The association of cardiovascular mortality with a first-degree family member history of different cardiovascular diseases

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ABSTRACT

OBJECTIVE   To investigate which history of cardiovascular disease [coronary heart disease (CHD), stroke, or peripheral arterial disease] in a first-degree family member predicts cardiovascular mortality.

METHODS   We studied a prospective cohort (the Lipid Research Clinics Prevalence Study) from ten primary care centers across North America. The primary outcome was cardiovascular mortality, assessed using Cox survival models.

RESULTS   There were 8,646 participants (mean age: 47.4 ± 12.1 years, 46% women, 52% of participants with hyperlipidemia) who were followed up for a mean duration of 19.4 ± 4.9 years. There were 1,851 deaths (21%), including 852 cardiovascular deaths. A paternal, maternal or sibling history of premature CHD (before 60 years) was present in 26% of participants, of stroke in 27% of participants, and of peripheral arterial disease in 24% of participants. After adjusting for risk factors (age, sex, systolic blood pressure, diastolic blood pressure, body mass index, smoking, fasting glucose, low-density lipoprotein cholesterol and triglycerides), only a paternal history of premature or any CHD, a maternal history of diabetes mellitus or premature or any CHD, and a sibling history of premature CHD, hypertension, or hyperlipidemia were individually predictive of cardiovascular mortality. After adjusting for risk factors and the mentioned familial factors, only paternal and maternal histories of CHD, especially before 60 years, remained predictive of cardiovascular mortality, with a somewhat higher association for a maternal history [adjusted hazard ratio (aHR) = 1.99, 95% CI: 1.36–2.92, *P* < 0.001 for maternal history of premature CHD; aHR = 1.52, 95% CI: 1.10–2.10, *P* = 0.011 for paternal history of premature CHD]. Family history of stroke or peripheral arterial disease did not predict cardiovascular mortality. Parental history of premature CHD predicted cardiovascular mortality independently of baseline age (< 60 years and ≥ 60 years), hypertension, or hyperlipidemia and carried more important prognostic value in men rather than women.

CONCLUSIONS   In this study, a parental history of CHD, especially before 60 years, best predicted cardiovascular mortality. This finding could help more accurately identify high-risk patients who would benefit from preventive strategies.

Cardiovascular mortality is defined as death due to diseases of the heart or blood vessels, most commonly coronary heart disease (CHD), sudden cardiac death, or stroke. CHD and stroke remain the leading causes of death worldwide.[1] Care for cardiovascular disease (CVD) and loss of productivity due to disability or death costs the United States around $219 billion yearly.[2] A variety of modifiable risk factors have been asso-

ciated with increased risk of CVD and mortality, namely hypertension, hyperlipidemia, diabetes mellitus (DM), obesity and smoking. The identification of such risk factors and their overall assessment along with other non-modifiable risk factors, mainly age and family history of CVD, is crucial to help estimate an individual's risk and ultimately guide therapy.[3]

The important role of family history in the devel-

opment of CVD has been shown in many prospective cohorts.[4-8] However, several controversies exist about the prognostic value of a family history of CVD. This is reflected in the variation of the definitions used across different studies and risk calculators.[9] Firstly, there is scarcity of data on what constitutes a clinically meaningful familial history of CVD. For instance, whether different cardiovascular conditions (e.g., CHD, stroke, or peripheral arterial disease) in different first-degree family members (parents, siblings, or children) carry distinct prognostic values remains unclear.[4,5] Secondly, whether a family history of CVD onset at any age (as opposed to a family history of premature CVD) is an important risk factor is unsure.[7] Thirdly, whether there are sex-based differences in the role of a familial history of CVD in individual risk assessment is also unclear.[7,8,10]

Given all these considerations, additional research is needed to further characterize the relationship between familial history and cardiovascular risk. Using patient data from the Lipid Research Clinics Prevalence Study[11] with up to twenty-three years of follow-up, we aimed to determine which specific first-degree familial histories of CVD (CHD, stroke, or peripheral arterial disease) predict cardiovascular mortality.

METHODS

Study Design and Participants

Participants took part in the Lipid Research Clinics Prevalence Study[11], a prospective cohort of North American individuals across ten geographic locations and diverse socioeconomic and occupational groups, as previously described.[12-14] The populations fell into three broad categories: occupational groups, household or residential groups, and parents of school children. At their first visit, individuals were screened from ten primary care centers in North America. A sample consisting of all visit 1 participants with elevated lipid levels, as well as an additional random sample of 15% of visit 1 participants were invited back for visit 2. The random sample constituted 58% of the total study participants, and the rest were individuals with elev-

ated lipid levels. Overall, 52% of participants invited to visit 2 had hyperlipidemia.

During visit 2 (between 1972 and 1976), participants underwent a medical interview, physical examination, fasting blood studies, and a treadmill exercise test. Six participants were lost to follow-up and were excluded from the current analysis, resulting in 8,646 participants. Follow-up was until death or December 31, 1995. All participants gave written informed consent at study enrollment. The Institutional Review Boards of the Brigham and Women's Hospital and the American University of Beirut approved the present study. This research was considered exempt.

Family History of CVD

Participants were asked during visit 2 about the presence of familial cardiovascular risk factors or diseases among first-degree family members (parents, siblings, or children). Familial factors assessed included history of hypertension, DM, hyperlipidemia, CHD (defined as history of heart attack or angina), premature CHD (before 60 years), stroke, and peripheral arterial disease. A sample question asked was: "Did your father have a heart attack or angina? If so, did this occur before he was 60 years?". We were not able to properly assess the association between cardiovascular mortality and history of disease in children, as the frequency of disease in offspring was low, given the younger age of the study population.

Participants' glucose and lipid levels were obtained after an overnight fast. Patients were considered to have hyperlipidemia if they had either low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL, total cholesterol ≥ 240 mg/dL, or triglycerides ≥ 200 mg/dL. Patients were considered to have DM if they had fasting glucose ≥ 126 mg/dL or used antidiabetic medications. Blood pressure was recorded as the mean value of two measurements at rest (supine). Hypertension was defined as a resting systolic blood pressure (SBP) ≥ 140 mmHg, resting diastolic blood pressure (DBP) ≥ 90 mmHg, or the use of antihypertensive medications. Participants were considered smokers if they had ever smoked cigarettes.

Cardiovascular Mortality

The primary outcome of this study was cardiovascular mortality. From 1976 to 1988, participant deaths were reported by mail or phone and then confirmed with either death certificates, family member or witness interviews, or via medical records. Reason of death was determined by cardiologists who were blinded to the identity of the departed. From 1988 to 1995, deaths were reported from death certificates by trained nosologists who used the National Death Index from 1998 to 1991 and then the Epidemiology Research Index from 1992 to 1995.[15]

Statistical Analysis

Baseline demographic and clinical characteristics were compared between groups with and without family history of premature CHD, using the Student's *t*-test for continuous variables and the Pearson's chi-squared test or Fisher's exact probability test for categorical variables (Table 1).

For survival analysis using Cox survival models, paternal, maternal and sibling history of diseases were first individually assessed for their association with time to cardiovascular mortality, after adjusting for risk factors (age, sex, SBP, DBP, body mass index, smoking, fasting glucose, LDL-C and triglycerides) (Table 2).

Only familial histories of disease that were significantly ($P < 0.05$) predictive of cardiovascular mortality after adjusting for risk factors were considered eligible to enter the final Cox survival model (Table 3). The final model thus aimed to identify which familial factors remain significant predictors of cardiovascular mortality after adjusting for risk factors and familial histories of disease that showed, at an individual level, significant associations with cardiovascular mortality. The proportional hazards assumption was satisfied using Schoenfeld residuals. Subgroup analyses were performed by sex, baseline age (< 60 years and ≥ 60 years), lipid and hypertensive statuses.

Harrell's C-index, the net reclassification index and the integrated discrimination index were used to evaluate the improvement in predicting cardiovascular mortality gained by adding familial history of CVD to standard clinical variables.

A two-sided P-value less than 0.05 was considered statistically significant, and statistical analyses were performed using STATA software (version 13.0).

Table 1   Baseline demographic and clinical characteristics grouped by presence of a family (paternal, maternal or sibling) history of premature coronary heart disease (before age 60 years).

Variables	Family history of premature coronary heart disease		
	Absent (*n* = 6,440)	Present (*n* = 2,206)	*P*-value
Age, yrs	47.1 ± 12.1	48.1 ± 12.1	< 0.001
Women	2,877 (44.7%)	1,126 (51.0%)	< 0.001
White race	6,092 (94.6%)	2,130 (96.6%)	< 0.001
Systolic blood pressure, mmHg	128.4 ± 20.1	129.8 ± 21.4	0.008
Diastolic blood pressure, mmHg	84.0 ± 11.3	84.5 ± 11.9	0.066
Hypertension	2,722 (42.3%)	991 (44.9%)	0.030
Smoking	4,104 (63.7%)	1,413 (64.1%)	0.783
Body mass index, kg/m^2	25.9 ± 4.2	26.2 ± 4.4	0.018
Body mass index ≥ 30 kg/m^2	937 (14.6%)	397 (18.0%)	< 0.001
Fasting glucose, mg/dL	98.5 ± 21.7	100.3 ± 27.0	0.004
Diabetes mellitus	225 (3.5%)	132 (6.0%)	< 0.001
Low-density lipoprotein cholesterol, mg/dL	144.9 ± 41.5	152.0 ± 44.0	< 0.001
High-density lipoprotein cholesterol, mg/dL	51.2 ± 16.5	50.0 ± 16.5	0.003
Total cholesterol, mg/dL	221.8 ± 46.3	229.3 ± 52.4	< 0.001
Triglycerides, mg/dL	122 (85–185)[*]	130 (91–192)[*]	0.024

Data are presented as means ± SD or *n* (%). [*]Presented as median (interquartile range).

Table 2 Adjusted hazard ratio of cardiovascular mortality for first-degree familial histories of different cardiovascular diseases.
Estimates were adjusted for age, sex, systolic blood pressure, diastolic blood pressure, body mass index, smoking, fasting glucose, low-density lipoprotein cholesterol and triglycerides.

Variables	Cardiovascular mortality	
	Adjusted hazard ratio (95% CI)	*P*-value
Paternal history of disease		
Hypertension	1.18 (0.93–1.49)	0.167
Diabetes mellitus	0.89 (0.61–1.30)	0.548
Hyperlipidemia	0.98 (0.52–1.84)	0.944
CHD	1.29 (1.07–1.55)	0.009[*]
CHD before 60 yrs	1.40 (1.08–1.82)	0.011[*]
Stroke	1.11 (0.90–1.37)	0.338
Peripheral arterial disease	1.05 (0.81–1.37)	0.708
Maternal history of disease		
Hypertension	1.00 (0.83–1.21)	0.981
Diabetes mellitus	1.32 (1.02–1.70)	0.032[*]
Hyperlipidemia	1.07 (0.62–1.87)	0.803
CHD	1.27 (1.03–1.56)	0.027[*]
CHD before 60 yrs	1.71 (1.25–2.35)	0.001[*]
Stroke	0.99 (0.80–1.23)	0.944
Peripheral arterial disease	1.20 (0.92–1.57)	0.181
Sibling history of disease		
Hypertension	1.43 (1.16–1.77)	0.001[*]
Diabetes mellitus	1.22 (0.94–1.58)	0.131
Hyperlipidemia	1.58 (1.11–2.25)	0.010[*]
CHD	Not available	Not available
CHD before 60 yrs	1.34 (1.09–1.64)	0.006[*]
Stroke	1.09 (0.79–1.49)	0.605
Peripheral arterial disease	1.05 (0.73–1.49)	0.803

[*]Refers to the $P < 0.05$. CHD: coronary heart disease.

RESULTS

There were 8,646 individuals (mean age: 47.4 ± 12.1 years, 46% women, 52% of participants with hyperlipidemia) who were followed up for a mean duration of 19.4 ± 4.9 years. There were 1,851 deaths (21%), including 852 cardiovascular deaths (46% of deaths). 2,206 of participants (26%) had either a father, mother, or sibling with a history of premature CHD, 2,302 of participants (27%) had either a father, mother or sibling with a history of stroke, and 2,049 of participants (24%) had either a father, mother or sibling with a history of peripheral arterial disease.

Participants with a family (paternal, maternal or sibling) history of premature CHD had higher rates of cardiovascular mortality during follow-up (12.8% *vs.* 8.8%, $P < 0.001$). They were also more likely to have significantly higher baseline levels of fasting glucose, LDL-C, total cholesterol, triglycerides, and lower levels of high-density lipoprotein cholesterol. They also had higher rates of hypertension and obesity (Table 1).

Cumulative incidence curves of cardiovascular mortality grouped by presence of paternal, maternal, or sibling history of premature CHD (Figure 1A) or stroke (Figure 1B) diverge very early (log rank $P < 0.001$). The cumulative incidence curves of cardiovascular mortality grouped by presence of paternal, maternal, or sibling history of peripheral arterial disease exhibit however substantial overlap (Figure 1C).

Table 3   Hazard ratio of cardiovascular mortality for standard clinical and familial factors included in the final model.

	Cardiovascular mortality	
	Adjusted hazard ratio (95% CI)	*P*-value
Clinical factors		
Age, yrs	1.11 (1.10−1.13)	< 0.001
Women	0.55 (0.43−0.71)	< 0.001
Fasting glucose, 10 mg/dL increments	1.06 (1.04−1.10)	< 0.001
Systolic blood pressure, 10 mmHg increments	1.08 (1.01−1.15)	0.024
Diastolic blood pressure, 10 mmHg increments	1.10 (0.98−1.24)	0.103
Smoking	1.50 (1.17−1.92)	0.001
Low-density lipoprotein cholesterol, 10 mg/dL increments	1.05 (1.02−1.07)	< 0.001
Triglycerides, 10 mg/dL increments	1.01 (1.00−1.01)	< 0.001
Body mass index, 1 kg/m² increments	1.03 (1.01−1.06)	0.018
Familial factors		
Father with CHD before 60 yrs	1.52 (1.10−2.10)	0.011
Mother with CHD before 60 yrs	1.99 (1.36−2.92)	< 0.001
Mother with diabetes mellitus	1.30 (0.94−1.79)	0.112
Sibling with CHD before 60 yrs	1.01 (0.76−1.35)	0.924
Sibling with hypertension	1.24 (0.94−1.64)	0.126
Sibling with hyperlipidemia	1.38 (0.93−2.05)	0.107

CHD: coronary heart disease.

Association Between Individual Familial Factors and Cardiovascular Mortality

After adjustment for participant risk factors (age, sex, SBP, DBP, body mass index, smoking, fasting glucose, LDL-C and triglycerides), only a history of CHD in parents and siblings, a history of DM in the mother, and a history of hypertension and hyperlipidemia in a sibling were significant predictors of cardiovascular mortality. Importantly, a familial history of stroke or peripheral arterial disease did not predict cardiovascular mortality after adjusting for risk factors (Table 2).

Familial Factors that Independently Predicted Cardiovascular Mortality

After adjusting for risk factors and for paternal, maternal and sibling histories of CHD before 60 years, maternal history of DM, and sibling history of hypertension or hyperlipidemia, only parental histories of premature CHD remained independent predictors of cardiovascular mortality, with somewhat higher associations for a maternal history of premature CHD [adjusted hazard ratio (aHR) = 1.99, 95% CI: 1.36−2.92, *P* < 0.001 for maternal history of premature CHD; aHR = 1.52, 95% CI: 1.10−

2.10, *P* = 0.011 for paternal history of premature CHD] (Table 3). Of note, replacing in the final model history of parental premature CHD with history of parental CHD at any age rendered similar results, albeit with more conservative estimates (aHR = 1.35, 95% CI: 1.02−1.78, *P* = 0.035 for maternal history of CHD; aHR = 1.28, 95% CI: 1.01−1.63, *P* = 0.043 for paternal history of CHD).

Adding parental history of premature CHD to a model that included age, sex, SBP, DBP, body mass index, smoking, fasting glucose, LDL-C and triglycerides resulted in statistically significant albeit small improvement in risk discrimination as indicated by Harrell's C-index (which improved from 0.8400 to 0.8446) and an integrated discrimination improvement index of 0.0049 (95% CI: 0.0027−0.0072). The improvement in the category-free net reclassification index was not significant (Table 4).

Subgroups Analyses

Subgroup analyses were performed according to categories of sex and baseline age (< 60 years and ≥ 60 years), hypertension, and hyperlipidemia. There was no significant difference in the ability of a parental history of premature CHD to predict cardiovascular mortality among those with and without
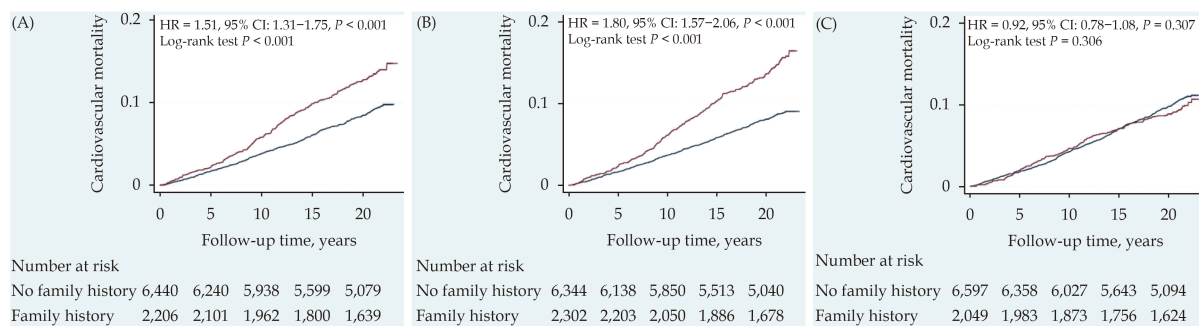
Figure 1　Cumulative incidence curves of cardiovascular mortality grouped by presence (red) or absence (blue) of a family (paternal, maternal or sibling) history of premature coronary heart disease (before age 60 years) (A), stroke (B), and peripheral arterial disease (C).

Table 4　Discrimination and reclassification statistics for a parental history of premature coronary heart disease with 23-year risk of incident cardiovascular mortality.

	Fully adjusted model[*]	Fully adjusted model[*] + parental history of premature coronary heart disease
Harrell's C-index (95% CI)	0.8400 (0.8253−0.8547), $P < 0.001$	0.8446 (0.8298−0.8593), $P < 0.001$
Integrated discrimination index (95% CI)	Reference	0.0049 (0.0027−0.0072), $P < 0.001$
Net reclassification index (95% CI)	Reference	0.0015 (−0.0148−0.0178), $P = 0.856$

[*]Refers to fully adjusted model includes age, sex, smoking, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein cholesterol, and triglycerides.

baseline hypertension or hyperlipidemia or among those in the younger (< 60 years) versus older (≥ 60 years) age subgroups, after adjusting for the full set of cardiovascular risk factors and as evidenced by $P_{interaction} > 0.05$ (Figure 2). Subgroup analysis by sex showed that the ability of a parental history of premature CHD to predict cardiovascular mortality was less significant in women (aHR = 1.10, 95% CI: 0.74−1.65) than in men (aHR = 1.79, 95% CI: 1.38−2.31), $P_{interaction} = 0.021$ (Figure 2).

DISCUSSION

In this study, we examined the risks of cardiovascular mortality that different first-degree familial histories of CVD carry. After adjusting for cardiovascular risk factors, only a parental history of CHD, especially before the age of 60 years, was a significant predictor of cardiovascular mortality. Importantly, the presence of stroke or peripheral arterial disease in first-degree relatives were not associated with increased risk of cardiovascular mortality. In this study, the importance of our findings lies in the ability to predict cardiovascular mortality using a simple, targeted question "Did your father or mother have a heart attack or angina? If so, did this occur before he or she was 60 years?". This is im-

portant given the evidence that a more detailed or complex familial history of CVD did not prove to be more effective at predicting cardiovascular events than more simple histories.[16]

While we did not find that a history of premature CHD in a sibling predicted cardiovascular mortality after adjusting for parental history in the final survival model, a previous study from the Framingham offspring cohort found that history of premature CVD in a sibling conferred increased risk of cardiovascular events after adjusting for risk factors and parental history of premature CVD.[4] Our findings might have been different due to differences in endpoints assessed (incidence of cardiovascular events versus cardiovascular mortality), definitions used for a significant family history of premature CVD (see next section), statistical methodology (logistic regression versus survival analysis), and potentially due to the younger mean baseline age of our cohort.

Another important point is that the additional prognostic value of a familial history of CVD beyond standard clinical risk factors seems to be limited in women. Our findings are in accordance with previous work showing that a positive family history of myocardial infarction (MI) in a parent, sibling, or child independently predicted cardiovascular mor-
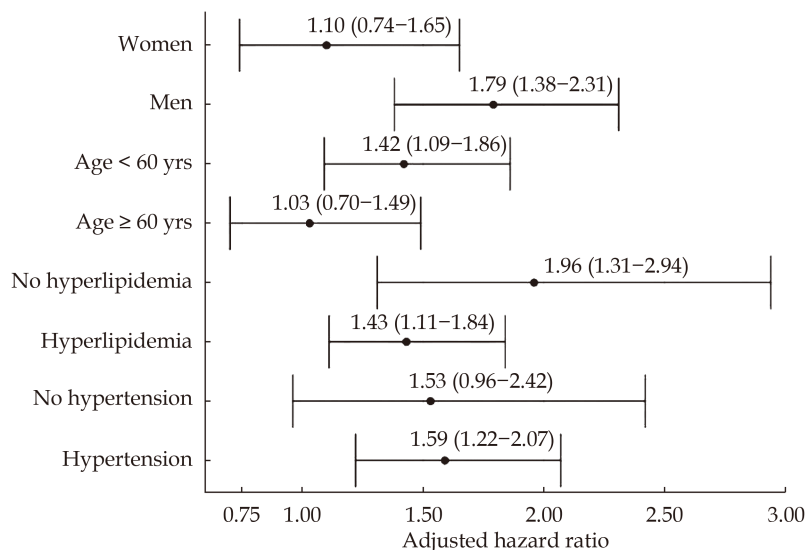
Figure 2   Plot of hazard ratio with 95% CI of cardiovascular mortality for a parental history of premature coronary heart disease, stratified by subgroups of sex, baseline age, lipid, and hypertensive statuses. Estimates were adjusted for age, sex, systolic blood pressure, diastolic blood pressure, smoking, body mass index and fasting glucose and lipids.

tality in men, but not in women.[10]

Familial History of Premature CVD

What precisely constitutes a familial history of premature CVD remains a debate. Studies from the Framingham offspring cohort defined it as any cardiovascular event (CHD, stroke, peripheral arterial disease, CHD mortality, CVD mortality) before 55 years in a father or brother, and before 65 years in a mother or sister.[4,5] Bachmann, et al.[6] used a more conservative cutoff of CHD before 50 years in their analysis of the Cooper Center Longitudinal Study in men. Risk score calculators that incorporate premature family history as a predictor of cardiovascular risk also exhibit variation in their definitions. The Joint British Societies 3 (JBS3) calculator defines it broadly as a close relative under 60 years suffering from CVD.[17] The QRISK2 calculator defines it as angina or heart attack in a first-degree relative younger than 60 years.[18] The Reynolds Risk Score for cardiovascular risk in women defines it as a parent with MI before 60 years.[19] The latter definition is in closest accordance with our findings.

Clinical Implications

Many widely used risk score calculators, such as the Framingham Risk Score,[3] the Pooled Cohort Equation,[20] and the European SCORE[21] do not incorporate family history of premature CVD as a risk predictor. This is not only due to the lack of agree-

ment on a specific definition; studies have shown that it only carries a minimal incremental prognostic value once other standard cardiovascular risk factors are adjusted for.[16,22] This finding was also replicated in our cohort. That is no surprise given that DM, hypertension, obesity and hyperlipidemia have strong genetic determinants. However, familial history captures important additional prognostic information that genetic history or precise genomic polygenic scores do not, that is, familial environmental determinants such as diet type, smoking habits and exposure, and living conditions.

There is recent compelling evidence about a growing list of non-traditional risk factors for CVD, namely socioeconomic status, particulate pollutants, noise exposure, and stressful lifestyle.[23-25] Familial history, in virtue of its encompassing and holistic nature, can be a simple tool to capture such factors before we are able to precisely quantify and routinely incorporate these non-traditional risk factors into cardiovascular prediction models. Interestingly, British prediction models have already incorporated area of residence (UK postcode) for QRISK2[18] and the Townsend deprivation score for JSB3[17] as surrogates for socioeconomic status.

While the decision to incorporate familial history as an integral part of prediction models remains debatable, it remains an important risk-enhancing factor to consider in clinical decision-making, espe-

cially in younger patients with no or few border-line traditional risk factors. Importantly, the final decision to initiate preventive measures remains a shared physician-patient decision.[22]

STRENGTHS AND LIMITATIONS

One major advantage provided by the Lipid Research Clinics Prevalence Study cohort is the richness of the information collected about familial history of CVD. This enabled us to study the prognostic value of each familial factor individually and then to understand which factors remain significant after all important familial factors are accounted for. Another unique aspect of this cohort is that it enabled us to study such associations while being relatively unaltered by a mix of cardiovascular medications. Statins, beta-blockers, and antihypertensives targeting the renin-angiotensin axis were not widely used at the time of study start. This provides insight into disease associations with mortality independently of modern interventions. Whether such interventions alter the association between familial factors and cardiovascular mortality remains to be investigated.

One limitation of this study is the subjective nature of how information about familial history was collected. Self-reporting of familial disease by participants is subject to recall bias. One other important consideration in the ascertainment of familial history is that maternal history of CHD might have been a stronger predictor of cardiovascular mortality than paternal history due to higher biological accuracy in determining the maternal relationship. The collection of genetic information could have provided more insight into the significance of this observation. Additionally, although data about offspring CVD was available, frequency of disease was low that reliable estimates could not be drawn.

An important point to mention is that half the participants had hyperlipidemia at baseline, which can potentially limit the generalizability of our findings. However, as shown in our subgroup analysis, a parental history of premature CHD predicted cardiovascular mortality independently of baseline hyperlipidemia. Finally, more precise and consistent definitions of premature CHD would allow for more refined estimates of the actual cardiovascular risk.

CONCLUSIONS

A parental history of CHD (defined as angina or MI), especially before age 60 years, was the best familial predictor of cardiovascular mortality in this study. This finding could help better identify high-risk patients and possibly initiate or intensify strategies to prevent cardiovascular mortality.

ACKNOWLEDGMENTS

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