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Family history as a risk factor for early onset myocardial infarction in young women

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Abstract

Background The relation between a family history of heart attack and the occurrence of early myocardial infarction (MI) has not been studied extensively in women In addition, whether recognized and newly-identified coronary heart disease (CHD) risk factors account for the familial aggregation of these events remains unknown We therefore examined these questions in a population-based case–control study among female 18- to 44-year-old residents of western Washington State *Methods and results* The patients consisted of 107 women with first acute MI, and the control subjects comprised 526 women similar in age identified from the community and without a history of recognized clinical coronary heart disease or stroke Trained interviewers used a structured questionnaire to elicit a detailed history of heart attack in first-degree relatives Information about other known MI risk factors was collected and biochemical measurements performed, and common polymorphisms in various candidate genes were determined The rate of MI among first-degree relatives of MI cases was twice as high as among first-degree relatives of controls (relative risk, 1 96, 95% confidence interval (CI), 1 46–2 48), this association was present for each familial relationship Sibling history of MI but not parental history was associated with MI, after controlling for established CHD risk factors In a subsample of subjects with blood measurements, further adjustment for lipids, lipoproteins and specific genetic risk factors slightly reduced the association with sibling MI history (from odds ratio (OR), 5 17, 95% CI, 1 93–13 85 to OR, 3 97, 95% CI, 0 92–17 17) *Conclusion* Family history of MI is positively associated with the risk of early MI in women While the association with parental history of MI is mediated through the clustering of other common risk factors, the association of sibling history of MI with early-onset MI in young women is only partially explained by the clustering of established and newly-identified risk factors © 2001 Elsevier Science Ireland Ltd All rights reserved

Keywords Family history, Women, Myocardial infarction, Early onset, Risk factors

1. Introduction

There is ample evidence that myocardial infarction (MI) tends to cluster in families [1,2] Since the major documented risk factors for the development of coronary heart disease (CHD) have important genetic determinants, the question arises whether aggregation of MI is due to the familial aggregation of these known risk factors or to genetic and/or environmental determinants that family members share, which exert their effects through as yet unknown mechanisms In several studies, a family history of MI or CHD was shown to be a strong predictor of CHD, even after adjustment for other risk factors [1–3], yet, this issue has remained

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controversial [4]. Extensive evidence suggests that hereditary determination may be particularly important in patients with early onset disease and in affected females [1,2,5]. Women and young men are intrinsically less susceptible and therefore must carry a heavier burden of predisposing genes to manifest early-onset MI and thereafter transmit a heavier 'genetic predisposition' to offspring. However, this possibility does not preclude alternative explanations for these age and maternal effects, such as shared lifestyle risk factors. We examined evidence for familial aggregation of MI risk associated with family history of heart attack within a case–control study of women with early-onset MI, and tested the hypothesis that this association is independent, at least in part, of other established and newly-identified CHD risk factors.

2. Methods

The basic design of the case–control study has been described in detail [6]. Briefly, the subjects were drawn from a study of incident cardiovascular disease among women 18–44 years of age residing in three contiguous counties of western Washington State. Eligible case patients were women diagnosed with a first fatal or nonfatal MI between 1 July 1991 and 28 February 1995. Cases were identified through the review of hospital discharge diagnoses provided by all hospitals within the study region, incident reports from emergency medical service systems and death certificates listing out-of-hospital deaths from cardiovascular disease and related conditions. Criteria for MI were adapted from the Cardiovascular Health Study [7], and were defined by evidence of symptoms, elevated enzymes, and electrocardiographic changes. Using these criteria, we identified 208 eligible MI patients, of whom 161 were living at the time that we initiated recruitment. One hundred and seven women were willing to participate in an in-person interview, a response rate of 66.5%.

We used random-digit telephone dialing to identify a control group of women 18–44 years old living in the same area during the time period of the study [8]. We recruited 526 such women, frequency matched on age. The estimated response rate, incorporating both the household screening and interview participation rates, was 72.8%.

Data on each woman's family health history were collected from both case patients and controls by trained interviewers using a structured questionnaire. Information about first-degree relatives (each biological parent, brother or sister) was obtained, including: age at the time of interview or age at death, occurrence of MI, and age of occurrence. In addition, participants were asked to describe the cause of death of their deceased relatives, particularly with regard to heart attack. In a small-scale validation study of family history, the interview data of 59 cases and 288 controls were compared with family history data ascertained through the ambulatory care medical records. This study detected a relatively strong concordance between reported family history and medical record evidence for both cases and controls (sensitivity, 0.69–0.70%; specificity, 0.74–0.82%).

The interview also covered other known or suspected cardiovascular risk factors such as: age, race, education, weight and height, physician-diagnosed diabetes, hypertension, or hypercholesterolemia, cigarette smoking, physical activity, coffee consumption and dietary fat intake. The structured interview elicited information for the time period preceding the MI or an equivalent date for controls. In addition to the in-person interview, we also collected nonfasting venous blood specimens from 79 MI case patients and 391 control subjects. Case blood samples were obtained at least 3 months after the event (mean, 8 months; median, 6.6 months). Plasma total cholesterol, triglyceride and high-density lipoprotein-cholesterol (HDL-C) were measured by enzymatic procedures on the Abbott Spectrum. HDL-C was measured directly from the plasma after precipitation of apoprotein B-containing lipoproteins. Plasma lipoprotein (a) (Lp(a)) was measured using an enzyme-linked immunosorbent assay technique that accounts for the potential influence of apolipoprotein (a) size on the accuracy of immunohistochemical detection [9]. These analyses were performed on a subset of case patients (69 cases with all lipid measurements) and controls subjects (220 subjects with all lipid measurements) selected at random. Since the plasma lipid measures we made were based on blood specimens obtained post-event for the cases, we were concerned that these levels might have changed after the acute coronary event and differ from those measured on these women earlier in life. We therefore compared the post-event plasma lipid concentrations to lipid level data abstracted from medical records completed prior to the reference dates of a subset of cases ($n = 48$) and controls ($n = 203$). We found moderate-to-strong, statistically significant correlations between plasma lipid levels and lipid levels from medical records. For total cholesterol, plasma measures were less strongly correlated with medical record levels among cases ($R = 0.41$, $P < 0.004$) than among controls ($R = 0.66$, $P < 0.0001$); whereas for HDL-C, the correlations were similar (cases, $R = 0.78$, $P < 0.0001$; controls, $R = 0.64$, $P < 0.0001$). For triglycerides, the correlations were somewhat stronger among cases ($R = 0.67$, $P < 0.0001$) than among controls ($R = 0.50$, $P < 0.0001$). These comparisons suggest that our data on post-event lipid levels are likely to capture the most important information regarding women's earlier (pre-event) lipid levels, and that the data are not systematically different among cases as compared with controls.

Polymorphisms in the genes for factor V (R506Q), prothrombin (G20210A), MTHFR (C677T) and platelet glycoprotein IIb (Ile843Ser) were determined as previously described [10–13]. Small, dense low-density lipoprotein (LDL) phenotype (A-predominance of large, buoyant LDL particles, or B-predominance of small, dense LDL particles) was determined by denaturing gradient gel electrophoresis [14]. All laboratory personnel were blinded to the case or control status of the samples.

For each participant, person-years accumulated by family members and the number of MI events within the family were counted. Person-years of relatives at risk were accumulated from birth until age at interview or age at death, or until age at event for relatives who experienced a MI. For each first-degree relative (parents and siblings), specific incidence rates were calculated and the relative risks were estimated by dividing the rate (history of MI among a relative per 1000 person-years) among the MI cases by the rate among the controls; confidence limits for these ratios were also calculated [15]. We then used unconditional logistic regression analysis to assess the relationship of family history with the risk of MI, while adjusting for differences in familial person-years and for potential confounding and mediating factors. Four sets of logistic regression models were fit with familial history of MI in first-degree relatives (number of events and familial person-years) as main predictors: (1) an unadjusted model; (2) a model that included as covariates the age of case and control subjects; (3) a model with additional adjustments for common CHD risk factors; and (4) a model similar to (3) with additional adjustments for lipids, lipoproteins and genotypic data variables which were examined on a subsample of 69 cases and 220 controls. Except for age, terms for other covariates were retained in the model if they were significant at the 0.1 level.

3. Results

The study subjects were predominantly white and cases were, on average, 1.8 years older than the sample of controls (Table 1). Cases exhibited a higher prevalence of diabetes, hypertension, hypercholesterolemia and current smoking. Case patients were less educated, weighed more given their height, had higher mean coffee intake and consumed more fat in their diet, and were less likely to participate in regular leisure-time vigorous physical activity than control subjects.

In the subsample of participants with blood measurements, case patients had higher mean total cholesterol, triglycerides and Lp(a) concentrations and lower mean levels of HDL-C than controls. The LDL subclass pattern B was more prevalent in MI patients (20.6%) than in controls (5.0%). The frequency of the factor V R506Q mutation, the prothrombin G20210A variant and the platelet glycoprotein IIb Ser843 variant were also higher in MI cases than in controls. No difference in the MTHFR C677T mutation was observed between MI cases and controls.

For each familial relationship, the rate of MI in family members among cases exceeded the corresponding rate among family members of controls (Table 2). The rate ratio was 1.68 (95% confidence interval (CI), 1.11–12.48) in fathers, 2.16 (95% CI, 1.07–4.12) in mothers and 1.73 (95% CI, 1.22–2.40) for MI in either mothers or fathers. The rate of MI among siblings of cases was 28.5 per 10 000 person-years, compared with a rate of 4.1 per 10 000 person-years in siblings of controls, resulting in a relative risk (RR) of 6.95 (95% CI, 3.29–15.37). Overall, the rate of MI among first-degree relatives of MI cases was almost 100% higher than the rate in first-degree relatives of controls (RR, 1.96; 95% CI, 1.46–2.84).

We assessed the relative odds of MI associated with a positive family history of MI in various family mem-

Table 1
Risk factors for myocardial infarction among case patients and control subjects

Risk factors[a]	Case patients ($n = 107$)	Control subjects ($n = 526$)
Age	39.5 ± 4.5	37.7 ± 5.3
White race (%)	86.0	87.6
Education ≤high school (%)	47.7	19.6
Marital status — married (%)	65.4	73.4
Diabetes (%)	15.9	2.7
Hypertension (%)	31.8	9.5
Hypercholesterolemia (%)	40.2	14.6
Current smoking (%)	69.2	20.9
No vigorous physical activity (%)	86.0	59.9
Coffee intake (cups/day)	4.8 ± 5.4	2.1 ± 3.0
Fat intake scale	21.8 ± 4.1	20.5 ± 3.8
Body mass index (kg/m^2)	29.3 ± 7.4	24.8 ± 5.4
Total cholesterol (mg/dl)	237.0 ± 38.7	190.0 ± 26.0
Triglyceride (mg/dl)	215.1 ± 94.8	119.5 ± 49.1
HDL-C (mg/dl)	48.9 ± 10.5	56.7 ± 8.4
Lp(a) (nmol/l)	110.2 ± 127.1	49.5 ± 64.6
LDL subclass (phenotype B) (%)	20.6	5.0
Factor V R506Q (any Q allele) (%)	10.1	4.1
Prothrombin G20210A (Any A allele) (%)	5.1	1.3
Platelet glycoprotein IIb (any Ser allele) (%)	71.8	59.5
MTHFR (TT) (%)	8.9	12.4

[a] Plus–minus values are means ± S.D. Lipids, lipoproteins and genotypic values derived from subsamples of cases and controls with blood samples.

Table 2
Familial person-years at risk, number of MI events and rates of events from MI in first-degree relatives

Relative	Case patients			Control subjects			Rate ratio	95% CI
	Person-years at risk[a]	Number of events	Rate[b]	Person-years at risk[a]	Number of events	Rate[b]		
Father	3394	34	100 2	20 144	120	59 6	1 68	1 11–2 48
Mother	4221	14	33 2	22 062	34	15 4	2 16	1 07–4 12
Parent	7615	48	63 0	42 206	154	36 5	1 73	1 22–2 40
Brother	3940	12	30 5	13 925	9	6 5	4 69	1 82–12 66
Sister	3775	10	26 5	15 254	3	2 0	13 25	3 47–76 17
Sibling	7715	22	28 5	29 179	12	4 1	6 95	3 29–15 37
First-degree relative	15 330	70	45 7	71 385	166	23 3	1 96	1 46–2 84

[a] Years were accumulated from birth until age at interview or age at death, or until age at event for those who survived their first MI
[b] Per 10 000 years

bers and examined the role of conventional risk factors on the familial aggregation of MI (Table 3). In the unadjusted model, the strength of the associations were in the order of sisters' history, brothers' history, mothers' history and fathers' history with odds ratios (ORs) (95% CI) of 8.78 (2.17–35.43), 4.84 (1.92–12.21), 2.21 (1.12–4.35), and 1 49 (0.88–2.53), respectively. While the associations with sibling history and any familial history were not altered upon the adjustment for age, parental history of MI was only marginally associated with subject's risk of MI following age adjustment. Inclusion of conventional risk factors as covariates in the multivariate adjusted model (Table 3, model B) appreciably altered the associations with any parental history and any first-degree family history. Based on this sample, the estimated odds of MI occurring in a subject increased by 1.52 times with each additional MI-affected first-degree relative (95%CI, 1.00–2.32), after adjustment for other risk factors and person-years at risk among first-degree relatives. This association is considerably lower than that obtained from the unadjusted (OR, 2.15) and the age-adjusted (OR, 2.12) logistic models. The introduction of the family history variables into the logistic model did not change considerably the coefficients for hypercholesterolemia, cigarette smoking and fat consumption, while a modest change was observed in the coefficients for low education, diabetes, physical activity, coffee consumption and body mass index (BMI) (data not shown).

Separately for cases and controls, we compared the risk factors between subjects with blood measurements and subjects without. For cases, only BMI slightly differed between those with blood measures and without ($P = 0.08$). Controls with blood measures were slightly older and were more likely to be diagnosed with high cholesterol. In addition, the significant positive association between age-adjusted family history and MI risk in the subgroup of cases and controls for whom blood measurements were available was similar to that observed in the total sample (i.e. the ORs associated with family history in first-degree relatives were 2.08 (95% CI, 1.37–3.16) and 2.12 (95% CI, 1.54–2.91), respectively). We therefore investigated the possible association of family history with myocardial infarction after additional adjustment for plasma lipids, lipoproteins and genotypes data. This further adjustment tended to reduce the strength and statistical significance of the point estimates for family history (e.g. the OR associated with risk of MI and parental history of MI decreased from 1.12 (Table 3, model B, observed in the total sample) and 1.28 (95% CI, 0.60–2.73; model B, observed in the subsample with blood measurements) to 0.89 (95% CI, 0.4–2.2)(Table 3, model C); and the OR associated with siblings history of MI decreased from 5.17 (Table 3 model B, observed in the total sample) and 4.58 (95% CI, 1.2–17.2; model B, observed in the subsample with blood measurements) to 3.97 (95% CI, 0.9–17.2) (Table 3, model C).

We also determined whether there was a differential pattern of familial clustering of MI risk according to the presence or absence of traditional risk factors. The combination of family history and hypertension resulted in a 2.9-fold increased risk compared with those without family history and hypertension, exceeding the separate effects of these two risk factors (OR, 1.14 and 0.67 for normotensive subjects with family history and hypertensive subjects without family history, respectively). Other interactions examined (e.g. family history with age, education, diabetes, hypercholesterolemia, smoking, physical activity, coffee, fat intake and BMI) did not show any such effect modification. In addition, we examined whether family history of early MI was more strongly related to the early onset of MI in women. Since most events occurring among siblings are early-onset events, we conducted this analysis among parents only. The odds ratios for early parental MI (fathers before age 60 years; mothers before age 65 years) were similar to those presented for the total group (Table 3).

4. Discussion

We found that a family history of MI, particularly sibling history of MI, is associated with an increased risk of early onset of MI in women. Our data also provide evidence that parental history of MI but not sibling history of MI may be primarily mediated by familial aggregation of common CHD risk factors. Although familial aggregation of CHD has been demonstrated in several retrospective [3] as well as prospective [1,2,5] studies, few have examined the role of parental and sibling history of CHD in young women [1,2,5,16,17]. The higher odds associated with sibling history than parental history also may indicate an increased risk associated with a family history of heart attack when the condition occurs early in life or when both genes and environmental/behavioral factors are shared.

Our results are consistent with other studies. In one study based on men and women, family history at young age was significantly associated with early onset of coronary artery disease as determined by arteriography [18]. In 520 female heart patients, the extent of coronary occlusive disease was also found to be correlated with parental history of MI [19]. Another study demonstrated that the risk of early-onset CHD was increased 2.7-fold for female and 1.6-fold for male first-degree relatives of women with confirmed coronary death before age 55, as compared with the risks of relatives of the controls [20]. This pattern of clustering of MI risk with respect to the gender of the family relatives is also supported by our study. In a 9-year follow-up of over 4000 men and women aged 40–79 years, positive family history in men, but not in women, was significantly associated with an excess risk of cardiovascular and CHD death [1]. Yet, in a large cohort of young women, parental history of early onset of MI, was a significant predictor of nonfatal and fatal MI [2]. A recent study reported a relative hazard of coronary death of 15.0 for female monozygotic twins and 2.6 for female dizygotic twins if their co-twins had died of CHD before the age of 65 [21]. However, this difference was not statistically significant if the co-twin died of CHD after the age of 75.

Although familial aggregation of CHD has been clearly demonstrated in women, the mechanisms underlying this aggregation are uncertain. In multivariate analysis, parental history appeared to be mediated by familial aggregation of other common risk factors. Such a finding suggests that, as the methodology of family history studies improves and more newly-identified risk factors are added to predictive models, the resulting independent effect of family history become much weaker and, even, nonsignificant. However, the introduction of sibling family history of MI as the last term in the stepwise logistic regression model did not alter considerably the coefficients for the risk factors in the antecedent model. While this suggests that the MI risk associated with sibling history was independent of other risk factors, it does not imply lack of a familial influence on diabetes, hypercholesterolemia, BMI, smoking or physical activity in our data. Rather, it suggests that familial aggregation of these risk factors accounts for, at most, only a small part of the clustering of MI in young family members (i.e. siblings). The clustering of early onset MI among siblings, therefore, appears to reflect characteristics other than the factors that were measured in our study. Yet, in the present study, the sample size provides a less stable estimate of the risk associated with sibling history of MI than the risk associated with parental history of MI.

Table 3
Risk of myocardial infarction associated with family history (FH) of myocardial infarction in first-degree relatives

	Unadjusted model		Adjusted models					
			A[a]		B[b]		C[c]	
	OR	CI	OR	CI	OR	CI	OR	CI
FH in fathers	1 49	0 88–2 53	1 21	0 70–2 09	0 91	0 44–1 86	0 47	0 15–1 44
FH in mothers	2 21	1 12–4 35	1 63	0 80–3 32	1 22	0 47–3 14	1 81	0 17–19 11
FH in parents	1 81	1 23–2 66	1 66	1 12–2 47	1 12	0 66–1 90	0 89	0 36–2 19
FH in brothers	4 84	1 92–12 21	4 96	1 98–12 44	5 61	1 54–20 46	5 62	0 88–35 88
FH in sisters	8 78	2 17–35 43	8 83	2 17–35 89	7 77	1 38–43 65	5 97	0 35–102 45
FH in siblings	5 03	2 35–10 75	5 10	2 41–10 81	5 17	1 93–13 85	3 97	0 92–17 17
FH in first-degree relatives	2 15	1 57–2 96	2 12	1 54–2 91	1 52	1 00–2 32	1 38	0 73–2 60

[a] Adjusted for age of case patients and control subjects

[b] Adjusted for age, education, diabetes, hypertension, hypercholesterolemia, smoking, physical activity, coffee and fat consumption, and body mass index

[c] Estimates (derived from a subsample of 69 cases and 220 controls) were adjusted for total cholesterol, triglyceride, HDL-C, Lp(a), LDL subclass, and polymorphisms in the genes for factor V, prothrombin, MTHFR and platelet glycoprotein IIb in addition to other covariables listed in footnote b

That aggregation of MI among siblings is largely unexplained by familial patterns in these risk factors is consistent with other retrospective [3,22], and prospective [2,16,23] studies. Yet, at least in some retrospective studies, the authors have concluded that the risk of CHD associated with a positive family history appears to be fully mediated by familial aggregation of common risk factors [4]. Methodological difficulties, related to identification of positive versus negative family history, complete assessment of known risk factors, and control for the covariation of elevated risk factor profiles and positive family history may account for much of the differences between studies regarding the MI risk attributed solely to family history.

Several alternative interpretations of the independent effect of a positive sibling history of myocardial infarction in the prediction of MI risk may be considered. First, the association may be operating via unobserved risk factors. We were able to determine total plasma cholesterol, triglyceride, HDL-C and Lp(a) on nonfasting specimens obtained from a subsample of cases and controls. The adjustment for these lipid variables and for allelic variation in various candidate genes had a small effect on the strength of the association between sibling history and the risk of MI. Nevertheless, residual confounding may account for some of our findings. Alternatively, this association may be due to genetic and/or environmental determinants that siblings share that exert their effects through yet unknown risk factors.

Positive family history also may be a marker for increased susceptibility to the deleterious effects of the traditional risk factors. For example, our results suggest that individuals from a family prone to MI may experience a greater risk of MI if they are hypertensive than someone with hypertension but without such family history. No evidence for other first-order interactions between family history and genotypic information and with other CHD risk factors was indicated.

In contrast, some studies have reported that family history may be most important in individuals who are otherwise at low risk for CHD [5,19,24]. Yet, in our study, no significant differences in odds ratios have been shown upon stratifying the study participants according to a composite risk score based on diabetes, hypertension, hypercholesterolemia, low education, smoking, physical activity, coffee drinking and fat consumption (probability value from the multivariate logistic regression model was 0.64 for family history $\times$ risk score interaction). Nonetheless, family history of MI could modify the risk associated with other risk factors not measured in the present study.

A number of limitations are inherent in the present study. A potential drawback of these data is the lack of a full validation of family history. In the Framingham study, analysis of the accuracy of reported paternal history of coronary artery disease death revealed that only 17% of the reports were discordant; the sensitivity was 0.59, and the specificity was high at 0.95 [5]. Other investigators have detected a relatively strong concordance between family history of MI/CHD ascertained by self-report and through medical records (a sensitivity of 67–85% and a specificity of 95–97%) [25–31].

We included only MI survivors, and therefore we cannot exclude the possibility that associations seen in our study are due in part to early case fatality among the MI patients without family history. Such a bias potentially could occur if MI patients without a family history tended to delay seeking medical care after the appearance of symptoms. We have, however, no data on this issue and no reason to assume this supposition to be true.

In retrospective studies, selection and recall biases are potential problems. Unfortunately, we did not collect data on family history from nonrespondents. However, we performed some analyses on variables for which we did collect data from nonrespondents and none of the differences was significant or overwhelmingly strong, and adjustment for nonresponse when estimating associations made little difference in the associations [32]. In addition, our comparison of self-report with medical records has shown that study participants provided an accurate information about family history variables that was essentially the same for cases and controls.

Based on this comparison between respondents and nonrespondents, the small validity study, and the fact that similar associations between family history and CHD have been seen in case–control studies and prospective studies that are less susceptible to selection and recall biases, we feel that these biases are not remarkable in the present study.

Our data indicate an overall positive association of family history of MI with the risk for MI in young women. While, the association with parental history is mediated through the clustering of other risk factors, the association of sibling history of MI is only partially explained by the clustering of established and newly-identified risk factors. Further identification of the genetic and/or environmental factors will provide a major tool for the understanding and prevention of the MI, especially among susceptible women with a positive family history of the disease.

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