Association between *Helicobacter pylori* infection and angiographically demonstrated coronary artery disease: A meta-analysis

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**Abstract.** Coronary artery disease (CAD) is a leading cause of mortality globally. However, the etiology and pathogenesis of CAD are not fully understood. The aim of the present meta-analysis was to estimate the association between the risk of CAD and *Helicobacter pylori* (*H. pylori*) infection. A literature search was performed to identify eligible studies published prior to August 14, 2014. Fixed or random effect meta-analytical methods were used to pool the data and perform the subgroup analyses. The effect measures estimated were the odds ratios (OR) for dichotomous data reported with 95% confidence intervals (95% CI). Of the 109 studies identified using the search parameters, 26 cross-sectional studies were eligible involving 3,901 CAD patients and 2,751 controls. *H. pylori* infection was associated with an increased risk of CAD (OR: 1.96, 95% CI: 1.47-2.63, P<0.00001). When the adjusted ORs were used to conduct another meta-analysis, the OR value decreased, but the association remained significant (OR: 1.42, 95% CI: 1.09-1.86, P=0.008). The association between *H. pylori* infection and CAD risk was stronger in younger individuals than in older individuals (OR: 2.36, 95% CI: 1.50-3.73 vs. OR: 1.59, 95% CI: 1.19-2.11). A significant association was observed in studies from Europe (OR: 2.11, 95% CI: 1.54-2.88, P=0.01) and the USA (OR: 1.43, 95% CI: 1.08-1.91, P=0.36). There is a potential association between *H. pylori* infection and the risk of CAD. The association may be influenced by age and ethnicity.

**Introduction**

Coronary artery disease (CAD), also known as ischemic heart disease (IHD), atherosclerotic heart disease, atherosclerotic cardiovascular disease and coronary heart disease, is a leading cause of mortality globally. It is reported to have caused 7.4 million mortalities (13.2% of all deaths) in 2012 worldwide (1). The etiology and pathogenesis of CAD are not fully understood. The common risk factors, including hypertension, diabetes mellitus, smoking, obesity, serum lipids, family history and socioeconomic status, do not fully account for all cases (2). Chronic infections, including *Helicobacter pylori* (*H. pylori*) infection, are assumed to play a role in the pathogenesis of CAD (3).

*H. pylori* is a gram-negative bacterium infecting more than half the world’s population (4). The infection results in chronic gastritis, peptic ulcer disease and gastric cancer (5). It is also associated with extra-gastrointestinal conditions, including diabetes mellitus and stroke (6,7). Previous studies have focused on the association between *H. pylori* infection and the risk of CAD. However, the role of *H. pylori* in CAD remains unclear (8,9).

Studies in which the potential association between *H. pylori* infection and CAD has been investigated have shown conflicting results. In the majority of studies, CAD was diagnosed using clinical questionnaires or on the basis of abnormalities on electrocardiograms. As patients with other diseases may also present with chest pain syndromes similar to CAD, these diagnostic methods would result in high confounding bias. Coronary angiography is a sensitive and specific technique for diagnosing CAD. It is considered to be a ‘gold standard’ for the diagnosis of CAD (10). Therefore, the present meta-analysis was conducted to determine the association between *H. pylori* infection and CAD risk. The data were obtained from studies in which CAD was diagnosed by coronary angiography to obtain a more comprehensive estimate of the putative influence of *H. pylori* on CAD.

**Materials and methods**

**Data search.** Studies were selected on the basis of a structured literature search in PubMed, EMBASE and the Cochrane library. Search terms were ‘coronary artery disease [All Fields]’ OR ‘coronary heart disease [All Fields]’ OR ‘coronary atherosclerosis [All Fields]’ OR ‘myocardial infarction [All Fields]’ OR ‘angina [All Fields]’ OR ‘atheroma [All Fields]’.
OR ‘ischemic heart disease [All Fields]’ OR ‘ischaemic heart disease [All Fields]’ AND ‘Helicobacter pylori [All Fields]’ AND ‘angiography [All Fields]’. The references in the articles were checked, and suitable studies identified from them were also used. The date of the most recent search was August 14, 2014.

Data selection. All selections were performed in duplicate. The final inclusion of studies was determined by consensus, and when this failed, a third author adjudicated. The following inclusion criteria were used: i) Studies that compared the incidence of angiographically demonstrated CAD in \( H. pylori \) infected subjects and uninfected subjects; and ii) studies that compared the incidence of \( H. pylori \) infection in angiographically demonstrated CAD patients and non-CAD controls. Studies that did not meet these inclusion criteria were excluded. Articles not in the English language were also excluded.

Data extraction. Two trained research personnel independently extracted the following data: First author, country, year of publication, mean age of patients, study size, study type, methods of \( H. pylori \) detection, matched variables and adjusted variables. All data were double-entered.

Statistical analysis. The meta-analysis was performed using Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, Oxford, UK). The effect measures estimated were the odds ratio (OR) and relative risk (RR) for dichotomous data reported with 95% confidence intervals (95% CIs). An OR/RR was considered statistically significant if the 95% CI did not include the value 1. An analysis of the heterogeneity of the studies was performed using the \( \chi^2 \)-based Q test. \( P<0.1 \) and I\(^2\)>50% were considered significant for heterogeneity. If the studies were shown to be homogeneous with \( P>0.1 \), a fixed-effects model (the Mantel-Haenszel method) was used, otherwise, the random-effects model (the DerSimonian and Laird method) was used. The potential publication bias was assessed with funnel plots. A sensitivity analysis was carried out to assess heterogeneity. Each study was sequentially removed from the analysis to determine its contribution to the overall effect size. All studies were scored using the modified Newcastle-Ottawa Scale system (11). This scoring system evaluated studies based on patient selection, comparability of the groups, and assessment of outcome. When an article received a score of \( \geq 6 \) in this scoring system, it was regarded as a high-quality article.

Results

Eligible studies. Of the 109 studies identified, 26 studies (12-37) were eligible. The reasons why other studies did not meet the inclusion criteria were as follows: They were reviews, comments, news, case reports or letters with no original data (n=18); non-English articles (n=4); studies of other topics (n=54); the full text could not be found (n=1); and studies on this topic, but did not use coronary angiography to diagnose CAD (n=6). A manual search of the listed references revealed no further studies. Of these 26 studies, 24 compared the incidence of \( H. pylori \) infection in angiographically diagnosed CAD patients and non-CAD controls, while only two studies [Lee et al (22) and Zhu et al (25)], involving <500 participants, compared the incidence of CAD in \( H. pylori \) infected subjects and uninfected subjects. A meta-analysis could not be conducted for these studies. The two studies also compared the incidence of \( H. pylori \) infection in CAD patients and non-CAD controls. Therefore, they were analyzed together with the other 24 studies. The characteristics of the selected studies are summarized in Table I.

\( H. pylori \) infection and CAD risk. Of these 26 studies, 13 indicated that \( H. pylori \) infection was associated with a higher risk of CAD, while the others showed no association. The total number of CAD patients was 3,901, and that of non-CAD controls was 2,751. The \( H. pylori \) positive rate in CAD patients and controls was 61.3% (2,390/3,901) and 42.5% (1,168/2,751), respectively. The random effect pooled OR was 1.96 (95% CI: 1.47-2.63, \( P<0.00001 \); Fig. 1). When excluding 12 studies that had a low score (≤6), 14 studies remained. Meta-analysis showed that the random effect pooled OR was 1.75 (95% CI: 1.39-2.19, \( P=0.008 \)). The studies with high scores (≥7) had adjusted some variables associated with CAD. The adjusted ORs were used to conduct another meta-analysis. The random effect pooled OR was 1.42 (95% CI: 1.09-1.86, \( P=0.008 \); Fig. 2). The adjusted effect pooled OR was lower than the unadjusted, but the association was still significant.

Subgroup analysis. To investigate the influencing factors of heterogeneity, the data were further stratified according to the year of publication, methods of \( H. pylori \) detection, and whether matched for gender, mean age, socioeconomic level and geographical region. Subgroup analyses according to the above factors were then conducted. The results are shown in Table II. The association between \( H. pylori \) infection and CAD risk was stronger in younger individuals (those <60 years old) than in older individuals (OR: 2.36, 95% CI: 1.50-3.73 vs. OR: 1.59, 95% CI: 1.19-2.11). A significant association was observed in studies from Europe (OR: 2.11, 95% CI: 1.54-2.88, \( P=0.01 \)) and the USA (OR: 1.43, 95% CI: 1.08-1.91, \( P=0.36 \)).

Sensitivity analysis and publication bias. A sensitivity analysis was performed to assess the influence of each individual study on the pooled ORs by omitting a single study each time. The results showed that there was no substantial change in the corresponding pooled OR. Publication bias was assessed using funnel plots. In the funnel plots, the largest studies were near the average, small studies were spread on both sides of the average and an asymmetric inverted funnel shape was obtained (Fig. 3). Therefore, funnel plots showed no evidence of significant publication bias in the meta-analyses.

Discussion

The studies included in the meta-analysis applied strict diagnostic criteria for CAD diagnosis, and the results were more reliable than those of a previous meta-analysis (38). All included studies during quality assessment achieved satisfactory scores (≥6). The meta-analysis including the high quality studies (scores ≥7) did not significantly change the pooled OR. Sensitivity analysis did not demonstrate that any single study would lead to a statistically significant effect size in the meta-analysis. Therefore, the included studies showed good
Table I. Characteristics of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Mean age (years)a</th>
<th>Study sizeb</th>
<th>Study type</th>
<th>H. pylori detectionc</th>
<th>Matched variablesd</th>
<th>Adjusted variablesd</th>
<th>Quality score</th>
<th>Ref.</th>
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<td>62/43</td>
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<td>1, 2, 4, 5, 6, 11, 13</td>
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<td>(13)</td>
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<td>100/93</td>
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<td>-</td>
<td>-</td>
<td>6</td>
<td>(14)</td>
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<td>500/500</td>
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<td>1</td>
<td>-</td>
<td>6</td>
<td>(15)</td>
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<td>1, 3, 4, 5, 6, 7</td>
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<td>CS</td>
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<td>4, 5, 6, 8, 11</td>
<td>-</td>
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<td>288/49</td>
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<td>-</td>
<td>1, 4, 5, 6, 8</td>
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<td>(18)</td>
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<td>3, 4, 5, 6, 11</td>
<td>-</td>
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<td>(19)</td>
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<tr>
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<td>33/66</td>
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<td>1, 2, 3, 4, 10</td>
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<td>1</td>
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<td>-</td>
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<td>(21)</td>
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<tr>
<td>Lee</td>
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<td>54/40</td>
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<td>1, 2, 3, 4, 5, 8, 9</td>
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<td>38/12</td>
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<td>6</td>
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<td>2, 5, 8, 9, 10</td>
<td>1, 2, 4, 5, 8, 9, 10, 11, 17</td>
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<td>(25)</td>
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<td>Stöllberger</td>
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<td>Austria</td>
<td>62.0</td>
<td>50/62</td>
<td>CS</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>6</td>
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<td>Iran</td>
<td>52.9</td>
<td>51/55</td>
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<td>(27)</td>
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<td>Osawa</td>
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<td>Japan</td>
<td>59.8</td>
<td>206/98</td>
<td>CS</td>
<td>1</td>
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<td>1, 4, 5, 6, 8</td>
<td>7</td>
<td>(28)</td>
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<td>Aydin</td>
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<td>114/56</td>
<td>CS</td>
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<td>165/127</td>
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<td>88/88</td>
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<td>1, 2, 3, 8</td>
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<td>Anderson</td>
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<td>Niemelä</td>
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<td>Finland</td>
<td>54.0</td>
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<td>CS</td>
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<td>1, 2</td>
<td>1, 2, 5, 8, 10</td>
<td>8</td>
<td>(37)</td>
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</table>

aMean age of the case group. bNumber of participants with CAD/number of participants without CAD. c1, detection of serum IgG by ELISA or chemiluminescence; 2, histological staining; 3, detection of antigens in stool samples. d1, age; 2, gender; 3, body mass index; 4, hypertension; 5, diabetes mellitus; 6, hypercholesterolemia; 7, family history; 8, smoking status; 9, socioeconomic status; 10, serum lipid; 11, C-reactive protein; 12, erythrocyte sedimentation rate; 13, interleukin-6; 14, high-density lipoprotein cholesterol and glycated hemoglobin; 15, alcohol consumption; 16, school education; 17, ethnicity; 18, peptic ulcer; CS, cross-sectional study; H. pylori, Helicobacter pylori; CAD, coronary artery disease.
The results showed that the risk of CAD increased ~2-fold in patients with *H. pylori* infection. However, when some variables associated with CAD were adjusted, the risk decreased...
This indicated that H. pylori infection was a potential independent risk factor for CAD, and may play a role in the pathogenesis of CAD.

Year of publication and H. pylori diagnostic method could affect homogeneity. Age, gender, ethnicity and socioeconomic level were associated with both H. pylori infection and CAD risk. Therefore, subgroup analyses according to the above factors were performed. During the subgroup analysis, the year of publication, H. pylori diagnostic method, gender and socioeconomic level did not influence the reliability of the results. However, the results indicated that the association between CAD risk and H. pylori infection was age- and ethnicity-dependent. The association was stronger in younger individuals than in older individuals. These results were consistent with those of previous studies, which demonstrated that the effect of most cardiovascular risk factors on cardiovascular diseases was stronger in younger than in older individuals (39, 40). The effect of H. pylori infection on CAD...
was stronger in Caucasians in this meta-analysis. It is generally acknowledged that the prevalence of *H. pylori* infection in younger individuals and Caucasians is lower than that in older individuals and other ethnicities. Therefore, *H. pylori* infection appears to have a greater impact on CAD risk in low prevalence populations.

This meta-analysis demonstrated that *H. pylori* infection was associated with the risk of CAD. CAD and *H. pylori* infection could potentially share common factors of genetic susceptibility. Genetic loci associated with host susceptibility to CAD or *H. pylori* infection have been identified using genome-wide association studies (GWAS) in recent years (41-46). GWAS represent an essentially unbiased approach capable of simultaneously assessing thousands of genetic variants across the whole genome for association with CAD or *H. pylori* infection. To date, multiple GWAS have identified >50 common genetic susceptibility loci independently associated with CAD (41-44). Two studies identified four single nucleotide polymorphisms (SNPs: rs4833095, rs10004195, rs368433 and rs10502974) located in different genes that were associated with *H. pylori* infection using GWAS (45,46). However, no genetic locus associated with both *H. pylori* infection and CAD risk has been found. Therefore, there is no good evidence to demonstrate that CAD and *H. pylori* infection share common factors of genetic susceptibility. *H. pylori* infection increases the risk of CAD and this may be due to the pathogenicity of *H. pylori*.

*H. pylori* infection can affect CAD risk in various ways. Two studies found *H. pylori* DNA in the aortic tissues and atherosclerotic plaques of patients with CAD (47,48). This may be an important indication of the direct role of *H. pylori* in the pathogenesis of CAD. Chronic *H. pylori* infection can reduce serum high-density lipoprotein (HDL) cholesterol and apolipoprotein-A, but elevate total cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride and apolipoprotein-B levels (49). These alterations in lipid profiles may promote the atherosclerotic process. Chronic *H. pylori* infection triggers the release of inflammatory cytokines and coagulation factors such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-α, fibrinogen and prothrombin fragments, resulting in vasosconstriction, endothelial dysfunction and slowed flow in the major epicardial coronary arteries (50). These factors link *H. pylori* infection to the development of CAD.

In conclusion, this meta-analysis demonstrated a potential association between *H. pylori* infection and the risk of CAD. The association may be influenced by age and ethnicity. More research is required to explore the mechanisms involved.

References


Yu et al: *Helicobacter pylori* and CORONARY ARTERY DISEASE


