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Prospective relations between *Helicobacter pylori* infection, coronary heart disease, and stroke in middle aged men

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Abstract

***Objective*—To determine whether *Helicobacter pylori*, a chronic bacterial infection often acquired in childhood, is associated with increased risk of coronary heart disease and stroke later in life.**

***Design*—Nested case-control study.**

***Setting*—Prospective study of cardiovascular disease in men aged 40–59 years at entry (1978–1980) in 24 British towns.**

***Subjects*—135 cases of myocardial infarction and 137 cases of stroke occurring before December 1991; 136 controls were identified, frequency matched to cases by town and age group.**

***Methods*—Serum samples stored at entry were analysed by an enzyme linked immunosorbent assay for the presence of *H pylori* specific IgG antibodies.**

***Results*—95 of the myocardial infarction cases (70%) and 93 (68%) of the stroke cases were seropositive for *H pylori* compared with 78 (57%) of the controls (odds ratio for myocardial infarction 1·77, 95% confidence interval (CI) 1·06 to 2·95, P = 0·03; odds ratio for stroke 1·57, 95% CI 0·95 to 2·60, P = 0·07). *Helicobacter pylori* infection was associated with manual social class, residence in Northern England or Scotland, cigarette smoking, higher systolic pressure and blood glucose, and a lower height-standardised forced expiratory volume in one second. Adjustment for these factors attenuated the relation between *H pylori* and myocardial infarction (odds ratio = 1·31, 95% CI 0·70 to 2·43, P = 0·40) and effectively abolished the relation with stroke (odds ratio = 0·96, 0·46 to 2·02, P = 0·92). The relation between helicobacter infection and fatal myocardial infarction was slightly stronger (odds ratio 2·41, 95% CI 1·13 to 5·12) but was also markedly attenuated after adjustment (1·56, 95% CI 0·68 to 3·61).**

***Conclusion*—In this prospective study the association between *Helicobacter pylori* infection and increased risk of myocardial infarction and stroke was substantially confounded by the relation between this infection, adult social class, and major cardiovascular risk factors.**

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Keywords: coronary heart disease; Helicobacter pylori; stroke

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Factors acting early in life may influence adult risk of coronary heart disease,[1 2] and play a part in determining its social class distribution.[3] *Helicobacter pylori* (*H pylori*) is a chronic bacterial infection which is usually acquired in childhood, particularly in socially deprived circumstances.[4 5] Its associations with peptic ulcer disease and gastric cancer are well recognised[6–8]; both of these conditions are associated with coronary heart disease.[9 10] A recent case-control study based on prevalent coronary heart disease in middle aged men provided some support for the possibility of an association between *H pylori* and coronary heart disease.[11] However, selection biases could not be excluded in that study, and only limited information was available on potential confounding factors. The problems of selection bias were addressed in a further cross-sectional study in south London men, which found a strong relation between *H pylori* seropositivity and electrocardiographic abnormalities suggestive of myocardial ischaemia or infarction, independent of a wide range of confounding variables.[12] However, no study has yet prospectively investigated the relation between *H pylori* infection and coronary heart disease. We have used a nested case-control study based on a longitudinal study of cardiovascular disease in middle aged men to examine the relation between *H pylori* seropositivity and subsequent coronary heart disease and stroke. The relations between *H pylori* and a range of cardiovascular risk factors have also been examined.

Subjects and methods

BRITISH REGIONAL HEART STUDY

The British Regional Heart Study is a longitudinal study of cardiovascular disease in 7735 middle aged men aged 40–59 years (response rate 78%) randomly selected from the age-sex registers of representative group general practices in each of 24 towns across England, Wales, and Scotland. The criteria for selecting the towns, the general practices, and the subjects, as well as the methods of data collection, have been presented in detail elsewhere.[13–16] At entry to the study in 1978–1980, a nurse administered a questionnaire to each man on occupation, smoking habits, alcohol intake, and medical history, including a modified WHO (Rose) chest pain questionnaire.[17] Social class was based on the longest-held occupation, using the Registrar General's 1971 classification and including a separate

category for armed forces. Cigarette smoking was classified into six groups, current smokers (1–19, 20, 21–39, 40+/day), ex-smokers, and never smokers. Alcohol intake was classified into five groups: none, occasional (< 1 unit/week), light (1–15 units/week), moderate (16–42 units/week), heavy (> 42 units/week).

Body mass index (weight/height^2) was used as an index of relative weight. Blood pressure was measured twice using a London School of Hygiene sphygmomanometer with the subject seated. The mean of the two readings was used in the analysis; all blood pressure readings were adjusted for observer variation within each town. Forced expiratory volume was measured twice with the subject seated using a Vitalograph spirometer (model J49-B2); data are based on the maximum value and have been standardised for height.[18] An orthogonal three-lead electrocardiogram was recorded,[19] from which heart rate was derived. A non-fasting blood sample was collected for laboratory analysis; in the last 18 towns serum was stored at −20°C for later analyses. Pre-existing coronary heart disease is based on the presence of one of the following: definite angina, possible or definite myocardial infarction on Rose questionnaire; recall of a previous doctor diagnosis of angina or myocardial infarction; and electrocardiographic evidence of possible or definite myocardial ischaemia or infarction.[14] Pre-existing stroke and diabetes are based on recall of a previous doctor diagnosis of the respective diagnoses.

All men have been followed up for all-cause mortality and for cardiovascular morbidity, with a follow up loss of less than 1% to date. Fatal cases of ischaemic heart disease and stroke were ascertained through the National Health Service Central Registers in Southport (England) and Edinburgh (Scotland) on the basis of a death certificate with ICD-9 codes 410–414 or ICD-9 codes 430–438 respectively. Ascertainment of non-fatal cardiovascular events was based on reports from general practitioners, supplemented by regular reviews of general practice records. Non-fatal myocardial infarction was diagnosed in accordance with World Health Organisation criteria[16]; non-fatal stroke included all cases with a reported neurological deficit lasting more than 24 hours and of presumed vascular origin. Death occurring within 28 days of the onset of symptoms led to reclassification as a fatal episode.

CASE-CONTROL STUDY DESIGN

The case-control study was based on first major cardiovascular events, fatal and non-fatal, occurring between the beginning of follow up and December 1991, but was restricted to subjects in 18 of the 24 study towns (n = 5661) for whom stored serum samples were available. The study was designed to be of sufficient size to detect a twofold increase in the odds of first myocardial infarction or stroke associated with *H pylori* infection with 80% power at P = 0·05, assuming a seropositivity rate of 40% in the control group.[11] Cases included were a random one-third sample of first myocardial infarctions and all cases of first stroke identified during follow up. Subjects with pre-existing disease were not excluded, but the influence of these subjects has been specifically examined in the analysis. Controls were subjects who survived to the end of the study period free from incident myocardial infarction and stroke. They were frequency matched to cases by town and by age group (in five year age bands).

LABORATORY METHODS

H pylori specific IgG antibody titres were measured in duplicate in the stored serum samples between August and October 1994 by an in-house enzyme linked immunosorbent assay (ELISA) and a partially purified antigen as described elsewhere.[4] Titres were dichotomised into seropositive and seronegative values using a cutoff value of 0·824 optical density units, defined in an endoscopy population to be 98% sensitive and 94% specific for the presence of infection in endoscopic biopsy samples.[4] The validity of the measurements obtained in serum stored for 14–16 years was supported by the observation that *H pylori* seropositivity rates were higher in subjects reporting the presence of overcrowding and the absence of a bathroom and hot water supply in the childhood home. This is consistent with earlier reports.[4] Moreover, the relation between *H pylori* and gastric cancer has previously been demonstrated using serum samples up to 13 years old.[7] Measurement of total serum cholesterol and of HDL cholesterol, carried out at the time of the original survey measurements, has been described in detail elsewhere.[20]

STATISTICAL ANALYSIS

Statistical analyses were carried out using the SAS statistical package.[21] Frequencies were compared by χ^2 tests. Standard linear regression techniques using PROC GLM were used to obtain age-adjusted mean values. Adjusted odds ratios were obtained using logistic regression. Age, systolic pressure, blood glucose, forced expiratory volume in 1s (FEV_1), and cholesterol were fitted as continuous variables (fitting each at five levels made no difference to the analysis). Smoking (six levels), alcohol intake (five levels), social class (seven levels), and town (18 levels) were fitted using dummy variables. Where appropriate, three geographical regions (Southern England, Northern England and Scotland) were defined; Southern and Northern England were separated by a line joining the Wash and the Bristol Channel.

Results

There were 135 cases of myocardial infarction, of which 54 (40%) were fatal, and 137 strokes, of which 29 (21%) were fatal, and 136 controls. Ninety-five of the myocardial infarct cases (70%) and 93 (68%) of the stroke cases were seropositive for *H pylori* compared with 78 (57%) of the controls. The unadjusted odds ratio for myocardial infarction was 1·77

Table 1 Cardiovascular risk factors in myocardial infarction and stroke cases

Risk factor	*Myocardial infarction*	*Stroke*	*Controls*
N	135	137	136
Age years (SE)	53·8 (0·4)	54·0 (0·4)	53·5 (0·4)
Systolic pressure (mm Hg) (SE)	152·5 (1·7)***	163·5 (1·9)***	141·5 (1·7)
Diastolic pressure (mm Hg) (SE)	85·7 (1·1)**	88·9 (1·1)***	80·6 (1·1)
Body mass index (kg/m²) (SE)	26·5 (0·3)***	25·7 (0·3)	25·2 (0·3)
Total cholesterol (mmol/l) (SE)	6·6 (0·1)	6·3 (0·1)	6·4 (0·1)
HDL cholesterol (mmol/l) (SE)	1·07 (0·02)***	1·12 (0·02)	1·20 (0·02)
Serum triglyceride (mmol/l) (SE)	2·25 (0·11)*	2·07 (0·10)	1·86 (0·10)
Serum glucose (mmol/l) (SE)	5·92 (0·13)*	5·99 (0·14)*	5·46 (0·14)
FEV_1 (l) (SE)	3·14 (0·05)*	3·00 (0·05)***	3·35 (0·05)
Heart rate (min^{-1}) (SE)	73·4 (1·0)	73·0 (1·1)	70·5 (1·1)
Height (cm) (SE)	171·6 (0·1)	172·0 (0·1)	172·2 (0·1)
White cell count (10^9/l) (SE)	7·44 (0·15)**	7·65 (0·14)**	6·79 (0·15)
Social class (% manual)	82/128 (64)	96/136 (71)*	74/134 (55)
Current cigarette smokers (%)	65/135 (48)*	82/137 (69)***	47/135 (35)
Heavy drinkers (%)	7/135 (5)	22/137 (16)*	7/135 (5)
Diabetes (%)	6/135 (4)*	5/137 (4)	0/136 (0)

All mean values are adjusted for age. *P < 0·05, **P < 0·005, ***P < 0·0005 for differences between cases and controls. Subjects whose longest-held occupation was in the armed forces are excluded from the social class analysis. Data on smoking and drinking were not available for two control subjects.

(95% CI 1·06 to 2·95, P = 0·03); that for stroke was 1·57 (95% CI 0·95 to 2·60, P = 0·07). Other characteristics of the cases and controls are shown in table 1. Mean blood pressures (systolic and diastolic), blood glucose, and white cell count and the prevalence of current smoking and diabetes were significantly higher both in myocardial infarction and in stroke cases when compared with controls; mean FEV_1 values were significantly lower. Statistically significant differences in mean body mass index, HDL cholesterol, and triglyceride between myocardial infarction cases and controls were also observed. The proportion of subjects in manual occupations was higher in both myocardial infarction and stroke cases than in controls, although the difference was only statistically significant for stroke.

The relations between *H pylori* seropositivity and cardiovascular risk factors were examined in the control population (table 2). *H pylori* infection was associated with a higher prevalence of current smoking, with manual social class, and with residence in Scotland and Northern England. Mean values for systolic blood pressure and serum glucose were higher in seropositive subjects, whereas FEV_1 values were lower. There were no important differences in body mass index, total or HDL cholesterol concentrations, height, white cell count, or heart rate. The relation between *H pylori* seropositivity and current smoking was slightly attenuated by adjustment for social class (adjusted odds ratio 2·08, P = 0·07). However, the differences in blood pressure, blood glucose, and FEV_1 were little affected by adjustment either for social class or for town.

Table 2 Helicobacter pylori and cardiovascular risk factors in controls

	Helicobacter pylori status		
	Positive	*Negative*	*P value*
N	78	58	
Age (yr) (SE)	53·8 (0·5)	53·1 (0·6)	0·18
SBP (mm Hg) (SE)	143·7 (1·9)	138·3 (2·2)	0·06
DBP (mm Hg) (SE)	81·5 (1·5)	79·5 (1·7)	0·37
Body mass index (kg/m²) (SE)	25·2 (0·3)	25·2 (0·4)	0·99
Total cholesterol (mmol/l) (SE)	6·32 (0·12)	6·55 (0·14)	0·23
HDL cholesterol (mmol/l) (SE)	1·22 (0·03)	1·17 (0·03)	0·36
Triglyceride (mmol/l) (SE)	1·82 (0·15)	1·93 (0·17)	0·63
Glucose (mmol/l) (SE)	5·66 (0·10)	5·20 (0·12)	0·006
FEV_1 (l) (SE)	3·21 (0·07)	3·56 (0·08)	0·0008
Heart rate (min^{-1}) (SE)	71·1 (1·3)	69·6 (1·5)	0·49
Height (cm) (SE)	172·6 (0·75)	171·8 (0·88)	0·47
White cell count (10^9/l) (SE)	6·89 (0·18)	6·68 (0·20)	0·45
Social class (% manual)	49/76 (64)	25/58 (43)	0·03
Current cigarette smokers (%)	33/77 (43)	14/58 (24)	0·04
Heavy drinkers (%)	5/77 (6)	2/58 (3)	0·35
Diabetes (%)	0/78 (0)	0/58 (0)	—
Region (%):			
Southern England	21/78 (27)	24/58 (41)	
Northern England	37/78 (47)	29/58 (50)	
Scotland	20/78 (26)	5/58 (9)	0·03

Values are mean (SE) or proportion (%). All mean values are adjusted for age. Subjects whose longest held occupation was in the armed forces are excluded from the social class analysis. Data on smoking and drinking not available for two control subjects.

Table 3 shows the effects of adjustment for age, cardiovascular risk factors, and adult social class on the relations between *H pylori* infection and risk of myocardial infarction and stroke. To correct for minor imbalances in the distribution of cases and controls between towns, these analyses have been standardised for town throughout. In the case of myocardial infarction, about one third of the increase in risk associated with *H pylori* seropositivity was removed after adjustment for social class and a slightly larger proportion after adjustment for the cardiovascular risk factors most strongly related to *H pylori* seropositivity (cigarette smoking, systolic pressure, blood glucose, FEV_1). Neither of these adjusted odds ratios was statistically significant. Simultaneous adjustment for both groups of factors reduced the increased risk by more than a half. Additional adjustment for total and HDL cholesterol, triglyceride, heart rate, alcohol intake, and pre-existing diabetes had no effect on the results. The relation between *H pylori* and stroke was markedly attenuated by adjustment for adult social class, with a corresponding loss of statistical significance. After adjustment for cardiovascular risk factors, the odds ratio for stroke was close to unity. There was no evidence of interaction between *H pylori* and any of the individual cardiovascular risk factors examined, either for stroke or for myocardial infarction.

The relation between *H pylori* seropositivity and coronary heart disease was examined after excluding men with pre-existing coronary heart disease (60 cases, five controls). While the age-adjusted odds ratio is only slightly lower than that for all men (1·69, 95% CI 0·92 to 3·10, P = 0·09), the odds ratio adjusted for risk factors and social class is close to unity (1·04, 95% CI 0·50 to 2·16, P = 0·91). The relation between *H pylori* and stroke is little affected by the exclusion of men with pre-existing coronary heart disease and stroke (60 cases, five controls; data not presented). We also examined the relation between *H pylori* seropositivity and coronary heart disease separately in men with fatal and non-fatal events. The odds ratios for fatal coronary heart disease were somewhat stronger than those for non-fatal coronary heart disease, both after age adjustment (OR [fatal] 2·41, 95% CI 1·13 to 5·12; OR [non-fatal] 1·42, 95% CI 0·79 to 2·54) and after adjustment for social class and risk factors (OR [fatal] 1·56, 95% CI 0·68 to 3·61; OR [non-fatal] 1·02, 95% CI 0·53 to 1·96). However, the differences in odds ratios between fatal and non-fatal outcomes were not

Table 3 Odds ratios for Helicobacter pylori seropositivity with myocardial infarction and stroke

Adjustment	*Odds ratio*	*95% CI*	χ^2 *(1 df)*	*P value*
		Myocardial infarction		
None	1·84	1·08 to 3·14	5·21	0·02
Age only	1·83	1·07 to 3·12	5·05	0·02
Age + social class	1·58	0·91 to 2·76	2·72	0·10
Age + risk factors*	1·46	0·81 to 2·64	1·55	0·21
Age + risk factors* + social class	1·31	0·70 to 2·43	0·72	0·40
		Stroke		
None	1·72	1·00 to 2·97	3·95	0·05
Age only	1·69	0·98 to 2·93	3·68	0·06
Age + social class	1·39	0·77 to 2·50	1·28	0·26
Age + risk factors*	1·08	0·53 to 2·20	0·05	0·83
Age + risk factors* + social class	0·96	0·46 to 2·02	0·01	0·92

All analyses are standardised for town. *Risk factors adjusted for include: cigarette smoking, systolic pressure, glucose and height-standardised FEV_1.

statistically significant, and no similar effect was observed for stroke.

Discussion

In this study, *H pylori* seropositivity was associated with an increased risk both of myocardial infarction and stroke before adjustment. However, *H pylori* seropositivity was strongly associated with adult social class and with several major risk factors for cardiovascular disease—particularly cigarette smoking, blood pressure, blood glucose, and FEV_1. After adjustment for these factors, the relation between *H pylori* and coronary heart disease was considerably weakened and the relation with stroke was effectively abolished.

The use of a case-control study nested within a cohort study has several advantages over the earlier studies. Cases are based on new coronary or stroke events, which in most cases were incident events. The assessment of cardiovascular risk factors and other potential confounders was carried out before the cardiovascular events defining the cases and was considerably more detailed than in the earlier studies. The seroprevalence rate in the control group of this study, which was higher than that in earlier population-based studies of middle aged British men,[8 11] may be partly accounted for by the marked regional variation in seroprevalence observed in this study and partly by the earlier dates of birth of the present cohort (1919 to 1939), compared with those of the other study populations.

The size of the age-adjusted increase in risk of coronary heart disease is similar to those reported in earlier studies,[11 12] when sampling error is taken into account. However, in contrast to the two previous studies, *H pylori* seropositivity was strongly related to recognised cardiovascular risk factors (particularly cigarette smoking, blood pressure, blood glucose, and FEV_1) to a degree which resulted in substantial confounding of the association between *H pylori* and coronary heart disease, and almost complete confounding in the case of stroke. These associations were not observed in the earlier case-control studies, although one other small study based in a general practice suggested an association between *H pylori* infection and risk of hypertension.[22] The interpretation of the associations between *H pylori* infection and cardiovascular risk factors (whether causal or not) is crucial, because this will determine whether adjustment for these factors is appropriate.[23] Taken together, the associations between *H pylori* infection and cardiovascular risk factors in studies conducted to date are not sufficiently consistent to provide strong evidence of a causal relation. However, poverty in early life, a strong predictor of *H pylori* infection,[4 5] has been postulated as a cause of an adverse cardiovascular risk profile in adult life,[3] possibly through its association with low birthweight.[24–27] If this is the case, adjustment for cardiovascular risk factors in the analysis would not necessarily be appropriate.

The results of our nested case-control study suggest that future studies will need to examine the relations between *H pylori* seropositivity and conventional cardiovascular risk factors and control rigorously for confounding where appropriate. Ideally, such studies should also include measurement of acute phase reactants including plasma fibrinogen, an independent marker of coronary risk,[28 29] which may be raised in the presence of *H pylori* infection.[12 30] Intervention studies are also required to assess the effect of therapeutic eradication of *H pylori* on cardiovascular risk factors.

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