Prospective Study of an Extensive Family History of Coronary Heart Disease

The Finnmark Study 1977-1989

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Abbreviations: CI, confidence interval; FHS, Family history score; R^2, generalised coefficient of determination.

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Running head: Family history of coronary heart disease

A family history of coronary heart disease is a consistent predictor of the disease, but the dichotomised family variable used in prospective studies, lacks detailed information on family structure and risk profile. The authors investigated family disease histories obtained from questionnaire and from an extensive interview about age, sex and heart disease status in all first-degree relatives. The positive interview reports were verified, and 2,203 men were followed 12 years for a first myocardial infarction. Adjusted for major risk factors the risk ratio for an enumerated family history score summarizing the interview was 1.14 (95% confidence interval (CI) 0.6-2.2). Risk ratios were small for simple dichotomised interview definitions of family disease history regarding age at disease onset (maximum 50 or 60 years) and male or female sex of the affected relative. Largest was the risk ratio of 1.55 (95% CI 1.0-2.4) for the common questionnaire response on whether or not heart disease had occurred in any parent or sibling. In the present study, elaborated family histories of heart disease taken from interviews seem to hold no potential to be more useful in defining disease risk in the general population than those obtained from questionnaires.

Keywords: coronary disease; family characteristics; prospective studies; risk factors

In several prospective studies, the relative risk of having a positive family history of heart disease has been found to vary around 1.5 (1-11). Usually, family histories of disease have been collected from self-administered questionnaires asking healthy participants whether or not heart disease has occurred in any of their first-degree relatives. There has been several concerns regarding the quality of such a simple, dichotomous family history variable. This relates both to the lack of detailed information regarding family age and sex structure, and the reliability of reported disease. Not only has excess risk been reported when the disease struck in young relatives (12), but case control studies have shown that risk tends to increase with the number of relatives affected (13, 14). It has also been suggested that heart disease in a female relative may be associated with higher risk than disease in a male relative, or that a family history of heart disease is a stronger risk factor for the disease in women than in men (15-17). A final problem has been that information on family diseases has proved to be inaccurate (18-21).

The general and observed family pattern of coronary heart disease appears to be best explained by a polygenic mode of inheritance (22). An underlying and continuous variable called the liability to diseases may express the hereditary basis for many diseases (23), and an enumerated score rather than a simple dichotomous variable thus would be more appropriate to express the family-conferred risk. Such a score would also possess the potential to identify a few families under extreme high risk.

In the present study we were able to compare the prognostic impact of the family disease history information collected from a questionnaire with that of a more detailed and validated interview. Data from the interview were used to construct simple family risk variables based on age, sex and number of relatives, and also to combine information into a continuous family history score.

MATERIALS AND METHODS

All inhabitants aged 23 to 52 years and a random 10 percent sample of men and women aged 20 to 22 years in four Finnmark municipalities were invited to a study in 1977. Body height and weight and blood pressure were measured and blood samples for determination of serum total cholesterol were taken. A questionnaire included questions on daily smoking (yes, no), physical activity during leisure (categories coded from 1 to 4 were inactive, active, moderate, and hard training, respectively), and the investigation was concluded with an interview (24-25).

Invited were 6,087 men and women, and 4,596 individuals were examined and completed the family interview. After the exclusion of subjects with missing information on their family, the responses regarding the total population of first-degree relatives of 4,343 men and women were used to estimate sex and age-specific rates for coronary heart disease.

The participants were followed for a first fatal or non-fatal myocardial infarction, imminent infarction or sudden death (26). By December 31, 1989, a total of 87 male events had been identified. Due to the limited number of 16 observed female events, our risk analysis was restricted to the 2,203 men who were free from heart disease at the time of the screening and had non-missing values on all included variables.

We used the Cox proportional hazards regression method to derive risk estimates for the different family history definitions (27). To compare their accuracy to predict heart disease, we applied the generalised coefficient of determination (R^2) (28). All handling and analyses of data were done with the SAS program package (29).

Family history definitions

On the self-administered questionnaire used at the investigation, there was a question

"Have one or more of your parents or siblings had a myocardial infarction (heart wound) or angina pectoris (heart cramp)"? Response alternatives were "yes", "no" or "don't know", and in this report the "don't know" answers were counted as "no".

The examinees were interviewed about sex, year of birth, and possible year of death and year of occurrence of "infarction" or "heart attack" for each first-degree relative (father, mother, brothers and sisters). Altogether 505 men reported on a total of 557 affected parents or siblings, and the positive reports were later checked in records of doctors and hospitals, and in the national death register. Of these reports, 52 could not be traced in any available register. Among the verified reports, 321 had obtained the diagnosis myocardial infarction, 20 imminent infarction, 42 sudden death and 37 angina pectoris, whereas 85 revealed other diagnoses. Reports which were verified as myocardial infarction, imminent infarction or sudden death were accepted and classified as myocardial infarction. The interview and verification procedures were in principal identical to those applied in an earlier survey (25).

Information from the interview was used in different ways to define family disease histories so that important elements of family structure and disease onset could be investigated regarding disease risk. Consequently, one dichotomous family history variable identified the participants with at least one case first-degree relative. Yet other simple family history variables took into account the age at disease onset (maximum of 50 or 60 years) or the sex of the affected relatives.

Finally, the family interview information was combined into a common continuous family history score (FHS) (30, 31). Comparing observed heart disease rates with values expected, the FHS was calculated for each participant as:

$$FHS = \sum_j \frac{O_j - E_j}{\sqrt{E_j}},$$

where O_j is the observed heart disease status (0 or 1) for the jth member in family and E_j is the expected risk for heart disease in that individual. The expected risk for each person was calculated from the sex and five-year age group specific information on relatives given in the interview. After calculating incidence proportions, the expected risks were derived from a life-table formula (32). Age at heart disease onset was observed to vary from 30 to 87 years. All relatives aged 30 years or more were counted until age of death, until occurrence of verified myocardial infarction, or until actual age at the time of survey. For 49 unaffected relatives aged 90 years or more, the expected values were set equal to that of the age group 85 to 89. For three men with relatives who experienced coronary heart disease in their early thirties, expected values were set identical to that of an older age group to modify unstable FHS values.

RESULTS

The response from the 4,343 family interviewees is shown in Table 1. More than 10,000 parents or siblings of each sex were reported. Altogether 621 male and 156 female first-degree relatives had experienced confirmed myocardial infarction. The expected risk values shown were those that were used in the derivation of the FHS.

Figure 1 shows the distribution of the FHS for the 2,203 men on a logarithmic scale. Most participants had a FHS value close to zero, and the highest bar represents a number of 1,547 subjects. The distribution had a long tail to the right, and values ranged from -3.0 to 39.8 with an average of 0.17. As seen from the FHS algorithm, the participants without a family history of heart disease all had negative values.

Table 2 shows the responses from the questionnaire and the family interview of the 2,203 men for the different family history definitions. Among the 625 men with a positive

questionnaire response, only 307 men were accepted from the interview with myocardial infarction ascertained in a parent or sibling. Altogether 52 men responded negatively on the questionnaire and positively on the verified interview. As seen, FHS values were especially high in instances where at least two family members had become affected or the disease had struck at an early age.

For the different definitions of family heart disease histories, responses are shown in Table 3 according to disease status after follow up together with the risk ratios. Among the 625 positive questionnaire respondents, the numbers of those who did and did not develop myocardial infarction during follow-up were 37 (42.5 percent of all case events) and 588 (27.8 percent of all who remained well), respectively. This definition of family heart disease thus was associated with a 65 percent increased age-adjusted risk of having the disease. The risk ratio was reduced to 1.55 after other major risk factors were taken into account. For the FHS, the confidence limits and the R^2 both showed that only a modest effect was present. Among the 21 participants with two or more affected relatives (Table 2), only a single man developed the disease during follow-up. Consequently, no separate analysis of this group was appropriate. Also, few cases had a relative who had become affected early or who were of female sex. As risk ratios are scale-dependent, they cannot be directly compared between dichotomous and continuous variables. However, the various interview definitions of family disease history had little predictive ability with fully adjusted risk ratios not far from unity.

DISCUSSION

The main result of the current investigation was the disappointingly small predictive power of the interview family heart disease histories. In fact, the only attempted definition reaching a level of statistical significance was that of the questionnaire. This or a similar question has

been used in many prospective studies, commonly seen referred to as the abbreviated, standard, simple or as here, questionnaire family history definition. The results came as a surprise because validated interview histories with its much more detailed information on family structure and age at heart disease onset have been thought to define risk more precisely than the simple questionnaire histories (33-36).

One reason for the increased number of positive questionnaire reports was that this definition, unlike that of the confirmed interview, included angina pectoris and histories that were either unverified or could not be traced. Another possibility may be that some men included their grandparents not only because they were in an age group especially susceptible to the disease, but also because the question was located in the last part of the questionnaire together with an item regarding grandparents' ethnic origin.

Despite the considerable number of false positive reports given in the questionnaire, it still picked out 307 of the 359 men (85.5 percent) who had a family history of confirmed myocardial infarction. The current risk ratio estimate of 1.55 also corresponded well with that of other prospective studies (1-11, 37).

A good quantitative family score should increase with increasing number of relatives affected and decreasing age at disease diagnosis. Moreover, as expected values were smaller for women, a female incident would count more than that developed in a male relative. Consequently, FHS would be extremely high for an imaginary individual with several female relatives who became affected at a young age. Various constructions of a family risk score have been suggested, but most scores compare observed and expected disease rates (31). Because no history of family disease inevitably leads to a negative FHS value, all such values could be set identical to zero (33). With this slight adjustment, recalculated risk ratios were not changed in the two decimals given in Table 3, and other common modifications are also

unlikely to impose notable changes in the FHS values or its predictive ability. The FHS contained information on male and female relatives added together, and analysing the sex specific contribution to the score separately, risk ratios for the male and female relatives were 1.13 and 1.15, respectively, as compared to that of 1.14 combined.

The current FHS values were based on heart disease rates derived from the relatives of the examined men and women. It might be argued that a better choice for the expected values would have been population rates. However, other data on heart disease morbidity and mortality for the relevant time period and geographic area were unavailable. Had such external rates existed, FHS values would have been slightly different, but there is no reason to expect a dramatic increase in predictive power. Neither is it likely that other definitions of disease endpoint would be important.

An advantage of a quantitative FHS variable is the opportunity to rank participants by score value and thereby identify relatively few individuals with the highest risk. We did that (results not shown in tables), and among the men with the 10 highest scores (FHS 15.6 or larger), a single case event was observed during follow-up. Correspondingly, among the 50 highest (FHS 7.85 or larger) and 100 highest (FHS 5.1 or larger) scores the number of case events were three and five, respectively. The percentages of men who developed the disease thus were 10, six and five, for those with the 10, 50 and 100 largest FHS values, respectively, as compared with the overall observed case percentage of 3.9 (87 out of 2,203). Consequently, the FHS was not a very efficient tool for identifying a few high-risk individuals eligible for preventive intervention.

Reports from prospective studies of a family history score for heart disease are scarcely found in the literature. An abstract concluded that incident coronary heart disease increases progressively with the level of a family risk score in African-American and white, men and

women (38). Another study that focused on statistical methods found a significant association for a family history score based on female relatives, but not for the one based on the male relatives (16). Case-control studies, on the other hand, have focused on various elements of a family history of heart disease and have shown that young age, female sex or more than one relative being affected all are associated with increased risk (13, 14).

In summary, the current study investigated 2,203 ostensibly well men of whom 87 developed heart disease during 12 years. We believe that this study was large enough to seriously question the role of a detailed family interview as a unique tool to identify individuals who will develop future disease. We conclude that taking the considerable effort of collecting detailed family histories does not seem worthwhile in routine screenings of the general population.

ACKNOWLEDGEMENTS

The study was carried out in co-operation with the National Health Screening Service, Oslo, Norway.

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TABLE 1. Age and sex specific incidence rates and expected risk of fatal or non-fatal myocardial infarction from family interview of 4,343 men and women. The Finnmark Study 1977-1989.

	10,049 fathers and brothers				10,192 mothers and sisters			
Age group (years)	No. of persons*	cases	Annual incidence rate (per 1,000)	Expected risk (per 1,000)†	No. of persons	cases	Annual incidence rate (per 1,000)	Expected risk (per 1,000)
30-34	9453	2	0.04	0.21	9618	1	0.02	0.10
35-39	8094	7	0.17	1.08	8345	0	0	0.10
40-44	6831	25	0.73	4.73	7052	0	0	0.10
45-49	5801	49	1.69	13.14	5937	3	0.10	0.61
50-54	4793	95	3.96	32.70	4775	16	0.67	3.96
55-59	3751	95	5.07	57.20	3581	30	1.68	12.30
60-64	2849	93	6.53	87.97	2547	31	2.43	24.32
65-69	1974	111	11.25	139.26	1684	28	3.33	40.55
70-74	1200	90	15.00	203.81	961	24	4.99	64.51
75-79	628	42	13.37	257.06	387	20	10.34	112.85
80-84	260	9	6.92	282.78	134	2	2.99	126.10
85-89	72	3	8.33	312.66	37	1	5.41	149.71

* Number of well subjects in the middle of age group.

† Expected risk for myocardial infarction by five-year age group $g = 1 - \prod_{k=1}^{g}(1 - 5 \cdot$ annual incidence rate for five-year age group $k)$.

TABLE 2. Correspondence between questionnaire and family interview responses. The Finnmark Study 1977-1989.

Family interview	No.	Mean age	Mean FHS*	Questionnaire: No. of answers to heart disease in any parent or sibling: Yes (n = 625)	Questionnaire: No. of answers to heart disease in any parent or sibling: No or do not know (n = 1,578)
No. of parents or siblings with verified myocardial infarction					
0	1844	36	-0.68	318	1526
1	338	38	4.10	287	51
≥ 2	21	41	11.57	20	1
Parent or sibling with verified myocardial infarction					
Onset at age ≤ 50 years	41	38	13.19	36	5
Onset at age ≤ 60 years	154	36	7.58	140	14
Male sex of parent or sibling	310	37	4.07	267	43
Female sex of parent or sibling	63	40	8.21	54	9

* FHS, family history score.

TABLE 3. Comparison of various definition of family heart disease history on the risk of myocardial infarction in 2,203 men. The Finnmark Study 1977-1989.

Definition of family history	Non-cases (n = 2,116) No.	%	Cases (n = 87) No.	%	Age adjusted Hazard ratio	95% CI†	R^2‡	Fully adjusted* Hazard ratio	95% CI	R^2
Questionnaire:										
Heart disease in any parent or sibling (yes vs. no or do not know)	588	27.8	37	42.5	1.65	1.1-2.5	0.0315	1.55	1.0-2.4	0.0478
Family interview:										
Family history score, FHS (per 10 units)	0.17§		0.21§		1.18	0.6-2.2	0.0294	1.14	0.6-2.2	0.0462
Parent or sibling with verified myocardial infarction										
Onset at any age (yes vs. no)	341	16.1	18	20.7	1.15	0.7-1.9	0.0294	1.06	0.6-1.8	0.0462
Onset at ≤ 50 years (yes vs. no)	39	1.8	2	2.3	1.05	0.3-4.3	0.0293	0.95	0.2-3.9	0.0461
Onset at ≤ 60 years (yes vs. no)	150	7.1	4	4.6	0.66	0.2-1.8	0.0296	0.57	0.2-1.6	0.0467
Male sex of parent or sibling (yes vs. no)	295	13.9	15	17.2	1.15	0.7-2.0	0.0294	1.04	0.6-1.8	0.0461
Female sex of parent or sibling (yes vs. no)	59	2.8	4	4.6	1.17	0.4-3.2	0.0293	1.20	0.4-3.3	0.0462

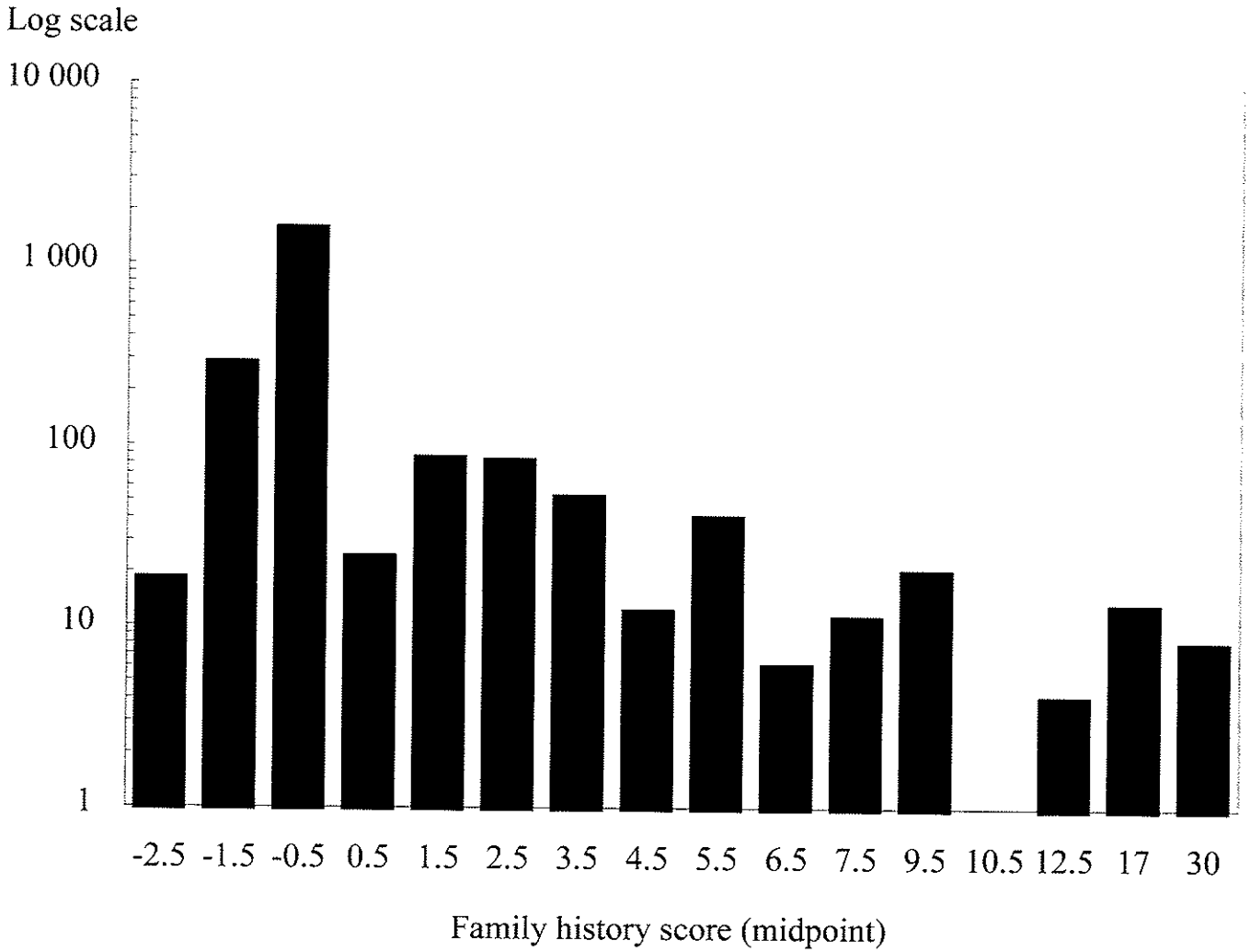
* Adjusted for age, total cholesterol, body mass index, systolic blood pressure, physical activity at leisure and daily smoking. For 45 men without body height and weight measurements, their values from a previous investigation in 1974 were used.

† CI, confidence interval.

‡ R^2, coefficient of determination.

§ Mean FHS.

FIGURE 1. Distribution of the family history score in 2,203 men. The Finnmark Study 1977-1989.


Log scale
10 000
1 000
100
10
1
-2.5
-1.5
-0.5
0.5
1.5
2.5
3.5
4.5
5.5
6.5
7.5
9.5
10.5
12.5
17
30
Family history score (midpoint)