A Prospective Study of *Helicobacter pylori* Seropositivity and the Risk for Future Myocardial Infarction among Socioeconomically Similar U.S. Men

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Background: **The role of *Helicobacter pylori* as a determinant of cardiovascular disease is controversial.**

Objective: **To determine whether previous exposure to *H. pylori* is associated with an increased risk for myocardial infarction.**

Design: **Prospective case-control study.**

Setting: **Physicians' Health Study.**

Participants: **Initially healthy U.S. men.**

Measurements: **Titers of IgG antibody against *H. pylori* and several inflammatory markers were measured in baseline blood samples obtained from 445 men who subsequently had a myocardial infarction (case-patients) and 445 men matched for age and smoking status who remained free of vascular disease (controls) during a mean follow-up of 8.9 years.**

Results: **Baseline seropositivity was similar among case-patients and controls (43.4% vs. 44.3%; rate ratio, 0.96 [95% CI, 0.7 to 1.3]). Minimal evidence of association was found between magnitude of seropositivity and subsequent risk and between seropositivity and levels of the inflammatory biomarkers.**

Conclusion: **In a socioeconomically homogeneous population, we found limited evidence of association between *H. pylori* exposure and risk for future myocardial infarction.**

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Infection with *Helicobacter pylori* may lead to a chronic low-grade inflammatory response, and it has been hypothesized that exposure to this agent promotes atherosclerotic initiation and progression. More than 25 cross-sectional and retrospective seroepidemiologic studies have evaluated the possible association between *H. pylori* infection and vascular disease, and collectively they indicate some positive association; however, the degree to which potential epidemiologic biases were avoided in these studies is uncertain. For example, low socioeconomic status is strongly associated with *H. pylori* infection and with coronary heart disease (1, 2), and failure to control properly for the effects of such factors could be responsible for at least some of the observed association between the prevalence of infection and the incidence of vascular disease (3–5).

Prospective epidemiologic studies in socioeconomically homogeneous groups could help control for social status and certain other potential sources of bias. We therefore sought to determine, in a large-scale cohort of socioeconomically similar U.S. men, whether baseline exposure to *H. pylori* is associated with an increased risk for future myocardial infarction and to compare the results of our investigation with the published literature.

METHODS

We determined levels of IgG antibody directed against *H. pylori* in a nested case–control study among participants in the Physicians' Health Study, a randomized trial of aspirin and β-carotene with long-term follow-up of 22 071 U.S. male physicians who had no history of coronary disease or stroke (6). At study entry, 14 916 participants provided a baseline plasma sample. For all incident events of myocardial infarction reported during 13-year follow-up, hospital records and autopsy reports were obtained and used to confirm or refute the diagnosis. Each study participant who provided a baseline blood sample and had a confirmed myocardial infarction during follow-up was then matched to a randomly selected control participant who had also provided a baseline blood sample but who had remained free of reported cardiovascular disease at the time the matched case-patient reported his event. Controls were matched to case-patients on the basis of age ($\pm$2 years), smoking status at study entry (past, current, or never), and length of follow-up (6-month intervals).

For each case-patient and control, the plasma samples that had been collected and stored at baseline were thawed and assayed by using enzyme-linked immu-

Table. **Baseline Clinical Characteristics of Study Participants, according to Participant Status and *Helicobacter pylori* Seropositivity***

Characteristic	Patients according to Participant Group			Patients according to Seropositivity		
	Controls (n = 445)	Case-Patients (n = 445)	P Value	*H. pylori*–Positive	*H. pylori*–Negative	P Value
Mean age ± SD, *y*	57.5 ± 8.4	57.8 ± 8.6	–†			
Smoking status, %			–†			
Never	44.1	44.1				
Past	40.3	40.3				
Current	15.5	15.5				
Body mass index ± SD, kg/m^2	24.9 ± 2.9	25.5 ± 3.4	0.01	25.1 ± 2.9	25.3 ± 3.4	>0.2
Blood pressure ± SD, *mm Hg*						
Systolic	126.6 ± 11.2	129.6 ± 12.3	<0.001	128.2 ± 12.2	127.9 ± 11.5	>0.2
Diastolic	79.3 ± 7.0	80.4 ± 7.6	0.03	79.4 ± 7.0	80.2 ± 7.6	>0.2
History of hypertension, %	18.1	25.1	0.01	21.9	21.4	>0.2
History of hyperlipidemia, %	7.1	13.9	0.002			
Diabetes mellitus, %	2.5	5.9	0.01	4.1	4.2	>0.2
Family history of coronary artery disease, %	13.9	17.4	0.2	13.9	17.0	0.2
Exercise > 1 time/wk, %	75.8	64.9	0.001	70.5	69.2	>0.2
Alcohol use, %			0.1			0.2
Daily	27.5	21.6		20.4	27.8	
Weekly	42.6	49.6		46.7	45.6	
Monthly	12.2	11.7		11.9	12.0	
Rarely or never	17.8	17.1		21.1	14.6	
Positive for *H. pylori*, %	44.3	43.4	>0.2			
Albumin level ± SD, *g/L*				45.7 ± 8.2	45.0 ± 7.8	0.2
Fibrinogen level ± SD, *g/L*				3.7 ± 1.4	3.5 ± 1.4	0.2
Median hs-CRP level (interquartile range), *mg/L*				1.40 (0.69, 2.46)	1.36 (0.66, 2.51)	>0.2
sICAM-1 concentration ± SD, *μg/mL*				238.7 ± 73.6	234.8 ± 66.8	>0.2
sVCAM-1 concentration ± SD, *μg/mL*				661.7 ± 217.6	650.4 ± 182.2	>0.2
Interleukin-6 level ± SD, *ng/mL*				2.2 ± 1.6	2.2 ± 1.8	>0.2

* hs-CRP = high-sensitivity C-reactive protein; sICAM-1 = soluble intercellular adhesion molecule-1; sVCAM-1 = soluble vascular cellular adhesion molecule-1.
† Matching variable.

nosorbent assay (Orion, Espoo, Finland) for IgG antibodies directed against *H. pylori*. As in the manufacturer's instructions, seropositivity was defined as an IgG titer of at least 300. Samples were also assayed for the inflammatory markers albumin, fibrinogen, high-sensitivity C-reactive protein, soluble intercellular adhesion molecule-1, soluble vascular cellular adhesion molecule-1, and interleukin-6 (7–9). All laboratory personnel were unaware of case-patient or control status.

Means and proportions for baseline clinical characteristics were computed for each study group, and any differences between groups were tested by using the Student *t*-test or the chi-square statistic. Logistic regression analyses, conditioned on the matching variables of age, smoking, and follow-up time, were used to test for any evidence of association between *H. pylori* seropositivity at baseline and the subsequent development of myocardial infarction; adjusted estimates of risk were additionally computed after adjustment for other baseline differences in cardiovascular risk factors. To test whether the risk for myocardial infarction might increase as levels of IgG antibody increased, we also computed the risks for subsequent myocardial infarction on the basis of increasing quartiles of antibody level. In these primary analyses, 95% CIs and two-tailed P values were used. All statistical analyses were performed by using SAS statistical software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Baseline characteristics of study participants are shown in the **Table**. Mean follow-up in the case-patient and control groups was 8.9 years. Because of matching, age and smoking status were similar in the two groups. As expected, participants who developed myocardial infarction during follow-up (case-patients) were significantly more likely than controls to have obesity, hypertension, hyperlipidemia, and diabetes mellitus.

Overall, the proportion of men who were seropositive for *H. pylori* at baseline was similar among case-

patients (43.4%) and controls (44.3%), yielding a rate ratio of 0.96 (95% CI, 0.7 to 1.3; $P > 0.2$). This risk estimate was not materially altered by adjustment for hypertension, hyperlipidemia, diabetes, body mass index, a family history of premature coronary artery disease, alcohol use, or exercise frequency (multivariate rate ratio, 0.97 [95% CI, 0.6 to 1.3]; $P > 0.2$). We found no significant evidence of increased risk across increasing quartiles of IgG antibody levels for the crude or for the adjusted relative risk (data not shown).

We observed no significant differences between *H. pylori*–positive and *H. pylori*–negative participants with respect to traditional cardiovascular risk factors, either in the cohort as a whole (**Table**) or in subgroup analyses stratified by case-patient or control status. Furthermore, we observed no significant differences with respect to baseline levels of the inflammatory biomarkers evaluated (**Table**).

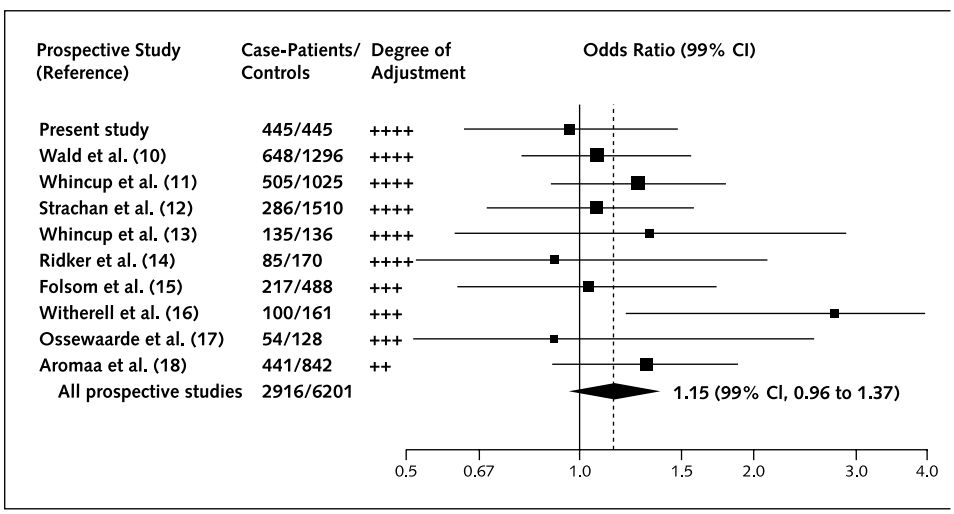
DISCUSSION

In this prospective study of apparently healthy and socioeconomically similar U.S. male physicians, we found little evidence of association between baseline IgG antibodies directed against *H. pylori* and the subsequent risk for developing myocardial infarction. Further, we found little evidence of association between *H. pylori* and the plasma levels of several inflammatory markers that have previously been shown to predict coronary risk in this cohort (7–9).

Several previous retrospective and cross-sectional studies have reported positive associations between chronic *H. pylori* infection and coronary heart disease. Interpretation of these studies, however, is complicated by potential confounding factors, of which low socioeconomic status is a general indicator, that are strongly associated both with infection and with coronary disease (3–5). By contrast, in the current study, the role of any such confounding is likely to be relatively small because all study participants were physicians and should therefore have similar socioeconomic status, at least in adulthood. Furthermore, although we could control for many additional potential confounding factors in our analysis, the adjusted and crude estimates of risk are almost identical.

As shown in the **Figure**, nine other prospective studies of *H. pylori* seropositivity and coronary death or nonfatal myocardial infarction have been reported (10–18), as has one study evaluating all cardiovascular events (19). Only two of these prospective studies, however, were conducted in socially homogeneous populations

Figure. **Odds ratios in prospective studies of *Helicobacter pylori* seropositivity and death from coronary heart disease or nonfatal myocardial infarction.**



Black squares indicate the odds ratio in each study; the square size is proportional to the number of cases, and the solid horizontal line represents the 99% CI. In each of the prospective studies shown in the figure, the investigators adjusted for the possible confounding variables of age, sex, and smoking status (++). Some studies also adjusted for other standard vascular risk factors (+++) and for information (or matching) on markers of socioeconomic status (++++). The studies are ordered according to degree of adjustment and sample size; odds ratios are plotted on a logarithmic scale.

(10, 14), and only three others (11–13) attempted statistical adjustments for indicators of social class. However, even if adjustments for social class are attempted, they may be less effective than adjustment for socioeconomic status by studying a homogenous group, since not all relevant markers of social class can be measured accurately.

Together with the present study, the available prospective studies include 2916 case-patients with coronary heart disease, with a weighted mean age of 67 years at the time of the event. Although these studies differed in the degree of adjustment for indicators of socioeconomic status, pooled results showed limited heterogeneity, and a combined analysis yielded an odds ratio of 1.15 (99% CI, 0.96 to 1.37) (**Figure**). In a subsidiary analysis restricted to the three prospective studies in socially homogeneous groups and a retrospective study that matched for childhood social status by comparing *H. pylori* seropositivity within sibling pairs (20), a total of 1688 case-patients had coronary heart disease; these results yield a pooled odds ratio of 1.11 (99% CI, 0.86 to 1.43). These epidemiologic studies, which primarily involved case-patients in their late middle-age years, suggest that any true association between *H. pylori* and coronary heart disease is likely to be of small magnitude.

Studies of early-onset coronary disease may, however, be more sensitive to the existence of any modest associations than are studies in persons of older age, because established vascular risk factors tend to be stronger at younger ages. Furthermore, the potential proinflammatory effects of *H. pylori* might also be of greater importance among such individuals. In this regard, a recent retrospective study of 1122 case-patients with early-onset myocardial infarction (mean age, 44 years) has reported an adjusted odds ratio of 1.87 (99% CI, 1.42 to 2.47) (20). Thus, it remains possible that associations between infection and vascular risk may be more substantial in certain patient subgroups, such as those with early onset of disease—a hypothesis that requires direct testing in other cohorts.

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