Intermittent Claudication, Heart Disease Risk Factors, and Mortality
The Whitehall Study

George Davey Smith, MB, MSc, MA, Martin J. Shipley, BA, MSc, and Geoffrey Rose, DM

In the Whitehall study, 18,388 subjects aged 40–64 years completed a questionnaire on intermittent claudication. Of these subjects, 0.8% (147) and 1% (175) were deemed to have probable intermittent claudication and possible intermittent claudication, respectively. Within the 17-year follow-up period, 38% and 40% of the probable and possible cases, respectively, died. Compared with subjects without claudication, the probable cases suffered increased mortality rates due to coronary heart disease and cerebrovascular disease, but the mortality rate due to noncardiovascular causes was not increased. Possible cases demonstrated increased mortality rates due to cardiovascular and noncardiovascular causes. This difference in mortality pattern may be due to chance. Possible and probable cases still showed increased cardiovascular and all-cause mortality rates after adjusting for coronary risk factors (cardiac ischemia at baseline, systolic blood pressure, plasma cholesterol concentration, smoking behavior, employment grade, and degree of glucose intolerance). Intermittent claudication is independently related to increased mortality rates. It is not a rare condition, and simple questionnaires exist for its detection. The latter can be usefully incorporated in cardiovascular risk assessment and screening programs. (Circulation 1990;82:1925–1931)

Follow-up studies of patients with intermittent claudication reveal a higher mortality rate than that in the general population.1–5 Such patients have a twofold increase in age-specific risk of death and a loss of 10 years in life expectancy. Premature cardiovascular disease accounts for most or all of this increased mortality.

The prevalence of intermittent claudication is increased in people with evidence of other forms of coronary artery disease, for example, angina, previous myocardial infarction, or electrocardiographic ischemic changes.6–8 Risk factors for coronary artery disease are related to the development of intermittent claudication9,10 and are elevated in patients with intermittent claudication.7,11,12 The increased prevalence of other forms of coronary artery disease and the coexisting unfavorable profile of risk factors may explain the increased cardiovascular mortality rates in subjects with intermittent claudication. Previous studies suggest that intermittent claudication uncomplicated by evidence of other ischemia is a benign condition,8,13 and after adjusting for existing disease and other cardiovascular risk factors, there may be no increased risk of death.7 These studies have been relatively small, and their power to detect independent effects has not been great. The Whitehall study of London civil servants14 provides an opportunity to examine the prognostic importance of intermittent claudication in a large cohort with long-term follow-up and to determine whether the elevated mortality risk is solely due to the associated ischemia and coronary artery disease risk factors.

A subsidiary objective of this report concerns the criteria required for the attribution of intermittent claudication in questionnaire-based studies. The Whitehall study used the questionnaire developed by the London School of Hygiene and Tropical Medicine (LSHTM).15–17 We have, therefore, examined the effect of varying the criteria for assessing intermittent claudication18 on associations with other risk factors and on mortality rates.

Methods

In the Whitehall study, 18,403 men aged 40–64 years were examined between 1967 and 1969. Clinical measurements included height, weight, blood pressure, forced expiratory volume in 1 second (FEV1),
forced vital capacity (FVC), and a limb lead electrocardiogram. Subjects were studied the morning after an overnight fast; 50 g oral glucose was administered; and 2 hours after this, a capillary blood sample was drawn for the measurement of glucose and cholesterol concentrations. A questionnaire on age, civil service employment grade, and smoking habits was completed. Full details of procedures used have been previously reported.\textsuperscript{14}

The electrocardiogram was coded according to the Minnesota system\textsuperscript{19} and was regarded as positive for ischemia if Q/QS items (codes 1.1–3), ST/T items (codes 4.1–4 or 5.1–3), or left bundle branch block (code 7.1) was present. A regression analysis of FEV\textsubscript{1.0} and FVC against height was performed, and the coefficients were used to adjust the measurements to a uniform height of 175 cm. Subjects with a plasma glucose concentration of 11.1 mmol/l or more (\geq 200 mg/100 ml) or with previously diagnosed diabetes constituted the diabetic group; nondiabetic subjects with glucose concentrations greater than the 95th centile point (5.4–11.0 mmol/l, 96–199 mg/100 ml) formed the group with impaired glucose tolerance, and other subjects were designated as being normoglycemic. Civil service employment grade is in four levels: administrators, professionals and executives, clerical, and other (mainly unskilled manual) grades. “Low work grade” refers to the clerical and other grades. For 873 subjects from the Diplomatic Service and British Council, employment grade was not comparable to the rest of the sample. These subjects have been categorized as a separate group in the analyses that involve grade. Subjects who smoke cigarettes have been categorized as “current smoker,” “exsmoker,” and “never smoker.” In addition, adjustment for smoking habits has included a term for the number of cigarettes per day smoked by current smokers. The 640 men who smoked pipes or cigars only have been categorized as a separate group in the analyses that involve smoking status.

The LSHTM chest pain and intermittent claudication questionnaire was administered by an interviewer to 938 men and was self-administered by the other subjects. The prevalence of positive response to the intermittent claudication section was similar in these two groups.\textsuperscript{17} Data regarding angina and possible myocardial infarction have been taken from this questionnaire for the present analysis. To be classified as having intermittent claudication, subjects had to report that they developed calf pain while walking, that they had not developed such pain when standing still or sitting, that they stopped walking or slowed down when pain developed, and that the pain had then usually disappeared within 10 minutes. In addition, if subjects reported that the pain had never disappeared while walking, they were classified as having “probable” intermittent claudication. If they reported that the pain had disappeared while they were walking (which may have been at a slow pace), they were classified as having “possible” intermittent claudication.

In previous reports from this study,\textsuperscript{14,17} only probable intermittent claudication has been discussed; however, in the present report we have studied both categories. Fifteen subjects failed to complete the intermittent claudication questionnaire and have been excluded from all analyses. In addition, for other variables, data were missing for the following number of subjects: blood pressure, five; plasma cholesterol, 684; glucose tolerance, 129; lung function, 18; body mass index, three; smoking status, seven; angina, five; possible myocardial infarction, 76; and electrocardiogram, 78. Subjects were only excluded from analyses for which they were missing specific data. When full adjustment for all risk factors was performed, 17,592 participants were included in the analyses.

Records from more than 99% of subjects were flagged at the National Health Service Central Registry. Death certificates were coded according to the eighth revision of the International Classification of Diseases (ICD), and this almost-complete mortality follow-up to January 31, 1985 provides the basis for this analysis. Death has been classified as being due to coronary heart disease (ICD codes 410–414), cerebrovascular disease (ICD codes 430–438), cardiovascular disease (ICD codes 390–458), lung cancer (ICD code 162), or any neoplasm (ICD codes 140–239). All-cause and noncardiovascular mortality have also been examined.

Mortality rates have been calculated using person-years at risk. These rates and also all means and proportions have been standardized for age by the direct method, using the total population as the standard. Tests of significance and confidence intervals for the age-adjusted rate ratios have been calculated by fitting models using the statistical package GLIM.\textsuperscript{20,21} Adjustment for other major risk factors and calculation of confidence intervals was done using Cox’s proportional hazards regression model.\textsuperscript{22}

Results

Probable and possible cases of intermittent claudication were reported by 0.8% (147) and 1% (175) of subjects, respectively. Each rate more than doubled from the age groups 40–44 to 60–64 years. The relations between reported symptoms and coronary heart disease risk factors are shown in Tables 1 and 2, which show slightly elevated average levels of plasma cholesterol concentration and body mass index and show lower average ventilatory measures. There are no significant relations with blood pressure or glucose intolerance. Smoking is more prevalent among subjects reporting intermittent claudication, as are angina and possible myocardial infarction according to questionnaire reports but not ischemia according to electrocardiography. The prevalence of any suspect ischemia, that is, angina, possible myocardial infarction, or electrocardiographic evidence of ischemia, is raised in both intermittent claudication groups. Any suspect ischemia is more prevalent among probable than possible cases; however, this latter difference is not significant (\(p=0.12\)). Analysis
TABLE 1. Mean and SEM of Age-Adjusted Risk Factors in Men With Probable, Possible, or No Intermittent Claudication

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No (n=18,066)</th>
<th>Possible (n=175)</th>
<th>Probable (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>135.9</td>
<td>0.15</td>
<td>137.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>84.5</td>
<td>0.10</td>
<td>83.5</td>
</tr>
<tr>
<td>Plasma cholesterol concentration (mmol/l)</td>
<td>5.11</td>
<td>0.01</td>
<td>5.27</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7</td>
<td>0.02</td>
<td>25.3*</td>
</tr>
<tr>
<td>FEV₁₀ (l)</td>
<td>3.13</td>
<td>0.004</td>
<td>3.02*</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>4.03</td>
<td>0.005</td>
<td>3.84†</td>
</tr>
</tbody>
</table>

FEV₁₀, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 3 also shows that the proportions of deaths due to cardiovascular or noncardiovascular causes among the possible cases of intermittent claudication is little different from the proportions shown by the nonintermittent claudication group ($\chi^2=1.16, p>0.2$). However, for the probable cases, there is a clear increased likelihood of deaths due to cardiovascular causes ($\chi^2=15.75, p<0.001$).

To examine whether the increased mortality rates among cases reflected only a short-term risk, we analyzed the data excluding deaths within 5 years of examination. For both the probable and the possible intermittent claudication groups, mortality rates due to all causes and cardiovascular causes were elevated by factors of approximately two and three times, respectively. For the possible, but not the probable, cases, the mortality rate due to noncardiovascular causes was elevated.

The relative mortality rates throughout the whole follow-up period for the probable and possible intermittent claudication groups are given in Table 4. The increases could be due to the higher prevalence of cardiac ischemia or to elevated coronary heart disease risk factors. Relative mortality rates adjusted for systolic blood pressure, plasma cholesterol concentration, smoking habits (including number of cigarettes

Table 2. Prevalence of Age-Adjusted Risk Factors in Men With Probable, Possible, or No Intermittent Claudication

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No</th>
<th>Possible</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Normoglycemic</td>
<td>93.3</td>
<td>16,745</td>
<td>89.6</td>
</tr>
<tr>
<td>Glucose intolerant</td>
<td>5.5</td>
<td>976</td>
<td>8.7</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.2</td>
<td>217</td>
<td>1.7</td>
</tr>
<tr>
<td>Never smokers</td>
<td>19.5</td>
<td>3,409</td>
<td>16.0</td>
</tr>
<tr>
<td>Exsmokers</td>
<td>37.9</td>
<td>6,595</td>
<td>26.3</td>
</tr>
<tr>
<td>Current smokers</td>
<td>42.6</td>
<td>7,422</td>
<td>57.7</td>
</tr>
<tr>
<td>Angina</td>
<td>4.6</td>
<td>837</td>
<td>12.9</td>
</tr>
<tr>
<td>Possible myocardial infarction</td>
<td>6.6</td>
<td>1,181</td>
<td>14.0</td>
</tr>
<tr>
<td>Abnormal electrocardiogram</td>
<td>6.3</td>
<td>1,127</td>
<td>5.8</td>
</tr>
<tr>
<td>Any suspect ischemia</td>
<td>15.1</td>
<td>2,696</td>
<td>25.0</td>
</tr>
<tr>
<td>Low work grade</td>
<td>24.8</td>
<td>4,278</td>
<td>30.4</td>
</tr>
</tbody>
</table>

p indicates whether the proportions in the possible or probable intermittent claudication groups are different from those in the group with no intermittent claudication.
smoked per day by current smokers), employment grade, and degree of glucose intolerance have, therefore, been calculated for all subjects (Table 4) and for the group with no evidence of other ischemia at baseline (Table 5). The same pattern of elevated mortality rates is seen after these exclusions and adjustments.

For comparison, the adjusted relative rates for subjects with angina compared with those without angina were 3.01 for coronary heart disease and 1.86 for all-cause mortality. The corresponding values for possible myocardial infarction were 2.57 and 1.71.

Discussion

The prevalence of probable intermittent claudication among these civil servants is lower than that seen in most studies using the LSHTM questionnaire.\textsuperscript{7,11,23–27} Intermittent claudication may lead to early retirement, and the consequent “healthy worker effect” may explain the higher prevalences seen in studies based on general populations.\textsuperscript{11,23,27} However, several studies of working populations have also revealed higher prevalence rates.\textsuperscript{7,25,26} The issue is complicated by the fact that small changes in the LSHTM questionnaire may produce large effects on responses.\textsuperscript{16} Several of the studies referred to above used translations of the questionnaire, which may change its sense. Indeed, the agreement between probable intermittent claudication and physician diagnosis has varied from 30\% in Sweden\textsuperscript{23} to more than 60\% in France\textsuperscript{24} and Britain.\textsuperscript{11} This might contribute to the higher prevalence estimates in Scandinavian studies.\textsuperscript{7,23,25,27}

The association between intermittent claudication and other evidence of cardiovascular disease that was

\begin{table}
\centering
\caption{Age-Adjusted Mortality Rates and Number of Deaths in Men With Probable, Possible, or No Intermittent Claudication}
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
\textbf{Cause of death} & \multicolumn{3}{c}{\textbf{No}} & \multicolumn{3}{c}{\textbf{Probable}} \\
& \textbf{Rate} & \textbf{n} & \textbf{Percent} & \textbf{Rate} & \textbf{n} & \textbf{Percent} \\
\hline
Coronary heart disease & 5.1 & 1,326 & 39 & 13.3* & 32 & 46 \\
Cerebrovascular disease & 0.8 & 204 & 6 & 2.5† & 6 & 9 \\
Cardiovascular disease & 6.9 & 1,788 & 53 & 17.1* & 42 & 60 \\
Noncardiovascular disease & 6.1 & 1,600 & 47 & 11.0‡ & 28 & 40 \\
Lung cancer & 1.5 & 380 & 11 & 2.8‡ & 8 & 11 \\
All cancers & 4.1 & 1,071 & 31 & 6.6‡ & 17 & 24 \\
All causes & 13.0 & 3,401 & 100 & 28.1* & 70 & 100 \\
\hline
\end{tabular}
\end{table}

Rates are for 1,000 person-years.

\begin{table}
\centering
\caption{Relative Mortality Rates and 95\% Confidence Intervals for Men With Probable or Possible Intermittent Claudication Versus No Intermittent Claudication}
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
\textbf{Cause of death} & \textbf{Adjustments} & \multicolumn{2}{c}{\textbf{Possible}} & \multicolumn{2}{c}{\textbf{Probable}} \\
& & \textbf{RR} & 95\% CI & \textbf{RR} & 95\% CI \\
\hline
Coronary heart disease & Age only & 2.54 & 1.7, 3.6 & 3.08 & 2.2, 4.3 \\
& Full & 2.12 & 1.4, 3.0 & 2.90 & 2.0, 4.1 \\
Cerebrovascular disease & Age only & 3.00 & 1.3, 6.8 & 2.79 & 1.1, 6.8 \\
& Full & 2.44 & 1.1, 5.6 & 2.53 & 0.9, 7.3 \\
Cardiovascular disease & Age only & 2.46 & 1.8, 3.3 & 2.92 & 2.2, 3.9 \\
& Full & 2.05 & 1.5, 2.8 & 2.69 & 2.0, 3.7 \\
Noncardiovascular disease & Age only & 1.83 & 1.3, 2.7 & 0.80 & 0.4, 1.4 \\
& Full & 1.70 & 1.2, 2.5 & 0.71 & 0.4, 1.3 \\
Lung cancer & Age only & 2.07 & 1.0, 4.2 & 0.58 & 0.1, 2.3 \\
& Full & 1.73 & 0.8, 3.7 & 0.46 & 0.1, 1.8 \\
All cancers & Age only & 1.66 & 1.0, 2.7 & 0.87 & 0.4, 1.7 \\
& Full & 1.58 & 1.0, 2.6 & 0.73 & 0.3, 1.5 \\
All causes & Age only & 2.15 & 1.7, 2.7 & 1.91 & 1.5, 2.5 \\
& Full & 1.86 & 1.5, 2.4 & 1.72 & 1.3, 2.3 \\
\hline
\end{tabular}
\end{table}

RR, relative rates.

Full, fully adjusted relative rates are adjusted for age, systolic blood pressure, cholesterol, smoking habits, employment grade, and degree of glucose intolerance.
shown in the present study is well established.5–8,13 The absence of a relation between intermittent claudication and electrocardiographic evidence of ischemia is surprising in the light of other studies, but it is based on relatively small numbers of subjects with both. Smoking has been consistently related to intermittent claudication in prevalence studies7,11 to a similar degree shown here. This relation is less strong than that seen in the clinical situation.

The relation between intermittent claudication and coronary heart disease risk factors other than smoking has been inconsistent in previous prevalence studies. Plasma cholesterol was elevated in some,7,27 but not all,11 studies. Similarly, blood pressure has been found to be elevated11,27 or else no higher.7 Negative findings have been reported for body mass index27 and both fasting glucose11 and glucose tolerance.7 The present results—small elevations in plasma cholesterol and body mass index, and no significant relation with blood pressure or glucose tolerance—add to the inconsistent set of previous findings.

The failure to detect a relation between claudication and diabetes may be a chance finding, or it may reflect selection out of employment in the civil service by participants who were both diabetic and had intermittent claudication. We cannot separate these two possibilities.

In the Framingham study,8,10,13 the presence of intermittent claudication was determined at each biennial examination. Smoking, glucose intolerance, and blood pressure were powerful independent predictors of intermittent claudication; serum cholesterol was a weak predictor, and relative weight was inversely associated with occurrence of intermittent claudication. The results from comparing the incidence data from Framingham with the data from prevalence studies suggests that in the latter a selective survival of individuals at lower risk may have led to underestimation of the importance of glucose tolerance and blood pressure.

There are no large differences between the two intermittent claudication groups in either their cross-sectional relations or their association with cardiovascular mortality. This rather unexpected finding suggests that the category of possible intermittent claudication has acceptable validity. In previous studies, the percentages of deaths from cardiovascular causes in subjects with intermittent claudication has ranged from 60–65%4 to more than 80%.2,3 Thus, the percentages of cardiovascular deaths in both the probable intermittent claudication group and in the possible intermittent claudication group lie within the previous boundaries.

It appears, however, that whereas probable and possible intermittent claudication cases have an increased risk of cardiovascular death, only possible cases have an increased risk of dying from other causes. This nonspecific mortality excess is little changed by excluding deaths within 5 years of the examination and, therefore, does not seem to be due to the inclusion of subjects with severe illnesses in this group. It could be that participants in the possible intermittent claudication group received less-aggressive treatment and risk factor intervention than did the probable group, leading to elevated rates of mortality from lung and other cancers among the former. In fact, the possible group did have marginally higher rates of smoking than did the probable group. However, the finding that only a small proportion of participants were under treatment by their physicians does not add support to the notion that differing degrees of intervention lead to the mortality pattern seen.

The difference in the criteria for classifying subjects as having possible or probable intermittent claudication is slight: in the former, the leg pain may have disappeared while subjects were walking; in the latter, pain could not have disappeared. While this small change approximately doubled the number of positive responses, it probably could not select groups of very different characteristics. We cannot explain the difference; possibly, it was due to chance. Data from other studies using the LSHTM questionnaire would help to answer this.

It has been reported that relaxing the criteria for intermittent claudication when using the LSHTM

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### TABLE 5. Relative Mortality Rates and 95% Confidence Intervals for Probable or Possible Intermittent Claudication Versus No Intermittent Claudication in Men With No Suspected Ischemia at Baseline

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Intermittent claudication</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2.82</td>
<td>1.8, 4.5</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5.22</td>
<td>2.1, 12.8</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2.81</td>
<td>1.9, 4.2</td>
</tr>
<tr>
<td>Noncardiovascular disease</td>
<td>2.06</td>
<td>1.3, 3.2</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>2.31</td>
<td>1.0, 5.2</td>
</tr>
<tr>
<td>All neoplasms</td>
<td>1.87</td>
<td>1.1, 3.2</td>
</tr>
<tr>
<td>All causes</td>
<td>2.41</td>
<td>1.8, 3.2</td>
</tr>
</tbody>
</table>

RR, relative rate.
Relative rates are adjusted for age, systolic blood pressure, cholesterol, smoking habits, employment grade, and degree of glucose intolerance.

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questionnaire leads to increased sensitivity and reduced specificity, when measured against clinical assessments of peripheral arterial disease. The group selected with relaxed criteria would be expected to contain more false-positive cases, that is, would contain a lower percentage of “real” cases and would, thus, demonstrate lower mortality rates. In fact, the possible intermittent claudication group did show a lower mortality rate due to cardiovascular causes than did the probable intermittent claudication group, but this was more than compensated for by a higher mortality rate due to noncardiovascular causes. It could be that an effect of relaxing the criteria for intermittent claudication was disguised by what may have been a chance increase in noncardiovascular mortality. Even if this is so, however, it is evident that the “possible” group contains many genuine cases.

The doubling of the mortality rate in those with intermittent claudication was similar to that shown in other population-based studies using interview or questionnaire methods of diagnosis. This elevation of mortality risk is less than that seen with peripheral arterial disease defined by more stringent criteria. The elevated mortality risk seen with large vessel peripheral arterial disease appears to be independent of coexisting cardiovascular disease and risk factors, as was the elevated mortality risk seen with intermittent claudication in the present study. Questionnaire-defined intermittent claudication and large-vessel peripheral arterial disease measured through more detailed assessments clearly overlap to a large degree and both appear to be related to diffuse atherosclerosis, which leads to a high risk of mortality.

Apparently, in population-based studies, intermittent claudication carries with it about the same risk as does angina or possible myocardial infarction assessed by questionnaire. Some, but not all, of this increased risk can be attributed to the associated levels of coronary risk factors. Intermittent claudication is not a rare disease; in men older than 60 years, it is two to three times as prevalent as diabetes mellitus. In the present sample, only 10% of subjects with probable intermittent claudication were under medical care for their condition. The LSHTM questionnaire can, therefore, identify a group of subjects, many of whom are not receiving medical care, whose increased risk of death may be partially preventable. The questionnaire does not require a physician to administer it, but it may be self-completed or administered by an interviewer after brief training. Thus, it could be usefully added to cardiovascular risk assessment and screening programs.

References


KEY WORDS * questionnaire * peripheral vascular disease * epidemiology
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