article

Expanding the definition of a positive family history for early-onset coronary heart disease

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Purpose: Assessing familial risk for early-onset coronary heart disease (CHD) is typically limited to first-degree relatives with early-onset CHD. To evaluate the impact of additional family history, we examined the associations between various family history definitions and early-onset CHD. **Methods:** By using the national HealthStyles 2003 survey data, we assessed associations between self-reported family history and personal history of early-onset CHD (diagnosed at or before age 60 years), adjusting for demographics, hypercholesterolemia, hypertension, and obesity. **Results:** Of 4035 respondents, 60% were female and 72% were white, with a mean age of 48.8 years; 4.4% had early-onset CHD. In addition to having at least one first-degree relative with early-onset CHD, other significant associations included having at least one first-degree relative with late-onset CHD, at least one second-degree relative with early-onset CHD, and two or more affected second-degree relatives regardless of age of onset of CHD. Early-onset stroke in at least one first-degree relative and, in women, having at least one first-degree relative with diabetes were also significantly associated with early-onset CHD. **Conclusions:** Family history beyond early-onset CHD in first-degree relatives is significantly associated with prevalent CHD diagnosed at or before age 60 years. ***Genet Med* 2006:8(8):491–501.**

Coronary heart disease (CHD) is the leading cause of premature death and disability in the United States and other developed countries.[1] Several risk factors are known to contribute to CHD. Global risk assessment is an approach to CHD prevention that estimates the absolute risk based on the summation of risks contributed by each risk factor.[2] Although not all risk factors are modifiable, all can contribute to the risk assessment, and the intensity of risk factor management can be adjusted according to the severity of the overall risk.

Family history is an important and independent CHD risk factor, especially for early-onset disease. Many studies have found a two- to threefold increase in CHD given a first-degree relative with CHD,[3–6] and the strength of this association increases as the number of affected first-degree relatives increases[7,8] and with younger ages of CHD onset in relatives.[7–10] Less is known about the effects of later-onset CHD in relatives, second-degree relatives with CHD, or the presence of stroke and diabetes among relatives. Furthermore, few studies have assessed the impact of the type of relative affected with CHD (e.g., parent or sibling) or the lineage of affected relatives (i.e., maternal or paternal) on CHD risk.

The Framingham Risk Score is a common global risk assessment method for CHD that is used to guide preventive interventions. Age is a prominent determinant of the Framingham risk estimate, and family history is not included as a risk factor.[11] Therefore, the Framingham score may underestimate CHD risk for individuals with family history, particularly at young ages when prevention could have substantial benefits given the risk for early-onset disease.

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) guidelines provide recommendations for CHD prevention, focusing on lipid lowering. The number of risk factors an individual has determines the low-density lipoprotein cholesterol goal. Family history is included as a risk factor, but is limited to premature CHD (age of onset $<$55 years for men and $<$65 years for women) in first-degree relatives.[12] If family history characteristics beyond premature CHD in first-degree relatives also increase CHD risk, the NCEP guidelines might underestimate CHD risk and the need for lipid-lowering therapies or other preventive interventions for individuals with such histories.

The goal of this study was further characterization of family history as a risk factor for CHD diagnosed at or before age 60 years (early onset) by a comprehensive assessment of associations between self-reports of prevalent early-onset CHD and various definitions of family history of CHD, stroke, and diabetes that include age at onset, number of affected relatives, degree of relationship, type, and lineage of affected relatives.

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MATERIALS AND METHODS

Subjects

The HealthStyles 2003 survey was the source of data for this cross-sectional study. HealthStyles is an annual mail survey of health-related attitudes and behaviors among the U.S. adult population.[13] It is a subset of a two-part consumer survey designed and conducted by Synovate, Inc. (Arlington Heights, IL), a marketing firm that annually recruits approximately 600,000 potential respondents. HealthStyles is used for health-communications planning by organizations (including the U.S. Centers for Disease Control and Prevention) that influence the design and administration of the questionnaire. In 2003, a stratified random sample of 5845 adults was selected, of whom 4035 (69%) agreed to participate. Questions about personal and family history of CHD, stroke, and diabetes were included in the survey. The Centers for Disease Control and Prevention Institutional Review Board approved this study.

Personal and family history assessment

Respondents provided information about their age, sex, ethnicity/race, education, income, marital status, and medical history. Personal history of CHD was considered present if a respondent reported that a doctor had diagnosed CHD, such as myocardial infarction (MI), coronary bypass graft surgery, or angioplasty. Angina was not included in the definition. Personal history of stroke was considered present if a respondent reported that a doctor had diagnosed stroke or transient ischemic attack (TIA). For both CHD and stroke, respondents indicated whether their diagnosis was made at or before age 60 years (early onset) or after age 60 years (late onset). We chose the age of 60 years because this is often used as a definition of premature CHD in epidemiologic studies of cardiovascular disease, and it is similar to the age cutoff used by the NCEP ATPIII guidelines, which describe family history of premature CHD as age of onset less than 55 years for men and less than 65 years for women in a first-degree relative.[12] Respondents were considered to have diabetes or to be obese if they reported having either condition currently or in the past year. Hypercholesterolemia was coded as present if respondents had ever been told by a health professional that they had high blood cholesterol or to take medication for high cholesterol. Hypertension was considered present if respondents reported ever being told on two or more office visits that they had high blood pressure or if they were ever prescribed medication to lower their blood pressure. Hypertension or diabetes diagnosed only during pregnancy was excluded.

Family history was obtained from respondents by asking about CHD or stroke/TIA diagnoses occurring at or before age 60 years (early onset) or after age 60 years (late onset) in first-degree relatives (mother, father, and siblings) and second-degree relatives (aunts, uncles, and grandparents). Response options included "yes," "no," and "don't know." Respondents also indicated if they had zero, one, or two or more siblings or second-degree relatives diagnosed with CHD or stroke/TIA. Family history of diabetes was positive if any first-degree relative had diabetes or high blood glucose levels, excluding pregnancy-related diagnoses. Response options were "yes," "no," and "don't know." Diabetes type and age at onset were not ascertained.

Statistical analyses

We used descriptive statistics to characterize respondents, chi-square tests to assess differences in proportions, and the Student *t* test to assess differences in means. Odds ratios (ORs) were calculated to assess the associations of individual family history characteristics with self-reported early-onset CHD compared with no CHD, with adjustment for age, sex, ethnicity/race, marital status, education, income, self-reported obesity, hypercholesterolemia, and hypertension. These individual family history characteristics describe differences in age at onset of CHD (early or late), number of affected relatives (only one or two or more), type of relative with CHD (parent or sibling), or lineage of affected relatives (nuclear, maternal, or paternal). Given the small number of observations for many of these individual family history characteristics, we could not assess associations between combinations of these characteristics and CHD. Because previous reports have found sex-specific effects on the association between family history and CHD,[14–17] the Breslow Day test for OR heterogeneity was performed to assess interactions between the various family history definitions and sex. When significant interactions ($P < .05$) were found, sex-specific associations are reported. Personal histories of stroke or diabetes were not included in the models because these diagnoses are considered CHD risk equivalents by the NCEP ATPIII guidelines.[12] According to these guidelines, because the magnitude of risk for CHD is so great for individuals with diabetes or stroke, regardless of the presence of other risk factors, the threshold for aggressive preventive intervention is reached and clinicians are advised to approach CHD prevention in these individuals as if CHD had already been diagnosed. Considering this perspective, we chose not to include these diagnoses in our models, because in practice knowing family history would not be relevant to the risk stratification and resulting preventive recommendations. In addition, because numerous studies have found significant associations between family history of CHD and personal history of stroke,[18–23] and because family history of diabetes is associated with family history of CHD,[24] it is unlikely that the overall patterns and strength of associations would change substantially if we included personal history of diabetes and stroke in our models. The 79 individuals with late-onset CHD were excluded from the analyses. "Don't know" responses were considered as "no" responses in the logistic regression models. All statistical analyses were performed using SAS v8.2 (SAS Institute, Cary, NC).

RESULTS

Respondent characteristics

There were 4035 respondents, including 178 with early-onset CHD, 79 with late-onset CHD, and 3778 with no personal history of CHD. The characteristics of respondents with early-onset CHD and no CHD are presented in Table 1. The mean age of respondents with no history of CHD was significantly less than the mean age of respondents with early-onset CHD: 47.5 years (standard

Table 1
Characteristics of respondents with early-onset coronary heart disease and no coronary heart disease (HealthStyles 2003 Survey of Health-related Attitudes and Behaviors Among the U.S. Adult Population)

Characteristic	Early-onset CHD (n = 178) n (%)	No CHD (n = 3778) n (%)	*P* values[a]
Female	81 (45.5)	2307 (61.1)	.002
Age group[b]			
18–34y	8 (4.5)	692 (18.3)	.00004
35–44y	16 (9.0)	28.8 (1088)	<.00002
45–54 y	54 (30.3)	956 (25.3)	.13
55–64 y	62 (34.8)	493 (13.0)	<.00002
65+ y	38 (21.3)	549 (14.5)	.2
Race/ethnicity			
White	127 (71.3)	2709 (71.7)	.91
African American	26 (14.6)	462 (12.2)	.33
Hispanic	15 (8.4)	428 (11.3)	.23
Asian	5 (2.8)	132 (3.5)	.62
Other race/ethnicity	5 (2.8)	47 (1.2)	.12
More than high school education	92 (51.7)	2321 (61.4)	.18
Ever married	166 (93.3)	3268 (86.5)	.18
Income >$35,000	71 (39.9)	2195 (58.1)	.00004
Stroke onset <60 y	29 (16.3)	87 (2.3)	<.00002
Stroke onset >60 y	30 (16.9)	127 (3.4)	<.00002
Diabetes	69 (38.8)	397 (10.5)	<.00002
Obesity	52 (29.2)	631 (16.7)	.00032
Hypertension	124 (69.7)	1158 (30.7)	<.00002
Hypercholesterolemia	130 (73.0)	1190 (31.5)	<.00002

CHD, coronary heart disease; early-onset CHD, disease at or before age 60 years.
[a]Corrected *P* values adjusted for 20 comparisons.
[b]Mean age (standard deviation) for early-onset CHD, 55.8 years (11.1 years) and no CHD, 47.5 years (14.1 years) ($P < .0001$).

deviation 14.1) and 55.8 years (standard deviation 11.1), respectively ($P < .0001$). There were also significantly fewer women among respondents with early-onset CHD compared with the respondents with no CHD, and respondents with early-onset CHD were significantly less likely to have annual incomes of $35,000 or more. As expected, reports of personal history of stroke, diabetes, hypertension, hypercholesterolemia, and obesity were significantly greater among respondents with early-onset CHD compared with respondents without CHD.

Prevalence of familial disease

Among all respondents, approximately half reported having at least one first- or second-degree relative with CHD, and approximately three quarters (76.6%) had a family history of CHD, stroke, or diabetes. Family history of stroke was reported more often by women (46.9%) than men (39.0%) ($P < .0001$). Frequency of family history of diabetes was similar for women (43.1%) and men (41.2%). The most prevalent family history reported by respondents included CHD, stroke, and diabetes in first- and/or second-degree relatives (15.8%), followed by CHD and stroke (14.6%), CHD only (11.8%), diabetes only (11.1%), CHD and diabetes (9.8%), stroke only (7.7%), and stroke and diabetes (5.6%).

Awareness of family history

In general, for both CHD and stroke, the respondents had significantly fewer "don't know" responses for disease status among first-degree relatives compared with second-degree relatives (data not shown). Respondents also had significantly greater awareness about disease status in mothers versus fathers and maternal compared with paternal second-degree relatives. Women and men had similar awareness of CHD, stroke, and diabetes among first- and second-degree relatives; however, women had fewer "don't know" responses (16.9%) than men (19.5%) concerning stroke in first-degree relatives ($P = .03$).

Family history of coronary heart disease

Prevalence ORs for individual characteristics of family history of CHD (e.g., age at onset, number of relatives affected, type or lineage of affected relatives) associated with personal history of early-onset CHD adjusted for demographic factors and self-reports of hypercholesterolemia, hypertension, and obesity are presented in Table 2. Combinations of these family history characteristics were not assessed. No significant sex-specific differences were found. In all analyses, the referent group was composed of respondents with no family history of CHD in first- or second-degree relatives.

In regard to age of onset, having at least one first-degree relative with early-onset CHD (OR = 5.0, 95% confidence interval [CI] 2.8–8.7) or at least one first-degree relative with late-onset CHD (OR = 2.5, 95% CI 1.2–5.3) was significantly associated with personal history of early-onset CHD. Regardless of the age of onset, having only one first-degree relative (OR = 3.0, 95% CI 1.7–5.4) or two or more first-degree relatives with CHD (OR = 5.1, 95% CI 2.8–9.4) was significantly associated with personal history of early-onset CHD. In regard to the type and lineage of first-degree relatives with CHD, the strength of association with early-onset CHD was similar (increased approximately threefold) given a mother, father, or sibling with CHD, and the strength of the association increased if a parent and a sibling had CHD (OR = 5.0, 95% CI 2.2–11.1) or if both parents were affected (OR = 6.2, 95% CI 2.9–13.3).

In regard to age of onset, regardless of number or lineage of affected second-degree relatives, having at least one second-degree relative (and no first-degree relative) with early-onset CHD was significantly associated with early-onset CHD (OR = 4.6, 95% CI 2.1–10.3). There were too few observations to assess the association between second-degree relatives with late-onset CHD and personal history of early-onset CHD. Having two or more second-degree relatives with CHD, regardless of the age of onset or lineage, was significantly associated with early-onset CHD (OR = 2.8, 95% CI 1.3–6.0).

Table 2
Associations between various definitions of family history of coronary heart disease and early-onset coronary heart disease

Definitions of family history of CHD	Early-onset CHD N = 178	No CHD N = 3778	Prevalence OR[a] for early-onset CHD (95% CI)
First-degree relatives only			
Having at least 1 first-degree relative with CHD (and no affected second-degree relative) regardless of age at onset, number, type, or lineage	53	566	3.8 (2.3–6.2)
No family history[b]	33	1701	1.0
Age of onset			
Regardless of number, type, or lineage of first-degree relatives with CHD, having at least 1 relative with:			
Early-onset CHD	33	256	5.0 (2.8–8.7)
Late-onset CHD	12	241	2.5 (1.2–5.3)
Early- and late-onset CHD	8	69	3.2 (1.2–8.5)
No family history[b]	33	1701	1.0
Number of affected relatives			
Regardless of age of onset, type, or lineage of first-degree relatives with CHD, having:			
1 relative with CHD	25	393	3.0 (1.7–5.4)
>2 relatives with CHD	28	173	5.1 (2.8–9.4)
No family history[b]	33	1701	1.0
Type of affected relatives			
Regardless of age of onset or number of first-degree relatives with CHD, having a:			
Sibling with CHD	10	88	3.1 (1.3–7.3)
Parent with CHD	30	390	3.8 (2.2–6.7)
Parent and sibling with CHD	13	88	5.0 (2.2–11.1)
No family history[b]	33	1701	1.0
Lineage of affected relatives			
Regardless of age of onset or number of first-degree relatives with CHD, having a:			
Nuclear relative with CHD[c]	10	88	3.1 (1.3–7.3)
Maternal relative with CHD[d]	10	144	2.8 (1.3–6.2)
Paternal relative with CHD[e]	18	255	3.5 (1.8–6.6)
Maternal and paternal relative with CHD[d,e]	15	79	6.2 (2.9–13.3)
No family history[b]	33	1701	1.0
Second-degree relatives only			
Having at least 1 second-degree relative with CHD (and no affected first-degree relative) regardless of age at onset, number, or lineage	20	667	2.2 (1.1–4.2)
No family history[b]	33	1701	1.0
Age of onset			
Regardless of number or lineage of second-degree relatives with CHD, having at least 1 relative with:			
Early-onset CHD	13	210	4.6 (2.1–10.3)
Late-onset CHD	2	215	NA
Early- and late-onset CHD	5	242	1.5 (0.5–4.3)
No family history[b]	33	1701	1.0

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Table 2
Continued

Definitions of family history of CHD	Early-onset CHD N = 178	No CHD N = 3778	Prevalence OR[a] for early-onset CHD (95% CI)
Number of affected relatives			
Regardless of age of onset or lineage of second-degree relatives with CHD, having:			
1 relative with CHD	5	290	1.3 (0.5–3.7)
>2 relatives with CHD	15	377	2.8 (1.3–6.0)
No family history[b]	33	1701	1.0
Lineage of affected relatives			
Regardless of age of onset or number of second-degree relatives with CHD, having a:			
Maternal relative with CHD	5	271	1.2 (0.4–3.6)
Paternal relative with CHD	6	205	2.3 (0.9–6.2)
Maternal and paternal relative with CHD	9	191	3.3 (1.3–8.0)
No family history[b]	33	1701	1.0
First- and second-degree relatives			
Having at least 1 first-degree and 1 second-degree relative with CHD regardless of age at onset, number, or lineage	72	666	4.5 (2.8–7.3)
No family history[b]	33	1701	1.0
Age of onset			
Regardless of number or lineage of first- and second-degree relatives with CHD, having at least 1 first-degree and 1 second-degree relative with:			
Early-onset CHD	21	117	9.8 (4.9–19.5)
Late-onset CHD	4	89	NA
Early- and late-onset CHD	47	460	4.1 (2.4–6.9)
No family history[b]	33	1701	1.0
Number of affected relatives			
Regardless of age of onset or lineage of first- and second-degree relatives with CHD, having:			
1 first- and 1 second-degree relative with CHD	8	116	3.0 (1.3–7.4)
>3 first- and second-degree relatives with CHD	64	550	4.7 (2.9–7.7)
No family history[b]	33	1701	1.0
Lineage of affected relatives			
Regardless of age of onset or number of first- and second-degree relatives with CHD, having:			
Maternal relatives with CHD	14	117	5.5 (2.7–11.4)
Paternal relatives with CHD	8	124	2.9 (1.2–7.1)
Maternal and paternal relatives with CHD	50	425	4.5 (2.7–7.6)
No family history[b]	33	1701	1.0

CHD, coronary heart disease; early-onset CHD, disease at or before age 60 years; OR, odds ratio; CI, confidence interval; NA, not available (because there were too few observations to calculate).
[a]Adjusted for age, race/ethnicity, marital status, education, income, self-reported obesity, hypercholesterolemia, and hypertension.
[b]No first- or second-degree relatives with CHD.
[c]Sibling(s) only.
[d]Mother only or mother and sibling(s).
[e]Father only or father and sibling(s).

Table 3
Associations between various definitions of family history of stroke and early-onset coronary heart disease

Definitions of family history of stroke	Early-onset CHD (N = 178)	No CHD (N = 3778)	Prevalence OR[a] for early-onset CHD (95% CI)
First-degree only			
Having at least 1 first-degree relative with stroke (and no affected second-degree relative) regardless of age at onset, number, type, or lineage	51	701	1.5 (1.0–2.3)
No family history[b]	81	2139	1.0
Age of onset			
Regardless of number, type, or lineage of first-degree relatives with stroke, having at least 1 relative with:			
Early-onset stroke	25	232	2.9 (1.7–5.0)
Late-onset stroke	25	420	1.2 (0.7–2.0)
Early- and late-onset stroke	1	49	NA
No family history[b]	81	2139	1.0
Number of affected relatives			
Regardless of age of onset, type, or lineage of first-degree relatives with stroke, having:			
1 relative with stroke	40	566	1.6 (1.0–2.5)
>2 relatives with stroke[c]	F:8	F:80	F:2.0 (0.8–4.7)
	M:3	M:55	NA
No family history[b]	81	2139	1.0
Type of affected relatives			
Regardless of age of onset or number of first-degree relatives with stroke, having a:			
Sibling with stroke	8	53	3.2 (1.2–8.3)
Parent with stroke	39	590	1.5 (1.0–2.3)
Parent and sibling with stroke	4	58	NA
No family history[b]	81	2139	1.0
Lineage of affected relatives			
Regardless of age of onset or number of first-degree relatives with stroke, having a:			
Nuclear relative with stroke[d]	8	53	3.2 (1.2–8.3)
Maternal relative with stroke[e]	23	276	1.6 (0.9–2.7)
Paternal relative with stroke[f]	14	287	1.2 (0.7–2.4)
Maternal and paternal relatives with stroke[e,f]	6	85	1.3 (0.5–3.2)
No family history[b]	81	2139	1.0
Second-degree only			
Having at least 1 second-degree relative with stroke (and no affected first-degree relative) regardless of age at onset, number, or lineage	22	567	1.6 (0.9–2.7)
No family history[b]	81	2139	1.0
Age of onset			
Regardless of number or lineage of second-degree relatives with stroke, having at least 1 relative with:			
Early-onset stroke	5	100	2.2 (0.7–6.6)
Late-onset stroke	10	340	1.3 (0.6–2.7)
Early- and late-onset stroke	7	127	1.5 (0.6–4.0)
No family history[b]	81	2139	1.0

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Table 3
Continued

Definitions of family history of stroke	Early-onset CHD (N = 178)	No CHD (N = 3778)	Prevalence OR[a] for early-onset CHD (95% CI)
Number of affected relatives			
Regardless of age of onset or lineage of second-degree relatives with stroke, having:			
1 relative with stroke	9	332	1.2 (0.5–2.6)
>2 relatives with stroke	13	235	0.3 (0.1–0.9)
No family history[b]	81	2139	1.0
Lineage of affected relatives			
Regardless of age of onset or number of second-degree relatives with stroke, having a:			
Maternal relative with stroke	10	262	1.4 (0.7–3.0)
Paternal relative with stroke	6	178	1.7 (0.7–4.4)
Maternal and paternal relative with stroke	6	127	1.4 (0.5–3.9)
No family history[b]	81	2139	1.0
First and second-degree relatives			
Having at least 1 first-degree and 1 second-degree relative with stroke regardless of age of onset, number, or lineage[c]	F:19 M:5	F:246 M:125	F:2.4 (1.3–4.4) M:0.7 (0.2–1.8)
No family history[b]	81	2139	1.0
Age of onset			
Regardless of number or lineage of first- and second-degree relatives with stroke, having at least 1 first-degree and 1 second-degree relative with:			
Early-onset stroke	0	34	NA
Late-onset stroke	5	114	1.1 (0.4–3.0)
Early- and late-onsetstroke[c]	F:15	F:105	F:3.1 (1.6–6.1)
	M:4	M:73	NA
No family history[b]	81	2139	1.0
Number of affected relatives			
Regardless of age of onset or lineage of first- and second-degree relatives with stroke, having:			
1 first- and 1 second-degree relative with stroke	6	130	1.2 (0.5–2.9)
>3 first- and second-degree relatives with stroke[c]	F:13	F:158	F:2.5 (1.2–5.2)
	M:5	M:83	M:0.9 (0.3–2.4)
No family history[b]	81	2139	1.0
Lineage of affected relative			
Regardless of age of onset or number of first- and second-degree relatives with stroke, having:			
Maternal relatives with stroke	2	108	NA
Paternal relatives with stroke	8	65	2.7 (1.1–6.3)
Maternal and paternal relatives with stroke	2	108	NA
No family history[b]	81	2139	1.0

CHD, coronary heart disease; early-onset CHD, disease at or before age 60 years; F, female; M, male; NA, not available (because there were too few observations to calculate).
[a]Adjusted for age, race/ethnicity, marital status, education, income, self-reported obesity, hypercholesterolemia, and hypertension.
[b]No first- or second-degree relatives with stroke.
[c]Significant interaction between sex and family history ($P < .05$) was found, and interaction term was included in the regression model.
[d]Sibling(s) only.
[e]Mother only or mother and sibling(s).
[f]Father only or father and sibling(s).

The most significant association with early-onset CHD was found when both first- and second-degree relatives had early-onset CHD (OR = 9.8, 95% CI 4.9–19.5). The strength of association increased with increasing numbers of affected first- and second-degree relatives, and given affected maternal relatives compared with paternal relatives, although the differences were not statistically significant.

Family history of stroke

The associations between various family history definitions of stroke and personal history of early-onset CHD adjusted for demographic factors and self-reports of hypercholesterolemia, hypertension, and obesity are presented in Table 3. Combinations of these family history characteristics were not assessed. In all analyses, the referent group was composed of respondents with no family history of stroke in first- or second-degree relatives.

History of early-onset stroke in at least one first-degree relative was significantly associated with personal history of early-onset CHD (OR = 2.9, 95% CI 1.7-5.0). Having two or more first-degree relatives with stroke, regardless of age of onset, was not associated with early-onset CHD in women, and there were too few observations of men with this family history to assess the association with early-onset CHD. When only first-degree relatives were affected with stroke, sibling history was significantly associated with personal history of early-onset CHD (OR = 3.2, 95% CI 1.2–8.3). However, stroke in one or both parents was not. The number of parent and sibling pairs with stroke was too small to assess associations with early-onset CHD.

No significant associations with early-onset CHD were observed given only second-degree relatives with stroke. When both first and second-degree relatives were affected, there was a significant association with early-onset CHD if these relatives were on the paternal side of the family (OR = 2.7, 95% CI 1.1–6.3). There were too few maternal first- and second-degree relatives with stoke to assess an association with early-onset CHD. Among female respondents, significant associations with early-onset CHD were observed given affected first- and second-degree relatives at any age of onset regardless of the lineage of affected relatives (OR = 2.4, 95% CI 1.3–4.4). There were too few male respondents with affected first- and second-degree relatives to assess an association with early-onset CHD.

Family history of diabetes

A family history of at least one first-degree relative with diabetes was reported by 67.9% (55/81) of women and 51.5% (50/97) of men with early-onset CHD, compared with 42.2% (973/2307) of women and 40.6% (597/1471) of men without CHD. This family history was significantly associated with early-onset CHD in women (OR = 2.4, 95% CI 1.5–4.0), but not in men (OR = 1.1, 95% CI 0.7–1.7).

DISCUSSION

In this cross-sectional survey, we found that family histories of CHD, stroke, and diabetes were prevalent and significantly associated with self-reported, early-onset CHD. We investigated various definitions of family history beyond early-onset CHD in first-degree relatives and identified several significant associations with CHD diagnosed at or before age 60 years (Table 4).

Table 4
Summary of significant associations between family history and early-onset coronary heart disease

Family history definitions
≥1 first-degree relative with early-onset CHD
≥1 first-degree relative with late-onset CHD
1 first-degree relative with CHD at any age of onset
≥2 first-degree relatives with CHD at any age of onset
≥1 sibling with CHD at any age of onset
≥1 parent with CHD at any age of onset
Parent and sibling pair with CHD at any age of onset
Maternal first-degree relatives[a] with CHD at any age of onset
Paternal first-degree relatives[b] with CHD at any age of onset
Maternal and paternal first-degree relatives[a, b] with CHD at any age of onset
≥1 second-degree relative with early-onset CHD
≥2 second-degree relatives with CHD at any age of onset
First- and second-degree relatives with CHD at any age of onset
≥1 first-degree relative with early-onset stroke
≥1 sibling with stroke at any age of onset
First- and second-degree relatives with stroke at any age of onset[c]
≥1 first-degree relative with diabetes[c]

CHD, coronary heart disease; early-onset CHD, disease at or before age 60 years; late-onset CHD, disease after age 60 years.
[a]Mother only or mother and siblings.
[b]Father only or father and siblings.
[c]Significant association among women only.

Early-onset versus late-onset coronary heart disease in relatives

Several studies have shown CHD risk is greater given younger ages of onset in relatives.[3,7–10,14,25,26] Studies that have investigated family history of late-onset disease have found positive associations with CHD, although comparatively the relative risks are smaller.[7–10,25,26] We found significant increases in early-onset CHD given early-onset CHD in either first- or second-degree relatives. Late-onset CHD in first-degree relatives was also significantly associated with early-onset CHD; however, the strength of association was reduced by half, 5.0-fold versus 2.5-fold increase, respectively. There were too few observations to assess associations between early-onset CHD given second-degree relatives with late-onset CHD.

Second-degree relatives with coronary heart disease

A recent study described a significant association between family history of premature CHD in second-degree relatives and coronary artery calcification in men aged 40 to 50 years.[27] We found that CHD in second-degree relatives, even in the absence of CHD in a first-degree relative, is significantly asso-

ciated with self-reports of early-onset CHD, and this seems to be attributable in large part to early-onset disease or having more than one affected second-degree relative. In addition, having second-degree relatives with early-onset CHD substantially increased the strength of association with CHD compared with having affected first-degree relatives only. To our knowledge, this is the first report of these key findings. These results have important implications for CHD risk assessment. Traditionally, assessment of family history has been limited to first-degree relatives. This limitation may be attributable in large part to a lack of data collection regarding second-degree relatives in large epidemiologic or clinical investigations of CHD, and as a result evidence about the impact of this information on CHD risk has been lacking.

Number of relatives with coronary heart disease

Several studies have shown increasing magnitude in CHD risk with increasing numbers of first-degree relatives with CHD.[7,8,14,15,26,28] Our results confirm this association, and we identified the same trend given increasing numbers of second-degree relatives with CHD regardless of age at onset or lineage.

Lineage of relatives with coronary heart disease

We found that when only first-degree relatives are affected, having an affected mother or father conferred a similar risk for early-onset CHD. However, when both first- and second-degree relatives are affected with CHD, there seemed to be a stronger association given affected maternal relatives compared with paternal relatives; however, the differences are not significant. Results from the Physicians' Health Study and the Women's Health Study found maternal history of MI was more strongly associated with MI at any age than was a paternal history of MI.[25] Other studies[6,14,28,29] have not identified an effect of lineage on CHD risk, perhaps because their definition of positive family history of CHD was restricted to first-degree relatives and, as in our analyses, considered only the outcome of early-onset CHD.

Type of relative with coronary heart disease

We did not find a substantial difference in risk for early-onset CHD given parental or sibling history of CHD. Our findings differ from those of other reports. A case-control study of women aged 18 to 44 years found sibling history of CHD was a stronger risk factor than parental history.[30] Silberberg et al.[8] also found greater risk with sibling history, and more recently, sibling history of CHD was described as a stronger risk factor for subclinical CHD.[31] The discrepancy in the results of these studies and ours may be explained by demographic differences, such as a younger age of study participants or different clinical end points in other studies (i.e., self-reports of CHD vs. subclinical CHD).

CHD is a complex disease because of interactions of genetic and environmental risk factors, and family history is currently the best method available to assess the interaction of these shared risk factors.[32] Given that shared environmental effects on CHD risk are stronger for sibling pairs than parent–offspring pairs,[33,34] results from previous studies seem to suggest a more important role for environmental/behavioral factors contributing to familial aggregation of CHD. However, the results of our study are not consistent with this notion; we found similar ORs for early-onset CHD given affected siblings or affected parents, and a stronger association if parents and siblings were both affected. These results suggest genetic factors that travel across generations play an important role in susceptibility to early-onset CHD. This idea is further supported by our finding of significant associations with CHD given first and second-degree relatives with CHD from one lineage (maternal or paternal).

Family history of stroke

Our results show that family history of early-onset stroke in first-degree relatives was significantly associated with early-onset CHD in all respondents. Unlike the situation with CHD, we did find that sibling history of stroke, but not parental history, was significantly associated with early-onset CHD. This finding suggests an important role for environmental or behavioral factors in explaining this association, or a recessive mechanism for a major gene or genes involved in CHD susceptibility might be responsible for the observation. However, a recessive gene or genes seem less likely given our observation that, at least among women, early-onset CHD was significantly more likely given an increasing number of relatives with stroke across generations (first- and second-degree relatives). The number of males with this type of family history was too small to assess an association. The Rancho Bernardo study found family history of stroke in any first-degree relative was an independent predictor of ischemic heart disease mortality in men, but not in women.[35] Because that study's family history data did not include age of stroke onset or second-degree relatives, the investigators may have been limited in detecting the significant associations that we found in women. Other reports investigating the effect of stroke family history on CHD risk have found positive associations, but none have assessed the association according to sex.[36–38]

Family history of diabetes

We found that family history of diabetes was significantly associated with early-onset CHD in women, but not in men. To our knowledge, this is the first report of this association. A previous study showed that family history of diabetes was associated with CHD in persons with type 1 diabetes.[39] Although family history of diabetes was not associated with CHD mortality in the Rancho Bernardo study, those participants with a family history of diabetes included a greater proportion with a family history of heart attack.[24]

Diabetes is a stronger risk factor for CHD in women than in men.[40,41] Our results suggest that genetic or environmental/behavioral factors shared by family members contribute to the CHD associated with diabetes in women, rather than factors solely associated with the internal milieu of females (e.g., hormones). Additional evidence for diabetes-related genetic factors contributing to CHD among women comes from a study that found the influence of genetic factors on body fat, insulin,

and cardiovascular disease differed between the sexes, with higher heritability estimates for women.[42]

Study strengths and limitations

The major strengths of this study are the large number of respondents to the HealthStyles survey and the equal representation of the sexes across a range of adult age groups. However, because of the limited number of respondents with late-onset CHD (n = 79) we were unable to assess associations between the various family history definitions investigated in this study and personal history of late-onset CHD. In addition, although the survey is population-based, it is subject to selection bias because the participants are voluntary respondents and thus not randomly drawn from the U.S. population. In addition, the cross-sectional design prohibits establishment of any temporal associations concerning family history as a risk factor, and because the data were obtained from prevalent cases the results may be confounded by survival.

Another potential limitation is lack of validation of self-reports. A previous study showed that self-reports of CHD and risk factors are reliable,[43] and several studies have investigated the validity of family history reports. For family history of CHD in first-degree relatives, sensitivity ranges from 67% to 89%, and specificity ranges from 59% to 97%, with most values greater than 90%.[8,30,44–47] Sensitivity values range from 56% to 87% for family history of diabetes, and specificity ranges from 97% to 98%.[44,47] For family history of stroke, sensitivity ranges from 42% to 51% with a specificity from 96% to 98%.[47] A personal history of CHD or having a CHD risk factor such as hypertension, diabetes, or hypercholesterolemia generally does not affect the accuracy of the family history report, nor does gender.[44,45,47] However, older individuals are more likely to give inaccurate family history compared with younger individuals.[44,47] 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 family history accuracy between whites and African Americans reporting on CHD, diabetes, and hypertension.[44] 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.[48] There are no available reports regarding the validity of family history of CHD, stroke, or diabetes in second-degree relatives; however, review of the cancer literature has shown decreased accuracy of reports with increasing degree of relationship, yet specificity tends to remain high.[48,49] Given these estimates of validity, a family history of CHD, stroke, or diabetes generally can be considered as accurate, with little overreporting of disease in close family members.

We found some sex-specific differences regarding certain types of family history associated with CHD. These differences might be attributable in part to differences in unmeasured demographic or cardiovascular risk factors, such as smoking and inactivity, that could affect the associations between family history and CHD. Alternatively, the sex-specific differences in family history reporting might reflect a reporting bias. However, such bias has not been observed in studies investigating accuracy of family history reporting.[8,44,47]

We also found differences in awareness of disease according to lineage. Respondents knew more about the presence or absence of disease (there were fewer "don't know" responses) for maternal relatives compared with paternal relatives. Other investigators studying family history reports of breast cancer have also found more reports of breast cancer among maternal relatives compared with paternal relatives, even after excluding cases with affected mothers.[50,51] However, the cause for these differences is not known and is deserving of further study. It may be that such differences reflect true biologic differences attributable to mitochondrial inheritance, epigenetic factors, or in utero effects, or it may be true reporting bias because of lack of information about paternal relatives or reduced family communication about disease in paternal relatives.

The impact of lifestyle risk factors could not be assessed in this study, such as smoking, inactivity, and diet, because these data were not collected in the HealthStyles 2003 survey. These risk factors are often shared by family members and could underlie some of the patterns of familial risk we observed in this study. However, we could not discern the contribution of these factors in our analyses, which also limited our ability to infer the possible benefit resulting from preventive interventions targeted to these risk factors. Tavani et al.[52] showed that individuals with increased familial risk for CHD may derive the greatest benefit from traditional preventive strategies.

SUMMARY AND IMPLICATIONS

Family histories of CHD, stroke, or diabetes are prevalent. We found significant associations between personal history of early-onset CHD and additional family history that goes beyond having first-degree relatives with early-onset CHD. For the first time we describe significant associations between personal history of early-onset CHD and having second-degree relatives with CHD, and we describe a significant association between family history of diabetes and personal history of early-onset CHD in women, but not in men. We also showed that the type or lineage of affected relatives can influence early-onset CHD, and that sex can affect associations between certain definitions of family history and CHD. We also confirmed an association between family history of stroke and early-onset CHD. Confirmation of our findings in large, population-based studies is needed. If replicated, these results may have important implications for risk assessment and prevention of CHD.

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