A Genetic Risk Score Is Associated With Incident Cardiovascular Disease and Coronary Artery Calcium

The Framingham Heart Study

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Background—Limited data exist regarding the use of a genetic risk score (GRS) for predicting risk of incident cardiovascular disease (CVD) in US-based samples.

Methods and Results—By using findings from recent genome-wide association studies, we constructed GRSs composed of 13 genetic variants associated with myocardial infarction or other manifestations of coronary heart disease (CHD) and 102 genetic variants associated with CHD or its major risk factors. We also updated the 13 single-nucleotide polymorphism (SNP) GRSs with 16 SNPs recently discovered by genome-wide association studies. We estimated the association, discrimination, and risk reclassification of each GRS for incident cardiovascular events and prevalent coronary artery calcium (CAC). In analyses adjusted for age, sex, CVD risk factors, and parental history of CVD, the 13 SNP GRSs were significantly associated with incident hard CHD (hazard ratio, 1.07; 95% CI, 1.00–1.15; $P=0.04$), CVD (hazard ratio per allele, 1.05; 95% CI, 1.01–1.09; $P=0.03$), and high CAC (defined as $>75^{th}$ age- and sex-specific percentile; odds ratio per allele, 1.18; 95% CI, 1.11–1.26; $P=3.4\times10^{-7}$). The GRS did not improve discrimination for incident CHD or CVD but led to modest improvements in risk reclassification. However, significant improvements in discrimination and risk reclassification were observed for the prediction of high CAC. The addition of 16 newly discovered SNPs to the 13 SNP GRSs did not significantly modify these results.

Conclusions—A GRS composed of 13 SNPs associated with coronary disease is an independent predictor of cardiovascular events and of high CAC, modestly improves risk reclassification for incident CHD, and significantly improves discrimination for high CAC. The addition of recently discovered SNPs did not significantly improve the performance of this GRS. **(*Circ Cardiovasc Genet*. 2012;5:113-121.)**

Key Words: genetics ■ single nucleotide polymorphisms ■ cardiovascular disease ■ coronary heart disease ■ risk prediction ■ reclassification

Current cardiovascular disease (CVD) risk prediction models, based on conventional risk factors, perform well and are frequently used to guide treatment decisions. However, nearly 15% of individuals who develop CVD have few risk factors and are deemed to be low risk, based on such models.[1] In addition, identifying higher-risk patients from the many who are deemed intermediate risk could also help target individuals for preventative treatment. Efforts to improve CVD risk prediction are needed, given that the first manifestation may be sudden death and that CVD is preventable. Although the familial nature of CVD has been documented for many years[2–4] and the addition of family history has improved risk prediction,[5,6] the genetic variants responsible for the increased familial risk were, until recently, unknown. Genome-wide association studies (GWASs) have uncovered several common genetic variants (single-nucleotide polymorphisms [SNPs]) that are robustly associated with myocardial infarction (MI), coronary heart disease (CHD), or CVD risk factors, including dyslipidemia and hypertension, and have been replicated in multiple independent samples.[7] The

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identification of these genetic variants provides an opportunity to evaluate whether addition of a genetic risk score (GRS) to risk models may improve predictive performance or lead to meaningful changes in risk classification. Recent studies evaluating the utility of adding genetic variants identified in GWASs to cardiovascular risk prediction have provided conflicting results about the utility of genetic information for CVD risk prediction.[8–10] These studies have focused on SNPs reported in GWASs before 2011 and have been limited to female health professionals[8] or to individuals from Scandinavian countries who may not be entirely generalizable to community-dwelling men and women in the United States.[10] Despite the increase in direct-to-consumer testing for genetic variants for CVD and other chronic diseases in the United States,[11] there are limited data evaluating the utility of adding genetic variants to CVD risk prediction in a US community-based sample of both men and women, in which such information would ultimately be used.

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Accordingly, we sought to evaluate whether a GRS composed of genetic variants from recent GWASs of MI and CHD that have been reported in other GRS studies, and variants identified in GWASs of CVD risk factors, is associated with incident CHD, incident CVD, and high coronary artery calcium (CAC), a measure of subclinical atherosclerosis,[12–15] in Framingham Heart Study participants. We specifically sought to evaluate whether the addition of a GRS improved discrimination or risk reclassification in this community-based sample.

Methods

Study Sample

In 1948, the Framingham Heart Study enrolled 5209 individuals into a longitudinal cohort study. Original cohort participants were examined approximately every 2 years. Subsequently, in 1971, the Framingham Offspring Study enrolled 5124 children and spouses of the children of the original cohort. In 2002, the Framingham Third Generation study enrolled 4095 children of the Offspring cohort. The study design and entry criteria for each cohort have been previously described.[16–18] Participants of the Framingham Offspring Study were evaluated approximately every 4 years. The sample included participants of the Offspring Cohort (baseline examinations 1 and 3, N=4073 individuals), as previously described,[19] as well as additional data from the 6th Offspring examination (N=301 individuals). Of these individuals, 847 were excluded for lack of DNA (refused to participate [n=795] or poor quality of DNA [n=52]) and an additional 488 participants were excluded for incomplete genotype data or other covariates. The final study sample size that was analyzed for incident events was 3014 participants contributing 6924 person-examination cycles. Of these participants, 1164 also participated in a Multi-Detector Computed Tomography (MDCT) substudy of CAC. Details of the MDCT substudy have been previously described.[20]

In a separate analysis of CAC, we analyzed participants from the Third Generation cohort who were also included in the MDCT substudy. A total of 2106 Third Generation participants underwent cardiac CT for evaluation of CAC as a measure of subclinical atherosclerosis. Of these participants, 42 were excluded for prevalent CVD and 102 were excluded for missing covariate data. The total sample analyzed for CAC from the Third Generation MDCT substudy was 1962. Although the Third Generation sample does not contain the same individuals as the Offspring sample previously described, individuals from these 2 samples are genetically related (ie, individuals in the Third Generation sample are the children of individuals in the Offspring sample). This study was approved by the institutional review board at Boston University, and written informed consent was obtained from all participants.

Incident CVD Events

Based on previously described Framingham Heart Study criteria, the primary outcome was *incident general CVD*, defined as cardiovascular death, MI, coronary insufficiency, angina pectoris, stroke, transient ischemic attack, intermittent claudication, or congestive heart failure during follow-up.[19] We also evaluated a more restrictive outcome of *hard CHD*, defined as coronary death or MI and denoted as "hard CHD" herein. All events were adjudicated by a panel of 3 physicians, including at least 1 cardiologist, using prespecified diagnostic criteria.

CAC Measurements

Participants underwent a chest scan on an 8-slice MDCT scanner (LightSpeed Ultra, General Electric; Milwaukee, WI) for quantification of CAC, as previously described.[20] Briefly, 48 contiguous 2.5-mm-thick slices were acquired, and each participant underwent a second scan after briefly being repositioned on the table. By using a dedicated off-line workstation (Aquarius, Terarecon; San Mateo, CA), each image was evaluated for the presence and amount of CAC by an experienced reader. We defined a *calcified lesion* as an area $\geq$3 connected pixels, with an attenuation $>$130 Hounsfield units, and an Agatston score was calculated, as previously described.[21]

Cardiovascular Risk Factors

Each participant underwent a routine medical history, a physical examination, and a fasting blood draw at each examination. By using conventional methods, total cholesterol and high-density lipoprotein (HDL) cholesterol levels were determined on fasting blood samples. Cigarette smoking and a complete medication history were obtained by participant interview. Blood pressure was determined in the left arm using a mercury sphygmomanometer in subjects who had been seated for at least 5 minutes. *Adult-onset diabetes mellitus* was defined as a fasting plasma glucose level $\geq$126 mg/dL or treatment with a hypoglycemic agent and/or insulin. *Premature parental occurrence of CVD* was defined as the occurrence of a validated parental CVD event before the age 65 years. At the time of this study, all parents in the original cohort were $>$65 years, allowing for complete ascertainment of parental history of CVD in offspring.

Construction of the GRS

We created 2 GRSs for primary evaluation. The 13-SNP GRS was based on SNPs reported in a recent GWAS of CHD or MI,[22–28] and consisted of 13 SNPs that have been robustly associated with this outcome ($P<5\times10^{-8}$) in a discovery sample with subsequent replication in 1 or more additional independent samples. These SNPs have been included in recent GRS studies of CHD and CVD. Details about these SNPs, listed under the trait "MI," are provided in online-only Data Supplement Table I. Participants were genotyped for 12 of these SNPs on an Illumina platform. The minimum call rate was 99.8%, and all SNPs were in Hardy-Weinberg equilibrium. Strand orientation was determined by comparing alleles and minor allele frequencies with those in the initial discovery report. For the *rs3798220* SNP in the *LPA* locus, we used the genotype from the Affymetrix 500K chip +50K molecular inversion probe chip genotypes, available from the SNP Health Association Resource. All SNPs in the final gene score were uncorrelated ($r^2<0.3$).

We also created a less restrictive GRS for evaluation, based on available GWASs of major CVD risk factors, that included 102 SNPs (13 CHD/MI SNPs from the 13-SNP GRS, in addition to 89 SNPs associated with the following cardiovascular risk factors (see Online Only Data Supplement Table I): low-density lipoprotein cholesterol, HDL cholesterol, triglycerides, diabetes (or fasting plasma glucose), systolic and diastolic blood pressured, and C-reactive protein). This score consisted of 85 (83.3%) directly genotyped SNPs. The remaining SNPs were imputed using HapMap

data as part of the SNP Health Association Resource, as previously described,[29] and had an imputation quality >0.65. All 102 SNPs in this final GRS were uncorrelated ($r^2<0.3$). For any correlated SNPs, a single SNP was selected for a given genomic region by giving preference to genotyped SNPs over imputed SNPs.

Each GRS was generated as a count of the risk alleles for each of the included SNPs (ie, 2 for homozygous, 1 for heterozygous, and 0 for absence of a risk allele), for total scores ranging from 0 to 26 and from 0 to 204 for the 13-SNP GRS and the 102-SNP GRS, respectively. In secondary analyses, we also computed a weighted 13-SNP GRS using the point estimate for the β coefficient reported in the original report as the weight for each risk SNP, and we also conducted a secondary analysis to evaluate a GRS that excluded the *LPA* SNP. Hazard ratios (HRs) for incident events, using the weighted score or after exclusion of the *LPA* SNP, did not differ substantially from the primary analysis and are, therefore, not presented.

After initial submission of this article, 17 novel, replicated genome-wide significant SNPs for MI and CHD were reported in 2011 from 2 large-scale GWASs.[30,31] Therefore, in secondary analyses, we have provided an updated version of our 13-SNP GRS incorporating these variants (Online Only Data Supplement Table II). We excluded 1 of these 17 SNPs for not being in Hardy-Weinberg equilibrium ($P=2\times10^{-25}$) and for a suboptimal call rate (90%), leaving a total of 16 new SNPs and the present results for this updated 29-SNP GRS (genotypes for 10 of these SNPs were imputed using HapMap data). For these additional analyses, we excluded an additional 127 individuals who did not have complete genotypes for these additional SNPs, reducing our sample to 2887 participants (1331 men and 1556 women).

Statistical Analysis

Kaplan-Meier rates were calculated for hard CHD and CVD at 10 years of follow-up. For incident events, we used Cox proportional hazard models to estimate the association between the GRSs and incident events at 10 years. Follow-up began at the baseline examination, and participants were censored at death, loss to follow-up, the next baseline examination, or 12 years, whichever was earlier. Baseline examinations were considered as examinations 1, 3, and 6, and follow-up windows were pooled. Each participant contributed a mean of 2.3 person-examination cycles. This method of pooling person-examinations has provided valid estimates of association similar to using time-dependent Cox regression, as demonstrated by D'Agostino et al.[32] Separate models were fit for each outcome (hard CHD and CVD). Three covariate adjustments were used: age and sex (model set 1); age, sex, and cardiovascular risk factors, including total cholesterol, HDL cholesterol, presence of diabetes, systolic blood pressure (and antihypertensive treatment), and cigarette smoking (model set 2); and age, sex, cardiovascular risk factors, and parental history of CVD (model set 3). For analyses using CAC as an outcome, we used logistic regression to estimate the association between the GRS and high CAC. *High CAC* was defined as Agatston score greater than the age- and sex-specific 75th percentile in a healthy reference population (free of clinically apparent CVD or CVD risk factors). Given that CAC is highly correlated with increasing age and male sex, we used an age- and sex-specific percentile based outcome measure to estimate whether the GRS improved discrimination for accelerated atherosclerosis for a given age and sex stratum. As previously reported, the 75th percentile Agatston score cutoffs for the <45, 45 to 54, 55 to 64, 65 to 74, and ≥75 years age groups were 0, 28, 177, 582, and 736 for men, respectively; and 0, 0, 26, 43, and 356 for women, respectively.[33]

All analyses were also performed accounting for the family structure of the sample. Incident event analyses were performed using a Cox regression with a frailty term clustering on family, and CAC logistic regression analyses were performed using generalized estimating equations clustering on family. Results adjusting for family structure did not materially change effect estimates or SEs and are, therefore, not shown. The HRs and 95% CIs are presented for each model.

To evaluate whether the addition of a GRS improved model performance, we evaluated changes in discrimination, as quantified by the C statistic, integrated discrimination improvement (IDI), and continuous net reclassification improvement (NRI). In addition, we evaluated changes in risk reclassification, measured by the traditional NRI with 3 risk categories (0%–6%, 6%–20%, and >20%), as previously described.[34] Furthermore, we calculated calibration statistics for models with and without GRS using the Nam and D'Agostino modification of the Hosmer and Lemeshow χ^2 statistic.[35] Only the primary 13-SNP GRS and the updated 29-SNP GRS were evaluated in these analyses, because the 102-SNP GRS was not a significant predictor of incident hard CHD or CVD events. To optimize sample size given the missing data on family history status (only 1560 participants had a complete validated parental history of CVD from both parents), we assumed that parental history was missing at random and used multiple imputation based on the clinical covariates and GRS to impute family history. Changes in performance measures with the addition of the GRS were evaluated across sets of nested models that included age and sex (model set 1); age, sex, and cardiovascular risk factors, including total cholesterol, HDL cholesterol, presence of diabetes, systolic blood pressure (and antihypertensive treatment), and cigarette smoking (model set 2); and age, sex, cardiovascular risk factors, and parental history of CVD (model set 3). For risk reclassification, we calculated the NRI and IDI for the addition of the GRS to a clinical model that included age, sex, and CVD risk factors. The following predicted risk cutoffs were used for these analyses: 0% to 6%, 6% to 20%, and >20%. We reported the NRI as a summary measure and separately for events and nonevents. We also used a novel continuous NRI that is independent of prespecified risk cutoffs and maximizes statistical power.[36] For this novel metric, any increase in predicted risk among those who develop events and any decrease among those who do not develop events correspond to improved reclassification. The CIs for NRI and IDI were computed using bootstrap with 999 replications. All analyses were performed in SAS 9.1 (SAS Institute, Cary, NC). A 2-tailed $P<0.05$ was used to indicate statistical significance.

Results

We included 1388 men (3168 person-examination cycles) and 1626 women (3756 person-examination cycles), with a mean age of 49±10 years, in the study sample. The median follow-up was 11 years. The follow-up rate was >85% at 12 years. A parental history of CVD was estimated to be 26%. Clinical characteristics of the sample for the incident CVD event analysis are described in Table 1. During follow-up, there were 539 CVD events and 182 hard CHD events. The mean 13 SNP GRS was 12.7±2.1 risk alleles, and the mean 102 SNP GRS was 108.2±6.3 risk alleles.

Association of GRSs With Incident CVD Events

After adjustment for CVD risk factors and parental history of CVD, the 13 SNP GRSs composed of risk variants for MI/CHD were associated with incident hard CHD (HR per risk allele, 1.07; 95% CI, 1.00–1.15; $P=0.04$) and incident CVD (HR per risk allele, 1.05; 95% CI, 1.0–1.09; $P=0.03$) events (Table 2). A total of 102 SNP GRSs composed of the 13 coronary disease variants and an additional 89 variants associated with several cardiac risk factors were not associated with incident CVD (HR per risk allele, 1.01; 95% CI, 1.01–1.02; $P=0.54$) or hard CHD events (HR, 1.01; 95% CI, 0.99–1.03; $P=0.48$).

Table 1. Characteristics of Offspring Participants in the Incident Events Analysis

Characteristics	Values
No. of participants*	3014
Median follow-up, y	11
Age, y	49±10.9
Male sex, %	46
Systolic blood pressure, mm Hg	124±16.7
Total cholesterol, mg/dL	206±38.2
HDL cholesterol, mg/dL	52±15.5
Smoking, %	26
Diabetes, %	5
HTN treatment, %	14
Parental occurrence of CVD, %	26
Kaplan-Meier event rate at 10 y of follow-up, % (No.)	
Hard CHD	2 (182)
CVD	7 (539)

All data are presented as mean±SD unless otherwise specified.

HDL indicates high-density lipoprotein; HTN, hypertension; CVD, cardiovascular disease; CHD, coronary heart disease.

*Data are based on 3168 person-examination cycles from 1388 men and 3756 person-examination cycles from 1626 women.

Changes in Discrimination, Calibration, and Risk Reclassification With the Addition of a 13 CHD/MI SNP GRS for the Prediction of Hard CHD and CVD Events

Improvements in discrimination were assessed for the addition of the 13 SNP CHD/MI GRSs to 3 separate models predicting risk of hard CHD and CVD (Table 3). First, we examined whether knowledge of a GRS with limited information improved the C statistic. The addition of the GRS to a model including only age and sex (C statistic, 0.732) offered marginal improvement (C statistic with GRS, 0.737) for incident CHD (model 1, Table 3). We also constructed a model predicting hard CHD that included age, sex, and cardiovascular risk factors. In this model, the C statistic increased marginally from 0.819 to 0.822 with the addition of the GRS (model 2, Table 3). Similar changes in the C statistic were seen when the GRS was added to a model, including the previously described risk factors and parental history of CVD (change in C statistic, 0.002; model 3, Table 3). Results did not materially change when the outcome was incident CVD (Table 3). All models with or without the CHD/MI GRS were well calibrated (data not shown).

Table 3. C Statistics for the Addition of a Coronary Disease GRS to Models Predicting 10-Year Risk of CVD or CHD

	CVD at 10 y		Hard CHD at 10 y	
Model	C Statistic	95% CI	C Statistic	95% CI
1				
Age and sex	0.728	0.706–0.750	0.732	0.696–0.768
+GRS	0.730	0.708–0.751	0.737	0.701–0.773
2				
Age, sex, cigarette smoking, total cholesterol, HDL, systolic blood pressure (and treatment), and diabetes	0.786	0.768–0.805	0.819	0.791–0.847
+GRS	0.786	0.768–0.805	0.822	0.794–0.850
3				
Age, sex, cigarette smoking, total cholesterol, HDL, systolic blood pressure (and treatment), diabetes, and parental history of CVD	0.787	0.769–0.806	0.820	0.792–0.848
+GRS	0.788	0.769–0.806	0.822	0.795–0.851

GRS indicates genetic risk score; CVD, cardiovascular disease; CHD, coronary heart disease; HDL, high-density lipoprotein.

In an assessment of risk reclassification, the addition of the CHD/MI GRS to a model including age, sex, and CVD risk factors did not lead to statistically significant changes in the NRI for incident hard CHD or CVD at 10 years using standard risk categories (Table 4). Because an increase in the C statistic may not be sensitive as a measure of improvement in model performance and the NRI is dependent on the risk categories selected, we also evaluated the IDI and a novel

Table 2. The HRs for the Association Between a GRS (per Allele) and Incident Events

GRS	No. of SNPs	Age- and Sex-Adjusted HR (95% CI)	*P* Value	Risk Factor–Adjusted HR (95% CI)*	*P* Value	Fully Adjusted HR (95% CI)†	*P* Value
Incident hard CHD							
1	13	1.09 (1.02–1.17)	0.02	1.07 (1.00–1.15)	0.04	1.07 (1.00–1.15)	0.04
2	102	1.02 (0.99–1.04)	0.14	1.01 (0.99–1.03)	0.48	1.01 (0.99–1.03)	0.47
Incident CVD							
1	13	1.06 (1.02–1.10)	0.006	1.05 (1.01–1.09)	0.03	1.05 (1.01–1.09)	0.03
2	102	1.01 (1.00–1.03)	0.07	1.01 (1.00–1.02)	0.54	1.00 (0.99–1.02)	0.52

HR indicates hazard ratio; GRS, genetic risk score; SNP, single-nucleotide polymorphism; CHD, coronary heart disease; CVD, cardiovascular disease.

*Adjusted for age, sex, total cholesterol, high-density lipoprotein, presence of diabetes, systolic blood pressure (and antihypertensive treatment), and cigarette smoking.

†Adjusted for age, sex, total cholesterol, high-density lipoprotein, presence of diabetes, systolic blood pressure (and antihypertensive treatment), cigarette smoking, and parental history of CVD.

Table 4. Risk Reclassification for the Addition of the Coronary Disease GRS to a Model Predicting 10-Year Risk of Hard CHD

Model	NRI	95% CI	Event/Nonevent NRI	IDI	95% CI	ContNRI	95% CI
1							
Age and sex (reference model)	. . .	. . .	. . .	. . .	. . .	. . .	. . .
+GRS	0.043	(−0.003 to 0.088)	0.041/0.002	0.001	(0.001 to 0.002)	0.22	(0.057 to 0.377)
2							
Age, sex, and CVD risk factors (reference model)	. . .	. . .	. . .	. . .	. . .	. . .	. . .
+GRS	0.001	(−0.040 to 0.039)	0.0003/0.0005	0.001	(−0.001 to 0.003)	0.17	(0.010 to 0.328)
3							
Age, sex, CVD risk factors, and parental history (reference model)	. . .	. . .	. . .	. . .	. . .	. . .	. . .
+GRS	−0.01	(−0.052 to 0.033)	−0.011/0.001	0.001	(−0.001 to 0.003)	0.19	(0.024 to 0.344)

NRI is calculated for the addition of the GRS to a reference model with the following risk cutoffs for 10-year risk of hard CHD: low (<6%), intermediate (6%–20%), and high (>20%).

GRS indicates genetic risk score; CHD, coronary heart disease; NRI, net reclassification index; IDI, integrated discrimination index; contNRI, continuous cutoff independent form of the NRI; CVD, cardiovascular disease.[36]

continuous NRI metric that is independent of risk categories and maximizes statistical power. Based on the IDI, the improvement in separation between events and nonevents was minimal for all models considered (Table 4). By using the continuous NRI metric, the addition of a GRS to a model predicting 10-year risk of hard CHD, including age, sex, and cardiovascular risk factors, led to a statistically significant, but modest, improvement in risk reclassification (NRI, 0.17; 95% CI, 0.01–0.33); these results were not affected when parental history of CVD was included in the baseline model (NRI, 0.19; 95% CI, 0.02–0.34).

Association Between a GRS and CAC and Improvements in Discrimination for High CAC

We examined the association of the 13 SNP CHD/MI GRSs with high CAC in the 1164 Offspring participants who were included in the incident analysis and also underwent an MDCT scan for assessment of CAC. In fully adjusted models, the odds ratio (OR) per allele of GRS for the presence of high CAC was 1.18 (95% CI, 1.11–1.26; $P=3.4\times10^{-7}$). There was a 2-fold increase in the odds of high CAC for individuals in the highest GRS tertile compared with those in the lowest tertile (OR, 2.04; 95% CI, 1.48–2.83) (Figure A). Moreover, the addition of the GRS to a model including age, sex, and CVD risk factors led to changes in the C statistic (change in C statistic, 0.03, from 0.64–0.67). The observed improvement in discrimination was not affected when parental history of CVD was included in the baseline model. The addition of the GRS to a model including age, sex, and cardiac risk factors led to improvements in both the IDI ($P=1.1\times10^{-7}$) and the continuous NRI (NRI, 0.29; 95% CI, 0.17–1.41; $P=2.7\times10^{-7}$) for the prediction of high CAC.

In a separate analysis of 1962 participants of the generation 3 cohort who underwent CAC scoring, we also observed a marked increase in the prevalence of high CAC across tertiles of the 13 SNP GRSs (OR, 1.41 [95% CI, 1.06–1.89] for highest versus lowest GRS tertile), which persisted after adjustment for cardiovascular risk factors (Figure 1B). The addition of the 13 SNP GRSs to a model including age, sex, and cardiac risk factors for prediction of high CAC in generation 3 participants led to improvement in the C statistic (change in C statistic, 0.05, from 0.66–0.71), the IDI ($P=0.001$), and the NRI (0.13; 95% CI, 0.03–0.24; $P=0.01$).

In analyses using the 102 SNP GRSs, the GRS remained modestly associated with high CAC in fully adjusted models (OR per allele, 1.03; 95% CI, 1.01–1.05; $P=0.003$), but we noted only marginal improvement in discrimination for high CAC (change in C statistic, 0.01, from 0.64–0.65).

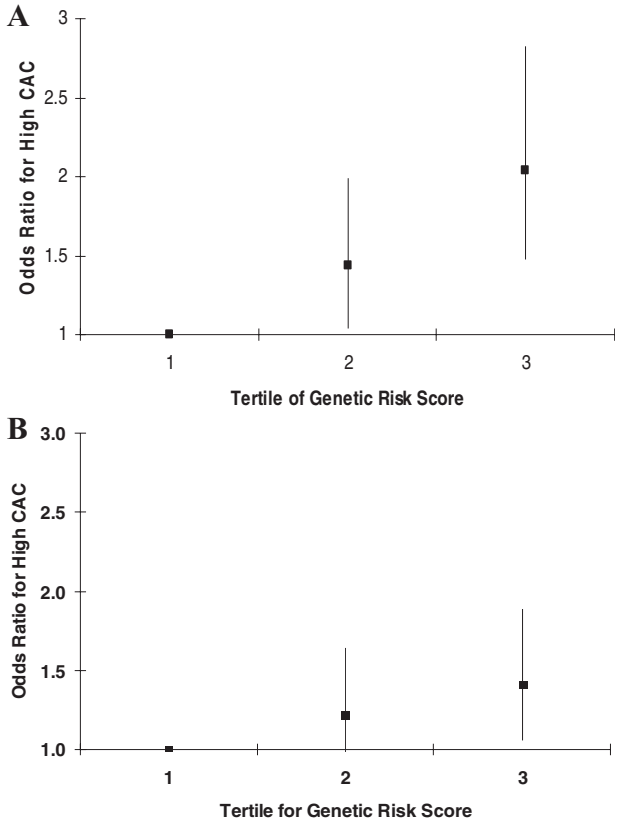

Figure. Fully adjusted odds ratios for high CAC in Offspring participants included in the incident events analysis (**A**) and in generation 3 participants (**B**).

Impact of Adding 16 Recently Discovered SNPs to the 13 SNP GRSs for Prediction of CVD, CHD, and CAC

To evaluate the impact of adding 16 recently discovered SNPs to the GRS, we created a new 29-SNP GRS. The mean score was 24.2±3.2 risk alleles. After adjustment for age, sex, cardiovascular risk factors, and parental history, the new 29-SNP GRS was associated with CHD (HR per allele, 1.06; 95% CI, 1.01–1.11; $P=0.02$) but was not associated with CVD (HR per allele, 1.00; 95% CI, 0.98–1.03; $P=0.86$). However, the 29-SNP GRSs remained significantly associated with CAC in offspring (OR per allele, 1.07; 95% CI, 1.03–1.12; $P=7.5\times10^{-4}$) and generation 3 samples (OR per allele, 1.04; 95% CI, 1.01–1.08; $P=0.01$) after adjustment for age, sex, and cardiovascular risk factors.

With respect to discrimination, the addition of the 16 novel SNPs to the original model, including age, sex, cardiovascular risk factors, and 13 SNP GRSs, did not lead to any significant improvement for CVD (no change in C statistic). For CHD, we noted a marginal improvement in C statistic (change in C statistic, 0.001). The addition of parental history to the baseline models did not affect these results. Last, for prediction of high CAC, the addition of the 16 SNPs to a baseline model, including age, sex, cardiovascular risk factors, and the 13 SNP GRSs, did not significantly improve the C statistic.

For risk reclassification, results for reclassification metrics using the 29-SNP GRS (data not shown) were similar to the results for the 13-SNP score data presented in Table 4.

Discussion

In this study of Framingham Heart Study participants, a GRS composed of 13 SNPs from recent GWASs of MI and other CHDs is significantly associated with incident hard CHD and incident CVD, even after adjustment for traditional cardiovascular risk factors and parental history of CVD. We found that, for each risk allele, there was a 5% increase in the risk of incident hard CHD or incident CVD at 10 years. In contrast, a more complex 102-SNP GRS, including SNPs associated with CVD and CVD risk factors, was not significantly associated with either incident hard CHD or incident CVD, suggesting that the addition of genetic variants for cardiovascular risk factors already captured in risk prediction models may be of limited utility. We also report that the 13-SNP GRS was significantly associated with increased CAC, an important subclinical marker of coronary artery atherosclerosis, which is also an important predictor of future cardiovascular events.[12–15] This represents a novel finding with potentially important mechanistic implications for the role of these genetic variants in CVD.

Despite these significant associations, the addition of the GRS to standard risk models did not lead to any significant improvements in discrimination or risk reclassification for incident CVD but did lead to a modest, significant improvement in 1 index of risk reclassification for incident hard CHD. On the contrary, the addition of a GRS to models for prediction of high CAC did lead to significant improvements in discrimination, suggesting that the GRS appears to be predictive for the presence of accelerated atherosclerosis.

We also updated our GRS with 16 novel SNPs recently discovered in GWASs of MI or CHD. The addition of these 16 SNPs led to marginal improvements in prediction, discrimination, or risk reclassification for CVD. The absence of improvement in prediction with the larger SNP score may be due to the low effect sizes of these additional SNPs. Alternatively, these SNPs may not be as specific for the more general CVD and CHD outcomes (which include other vascular events), compared with the more restrictive MI outcome for which they were discovered. In addition, not all the SNPs were associated individually with hard CHD or CVD (results not shown) in our sample. Future studies will need to address whether future iterations of a GRS incorporating additional genetic risk variants, including both common and low-frequency variants, would lead to clinically useful improvements in clinically relevant metrics of risk prediction and whether such information will be most useful for prediction in children, young adults, or older individuals.

Several studies[8–10,26,37–45] have previously incorporated genetic information for the purpose of risk prediction of CVD. However, several of these studies relied on genetic variants from the candidate gene era, many of which have failed further replication and may represent largely spurious false-positive genetic associations, limiting the validity of many prior GRSs.[46,47] Only a few studies have evaluated the utility of adding GWAS-based genetic variants to risk prediction models. Talmud et al[43] reported that the addition of 9p21 variants led to significant improvements in reclassification; however, these findings have not been confirmed by others.[42] Kathiresan et al[40] created a GRS using SNPs strongly associated with lipid levels; this GRS was associated with a 15% increase in CHD risk per lipid-associated SNP allele but did not improve discrimination over and above traditional risk factors and showed only modest improvement in risk reclassification. Paynter et al[8] created 2 separate risk scores based on SNPs identified from GWASs of CVD and cardiovascular risk factors. After adjustment for risk factors, neither GRS was associated with incident CVD in the Women's Genome Health Study; therefore, further improvements in discrimination and risk reclassification were also not observed. Although our GRS consisted of a similar set of SNPs to that in the study by Paynter et al, several important differences exist between these studies that may explain the disparate results. First, the GRS used in our study was composed primarily of in silico, not imputed, genotypes, and we also included variants in *LPA* that were not included in previous studies. In addition, our community-based population of Framingham Offspring included men and women who may have been at a higher baseline risk for CVD than the relatively young women in the Women's Health Study. Our findings are in agreement with those of a recent study evaluating the utility of a GRS consisting of a similar set of SNPs in a large community cohort of men and women from Finland and Sweden, which demonstrated a significant increase in risk of CVD in individuals in the top GRS quintile but did not improve measures of discrimination or reclassification.[10] Although we found similar associations between the GRS and incident events, the modest improvements we report for discrimination and reclassification confirm that genetic

testing for cardiovascular risk prediction is of limited clinical utility.

Limited functional information exists regarding the novel genetic variants associated with coronary artery disease identified from GWASs. Animal studies have recently increased our understanding of the 9p21 variant by demonstrating that a knockout of the mouse ortholog of the *CDKN2A/2B* locus led to a vascular phenotype of accelerated smooth muscle proliferation.[48] Our findings of marked associations with the GRS and high CAC are, therefore, noteworthy, suggesting that the presence of multiple risk alleles is highly predictive of an increased propensity to coronary atherosclerosis and vascular wall calcification and implying that several risk variants may act via a vascular phenotype captured by CAC.

Thus far, GRSs for the prediction of diabetes,[49] breast cancer,[50] and CVD,[8,10] based on recent GWAS discoveries, have not yielded important improvements in risk prediction. Although this has been seen by some as a failure of the concept of personalized medicine using genomics, the relatively low levels of genetic variance explained by the variants discovered to date suggest that much of the genetic predisposition underlying complex disease remains to be discovered.[51] Simulation studies[52,53] have shown that, for CVD, 100 to 400 common SNPs with modest effect sizes would be needed to improve risk prediction. Fewer SNPs would be needed if a few rare variants with relatively strong effects were also identified. It is, therefore, encouraging that the limited number of genetic variants identified appear strongly associated with clinical events and intermediate phenotypes, such as CAC, and lead to modest improvement in reclassification (for cardiovascular events, using the continuous NRI metric[36]) and discrimination (for high CAC) when added to models that include traditional cardiovascular risk factors. Our results demonstrate that, although major advances have been made in our understanding of the genetics of coronary artery disease and atherosclerosis, genetic screening for CVD is unlikely to be clinically useful at present. However, GWASs with larger sample sizes[54] and other novel approaches, including whole-exome[55] and whole-genome sequencing, are ongoing and will undoubtedly identify additional variants that may improve future iterations of a GRS, leading to clinically useful improvements in risk prediction. In addition, a GRS may also be most useful earlier in the life course, when knowledge of other risk factors is limited.[49] Whether the improvements in prediction at this early age could lead to changes in lifestyle, risk factor development, and outcomes by more aggressive primary prevention strategies remains to be seen. Further studies evaluating the utility of genetic information to predict lifetime risk and the impact of providing such estimates to individuals (including cost-benefit analyses) are required.

Our study has several strengths, including the use of a community-based sample of the US population with a long follow-up and the use of primarily in silico genotyped SNPs. However, several limitations deserve mention. First, the genotype score relied only on the few SNPs discovered from GWASs that likely account for a small proportion of the genetic variance of CVD. Furthermore, the gene score used for most analyses was constructed using a simple allele count instead of a more complex weighted score based on effect sizes. Although we also computed a weighted score based on effect sizes from published reports, this score was not significantly better than the allele count score, suggesting that the effect sizes may not be of adequate precision for the purpose of risk prediction. Second, we did not consider gene-gene and gene-environment interactions in the prediction models because no specific interaction has been robustly identified in large populations. The addition of interactions rigorously identified in large-scale studies could significantly improve genetic risk prediction. Third, although we had $>$500 events for CVD and $>$180 events for CHD, because of the relatively low effect sizes for each allele in the GRS, it is possible that the limited impact of the GRS could be because of the relatively low power of our study in detecting any improvements with the GRS. Further studies evaluating the clinical utility of adding a GRS in large samples of individuals are warranted. Fourth, our sample consisted of predominantly white individuals of European descent, which limited population stratification; however, the results of the GRS may not apply to other races or ethnicities, with different risks for CVD or different allele frequencies.

In summary, we have shown that a GRS composed of 13 SNPs for coronary disease, identified in GWASs, is significantly associated with incident cardiovascular events but provides only marginal incremental information to risk prediction when added to standard cardiovascular risk factors. Nevertheless, the GRS is strongly associated with prevalent high CAC, a marker of subclinical atherosclerosis, and significantly improves the discrimination of individuals for having high CAC, even after consideration of standard risk factors. In addition, we also show that the addition of 16 new SNPs, recently discovered in GWASs of MI and CHD, do not appreciably improve the performance of a GRS in prediction, discrimination, or risk reclassification. Our results suggest that, although genetic information has limited clinical utility currently for the prediction of future events, the variants identified appear to provide incremental information for the presence of accelerated coronary atherosclerosis and calcification. As additional variants explaining more of the genetic variants are identified, future iterations of a GRS will warrant further investigation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Several major discoveries in the genetics of cardiovascular disease (CVD) have been made in recent years. However, whether the addition of genetic information can improve current risk prediction models for CVD (eg, Framingham Risk Score) has not been well established. By using data from >3000 individuals from the Framingham Offspring Study, we demonstrate that a genetic risk score (GRS) composed of 13 genetic variants associated with myocardial infarction is associated with both incident coronary heart disease and CVD. Furthermore, we also show that the GRS is also associated with high coronary artery calcium, a subclinical marker of atherosclerosis. However, the addition of these genetic variants only led to modest improvements to risk assessment when added to the Framingham Risk Score. Our results suggest that the addition of available genetic information does not appreciably improve the assessment of future cardiovascular risk at present. As additional genetic variants are discovered, future iterations of a GRS will require further investigation.