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Family history in "low risk" men with coronary heart disease

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SUMMARY A detailed family history was obtained from men who had earlier been participants in a longitudinal study of coronary heart disease (CHD). Men who developed CHD during the 5–6 years' course of that study were matched with those who had remained free of CHD, using age and initial risk characteristics (blood pressure, plasma cholesterol concentration, smoking habits, and physical activity at work) for the matching criteria. Men who developed CHD were more likely to report a family history of CHD than their controls, and the excess was greater in those who had been at low risk initially than in those at initially high risk. This suggests that a clue to the reason why men at low conventional risk develop CHD may lie in their family history, and that there may be an explanation other than the familial aggregation of conventional risk factors for CHD to run in families.

Although many studies have shown that coronary heart disease (CHD) may run in families,[1–3] there has been debate[4 5] about whether this is due to anything more than the fact that family members show similarities in the conventional risk factors such as levels of blood pressure, plasma cholesterol concentrations, and cigarette smoking habits or whether there is an additional genetic or environmental factor. If CHD runs in families only because of the aggregation of known risk factors we would expect family history to be stronger in people with high risk factor levels. An opportunity arose to study the family history of CHD in people with different risk factor levels as part of a study designed to explore the reasons why people develop CHD despite being at apparently low risk.

Methods

This study was performed among men who had participated in a longitudinal industry based study of the prevention of CHD two years after its completion.[6] All subjects had been seen at the initial screening examination (1971–3), were free of CHD at that time (normal ECG, no history, and no angina), had attended a final screening examination (1978–9), and were still employed in their original factories at the time of this study in 1980.

Cases were men who had either developed a myocardial infarction between initial screening and the final screening examination or who at final screening had an abnormal ECG or reported angina. Each case was matched with a control who was a man working in the same factory, was within one year of age, and had a similar risk score, calculated by the addition of weights assigned on the basis of age, concentration of plasma cholesterol, level of systolic blood pressure, cigarette smoking, and physical activity at work at the time of initial screening.[6 7] In 1980 subjects were asked to atttend the factory medical department, having previously been sent a questionnaire that included detailed questions to obtain information on cause of death and occurrence of non-fatal heart attacks in parents and siblings. At the time of the visit the questionnaire was checked for completeness, and permission was obtained from subjects to trace death certificates of any relatives. From the information suppled by subjects, causes of death in relatives were coded according to the ICD 8th revision. Non-fatal heart attacks were coded as yes or no. Each relative could appear only once in the numerator, those who had a non-fatal attack but later died of a heart attack were classified as having had a fatal attack.

Where information suppled for relatives was adequate and permission had been granted, the Office of Population Censuses and Surveys was sent a list of those relatives who had died and asked to provide a copy of the death certificate so that the causes of death supplied by subjects could be compared with the actual certified cause of death. The single coder did not know the risk status of the

index subject, nor whether they were a case or control, either at the time of coding or at the time of comparing the information given on the questionnaire with that on the death certificates. The coding was independently checked by a second coder who was also unaware of the risk status or whether they were a case or control. Death certificates were obtained for only 119 relatives, the others were impossible to trace owing to inadequate information or they had died in childhood or in other countries. There was underreporting of heart attacks as a cause of death among relatives: of 20 certificates coded as ischaemic heart disease only 13 had been so reported. Although numbers were small, cases and controls did not appear to differ in this regard, since heart attack was reported to be the cause of death in five relatives of cases compared with seven on the death certificate and in nine relatives of controls compared with 13 on the certificate.

Results

Of 173 cases invited to this study, 142 attended (82%) while 153 of the 184 controls attended (83%) (11 control subjects had inadvertently been invited without their case pairs). Not all the assigned pairs were complete as sometimes only one member of the pair attended and for this reason analysis has ignored the pairings. By the time of final screening 70 of the cases had developed major manifestations of CHD—that is, a proved heart attack, or an ECG with Q waves, large ST-T wave changes, or left bundle branch block (Minnesota codes 1:1–3, 4:1–2, 5:1–2, or 7:1)—while 72 had minor manifestations of either minor ST-T changes (Minnesota codes 4:3 or 5:3) or angina only without ECG changes. Similarly 76 of the controls came from pairs in which the cases had major manifestations of CHD and 77 from pairs in which the cases had minor manifestations. ECG examinations performed at the time of this survey showed that two of the control subjects had developed major manifestations of CHD and a further seven had either minor ST-T changes or now reported angina: these subjects were left in their original control category for analysis.

For the purposes of analysis the subjects attending were designated either "high risk" or "low risk" according to their originally assigned risk score, the dividing line being the 50th centile on the risk score distribution. The characteristics of the subjects (table 1) indicate that cases and controls were well matched. Information on heart attacks was available on 1246 first degree relatives (parents or brothers or sisters) and of these, 531 had died. Table 2 shows the numbers of first degree relatives who were reported to have had a heart attack and the proportions of deaths thought to be due to heart attack. Overall, heart attacks were most likely to have been reported among relatives of low risk cases, where the proportion of the deaths from this cause was almost double that among relatives of their controls ($p=0{\cdot}06$, difference between proportions corrected for continuity). The difference between high risk cases and controls was smaller, as were the differences between cases and controls for non-fatal heart attacks in both risk categories. When the analysis was confined to the cases with major manifestations of CHD and their controls, the excess in the proportion of deaths due to CHD among relatives of low risk cases persisted (12 of 71 relatives of cases compared with two of 68 relatives of controls) and was statistically significant at the 1% level. Again the difference between high risk cases and controls was smaller and not significant (seven of 69 and eight of 77 relatives respectively).

Discussion

The advantage of this study design is that it permits the importance of various possible aetiological agents to be tested in relation to "conventional" risk factors (and may be particularly useful at the end of a longitudinal study where it was not possible to measure everything at the start). The recall of family history may be "stimulated" by having the disease

Table 1 *Initial characteristics of study subjects*

	No	*Mean risk score**	*Mean age (year)*
Low risk:			
Cases	75	3·3	45·8
Controls	80	3·3	45·7
High risk:			
Cases	67	6·1	47·8
Controls	73	6·0	48·0

*Based on age, concentration of plasma cholesterol, systolic blood pressure, cigarette smoking, and physical activity at work (range 0–11).

Table 2 *Reported heart attacks in relatives of cases and controls*

	All relatives		*Dead relatives*	
	No	*Heart attacks**	*No*	*Died of heart attack*
Low risk:				
Cases	315	41 (13·0%)	137	24 (17·5%)
Controls	366	31 (8·5%)	151	14 (9·3%)
High risk:				
Cases	293	29 (9·9%)	122	13 (10·7%)
Controls	271	21 (7·7%)	121	10 (8·3%)

*Includes fatal and non-fatal: those with both counted only once.

oneself, and another advantage of this design is that it enables us to compare low with high risk men between whom the biases should not differ. Biased recall is unlikely to be responsible for our findings since an examination of death certificates suggested that, although numbers are small, cases and controls are similar in their under reporting of heart attack as a cause of death in their relatives.

The results of this study appear to suggest that a clue to the reason why low risk men develop CHD may be in their family history. Since low risk men had a stronger family history of CHD than high risk men a search for other similarities between members of families who share a tendency to develop CHD may help discover some extra aetiological factors for CHD. It would appear that the familial aggregation of conventional risk factors is not enough to explain the fact that CHD runs in families. If this had been the case, since risk factors certainly do aggregate in families, we would have expected a stronger family history among high risk men than low risk men. Support for this comes from a recent report from the Framingham study, where having a brother with heart disease increased the chance of developing CHD irrespective of other risk factors[8]: further studies should be designed to explore the nature of additional familial factors, which seem to operate to produce CHD in men at otherwise low risk.

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