Family history — and independent risk factors for coronary heart disease, it is time to be practical

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Epidemiological studies indicate that family or parental history of myocardial infarction is a risk factor for coronary heart disease (CHD)\(^1\)-\(^2\). The innate susceptibility to CHD was suggested 20 years ago in the Framingham cohort, which showed that family history of premature CHD conferred excess risk\(^3\)-\(^4\). A history of death due to CHD in parents of the cohort was found to be associated with a 30% increased risk of CHD, a risk which was not mediated by other risk factors.

The common disorders such as CHD, diabetes, Alzheimer’s disease or bronchial asthma are considered complex diseases arising from interactions between genes and environment\(^5\). The usual measure of the effect of gene–environment interaction is the ratio of disease incidence between exposed and unexposed individuals i.e. individuals with a positive or negative family history of disease. But very important questions remain: how to define a positive family history? Usually, how far both parents and siblings are affected is considered together, and the age limit at which they were affected is given. It is well known that females are prone to CHD at least 10 years later than men. A positive family history is seen as fathers who succumb earlier than 55 years of age, and mothers before 65 years\(^6\). The answers always depend on the level of information available, and the intellectual power of the probands. Those with higher education may be considered better informed in this matter.

The maternal and paternal history of myocardial infarction (MI) and risk of cardiovascular disease in men and women was recently studied in the Physician’s Health Study and the Women’s Health Study\(^1\). Compared with men with a negative family history, of those affected either only maternal or paternal, or both maternal and paternal conferred for first-degree relatives the relative risk (RR) of 1·71, 1·40 and 1·85. Among women, the RR was, respectively, 1·4, 1·15 and 2·05. It means, that women with both parents affected are at particularly high risk.

In this issue the coronary risk associated with a reported family history of MI and/or sudden death was assessed in a large population of 19 390 male and female participants of the Reykjavik Cohort Study\(^7\). A random sample of men born 1907–1934 and women born 1908–1935 was examined during a 30-year period 1967–1996 and followed until 31 December 1998. The participants were asked about any history of acute MI or coronary death in parents or siblings. Risk factor levels were compared in participants with and without a positive family history in a risk period between initial examination until 31 December 1998. Average follow-up was about 19 years. Of 9328 male and 10 62 female participants, 14% of men and 14% of women had a personal history of CHD prior to entry into this study. This personal history of CHD was based only on a positive Rose Chest Pain Questionnaire\(^8\). During this follow-up period, 2700 men and 1070 women suffered a MI or sudden death. A large set of traditional risk factors was assessed at the entry. Higher education and leisure time physical activity were inversely associated with coronary risk, as well as with prevalence of smoking, blood pressure and blood cholesterol levels in probands. A positive family history in the whole cohort was associated with about a 75% increase of risk in men and an 84% increase in women, as well as with a significantly higher total cholesterol, impaired glucose tolerance, triglycerides levels and prevalence of antihypertensive treatment. At follow-up they also showed a higher prevalence of chest pain assessed by the Rose Questionnaire for possible MI and/or angina pectoris. Family history in this study included heart attacks irrespective of age, but it has not been established whether only the father or mother or both parents were affected, or whether only siblings and not parents were affected. In spite of these limitations the published data confirm previous findings of an independent effect of family history on the risk of cardiovascular disease. Due to the design of this cohort study whether paternal or maternal history of MI is more strongly associated with coronary risk could not be revealed. As was recently shown\(^1\), a

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history of maternal MI at any age up to 79 years was associated with excess risk for both sons and daughters. In contrast, paternal MI at any age confers excess risk for sons, but only premature MI (<50 years) for daughters. Prematurity of coronary disease in both parents jointly is a very important estimate of risk. Joint association of paternal and maternal history of premature MI may increase the risk for descendants almost sevenfold.

Many questions remain about the actual role of inheritance on risk-phenotypes of affected family members including lifestyle. It has been shown many times that family members are clustered for blood pressure, particular types of hyperlipidemias and diabetes. Inheritance may even play a role in such behavioural traits as smoking. Members of families may find it difficult to stop smoking due to the inherited rapid conversion of nicotine to cotinine associated with polymorphisms in the CYP-2A6 genes, which encode a cytochrome P450 enzyme. They may require nicotine substitutes for smoking cessation. Inherited polymorphisms or mutations of coagulation factor-genes such as beta-fibrinogen, Leiden mutation of factor V and enzymes responsible for homocysteine metabolism such as thermolabile mutation of methylen-tetrahydroxy-folate reductase may interfere in multistage interactions of hereditary background and acquired lifestyles.

Taking family history is one of the traditional tools in clinical medicine, however, it is frequently neglected. Case-finding through affected probands may identify not only people at risk of disorders with classical Mendelian inheritance, but also individuals at high risk of common diseases, as was shown in the Reykjavik Cohort Study. Family members of affected probands are an ideal target population for primary prevention of CHD, as recommended in the European Guidelines for prevention of CHD in clinical practice.

In spite of it, the results from the EUROASPIRE II family survey have shown that European physicians rarely screen family members of patients with premature CHD and, moreover, general lifestyle advice or treatment for risk factors are rarely provided. Without regard to particular phenotypes or genotypes of individual members of affected families we have to be practical. A family history of CHD requires physicians to advise on lifestyle and appropriate management of risk in all family members, moreover, regular follow-ups of all still evidently healthy descendants is essential.

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