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Basic vs 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 and Methods: Participants who provided FH data from July 17, 2000, through February 24, 2004, were identified. Definitions of FH were any, premature, and Familial Risk Assessment (FRA). 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 the net reclassification index examined the incremental prognostic contribution of each definition.

Results: In 6200 participants, the proportions of any FH and premature FH were 36% and 16%, respectively, and of weak, moderate, and strong familial risk were 20%, 16%, and 20%, respectively. Over median follow-up of 10.1 years (range, 0.02-11.5 years), 741 participants experienced a composite event. Compared with no FH, any FH was associated with incident CHD, angina, and composite ASCVD (hazard ratios [95% CIs]: 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 with no FH and for strong compared with weak FRA for these 3 outcomes. There was no association between the FH definitions and noncoronary cardiovascular events. Compared with 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* statistics among any FH (0.743), premature FH (0.742), and FRA (0.744) were numerically small, as were differences in the net reclassification index.

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

Trial Registration: clinicaltrials.gov Identifier: NCT00005487.

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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 of coronary heart disease (FH) 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 coronary heart disease (CHD) when the decision to initiate pharmacologic 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]

Although FH is an established risk factor for developing future ASCVD events, previous studies have differed widely in the applied

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definition of FH, have been racially homogenous, have not considered sex differences, or have exclusively evaluated CHD or stroke as the ASCVD end point.[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 the Framingham risk score (FRS) or the pooled cohort equations (PCE).[2,15]

Given these considerations, further characterization of the association between various definitions of FH and ASCVD in 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 10-year follow-up.

METHODS

Study Population and Data Collection

The Multi-Ethnic Study of Atherosclerosis (MESA) recruited 6814 participants between 2000 and 2002 across 6 field centers, with full details previously published.[16] Participants were aged 45 to 84 years; identified their race/ethnicity as white, black, Hispanic, or Chinese American; and were free of clinical ASCVD at baseline. Data pertaining to FH were obtained at the baseline visit (July 17, 2000, through September 5, 2002) and at visit 2 (September 9, 2002, through February 24, 2004). As such, only persons who attended both visits ($n = 6201$) were included. Overall, the final analysis consisted of 6200 participants, with 1 person excluded due to unavailable FH data. Institutional review boards at each site approved the study, and all the 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 the weight in kilograms divided by the height in meters squared. High-density lipoprotein cholesterol (HDL-C) level was measured using the cholesterol oxidase method. Low-density lipoprotein-cholesterol (LDL-C) level was calculated using the Friedewald equation.[17] Diabetes mellitus (DM) was defined as the use of insulin or oral hypoglycemic medications or a fasting glucose level of 126 mg/dL or greater (to convert to mmol/L, multiply by 0.0555).[18] Hypertension was defined as a history of physician-diagnosed hypertension, taking a medication for hypertension, a systolic blood pressure (BP) of 140 mm Hg or greater, or a diastolic BP of 90 mm Hg or greater.[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 an 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 1 relative with CHD occurring before age 55 years in men and 65 years in women. 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 were required to have physician-diagnosed typical or atypical symptoms of chest pain. Definite angina further required a history of a coronary artery bypass graft or revascularization procedure, at