Coronary Disease and Risk Factors in Close Relatives of Utah Women With Early Coronary Death

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Familial aggregation of coronary heart disease (CHD) and specific major risk factors were determined among 639 first-degree relatives of 73 women with confirmed coronary death before age 55. They were compared with 1,151 persons in 141 control families. Of women with early coronary death, 62% had first-degree relatives with early coronary disease compared with 12% of affected control family members. In the proband families, coronary incidence rates were 2.7 times the control population rates for women (P < .001) and 1.6 times the control population rates for men (P < .05). An excess incidence of coronary disease was observed for ages 45 to 74 in both men and women.

Smoking, hypertension, diagnosed hyperlipidemia and diabetes were all two to three times more common in the female probands with early coronary death than in healthy controls. Hypertension was more common in all proband relatives (both sexes with and without coronary disease). Smoking was more common among female relatives of probands when compared with the controls.

These data suggest that early coronary disease in women is often familial and associated with smoking and hypertension. The familial aggregation seems to be stronger in female relatives of female probands with early CHD than in male relatives. Genetic factors or shared family life-style or both likely account for these observations.

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It is generally accepted that premature coronary heart disease (CHD) is strongly familial. Most studies showing this have used men as probands or have included few women with CHD. We undertook this investigation to expand this important body of data. The conception of this study parallels work on a set of male probands we have previously described.[1] Reported here are CHD incidence rates in first-degree relatives of women with early CHD and controls and reported risk factor patterns in the two groups of relatives and in a subset of the families selected for pronounced aggregation of early CHD. We hope these efforts will serve to further elucidate factors contributing to the familiality of coronary disease.

Methods

Probands were selected, relatives contacted and data collected in a fashion completely analogous to methods described for our study of male probands with early CHD.[1] Briefly, from 180 Utah death certificates representing all white female Utah residents dying before age 55 of CHD (*International Classification of Diseases* codes 420 for the sixth and seventh revisions and 410 to 414 for the eighth revision) in Salt Lake

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County between the years 1956 and 1975, data on 73 probands and their families were obtained. Control families were in-laws to the proband family as described previously[1] and shown in Figure 1.

Family informants supplied data for 73 proband families and 141 control families. The informants included 50 proband offspring, 19 proband siblings, 3 proband spouses and 1 parent. The one parent reported only on his wife and offspring and did not provide control information. In each instance where possible, wives or husbands of the informant supplied control family information on an identical set of their own relatives. The 50 offspring informants and their spouses provided control information on up to three nuclear family sets, while the other informants' spouses provided control information on only one family (Figure 1). In all, data for about 41,000 person-years were obtained. Exclusions from the 180 identified probands included 88 probands whose relatives could not be found by phone or mail contacts within the duration of the study and 18 probands with questionable deaths from coronary disease (six with rheumatic heart disease, five with stroke, three with renal failure, two with drug or alcohol overdose and one each with pulmonary embolus and surgical complications of peptic ulcer disease). One person refused to participate.

Data collected for probands, their first-degree relatives and controls included name; birth and death dates and locations; weight status (slender, average, 9 to 22 kg [20 to 49 lb] overweight and 23 kg and more [50-plus lb] overweight); cigarette smoking history (never, former or current), and age at first diagnosis for the following: heart attack, coronary bypass operation or angina pectoris on medical treatment, stroke, diabetes treated with diet or medication, hypertension, elevated serum cholesterol or triglyceride levels and cancer.

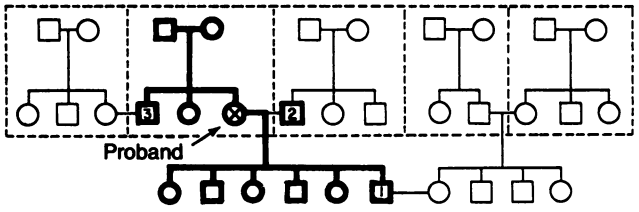


Figure 1.—A pedigree diagram shows the proband families (bold symbols) and matched control families. The three types of primary informants are indicated by numbers in the symbols and include the proband's offspring (1), spouse (2) or sibling (3).

The definition of a positive family history used in this report is identical to that used in our previous study.[1] A family history was positive for CHD if at least two first-degree relatives (not a father and mother only) had CHD, one occurring at a very early age and the other(s) occurring by at least a moderately early age. Very early CHD was, for men, a heart attack by age 55 or treated angina or a bypass operation by age 50. The same events up to five years later were considered very early CHD for women. Moderately early CHD included the same events up to ten years later.

Incidence rates were calculated by adding up the person-years of experience into 15-year age groups. Estimates of relative risk were calculated from the ratio of these rates with exact two-sided 95% confidence intervals calculated by the method described by Mulder.[2] Summary incidence density ratios over age were calculated by the Mantel-Haenszel method.[3]

Results

Familial aggregation of CHD was stronger among women than among men. Striking increases in CHD rates were observed among sisters, mothers and aunts of proband women with early CHD death. Only modest increases of CHD were observed among male first-degree relatives. Incidence rates for CHD death, heart attack incidence and all CHD including treated angina are given in Table 1. Relative risks of CHD comparing male relatives of the probands and controls were significantly greater than 1 for all CHD and all heart attacks, but not for CHD death. The relative risks of CHD for female relatives were significant for all three disease categories. Also, the relative risks for women were consistently higher than the relative risks for men with nearly nonoverlapping 95% confidence intervals, lending statistical support for stronger female than male CHD aggregation in this population. For both male and female proband relatives there appears to be a deficit of relatives with CHD at older ages (75 to 89) compared with the control relatives (Figures 2 and 3), indicating that relatives of female probands with early CHD also tend to have their disease onset at earlier ages. Figures 2 and 3 also show a greater relative increase in CHD risk for

TABLE 1.—*Incidence of Coronary Heart Disease (CHD) in Proband and Control Families**

Age Groups, Years	Total CHD Incidence			All Cases of 'Heart Attack'			Death Due to CHD		
	Proband	Control	RR	Proband	Control	RR	Proband	Control	RR
Men									
30-44	1.8 (6)	1.9 (14)	0.9	1.5 (5)	1.6 (12)	0.9	0.3 (1)	0.7 (5)	0.4
45-59	11.8 (27)	6.3 (36)	1.9	9.4 (22)	6.1 (35)	1.5	4.1 (10)	3.9 (23)	1.1
60-74	29.5 (28)	12.4 (36)	2.4	31.2 (30)	12.0 (35)	2.6	20.9 (22)	9.6 (30)	2.2
75-89	13.8 (2)	40.6 (22)	0.3	6.8 (1)	39.9 (22)	0.2	11.9 (2)	24.6 (15)	0.5
Summary RR and 95% CI†	1.6 (1.3,2.1)			1.6 (1.2,2.0)			1.3 (0.9,1.9)		
Women									
30-44	1.1 (4)	0.8 (5)	1.4	1.4 (5)	0.8 (5)	1.8	0.5 (2)	0.3 (2)	1.7
45-59	5.5 (13)	1.8 (10)	3.1	3.7 (9)	1.1 (6)	3.4	2.5 (6)	0.5 (3)	5.0
60-74	18.0 (21)	3.4 (11)	5.3	17.7 (21)	2.7 (9)	6.6	10.4 (13)	2.1 (7)	5.0
75-89	8.6 (2)	14.9 (12)	0.6	8.5 (2)	13.3 (11)	0.6	11.9 (3)	10.5 (9)	1.1
Summary RR and 95% CI†	2.7 (2.0,3.7)			3.1 (2.2,4.3)			3.1 (2.0,4.6)		

*Incidence rates are new cases per 1,000 person-years (probands are excluded). Numbers in parentheses are number of cases.
†RR = relative risk estimates, CI = two-sided confidence intervals.

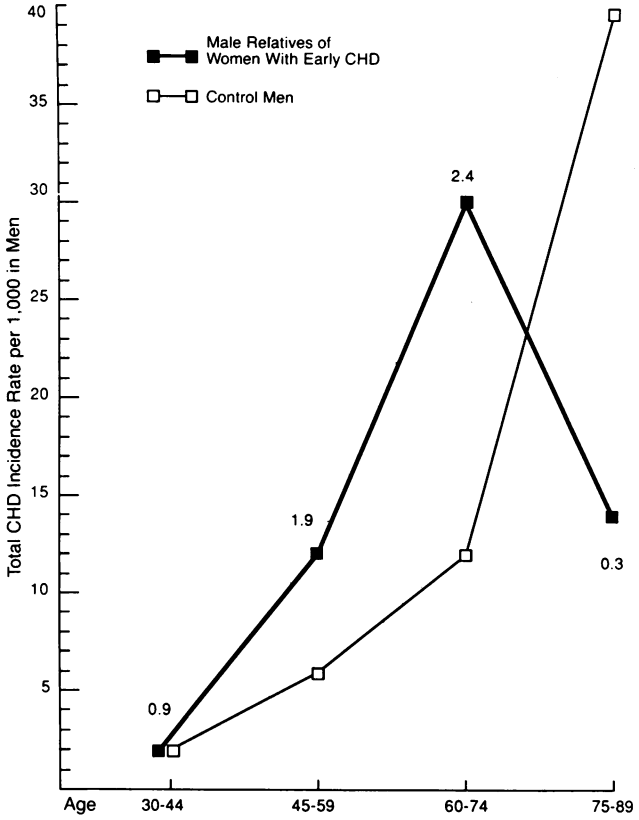
female relatives than for male relatives of each female CHD proband.

Hypertension and cigarette smoking were both more prevalent in the women with early CHD and in their female relatives compared with non-CHD control women as shown in Table 2. These two major risk factors likely account for much of the familial CHD aggregation observed. Within each of the four groups of relatives in Table 2, the proband relatives had a higher prevalence of hypertension than the control relatives, indicating a strong general association of hypertension with a family history of CHD. This higher prevalence of hypertension in the proband relatives was observed even though the proband relatives were younger than the control relatives.

Table 3 shows similar relative risks for CHD among smokers and persons with hypertension in proband and control families. In contrast to the previous study of male CHD proband families,[1] which showed an interaction of smoking and family history—that is, a greater relative risk for smoking among proband relatives than among controls—there was no interaction between cigarette smoking and being related to a female proband in the present study. Similarly, hypertension risk did not interact with being related to the female probands.

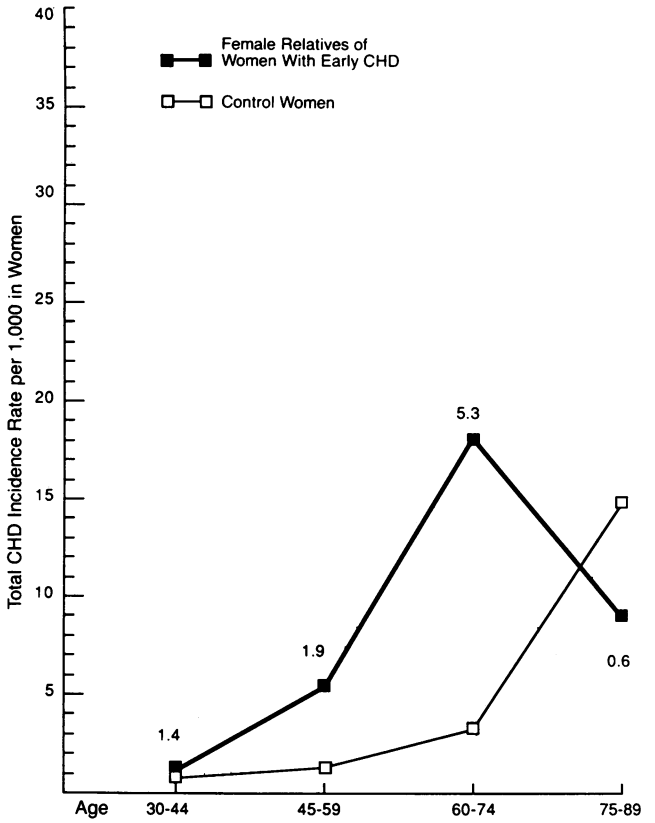
Applying our definition of a positive CHD family history to the 73 proband and 141 control families, we found that 62% of the proband family histories were positive for CHD when probands were included and that 21% were positive when probands were excluded. This compares with only 12% with a positive family history for CHD among the control families.

If a given risk factor is responsible for the aggregation of early CHD in a family, all family members with early CHD would be expected to share that risk factor. To determine the possible contribution of reported risk factors to a familial aggregation of early CHD, concordance was calculated between risk factors and early CHD occurrence. Only those affected persons contributing to the positive family history (two or more relatives per family with very early or moderately early CHD) were included in the concordance tabulations. Probands were included in this table because other affected relatives should share the same risk factors as the proband if there is a common cause of the disease. A family was considered "concordant" for a given risk factor if two



		30-44	45-59	60-74	75-89
Number of CHD Events	■	6	27	28	2
	□	14	36	36	22
Number of Persons at Risk	■	255	191	110	22
	□	519	440	293	96

Figure 2.—Coronary heart disease (CHD) incidence in male first-degree relatives of women with CHD death before age 55 and in control men. Relative risks listed on the graph for each age show about a *twofold increase* in CHD in middle ages for men in the coronary-prone families of female early-CHD probands. By older ages (75-89), few men in the coronary-prone families have CHD, presumably because most of the CHD occurred at an earlier age in these families.



		30-44	45-59	60-74	75-89
Number of CHD Events	■	4	13	21	2
	□	5	10	11	12
Number of Persons at Risk	■	270	204	115	35
	□	469	404	292	123

Figure 3.—Coronary heart disease (CHD) incidence in female first-degree relatives of women with CHD death before age 55 and in control women. Relative risks listed on the graph for each age show a threefold to fivefold increase in CHD in middle ages for women (higher relative risks than in men), suggesting some sex-specificity for underlying risk factor mechanisms. As in men, older women in high-risk families had less CHD than controls.

or more persons with early CHD had the risk factor or, in the case of smoking, if greater than 50% of the affected persons smoked.

Results in Table 4 show smoking and hypertension were the most commonly concordant risk factors—that is, two or more persons with early CHD from families with an early-CHD-positive family history also had hypertension, smoking or both in common. Hyperlipidemia, diabetes and obesity were concordant less often, suggesting, within the limitations of the data, that smoking and hypertension are the most common contributors to positive family histories of coronary disease in families of women with early CHD. More than a third of the coronary cluster families reported no risk factors that could account for their positive family history of CHD. Because the control families in Table 4 are required to have two or more relatives with CHD, they are also families with positive family histories. Therefore, it is not surprising to see a similar concordance of risk factors between the proband and control families.

Discussion

This study of coronary disease and risk factor aggregation in relatives of female victims of early CHD parallels earlier work among male probands and their relatives.[1] In both studies, probands, their families and controls were identified in precisely the same manner. Methods of data collection in the two studies were also identical. The studies, therefore, share the same strengths and weaknesses. Data reliability was assessed in the male proband study where the reporting of CHD end points in the relatives was 89% accurate as verified by death certificates and clinic screening, with no difference between proband and control family reporting accuracy. Reporting of smoking and hypertension was similarly accurate, while reporting sensitivity was below 50% for diabetes mellitus and obesity (>23 kg [50 lb] overweight) and only 24% for hyperlipidemia. Specificity of reporting was greater than 90% for all disease and risk factor data. Although the sensitivity was low for diabetes, obesity and hyperlipidemia, the high specificity made the variables useful and predictive in other analyses of the male and female data (S.C. Hunt, R. R. Williams, unpublished results, May 1984).[1] An association in this study, however, could easily have been missed because of the low sensitivity of these variables.

A major finding in this study was the increased female

TABLE 2.—*Risk Factor Prevalence in Persons With and Without Coronary Heart Disease (CHD) in Proband and Control Families*

Subjects	Number	Mean Age, Years	Prevalence Rates, Percent					
			Smoking	Hypertension	Hyperlipidemia	Obesity	Diabetes	Stroke
Female Proband	73	49	48	27	7	10	14	4
Early Male CHD*								
Proband Relatives	64	61	53	25	9	8	8	2
Controls	102	62	51	15	4	7	13	10
Early Female CHD*								
Proband Relatives	40	60	20	55	3	23	13	13
Controls	38	71	6	42	3	16	29	18
Men Without CHD†								
Proband Relatives	252	44	41	14	2	4	5	3
Controls	507	51	40	9	1	4	4	3
Women Without CHD†								
Proband Relatives	283	47	26	18	2	7	5	5
Controls	504	56	16	13	1	8	4	4

*Early CHD is defined in this table as men with heart attacks before age 60 or treated angina pectoris (including a coronary bypass operation) by age 55. For women, the same events up to 5 years later were considered early CHD. Early female CHD refers to women other than the probands in whom early CHD developed.
†Persons free of CHD at any age.

TABLE 3.—*Associations of Cigarette Smoking and Hypertension With Coronary Heart Disease (CHD) Incidence in Proband and Control Relatives**

Age Category, Years	CHD Incidence in Proband Relatives			CHD Incidence in Controls		
	Smokers	Nonsmokers	Relative Risk	Smokers	Nonsmokers	Relative Risk
30-44	3.0 (8)	0.5 (2)	6.0 (2.6,11.8)	2.0 (9)	1.1 (10)	1.8 (0.8,3.5)
45-59	12.7 (21)	6.3 (19)	2.1 (1.3,3.2)	7.7 (26)	2.6 (20)	3.0 (1.9,4.3)
60-74	22.8 (14)	23.3 (35)	1.0 (0.6,1.7)	8.8 (13)	7.3 (34)	1.2 (0.6,2.1)
75-89	0.0 (0)	13.2 (4)	...	51.3 (10)	20.8 (24)	2.4 (1.2,4.5)
Summary RR and 95% CI			1.6 (1.2,2.2)			2.0 (1.5,2.6)
	Hypertensives	*Normotensives*		*Hypertensives*	*Normotensives*	
30-44	1.7 (3)	1.3 (7)	1.3 (0.3,3.8)	1.9 (4)	1.3 (15)	1.5 (0.4,3.7)
45-59	13.5 (18)	6.6 (22)	2.0 (1.2,3.1)	8.2 (15)	3.3 (31)	2.5 (1.4,4.1)
60-74	36.8 (19)	18.8 (30)	2.0 (1.2,3.1)	10.1 (11)	7.1 (36)	1.4 (0.7,2.5)
75-89	0.0 (0)	13.5 (4)	...	15.6 (4)	27.5 (30)	0.6 (0.2,1.4)
Summary RR and 95% CI			1.9 (1.4,2.6)			1.4 (1.0,2.0)

CI = confidence interval, RR = relative risk

*CHD incidence rates are "all CHD" new cases per 1,000 person-years. Numbers in parentheses are number of affected persons.

aggregation of CHD among female proband relatives. Female relatives of the female probands had a relative risk of 2.7 (2.0 to 3.7 95% confidence interval; $P < .001$) for all CHD compared with control relatives, whereas male relatives of the probands had a relative risk of only 1.6 (1.3 to 2.1 95% confidence interval; $P < .05$). Sex differences in coronary risk among first-degree relatives have been reported by several other authors.[4-11] Most of these studies, however, were focused on early coronary disease in men.[6-11] Data for relatives of female victims of early CHD are scarce. The few studies on relatives of female victims of early coronary death[4,5] had very few female CHD cases reported among the family history data. Even in this study, the confidence intervals for CHD risk in men and women are barely nonoverlapping and do not give definitive answers. Using data from abstracted hospital charts of early CHD death in men and women, we have previously noted a tendency for female relatives of female fatal CHD cases to have a higher risk for CHD than their male counterparts and vice versa.[12] Data from the present study confirm and extend these findings.

When early CHD in women in this study is compared with early CHD in men in our previous study,[1] we find some interesting similarities and contrasts. A positive family history of CHD was present in more than 60% of both men and women with early CHD. Among coronary cluster families, concordance for risk factors suggested smoking and hypertension each may play a major role in about a third of the coronary-prone families. Hyperlipidemia was also implicated for about a fourth of the male proband families but in only 4% of the female proband families. No concordant risk factor was detected for 44% of the coronary-prone families of female CHD probands and for 14% of the families of male CHD probands. Some of these may be due to unknown hyperlipidemia, diabetes mellitus or other factors such as low high-density-lipoprotein-cholesterol levels. The lack of a difference in CHD aggregation between male and female relatives of male CHD probands in our previous study is interesting. In that study, cigarette smoking acted in a possibly synergistic way to elevate the risk among smoking proband relatives. This was true for both men and women.

In families in which smoking interacts with a positive family history of CHD, both men and women may be susceptible to the effects of smoking. For those families in which women have an early expression of CHD in the absence of a smoking interaction, hypertension seems to play the dominant role. The female relatives with CHD of the female probands had hypertension twice as often as the male relatives with CHD, whereas there were less than half as many smokers. Therefore, different risk factors may be involved in the early expression of CHD depending on the sex of the person(s) with the early CHD. In the present study, the only synergistic interaction of risk factors was between female sex and positive family history. There was an excess incidence of hypertension among female relatives of the female probands, especially among those with CHD. There was also an excess of obesity among both probands and control relatives with CHD compared with those without CHD. In the Framingham study, obesity-related risk factors such as hypertension and low high-density-lipoprotein levels were especially strong predictors for CHD among women.[13] One hypothesis suggested by these findings is that a predisposition to CHD may be passed on to female relatives via hypertension due to obesity-related factors whereas among male relatives, a susceptibility to smoking may be more important. Testing these hypotheses will require extensive screening data.

TABLE 4.—*Risk Factors Associated With a Positive Family History for Coronary Heart Disease (CHD)*

Risk Factors†	Percent of Families With Positive Family History of CHD Showing Concordance for Each Listed Risk Factor*: Proband Families N = 45 (62%)	Control +FH× Families N = 17 (12%)
Smoking	36	35
Hypertension	29	24
Hyperlipidemia	4	0
Diabetes	2	12
Obesity	4	0
None	44	35

*See text in Results Section for definition of risk factor concordance. 62% and 12% are percentages of proband and control families, respectively, with a positive family history (+FH×).

†Risk factor categories are not mutually exclusive. Several families were concordant for more than one risk factor.

The high prevalence of risk factors reported among female probands in this study is consistent with reports by other investigators.[14-17] In the study by Oliver,[15] of women with myocardial infarction before age 45, 43% smoked, 39% had diastolic hypertension, 48% had hypercholesterolemia, 4% were obese and 2% had diabetes mellitus. Underreporting probably accounts for the relatively few cases of hyperlipidemia among probands (7%) reported for the present study.

Rosenberg and co-workers[18] found in a large sample of female patients with early CHD that 80% were smokers and that smokers had a smaller but significantly increased risk of CHD if they had a positive family history of a myocardial infarction or stroke compared with those who did not have a positive family history. Shea and associates[19] have found that a family history of CHD has a more important role in CHD occurrence in persons who have a lower baseline risk. This may also be the case in our study. Comparing the relative risks of CHD between proband and control relatives (Figures 2 and 3) shows that the relative increase in risk was greater among the women than the men, with the women having a lower baseline incidence of CHD.

Ten Kate and colleagues[20] found that there was no difference in CHD rates between relatives of male CHD probands and relatives of the probands' spouses. The relatives of the spouses had an increased CHD incidence over a group of control relatives, and they suggested that there was assortative mating for CHD risk factors. In both our male and female proband studies, we found an increased CHD incidence in the relatives of the probands compared with relatives of the informants' spouses. Only 17% and 2%, however, of the control families used in our male and female proband studies, respectively, were families of the spouses of the probands. The others were the families of an offspring's or sibling's spouse. They would be more similar to the control relatives used by ten Kate and co-workers than the spouses' relatives and should not be affected by assortative mating unless both the probands' and the informants' spouses were chosen according to the same risk factors.

Also, the informants themselves were often unaffected by CHD. If there is any assortative mating in our studies of this sort, the magnitude of the results presented would be conservative.

The increased incidence of CHD in families of early CHD probands has important public health implications. Extra emphasis on prevention should clearly be focused on such high-risk families. The fact that potentially modifiable risk factors were concordant with coronary disease in nearly two thirds of these families gives hope that intervention may be especially fruitful in coronary-prone families. On the other hand, the more than one third of families who reported no associated risk factors that could potentially account for their high CHD risk represents a fascinating and challenging group that may provide important insights into the pathogenesis and prevention of the number one killer in the United States and other western nations.

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