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A Comparison of Basic versus more Complex Definitions of Family History in the Prediction of Coronary Heart Disease: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—To determine whether family history of coronary heart disease (FH) definitions differ in their association with atherosclerotic cardiovascular disease (ASCVD) events.

Patients/Methods—Participants who provided FH data between July 17, 2000 to February 24, 2004 were identified. FH definitions were: any, premature, and a familial-risk-assessment (FRA) tool. Outcomes included coronary heart disease (CHD), stroke, peripheral artery disease, angina, and congestive heart failure. Multivariable-adjusted Cox models examined the association of FH definitions with events. C-statistics and net reclassification improvement (NRI) examined the incremental prognostic contribution of each definition.

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COMPETING INTERESTS

Drs. Patel, Al Rifai, Shea, Blumenthal, Blaha, and McEvoy do not have any disclosures to report.

Results—In 6,200 participants, the proportion of any-FH and premature-FH were 36% and 16%, respectively. Using the FRA, the proportions for weak, moderate, and strong-familial-risk were 20%, 16%, and 20%, respectively. Over 10.1-years median follow-up (range 0.02–11.5 years), 741 participants suffered a composite event. Compared to no-FH, any-FH was associated with incident CHD, angina, and composite ASCVD [HR (95% CI)]: 1.4 (1.1–1.8), 1.6 (1.2–2.1), and 1.3 (1.1–1.5), respectively]. Similar results were obtained for premature-FH compared to no-FH, and for strong compared to weak-FRA for these three outcomes. There was no association between the FH definitions and non-coronary cardiovascular events. Compared to traditional risk-factors (C-statistic 0.740), any-FH, premature-FH and FRA all improved discrimination of composite ASCVD (all $P < .01$); however, the differences in C-statistic between any-FH (0.743), premature-FH (0.742), and FRA (0.744) were numerically small, as were differences in NRI.

Conclusions—A single question of the presence of FH in any first-degree relative performs just as well as more complicated assessments in predicting CHD.

Clinical Trials Registration Number—NCT00005487

Keywords

prevention; ethnic; genetic; atherosclerosis; inflammation

INTRODUCTION

Primary prevention of atherosclerotic cardiovascular disease (ASCVD) is based on the accurate identification of adults who will benefit from lifestyle and pharmacologic interventions that are aimed at risk reduction. In this context, the collection of information regarding family history (FH) of coronary heart disease (CHD) may represent an inexpensive and evidence-based tool to improve the assessment of ASCVD risk and guide preventive therapies.¹ Current guidelines recommend considering the presence of premature CHD when the decision to initiate pharmacological therapy remains uncertain after considering other risk factors.² However, the collection and assessment of familial risk is often not performed in routine clinical practice and, when it is, providers differ in how much detail they obtain.³

While FH is an established risk factor for developing future ASCVD events, prior studies have differed widely in the applied definition of FH, have been racially homogenous, have not considered gender differences, or have exclusively evaluated CHD and/or stroke as the ASCVD endpoint.^{4–13} Possibly resulting in part from these limitations, minimal prognostic discrimination is typically seen with the addition of FH to models containing traditional risk factors.^{5–7,14} For this reason, information on FH is not included in standard ASCVD risk equations, such as Framingham risk score (FRS) or the Pooled Cohorts Equation (PCE).^{2,15}

Given these considerations, further characterization of the association between various definitions FH and ASCVD among an ethnically diverse population could provide stronger evidence for the routine incorporation of FH assessment into primary prevention efforts. We also hypothesized that FH definitions may differ in their association with various ASCVD outcomes over extended follow-up out to 10-years.

METHODS

Study Population and Data Collection

The Multi-Ethnic Study of Atherosclerosis (MESA) recruited 6,814 participants between 2000 and 2002 across 6 field centers, with full details previously published.¹⁶ Participants were between 45 and 84 years of age, identified themselves as white, black, Hispanic, or Chinese American, and were free of clinical ASCVD at baseline. Data pertaining to FH was obtained at the baseline visit (July 17, 2000 to September 5, 2002) and visit 2 (September 9, 2002 to February 24, 2004). As such, only persons who attended both visits (n=6201) were included. Overall, the final analysis consisted of 6,200 participants, with one person excluded due to unavailable FH data. Institutional Review Boards at each site approved the study and all participants gave written informed consent.

At the baseline visit, demographic information, medical history, anthropometric measurements, and laboratory data were collected. Body mass index was calculated as weight in kilograms divided by height in meters squared. High-density lipoprotein-cholesterol (HDL-C) was measured using the cholesterol oxidase method. Low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald equation.¹⁷ Diabetes mellitus (DM) was defined as use of insulin or oral hypoglycemic medications, or a fasting glucose ≥ 126 mg/dL.¹⁸ Hypertension was defined as either a history of physician-diagnosed hypertension, taking a medication for hypertension, a systolic blood pressure (SBP) ≥ 140 mmHg, or a diastolic blood pressure (DBP) ≥ 90 mmHg.¹⁹ Study participants also self-reported personal habits, such as alcohol and current tobacco use (defined as having smoked a cigarette in the past 30 days and >100 cigarettes in a lifetime).

Family History Assessment

At baseline (visit 1), participants reported on the presence or absence of a FH of heart attack or stroke in any first-degree relative: mother, father, siblings, or child. Response options were “yes”, “no”, and “do not know”. At visit 2, participants were asked if any relative had CHD, stroke or cerebral hemorrhage, or DM; with response options the same as those at visit 1. If a participant reported a disease in a relative, the age at diagnosis was ascertained. For the purposes of this analysis, “do not know” responses were counted as “no” responses.

We defined “any-FH” as CHD occurring in a first-degree relative, irrespective of age, and “premature-FH” as having at least one relative with CHD occurring before the age of 55 years in males and 65 years in females, respectively. We also used the validated Familial Risk Assessment (FRA) tool to categorize FH risk as strong, moderate, or weak. The FRA is based on the number, sex, lineage, and age at onset of relatives with CHD, stroke, and DM (Table 1).^{20,21}

Ascertainment of Incident ASCVD

A detailed description of the event adjudication process in MESA has been previously published.²² We analyzed 5 separate clinical end-points. First, hard CHD: defined as myocardial infarction, resuscitated cardiac arrest, or CHD death. Second, angina: defined as definite, probable, or absent. For definite or probable angina, participants required physician

diagnosed typical or atypical symptoms of chest pain. Definite angina further required history of a CABG or revascularization procedure, 70% obstruction on angiography, or evidence of ischemia by stress testing or resting ECG.^{23,24} Third, stroke: defined as fatal or nonfatal due to hemorrhage or infarct. Fourth, peripheral artery disease (PAD): defined as an ABI value of <0.9 and did not require symptoms.²⁵ Fifth, congestive heart failure (CHF): defined as having shortness of breath or peripheral edema, plus pulmonary edema by chest X-ray, and/or dilated ventricle or poor left ventricular (LV) function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction.²⁶

Statistical Analysis

Baseline characteristics of the study participants in each of the family history status groups (none, any, and premature) and for each of the familial risk assessment categories (weak, moderate, strong) were compared using ANOVA for continuous variables and chi square test for categorical variables, respectfully.

We used Cox proportional hazard regression models to study the association of FH status and outcomes. The proportionality assumption was tested and satisfied using graphical methods (log-log plots). Models were adjusted for age, sex, race, education, MESA site, body mass index (BMI), cigarette smoking, SBP, LDL-C, HDL-C, anti-hypertensive medication use, and lipid-lowering therapy. We also tested for multiplicative interaction between FH status and either sex or race/ethnicity in the association with ASCVD risk.

Area under the receiver operating characteristic curves (AUC) was used to assess discrimination of ASCVD events. The likelihood ratio test examined the improvement in discrimination when FH information was added to variables included in the 2013 PCE for ASCVD risk estimate (age, sex, race, SBP, treatment for hypertension, HDL-C, total cholesterol, diabetes mellitus, and smoking). Net reclassification improvement (NRI) was used to assess the incremental contribution of FH information for reclassification of ASCVD events when added to categories of the FRS (calibrated for individual CVD outcomes), plus race/ethnicity.²⁷

In a sensitivity analysis, we assessed the incremental contribution of traditional risk factor elements of the FRS for ASCVD reclassification when added to baseline models containing the various FH definitions, plus race/ethnicity. Additionally, we calculated the same NRI analyses among only those categorized as intermediate risk by the FRS. Lastly, we used Cox proportional hazard regression models to study the association of the number of relatives with any-FH and premature-FH, and composite ASCVD events, respectively. All statistical analysis was performed using Stata version 13 (StataCorp). A 2-tailed $P < .05$ was considered statistically significant.

RESULTS

Our study population consisted of 6,200 individuals (mean age 62 ± 10 years, 48% men, 40% White). Overall, 36% ($n=2211$) and 16% ($n=983$) MESA participants reported any-FH or premature-FH, respectively. The corresponding proportions for weak, moderate, and strong FHA were 20%, 16%, and 20%, respectively (Supplementary Table 1). Compared to no FH,

those with any-FH had a higher percentage of individuals who were white, overweight, current smokers, and on blood pressure and lipid lowering therapy (Table 2). In the premature-FH group, a higher percentage of individuals were younger, female, black or Hispanic, overweight, current smokers, and on therapy for blood pressure and lipid management. When stratified by FRA, individuals with a strong FH had a higher percentage of individuals who were female, black, diabetic, and on therapy for blood pressure and lipid management (Supplementary Table 1).

After a median of 10.1 years follow up (range 0.02–11.5 years), a total of 741 composite ASCVD events occurred overall (not accounting for repeat events occurring after the first occurrence of any of the individual components of the composite in a given participant) (Supplementary Table 2). For individual outcomes, there were 250 CHD, 258 angina pectoris, 150 stroke, 75 PAD, and 206 CHF events, respectively. Among those with any-FH and premature-FH, a total of 317 and 142 composite events occurred, representing a cumulative incidence of 14% and 14%, respectively (Supplementary Table 2 for individual outcomes). In unadjusted analyses, point estimates for incident event rates (IR) (per 1000 person-years) for composite and individual outcomes were qualitatively similar between any-FH and premature-FH, respectively (Supplementary Table 2).”

Family History Status and ASCVD Risk

A) Adjusted HR based on Any Family History—Relative to persons without a FH, any-FH was significantly associated with composite ASCVD, hard CHD, and angina in all models, respectively (Table 3). No significant associations were found for stroke, PAD, or CHF (Supplementary Table 3). Associations between any-FH and ASCVD events were also calculated within each race/ethnicity category (HR [95% CI]): 1.27 (1.02–1.58) in Whites, 1.34 (0.99–1.81) in Blacks, 1.21 (0.88–1.68) in Hispanic, and 1.39 (0.61–3.14) in Chinese Americans). There was no significant interaction between any-FH and either ethnicity or sex in the association of composite ASCVD, CHD, and angina (data not shown).

B) Adjusted HR based on Premature Family History—Among those who reported a premature-FH (compared to no FH), significant associations were seen with composite ASCVD and angina in all models, respectively (Table 3). No significant association was found between premature-FH and incident CHD. Similar to any-FH, no significant association was found with any of the non-coronary cardiovascular events (Supplementary Table 3). According to each ethnicity, associations between premature FH and total ASCVD events were as follows (HR [95% CI]): 1.31 (0.99–1.72) in Whites, 1.75 (1.26–2.45) in Blacks, 0.79 (0.51–1.23) in Hispanic, and 0.59 (0.08–4.36) in Chinese Americans. There was no significant interaction between premature-FH and either ethnicity or sex in the association of composite ASCVD, CHD, and angina (data not shown).

C) Adjusted HR based on Number of Relatives with a Family History—Among those who reported any-FH, similar significant associations were seen with composite ASCVD when one of or multiple relatives were affected (Supplementary Table 4). Among those who reported a premature-FH, the presence of multiple affected relatives predicted composite ASCVD events.

Familial Risk Assessment and ASCVD Risk

When participants were stratified by the FRA, a significant graded relationship was seen for crude IR of the composite ASCVD outcome, hard CHD, and angina (Figure 1). For example, the highest IR was in those with a strong FH (16.6 per 1000 person-years). Additionally, the highest IRs were found in outcomes for CHD and angina in those with a strong FH: 5.1 and 6.6 (per 1000 person-years), respectively.

Relative to a weak FH, a strong FH by FRA was associated with composite ASCVD, CHD, and angina in all models, respectively (Table 3). For moderate FRA, associations were seen in demographic adjusted models for composite ASCVD, CHD, and angina; however, this relationship persisted only for CHD after risk factor adjustment. Similar to FH status, none of the FRA categories were significantly associated with non-coronary cardiovascular events in all models. Furthermore, there was no significant interaction for any event between FRA and either ethnicity or sex (data not shown).

In a sensitivity analysis, we repeated the models reported above for each of the three FH definitions after stratification by whether the source of the FH was a sibling, parent, child, or spouse (the latter was only used in the FRA analyses). These demonstrated qualitatively similar findings, though having a child or parent with a FH (any and premature) appeared to indicate a higher-risk for composite ASCVD and angina (Supplementary Table 5).

Addition of FH Status and Familial Risk Assessment for the Discrimination of CHD and composite ASCVD Events

For CHD events, the addition of FH status to the base model comprising traditional risk factors led to an increase in the C-statistic from 0.736 to 0.738 ($P=.02$) for any-FH, and from 0.736 to 0.737 for premature-FH ($P=.09$) (Figure 2a). The FRA also improved the c-statistic from 0.736 to 0.739 ($P=.05$) when added to the base model.

For composite ASCVD events, the addition of FH status to the base model comprising traditional risk factors led to an increase in the C-statistic from 0.740 to 0.743 ($P<.001$) for any-FH, and from 0.740 to 0.742 for premature-FH ($P<.05$) (Figure 2b). The FRA also improved the c-statistic from 0.740 to 0.744 ($P=.001$) when added to the base model and provided further discrimination over and above premature FH status for composite ASCVD (c-statistic from 0.742 to 0.744, $P=.05$).

Reclassification Based on FH Status and Familial Risk Assessment

Table 4 displays the net reclassification for the various FH definitions. The addition of any-FH and FRA to traditional Framingham risk factors reclassified incident CHD. For the composite ASCVD outcome, similar results were found for any-FH and FRA, however premature-FH also reclassified this outcome. Among intermediate risk participants, any-FH reclassified risk for the composite outcome. In a sensitivity analysis (Supplementary Table 6), the addition of Framingham risk factors to a base model including each FH definition, resulted in a significant and larger reclassification improvement for incident CHD and ASCVD events, respectfully, in the total population and among those at intermediate risk by the FRS.

DISCUSSION

In this contemporary, multi-ethnic cohort, FH definitions of differing complexity were all demonstrated to be independent risk factors for ASCVD events. Interestingly, the magnitude of these associations was similar for each FH definition. While statistically significant, the incremental prognostic contribution to the C-statistic for ASCVD was qualitatively similar for each FH definition. The association of FH and events was limited to CHD and angina, while other non-coronary cardiovascular outcomes were not significantly associated. As such, our main finding is that all of the approaches to defining FH considered in this analysis appeared to perform similarly in improving CHD risk prediction, supporting the use of a simple and practical approach to defining FH in routine clinical practice towards CHD prevention.

The comparison between simple and other more comprehensive assessments of FH has been described in other populations.^{28–31} However, comparisons between studies can be challenging given the different definitions of FH used, variable study designs, and duration of follow-up. For example, ORs have been reported from cross-sectional and retrospective studies for the association between premature-FH (applying various definitions) and CHD ranging from 1.4 to 5.9.^{5,10,11,13,30,31} This study has a lower (and perhaps more valid) risk ratio for any-FH or premature-FH (both RRs were 1.3) given its prospective nature.³² Consistent with this, the association of FH with CHD in our study is similar in magnitude to other prospective studies, which reported HRs ranging from 1.3 to 1.7.^{8,9}

Adoption of FH into risk prediction models has been limited as: 1) FH risk is often not independent of other established risk factors, 2) FH is non-modifiable, and 3) because of the varied temporal association between FH and ASCVD events (i.e. greater influence of shared, genetic component for premature events, and a more balanced contribution of environmental and acquired CVD risk factors for later onset events).^{4,8,33–35} Indeed, traditional risk factors account for the majority of attributable CHD risk, with only 1% contributed by FH, which provides a plausible explanation for the limited improvement in discrimination and reclassification with FH seen in the current study.³⁵ Despite these limitations, current guidelines recommend that clinicians assess *premature*-FH status, particularly among intermediate risk individuals to potentially reclassify risk.^{2,36} However, some providers may be dissuaded from querying FH status given time-constraints and the perceived complexity and unreliability of premature-FH assessment.³ Given our results and the historical challenges implementing FH information into risk assessment tools, it may be reasonable to consider using a simple definition of “any-FH” to identify individuals at increased risk for CHD, both in clinical practice and for research purposes.

Notably, the application of our results is most valid in the routine care of patients drawn from the general community when traditional risk factors are already known and CHD is the outcome of primary interest. We are unable to speculate whether detailed FH assessments may have added value at the individual treatment level in high risk subsamples of the population.³⁷ For example, by incorporating the FRA, the Family Healthcare™ tool accounts for the number, sex, onset, and lineage relatives with CHD, with classification into three risk categories, and has been developed by the Center for Disease Control.³⁸ This

MESA study cannot rule out that more detailed FH tools like the FRA have value in some high risk pedigrees. For example, we found that the number of relatives with premature FH (a form of high risk pedigree) was incrementally associated with outcomes in this analysis, a situation where these more detailed tools may have value. Additionally, depending on the definition used, a vastly different number of patients could fall into different categories of risk. This has implications when considering how the FH assessment may change the care being offered a given patient. For example, recent Society of Cardiovascular Computed Tomography guidelines recommend CAC imaging if ASCVD risk by the PCE is <5% in patients with a premature-FH.³⁹ However, many more people would have been eligible using the any FH definition. Thus, for certain applications that have cost or safety implications, an assessment of premature FH may be preferred.

LIMITATIONS

The results of our study should be interpreted in the context of several limitations. Self-reports of CHD in a first-degree relative are subject to a high specificity and comparatively lower sensitivity, limiting accurate FH assessment by reporting errors.⁴⁰ Selection bias may have been introduced, as detailed information on FH was collected at visit 2. As a result, participants who died from an ASCVD related event before visit 2 were excluded from the analysis. However, of those who did die (n=159), the proportion of those with any-FH was statistically similar to the proportion of those with any-FH included in our analysis and the time between visits was short (median time, 1.6 years).⁴¹ Given the number of ASCVD outcomes compared, multiple comparisons would have to be considered. Data collection may have been affected by recall bias (if participants were unable to accurately recollect the number family members who suffered a CHD event) and by ascertainment bias related to the participant's age. Another limitation is the inclusion of persons responding 'do not know' in the no FH group. However, we conducted a sensitivity analysis excluding such 'do not know' individuals from the analysis and the results were all quantitatively similar (data not shown). Our definition of PAD may not have allowed for an accurate assessment with various FH-phenotypes, as the ABI measurement is limited by non-compressible arteries, rendering it a sensitive but not specific test.⁴² Given the age cutoff used for this study, our results may not be generalizable to those less than age 45 who may have a strong premature family history.

CONCLUSIONS

Various definitions for a family history of CHD can add significant prognostic information to traditional risk factors in the prediction of CHD events. Current prevention guidelines endorse the assessment of premature-FH to guide ASCVD risk prevention, particularly when therapeutic uncertainty exists. Our MESA data would suggest that, in aggregate and when other traditional risk factors are already known, a simple and single-question assessment of family history in a first-degree relative of any age may be more efficient and as effective as more complex FH definitions for identifying individuals with heightened CHD risk; a finding that should motivate more routine assessment of FH in ASCVD prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Dr. Scheuner hold two patents for familial risk assessment algorithms: 1) US 7,951,078 B2 - Method and apparatus for determining familial risk of disease; and 2) US 8,719,045 - Personal assessment including familial risk analysis for personalized disease prevention plan. Dr. Nasir has reported consulting for Regeneron; and is on the advisory board of Quest Diagnostics.

ABBREVIATIONS

ABI	ankle brachial index
ASCVD	atherosclerotic cardiovascular heart disease
CHD	coronary heart disease
CHF	congestive heart failure
DM	diabetes mellitus
FH	family history of coronary heart disease
FRA	familial risk assessment
FRS	Framingham risk score
MESA	Multiethnic Study of Atherosclerosis
NRI	net reclassification index
PAD	peripheral artery disease
PCE	pooled cohorts equation

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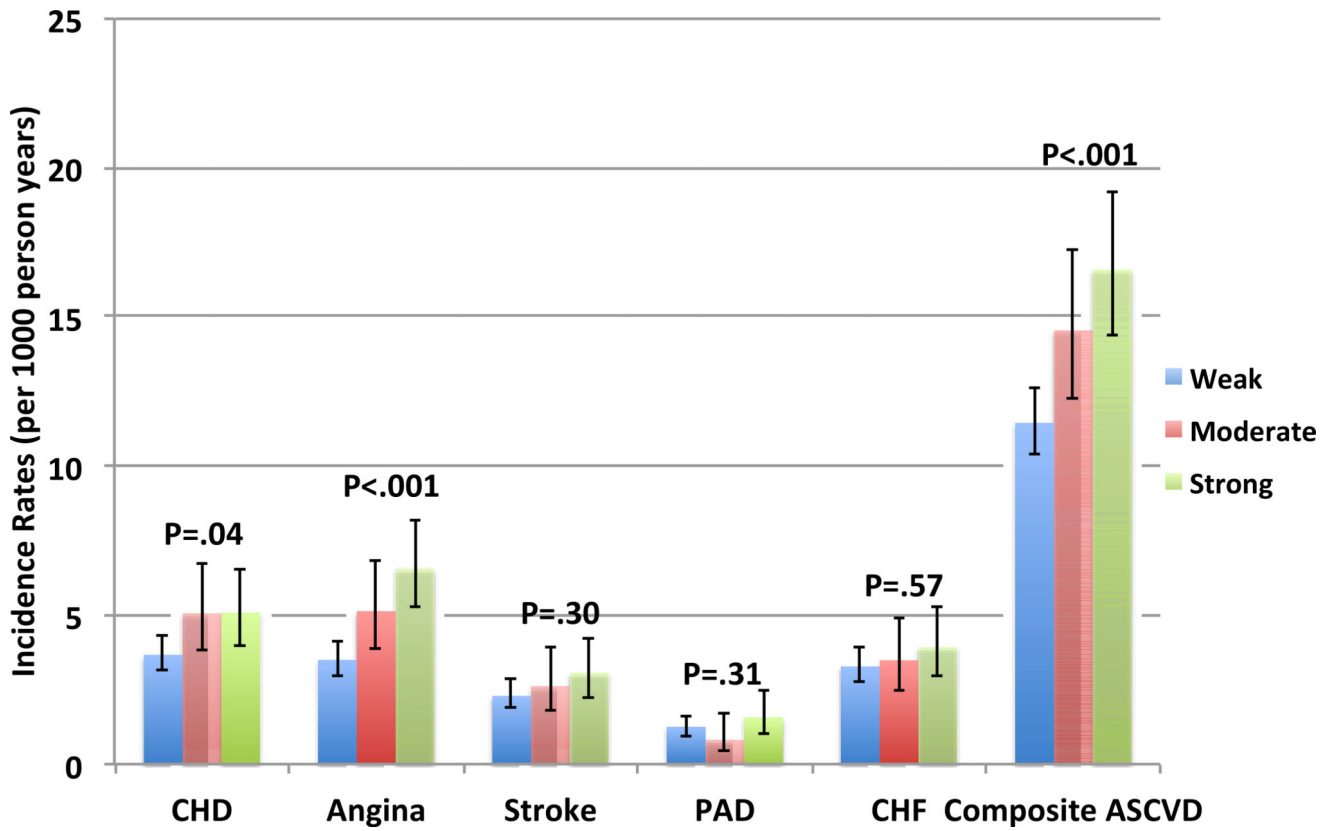
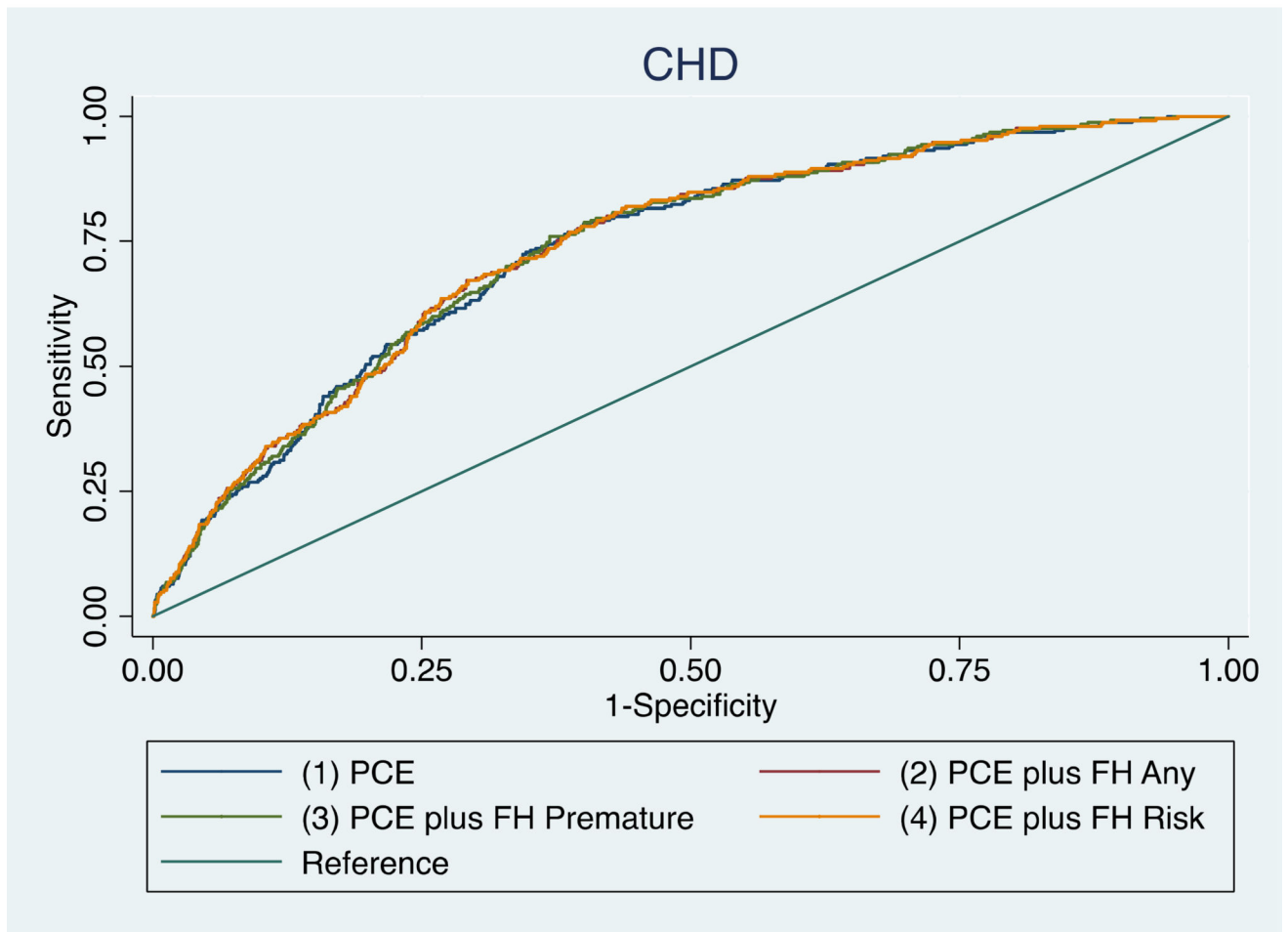


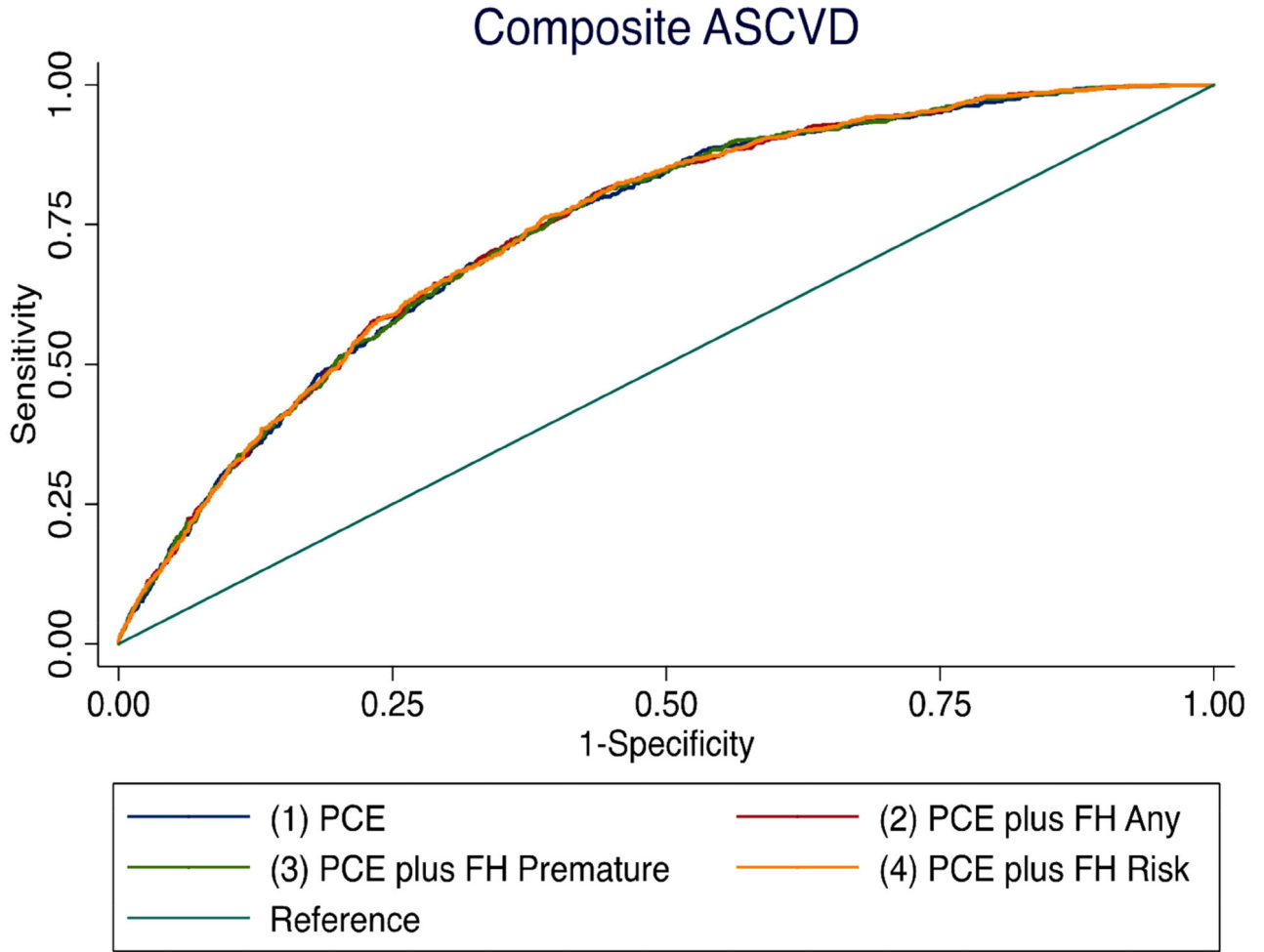
Figure 1. Crude incidence rates of cardiovascular outcomes by familial risk stratification*†
 * ASCVD = atherosclerotic cardiovascular disease, CHD = Coronary Heart Disease, CHF = Congestive Heart Failure, PAD – Peripheral Artery Disease
 † P-value refers to the comparison of incidence rates using non-parametric testing

a:



Area under the curve values: (1) = 0.736, (2) = 0.738, (3) = 0.737, (4) = 0.739

b:



Area under the curve values: (1) 0.740; (2) 0.743; (3) 0.742; (4) 0.744

Figure 2.

a: Receiver operator curves showing area under the curve for incident CHD among those with any-FH, premature-FH, and FRA *

*ASCVD – atherosclerotic cardiovascular disease, FH = family history of coronary heart disease, FRA – familial risk assessment, PCE – pooled cohorts equation

b: Receiver operator curves showing area under the curve for incident ASCVD among those with any-FH, premature-FH, and FRA *

*ASCVD – atherosclerotic cardiovascular disease, FH = family history of coronary heart disease, FRA – familial risk assessment, PCE – pooled cohorts equation.

Table 1

Familial risk stratification rules considered the presence of coronary heart disease, stroke, and diabetes in first-degree relatives^a

Strong Familial Risk	Moderate Familial Risk	Weak Familial Risk
<ul style="list-style-type: none"> At least one relative with early-onset-CHD. At least one relative with late-onset CHD, diabetes, and stroke. At least two relatives from the same lineage with late-onset CHD. At least one relative with both late-onset CHD and diabetes, and from the same lineage, at least one relative with both stroke at any age of onset and diabetes. At least one relative with both late-onset CHD and stroke at any age of onset, and from the same lineage, at least one relative with both stroke at any age of onset and diabetes. 	<ul style="list-style-type: none"> Only one relative with both late-onset CHD and diabetes, and from the same lineage, only one relative with either stroke at any age of onset of diabetes. Only one relative, on one or both sides of the family, with both late-onset CHD and diabetes. Only one relative with both late-onset CHD and stroke at any age of onset, and from the same lineage, only one relative with either stroke at any age of onset or diabetes. Only one relative, on one or both sides of the family, with both late-onset CHD and stroke at any age of onset. Only one relative with late-onset CHD, and from the same lineage, only one relative with either stroke at any age of onset or diabetes. Only one relative with both stroke at any age of onset and diabetes, and from the same lineage, only one relative with either stroke at any age. 	<ul style="list-style-type: none"> No relatives with CHD (includes families with one or more relative with either diabetes or stroke).

Familial risk stratification rules considered the presence of coronary heart disease (CHD), stroke, and diabetes in first-degree relatives. Information regarding second-degree relatives was not collected, although this information may have contributed further to the risk stratification. Early-onset CHD was defined as occurring before the age of 65 years in women and before the age of 55 years in men. Early-onset stroke was defined as occurring before the age of 50 years in both women and men. CHD and stroke occurring before the age of 25 years were not considered, because we suspected that these were most likely cases of congenital or hereditary forms of CVD. CHD or stroke after the age of 85 years was also not considered. From the same lineage refers to maternal (mother and siblings or children), paternal (father and siblings or children), or nuclear (siblings or children) lineage.²⁰

^aCHD = Coronary Heart Disease

Table 2

Baseline characteristics of the study population stratified by familial history status^{a,b}

	Total population (N= 6200)	No FH (N= 3989)	Any FH (N= 2211)	Premature FH (N= 983)	p-value ^c	p-value ^d
Age, years	62 (10)	62 (10)	62(10)	61(10)	.64	.003 ^e
Males, %	2954 (48)	1984 (50)	970 (44)	406 (41)	<.001 ^e	<.001 ^e
Ethnicity, %					<.001 ^e	<.001 ^e
White	2453 (40)	1378 (35)	1075 (49)	433(44)		
African American	1673 (27)	1092 (27)	581 (26)	305 (31)		
Hispanic	1347 (22)	890 (22)	457 (21)	216 (22)		
Chinese-American	727 (12)	629 (16)	98 (4)	29 (3)		
BMI, kg/m2	28.2 (5.4)	28.0 (5.3)	28.9 (5.6)	29.4 (5.7)	<.001 ^e	<.001 ^e
LDL, mg/dL	117 (31)	116 (31)	119 (31)	118 (31)	.002 ^e	.19
HDL, mg/dL	51 (15)	51 (15)	51 (15)	51 (15)	.10	.57
SBP, mmHg	126 (21)	126 (21)	127 (21)	126(20)	.12	.73
Diabetes mellitus, %	741 (12)	478 (12)	263 (12)	130 (13)	.93	.19
Cigarette smoking, %					<.001 ^e	<.001 ^e
Never	3124 (51)	2077 (52)	1047 (47)	459(47)		
Former	2283 (37)	1417 (36)	866 (39)	367 (37)		
Current	776 (13)	482 (12)	294 (13)	155(16)		
Lipid-lowering therapy, %	1008 (16)	585 (15)	423 (19)	191 (19)	<.001 ^e	.003 ^e
Antihypertensive therapy, %	2277 (37)	1397 (35)	880 (40)	395 (40)	<.001 ^e	.02 ^e

^aBMI = body mass index, FH = family history, HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol, SBP = systolic blood pressure.

^bBaseline characteristics expressed as means (standard deviation) for continuous variables and numbers, percentages for categorical variables. P-value for difference calculated using ANOVA test for continuous variables and chi-square test for categorical variables.

^cP-value comparing presence of any FH to no FH.

^dP-value comparing presence of premature FH to no FH.

Indicates statistically significant results.

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Table 3 Hazard ratios (95% confidence interval) for the association of family history definitions and cardiovascular events^a

	CHD			Angina			Composite ASCVD		
	Unadjusted	Model 1 ^b	Model 2 ^c	Unadjusted	Model 1 ^b	Model 2 ^c	Unadjusted	Model 1 ^b	Model 2 ^c
	Family History Status								
No FH (ref)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Any	1.37 (1.07,1.76) ^d	1.39 (1.07,1.79) ^d	1.37 (1.06,1.77) ^d	1.71 (1.34,2.18) ^d	1.76 (1.37,2.26) ^d	1.60 (1.24,2.06) ^d	1.37 (1.19,1.59) ^d	1.34 (1.16,1.56) ^d	1.28 (1.10,1.49) ^d
Premature	1.26 (0.92,1.73)	1.33 (0.97,1.83)	1.33 (0.96,1.83)	1.52 (1.13,2.04) ^d	1.66 (1.23,2.22) ^d	1.58 (1.17,2.14) ^d	1.28 (1.06,1.53) ^d	1.34 (1.10,1.61) ^d	1.29 (1.07,1.55) ^d
	Familial Risk								
Weak (ref)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	1.38 (0.99,1.92)	1.41 (1.01,1.97) ^d	1.40 (1.00,1.96) ^d	1.47 (1.06,2.04) ^d	1.48 (1.06,2.06) ^d	1.33 (0.94,1.87)	1.27 (1.05,1.55) ^d	1.24 (1.01,1.51) ^d	1.20 (0.98,1.47)
Strong	1.39 (1.03,1.88) ^d	1.40 (1.03,1.90) ^d	1.37 (1.00,1.87) ^d	1.88 (1.42,2.49) ^d	1.98 (1.49,2.64) ^d	1.80 (1.35,2.40) ^d	1.45 (1.22,1.72) ^d	1.43 (1.20,1.70) ^d	1.35 (1.13,1.61) ^d

^aASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease, FH = family history

^bModel 1: Adjusted for age, sex, ethnicity, education, and MESA study site

^cModel 2: Adjusted for Model 1 covariates + body mass index, diabetes mellitus, cigarette smoking status, systolic blood pressure, LDL-C, HDL-C, lipid-lowering therapy, and anti-hypertensive medication use.

^dIndicates statistically significant results.

Table 4

Net reclassification improvement analysis for incident cardiovascular events with addition of FH definitions to models adjusted for FRS in the entire study population and those at intermediate risk, respectively^a

FH Variable	CHD NRI (95%CI)	Composite ASCVD NRI (95%CI)
Total Population		
FRS+ FH Any	0.162 (0.061,0.264) ^b	0.166 (0.094,0.243) ^b
FRS+ FH Premature	0.069 (-0.106,0.179)	0.076 (0.014,0.135) ^b
FRS+ FH Risk Strata	0.164 (0.067,0.260) ^b	0.165 (0.090,0.237) ^b
Population at Intermediate Risk by FRS		
FRS+ FH Any	0.160 (-0.200, 0.323)	0.143 (0.041, 0.244) ^b
FRS+ FH Premature	0.064 (-0.190, 0.206)	0.036 (-0.108, 0.111)
FRS+ FH Risk Strata	0.159 (-0.201, 0.318)	-0.209 (-0.155, 0.205)

^aASCVD= atherosclerotic cardiovascular disease, CHD = coronary heart disease, FH = family history, FRS = Framingham Risk Score, NRI = net reclassification index.

^b Indicated statistically significant results.