAD and provided modest predictive utility for incident CAD. Despite comparable predictive power with family history and improved ability to discriminate prevalent cases of CAD when added to a model with traditional risk factors, FDR_{267} does not improve on risk assessment. The clinical use of FDR_{267} is further limited by its inconsistent assessment of risk in a non-European population.

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjco.2019.01.003.