hospitalizations in 10 French AIDS reference centres. *AIDS* 1997; 11:F101-5.
13 Rückläufige Aidsmeldungen—gibt es tatsächlich weniger Fälle? *Bulletin des Bundesamt für Gesundheitswesen* 1997; Jan 27:10-2.
14 Whitmore-Overton SE, Tillet HE, Evans BG, Allardice GM. Improved survival from diagnosis of AIDS in adult cases in the United Kingdom and bias due to reporting delays. *AIDS* 1993;7:415-20.
15 Ledergerber B, von Overbeck J, Egger M, Lüthy R. The Swiss HIV cohort study: rationale, organization and selected baseline characteristics. *Soz Präventivmed* 1994;39:387-94.
16 Von Overbeck J, Egger M, Davey Smith G, Schoep M, Ledergerber B, Furrer H, et al. Survival in HIV infection: do sex and category of transmission matter? *AIDS* 1994;8:1307-13.
17 Centers for Disease Control. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR* 1992;41:1-20.
18 Cox DR. Regression models and life tables. *J R Stat Soc* 1972;34:187-220.
19 Tibshirani R. A plain man's guide to the proportional hazards model. *Clin Invest Med* 1987;5:63-8.
20 Glesby MJ, Hoover DR. Survivor treatment selection bias in observational studies: examples from the AIDS literature. *Ann Intern Med* 1996; 124:999-1005.
21 Perneger TV, Sudre P, Lundgren JD, Hirschel B. Does the onset of tuberculosis in AIDS predict shorter survival? Results of a cohort study in 17 European countries over 13 years. AIDS in Europe Study Group. *BMJ* 1996;311:1468-71.
22 Staszewski S, Hill AM, Bartlett J, Eron JJ, Katlama C, Johnson J, et al. Reductions in HIV-1 disease progression for zidovudine/lamivudine relative to control treatments: a meta-analysis of controlled trials. *AIDS* 1997;11:477-83.
23 Lundgren JD, Phillips AN, Pedersen C, Clumeck N, Gatell JM, Johnson AM, et al. Comparison of long-term prognosis of patients with AIDS treated and not treated with zidovudine. *JAMA* 1994;271:1088-92.
24 Dorrucci M, Pezzotti P, Phillips AN, Alliegro MB, Rezza G, and the Italian Seroconversion Study. Antiretroviral treatment and progression to AIDS in HIV seroconverters from different risk groups. *AIDS* 1997;11:461-7.
25 Feinstein A. The role of observational studies in the evaluation of therapy. *Stat Med* 1984;3:341-5.
26 Fleming TR, Demets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* 1996;125:605-13.
27 Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994;343:871-81.
28 Brun-Vézinet F, Boucher C, Loveday C, Descamps D, Fauveau V, Izopet J, et al. HIV-1 viral load, phenotype, and resistance in a subset of drug-naive participants from the Delta trial. *Lancet* 1997;350:983-90.
29 Babiker A. Can HIV viral load be used as a surrogate for clinical endpoints in HIV disease? In: *6th European conference on clinical aspects and treatment of HIV infection, Hamburg, 11-15 October 1997*. Hamburg: 1997. (Abstract 103.)
30 Feinberg M. Hidden dangers of incompletely suppressive antiretroviral therapy. *Lancet* 1997;349:1408-9.

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Helicobacter pylori infection and mortality from ischaemic heart disease: negative result from a large, prospective study

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Abstract

Objective—To determine whether there is an independent association between *Helicobacter pylori* infection of the stomach and ischaemic heart disease.
Design—Prospective study with measurement of IgG antibody titres specific to *H pylori* on stored serum samples from 648 men who died from ischaemic heart disease and 1296 age matched controls who did not (nested case-control design).
Subjects—21 520 professional men aged 35-64 who attended the British United Provident Association (BUPA) medical centre in London between 1975 and 1982 for routine medical examination.
Main outcome measure—Death from ischaemic heart disease.
Results—The odds of death from ischaemic heart disease in men with *H pylori* infection relative to that in men without infection was 1.06 (95% confidence interval 0.86 to1.31). In a separate group of 206 people attending the centre, plasma fibrinogen was virtually the same in those who were positive for *H pylori* (2.62 g/l) and those who were negative (2.64 g/l).
Conclusions—A study that by its size and design minimised both random error and socioeconomic bias found no relation between *H pylori* infection and ischaemic heart disease. The validity of the study was shown by its confirmation of the recognised association between *H pylori* infection and stomach cancer (odds ratio 4.0 (1.9 to 8.2); $P < 0.001$). Eradication of *H pylori* infection may greatly reduce the incidence of stomach cancer, one of the most common causes of death from cancer worldwide, but it cannot be expected to have any effect in preventing ischaemic heart disease.

Introduction

Mendall et al showed an association between *Helicobacter pylori* infection of the stomach and ischaemic heart disease in 1994-5,[1 2] and 18 studies have reported on the relationship over the subsequent two years.[3–20] The position remains uncertain, an assessment supported by a recent review.[21] Since the risk of acquiring *H pylori* infection in childhood increases with socioeconomic deprivation and overcrowding,[3 22] the association may be indirect; *H pylori* infection and ischaemic heart disease are both related to social class. Some studies have shown little or no excess risk,[4–9] but others reported a fourfold to fivefold increased risk without adjustment for measures of social class and other risk factors for ischaemic heart diseases[10–11] or a twofold to threefold increased risk after such adjustment.[1–3]

We report the results of an investigation using a prospective study of the determinants of major chronic disease.This study is well suited to determine whether there is an independent relationship between *H pylori* infection and ischaemic heart disease. With 648 deaths from ischaemic heart disease it is much the largest study to report on the association. The likelihood of an indirect association arising through social class differences is minimised by the homogeneity of the study population: the subjects were all professional men attending for a routine medical examination. Random error and systematic error are therefore likely to be small.

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Table 1 Risk factors for heart disease and *H pylori* antibody status in men who subsequently died of ischaemic heart disease (cases) and men who did not (controls). Values are means (SD) unless indicated otherwise

Variable	Cases (n=648)	Controls (n=1296)	P value*
Age (years)	53.6 (7.1)	53.5 (7.1)	NS
Body mass index (kg/m^2)	25.9 (3.2)	25.4 (2.7)	<0.001
Height (m)	1.75 (0.06)	1.75 (0.06)	NS
Weight (kg)	79.3 (10.7)	78.1 (9.9)	<0.05
Total cholesterol (mmol/l)	7.1 (1.2)	6.7 (1.1)	<0.001
Triglycerides (mmol/l)	1.72 (1.67)†	1.50 (1.67)†	<0.001
Systolic blood pressure (mm Hg)	144 (22)	135 (19)	<0.001
Diastolic blood pressure (mm Hg)	89 (13)	84 (12)	<0.001
No (%) current cigarette smokers	329 (50.8)	503 (38.8)	<0.001
No (%) father died of heart disease	124 (19.1)	176 (13.6)	<0.001
No (%) mother died of heart disease	76 (11.7)	86 (6.6)	<0.001
No (%) positive for *H pylori*	308 (47.5)	595 (45.9)	NS

†Geometric mean (SD expressed as multiple of geometric mean).
*t tests and χ^2 tests.

Table 2 Values of risk factors for heart disease according to *H pylori* antibody status in 1296 men who did not die of ischaemic heart disease (controls). Values are means (SD) unless indicated otherwise

	H pylori antibody status		
Variable	Positive (n=595)	Negative (n=701)	P value*
Age (years)	54.8 (6.7)	52.4 (7.2)	NS
Body mass index (kg/m^2)	25.4 (2.7)	25.3 (2.7)	NS
Height (m)	1.75 (0.06)	1.76 (0.07)	<0.05
Weight (kg)	77.8 (9.7)	78.4 (10.0)	NS
Total cholesterol (mmol/l)	6.7 (1.1)	6.7 (1.1)	NS
Triglycerides (mmol/l)	1.50 (1.66)†	1.50 (1.68)†	NS
Systolic blood pressure (mm Hg)	135 (20)	135 (19)	NS
Diastolic blood pressure (mm Hg)	84 (12)	84 (12)	NS
No (%) current cigarette smokers	243 (40.8)	260 (37.1)	NS
No (%) father died of heart disease	111 (18.7)	65 (9.3)	<0.001
No (%) mother died of heart disease	44 (7.4)	42 (6.0)	NS
No (%) positive for *H pylori*	595 (100)	0	

*t tests and χ^2 tests.
†Geometric mean (SD expressed as multiple of geometric mean).

Table 3 Odds of death from ischaemic heart disease in men who were *H pylori* positive relative to that in men who were negative (648 cases and 1296 controls; matching analysis*)

	Odds ratio (95% CI)
Unadjusted	1.09 (0.89 to 1.33)
Adjusted for father dying of smoking; height; and heart disease	1.06 (0.86 to 1.31)

*Method of analysis took account of matching for age and duration of storage of serum sample.

Methods

The British United Provident (BUPA) study is a prospective study of 21 520 professional men aged 35-64 who attended the BUPA medical centre in London between 1975 and 1982 for a routine medical examination. Serum cholesterol concentration and other risk factors for ischaemic heart disease were measured[23 24] and serum samples were stored at −40°C. The cohort consisted of men resident in Britain, so all records could be flagged at the NHS central register in Southport, permitting automatic notification of death (with the certified cause) and cancer incidence by the Office of Population Censuses and Surveys (now the Office for National Statistics). Further information on the causes of death was obtained by writing to each certifying doctor.

This analysis is based on follow up to the end of December 1994; the average follow up was 15.6 years. In this period 648 men died from ischaemic heart disease (international classification of diseases, 9th revision, codes 410-414) but had no history of ischaemic heart disease on entry. For each case, two controls (who did not die of ischaemic heart disease and did not have a history of ischaemic heart disease on entry) were selected; they were matched for age and duration of storage of the serum sample, each to one year.

In 1997 the frozen serum samples were retrieved. IgG antibody titres specific to *H pylori* were measured with an enzyme linked immunosorbent assay (ELISA) kit (HelicoG2; Shield Diagnostics, Dundee). This quantified the results in arbitrary units; we designated a result of 10 units/ml as positive, as suggested by the manufacturer of the test. In our laboratory the within-assay coefficient of variation was 2.6% and the between-assay coefficient of variation was 10.0%. Linear models were used for all the variables except triglycerides, which were log transformed to correct for skewness. Blood pressure was somewhat skewed, but analyses using log transformed and untransformed data yielded almost identical results. Cox's proportional hazards models (with strata to identify each case with its two controls) were used to estimate the independent association of risk factors with ischaemic heart disease; the statistical analysis takes account of both the matching and the survival time.

Results

Table 1 shows characteristics of the men at the time of entry to the prospective study. The established risk factors for ischaemic heart disease were more common or more extreme in the men who subsequently died of ischaemic heart disease than in those who did not, as reported previously.[23] The prevalence of *H pylori* infection did not differ significantly between the two groups (47.5% in cases, 45.9% in controls; P = 0.50). The study indicated no association between *H pylori* infection and ischaemic heart disease.

Table 2 summarises risk factors for ischaemic heart disease in controls with and without *H pylori* infection. Risk factors were almost identical in the two groups, confirming that the study population was ideal in that it avoided the opportunity for confounding.

Table 3 shows the odds of death from ischaemic heart disease in men infected with *H pylori* relative to that in men not infected. Adjustment for potential confounding factors that may have been associated with *H pylori* infection (those with P values <0.2 in table 1—height, smoking, and father dying of heart disease)—had negligible effect. The adjusted odds ratio was 1.06 (0.86 to 1.31), indicating no material association. Further adjustment for the other risk factors shown in table 1 did not affect this estimate.

Discussion

This study is the largest published study on *H pylori* and ischaemic heart disease. It avoids confounding by socioeconomic status because the study population came from the same socioeconomic group; this is confirmed by the minimal effect of adjustment for potential confounding factors. The results show no significant association, and the upper confidence limit indicates that any excess risk is unlikely to exceed 30%. Reports of positive associations have come mainly

from small retrospective studies, and it seems likely that these were due to a combination of chance and confounding.

Our negative result cannot be explained by error in the assay determining *H pylori* status because the same assay showed a strong association between *H pylori* infection and stomach cancer. With 50 cases and three controls per case (updating an earlier report[25]), 68% and 37% respectively were positive for *H pylori* (odds ratio = 4.0 (1.9 to 8.2); $P < 0.001$). The assay also confirmed the expected increasing prevalence of *H pylori* infection with age (30%, 42%, 52%, and 70% in control men who were aged 35-44, 45-54, 55-64, and ≥65 on entry). These rates are higher than might be expected today because they relate to blood samples collected about 18 years ago.

One of the studies originally linking *H pylori* infection with ischaemic heart disease suggested that the infection increased plasma fibrinogen,[2] a plausible mechanism for the association with heart disease. We were unable to measure fibrinogen concentrations in the samples from the men who died of heart disease and their controls (because serum, not plasma, was stored), but it was measured in 206 people who attended for a routine medical examination in 1996. The mean plasma fibrinogen (measured by the Medical Research Council Epidemiology and Medical Care Unit, using the Clauss fibrinogen assay[26]) was virtually the same in the 55 people who were positive for *H pylori* and in the 151 who were negative (2.64 and 2.62 g/l respectively, age adjusted); the 95% confidence interval on the difference was −0.16 to 0.19 g/l ($P = 0.84$). Other studies have also shown no relation between *H pylori* infection and plasma fibrinogen.[7 11–13 27]

Implications

Our finding no relationship between *H pylori* and ischaemic heart disease strengthens the evidence that the relationship between *H pylori* and stomach cancer is one of cause and effect: the absence of confounding by social class in the association with heart disease indicates that such confounding will not affect the association with stomach cancer.

The negative result is disappointing in that it indicates that screening people for *H pylori* infection and treating those found to be infected will do little to prevent ischaemic heart disease. It does, however, reinforce the evidence on stomach cancer and indicates that eradicating *H pylori* infection may greatly reduce one of the most common cancers worldwide.

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Conflict of interest: None.

Key messages

- A cohort study found no association between *Helicobacter pylori* infection and death from ischaemic heart disease
- The study is much the largest to report on the association, with 648 deaths from ischaemic heart disease in men
- An important source of confounding which may have led to positive results in previous studies was avoided because all the subjects were of similar socioeconomic status
- The validity of the study was demonstrated by its ability to show the recognised association between *H pylori* infection and stomach cancer
- Men with *H pylori* infection had no increase in plasma fibrinogen (a proposed mechanism for infection causing heart disease)
- The study indicates that *H pylori* infection is not a cause of ischaemic heart disease

1 Mendall MA, Goggin PM, Molineaux N, Levy J, Toosy T, Strachan D, et al. Relation of Helicobacter pylori infection and coronary heart disease. *Br Heart J* 1994;71:437-9.
2 Patel P, Mendall MA, Carrington D, Strachan DP, Leatham E, Molineaux N, et al. Association of Helicobacter pylori and Chlamydia pneumoniae infections with coronary heart disease and cardiovascular risk factors. *BMJ* 1995;311:711-4.
3 Balaban DH, Peura DA, Watson D, Rembold C, Shifflett J. Relationship between H pylori infection and ischaemic heart disease. *Gastroenterology* 1996;110(suppl):A55.
4 Whincup PH, Mendall MA, Perry IJ, Strachan DP, Walker M. Prospective relations between Helicobacter pylori infection, coronary heart disease and stroke in middle aged men. *Heart* 1996;75:568-72.
5 Rathbone BJ, Martin D, Stephens J, Thompson JR, Samani NJ. Helicobacter pylori seropositivity in subjects with acute myocardial infarction. *Heart* 1996;76:308-11.
6 Niemela S, Karttunen T, Korhonen T, Laara E, Karttunen R, Ikäheimo M, et al. Could Helicobacter pylori infection increase the risk of coronary heart disease by modifying serum lipid concentrations? *Heart* 1996;75:573-5.
7 McDonagh TA, Woodward M, Morrison C, McMurray J, Tunstall-Pedoe H, Lowe GDO, et al. Lack of independent association of H pylori and coronary heart disease. *Gut* 1996;38(suppl 1):A1.
8 Murray LJ, Bamford KB, O'Reilly DPJ, McCrum EE, Evans AE. Helicobacter pylori infection:relation with cardiovascular risk factors, ischaemic heart disease, and social class. *Br Heart J* 1995;74:497-501.
9 Strandberg TE, Tilvis RS, Vuoristo M, Lindroos M, Kosunen TU. Prospective study of Helicobacter pylori seropositivity and cardiovascular diseases in a general elderly population. *BMJ* 1997;314:1317-8.
10 Aceti A, Mazzacurati G, Amendolea MA, Pennica A, Zechini B, Trappolini M, et al. Relation of reactive protein to cardiovascular risk factors. *BMJ* 1996;313:428-9.
11 Ponzetto A, la Rovere MT, Sanseverino P, Bazzoli F. Association of Helicobacter pylori infection with coronary heart disease. *BMJ* 1996;312:251.
12 Martin-de-Argila C, Boixeda D, Canon R, Gisbert JP, Fuertes A. High seroprevalence of Helicobacter pylori infection in coronary heart disease. *Lancet* 1995;346:310.
13 Gerning NO, Moayyedi P, Axon ATR, Grant PJ. The association between Helicobacter pylori and ischaemic heart disease assessed by coronary angiography. *Gut* 1996;39(suppl 2):A91.
14 Lipp GYH, Wise R, Beevers G. Association of Helicobacter pylori infection with coronary heart disease. *BMJ* 1996;312:250.
15 Morgando A, Sanseverino P, Perotto C, Molino F, Gai V, Ponzetto A. Helicobacter pylori seropositivity in myocardial infarction. *Lancet* 1995;345:1380.
16 Aromaa A, Knekt P, Reunanen A, Rautelin HI, Kosunen TU. Helicobacter pylori and the risk of myocardial infarction. *Gut* 1996;3 (suppl 2):A91.
17 Vakil N, Khurshid A, Fenske T, Bajwa T. H pylori infection in patients with and without coronary artery disease. *Gut* 1996;39(suppl 2):A91.
18 Caselli M, Kubbajeh M, Ruina M, Gaudenzi P, Trevisani L, Marangoni MG. Helicobacter pylori and heart. *Gut* 1996;39(suppl 2):A91.
19 Strandberg TE, Tilvis RS, Vuoristo M, Kosunen TU. H pylori infection and cardiovascular diseases in elderly population. *Gut* 1996;39(suppl 2):A92.
20 Malnick SDH, Adlan K, Goland S, Bass DD, Beergabell M, Fink A, et al. High incidence of H pylori seropositivity in young patients with coronary artery disease. *Gut* 1996;39(suppl 3):A63.
21 Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is ther a link? *Lancet* 1997;350:430-6.
22 Webb PM, Knight T, Greaves S, Wilson A, Newell DG, Elder J, et al. Relation between infection with Helicobacter pylori and living conditions in childhood:evidence for person to person transmission in early life. *BMJ* 1994;308:750-3.
23 Wald NJ, Law M, Watt HC, Wu T, Bailey A, Johnson MA, et al. Apolipoproteins and ischaemic heart disease: implications for screening. *Lancet* 1994;343:75-9.
24 Wald N, Idle M, Boreham J, Bailey A. Low serum vitamin A and subsequent risk of cancer. Preliminary results of a prospective study. *Lancet* 1980;2:813-5.
25 Forman D, Newell DG, Fullerton F, Yarnell JWG, Stacey AR , Wald NJ, et al. Association between infection with Helicobacter pylori and risk of gastric cancer: evidence from a prospective investigation. *BMJ* 1991;302:1302-5.
26 Clauss VA. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. *Acta Haemat* 1957;17:237-46.
27 Parente F, Maconi G, Imbesi V, Sangaletti O, Poggio M, Rossi E, et al. Helicobacter pylori infection and coagulation in healthy people. *BMJ* 1997;314:1318-9.

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