Relation of familial patterns of coronary heart disease, stroke, and diabetes to subclinical atherosclerosis: the multi-ethnic study of atherosclerosis

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Purpose: To investigate the possibility that family history beyond early-onset coronary heart disease might contribute to coronary heart disease susceptibility, we studied associations between additional family history and the coronary artery calcium score. **Methods:** Associations between coronary artery calcium score and self-reports of coronary heart disease, stroke, and diabetes in first-degree relatives of 5264 nondiabetic subjects were assessed using logistic and linear regression adjusting for risk factors; adjusted mean coronary artery calcium score estimates were determined by pooling results. **Results:** Family history of coronary heart disease alone and in combination with diabetes and/or stroke was significantly associated with a positive coronary artery calcium score compared with no family history with odds ratios ranging from 1.7 (95% CI: 1.3–2.3) to 1.9 (95% CI: 1.6–2.3) and adjusted mean coronary artery calcium score estimates ranging from 137 (95% CI: 101–173) to 184 (95% CI: 143–226). Associations between family history of coronary heart disease and coronary artery calcium score were significant regardless of age at onset, sex, lineage, or number of relatives with coronary heart disease. The association between family history of diabetes only and coronary artery calcium score was also significant (OR, 1.3; 95% CI: 1.1–1.7) with an adjusted mean coronary artery calcium score estimate of 122 (95% CI: 93–151). Generally, family history of stroke had nonsignificant associations with coronary artery calcium score. **Conclusions:** Numerous family history variables in addition to early-onset coronary heart disease are associated with subclinical atherosclerosis. Our results have implications for improving coronary heart disease risk assessment. *Genet Med* 2008;10(12):879–887.

Key Words: family history, coronary heart disease, stroke, diabetes, subclinical atherosclerosis

Family history is a well-known and significant risk factor for coronary heart disease (CHD). However, many studies that have investigated family history as a risk factor have limited the definition of a positive family history to premature CHD in first-degree relatives (defined as CHD occurring before age 55 years in men and before age 65 years in women). Few studies have considered other definitions of a positive family history for the outcome of CHD,¹ and none have assessed a broader definition of a positive family history for the outcome of sub-

clinical atherosclerosis, which is increasingly becoming the target for risk factor modification.^{2–4}

Understanding how risk factors contribute to cardiovascular disease risk is important to risk assessment and tailoring recommendations for risk factor modification. However, widely used risk stratification guidelines for the primary prevention of CHD lack family history altogether or they include a limited definition of positive family history. For example, the Framingham risk score, which predicts the 10-year risk of a clinical CHD event such as myocardial infarction or sudden death, is based on the traditional risk factors of age, gender, total or low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, and smoking—family history is not included.⁵ The National Cholesterol Education Program Adult Treatment Panel III guidelines⁶ only consider family history of early-onset CHD (age of onset <55 years for men and <65 years for women) in a first-degree relative as a risk factor. CHD at later ages of onset is not included, nor is a family history of related conditions such as stroke and diabetes.

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To investigate the possibility that family history beyond early-onset CHD in first-degree relatives might contribute to subclinical atherosclerosis, we studied the associations between coronary artery calcium scores (CACS) and self-reports of CHD, stroke, and diabetes in first-degree relatives among nondiabetic subjects participating in the Multi-Ethnic Study of Atherosclerosis (MESA). Positive associations could provide the rationale for evaluating the added value of family history variables within existing cardiovascular risk stratification models.

MATERIALS AND METHODS

This study is an ancillary study to MESA, a cohort study that enrolled 6814 subjects without clinically apparent atherosclerotic vascular disease (e.g., no history of heart attack, angina, stroke, transient ischemic attack, or heart failure), age 45–84, from six sites across the United States (Columbia University, Johns Hopkins University, Northwestern University, University of Minnesota, UCLA, and Wake Forest University); 53% of enrolled subjects were women, and 62% were ethnic/racial minorities. The purpose of MESA is to study the relationship between cardiovascular risk factors and subclinical atherosclerosis measured periodically using electron beam computed tomography (EBCT) or multidetector computed tomography (MDCT) and other modalities such as ultrasound and magnetic resonance imaging over a 10-year period (1999–2009) with four clinical examinations scheduled 18–24 months apart.

This study utilized data collected in exams 1 and 2 from nondiabetic MESA subjects to assess the relationships between family history and baseline measures of CACS using regression analyses adjusting for demographic and personal risk factors. MESA subjects were excluded if they had previously diagnosed diabetes, a fasting glucose ≥ 126 mg/dL, or used a hypoglycemic medication ($n = 995$) and if information regarding family history ($n = 483$) or covariates included in the regression models ($n = 72$) was missing. This study has been reviewed and approved by the RAND Human Subjects Protection Committee.

Demographic factors

Information about age, gender, ethnicity, marital status, educational level, income level, and medical history was obtained by questionnaires in exam 1. Laboratory test results were also measured in exam 1 and included fasting lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) and glucose. Current smoking was defined as having smoked a cigarette in the last 30 days. Resting blood pressure was measured three times in the seated position, and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of medication prescribed for hypertension. Hypercholesterolemia was defined as those participants taking medication to lower cholesterol. Use of medications was based on clinical staff entry of prescribed

medications verified by the staff. Body mass index was calculated as weight (kg)/height² (m²).

Family history

Detailed information on family histories of CHD, stroke, and diabetes was ascertained in exam 2 using a structured survey instrument. Subjects were asked if their mother, father, siblings, or children have had CHD defined as a heart attack, myocardial infarction, or cardiac procedures (coronary bypass surgery, balloon angioplasty, intracoronary stenting); stroke, cerebral hemorrhage, or brain attack; or diabetes or high blood sugar. Response options were yes, no, and don't know. If a subject reported a disease in a relative, the age at diagnosis was also ascertained. Reports of CHD and stroke occurring in relatives before age 25 were excluded in our family history assessment, as we suspected these were most likely cases of congenital heart disease, congenital cerebrovascular malformations, or single gene forms of cardiovascular disease. Relatives with a first occurrence of CHD or stroke after age 85 were not included. For diabetes, we excluded diagnoses occurring in relatives before age 20 as we considered this history more consistent with type 1 diabetes than type 2 diabetes. The latter was of greater interest because it is closely linked to atherosclerosis through insulin resistance.

Eight different family history variables were developed that considered the presence or absence of CHD, diabetes, and/or stroke at any age of onset in first-degree relatives including (1) no family history of CHD, diabetes, or stroke; (2) family history of CHD only; (3) family history of diabetes only; (4) family history of stroke only; (5) family history of CHD and diabetes; (6) family history of CHD and stroke; (7) family history of stroke and diabetes; and (8) family history of CHD, stroke, and diabetes.

We also conducted analyses that assessed the association between CACS and the number (0, 1, 2, 3, or more), type (parent, siblings, children), lineage (maternal, paternal, nuclear), and youngest age of onset of relatives with CHD, stroke, or diabetes compared to having no affected relative. Maternal lineage included families with an affected mother with or without affected siblings or children. Paternal lineage included families with an affected father with or without affected siblings or children. Nuclear lineage included families with affected siblings or children and no affected parent. To investigate the influence of age of disease onset thresholds in relatives, we used the non-parametric technique of generalized additive models⁷ to explore the functional form of the relationship between age of disease onset and a positive CACS. This relationship is estimated using smoothing operations, and graphic displays were used to select the different age of onset thresholds. For all three conditions, three age of onset thresholds were identified as age <40 years, 40–60 years, and 60 years and older. We observed increasing, flat, and then decreasing linear associations across these age groups. We did not observe differences when we assessed the age of onset thresholds for each condition according to the sex of the relative or the sex of the MESA participant.

Coronary artery calcium score

The mean Agatston, phantom-adjusted CACS was the outcome measure used in the analyses of this study. Computed tomography scanning of the chest was performed on the MESA cohort either with an ECG-triggered (at 80% of the RR interval) EBCT scanner (Chicago, Los Angeles, and New York field centers; Imatron C-150, Imatron) or with prospectively ECG-triggered scan acquisition at 50% of the RR interval with a MDCT system that acquired four simultaneous 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (Baltimore, Forsyth County, and St. Paul field centers; Lightspeed, General Electric or Siemens, Volume Zoom). Each participant was scanned twice. Scans were read centrally at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center to identify and quantify coronary calcification. The CACS measurements among scanning centers and between participants were adjusted with a standard calcium phantom scanned simultaneously with each participant. The mean Agatston score was used in all analyses. Agreement with regard to presence of CACS was high (kappa statistic 0.90–0.93 between and within readers), and the intraclass correlation coefficient for the Agatston score between readers was 0.99. Concordance for presence of coronary artery calcification between duplicate scans was high and similar for both EBCT and MDCT (96%, kappa = 0.92).⁸

Statistical analyses

SAS software (version 9.1) was used for all statistical analyses. Basic descriptive statistics were performed to describe the distribution, mean value, and range of the demographic factors, personal risk factors, family histories, and CACS. Chi-square and *t* tests were used to test for any difference in the outcomes between different ethnic/racial groups and any other group stratification. When appropriate, the significance of the results presented in the text and tables has been adjusted for multiple comparisons. The Bonferroni method was applied to adjust the threshold of statistical significance when multiple comparisons were made.

The association between CACS and family history was assessed using a two-part model structure.^{9–11} Because many participants had a CACS of zero, we first assessed the association between having a positive CACS and family history using logistic regression, and then for those subjects with a positive CACS, we modeled their continuous score using a linear regression model. The positive scores were skewed, therefore a log transformation of the outcome was used to help stabilize the error variance and improve the fit with the linearity and normality assumptions. To appreciate the magnitude of the different estimates derived from both the logistic and the linear regression models, we report predictive margins or adjusted mean estimates for the CACS.¹² These adjusted mean estimates represent average predicted outcomes if every participant in the sample would have the risk factor of interest (e.g., family history of CHD only), and these estimates are equivalents of the model coefficient estimates in the outcome scale. So, for the

first part of the two-part model (logistic), adjusted proportions or probabilities equivalent to the estimated odds ratios are used, and for the second part of the two-part model (linear), predictions were back-transformed into the CACS scale (where the score was >0) using the smearing estimate technique¹³ and again presented as adjusted means. The combined associations between family history and CACS using both the zero and the nonzero scores were also estimated considering that at a participant prediction level the combined estimated score can be obtained as the product of the probability of having a nonzero score and the estimate of the participant's score using the two-part model: $E(\text{CACS} \mid \text{Covariates}) = \text{Prob}(\text{CACS} > 0) \times E(\text{CACS} \mid \text{Covariates}, \text{CACS} > 0)$.

In all of the models, we adjusted for age, sex, education, income, marital status, ethnicity/race, study site, family size, current smoking, LDL cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, and body mass index. Models adjusted for sociodemographic factors only, excluding cardiovascular risk factors, produced similar results to the fully adjusted models, and are therefore not presented. Interactions between family history of CHD, stroke and/or diabetes and age, sex and ethnicity/race on the outcome of CACS were evaluated by the addition of interaction terms into regression models.

RESULTS

Table 1 provides a description of the 5264 nondiabetic MESA subjects eligible for this study. The mean age was 61.6 years (range, 44–84), 47% were men, and 57% were nonwhite. The majority (67%) had more than a high school education, and a range of annual incomes was represented. The mean number of first-degree family members per subject was 7.8 (range 1–35). About 37% of the subjects were current cigarette smokers. Personal history of hypertension or use of blood pressure-lowering medication was reported by 41%, and use of cholesterol-lowering medication was reported by 14.4%. Slightly more than half (53%) of subjects had a CACS of 0. The mean CACS was 124 (SD, 371; median, 0; range, 0–6316), and the mean value for subjects with a positive CACS (i.e., CACS >0) was 264 (SD, 505; median, 79; range, 1–6316). Subjects with a positive CACS were more likely to be older, men, white, current smokers, and to have lower annual incomes and personal history of hypertension and lipid disorders.

Tests for goodness of fit for both the logistic and the linear regression models comparing likelihood ratios and R^2 values found that models including family history defined as having at least one first-degree relative with CHD, stroke, or diabetes were significantly better than models that did not include family history ($P < 0.0001$ and $P < 0.001$, respectively). The odds ratios and CACS estimates describing the associations of family history of CHD, stroke, and/or diabetes in at least one first-degree relative at any age of onset compared with no family history and adjusted for demographic factors, personal risk factors, and multiple comparisons are shown in Table 2. Family history of CHD alone and in combination with diabetes

Table 1
Characteristics of nondiabetic MESA subjects at baseline

Characteristics	CAC = 0 (N = 2780)	CAC >0 (N = 2484)	Total (N = 5264)
Age: mean (SD), range (yr) ^a	57.6 (9), 44–84	66.1 (9.7), 44–84	61.6 (10.2), 44–84
Male (%) ^a	36.5	58.2	46.7
Ethnicity/race (%) ^a			
African-American	29.1	21.4	25.5
Asian-American	11.7	11.4	11.6
White	36.7	49.4	42.7
Hispanic	22.4	17.9	20.3
Education (%) ^b			
Less than high school	15.1	14.6	14.9
High school graduate	16.2	19.6	17.8
More than high school	68.7	65.8	67.3
Marital status (%)			
Married or living as married	61.8	61.8	61.8
Divorced, widowed or separated	28.7	29.3	29.0
Never married	8.5	8.3	8.4
Income (%) ^a			
Less than \$25,000	24.5	30.2	27.2
\$25,000–\$49,999	28.3	27.7	28.1
\$50,000–\$74,999	18.5	15.9	17.3
\$75,000–\$99,999	10.4	9.1	9.8
More than \$100,000	15.5	13.7	14.7
Number of relatives: mean (SD), range ^c	7.9 (3.6), 1–35	7.7 (3.5), 1–21	7.8 (3.5), 1–35
Smoking status (%) ^a			
Current	30.9	43.5	36.9
Former	12.9	12.4	12.6
Never	56.2	44.1	50.4
Personal history of hypertension (%) ^{a,d}	31.5	50.8	
Systolic blood pressure: mean (SD), range (mm Hg) ^a	121 (20), 78–231	129 (21), 75–218	125 (21), 75–231
Diastolic blood pressure: mean (SD), range (mm Hg) ^a	71 (10), 41–106	73 (10), 41–110	72 (10), 41–110
Personal history of lipid disorder (%) ^{a,e}	9.8	19.7	14.5
LDL cholesterol: mean (SD), range (mg/dL) ^a	117 (30), 21–252	119 (31), 20–284	118 (31), 20–284
HDL cholesterol: mean (SD), range (mg/dL) ^a	53 (15), 21–142	50 (15), 15–127	52 (15), 15–142
Triglycerides: mean (SD), range (mg/dL) ^a	120 (63), 21–400	126 (64), 23–391	123 (64), 21–400
BMI: mean (SD), range (kg/m ²)	28 (6), 15–54	28 (5), 16–55	28 (5), 15–55
Coronary calcium score: mean (SD), median, range ^a	0	264 (505), 79, 1–6316	124 (371), 0–6316

^aComparison of CAC = 0 to CAC > 0 group, $P < 0.001$.

^bComparison of CAC = 0 to CAC > 0 group, $P < 0.01$.

^cComparison of CAC = 0 to CAC > 0 group, $P < 0.05$.

^dIncludes use of blood pressure-lowering medication.

^eIncludes use of cholesterol-lowering medication.

MESA, multi-ethnic study of atherosclerosis; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index.

Table 2
Associations between CACS and family history of CHD, stroke, and diabetes in MESA subjects at baseline

Family history of:	Odds ratio (95% CI) ^a CACS > 0 vs. CACS = 0	CACS estimate (95% CI) when CACS > 0 ^b	Adjusted mean CACS estimate ^c
No CHD, diabetes, or stroke (<i>n</i> = 1,688)	1.00	241 (206–275)	105 (91–119)
CHD only (<i>n</i> = 966)	1.9 (1.6–2.3) ^d	332 (275–389) ^d	169 (143–195)
Diabetes only (<i>n</i> = 523)	1.3 (1.1–1.7) ^e	259 (197–321)	122 (93–151)
Stroke only (<i>n</i> = 515)	1.1 (0.9–1.4)	225 (174–275)	101 (79–124)
CHD and diabetes (<i>n</i> = 477)	1.8 (1.4–2.2) ^d	367 (280–454) ^d	184 (143–226)
CHD and stroke (<i>n</i> = 502)	1.8 (1.4–2.3) ^d	327 (254–400) ^f	164 (130–199)
Stroke and diabetes (<i>n</i> = 236)	1.1 (0.8–1.5)	221 (143–298)	99 (64–134)
CHD, diabetes, and stroke (<i>n</i> = 357)	1.7 (1.3–2.3) ^d	273 (199–347)	137 (101–173)

For each analysis, all *P* values were adjusted for two comparisons (i.e., the two models used—logistic regression and linear regression) using the Bonferroni method with a significance threshold value of 0.025.

^aPart 1 of the two-part model: odds ratios for a positive CACS derived from logistic regression adjusting for age, sex, ethnicity/race, education, income, marital status, study site, family size, current smoking status, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, and body mass index.

^bPart 2 of the two-part model: CACS estimates derived from linear regression adjusting for age, sex, ethnicity/race, education, income, marital status, study site, family size, current smoking status, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, and body mass index.

^cAdjusted mean CACS estimate is the mean value calculated by pooling the results from the logistic and the log-transformed linear regression models. All *P* values were adjusted for multiple comparisons (i.e., the two models used—logistic regression and linear regression).

^d*P* < 0.01, statistically significant after adjustment for two comparisons using the Bonferroni method.

^e*P* = 0.02, statistically significant after adjustment for two comparisons using the Bonferroni method.

^f*P* = 0.01, statistically significant after adjustment for two comparisons using the Bonferroni method.

CACS, coronary artery calcification score; CHD, coronary heart disease; MESA, multi-ethnic study of atherosclerosis; CI, confidence interval.

and/or stroke was significantly associated with a positive CACS with odds ratios ranging from 1.7 (95% CI: 1.3–2.3) to 1.9 (95% CI: 1.6–2.3) and adjusted mean CACS estimates ranging from 137 (95% CI: 101–173) to 184 (95% CI: 143–226). A significant association of lesser magnitude was also observed between family history of diabetes only and a positive CACS (OR, 1.3; 95% CI: 1.1–1.7) with an adjusted mean CACS estimate of 122 (95% CI: 93–151) for these participants. However, the addition of family history of diabetes to family history of CHD did not substantially change the odds ratios or CACS estimates observed given family history of CHD alone. Family history of stroke only was not significantly associated with a positive CACS, and adjusted mean CACS estimates observed with family history of CHD and/or diabetes were if anything diminished by including family history of stroke. Because CHD has different prevalence rates according to age, sex, and ethnicity, we evaluated potential interactions between these demographic variables and the different family history combinations of CHD, stroke, and/or diabetes for the outcome of a positive CACS. We found no significant interactions and for this reason we did not present the results stratified by these variables, because any heterogeneity of associations by ethnicity/race, sex, or age could be due to chance.

To examine whether specific CHD, stroke, and diabetes family history variables—such as the youngest age of onset, number, sex, type, or lineage of affected relatives—had significant associations with CACS, we assessed the odds ratios for a positive CACS and calculated the mean CACS given these different family history variables compared to having no family history of each condition adjusting for demographics, personal risk factors, and multiple comparisons.

All of the associations between CACS and the specific CHD family history variables relating to youngest age at onset, number of affected relatives, and sex of affected relatives were significantly associated with a positive CACS (Table 3). The magnitude of the adjusted mean CACS estimates and associations with a positive CACS increased as the age of onset decreased and the number of relatives with CHD increased. Adjusted mean CACS estimates were >200 when there were both parents and siblings affected, both maternal and paternal relatives affected, three or more affected relatives, and when the youngest age of CHD onset was <40. This was about twice the CACS estimated in the absence of a family history of CHD. For the family history variables describing the type of affected relatives and lineage of affected relatives, all were significantly associated with a positive CACS; however, when only siblings were affected with CHD and when both maternal and paternal relatives were affected, the significance was at the threshold level when correcting for multiple comparisons.

There were no significant associations between a positive CACS and the specific stroke family history variables relating to age at onset, and number, sex, type, and lineage of affected relatives. The adjusted mean CACS estimates given a family history of stroke were generally similar to or less than the CACS estimate of about 133 for subjects without a family history of stroke. The stroke family history variable having the greatest adjusted mean CACS estimate of 151 (95% CI: 114–188) was observed when the youngest age at stroke onset was between 40 and 60 years.

In considering the different diabetes family history variables, only one was significantly associated with a positive CACS, and that was having male relatives with diabetes, which

Table 3

Odds ratios and CACS estimates according to number, sex, type, lineage, and age at onset of relatives with CHD, stroke, or diabetes in MESA subjects at baseline

Family history variables	N	Odds ratio ^a CAC > 0 (95% CI)	Mean adjusted CACS estimate ^b (95% CI)
Youngest age at onset			
No affected relative	2962	1.0	106 (94–117)
Age <40	108	2.7 (1.7–4.2) ^g	220 (125–315)
Age 40–60	881	1.7 (1.4–2.0) ^g	173 (144–203)
Age >60	1287	1.6 (1.4–1.9) ^g	160 (138–182)
Number of affected relatives			
No affected relative	2962	1.0	105 (94–117)
1	1589	1.6 (1.4–1.8) ^g	148 (128–167)
2	506	1.8 (1.5–2.3) ^g	193 (152–233)
3+	207	2.4 (1.7–3.4) ^g	244 (172–316)
Sex of affected relative			
No affected relative	2962	1.0	106 (95–118)
Male	1241	1.5 (1.3–1.8) ^g	154 (131–176)
Female	603	1.8 (1.5–2.2) ^g	155 (125–185)
Male and Female	458	2.0 (1.5–2.5) ^g	222 (173–270)
Type of affected relative			
No affected relative	2,962	1.0	106 (94–117)
Parents and no siblings ^c	1,306	1.6 (1.4–1.9) ^g	156 (133–180)
Siblings and no parents ^{c,d}	580	1.6 (1.3–2.0) ^h	158 (128–187)
Parents and siblings ^c	416	2.1 (1.6–2.7) ^g	206 (160–251)
Lineage of affected relative			
No affected relative	2,962	1.0	106 (95–118)
Maternal ^e	560	1.8 (1.4–2.2) ^g	169 (134–204)
Paternal ^e	956	1.7 (1.4–2.0) ^g	155 (130–181)
Maternal and paternal ^e	206	1.6 (1.2–2.3) ^h	264 (174–353)
Nuclear ^f	580	1.6 (1.3–2.0) ^g	157 (127–187)

For each analysis, all *P* values were adjusted for five comparisons (i.e., the models considering the five different family history variables of youngest age at onset, number of relatives affected, sex of affected relatives, type of affected relatives, and lineage of affected relatives) using the Bonferroni method with a significance threshold value of 0.01.

^aAdjusted for age, sex, education, income, marital status, study site, family size, current smoking status, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, and body mass index.

^bMean CACS estimate is the mean value calculated by pooling the results from the logistic and the log-transformed linear models.

^cCan include children.

^dIncludes 48 subjects with only children affected with CHD.

^eCan include siblings and children with CHD.

^fIncludes siblings and/or children with CHD but no affected parents.

^g*P* < 0.01, statistically significant after adjustment for five multiple comparisons using the Bonferroni method.

^h*P* = 0.01, at the threshold of statistical significance after adjustment for five comparisons using the Bonferroni method.

CACS, coronary artery calcification score; CHD, coronary heart disease; CI, confidence interval.

was associated with a 1.4-fold (95% CI: 1.1–1.7) increase for a positive CACS. The greatest adjusted mean CACS estimate of 157 (95% CI: 125–188) was observed when male relatives were affected compared with a CACS estimate of about 129 when

there was no family history of diabetes. We observed a similar trend when fathers were affected with diabetes (OR = 1.4; 95% CI: 1.0–1.7); however, the association did not reach significance after adjustment for multiple comparisons, and the ad-

justed mean CACS estimate was not substantially increased (132; 95% CI: 95–169). There was no significant association with a positive CACS and the adjusted mean CACS estimate was only 127 (95% CI: 101–153) when female relatives had diabetes, despite increased numbers of diabetic female-only pedigrees (621) versus male-only pedigrees (539). The number of relatives with diabetes, type of relative, or youngest age at onset did not affect adjusted mean CACS estimates or associations with a positive CACS.

DISCUSSION

We have found numerous family history variables describing CHD in first-degree relatives that have greater CACS estimates and are significantly associated with a positive CACS compared with no family history of CHD, even after adjusting for demographic and personal cardiovascular risk factors. This includes having relatives with CHD diagnosed before or after age 60, in men or women, or relatives from the maternal or paternal lineage. We also observed an increasing adjusted mean CACS estimate and magnitude of association with a positive CACS as the number of relatives with CHD increased and the age of onset decreased.

Previous studies have described significant associations between clinical outcomes of CHD or self-reports of CHD and increasing number of relatives with CHD^{14–19} and younger ages of CHD onset.^{14–17,20–22} An earlier study of MESA subjects has also found a significant association between a positive CACS and family history of premature CHD (defined as occurring before age 55 years in men and before age 65 years in women).²³ However, this study did not assess associations between CACS and family history of later onset CHD, diabetes, or stroke. This is the first time that family history characteristics beyond premature CHD in a first-degree relative have been associated with the presence of coronary artery calcium.

Previous studies that have limited the definition of a positive family history to premature CHD in first-degree relatives (i.e., defined as occurring before age 55 years in men and before age 65 years in women) have found greater associations between family history and clinical CHD or subclinical atherosclerosis when siblings are affected compared to parents^{16,23,24} or when paternal relatives are affected compared to maternal relatives.²⁵ We have shown the adjusted mean CACS estimate and strength of association with CACS were similar given affected parents or siblings, or maternal or paternal relatives, regardless of the age at onset. Thus, our findings suggest that familial risk assessment should not be limited to early-onset disease in siblings or paternal relatives as suggested by these previous studies.

Previous studies have found an association between family history of diabetes and cardiovascular disease as measured by endothelial dysfunction,²⁶ common carotid artery intima-media thickness,^{27,28} and self-reports of CHD,^{1,29} and the Rancho Bernardo study found participants with family history of diabetes were more likely to have a family history of heart attack.³⁰ However, none of these studies assessed family history of dia-

betes only, that is, in the absence of a family history of cardiovascular disease. Therefore, for the first time, we have described family history of diabetes only as a significant cardiovascular risk factor. Our findings provide further support to the “common soil” hypothesis that asserts genetic, environmental, and behavioral diabetes risk factors that are shared by family members contribute to CHD susceptibility.^{31,32} Interestingly, we have found that the specific diabetes family history variable of greatest significance for a positive CACS is having a male relative with diabetes. This suggests that men and women may express diabetes-related familial risk factors differently, which in turn could have differential effects on relatives at risk.

Several studies have found family history of stroke is a significant risk factor for CHD.^{1,33–36} We found that a family history of stroke generally had no significant associations with the adjusted mean CACS estimates or with a positive CACS. This discrepancy between reports in the literature and our results may relate to the different outcomes assessed. Previous studies have examined outcomes of clinical CHD events, such as heart attack, that are often precipitated by a thrombus superimposed on a disrupted plaque, similar to stroke. Thromboembolic factors probably do not come into play for the outcome of subclinical atherosclerosis, and this may explain why we did not find strong associations between family history of stroke and the CACS.

A major strength of this study is the large, ethnically diverse, and well-phenotyped MESA cohort. However, these MESA participants are relatively healthy, as subjects with preexisting cardiovascular disease were excluded and, therefore, this cohort is not representative of the US population. By excluding subjects with preexisting cardiovascular disease, subjects with the strongest risk factors for CACS could have been excluded, which could potentially underestimate the significance of certain familial risk factors and could potentially diminish the strength of associations we have observed between family history and CACS. Another limitation is the cross-sectional design of our study, which prohibits establishment of any temporal associations concerning family history as a risk factor.

In our study we used a measure of subclinical atherosclerosis as our outcome of interest rather than hard clinical coronary events, such as myocardial infarction, need for revascularization, or cardiovascular death. Thus, our findings are limited to this outcome. However, coronary artery calcium accumulation is part of the development of atherosclerosis, and this occurs almost exclusively in atherosclerotic arteries, particularly in advanced lesions and with older age, and is absent in the normal vessel wall.^{37–42} Recent studies have also shown that the CACS provides prognostic information of proven value regarding the risk of hard cardiovascular events.^{2–4,40,43–46} Given this evidence, several organizations, including the American Heart Association, the National Cholesterol Education Program Expert Panel, and the European Third Joint Task Force, have recommended the addition of measures of subclinical atherosclerosis as a means to improve CHD risk stratification because of the limitations of the current clinical guidelines for

primary prevention.^{6,47,48} Currently in clinical practice, CACS measurement has a role as a screening or risk assessment tool that complements global risk assessment in asymptomatic patients, for the primary purpose of modifying and potentially improving selection of patients for risk-reducing therapies.^{2–4}

Another potential limitation of our study is lack of validation of self-reports of family history. Numerous studies have estimated the accuracy of these reports. For CHD in first-degree relatives, sensitivity of self-reports range from 67% to 89%, and specificity ranges from 59% to 97%, with most values >90%.^{16,24,49–52} Sensitivity values range from 56% to 87% for family history of diabetes, and specificity ranges from 97% to 98%.^{49,52} For family history of stroke, sensitivity ranges from 42% to 51% with specificity from 96% to 98%.⁵² A personal history of CHD or CHD risk factors generally does not affect the accuracy of the family history report, nor does sex.^{49,50,52} However, older individuals are more likely to give inaccurate family history compared with younger individuals.^{49,52} Limited information is available regarding the influence of ethnicity/race on accuracy of family history reports. However, in the National Heart, Lung, and Blood Institute Family Heart Study, there were no significant differences in accuracy of self-reports of family history between whites and African-Americans reporting on CHD, diabetes, and hypertension.⁴⁹ Similar results were found in a study investigating the validity of cancer family history data; race or ethnicity did not influence the accuracy of reporting.⁵³ Thus, in general, individuals are more likely to under-report and less likely to over-report disease in their relatives. Yet, despite under-reporting, positive disease associations are consistently observed, and as a result, use of family history can help to stratify disease risk in the population. However, given the lower sensitivity values and potential differences in reporting associated with age or other demographic variables, when assessing individual risk, validation of self-reports of family history is desirable, and in the clinical setting validation may be necessary if the familial risk substantially affects management decisions.

In summary, our results provide further evidence that family history is an important risk factor for CHD susceptibility. Moreover, when assessing familial risk, the family history should be considered as a categorical or continuous variable that accounts for the number of relatives with CHD and age of CHD onset, as well as family history of diabetes particularly in men. Application of rules derived from these findings could improve stratification of CHD susceptibility associated with the family history. Studies are needed to demonstrate whether adding family history could improve overall risk assessment for CHD, which could influence CHD prevention guidelines including indications for screening to detect subclinical atherosclerosis.

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