An Updated Meta-Analysis of the Relationship Between Helicobacter pylori Infection and the Risk of Coronary Heart Disease

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Background: Coronary heart disease (CHD) is one of the leading causes of mortality in the world. Although the traditional risk factors for CHD have been identified, it seems that there are still many CHD cases without these factors. Previous studies have hypothesized that Helicobacter pylori (H. pylori) infection was associated with the risk of CHD.

Objective: The association between H. pylori infection and the risk of CHD was studied using a systematic evaluation and meta-analysis method.

Methods: In order to find relevant studies, four electronic databases were systematically searched until August 2021. According to the inclusion and exclusion criteria, studies were screened and data were extracted. Under the random-effects or the fixed-effects model, the odds ratio (OR) and 95% confidence interval (95% CI) were combined. All analyses were conducted using Review Manager software (RevMan 5.4).

Results: Among the included studies, 2 studies were analyzed for H. pylori stool antigen test, 2 studies were analyzed for H. pylori histological staining test, 13 studies were analyzed for the anti-CagA test, and 38 studies were analyzed for the anti-H. pylori IgG test. The pooled results revealed that positive anti-H. pylori IgG was significantly associated with an increased risk of CHD (OR, 1.58; 95% CI: 1.34–1.87). Similarly, positive anti-CagA, positive H. pylori stool antigen, and positive H. pylori histological staining were significantly associated with the development of CHD with (OR: 1.33, 95% CI: 1.16–1.53), (OR: 3.50, 95% CI: 1.60–7.66), and (OR: 1.78, 95% CI: 1.12–2.83), respectively.

Conclusion: This meta-analysis showed that H. pylori infection increased the risk of CHD. However, more studies are needed to further investigate whether early eradication of H. pylori may reduce the morbidity of CHD.

Keywords: coronary heart disease, Helicobacter pylori, anti-H. pylori IgG test, anti-CagA test, H. pylori stool antigen test, H. pylori histological staining test, systematic review, meta-analysis
INTRODUCTION

Helicobacter pylori (H. pylori), a gram-negative bacterium, is one of the common infections in human. More than the half of population in the world suffers from the infection (1). H. pylori infection causes a wide range of gastrointestinal diseases including chronic gastritis, gastric cancer, and duodenal ulcer (2, 3). Moreover, researchers have also recently found that H. pylori infection was closely related to atherosclerotic cardiovascular diseases, including coronary heart disease (CHD), peripheral arterial disease, and stroke (4–7).

CHD is the most common type of organ disease caused by atherosclerosis, the leading cause of mortality in many countries (8). The etiology and pathogenesis of CHD have not been fully understood until now. The classical risk factors, including diabetes, hypertension, obesity, smoking, dyslipidemia, socioeconomic status, and family history, cannot fully explain all causes (9). Chronic inflammation caused by chronic infection, such as H. pylori infection, plays an important role in the pathogenesis of CHD. Some studies have shown that H. pylori infection increased the risk of CHD (10, 11). However, other studies have shown that H. pylori infection was not closely related to CHD (12, 13). Previous meta-analyses have also provided evidence for or against the relationship between H. pylori infection and the risk of CHD (14, 15).

Previous studies have been controversial, even from earlier published meta-analyses with no clear final conclusions. Therefore, we conducted a large-scale systematic review and meta-analysis to establish specific evidence about the relationship between H. pylori infection and the risk of CHD.

MATERIALS AND METHODS

This meta-analysis strictly followed the recommendations of the systematic review and meta-analysis (PRISMA) list (16) of the preferred reporting items.

Literature Search

We searched four electronic databases including Web of Science, Embase, PubMed, and Cochrane Library until August 2021. We used the following search string: “ischemic heart disease (IHD)” OR “coronary heart disease (CHD)” OR “coronary artery disease (CAD)” OR “coronary atherosclerosis” OR “angina” OR “unstable angina (UA)” OR “acute myocardial infarction (AMI)” OR “Acute coronary syndrome (ACS)” OR “myocardial infarction (MI)” OR “atheroma” AND “Helicobacter” OR “Helicobacter pylori” OR “Campylobacter pylori” OR “H. pylori.” The references in the included studies were checked, and suitable studies were identified.

Literature Selection and Data Extraction

Eligible studies that reported the relationship between H. pylori infection and the risk of CHD were included in this meta-analysis. In addition to studies with unreliable data, we excluded abstract-only articles, book chapters, conference papers, theses, reviews, letters, editorials, and posters. There were no restrictions for included studies on publication year, language, place, or demographics of patients. Any discrepancy in the screening step was agreed by two reviewers. If necessary, a third reviewer was consulted. Then, the full-text screening was carried out to identify the related studies for data extraction. The extracted data included the following: the first author, publication year, category of CHD, country, settings, study design, sample size, agent, and adjustment status.

Quality and Assessment

All studies were evaluated using the modified Newcastle-Ottawa Scale (NOS). This scoring system assessed studies according to the comparability of groups, patient selection, and assessment outcomes. When an article scored >7 points in this scoring system, it was considered a high-quality article.

Statistical Analysis

The most adjusted hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI) was extracted and combined into an equivalent measure which was expressed in the form of combined OR. The original data was extracted and used to calculate the original OR when a study did not contain the most adjusted HR or OR with 95% CI. Heterogeneity among studies was assessed by using the I-statistic ($I^2$) test (17). When there was substantial heterogeneity ($I^2 > 50$%), the random-effects model was used. Otherwise, the fixed-effects model was selected (18). In order to test the robustness of the results, the sensitivity analysis was evaluated by excluding one study at a time (19). In addition, several subgroup meta-analyses were performed based on study design, setting, adjustment status, quality assessment score, category of CHD, and country. All analyses were conducted using Review Manager (RevMan 5.4), and a p-value of less than 0.05 was regarded as statistically significant.

RESULTS

Search Results

Using predefined keywords, 3,245 studies were identified from four electronic databases. After excluding duplicate studies, 1,234 studies were included and screened, of which 643 were deleted by title and abstract. We screened the remaining 591 studies and excluded 551 studies according to the exclusion criteria. In addition, the manual search yielded 4 other studies. We then extracted useful data from 44 qualified studies (20–63) (Figure 1).

Characteristics of the Included Studies

Among the included studies, 13 studies were prospective studies with a total sample size of 16,236 participants. Thirty-one studies were cross-sectional studies with 14,689 participants. Included studies were published between 1995 and 2017. The number of included studies per type of CHD were as follows: 19 studies on CHD, 12 studies on AMI, 10 studies on MI, 2 studies on IHD, and 1 study on ACS. Ten studies were conducted in the United Kingdom, 5 in Iran, 4 in the United States, 4 in Italy, 4 in Japan, 3 in India, 3 in Turkey, 2 in China, 2 in South Korea, 1 in New Zealand, 1 in the Netherlands, 1 in Sweden, 1...
in Germany, 1 in Greece, 1 in Pakistan, and 1 in Croatia. We found 27 studies that were conducted in hospital-based settings and 17 studies conducted in a community-based setting. *H. pylori* detection method included anti-*H. pylori* IgG, anti-CagA, *H. pylori* stool antigen, and *H. pylori* histological staining. According to the adjustment status, there were 17 adjusted studies and 27 unadjusted studies. Moreover, the included studies were divided into 21 studies with ≥7 points and 23 studies with <7 points according to the quality score (Table 1).

**Main Results**

We revealed the relationship between the risk of CHD and *H. pylori* infection by using different *H. pylori* detection methods.

**Anti-*Helicobacter pylori* IgG Test and Coronary Heart Disease**

A meta-analysis of 38 studies, of which 2 studies used HR and 36 studies used OR, indicated a statistically significant
TABLE 1 | Description of included studies.

| References          | CHD type | Country     | Setting         | Sample size<sup>a</sup> | Study design | Agent | Adjustment state | Quality score |
|---------------------|----------|-------------|-----------------|--------------------------|--------------|-------|------------------|---------------|
| Patel et al. (20)   | CHD      | United Kingdom | Community       | 26/341                   | CS           | 1     | N                | 8             |
| Whincup et al. (21) | MI       | United Kingdom | Community       | 135/136                  | PS           | 1     | Y                | 7             |
| Rathbone et al. (22) | AMI     | United Kingdom | Hospital        | 342/236                  | CS           | 1     | Y                | 7             |
| Folsom et al. (23)  | CHD      | United States | Community       | 217/498                  | PS           | 1     | Y                | 8             |
| Pellegrino et al. (24) | AMI    | Italy        | Hospital        | 44/310                   | CS           | 1     | N                | 6             |
| Danesh et al. (25)  | MI       | United Kingdom | Community       | 1,122/1,122              | CS           | 1     | Y                | 7             |
| Galante et al. (26) | MI       | Italy        | Hospital        | 63/81                    | CS           | 1     | N                | 6             |
| Kahan et al. (27)   | AMI      | Sweden       | Hospital        | 100/100                  | CS           | 1     | Y                | 6             |
| Gunn et al. (28)    | AMI      | United Kingdom | Hospital        | 342/214                  | CS           | 1     | N                | 7             |
| Ricker et al. (29)  | MI       | United States | Community       | 445/445                  | PS           | 1     | N                | 7             |
| Kinjo et al. (30)   | AMI      | Japan        | Hospital        | 618/967                  | CS           | 1     | Y                | 7             |
| Fraser et al. (31)  | MI       | New Zealand  | Community       | 341/831                  | CS           | 1     | Y                | 6             |
| Ozdogru et al. (32) | MI       | Turkey       | Hospital        | 353/163                  | CS           | 1     | N                | 5             |
| Nikolopoulou et al. (33) | AMI | Greece      | Hospital        | 138/49                   | CS           | 1     | N                | 6             |
| Jafarzadeh et al. (34) | CHD | Iran        | Hospital        | 120/60                   | CS           | 1, 2  | N                | 6             |
| Guan et al. (35)    | AMI      | China        | Community       | 150/102                  | CS           | 1     | N                | 5             |
| Nakić et al. (36)   | AMI      | Croatia      | Hospital        | 93/100                   | PS           | 1     | N                | 6             |
| Khodai et al. (37)  | AMI      | Iran         | Hospital        | 500/500                  | CS           | 1, 2  | N                | 5             |
| Padmavati et al. (38) | CHD    | India       | Hospital        | 108/100                  | CS           | 1     | N                | 6             |
| Schöttker et al. (39) | MI    | Germany     | Community       | 8,482/154                | PS           | 1, 2  | Y                | 7             |
| Ikeda et al. (40)   | MI       | Japan        | Community       | 106/212                  | PS           | 1, 2  | N                | 8             |
| Sunanda et al. (41) | AMI      | India        | Community       | 261/261                  | CS           | 1     | N                | 6             |
| Witherell et al. (42) | MI    | United States | Community       | 121/201                  | PS           | 1     | N                | 6             |
| Singh et al. (43)   | CHD      | United Kingdom | Hospital        | 201/414                  | PS           | 2     | Y                | 7             |
| Ossewaarde et al. (44) | CHD | Netherlands | Community       | 54/108                   | PS           | 1     | N                | 6             |
| Whincup et al. (45) | CHD      | United Kingdom | Community       | 505/1,025                | PS           | 1, 2  | Y                | 7             |
| Wald et al. (46)    | CHD      | United Kingdom | Community       | 648/1,296                | PS           | 1     | N                | 8             |
| Stone et al. (47)   | CHD      | United Kingdom | Community       | 172/205                  | PS           | 1, 2  | N                | 8             |
| Danesh et al. (48)  | CHD      | United Kingdom | Community       | 288/704                  | CS           | 1     | Y                | 7             |
| Azarkar et al. (49) | MI       | Iran         | Hospital        | 73/78                    | CS           | 1     | N                | 6             |
| Khurshid et al. (50) | CHD    | United States | Hospital        | 58/121                   | CS           | 1     | Y                | 7             |
| Pascrei et al. (51) | IHD      | Iran         | Hospital        | 88/88                    | CS           | 1, 2  | Y                | 8             |
| Bonaventura et al. (52) | IHD | Iran        | Hospital        | 58/52                    | CS           | 2     | N                | 6             |
| Lenz et al. (53)    | CHD      | Italy        | Hospital        | 80/160                   | CS           | 2     | N                | 5             |
| Zodpey et al. (54)  | AMI      | India        | Hospital        | 265/265                  | CS           | 1     | Y                | 6             |
| Aceti et al. (55)   | CHD      | Italy        | Hospital        | 40/40                    | CS           | 2, 3  | N                | 7             |
| Tsai and Huang (56) | CHD      | China        | Hospital        | 165/127                  | CS           | 1     | Y                | 5             |
| Jin et al. (57)     | CHD      | South Korea  | Hospital        | 175/88                   | PS           | 3     | N                | 6             |
| Miyazaki et al. (58) | ACS  | Japan        | Hospital        | 33/66                    | CS           | 1, 2  | Y                | 7             |
| Adiloglu et al. (59) | CHD   | Turkey       | Hospital        | 38/12                    | CS           | 4     | N                | 5             |
| Adiloglu et al. (60) | CHD   | Turkey       | Hospital        | 88/91                    | CS           | 1, 2  | N                | 6             |
| Lee et al. (61)     | CHD      | South Korea  | Hospital        | 54/40                    | CS           | 4     | N                | 6             |
| Lin et al. (62)     | CHD      | Japan        | Community       | 627/827                  | CS           | 1     | Y                | 7             |
| Bai and Hashmi (63) | AMI      | Pakistan     | Hospital        | 109/109                  | CS           | 1     | N                | 7             |

CHD, coronary heart disease; ACS, acute coronary syndrome; AMI, acute myocardial infarction; IHD, ischemic heart disease; MI, myocardial infarction; CS, cross-sectional study; PS, prospective study; Y, adjusted articles; N, unadjusted articles.

<sup>a</sup>No. of participants with CHD/No. of participants without CHD.

1, detection of H. pylori IgG by ELISA or chemiluminescence; 2, H. pylori CagA positive strains by immunoenzymatic method; 3, H. pylori stool antigen by enzyme immunoassay; 4, H. pylori histological staining by Warthin–Starry silver stain.

Diagnosis of CHD, IHD, ACS, AMI and MI by medical history, symptoms, signs, ECG, cardiac ultrasound and coronary angiography, etc.
relationship between the risk of CHD and positive anti-\textit{H. pylori} IgG (OR, 1.58; 95% CI: 1.34–1.87; Figure 2). In addition, the meta-analysis of studies reporting OR also showed a statistically significant relationship (OR, 1.65; 95% CI: 1.39–1.95; Figure 3). However, the meta-analysis of studies reporting HR showed a statistically non-significant relationship (HR 0.74; 95% CI: 0.52–1.06; Figure 4). Subgroup analyses based on study design, setting, adjustment, quality assessment score, the category of CHD, and country are presented in Table 2. A leave-one-out sensitivity analysis showed robust results, and none of the studies had a significant impact on the pooled results.

**Anti-CagA Test and Coronary Heart Disease**

Our analysis of 13 studies showed a significant correlation between the risk of CHD and positive anti-CagA (OR, 1.33; 95% CI: 1.16–1.53; Figure 5). One study was reported using an adjusted result. Subgroup analyses based on study design, setting, adjustment, quality assessment score, the category of CHD, and country are presented in Table 3. A leave-one-out sensitivity analysis also indicated that the results were robust, and none of the studies had a significant influence on the overall results.

**\textit{Helicobacter pylori} Stool Antigen Test and Coronary Heart Disease**

We observed a statistically significant association between positive \textit{H. pylori} stool antigen and the development of CHD (OR, 3.50; 95% CI: 1.60–7.66; Figure 6). Because of the lack of data, subgroup meta-analyses and sensitivity analysis could not be conducted for \textit{H. pylori} stool antigen.

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**FIGURE 2** | Relationship anti-\textit{H. pylori} IgG test and coronary heart disease [CHD; studies reporting OR + studies reporting hazard ratio (HR)].
Helicobacter pylori Histological Staining Test and Coronary Heart Disease

We also observed that positive H. pylori histological staining was significantly associated with the risk of CHD (OR, 1.78; 95% CI: 1.12–2.83; Figure 7). Due to limited data, subgroup meta-analyses and sensitivity analysis of H. pylori histological staining also could not be performed.

DISCUSSION

Over the past 30 years, there has been controversy in the literature about the impact of H. pylori infection on the risk of CHD. Therefore, we conducted this updated meta-analysis based on all available studies in order to establish a more comprehensive and stronger analysis. The final results of our meta-analysis showed...
TABLE 2 | Subgroup analyses about between anti-\(H.\) pylori IgG and CHD.

| Category of subgroups | Subgroups | Number of studies | OR   | 95% CI         | \(I^2\) | \(P\)-value |
|-----------------------|-----------|------------------|------|----------------|--------|------------|
| Study design          | PS        | 11               | 1.21 | 0.96–1.53      | 67     | 0.12       |
|                       | CS        | 27               | 1.78 | 1.45–2.18      | 77     | <0.0001    |
| Setting               | Hospital  | 21               | 1.79 | 1.38–2.32      | 77     | <0.0001    |
|                       | Community | 17               | 1.39 | 1.12–1.72      | 77     | 0.002      |
| Adjustment state      | Adjusted  | 16               | 1.31 | 1.05–1.62      | 72     | 0.02       |
|                       | Not adjusted | 22           | 1.86 | 1.45–2.39      | 81     | <0.00001   |
| Quality assessment    | ≥7        | 19               | 1.33 | 1.09–1.63      | 74     | 0.006      |
|                       | <7        | 19               | 1.88 | 1.47–2.42      | 75     | <0.00001   |
| Category of CHD       | MI        | 10               | 1.24 | 0.96–1.62      | 75     | 0.01       |
|                       | AMI       | 12               | 2.06 | 1.56–2.71      | 78     | <0.00001   |
|                       | ACS       | 1                | 4.09 | 1.10–15.21     | –      | 0.04       |
|                       | CHD       | 13               | 1.41 | 1.02–1.93      | 79     | 0.03       |
|                       | IHD       | 2                | 1.98 | 1.16–3.39      | 35     | 0.01       |
| Country               | United Kingdom | 9              | 1.34 | 1.11–1.62      | 60     | 0.003      |
|                       | United States | 4              | 0.99 | 0.79–1.25      | 48     | 0.96       |
|                       | Iran      | 5                | 2.68 | 2.12–3.39      | 42     | <0.00001   |
|                       | India     | 3                | 2.15 | 1.35–3.43      | 68     | 0.001      |
|                       | Japan     | 4                | 1.49 | 0.72–3.09      | 76     | 0.28       |
|                       | China     | 2                | 1.04 | 0.33–3.28      | 83     | 0.94       |
|                       | Turkey    | 2                | 0.85 | 0.52–1.39      | 31     | 0.52       |
|                       | Italy     | 2                | 1.76 | 1.04–2.98      | 0      | 0.03       |
|                       | New Zealand | 1              | 1.34 | 1.00–1.80      | –      | 0.05       |
|                       | Netherlands | 1              | 5.50 | 2.70–11.20     | –      | <0.00001   |
|                       | Sweden    | 1                | 1.35 | 1.01–1.80      | –      | 0.04       |
|                       | Germany   | 1                | 0.70 | 0.46–1.07      | –      | 0.10       |
|                       | Croatia   | 1                | 1.17 | 0.62–2.21      | –      | 0.63       |
|                       | Greece    | 1                | 4.25 | 1.97–9.17      | –      | 0.0002     |
|                       | Pakistan  | 1                | 4.32 | 2.42–7.70      | –      | <0.00001   |

CHD, coronary heart disease; ACS, acute coronary syndrome; AMI, acute myocardial infarction; IHD, ischemic heart disease; MI, myocardial infarction; CS, cross-sectional study; PS, prospective study.

FIGURE 5 | Relationship anti-CagA test and CHD.

that the positive anti-\(H.\) pylori IgG was closely related to the risk of CHD. In addition, this relation was also significant in analysis of positive anti-CagA, positive \(H.\) pylori stool antigen, and positive \(H.\) pylori histological staining.

Earlier studies showed that there may be a weak association between \(H.\) pylori infection and the risk of CHD (64, 65). Currently, our results are similar to those of recent meta-analyses (4, 15, 66–68) in which positive anti-\(H.\) pylori IgG was
TABLE 3 | Subgroup analyses about between anti-CagA test and CHD.

| Category of subgroups | Subgroups | Number of studies | OR  | 95% CI        | P  | P-value |
|-----------------------|-----------|------------------|-----|---------------|----|---------|
| Study design          | PS        | 5                | 1.16| 0.96–1.40     | 57 | 0.13    |
|                       | CS        | 8                | 1.56| 1.27–1.91     | 55 | <0.0001 |
| Setting               | Hospital  | 10               | 1.47| 1.25–1.73     | 49 | <0.0001 |
|                       | Community | 3                | 1.02| 0.78–1.33     | 67 | 0.88    |
| Adjustment            | Adjusted  | 6                | 1.35| 1.12–1.62     | 75 | 0.002   |
|                       | Not adjusted | 7        | 1.31| 1.06–1.62     | 33 | 0.01    |
| Quality assessment    | ≥7        | 9                | 1.31| 1.11–1.54     | 9  | 0.001   |
|                       | <7        | 4                | 1.40| 1.07–1.84     | 4  | 0.01    |
| Category of CHD       | MI        | 2                | 0.92| 0.65–1.31     | 2  | 0.64    |
|                       | AMI       | 2                | 0    | 1.18–1.96     | 2  | 0.001   |
|                       | ACS       | 1                | 3.58| 1.04–11.87    | NG | 0.04    |
|                       | CHD       | 8                | 1.34| 1.10–1.63     | 54 | 0.003   |
| Country               | United Kingdom | 4    | 1.31| 1.08–1.58     | 0  | 0.007   |
|                       | Italy     | 2                | 2.53| 1.31–4.86     | 0  | 0.005   |
|                       | Iran      | 4                | 1.47| 1.12–1.93     | 72 | 0.006   |
|                       | Japan     | 2                | 2.02| 1.15–3.55     | 11 | 0.01    |
|                       | Germany   | 1                | 0.70| 0.46–1.07     | NG | 0.10    |

CHD, coronary heart disease; ACS, acute coronary syndrome; AMI, acute myocardial infarction; IHD, ischemic heart disease; MI, myocardial infarction; CS, cross-sectional study; PS, prospective study.

positively related to the risk of CHD. However, our study avoided the main limitations of these meta-analyses. For example, the meta-analyses performed by Wang et al. (4), Liu et al. (66), and Rahmani et al. (67) only involved myocardial infarction and did not mention other types of CHD. A meta-analysis (67) conducted in 2017 showed that H. pylori infection was associated with an increased risk of CHD, but the meta-analysis was based on Iranians and the number of studies was limited. In addition, a meta-analysis by Sun et al. (15), published in 2016, was based only on prospective studies, excluding cross-sectional studies with stronger evidence. Therefore, the sample size of the included studies was small, which makes the results more prone to confounding factors and selection bias. Similarly, our results are consistent with a previous meta-analysis that indicated a significant association between positive anti-CagA and the risk of CHD. However, our meta-analysis avoided many defects of previous studies (68, 69). For instance, a meta-analysis conducted by Zhang et al. (68) was based only on cross-sectional studies, excluding more meaningful prospective studies. A meta-analysis (69), published in 2006, had a limited number of studies included and had no subgroup analysis for finding the source of heterogeneity. In addition, we also found that positive H. pylori stool antigen and positive H. pylori histological staining were significantly associated with the risk of CHD. Subgroup analysis and sensitivity analysis were not performed due to the small number of studies.
The mechanism of *H. pylori* infection causing CHD mainly consists of the following aspects. *H. pylori* in atherosclerotic plaque can stimulate inflammatory cells and cause excessive production of cytokines, which leads to local endothelial and vascular dysfunction (30). *H. pylori* infection leads to non-specific stimulation of inflammatory mediators *in vivo*, such as interleukin-1 (IL-1), interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-α), which promote plaque instability (70). Lastly, it can not only enter endothelial cells through CagA containing exosomes, resulting in endothelial damage (71) but also secrete another virulence factor, vacuolating cytotoxin A (VacA), which can reduce nitric oxide (NO), resulting in endothelial function damage (72).

The expression of P-selectin increases after *H. pylori* infection, and the adhesion between von Willebrand factor (vWF) released by platelets and P-selectin eventually leads to platelet aggregation (73). In addition to this, *H. pylori* infection can affect the risk factors for CHD, such as hypertension, dyslipidemia, hyperhomocysteinemia, diabetes, and impaired glucose tolerance. A recent meta-analysis (74) showed that *H. pylori* infection was significantly associated with arterial hypertension. Aslan et al. (75) found that the levels of total cholesterol, triglyceride, and low-density lipoprotein cholesterol in patients infected with *H. pylori* increased significantly, while high-density lipoprotein cholesterol decreased significantly. The interaction between *H. pylori* infection and diabetes leads to the occurrence of CHD (76). After persistent infection with *H. pylori*, low levels of serum vitamin B12 and folic acid will lead to hyperhomocysteinemia (77).

From our perspective, our meta-analysis is by far the most comprehensive and largest study supported by its statistical ability, leading to a more reliable overall evaluation. Our meta-analysis proved the positive relationship between positive anti-*H. pylori* IgG and development of CHD by subgroup analyses based on setting, category of CHD, adjustment status, and quality assessment score, but this relationship did not appear in prospective studies and some countries. Similarly, we also observed a positive association between the positive anti-CagA and the risk of CHD based on subgroup analyses of adjustment status and quality assessment score, but this association did not exist in prospective studies, community, MI, and Germany. Our results are similar to a previous meta-analysis (15) based on prospective studies, which indicated that *H. pylori* infection increased CHD risk, but this relationship weakens over time. The development of CHD is a multi-effect, long-term process. Over time, other CHD risk factors may attenuate the risk of CHD from the infection. Reasons for other subgroups without *H. pylori* infection increasing the risk of CHD might be associated with fewer studies. In addition, except for the fixed model for studies on anti-*H. pylori* IgG studies reporting HR, *H. pylori* stool antigen, and *H. pylori* histological staining, there is substantial heterogeneity among other studies, which may be attributed to the different participants and different study designs. Hence, the random model is adopted.

### Strengths and Limitations

This is the first attempt to use a meta-analysis to evaluate the relationship between the risk of CHD and *H. pylori* infection through different *H. pylori* detection methods. Most previous meta-analyses used the anti-*H. pylori* IgG test to detect bacterial infection. In fact, this approach fails to detect current infections and may overestimate the association between bacteria and the risk of CHD. However, *H. pylori* stool antigen and *H. pylori* histological staining tests can detect current infection, which accurately assess the relationship between bacteria and the risk of CHD. Since positive anti-CagA has a strong inflammatory response, we also analyzed its association with the risk of CHD. More importantly, the included studies did not adequately consider traditional risk factors for CHD and other microbial infections. In the future, we strongly recommend conducting more well-designed intervention trials and investigating the relationship between other sources of infection and the risk of CHD.

### CONCLUSION

This meta-analysis revealed an evidence-based relationship between *H. pylori* infection and the risk of CHD, which may contribute to the arguments established in the literature to provide strong evidence. Therefore, we suggest that *H. pylori* infection should be regarded as a new risk factor for CHD in future guidelines related to CHD. Future clinical application needs to be further studied to determine whether early eradication of *H. pylori* can reduce the incidence of CHD.

### DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

### AUTHOR CONTRIBUTIONS

X-JD and LT designed and analyzed the meta-analysis, and contributed to the revision of the manuscript. X-JD, LT, B-BW, F-HL, S-PL, and F-FP collected the data. All authors have read and approved the manuscript.

### REFERENCES

1. Kotilea K, Bontems P, Touat E. Epidemiology, diagnosis and risk factors of *Helicobacter pylori* infection. *Adv Exp Med Biol.* (2019) 1149:17–33. doi: 10.1007/58584_2019_357
2. Watari J, Chen N, Amenta PS, Fukui H, Oshima T, Tomita T, et al. *Helicobacter pylori* associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. *World J Gastroenterol.* (2014) 20:5461–73. doi: 10.3748/wjg.v20.i18.5461
3. Holleczek B, Schöttker B, Brenner H. *Helicobacter pylori* infection, chronic atrophic gastritis and risk of stomach and esophagus cancer: results from the prospective population-based ESTHER cohort study. *Int J Cancer.* (2020) 146:2773–83. doi: 10.1002/ijc.32610
13. Rothenbacher D, Brenner H, Hoffmeister A, Mertens T, Persson K, Koenig W.

18. DerSimonian R, Laird N. Meta-analysis in clinical trials.

16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis of 273,135 patients.

22. Rathbone B, Martin D, Stephens J, Thompson JR, Samani NJ.

5. Doheim MF, Altaweel AA, Elgendy MG, Elshanbary AA, Dibas M, Hegil Abo Ali AA, et al. Association between Helicobacter pylori and Cytomagalovirus infections and the risk of peripheral arterial disease in young women. Atherosclerosis. (2002) 163:149–56. doi:10.1016/s0022-5108(01)00761-4

8. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AJ, et al. Association of Helicobacter pylori infection with cardiovascular disease.

H. pylori

13. H. pylori infection and risk of atherosclerotic cardiovascular disease. Helicobacter. (2020) 25:e12761. doi:10.1111/hel.12761

16. H. pylori infection and early onset myocardial infarction: case-control and sibling pairs study. BMJ. (1999) 319:1157–62. doi:10.1136/bmj.319.7128.1157

25. Danesh J, Youngman L, Clark S, Parish S, Peto R, Collins R. Helicobacter pylori infection and early onset myocardial infarction: case-control and sibling pairs study. BMJ. (1999) 319:1157–62. doi:10.1136/bmj.319.7128.1157

26. Galante A, Pietrouisti A, Carta S, Franceschelli L, Piccolo P, Mastino A, et al. Infection with Helicobacter pylori and leucocyte response in patients with myocardial infarction. Eur J Clin Microbiol Infect Dis. (2000) 19:298–300. doi:10.1007/s100960050479

27. Kahan T, Lundman P, Olsson G, Wendt M. Greater than normal prevalence of seropositivity for Helicobacter pylori among patients who have suffered myocardial infarction. Coron Artery Dis. (2000) 11:523–6. doi:10.1097/00001950-200010000-00002

28. Gunn M, Stephens JS, Thompson JR, Rathbone BJ, Samani NJ. Significant association of cagA positive Helicobacter pylori strains with risk of premature myocardial infarction. Heart. (2000) 84:267–71. doi:10.1136/heart.84.3.267

29. Rudker PM, Danesh J, Youngman L, Collins R, Stämpfer MJ, Peto R, et al. A prospective study of Helicobacter pylori seropositivity and the risk for future myocardial infarction among socioeconomically similar U.S. men. Ann Intern Med. (2001) 135:184–8. doi:10.7326/0003-4819-135-3-200108070-00010

33. Kinjo K, Sato H, Sato H, Shiotani I, Kurotobi T, Ohnishi Y, et al. Prevalence of Helicobacter pylori infection and its link to coronary risk factors in Japanese patients with acute myocardial infarction. Circ J. (2002) 66:805–10. doi:10.1253/circj.66.805

30. Nakić D, Vcev A, Jović A, Patrk J, Zekanović D, Klarin I, et al. Association of Helicobacter pylori infection with acute myocardial infarction. Helicobacter. (2007) 36:199–212. doi:10.1111/j.1071-0744.2007.000757

31. Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, Fleming C, et al. Meta-analysis for the primary care clinician: a guide for clinicians. Ann Intern Med. (1998) 128:184–9. doi:10.7326/0003-4819-128-2-199801130-00010

32. Jafarzadeh A, Esmaeili-Nadimi A, Nemati M, Tahmasbi M, Ahmadi P. Serum concentrations of Helicobacter pylori IgG and the virulence factor CagA in patients with ischaemic heart disease. East Mediterr Health J. (2010) 16:1039–44. doi:10.26719/2010.16.10.1039

33. Guan XR, Jiang LX, Ma XH, Wang LF, Quan H, Li HY. Respiratory syncytial virus infection and risk of acute myocardial infarction. Am J Med Sci. (2010) 340:356–9. doi:10.1097/MAJ.0b013e3181eecf29

34. Nakić D, Vicz N, Jovčić A, Patrk J, Zekanović D, Klarin I, et al. Helicobacter pylori infection and acute myocardial infarction. Coll Antropol. (2011) 35:781–5.

35. Khodaei Z, Vakili H, Ghaderian SMH, Najar RA, Panah AS. Association of Helicobacter pylori infection with acute myocardial infarction. Coron Artery Dis. (2011) 22:6–11. doi:10.1097/MCA.0b013e3283402360

36. Padmavathi S, Gupta U, Agarwal HK. Chronic infections & coronary artery disease with special reference to Chlamydia pneumoniae. Indian J Med Res. (2012) 135:228–32.

37. Schöttker B, Adamu MA, Weck MN, Müller H, Brenner H. Helicobacter pylori infection, chronic atrophic gastritis and major cardiovascular events: a population-based cohort study. Atherosclerosis. (2012) 220:569–74. doi:10.1016/j.atherosclerosis.2011.11.029

38. Ikeda A, Iso H, Sasazuki S, Inoue M, Tsugane S, Jphc Study Group. Association of Helicobacter pylori infection and acute myocardial infarction. Coron Artery Dis. (2011) 22:6–11. doi:10.1097/MCA.0b013e3283402360

39. Sunanda N, Shrikhande, Zodepy SP, Negandhi H. A case-control study examining association between infectious agents and acute myocardial infarction. Indian J Public Health. (2014) 58:106–9. doi:10.4103/0019-557X.13285

40. Witherell HL, Smith KL, Friedman GD, Ley C, Thom DH, Orentreich N, et al. C-reactive protein, Helicobacter pylori, Chlamydia pneumoniae, cytomegalovirus and risk for myocardial infarction. Ann Epidemiol. (2003) 13:170–7. 00276-4 doi:10.1016/s1047-2797(02)
43. Singh PK, McMahon AD, Patel H, Packard CJ, Rathbone BJ, Saman NJ. Prospective analysis of the association of infection with CagA bearing strains of Helicobacter pylori and coronary heart disease. Heart. (2002) 88:43–6. doi: 10.1136/heart.88.1.43
44. Ossewaarde JM, Festken EL, Vries AD, Vallinga CE, Kromhout D. Chlamydia pneumoniae is a risk factor for coronary heart disease in symptom-free elderly men, but Helicobacter pylori and cytomegalovirus are not epidemiology and infection. Epidemiol Infect. (1998) 120:93–9. doi: 10.1017/S0954422498003830
45. Whincup P, Danesh J, Walker M, Lennon I, Thomson A, Appleby P, et al. Prospective study of potentially virulent strains of Helicobacter pylori and coronary heart disease in middle-aged men. Circulation. (2000) 101:1647–52. doi: 10.1161/01.cir.101.14.1647
46. Wald NJ, Law MR, Morris JK, Bagnall AM. Helicobacter pylori infection and mortality from ischaemic heart disease: negative result from a large, prospective study. BMJ. (1997) 315:1199–201. doi: 10.1136/bmj.315.7117.1199
47. Stone AF, Risley P, Markus HS, Butland BK, Strachan DP, Elwood PC, et al. Helicobacter pylori infection and myocardial infarction. Caspian J Intern Med. (2011) 2:222–5.
48. Khurshid A, Fenske T, Bajwa T, Bourgeois K, Vakil N. A prospective, controlled study of Helicobacter pylori and systemic arterial hypertension: a meta-analysis. Ethio J Health Sci. (2017) 27:433–40. doi: 10.4314/ejhs.v27i4.15
49. Azarkar Z, Jafarnejad M, Sharifzadeh G. The relationship between Helicobacter pylori infection and ischemic heart disease. BMJ. (2011) 343:3184. doi: 10.1136/bmj.d1875
50. Fang ZM, Chen Y, Yao YS. Association between Helicobacter pylori infection and acute myocardial infarction in Chinese population. Adv Biomed Res. (2015) 27:433–40. doi: 10.4314/abr.j_2015.04.011
51. Xia XJ, Zhang LF, Li H, Liu XM, Hu TZ, et al. Helicobacter pylori infection impairs endothelial function through an exosome-mediated mechanism. J Am Heart Assoc. (2020) 9:e014120. doi: 10.1161/JAHA.119.014120
52. Tobin NP, Henehan GT, Murphy RP, Atherton JC, Guinan AF, Kerrigan SW, et al. Helicobacter pylori-induced inhibition of vascular endothelial cell functions: a role for VacA-dependent nitric oxide reduction. Am J Physiol Heart Circ Physiol. (2008) 295:H1403–13. doi: 10.1152/ajpheart.00240.2008
53. Xia XJ, Zhang LF, Chi JS, Li H, Liu XM, Hu TZ, et al. Helicobacter pylori infection increases the risk of acute myocardial infarction. Blood. (2010) 115:2427–3. doi: 10.1182/blood-2009-04-214616
54. Huang MY, Zhu L, Jin YL, Fang ZM, Chen Y, Yao YS. Association between Helicobacter pylori infection and systemic arterial hypertension: a meta-analysis. Arq Bras Cardiol. (2021) 117:626–36. doi: 10.36600/abcc.20200186
55. Aslan M, Nazligul Y, Horoz M, Bolubas C, Bolubas FF, Gur M, et al. Serum paraoxonase-1 activity in Helicobacter pylori infected subjects. Atherosclerosis. (2008) 196:270–4. doi: 10.1016/j.atherosclerosis.2008.03.014
56. Nodoubesh S, Nabavi A. The interaction of Helicobacter pylori infection and type 2 diabetes mellitus. Adv Biomed Res. (2019) 8:15. doi: 10.4103/abr.abr_.37_18
57. Chen YH, Xu CL, Xu HF, Chen WL, Wang HH, Wang ZT, et al. Persistent Helicobacter pylori infection for more than 3 years leads to elevated serum homocysteine concentration: a retrospective cohort study based on a healthy Chinese population. J Gastroenterol Hepatol. (2021) 36:3077–83. doi: 10.1111/jgh.15603

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