Circulation VOL 69 NO 6
JUNE 1984
An Official Journal of the American Heart Association, Inc.®

CLINICAL INVESTIGATION

Family history of heart attack as an independent predictor of death due to cardiovascular disease

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ABSTRACT Although a family history of ischemic heart disease is a well-accepted risk factor for cardiovascular disease, only three prospective studies — all in men — have examined the predictive strength of a positive family history after adjusting for other heart disease risk factors. The present analysis is based on a 9 year follow-up of 4014 men and women from 40 to 79 years old who resided in Rancho Bernardo, CA, and who reported no known cardiovascular disease in response to a standardized interview. At baseline 38% of this group reported a family history of a heart attack in a parent, sibling, or child; 15% of those with a positive family history in a first-degree relative indicated that the heart attack had occurred before the relative was 50 years old. Younger men (<60 years) with a positive family history at any age had significantly higher mean blood pressures and total plasma cholesterol levels; older men were more likely to have diabetes mellitus. Younger women with a positive family history were more likely to smoke cigarettes and older women had higher cholesterol levels and were more likely to use exogenous estrogens. The independent contribution of a positive family history of heart attack to subsequent cardiovascular death was determined by the Cox model after adjusting for age, systolic blood pressure, total plasma cholesterol level, obesity, cigarette smoking, personal history of diabetes, and estrogen use (in women). In men, but not in women, a positive family history of heart attack was independently predictive of death from all causes and from cardiovascular and ischemic heart disease. Significant differences were restricted to younger men; those with a positive family history had a fivefold excess risk of cardiovascular death independent of other risk factors. A family history of premature heart attack (<50 years) was not predictive of mortality in men or women. The differences between younger and older men probably reflect survivorship, but the differences between men and women are unexplained.
Circulation 69, No. 6, 1065–1069, 1984.

A NUMBER OF STUDIES have demonstrated clustering of individuals with coronary heart disease and with heart disease risk factors in families.[1–12] However, surprisingly few studies[13–15] have examined the predictive strength of a positive family history in relation to the incidence of new cases of cardiovascular disease after adjusting for differences in risk factor distribution.

In this report data from a previously defined adult community[16] that was followed for 9 years were used to assess the independent contribution of a family history of heart attack in members who are younger and older than 50 years of age to the risk of death from all causes and from cardiovascular and ischemic heart disease.

Methods

Between 1972 and 1974, 82% of all 40- to 79-year-old residents of Rancho Bernardo, CA were studied for the prevalence of heart disease risk factors. This survey was conducted as part of the baseline visit protocol of the La Jolla Lipid Research Clinic Prevalence Study, but a number of questions and measurements were added to enrich the data base. At their interviews, all participants completed a standardized questionnaire that included questions concerning current cigarette smoking; the use of exogenous estrogens; personal history of heart attack, heart failure, stroke or diabetes; and family history of heart attack before or after age of 50 years in parents, siblings, or children. No attempt was made to determine which first-degree relative experienced a heart attack or to validate the diagnosis of reported heart attack in family members.

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Supported by the Lipid Research Clinics Program, National Institutes of Health contract No. NIH-NHLBI-HV-1-2160-L.
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Received Nov. 14, 1983; revision accepted Feb. 16, 1984.
K. Khaw is a Research Fellow supported By Wellcome Trust, London, England.

Height and weight were measured in subjects in light clothing and without their shoes; obesity was estimated with the body mass index weight/height^2. Blood pressure was measured with a standard sphygmomanometer after the participant had been seated at least 5 min and was repeated in those whose initial reading exceeded 160/90 mm Hg, the lower of the two readings being recorded. Total plasma cholesterol level was determined in a standardized lipid research clinic laboratory with an Auto-Analyzer.

With the use of follow-up methods detailed elsewhere,[17] 99.8% of this group was followed for vital status for an average of 9 years. Death certificates were obtained for all decedents and coded by a certified nosologist who used the eighth revision of the International Classification of Diseases. Codes 400 to 438 encompass cardiovascular death and codes 410 to 414 myocardial infarction. In 30% of this cohort (a 15% random sample and all hyperlipidemic subjects) validation of data on the death certificate was attempted whenever cardiovascular disease was mentioned anywhere on the death certificate. This was accomplished by interview of the next of kin and/or physician, and by review of hospital records. A panel of cardiologists determined that validation data agreed with the death certificate in approximately 85% of cases.

The present analysis included all subjects who were 40 to 79 years old and who were not pregnant and had no personal history of heart attack, heart failure, or stroke. Death rates and risk factor distribution were determined separately for men and women and for age groups of those 40 to 59 and 60 to 79 according to the presence or absence of a history of a heart attack in any first-degree relative before or after the age of 50. The Cox proportional-hazards model[18] was used to determine the independent contribution of a positive family history to death from all causes and from cardiovascular and ischemic heart disease after adjusting for differences in age, cigarette smoking, systolic blood pressure, cholesterol level, obesity, personal history of diabetes, and, in women, estrogen use.

Results

There were 4014 men and women 40 to 79 years old with no known cardiovascular disease in this study group; 34% of the men and 42% of the women reported a positive family history of heart attack. Of the 1538 subjects with positive family histories, 15% indicated that at least one first-degree relative had experienced premature coronary artery disease, here defined as a heart attack before the age of 50. Sex- and age-specific death rates for death from all causes and from cardiovascular and ischemic heart disease according to family history of heart attack status are shown in table 1. For the group of all men combined a positive family history of heart attack at any age was significantly associated with an excess risk of death from all causes and from cardiovascular and ischemic heart disease; differences were not statistically significant for the subset of men whose positive family histories included heart attack before the age of 50. A significant excess risk associated with a positive family history was seen only in men less than 60 years of age; a positive family history was not predictive of death in men 60 or more years of age. In women death rates were similar in those with and without positive family histories; in fact, in some categories death rates were slightly higher in the absence of a family history of heart attack.

Age- and sex-specific risk factor distribution according to family history status are listed in tables 2 and 3. In younger men positive family history was associated with significantly higher mean blood pressure and mean total plasma cholesterol levels. Older men with positive family histories were significantly more likely than those without them to have diabetes. In contrast, in women family history was not significantly related to diabetes or blood pressure, and cho-

TABLE 1

Age-adjusted 9 year mortality for all causes, cardiovascular disease (CVD), and ischemic heart disease (IHD) for men and women 40 to 79 years old by family history of heart attack at any age, before age 50, and after age 50

	Age-adjusted death rate per 100															
	No family history of heart attack				Family history of heart attack at any age				Family history of heart attack before age 50				Family history of heart attack after age 50			
Ages (yr)	IHD	CVD	All causes	n	IHD	CVD	All causes	n	IHD	CVD	All causes	n	IHD	CVD	All causes	n
Men																
40–59	0.5	0.5	3.0	405	3.4$^{\wedge}$	3.8^{B}	7.0$^{\wedge}$	220	5.6	5.6	5.6	37	3.4$^{\wedge}$	3.9$^{\wedge}$	7.6$^{\wedge}$	182
60–79	6.2	8.7	21.8	773	8.4	11.3	26.3	376	9.6	9.6	26.9	42	8.1	11.4	25.6	330
40–79	4.1	5.6	14.6	1178	6.5$^{\wedge}$	8.5$^{\wedge}$	19.1$^{\wedge}$	596	8.4	8.4	18.9	79	6.3	8.6	18.9	512
Women																
40–59	0	0.4	3.3	476	0	0	4.1	367	0	0	3.5	64	0	0	4.4	302
60–79	2.9	4.8	13.5	822	2.7	4.0	13.3	575	1.2	4.1	17.5	90	2.4	3.5	12.1	477
40–79	1.8	3.2	9.7	1298	1.7	2.5	9.9	942	0.8	2.6	12.3	154	1.5	2.2	9.2	779

Totals in family history before and family history after age 50 do not add up to total family histories at any age because of missing (unknown) values (five men and nine women did not know when cardiac event in family member occurred).

No family history vs positive family history: $^{\wedge}p < .05$; $^{B}p < .01$.

TABLE 2

Distribution of risk factors among men and women from 40 to 59 years old by family history of heart attack at any age, before age 50, and after age 50

Factor	No family history of heart attack	Family history of heart attack at any age	Family history of heart attack before age 50	Family history of heart attack after age 50
Men	n = 405	n = 220	n = 37	n = 182[B]
Age (yr)[A]	49.6 (6.0)	50.6 (6.0)	49.4 (6.4)	50.8 (5.9)
SBP (mm Hg)[A]	126.5 (16.8)	129.7 (18.6)[B]	127.3 (15.9)	130.2 (19.2)[B]
DBP (mm Hg)[A]	79.9 (10.5)	81.0 (11.3)	79.7 (10.9)	81.2 (11.4)
Obesity index (pounds/in^2 × 100)[A]	3.7 (0.4)	3.7 (0.4)	3.6 (0.3)	3.7 (0.4)
Cholesterol (mg%)[A]	206.8 (34.4)	219.4 (39.7)[C]	218.4 (37.4)	219.7 (40.3)[C]
Smokers (% current)	30.6	30.0	35.1	29.1
Personal history of diabetes (% positive)	3.7	5.5	2.7	6.0
Women	n = 476	n = 367	n = 64	n = 302
Age (yr)[A]	50.6 (5.7)	51.2 (5.7)	50.6 (5.9)	51.3 (5.6)
SBP (mm Hg)[A]	123.6 (20.9)	123.9 (20.5)	126.3 (21.3)	123.4 (20.3)
DBP (mm Hg)[A]	77.2 (11.8)	77.7 (11.0)	80.3 (13.6)	77.2 (10.3)
Obesity index (pounds/in^2 × 100)[A]	3.3 (0.5)	3.4 (0.6)	3.4 (0.7)	3.4 (0.6)
Cholesterol (mg%)[A]	213.1 (37.3)	212.2 (35.6)	209.2 (32.3)	213.0 (36.3)
Smokers (% current)	37.0	35.4	50.0[B]	32.5
Personal history of diabetes (% positive)	2.1	2.2	1.6	2.3
Estrogen use (% current)	46.0	47.1	42.2	48.0

[A]Mean (± SD).

No family history vs positive family history: [B]$p < .05$; [C]$p < .001$.

TABLE 3

Distribution of risk factors among men and women from 60 to 79 years old by family history of heart attack at any age, before age 50, and after age 50

Factor	No family history of heart attack	Family history of heart attack at any age	Family history of heart attack before age 50	Family history of heart attack after age 50
Men	n = 773	n = 376	n = 42	n = 330
Age (yr)[A]	68.8 (4.6)	68.0 (4.7)[C]	67.5 (5.4)	67.9 (4.6)[C]
SBP (mm Hg)[A]	146.3 (22.6)	145.3 (23.0)	145.5 (26.7)	145.3 (22.5)
DBP (mm Hg)[A]	82.7 (11.6)	83.0 (11.3)	82.1 (12.9)	83.1 (11.1)
Obesity index (pounds/in^2 × 100)[A]	3.6 (0.4)	3.7 (0.4)	3.6 (0.3)	3.4 (0.4)
Cholesterol (mg%)[A]	210.1 (33.4)	213.6 (33.8)	219.1 (35.8)	213.0 (33.6)
Smokers (% current)	17.5	16.5	21.4	16.1
Personal history of diabetes (% positive)	5.6	9.6[B]	9.5	9.4[B]
Women	n = 822	n = 575	n = 90	n = 477
Age (yr)[A]	67.8 (4.9)	67.0 (4.7)[C]	66.7 (5.0)	67.0 (4.6)[C]
SBP (mm Hg)[A]	140.6 (22.3)	144.1 (21.4)	141.9 (21.8)	141.1 (21.4)
DBP (mm Hg)[A]	81.5 (10.9)	81.3 (10.6)	80.9 (10.1)	81.5 (10.7)
Obesity index (pounds/in^2 × 100)[A]	3.4 (0.5)	3.4 (0.5)	3.4 (0.5)	3.4 (0.5)
Cholesterol (mg%)[A]	225.9 (37.7)	230.1 (37.9)[B]	222.6 (33.9)	231.1 (38.4)[C]
Smokers (% current)	21.4	20.2	21.1	20.1
Personal history of diabetes (% positive)	3.4	3.7	2.2	4.0
Estrogen use (% current)	33.9	33.6	46.7[B]	31.0

[A]Mean (± SD).

No family history vs positive family history: [B]$p < .05$; [C]$p < .01$.

TABLE 4
Relative risk[A] of selected factors for death from all causes, cardiovascular disease, and ischemic heart disease among men and women from 40 to 79 years old, based on Cox proportional-hazards model

Risk factor	Independent relative risk		
	All causes	Cardiovascular diseases	Ischemic heart disease
Men			
Age (per 5 yr)	1.61[D]	1.65[D]	1.54[D]
SBP (per 20 mm Hg)	1.18[C]	1.29[D]	1.22[B]
Smoking (current/never)	1.75[C]	1.37	0.91
Obesity (per 0.5 pounds/in^2 × 100)	1.00	1.11	1.22
Cholesterol (per 40 mg%)	1.14	1.43[D]	1.62[D]
Personal history of diabetes (yes/no)	1.30	1.02	1.29
Family history of heart attack (yes/no)	1.30[B]	1.50[B]	1.56[B]
Women			
Age (per 5 yr)	1.62[D]	2.36[D]	2.40[D]
SBP (per 20 mm Hg)	1.10	1.19	1.15
Smoking (current/never)	1.89[D]	2.42[C]	0.98
Obesity (per 0.5 pounds/in^2 × 100)	0.93	0.94	1.14
Cholesterol (per 40 mg%)	1.09	1.23	1.77[C]
Personal history of diabetes (yes/no)	2.21[B]	3.31[B]	3.07
Family history of heart attack (yes/no)	1.08	0.82	0.87
Estrogen use (yes/no)	0.73	0.86	1.13

[A]For continuous variables apart from age, intervals represent approximately 1 SD.
[B]$p < .05$; [C]$p < .01$; [D]$p < .001$.

lesterol levels were significantly higher only in older women with positive family histories. Younger women with family histories of premature heart attack were significantly more likely to smoke and older women reported more exogenous estrogen use.

The independent contribution of each risk factor to death from all causes and from cardiovascular and ischemic heart disease for the group of men and women at all ages combined is listed in table 4. In men only family history of heart attack, age, and systolic blood pressure were independently predictive of death from causes in all three categories. In addition, cigarette smoking was independently associated with "all cause" mortality and cholesterol with death from cardiovascular and ischemic heart disease. When the Cox model was restricted to younger men (<60 years old) the independent relative risk for cardiovascular disease was five times ($p < .05$) that in younger men without positive family histories, but there were too few deaths from ischemic heart disease for analysis. In the same model, multiply adjusted relative risks for older men with positive family histories were not statistically significant: 1.3 for death from all causes, 1.3 for death from cardiovascular, and 1.4 for that from ischemic heart disease.

Results were very different in women in whom a family history of heart attack was not associated with an increased risk of death from all causes, from cardiovascular disease, or from ischemic heart disease (table 4). In women only age was independently predictive of death from causes in all three categories; smoking and diabetes were predictive of death from all causes and from cardiovascular disease and cholesterol of death from ischemic heart disease.

Discussion

In 1970 the Intersociety Commission for Heart Disease Resources stated that there is ". . . an increased risk of coronary heart disease in close relatives of persons who experience a heart attack early in life, e.g., prior to age 50 . . . In contrast, there is little evidence for familial aggregation when the disease first occurs late in life."[19] Many case-control studies have shown the frequency of myocardial infarction to be two to four times higher in first-degree relatives of patients with myocardial infarction than among first-degree relatives of healthy control subjects.[1-7, 11] A positive family history was not significantly associated with heart disease in some studies of older subjects.[3, 4] Several of these case-control studies did not examine the independence of the association after adjusting for other heart disease risk factors and all suffer from recall bias in that people who have suffered heart attacks may be more apt to learn about and report a family history of heart disease.

The three reported prospective studies of family history as a predictor of cardiovascular disease that considered other heart disease risk factors all dealt with subjects in a restricted age range and were limited to men, and none considered the age of onset of coronary heart disease in the first-degree relatives. The Western Collaborative Group Study[14] included 3154 men who were 39 to 59 years old and in this study it was found that a parental history of coronary heart disease was independently predictive of symptomatic myocardial infarction and angina pectoris only in men less than 50 years of age. In a Framingham study of 186 pairs of brothers[13] coronary heart disease in an older brother was predictive of myocardial infarction and death from coronary heart disease in the younger brother after controlling for total cholesterol, cigarette smoking,

and blood pressure. In the Paris Prospective Study[15] of 7484 men from 43 to 54 years old who were followed for 6.5 years it was found that a paternal, but not maternal, history of coronary heart disease was independently predictive of coronary heart disease.

In our study men less than 60 years old with positive family histories of heart attack had significantly higher blood pressures and cholesterol levels and an increased risk of cardiovascular death that was independent of all risk factors studied. In contrast, older men with positive family histories did not have significantly higher plasma cholesterol and systolic blood pressure levels or mortality rates, suggesting selective mortality: Men with high blood pressures or cholesterol levels or positive family histories may die at earlier ages, and older surviving men either have lower levels of such factors or are more resistant to their effects. The fivefold excess risk of cardiovascular death in younger men with positive family histories of heart disease, independent of all major heart disease risk factors, supports the notion that other possibly heritable factors are important determinants of cardiovascular mortality.

A family history was not predictive of mortality in women in this population. Others have reported higher levels of cardiovascular risk factors in women with positive family histories of cardiovascular disease[9, 10] and that the relatives of female patients show a more pronounced risk of death from ischemic heart disease than the relatives of male patients.[3, 7] No previous study has examined the independent effect of family history on mortality in women, and the lack of an association in our subject group needs confirmation. Nevertheless, these results are reminiscent of those of Slack and Evans,[3] who noted that female relatives of male patients were at less excess risk of death from ischemic heart disease than were male relatives; they postulated that familial causes of ischemic heart disease in men do not cause ischemic heart disease in women. Other possible explanations include limited statistical power as a result of the small number of deaths in women (which is unlikely given that the relative risk of cardiovascular mortality in women with positive family histories was actually negative) or less concern (and less knowledge) about heart disease in women (which is unlikely because more women than men reported a positive family history).

The results of this study suggest that family history may be a useful tool for identifying high-risk younger men for risk factor intervention, and points to the need for investigation into other possible environmental or genetic determinants of cardiovascular disease in men. The sex differences are unexplained and warrant further investigation.

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