Relati of Helicobacter pylori Infection to 13-Year Mortality and Incident Ischemic Heart Disease in the Caerphilly Prospective Heart Disease Study

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Background—Associations have been suggested between Helicobacter pylori seropositivity, cardiovascular risk factors, and ischemic heart disease (IHD). The effect of this common infection on mortality is uncertain.

Methods and Results—Plasma specimens collected during 1979 to 1983 from 1796 men in Caerphilly, South Wales, were analyzed for IgG antibodies to H pylori. Cause of death and occurrence of incident IHD events were ascertained over an average of 13.7 years from death certificates, hospital records, and ECG changes at 5-yearly follow-up examinations. Seventy percent of men were seropositive. The prevalence of IHD at entry was similar in men with and without H pylori antibodies (odds ratio [OR], 1.10; 95% CI, 0.87 to 1.40). Seropositivity was significantly (P<0.05) associated with poorer socioeconomic status currently and in childhood, shorter stature, and poorer ventilatory function at entry but not with age, smoking, body mass index, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, fibrinogen, plasma viscosity, or heat shock protein antibodies. Thirteen-year incidence of IHD was not significantly associated with H pylori (OR, 1.05; 95% CI, 0.80 to 1.39), but there was a stronger relationship with all-cause mortality (OR, 1.46; 95% CI, 1.12 to 1.92) and fatal IHD (OR, 1.54; 95% CI, 1.03 to 2.30). After adjustment for cardiovascular risk factors and both adult and childhood socioeconomic status, ORs were slightly reduced and lost statistical significance (OR=1.32 [95% CI, 0.99 to 1.78] for all-cause mortality and OR=1.52 [95% CI, 0.99 to 2.34] for fatal IHD).

Conclusions—H pylori infection is unlikely to be as strong a risk factor for IHD as some previous studies have suggested, but its relationship to mortality, including fatal IHD, deserves further investigation. The mechanism underlying these associations is unlikely to involve hypertension, circulating lipid profile, fibrinogen, or cross-reacting antibodies to bacterial heat shock proteins. (Circulation. 1998;98:1286-1290.)

Key Words: heart diseases ■ epidemiology ■ mortality ■ infection ■ Helicobacter pylori

H elicobacter pylori is a chronic infection of the human stomach that is an established cause of gastritis and peptic ulceration. Infection often occurs in childhood and persists into late adult life unless treated by combinations of broad-spectrum antibiotics and gastric acid suppressants. Between one third and two thirds of middle-aged adults in European countries have circulating IgG antibodies against H pylori.

Previous studies have suggested that a low-grade systemic inflammatory response may occur in association with H pylori seropositivity, with elevated concentrations of acute-phase reactants such as C-reactive protein and sialic acid and an increase in the white blood cell count. One study, but not others, reported an association with fibrinogen levels. In prospective studies, these acute-phase reactants have been related in turn to ischemic heart disease (IHD) or cardiovascular mortality. More recently, other mechanisms have been proposed whereby H pylori infection might influence cardiovascular risk, including reduction in HDL cholesterol, vitamins B6 and B12, and folate deficiency, leading to elevation of circulating homocysteine levels; immunologic cross-reactivity between bacterial and human heat shock proteins; and effects on growth in childhood. An association of H pylori infection with hypertension has also been reported, although no biological mechanism has yet been proposed for a direct causal link.

Reported associations of atheroma and IHD with a variety of chronic infections (dental sepsis, cytomegalovirus, and Chlamydia pneumoniae) led us to investigate whether IHD might also be related to H pylori. Early findings of an increased prevalence of H pylori seropositivity among men with angiographically confirmed IHD were open to a number of criticisms, including selection bias and residual confounding by unmeasured socioeconomic factors. Subse-
frequently, a number of studies of cross-sectional and case-control design and 4 prospective investigations have reported associations of variable strength between H pylori seropositivity and IHD or cardiovascular disease. The published findings are generally consistent with a true relative risk in the range of 1.0 to 2.0. Only 1 study has reported on the relationship of H pylori with all-cause mortality, among elderly subjects.

We report herein findings from a longitudinal study relating H pylori seropositivity prospectively to the incidence of IHD and to all-cause mortality among middle-aged men.

Methods

The Caerphilly Prospective Heart Disease Study recruited 2512 men aged 45 to 59 years in the Caerphilly area of South Wales during 1979 to 1983. Symptoms and ECG abnormalities suggestive of past or current IHD were ascertained, and a range of cardiovascular risk factors were measured, including smoking history; standing height; body weight; blood pressure; forced expiratory volume in 1 second (FEV1); total, HDL, and LDL cholesterol; fibrinogen; plasma viscosity; and leukocyte count. Socioeconomic status was classified according to the registrar-general’s social class of current occupation and father’s occupation during childhood.

The sample subjects have been followed up at 5-yearly intervals, and the fourth round of field work (phase IV) was completed during 1994 to 1997, an average of 13.7 years (SD, 0.5 year) after the entry examination. Deaths were classified according to the ninth revision of the International Classification of Diseases (ICD9) as due to IHD (ICD9 410-414) and further classified as circulatory (ICD9 390-459) or noncirculatory causes. Incident IHD was ascertained from death certificates, review of hospital notes, and ECG changes by use of the same conventions as in previous prospective analyses of this cohort.

Three groups were thus included as incident cases of IHD: fatal IHD (death coded as ICD9 410-414); clinical myocardial infarction (hospitalized episodes meeting WHO criteria of combinations of serial ECG changes, cardiac enzyme abnormalities, and acute symptoms); and development of new Q or QS waves (Minnesota codes 1-1-1 through 1-2-5, or 1-2-7) on follow-up ECG in the absence of Q or QS waves on the ECG recorded at entry. Follow-up for mortality is considered complete. More than 98% of survivors were seen at the 5-year reexamination, 95% at 10 years, and 93% at 13.7 years.

Frozen plasma specimens banked at the entry (phase I) examination were available for 1796 (71%) of the 2512 men. They had been stored at −20°C since collection in 1979 to 1983, with 1 thaw cycle. The main reason for specimens being missing was depletion of material during previous seroepidemiological studies involving ~25% of the cohort. All available specimens were analyzed for H pylori IgG by commercial ELISA (Launch Diagnostics). In-house ELISA assays were developed to measure C-reactive protein and IgG antibodies to mycobacterial heat shock protein.

Statistical analysis was performed with STATA software. The cross-sectional relations of H pylori seropositivity to levels of cardiovascular risk factors measured at entry were analyzed by tabulations and comparisons of means. Associations of H pylori seropositivity with prevalent IHD at entry, incident IHD (fatal and nonfatal), and mortality (circulatory and noncirculatory) were analyzed. Multiple logistic regression was used to derive odds ratios (ORs) for incident IHD, fatal IHD, and all-cause mortality both

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Percentage Seroprevalence</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–49</td>
<td>69.3 (406/586)</td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>68.7 (287/423)</td>
<td>0.15*</td>
</tr>
<tr>
<td>55–59</td>
<td>73.0 (472/647)</td>
<td></td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>68.8 (205/298)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>70.4 (359/510)</td>
<td></td>
</tr>
<tr>
<td>Cigar/pipe</td>
<td>68.9 (133/193)</td>
<td>0.70†</td>
</tr>
<tr>
<td>1–14/d</td>
<td>74.4 (195/262)</td>
<td></td>
</tr>
<tr>
<td>15–24/d</td>
<td>71.7 (223/311)</td>
<td></td>
</tr>
<tr>
<td>25+/d</td>
<td>69.2 (148/214)</td>
<td></td>
</tr>
<tr>
<td>Social class at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>60.9 (220/361)</td>
<td></td>
</tr>
<tr>
<td>IIIM</td>
<td>65.8 (127/193)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>IIIM</td>
<td>72.7 (67/928)</td>
<td></td>
</tr>
<tr>
<td>IV/V</td>
<td>76.7 (21/275)</td>
<td></td>
</tr>
<tr>
<td>Father’s social class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>63.2 (74/117)</td>
<td></td>
</tr>
<tr>
<td>IIIM</td>
<td>58.3 (42/72)</td>
<td>0.013*</td>
</tr>
<tr>
<td>IIIM</td>
<td>71.0 (824/1160)</td>
<td></td>
</tr>
<tr>
<td>IV/V</td>
<td>72.2 (174/241)</td>
<td></td>
</tr>
</tbody>
</table>

*Test for linear trend (single years of age, 6 social classes). †Test for heterogeneity. ‡I and II, professional and managerial occupations; III, skilled occupations (subdivided as manual and nonmanual); IV and V, semiskilled and unskilled occupations.
before and after adjustment for age, body mass index, systolic blood pressure, total cholesterol, height, and FEV1 (all as continuous variables) and for smoking history (6 categories), own social class (6 categories), and father’s social class (5 categories). Kaplan-Meier survival curves and proportional hazards regression were also used to confirm the association of H pylori seropositivity with all-cause mortality and fatal IHD.

Results

Among the 1796 men included in the present study, 1265 (70%) were seropositive for H pylori. Table 1 shows the numbers of prevalent and incident cases of IHD and deaths among the 1265 seropositive men, 531 seronegative subjects, and 716 men with missing specimens.

Before adjustment for other variables, H pylori seropositivity was significantly associated with mortality from all causes (OR, 1.46; 95% CI, 1.12 to 1.92) and circulatory diseases (OR, 1.50; 95% CI, 1.04 to 2.14). The association with noncirculatory mortality was not statistically significant at the 5% level (OR, 1.32; 95% CI, 0.91 to 1.92). There were 5 deaths of stomach cancer, 3 among men who were seronegative at entry, and 1 death of peptic ulceration in a seropositive subject. The excess of noncirculatory deaths among seropositive deaths was mainly attributable to lung cancer (2.45% [31/1265] versus 1.32% [7/531]) and respiratory diseases (1.11% [14/1265] versus 0.56% [3/531]).

In contrast, there was no significant association of seropositivity with past or prevalent IHD at entry (OR, 1.10; 95% CI, 0.87 to 1.40) or with all incident IHD (fatal and nonfatal combined) during 13.5 years of follow-up (OR, 1.05; 95% CI, 0.80 to 1.39). However, H pylori was associated with a significantly increased risk of fatal IHD (OR, 1.54; 95% CI, 1.03 to 2.30). Thus, among men who developed incident IHD events, the proportion who died of IHD was greater among seropositive subjects (57% [117/204]) than among seronegative subjects (40% [33/82]), a significant difference (OR, 2.00; 95% CI, 1.19 to 3.36). The association of fatal IHD with H pylori was apparent among men with and without past or prevalent IHD at entry; ORs (95% CI) 1.75 (0.94 to 3.27) and 1.36 (0.80 to 2.31), respectively. These ORs do not differ significantly (χ² test for interaction=0.37, df=1). There was a stronger association of H pylori with fatal IHD among 554 men with nonmanual occupations (OR, 3.00; 95% CI, 1.13 to 7.99) than among 1203 men with manual occupations (1.11, 0.71 to 1.74). This statistical interaction (effect modification) is of borderline statistical significance (χ²=3.69, df=1, \( P=0.055 \)).

Table 2 shows the relationship of seropositivity to age, smoking habit, and social class. Within the limited age range of the cohort, seroprevalence did not vary greatly with age. Strong associations emerged with both current and childhood socioeconomic status. Table 3 shows the levels of major cardiovascular risk factors in men with and without H pylori antibodies. Differences in body mass index, systolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, fibrinogen, and plasma viscosity were small and nonsignificant, but there was a slightly higher mean white blood cell count among seropositive men. The associations with C-reactive protein and heat shock protein antibodies were in both cases weak and nonsignificant. Highly significant differences emerged for risk factors closely related to socioeconomic status: height and FEV1. The association of H pylori with FEV1 persisted after adjustment for height.

Table 4 shows the effect of adjustment for major cardiovascular risk factors on the associations of H pylori seropositivity with all incident IHD, fatal IHD, and all-cause mortality. These analyses are based on 1717 men with complete information on the cardiovascular risk factors in model 2. Results are presented before and after adjustment for height and FEV1 because these variables may be considered either as markers of socioeconomic circumstances during childhood or as intermediate mechanisms linking H pylori infection to adult disease.

The magnitudes of the associations of seropositivity with all-cause mortality and fatal IHD were diminished slightly and just lost statistical significance at the 5% level after adjustment for conventional cardiovascular risk factors, including current socioeconomic status. Further adjustment for markers of socioeconomic status in childhood (including height and FEV1) had little effect on the OR estimates. The OR relating H pylori to all incident IHD was little changed by adjustment for multiple covariates (Table 4). Further adjustment for fibrinogen and leukocyte count reduced the OR for fatal IHD slightly to 1.46 (95% CI, 0.95 to 2.26), but the OR for total mortality was little changed at 1.30 (95% CI, 0.97 to 1.74).

When all-cause mortality and fatal IHD were modeled by proportional hazards regression, the unadjusted hazard ratios (95% CIs) for H pylori seropositivity were, respectively, 1.41 (1.10 to 1.82) and 1.53 (1.03 to 2.29). After adjustment for age, body mass index, systolic blood pressure, total cholesterol, smoking history, current and childhood social class, height, and FEV1, the hazard ratios became nonsignificant
and were reduced slightly to 1.29 (1.00 to 1.66) for all-cause mortality and 1.44 (0.96 to 2.15) for fatal IHD. These models were also based on 1717 subjects.

**Discussion**

This is the first study to relate *H pylori* infection prospectively to risk of mortality from all causes among middle-aged men. Over 13.5 years of follow-up, both circulatory and noncirculatory deaths occurred more commonly among seropositive men, and these associations were only partially explained by the confounding effect of measured risk factors. However, after adjustment for multiple covariates, the difference in mortality risk, whether analyzed by logistic regression or proportional hazards modeling, was of borderline statistical significance. The only other study that has related *H pylori* seropositivity to all-cause mortality\(^5\) reported a hazard ratio of 1.08 (95% CI, 0.83 to 1.42) among men and women aged 75 to 85 years at the commencement of a 5-year follow-up period. This CI overlaps with ours, and both studies would be consistent with a weak association of *H pylori* infection and mortality or with no true association.

Residual confounding by socioeconomic factors seems an unlikely explanation for our findings because adjustment for 3 indicators of early growth and childhood socioeconomic status had little impact on the association of *H pylori* and total mortality (Table 4). Nevertheless, the excess of lung cancer and respiratory disease deaths among the seropositive men raises the possibility of unmeasured differences in smoking habits, despite the similarity in smoking history and current smoking habits reported by seronegative and seropositive men at entry to the study.

Most previous studies of the association of *H pylori* and IHD have recruited surviving case subjects.\(^5,6,14,26,28–33\) We found almost no cross-sectional association between *H pylori* past and current IHD at entry and only a slight elevation in risk of incident IHD events among seropositive men during 13.5 years of follow-up. Nevertheless, there was a significantly increased risk of fatal IHD among seropositive subjects, consistent with the findings of the British Regional Heart Study,\(^34\) in which *H pylori* was more strongly associated with fatal IHD events than with nonfatal IHD ascertained by general practitioners.

Our results may be compared with those of 2 case-control studies nested within British cohorts that have assessed the relationship of *H pylori* antibodies and fatal IHD among men free of IHD at entry, with adjustment for major cardiovascular risk factors. Among a general population sample recruited to the British Regional Heart Study,\(^34\) the adjusted OR was 1.56 (95% CI, 0.68 to 3.61), whereas among professional men attending for routine medical examination in the British United Provident Association (BUPA) study,\(^37\) the adjusted OR was 1.06 (95% CI, 0.86 to 1.31). The corresponding result for Caerphilly men with no past or prevalent IHD at entry is 1.36 (95% CI, 0.80 to 2.31). These 3 ORs do not differ significantly ($\chi^2$ for heterogeneity=1.12, $df=2$), and when pooled with weights inversely proportional to variance, the summary OR is 1.12 (95% CI, 0.92 to 1.35).

Our study addressed a number of biological mechanisms proposed as links between *H pylori* and IHD. Hypertension, fibrinogen, and HDL cholesterol are clearly excluded as possible intermediates. The association of leukocyte count with *H pylori* infection, although statistically significant, was weak and explained little of the increase in total mortality or fatal IHD. Although our measurements of mycobacterial heat shock protein antibodies were based on smaller numbers, there was no significant relationship with either *H pylori* infection or incident IHD (data not shown), so this mechanism seems unlikely. Men infected with *H pylori* tended to be shorter and to have lower values of FEV\(_1\) than their seronegative peers, despite similar age and smoking histories. However, the effect of seropositivity on total mortality and fatal IHD was essentially independent of these associated factors. Thus, effects of *H pylori* on growth are unlikely to explain associations with adult disease.

Our results suggest that *H pylori* infection is unlikely to be as strong a risk factor for IHD as some previous studies have reported,\(^25\) but they raise the possibility of an increased risk of death, from both IHD and other causes, among seropositive men. Failure to identify a plausible mechanism linking this chronic infection to adult IHD or mortality favors chance or confounding rather than causality as the explanation for our findings. However, because *H pylori* infection is potentially treatable, even a small elevation in risk would be of epidemiological relevance. Thus, there is a need for further

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**TABLE 4. Odds Ratios for Incident IHD and Mortality Comparing *H pylori* Seropositive and Seronegative Subjects Before and After Adjustment for Cardiovascular Risk Factors**

<table>
<thead>
<tr>
<th>Risk Factors Adjusted for</th>
<th>Incident IHD, OR (95% CI)</th>
<th>Fatal IHD, OR (95% CI)</th>
<th>Total Mortality OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No adjustments</td>
<td>1.05 (0.79–1.39)</td>
<td>1.56 (1.04–2.36)(^*)</td>
<td>1.46 (1.10–1.92)(^†)</td>
</tr>
<tr>
<td>2. Age, smoking history, BMI, systolic BP, and total cholesterol</td>
<td>1.03 (0.77–1.39)</td>
<td>1.54 (1.01–2.35)(^*)</td>
<td>1.41 (1.06–1.88)(^*)</td>
</tr>
<tr>
<td>3. Model 2 plus current social class(‡)</td>
<td>1.01 (0.75–1.36)</td>
<td>1.49 (0.98–2.28)</td>
<td>1.33 (1.00–1.78)</td>
</tr>
<tr>
<td>4. Model 3 plus father’s social class(§)</td>
<td>1.02 (0.76–1.37)</td>
<td>1.51 (0.98–2.30)</td>
<td>1.34 (1.00–1.79)</td>
</tr>
<tr>
<td>5. Model 4 plus height and FEV(_1)(|)</td>
<td>1.02 (0.76–1.37)</td>
<td>1.52 (0.99–2.34)</td>
<td>1.32 (0.99–1.78)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure.

*P<0.05; †P<0.01.

\(‡\)Modelled as 6 levels: I/II, III nonmanual, III manual, IV, V, missing.

\(§\)Modelled as 5 levels: I/II, III nonmanual, III manual, IV, V, missing/unemployed.

\(\|\)Subjects with missing FEV\(_1\) retained in the model by use of a dummy variable representing missing data.
longitudinal studies to quantify more precisely its association with total mortality in both men and women and with survival in patients with IHD.

Acknowledgments

This study was supported by the British Heart Foundation (PG/95041). We are deeply indebted to the men of Caerphilly who participated in the multiple follow-up examinations and to many unnamed field-workers who collected data and specimens during phases I to IV of the study. We are also particularly grateful to Lydia Ballam and Julia Morris for their diligent attention to specimen handling and laboratory analyses.

References

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