Families of patients with premature coronary heart disease: an obvious but neglected target for primary prevention

Risk of premature coronary heart disease is increased in the families of affected patients.

C K Chow and colleagues argue that targeting relatives for primary prevention would be an effective policy

First degree relatives of patients with premature coronary heart disease are at increased risk of the disease. Compared with the general population, siblings have at least double the risk, because of shared lifestyle risk factors and genetic predisposition. Offspring and partners are also at increased risk. Relatives have an increased prevalence of modifiable risk factors including hypertension, dyslipidaemia, and smoking. Some guidelines recommend screening of relatives, but surveys indicate that this does not occur in practice. We propose that first degree relatives of patients admitted for premature myocardial infarction should be identified and then offered screening and treatment for risk factors of coronary heart disease.

Sources and selection

We searched OVID, Medline, and PubMed databases using combinations of the terms “family history”, “coronary heart disease”, “sibling”, “relative”, “premature coronary heart disease”, and “cardiovascular risk factors”. We cross checked the reference lists of papers identified as relevant. We undertook a web search using the same terms and searched the publication lists of relevant organisations such as the British Heart Foundation, European Society of Cardiology, and American Heart Association.

Increased risk of coronary heart disease

Coronary heart disease aggregates in families.¹ In a cross sectional European survey (Euroaspire II), 10% of the siblings of 1289 patients with premature coronary heart disease also had the disease.² In another study, 16% of first degree relatives of survivors of myocardial infarction reported previous myocardial infarction, compared with 9% of the relatives of controls.¹ Similarly, 12% of siblings of 325 patients with premature coronary heart disease in a Danish registry already had the disease, and 30% had substantial risk ($\geq 20\%$ at 10 years) of a cardiovascular event.²

Family history of coronary heart disease significantly increases risk of the disease in all first degree relatives.^{3 4} Myocardial infarction in a sibling increases the risk of coronary heart disease by twofold to 15-fold (table 1).¹⁵ Risk varies according to age at presentation, number of relatives affected, and degree of genetic concordance.

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Premature coronary heart disease—before 55 years in men and 60 in women—is more likely to reflect a genetic predisposition, so relatives of patients with premature onset are at greater risk than those of patients with late onset disease.^{15 17} Among 45 317 health professionals, paternal history of myocardial infarction before 70 years conferred a relative risk of 1.7,¹⁵ whereas a paternal history before 50 years carried a relative risk of 2.3. The corresponding figures for maternal history were 2.2 and 3.6. Increased risk is also due to shared lifestyle. Mothers exert a greater influence over the lifestyle of their offspring than fathers,²⁰ which accounts for the higher risk associated with maternal family history.^{10 15} Risk is higher if more than one first degree relative is affected.¹⁰ In a study of 1310 people with myocardial infarction, the odds ratio was 1.8 for a history of coronary heart disease in one family member, compared with 3.5 for a history in two. In a study of 21 004 twins, the risk among dizygotic twins (odds ratio 2.2) was similar to other first degree relatives (table 1) but was much higher among monozygotic twins (14.9).¹⁶

In another study, the relative risks of coronary heart disease in young men were 3.9 for a family history of premature coronary heart disease, 5.9 for a history of the disease in more than one relative, and 12.7 if both were true.²¹ The corresponding figures in an Italian case-control study were 2.7, 3.5, and 20.0; these results suggest that the combined effects of these factors may be more than additive.²²

Increased prevalence of modifiable risk factors

The relative contributions of genetic predisposition and shared lifestyle are unclear and probably vary between families. None the less, the high prevalence of modifiable risk factors suggests that affected families would benefit from modifying risk factors. High levels of cardiovascular risk factors have been noted in siblings, children, and even partners of patients with premature coronary heart disease.²³ In Euroaspire II, 30% of siblings smoked, 20% were obese, 23% had hypertension, and 8% had diabetes.²⁴ One study compared mean levels of risk factors between siblings of patients with premature coronary heart disease and the general population of the United States.²⁵ Total cholesterol concentrations, low density lipoprotein

Table 1 | Risk of coronary heart disease associated with a family history of premature coronary heart disease

Reference	Location	Number	Relationship	Risk factor adjustment	Odds ratio		
					Overall	Men	Women
Case-control studies							
Nora 1980 ⁵	USA	207 cases, 621 controls	1st degree relatives	No	10.4	—	—
Ten Kate 1982 ¹	USA	145 cases, 145 controls	1st degree relatives	No	2.1	—	—
Shea 1984 ⁶	USA	223 cases, 57 controls	1st degree relatives	Yes	2.1	—	—
Friedlander 1985 ⁷	Israel	123 cases, 921 controls	1st degree relatives	No	1.7	—	—
Roncaglioni 1992 ⁸	Italy	916 cases, 1106 controls	1st degree relatives	No	2.0	2.0	1.9
Roncaglioni 1992 ⁸	Italy	916 cases, 1106 controls	1st degree relatives	No	3.1	—	—
Ciruzzi 1997 ⁹	Argentina	1060 cases, 1071 controls	1st degree relatives	Yes	2.5	2.4	3.1
Leander 2001 ¹⁰	Sweden	954 cases, 1351 controls	Offspring/siblings	No	—	2.0	2.1
Cohort studies							
Sholtz 1975 ¹¹	USA	3524	Offspring	No	—	2.2	—
Barrett-Connor 1984 ¹²	USA	4014	1st degree relatives	Yes	—	1.6	0.9
Colditz 1986 ¹³	USA	117 156	Offspring	No	—	—	2.8
Myers 1990 ¹⁴	USA	4847	Offspring	Yes	1.3	1.4	1.2
Colditz 1991 ¹⁵	USA	45 317	Offspring	No	—	2.2	—
Marenberg 1994 ¹⁶	Sweden	7310	Twins	No	—	13.4	14.9
Marenberg 1994 ¹⁶	Sweden	13 694	Twins	No	—	4.3	2.2
Jousilahti 1996 ¹⁷	Finland	15 620	Offspring	No	—	1.6	1.9
Boer 1999 ¹⁸	Netherlands	46 356	1st degree relatives	Yes	—	1.6	2.1
Boer 1999 ¹⁸	Netherlands	46 356	1st degree relatives	No	—	1.7	2.3
Andresdottir 2002 ¹⁹	Iceland	19 390	1st degree relatives	No	—	1.8	1.8
Hawe 2003 ³	UK	2827 men	Any relatives	Yes	1.9	1.9	—
Hawe 2003 ³	UK	2827 men	Any relatives	No	1.7	1.7	—

cholesterol concentrations, and systolic and diastolic blood pressure were all higher in siblings.

The offspring of patients with premature coronary heart disease also have higher levels of modifiable risk factors than age and sex matched controls. Of 87 asymptomatic offspring of women with such disease, 29% of sons and 30% of daughters exceeded their age and sex specific risk for developing the disease within 10 years.¹⁵ Carotid intima media thickness, an indicator of global cardiovascular risk, is higher in offspring of patients with premature coronary heart disease.^{27 28} The role of shared lifestyle is clearly shown by studies of unrelated family members. Wives of patients with myocardial infarction had significantly higher levels of modifiable risk factors than wives of healthy men.²⁹

Guidelines versus current practice

Several published guidelines have recommended screening of first degree relatives of patients with premature coronary heart disease (table 2).¹⁹⁻²³ Surveys suggest that this is not done in practice. Among siblings of 325 patients with premature coronary heart disease in a Danish registry, only 83% of those with hypertension and 33% of those with hypercholester-

laemia were receiving medical treatment.² Furthermore, treatment targets were reached in only 28% and 7%, respectively. When 859 siblings of 490 patients with premature coronary heart disease in the John Hopkins study were compared with the US general population, siblings had a lower awareness about hypertension (60% *v* 69%), its treatment (45% *v* 53%), and its control (16% *v* 24%).²³ In Euroaspire II, 54% of siblings and 71% of offspring had not been screened. Where screening had occurred, it was mostly opportunistic—part of a general check-up.²⁴ In an international survey of patients with myocardial infarction, only 61% of relatives had altered their lifestyle; only 39% had reduced or quit smoking and less than half had reduced their fat intake.³⁵ Few studies have examined why relatives are not screened, but lack of public awareness and lack of systems to identify them may play a part. Of 5553 patients admitted with coronary heart disease to 53 US hospitals, less than 1% had a discharge plan recommending screening of family members.³⁶ Only 20% of the 5553 patients had family members screened within six months. Predictors of screening were education level, cholesterol value, marital status, smoking status, and ethnic group.³⁶

Primary prevention strategies

In the past, the main approach to primary prevention was to identify and treat very high levels of individual risk factors. This approach was ineffective at a population level because most events occur in people with moderate levels of risk.³⁷ A small shift in the population distribution of a risk factor, such as blood pressure, prevents more deaths.³⁷ Recently, a hybrid approach has been championed, whereby people are treated for one or more risk factor on the basis of their overall cardiovascular risk. Targeting interventions in this way is more than twice as effective as treating individual factors.³⁸ Similarly, studies of the “polypill concept” (a pill combining low doses of many cardiovascular preventative drugs) suggest that this multifactorial approach could be very effective—reducing the risk of a cardiovascular event in high risk subgroups by up to 88%.³⁹

The cost effectiveness of this strategy depends on how easily we can identify asymptomatic people with high overall risk. Few people have occupational health checks. Socioeconomically deprived people are at highest risk but are least likely to be screened. Opportunistic screening while patients visit primary care for another reason is possible, but middle aged men visit infrequently. Inviting unselected people for primary care screening is feasible,⁴⁰ but the yield is low. Such an approach is of borderline cost effectiveness,⁴¹ but the overall cost may be prohibitive.⁴²

Family history can identify a large proportion of people at high overall risk. In the Utah family health tree study, the 14% of families with a positive family history accounted for 48% of all coronary heart disease events and 72% of all premature coronary heart disease events.⁴³ Targeting relatives of patients with premature coronary heart disease would improve yield and cost effectiveness. Attempts have been made to identify high risk families via school based, work based, or online questionnaires. We believe that wide coverage could be achieved by identifying relatives whenever someone is admitted to hospital for premature myocardial infarction. Such people may be motivated by their relative's illness to modify their lifestyle.

Burden of preventable disease

The 2001 census shows that 29.2 million adults may be at risk of premature myocardial infarction in England and Wales (men 20–54 years, women 20–64 years; figure). In 2004, 15 616 hospital admissions for a principal diagnosis of myocardial infarction occurred in this age group (Hospital Episode Statistics (www.hesonline.nhs.uk); Scottish Morbidity Record (www.isdscotland.org))—20% of all admissions for myocardial infarction.

By applying the results of a northern European cohort study, we estimated that 25% (7.3 million) of people in this age group had a family history of coronary heart disease, and that their relative risk of this disease was 1.7 for men and 2.1 for women.¹⁷ By applying these relative risks to the age and sex specific population incidence, we estimated that people

Table 2 | Guidelines recommending screening of first degree relatives of patients with premature coronary heart disease

Year	Organisation	Recommendation
1993	Second report of the National Cholesterol Education Program (NCEP) ATP II	Family history of premature coronary heart disease (definite myocardial infarction or sudden death before 55 years of age in father or in other male first degree relative, or before 65 years of age in mother of other female first degree relative) is a high risk category for cholesterol monitoring and lowering ³⁰
1994	Task force of the European Society of Cardiology, European Atherosclerosis Society, and European Society of Hypertension	Close relatives of patients with premature coronary heart disease or other atherosclerotic vascular disease are a high risk group requiring action to reduce their risk factor levels ³¹
1998	Second joint task force of European and other societies on coronary prevention	Close relatives of patients with premature coronary heart disease (men <55 years and women <65 years) should be screened for coronary risk factors as they are at increased risk of developing coronary heart disease ³²
2002	American Heart Association guidelines for primary prevention of cardiovascular disease and stroke	Risk factor assessment in adults should begin at age 20 years; family history of coronary heart disease should be regularly updated ³³

with a family history had 7369 premature myocardial infarctions in 2004.

On the basis of the polypill study, aggressive cardiovascular risk management might have decreased the risk by up to 88%³⁹ and prevented 6485 premature myocardial infarctions in 2004. Thus, screening and treating middle aged people with a family history of coronary heart disease could have prevented 42% of premature myocardial infarctions and 8% of all myocardial infarctions.

Potential impact of a hospital admission strategy

We estimated the potential impact of using hospital admissions for premature myocardial infarction to identify and screen high risk relatives. Data from a population based family cohort study were used to determine the average numbers of live siblings by age-sex strata.⁴⁴ We calculated that the 15 616 patients admitted for premature myocardial infarction in 2004 had a total of 32 074 siblings (mean 2.4). Using relative risks of 4.3 and 2.2 for male and female siblings, respectively,¹⁶ and the population age specific incidence of myocardial infarction, we calculated that 218 siblings would have premature myocardial infarction within one year of the index admission and 1148 within five years (figure). By applying the polypill risk reduction,³⁹ we estimated

Potential impact of using hospital admissions for premature myocardial infarction to identify and screen high risk relatives based on data from 2004 in England and Wales

that for every 14 patients admitted with premature myocardial infarction, one additional premature myocardial infarction could be avoided in siblings within five years. Inclusion of other first degree relatives would increase the yield further.

Conclusions

Primary prevention of coronary heart disease should be targeted at people with a high overall risk. Identifying such people from the general population is difficult. First degree relatives of patients admitted with premature myocardial infarction have a high overall risk and account for a large proportion of premature myocardial infarctions. At risk relatives could be identified easily at the time the index patient presents to hospital. Patients with premature coronary heart disease usually present acutely to the accident and emergency department or are referred to the outpatient clinic. Such patients could be flagged in these settings as needing family counselling. A similar practice is in use for inherited cancers, where relatives are identified, counselled, and offered screening. Motivation to attend cancer screening is higher in people with a positive family history.⁴⁵ However, familial risk in cardiovascular disease is complex, and overemphasising the genetic component may reduce motivation to change lifestyle.⁴⁶ Further research is needed to identify barriers and determine the most effective approach. In England and Scotland alone, 7369 premature myocardial infarctions occur each year in people with a family history of the disease, and 6485 may be preventable. First degree relatives are an obvious, but neglected, group at which primary prevention should be targeted.

Contributors and sources: AFD has a longstanding research interest in genetics of cardiovascular disease. JPP has a longstanding research interest in cardiovascular epidemiology and health services research. CKC is a cardiologist with a research interest in cardiovascular epidemiology. ACHP has considerable experience of managing patients with premature coronary heart disease. AW and CO'D have a longstanding interest in the health economics of cardiovascular disease. JPP and ACHP had the original idea. CKC and JPP did the literature review. CKC, JPP, AW, and CO'D agreed the model. CKC and JPP obtained the data for the model. CKC did the modelling. CKC and JPP drafted the paper. All authors helped with redrafting and agreed the final version. JPP is guarantor.

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SUMMARY BOX

Prevention of coronary heart disease is most effective if targeted at people with high overall risk

First degree relatives of patients with premature myocardial infarction have double the risk of the condition

In the UK, about 20% of all admissions for myocardial infarction occur in patients with premature myocardial infarction

More than a third of admissions for premature myocardial infarction could be prevented by screening and treating first degree relatives

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