Family history, longevity, and the risk of coronary heart disease: the PRIME study


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Numerous epidemiological studies have identified the major classical\(^1\) and many putative\(^3,4\) risk factors for coronary heart disease (CHD). A family history of coronary disease is one such factor and several studies\(^5\) have examined its contribution to subsequent risk.

We have previously reported cross-sectional associations between classical risk factors and coronary disease in Northern Ireland and France, two countries at contrasting risk for myocardial infarction.\(^9\) Predicted risk of coronary disease as estimated from logistic regression equations using the classical risk factors could not explain the much higher level of coronary incidence experienced in Northern Ireland compared with that in France.\(^10\)

In this report we examine the influence of a family history of premature coronary disease and also the effect of parental longevity, although related, act independently of one another and of other major cardiovascular risk factors in predicting 5-year risk of subsequent coronary events.

Conclusions These results indicate that a family history of coronary disease and parental longevity, although related, act independently of one another and of other major cardiovascular risk factors in predicting 5-year risk of subsequent coronary events.

Keywords Coronary heart disease, cohort study, family history, longevity, men, France, Northern Ireland, risk factors, heredity

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longevity on the incidence of coronary events over a 5-year period of follow-up in middle-aged men from these populations who had no historical or clinical evidence of coronary disease when initially examined.

Subjects and Methods

Study design

Between 1991 and 1994, a sample of 10,600 men aged 50–59 years were included in three centres in France (Lille in the north, Strasbourg in the east, and Toulouse in the southwest), and one centre in Northern Ireland (Belfast). The sample was recruited in factories and in various firms, in occupational medicine, health screening centres, and general practice. Subjects were informed of the aim of the study and agreed to an annual follow-up. Approval from the appropriate local Ethical Committee was obtained in each study centre. The PRIME Study (étude PRospective du l’Infarctus MyocardE prospective epidemiological study of myocardial infarction) has the general aim of evaluating the contribution of nutritional, metabolic, and genetic risk factors in the development of ischaemic heart disease in Europe and a more detailed description of the study populations and general methodology has been reported elsewhere. In each centre the sample broadly matched the social class structure of the background population.

Personal/family history and examination

Each subject completed self-administered questionnaires. These questionnaires on demographic, socioeconomic factors, and dietary habits were checked by specially trained medical staff. Additional questionnaires were administered at the clinic: information was collected on tobacco consumption, family and personal medical history, symptoms, and medication(s). The London School of Hygiene and Tropical Medicine chest pain questionnaire was also administered. A detailed family history was requested using a self-administered questionnaire. The following information was requested for all family members: vital status, current age or age at death, history of heart attack, age at heart attack, and whether or not hospitalized for heart attack. Only first-degree family relatives were included in the present analysis (parents, siblings, and offspring). Baseline investigations included anthropometric measurements, waist/hip ratio, a 12-lead electrocardiogram, and standardized blood pressure measurements using an automatic sphygmomanometer (Spengler SP9) as reported in detail previously. Subjects were considered as having a history of coronary disease at entry if they reported one of the following events: (1) myocardial infarction and/or angina pectoris diagnosed by a physician; (2) electrocardiographic evidence of myocardial infarction, defined as major or moderate Q waves coded using the Minnesota system, and (3) a positive chest pain questionnaire.

Venous blood samples were collected after a 10-hour fast and centrifuged within 4 hours. Blood samples were stored at +4°C, and were shipped at the same temperature, weekly, to the co-ordinating laboratory in Lille. All measurements were performed blind to the originating centre and by consecutive numbers, to include samples from the four centres in each analytical run. All procedures were standardized between centres. Plasma lipid analyses were conducted at SERLIA-INSERM U325 (Pasteur Institute, Lille, France). Total cholesterol and triglycerides were measured by enzymatic methods using commercial kits in an automatic analyser (Boehringer, Mannheim, Germany). High-density lipoprotein (HDL) cholesterol was determined after precipitation of apolipoprotein (apo) B-containing lipoproteins with phosphotungstic acid/magnesium chloride by an enzymatic method (Boehringer).

Calculation of family risk score (FRS)

This was calculated from the observed events in each subject’s family using established methods to adjust for family size and background incidence in the population. Data from the questionnaire on the age of onset of coronary events in first-degree relatives and the expected background incidence in the general population at different ages (which we estimated using data from the MONICA Project14 and the World Health Organization mortality data15) were used as follows. Use O to denote the observed number of individuals in the family that had had a coronary event. Then E, the expected number of individuals, is obtained by summing over all first-degree relatives the cumulative risk up to the date of interview or death, whichever occurred first. These incidence rates required to estimate the cumulative risks were obtained as follows. For men and women aged 35–64 years, the incidence rates were taken from MONICA project population studies for the years 1991–1994, 1992–1994, and the years of the present study. For men and women aged ≤34 and ≥65 years, the incidence rates were estimated from mortality rates of acute myocardial infarction—International Classification of Diseases, Ninth Revision (ICD-9, 270) and other ischaemic heart disease (ICD-9, 279), and assuming a mortality to incidence ratio of 50%. In performing these calculations we noted that the observed number of events in parents of the subjects was considerably less than the number of expected events, probably because the incidence rates we used in the calculations were too high for this earlier generation. For this reason we scaled down the number of events expected in parents by making the expected number of events (totalled over all families) match the observed number of events (totalled over all families).

The FRS was then calculated as:

\[
FRS = \frac{O - E}{\sqrt{E}} + \frac{0.5}{O - E} \times \frac{|O - E|}{O - E} \quad \text{if} \quad |O - E| > 0.5
\]

To adjust for instability of the FRS due to small family size and/or small expected numbers of events, FRS was set to 0 if \(|O - E| \leq 0.5\) and was set to 0.99 if the FRS > 1.0 but fewer than two members of the family were affected.

The distribution of the FRS was highly skewed (the majority of subjects having a low score) and was grouped into categories for further analysis as follows:

<table>
<thead>
<tr>
<th>FRS category</th>
<th>FRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 ≤ FRS &lt; 0.5</td>
<td>1 none (or minimal)</td>
</tr>
<tr>
<td>0.5 ≤ FRS &lt; 1.0</td>
<td>2 suggestive</td>
</tr>
<tr>
<td>1.0 ≤ FRS</td>
<td>3 positive</td>
</tr>
</tbody>
</table>

Follow-up

Subjects were contacted annually by letter and a clinical event questionnaire was filled up and sent to the centre. If the subject did not respond, a phone contact was established with the
subject or with his general practitioner. For all subjects reporting a possible clinical event, clinical information was sought directly from hospital or general practitioner notes. All details of electro-cardiographs, hospital admissions, enzymes, surgical operations, angioplasty, treatment, etc. were collected. Death certificates were checked for supporting clinical and post-mortem information on cause of death. Whenever necessary, death circumstances were obtained from the practitioner or the family.

A medical committee was established, comprising one member of each PRIME centre, including the co-ordinating centre, and three independent cardiologists (two from France and one from the UK) in order to provide an independent validation of coronary events in the PRIME Study. Coronary events were defined as ‘hard’ coronary events (myocardial infarction or coronary deaths) and angina pectoris, which were validated using clinical records as described in detail previously. Total coronary events included both ‘hard’ and angina events.

Statistical analysis

Hard coronary events were counted only once, whether or not preceded by a diagnosis of angina. Conversely, angina pectoris events were counted once (stable or unstable according to which occurred first), but only when they were not preceded by a myocardial infarction. Results were expressed as mean (SD), median (interquartile range), or number of subjects (percentage). Statistical significance was assessed at the $P < 0.05$ level. Relative odds were computed using logistic regression analyses with coronary incidence as the dependent variable. For the comparison of the two outcomes ‘hard’ coronary disease and angina, multinomial logistic regression was used as described elsewhere. Statistical analysis was performed using the SPSS and STATA software packages.

Results

On baseline screening 842 subjects were considered to have clinical or historical evidence of coronary disease as defined in Methods (346 [13%] men in Belfast and a total of 496 [6%] in the three French centres). Only subjects without evidence of coronary disease at baseline were considered further in this report (2399 in Belfast; 7359 in France).

Table 1 shows the distribution of subjects with a family history of coronary disease as defined in Methods (346 [13%] men in Belfast and a total of 496 [6%] in the three French centres). Only subjects without evidence of coronary disease at baseline were considered further in this report (2399 in Belfast; 7359 in France).

Table 1 Number (%) of subjects with family history of coronary disease and number of parental longevity in Northern Ireland and France among men aged 50–59 years at entry

<table>
<thead>
<tr>
<th>Family history of coronary disease</th>
<th>Northern Ireland</th>
<th>France</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRS1 none</td>
<td>2056 (86)</td>
<td>6450 (88)</td>
</tr>
<tr>
<td>FRS2 suggestive</td>
<td>153 (6)</td>
<td>752 (10)</td>
</tr>
<tr>
<td>FRS3 positive</td>
<td>185 (8)</td>
<td>139 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>2394 (100)</td>
<td>7341 (100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parental longevity</th>
<th>Northern Ireland</th>
<th>France</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both parents dead by 80 years</td>
<td>857 (36)</td>
<td>1887 (26)</td>
</tr>
<tr>
<td>1 parent alive at 80 years</td>
<td>941 (39)</td>
<td>3029 (41)</td>
</tr>
<tr>
<td>Both parents alive at 80 years</td>
<td>244 (10)</td>
<td>1033 (14)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>357 (15)</td>
<td>1410 (19)</td>
</tr>
<tr>
<td>Total</td>
<td>2399 (100)</td>
<td>7359 (100)</td>
</tr>
</tbody>
</table>

* $\chi^2 = 214.3$, d.f. = 2, $P < 0.001$. See text for explanation of family risk score (FRS) terms.
* Information missing for 23 subjects.
* $\chi^2 = 106.0$, d.f. = 3, $P < 0.001$.
* One parent either alive aged <80 years or unknown age at death.
cholesterol shows a significant difference between those with a positive and negative family history. The lipid profile is more adverse in subjects from Northern Ireland compared to that in France.

Table 4 shows the distribution of non-lipid and lipid risk factors by longevity of parents. In contrast to the data on family history most non-lipid risk factors show an adverse profile in subjects whose parents had both died early, before the age of 80 years compared with subjects with one or both parents surviving.

In the case of parental longevity, triglycerides was the only lipid risk factor which differed significantly, higher values occurring in the subjects whose parents had both died by the age of 80 years.

Table 5 shows the multivariate adjusted relative odds of coronary events according to the FRS. Family risk score scaled at 1 is used as the baseline for relative odds. After adjustment for 10 other risk factors including parental longevity the association is stronger in Northern Ireland than in France, but combining the results for the two countries produces a graded relationship from low to high family risk, both relative odds achieving statistical significance. These findings are mirrored in the results for parental longevity also shown in Table 5. Tests for interaction in the logistic model between FRS and centre and between parental longevity and centre were non-significant, indicating that the risks associated with these factors were of similar magnitude in Northern Ireland and France. Also shown are relative odds for other major cardiovascular risk factors (unstandardized in the case of continuously distributed variables).

Table 6 shows the separate effects for risk of ‘hard’ coronary events and angina according to the degree of family history or parental longevity adjusted for nine other risk factors including parent longevity.
adjustment for either family history or parental longevity as appropriate. Multinomial logistic regression was used for this analysis, providing a comparison of the relative odds for the two separate outcomes: ‘hard’ coronary disease, and angina.

Statistical tests indicated that the relative odds for neither FRS nor parental longevity differed significantly between ‘hard’ coronary events and angina.

### Discussion

In this large cohort the incidence of coronary events in men without pre-existing coronary disease was almost twice the rate in Northern Ireland (Belfast) compared with that in the combined three French centres. These results are reported in detail elsewhere\textsuperscript{17} but the calculation of the FRS had the effect of adjusting for the background incidence. Although there are small differences in the incidence of coronary events between the French centres, tests for heterogeneity between the French centres did not show significant differences for the results shown in Tables 3–5.

As in the UK, France is experiencing a slow decline in coronary mortality but UK rates remain much higher than those in France.\textsuperscript{15} Similarly the higher proportion of individuals with both parents dead by 80 years in Northern Ireland reflects the higher mortality rates for the UK and Northern Ireland in particular; for 1991/92 the difference in life expectancy at birth was 0.8 years and at 65 years was 2.4 years between France and Northern Ireland.\textsuperscript{15}

In this study it was not possible to validate the family histories of heart attacks, but a careful family history was recorded, detailing all first-degree relatives and some second-degree relatives which would provide less opportunity for systematic bias. Recall bias has been calculated previously in case-control studies and was generally found to be small\textsuperscript{19,20} but is likely to be smaller in a cohort of men initially free of clinical or historical evidence of coronary disease.

For parental longevity almost all of the non-lipid risk factors differed between subjects with and without a history of parental longevity but this was not true for lipids. For family history only total cholesterol differed between those with and without such a history and only blood pressure and age of the other risk factors. Fibrinogen showed no association with family history in such a history and only blood pressure and age of the other risk factors. Fibrinogen showed no association with family history in contrast to findings reported in other studies.\textsuperscript{21–23}

Although many of the cardiovascular risk factors differed between Northern Ireland and France in the expected direction, some, such as hypertension and body mass index, had a higher prevalence in France; yet, according to logistic regression models, prevailing levels of cardiovascular risk could not explain the differences in coronary event rates between Northern Ireland and France.\textsuperscript{10} Full adjustment for all non-lipid and lipid risk factors did not markedly reduce the strength of the associations between either family history of coronary disease or parental longevity. Although these factors are associated, each of these parameters is also adjusted for the other, indicating that the effects are independent.

For parental longevity the effect also appears to be stronger in Northern Ireland than in France, but, as there was a large group for whom there was insufficient information or whose parents were younger than the age of 80 years, these parameters do not apply to a significant proportion of the population at this age. It has been estimated that the genetic contribution to longevity is in the order of 25%.\textsuperscript{24}

In this study, family history and parental longevity act independently of each other and of other risk factors in predicting

### Table 4 Distributions of risk factors for coronary disease according to parental longevity (one or both parents alive at 80 years) and centre among men aged 50–59 years at entry

<table>
<thead>
<tr>
<th></th>
<th>Northern Ireland Parental longevity</th>
<th>France Parental longevity</th>
<th>Test of differences\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both dead by 80 years</td>
<td>One or both alive at 80 years</td>
<td>Both dead by 80 years</td>
</tr>
<tr>
<td></td>
<td>n = 857</td>
<td>n = 1185</td>
<td>n = 1887</td>
</tr>
<tr>
<td>Non-lipid factors\textsuperscript{b}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.8 (2.9)</td>
<td>55.2 (2.8)</td>
<td>55.3 (2.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m\textsuperscript{2})</td>
<td>26.2 (3.5)</td>
<td>26.2 (3.4)</td>
<td>27.0 (3.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.8 (20.8)</td>
<td>132.9 (20.4)</td>
<td>135.8 (18.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.8 (12.0)</td>
<td>81.5 (11.3)</td>
<td>85.4 (12.0)</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.94 (0.06)</td>
<td>0.94 (0.05)</td>
<td>0.97 (0.06)</td>
</tr>
<tr>
<td>Alcohol (ml/week pure alcohol)</td>
<td>77 (0–264)</td>
<td>85 (0–265)</td>
<td>234 (72–435)</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.62 (1.02)</td>
<td>3.60 (0.99)</td>
<td>3.22 (0.97)</td>
</tr>
<tr>
<td>Former or current smoker</td>
<td>574 (67.0%)</td>
<td>753 (65.5%)</td>
<td>1360 (72.1%)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>16 (1.9%)</td>
<td>15 (1.3%)</td>
<td>96 (5.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Northern Ireland Parental longevity</th>
<th>France Parental longevity</th>
<th>Test of differences\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cholesterol (mmol/l)</td>
<td>HDL\textsuperscript{c} cholesterol (mmol/l)</td>
<td>Triglycerides (mmol/l)</td>
</tr>
<tr>
<td></td>
<td>5.86 (1.04)</td>
<td>1.19 (0.33)</td>
<td>1.66 (1.17–2.39)</td>
</tr>
<tr>
<td></td>
<td>5.88 (0.99)</td>
<td>1.20 (0.32)</td>
<td>1.63 (1.19–2.36)</td>
</tr>
<tr>
<td></td>
<td>5.69 (1.00)</td>
<td>1.28 (0.35)</td>
<td>1.32 (0.98–1.82)</td>
</tr>
<tr>
<td></td>
<td>5.68 (0.96)</td>
<td>1.29 (0.33)</td>
<td>1.30 (0.98–1.78)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Significance by two-way analysis of variance or log-linear modelling with adjustment for age. NS, not significant; *P < 0.05; **P < 0.01; ***P < 0.001.

\textsuperscript{b} Values are mean (standard deviation), median (interquartile range), or number (percentage).

\textsuperscript{c} High density lipoprotein.
5-year risk of coronary events in men with no evidence of coronary disease at baseline. This suggests that new risk factors, including heritable risk factors, may be relevant to the aetiology of CHD.

**Acknowledgements**

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FAMILY HISTORY AND CORONARY HEART DISEASE: THE PRIME STUDY

KEY MESSAGE

- Family history and parental longevity are each independent predictors of subsequent coronary heart disease in this large cohort study, particularly in the population from Northern Ireland.

References


