Association between *H. pylori* infection and health Outcomes: an umbrella review of systematic reviews and meta-analyses

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ABSTRACT

Objective Systematic reviews and meta-analyses have revealed the associations between *H. pylori* infection and various health outcomes. We aimed to evaluate the strength and breadth of evidence on the associations.

Design Umbrella review of systematic reviews and meta-analyses.

Setting No settings.

Participants No patients involved.

Data sources Embase, PubMed, Web of Science, Cochrane Library Databases, CNKI, VIP database and Wangfang database from inception to February 1, 2019.

Outcomes measures Diverse diseases (such as cancer and ischaemic heart disease).

Results Sixty articles reporting 88 unique outcomes met the eligibility criteria. 74 unique outcomes had nominal significance (p<0.05). Of the outcomes with significance, 61 had harmful associations and 13 had beneficial associations. Furthermore, 73% (64) of the outcomes exhibited significant heterogeneity. Of the these meta-analyses, 32 had moderate to high heterogeneity (I²=50%–75%) and 24 had high heterogeneity (I²>75%). Moreover, 20% exhibited publication bias (p<0.1). In addition, 97% of the methodological qualities were rated ‘critically low’. 36% of the evidence qualities of outcomes were rated ‘low’, 56% of the evidence qualities were rated ‘very low’ and 8% of the evidence qualities were rated ‘moderate’. *H. pylori* infection may be associated with an increased risk of five diseases and a decreased risk of irritable bowel syndrome.

Conclusion Although 60 meta-analyses explored 88 unique outcomes, moderate quality evidence only existed for six outcomes with statistical significance. *H. pylori* infection may be associated with a decreased risk of irritable bowel syndrome and an increased risk of hypertiglyceridemia, chronic cholecystitis and cholelithiasis, gestational diabetes mellitus, gastric cancer and systemic sclerosis.

Trial registration CRD42019124680.

INTRODUCTION

*H. pylori* is a Gram-negative bacterium that affects human health worldwide, and its prevalence ranges from 50.8% to 84%.1–4 Earlier studies demonstrated that *H. pylori* infection contributes to the development of several digestive diseases (e.g. gastric cancer,5, 6 peptic ulcer disease (PUD)7 and dyspepsia).8 These conclusions were supported by recent studies.9–12 Over the last 20 years, the associations between *H. pylori* infection and a sequence of non-digestive disorders have been investigated extensively. Multiple studies and meta-analyses have revealed that *H. pylori* infection is harmful to human health by increasing the risk of diverse diseases, including cancers, cardiovascular and cerebrovascular diseases, respiratory disorders, endocrine diseases and neurocognitive disorders. Meta-analyses have further reported that *H. pylori* infection increases the risk of acquiring hepatocellular carcinoma (HCC) by more than 16-fold,13 cholangiocarcinoma by approximately 9-fold and myocardial infarction (MI) nearly 2-fold.15 Subsequently, with further research on *H. pylori* infection, it may be beneficial to health

Strengths and limitations of this study

- This umbrella review is the first synthesis of systematic reviews and meta-analyses to consider the associations between *H. pylori* infection and various health outcomes.
- These results provide recommendations about the relationships between *H. pylori* infection and various health outcomes.
- The associations observed in the meta-analyses included in this umbrella review may reflect the uncertainty of most diseases related to *H. pylori* infection.
- Only evidence derived from systematic reviews and meta-analyses was included in our umbrella review. Evidence from original observational studies and/or randomised controlled trials that were not included in the meta-analyses was beyond our scope of discussion. This condition might result in conclusion bias of association between *H. pylori* infection and human health.
in some conditions by decreasing the risk of diseases (e.g., asthma, inflammatory bowel disease and oesophageal cancer). Therefore, the causal role of *H. pylori* infection in these diseases has been widely queried.

The observed associations between *H. pylori* infection and health outcomes can be causal, indicating that *H. pylori* infection elicits adverse effects on human health. However, the publication bias, scheme design defects or inconsistencies of studies can lead to a decrease in the strength and validity of evidence. Furthermore, confounding factors, such as age, sex, smoking or drinking status, can affect causality. The lack of adequate controls for confounders may cause reverse causality. Therefore, evidence from meta-analyses may also have uncertainty. If causal, the association of *H. pylori* infection and public health should be reconsidered, and the role of *H. pylori* infection in human health must be reanalyzed.

Once strong associations between *H. pylori* infection and diseases are confirmed, findings provide an important guidance both for conducting disease diagnosis and treatment. Therefore, the associations of *H. pylori* infection and health outcomes must be further evaluated.

To provide an overview of the length, validity and credibility of the evidence on the associations between *H. pylori* infection and human health outcomes, we systematically and comprehensively re-evaluated these pieces of evidence to make them concise for decision-makers and guideline developers. We conducted an umbrella review to estimate the findings and content of meta-analyses that investigated these associations and to estimate the evidence of potential bias and consistency of findings.

**METHODS**

**Literature search**

Computerised searches on Embase, PubMed, Web of Science, Cochrane Database of Systematic Reviews, CNKI, VIP database and Wangfang database were independently and comprehensively performed by two researchers (Guangwen Chen and Mingbing Chen) to identify the systematic reviews and meta-analyses of epidemiological studies investigating the associations between *H. pylori* infection and diverse health outcomes. Studies published from inception to February 1, 2019 were collected using a comprehensive search strategy, and the language was limited to English and Chinese. Medical subject heading (MeSH) terms and free-text words were used: meta-analysis, meta analysis, meta-analyses, meta analyses, systematic review, *Helicobacter pylori*, *Campylobacter pylori*, Pylorus spirillum and *H. pylori*. The search strategies are described in online supplementary appendix 1. References from eligible systematic reviews were also manually reviewed. All identified publications were managed with EndNote X7. Two reviewers (Qingzeng Song and Jieru Xie) independently screened the titles, abstracts and full texts for eligible articles based on the inclusion and exclusion criteria. Any discrepancy was resolved by discussion, and all discrepancies that could not be resolved through a discussion were arbitrated by Sheng Xie.

**Eligibility criteria and exclusion criteria**

Only systematic reviews and meta-analyses of epidemiological studies investigating the associations between *H. pylori* and multiple diseases were included in this umbrella review. The included systematic reviews and meta-analyses should present the data of pooled summary effects (i.e. relative risks (RRs), odds ratios (ORs), mean difference (MD), standard mean difference (SMD) and their 95% confidence intervals (CIs)), number of included studies, number of cases and participants, publication bias and heterogeneity. Table data (2×2) should be presented if pooled summary effects were unavailable. The population included was not limited to age, sex, ethnicity or country of origin. Articles were not limited to clinical setting, study region or research institution. When more than one meta-analyses were performed for the same review question, the concordance of the main conclusions was checked. If conclusions were inconsistent, the meta-analysis with the largest sample size and the latest date of publication was selected. The meta-analyses of interventional trials and diagnostic trials were unavailable for our research question. Conference abstracts on review questions were also excluded.

**Patient and public involvement**

Our study is a review of literature, so no patient was involved.

**Data extraction**

Data from each eligible systematic review and meta-analysis were independently extracted by two investigators (Liqun Li and Jinjing Tan). All of the results were carefully checked by a third investigator (Xiaoyan Huang). Any discrepancy was resolved by discussion, and all discrepancies were arbitrated by a fourth reviewer (Sheng Xie). The name of the first author, the year of publication, outcomes examined, the number of included studies, the total numbers of participants and cases, study design, study region and detection method of *H. pylori* were extracted by using a predesigned data extraction form. For each eligible systematic review and meta-analysis, the reported relative summary risk estimates (RRs, ORs, SMD or MD) and their 95% CIs were extracted. The *p* values of the overall pooled effects, Egger’s test and Cochran Q test were extracted. The results of I² were also extracted. However, if the eligible systematic reviews or meta-analyses did not assess the quality of the included studies, assessing the quality was beyond our task in this umbrella review. If systematic reviews or meta-analyses examined more than one health outcome of interest, each outcome was recorded separately. If the included meta-analyses did not present the results of pooled meta-analysis (RRs, ORs, SMD or MD), I², Egger’s test or publication bias, the 2×2 table data from studies included in those meta-analyses were extracted for reanalysis.
Assessment of methodological quality

The methodological quality of the included studies was independently assessed by two investigators (Liqun Li and Jianfeng Li) using AMSTAR 2 (A Measurement Tool to Assess systematic Reviews), and the results were checked by a third investigator (Xiaoyan Huang). Inconsistencies were resolved through a discussion or consultation with a fourth reviewer (Sheng Xie). AMSTAR 2 is a reliable, valid and critical assessment tool developed from AMSTAR in 2017. It contains 16 checklists (7 critical checklists and 9 non-critical checklists) for assessing systematic reviews and meta-analyses, including randomised controlled trial (RCT) studies, observational studies on exposures or both. The rating criteria of AMSTAR 2 were as follows: zero or one non-critical weakness was defined as high quality; more than one non-critical weakness was defined as moderate quality; one critical flaw with or without non-critical weaknesses was defined as low quality; and more than one critical flaw with or without non-critical weaknesses was defined as critically low quality.

Assessment of the quality of evidence

In this umbrella review, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system to evaluate the quality of evidence for each outcome. The GRADE system includes five factors for downgrading and three factors for upgrading the quality of evidence. The baseline quality of evidence of health outcomes depends on the design of the primary studies. The summary estimate result of the random-effect model was used if potential heterogeneity was observed. Otherwise, the result of the fixed-effect model was used. When a serious or very serious defect could occur because of downgrading factors, the evidence quality was downgraded by one or two levels, respectively. If the effect was large (RR/OR either >2.0 or <0.5) or very large (RR/OR either >5.0 or <0.2), the evidence quality was upgraded by one level or two levels, respectively. If there was evidence that the influence of all plausible confounding would reduce a demonstrated effect or suggest a apurious effect when results show no effect, the evidence quality was upgraded by one level. The rating criteria of GRADE22 23 were as follows: the primary evidence quality of an observational study was considered ‘low’; the evidence quality was downgraded to ‘very low quality’ by downgrading one level, upgraded to ‘moderate quality’ by increasing one level and upgraded to ‘high quality’ by increasing two levels. The GRADE system approach classifies the evidence quality of outcomes from eligible articles as high, moderate, low and very low. GRADE classification was independently performed by two investigators (Liqun Li and Jinjing Tan), and the results were checked by a third researcher (Xiaoyan Huang). Any discrepancy was resolved via a discussion, and all discrepancies that could not be resolved through a discussion were arbitrated by Sheng Xie.

Data analysis

If the included meta-analyses did not present results of pooled meta-analysis, they were reanalysed. For example, a study was reanalysed if it did not present the results of pooled meta-analysis (RRs, ORs, SMD or MD), Egger’s test, publication bias or I^2. The heterogeneity between different studies was assessed using the I^2 metric of inconsistency and the p value of χ^2 based on the Cochran Q test. If heterogeneity was observed, a random-effect model was used to calculate the relative summary risk estimates. Otherwise, a fixed-effect model was used. Publication bias was estimated by using Egger’s test. The overall effects of pooled meta-analysis, heterogeneity was considered significant at p value <0.1. Publication bias was considered significant at p<0.1. Statistical analyses were conducted using Stata V.15.

RESULTS

Description of the meta-analyses

Overall, 3036 articles that met our search criteria were first identified from the seven databases. Sixty articles9–18 27–76 of observational studies were finally selected, covering 88 unique outcomes (figure 1). Fifty-four meta-analyses10–17 28–34 38–40 42–44 47–50 54–60 64–70 72–75 were reanalysed because they did not present all of the results of estimates (i.e. OR, RR), Egger’s test, I^2 or publication bias. These 60 eligible non-overlapping meta-analyses are summarised in table 1. A total of 1239 individual study estimates were included in the included meta-analyses. Various measurement methods, including serology, histology, rapid urease test and 18 other detection methods were included.
| Included meta-analyses | Outcomes | HP detection method | Number of studies | Number of participants | Number of cases | Type of metric | Relative risk (95% CI) | P value | P value | I² (%) | P value | Whether exist publication bias |
|------------------------|----------|---------------------|-------------------|-----------------------|----------------|--------------|----------------------|---------|---------|--------|---------|-----------------------------|
| Cancer outcomes        |          |                     |                   |                       |               |              |                      |         |         |        |         |                             |
| Xuan et al<sup>13</sup> | Hepatocellular carcinoma | HP DNA | 9 CCS; 1 CSS     | 522                   | 129            | OR            | 16.52 (6.63 to 41.12) | 0.00    | 0.07    | 44     | 0       | Yes                                        |
| Mounika<sup>44</sup>   | Lung cancer | ELISA              | 5 CCS; 1 PNCCS; 1 PCS | 17 951              | 16244         | OR            | 2.29 (1.34 to 3.91)  | 0.032   | <0.01  | 83.9   | NA      | No<sup>5</sup>                |
| Xie et al<sup>18</sup> | ESCC in Eastern populations | S; H; R; His<sup>+</sup>; HpSe<sup>+</sup> | 16 OS             | 7665                 | 1961           | OR            | 0.66 (0.43 to 0.98)  | NA      | <0.01  | 74.5   | 0.42    | No                                         |
| Xie et al<sup>18</sup> | EAC in the overall population | S; H; U; His<sup>+</sup>; HpSe<sup>+</sup> | 15 OS             | 6035                 | 1330           | OR            | 0.59 (0.51 to 0.68)  | NA      | 0.13    | 29.9   | 0.37    | No                                         |
| Wang et al<sup>40</sup> | Colorectal adenomatous polyp | S; H; several    | 12 CS             | 2678                 | 1783           | OR            | 1.89 (1.59 to 2.25)  | 0       | 0.10    | 35.9   | 0.61    | No                                         |
| Xiao et al<sup>14</sup> | Cholangiocarcinoma | PCR; ELISA; WB   | 10 CCS            | 489                  | 220            | OR            | 8.88 (3.67 to 21.49) | 0       | 0.02    | 56     | 0.01    | Yes                                        |
| Dong and Hao<sup>75</sup> | Colorectal cancer | IgG; UBT; CagA | 21 CCS; 2 CSS     | 182561              | 24295         | OR            | 1.42 (1.38 to 1.46)  | 0       | 0.00    | 71     | 0.74    | No                                         |
| Zhou et al<sup>76</sup> | Laryngeal carcinoma | ELISA; H; PCR  | 11 CCS            | 1030                | 418            | OR            | 2.87 (1.7 to 4.88)   | 0       | 0.00    | 67.1   | 0.62    | No                                         |
| Liu<sup>28</sup> | Colon neoplasia | IgG; IgA; UBT; CagA | 24 CCS; 7 CSS; 2 NCCS | 25 897              | 12145         | OR            | 1.63 (1.39 to 1.90)  | 0       | <0.01  | 80     | 0.14    | No                                         |
| Li et al<sup>12</sup> | Gastric cancer | WB; Chip; ELISA; neutralisation assay; ElA | 10 CCS | 1094 | 664 | OR | 2.78 (1.98 to 3.88) | 0 | 0.23 | 22.8 | 0.1 | No |
| Ma et al<sup>42</sup> | Oesophagogastric junction adenocarcinoma | NA | 9 CCS; 4 PCS | 5547 | 2893 | OR | 0.95 (0.06 to 1.36) | 0.769 | 0.00 | 78 | 0.61 | No |
| Liu et al<sup>11</sup> | Pancreatic cancer | ELISA | 6 NCCS; 2 PCS | 44 193 | NA | OR | 1.09 (0.81 to 1.47) | 0.58 | <0.01 | 76 | 0.59 | No |
| Cardiovascular and cerebrovascular diseases |          |                     |                   |                       |               |              |                      |         |         |        |         |                             |
| Pasceri et al<sup>47</sup> | Ischaemic heart disease | CagA | 3 PCS | 2140 | 966 | OR | 1.26 (1.05 to 1.51) | <0.00001 | 0.01 | 53 | NA | No<sup>5</sup> |
| Pasceri et al<sup>47</sup> | Cerebral ischaemia | CagA | 4 RCCS | 1103 | 446 | OR | 2.43 (1.89 to 3.13) | <0.00001 | 0.43 | 0 | NA | No<sup>5</sup> |
| Wang et al<sup>65</sup> | Diabetic IHD | S; H | 5 CS | 1805 | 469 | RR | 1.12 (0.95 to 1.32) | 0.172 | 0.14 | 42.30 | 0.21 | No |
| Liu et al<sup>6</sup> | Myocardial infarction | NA | 19 CCS; 7 PCS | 21 960 | 11156 | OR | 1.73 (1.37 to 2.17) | 0 | 0.00 | 87.9 | 0.71 | No |
| Chen et al<sup>48</sup> | Coronary heart disease | NA | 12 CS; 5 PCS; 1 NA | 17 514 | 9165 | OR | 1.64 (1.22 to 2.23) | 0.001 | <0.01 | 90 | 0.58 | No |
| Saburi et al<sup>43</sup> | Atherosclerosis | PCR | 4 CCS | 222 | 102 | OR | 5.98 (0.69 to 51.99) | 0.105 | 0.03 | 67.6 | 0.04 | Yes |
| Yan et al<sup>47</sup> | Arrhythmia | IgG; 13C-UBT; UBT | 7 CCS | 2014 | 1032 | OR | 1.81 (1.08 to 2.99) | 0.024 | <0.001 | 80 | 0.28 | No |
| Dong et al<sup>76</sup> | Carotid intima thickness | NA | 9 CCS | 1370 | 694 | SMD | 0.80 (0.69 to 0.92) | <0.01 | 0.00 | 89.7 | NA | No<sup>5</sup> |
| Respiratory disorders |          |                     |                   |                       |               |              |                      |         |         |        |         |                             |
| Wang et al<sup>67</sup> | COPD | S; 13C-UBT | 9 CCS | 9465 | 3192 | OR | 2.25 (1.73 to 2.92) | 0 | 0.00 | 75.5 | 0.27 | No |
| Wang et al<sup>67</sup> | Chronic bronchitis | S; 13C-UBT | 5 CCS | 5674 | 1824 | OR | 1.57 (1.33 to 1.86) | 0 | 0.04 | 58.2 | 0.51 | No |

*Continued*
| Included meta-analyses | Outcomes | HP detection method | Number of studies | Number of participants | Number of cases | Type of metric | Relative risk (95% CI) | P value | P value† | I² (%) | P value‡ | Whether exist publication bias |
|------------------------|----------|---------------------|------------------|-----------------------|----------------|---------------|---------------------|---------|---------|---------|---------|-----------------------------|
| Chen et al  16          | Asthma   | SA; ELISA; IgG; ¹³C-UBT | 5 CCS; 16 CSS    | 53 947                | 5648           | OR            | 0.83 (0.74 to 0.94) | 0.002   | 0.00    | 53.4    | 0.67    | No                          |
| Endocrine disease       |          |                     |                  |                       |                |               |                     |         |         |         |         |                |
| Upala et al  54         | Metabolic syndrome | S; R; H; SA; UBT; biopsy | 5 CSS; 1 CS      | 19 771                | NA             | OR            | 1.34 (1.17 to 1.53) | NA      | <0.01  | 39      | 0.92    | No                          |
| Upala et al  54         | Fasting blood glucose | S; R; H; SA   | 11 CSS; 3 CS     | 79 05                | NA             | MD            | 2.37 (0.98 to 3.77) | NA      | 0.04    | 55      | 0.92    | No                          |
| Upala et al  54         | HDL-C    | UBT; biopsy        | 9 CSS; 3 CS      | 7701                 | NA             | MD            | -2.43 (-3.75 to -1.12) | NA      | <0.01  | 92      | 0.92    | No                          |
| Upala et al  54         | Triglyceride level | S; R; H; SA | 8 CSS; 3 CS      | 75 96                | NA             | MD            | 8.12 (0.05 to 13.2) | NA      | 0.04    | 71      | 0.92    | No                          |
| Upala et al  54         | Systolic blood pressure | UBT; biopsy; culture | 5 CSS; 1 CS | 7 172                | NA             | MD            | 2.88 (0.20 to 5.57) | NA      | 0.01    | 89      | 0.92    | No                          |
| Upala et al  54         | Body mass index | S; R; H; SA | 8 CSS; 2 CS      | 10 707               | NA             | MD            | 0.30 (0.01 to 0.59) | NA      | <0.01  | 57      | 0.92    | No                          |
| Upala et al  54         | HOMA-IR  | UBT; biopsy       | 7 CSS; 3 CS      | 7 935                | NA             | MD            | 0.38 (0.03 to 0.73) | NA      | 0.03    | 85      | 0.92    | No                          |
| Li et al  39            | DM       | ¹³C-UBT; R; ¹⁴C-UBT; SA; biopsy; culture; H | 8 CSS; 68 CCS; 3 PCS | 57 397               | 28 542         | OR            | 1.69 (1.47 to 1.96) | 0       | <0.00001 | 86 | 0 | Yes |
| Li et al  39            | T2 DM    | ¹³C-UBT; R; ¹⁴C-UBT; SA; biopsy; culture; H | 8 CSS; 57 CCS; 2 PCS | 41 684               | 21 286         | OR            | 2.05 (1.67 to 2.52) | 0       | <0.00001 | 89 | 0 | Yes |
| Li et al  39            | T1 DM    | ¹³C-UBT; R; ¹⁴C-UBT; biopsy; H | 1 PCS; 11 CCS | 3 175                | 9 69         | OR            | 1.23 (0.77 to 1.96) | 0.499   | <0.00001 | 82 | 0.46 | No |
| Urinary disease         |          |                     |                  |                       |                |               |                     |         |         |         |         |                |
| Wang et al  56          | Diabetic nephropathy | ¹³C-UBT; ELISA; H | 6 CCS | 636                  | 211            | OR            | 1.6 (1.1 to 2.33)   | 0.018   | 0.44    | 0.98    | No      | No                        |
| Wijamprecha et al  56   | ESRD in adult | A; H; R; UBT; SA; culture | 33 CCS | NA                  | NA             | RR            | 0.71 (0.55 to 0.94) | NA      | <0.00001 | 79 | NA | No§ |
| Digestive disorders     |          |                     |                  |                       |                |               |                     |         |         |         |         |                |
| Eriss et al  32         | Barrett’s oesophagus | S; H; UBT; PCR; R; SA | 70 CCS | 91 656               | 12 134         | OR            | 0.68 (0.58 to 0.79) | 0       | 0.00    | 84      | <0.001  | Yes                         |
| Li et al  54            | Gastric ulcer | WB; Chip; ELISA; neutralisation assay; EIA | 8 CCS | 517                  | 260            | OR            | 1.64 (1.02 to 2.62) | 0.042   | 0.26    | 20.8    | 0.96    | No                          |
| Li et al  52            | Duodenal ulcer | WB; Chip; ELISA; neutralisation assay; EIA | 17 CCS | 2 359                | 1 333         | OR            | 2.06 (1.50 to 2.84) | 0       | 0.01    | 51.3    | 0.63    | No                          |
| Cremonini et al  53     | GERD in population with HP-negative status | R; S; biopsy; H; UBT; Gram stain; culture; H&E; Giemsa stain | 14 CCS | 2 010                | 1 683         | OR            | 1.34 (1.15 to 1.55) | 0       | <0.001  | NA | NA | No§ |
| Weck and Brenner  13    | Chronic atrophic gastritis | NA | 34 OS | 7 726                 | 5 048         | OR            | 6.37 (4.01 to 10.11) | 0       | 0.00    | 91.2    | 0.01    | Yes                         |
| Zhou et al  73          | Biliary lithiasis | ELISA; PCR; culture | 13 CCS | 1 333                | 432           | OR            | 2.59 (1.21 to 5.55) | 0.014   | <0.0001 | 69.5 | 0.18 | No |
| Shioota et al  59       | Peptic ulcer disease | PCR | 42 CCS | 4 601                | 2 524         | OR            | 1.25 (1.09 to 1.44) | 0.002   | 0.39    | 4.6     | 0.78    | No                          |
| Jiang et al  57         | Ammonia levels in cirrhotic patients | ¹⁴C-UBT; R; H; culture; IgG | 6 OS | 396                  | 6 32          | SMD           | 0.34 (0.21 to 0.47) | NA      | 0.12    | 42.1    | 0.11    | No                          |
| Ford et al  68          | Dyspepsia | NA | 13 CSS | 2 305                 | 9 010         | OR            | 1.18 (1.04 to 1.33) | NA      | <0.001  | 63      | 0.3     | No                          |
| Feng et al  50          | Alcoholic cirrhosis in all population | R; UBT; H; ELISA | 8 CCS | 14 226               | 10 053        | OR            | 0.82 (0.35 to 1.91) | 0.648   | 0.00    | 84.5    | 0.67    | No                          |
| Included meta-analyses | Outcomes | HP detection method | Number of studies | Number of participants | Number of cases | Type of metric | Relative risk (95% CI) | P value | P value | I² (%) | P value | Whether exist publication bias |
|------------------------|----------|---------------------|-------------------|-----------------------|----------------|----------------|------------------------|---------|---------|---------|---------|-------------------------------|
| Feng et al\(^{23}\) | Alcoholic cirrhosis in European | R; H; ELISA | 3 CCS | 1171 | 516 | OR | 2.14 (1.19 to 3.86) | 0.011 | 0.31 | 15.5 | 0.74 | No |
| Wu et al\(^{17}\) | Inflammatory bowel disease | IgG; UBT; H; culture | 10 OS | 3116 | 1202 | RR | 0.48 (0.43 to 0.54) | 0 | 0.25 | 21 | 0.2 | No |
| Wang et al\(^{60}\) | Chronic hepatitis C | PCR; S | 12 CCS | 3826 | 2185 | OR | 2.93 (2.30 to 3.75) | 0 | 0.05 | 45 | 0.31 | No |
| Wang et al\(^{69}\) | Chronic hepatitis B | S | 15 CCS | 5129 | 2845 | OR | 3.17 (2.38 to 4.22) | 0 | 0.00 | 77.9 | 0.02 | Yes |
| Wijiannecha et al\(^{66}\) | NAFLD | EIA; IgG; \(^{13}\)C-UBT; H; S | 5 CCS; 1 CCS | 38 594 | NA | OR | 1.21 (1.07 to 1.37) | 0.002 | 0.08 | 49 | NA | No |
| Cen et al\(^{11}\) | Chonic cholecystitis and cholelithiasis | H; PCR; culture | 18 CCS | 1544 | NA | OR | 2.02 (1.90 to 4.82) | NA | 0.21 | 20.1 | 0.43 | No |
| Shah et al\(^{69}\) | Eosinophilic oesophagitis | Biopsy; R; H; IgG; ELISA; EIA; H&E; SA; \(^{13}\)C-UBT | 5 CCS; 3 CS or CCS | 371274 | 26442 | OR | 0.63 (0.51 to 0.78) | 0.00 | 0.02 | 57.9 | 0.77 | No |
| Shah et al\(^{69}\) | Oesophageal eosinophilia | Biopsy; R; H; IgG; ELISA; EIA; H&E; SA; \(^{13}\)C-UBT | 5 CCS; 6 CS or CCS | 377976 | 28007 | OR | 0.64 (0.52 to 0.78) | 0.00 | 0.00 | 69.4 | 0.7 | No |
| Neurocognitive disorders | Wang et al\(^{55}\) | Diabetic neuropathy | S; H | 5 CS | 1607 | 530 | RR | 1.20 (1.03 to 1.40) | 0.018 | 0.29 | 19.1 | 0.99 | No |
| Wang et al\(^{61}\) | Ischaemic stroke | IgG; CagA; C-UBT | 13 CCS | 4041 | NA | OR | 1.60 (1.21 to 2.11) | NA | 0.00 | 65.2 | 0.01 | Yes |
| Yu et al\(^{50}\) | Stroke | S | 6 CS; 4 CCS | 166041 | 1769 | OR | 0.96 (0.74 to 1.24) | NA | 0.03 | 48 | 0.68 | No |
| Shindler-Itskovitch et al\(^{61}\) | Dementia | Biopsy; IgG; IgA; R; H; CagA | 1 CS; 6 CCS | 86 606 | NA | OR | 1.71 (1.17 to 2.48) | 0.01 | <0.001 | 76.1 | 0.33 | No |
| Shen et al\(^{60}\) | Parkinson’s disease | ELISA; PCR; \(^{13}\)C-UBT; H; prescriptions for HP eradication drug | 6 CCS; 2 CSS | 28 201 | 1101 | OR | 1.59 (1.37 to 1.85) | 0 | 0.55 | 0 | 0.02 | Yes |
| Pregnancy-related disorders | Ng et al\(^{65}\) | Hyperemesis gravidarum | Biopsy; H; ELISA; IgG; CagA; EIA; \(^{13}\)C-UBT; SA | 33 CCS; 4 CSS; 1 CS | 10 289 | NA | OR | 1.35 (1.16 to 1.54) | <0.01 | 0.06 | 28 | 0.76 | No |
| Zhan et al\(^{72}\) | Pre-eclampsia | ELISA; CUA; Heli-Blot assay; SA; UBT; WB | 3 CS; 12 CCS; 1 CSS | 10 402 | 1077 | OR | 2.51 (1.18 to 3.34) | 0 | 0.00 | 63 | 0.02 | Yes |
| Zhan et al\(^{72}\) | Fetal growth restriction | Heli-Blot assay; ELISA; SA | 3 CCS; 2 CS | 6099 | 202 | OR | 2.28 (1.21 to 4.32) | 0.011 | 0.02 | 66 | 0.17 | No |
| Zhan et al\(^{72}\) | Gestational DM | ELISA; SA; WB; UBT | 2 CCS; 3 CS | 3697 | 270 | OR | 2.03 (1.56 to 2.64) | 0 | 0.81 | 0 | 0.77 | No |
| Zhan et al\(^{72}\) | Spontaneous abortion | ELISA; SA | 2 CS; 3 CCS; 1 CSS | 5909 | 226 | OR | 1.5 (1.05 to 2.14) | 0.024 | 0.23 | 27 | 0.76 | No |
| Zhan et al\(^{72}\) | Birth defect | ELISA; CUA | 1 CS; 2 CCS | 737 | 132 | OR | 1.63 (1.05 to 2.54) | 0.031 | 0.48 | 0 | 0.14 | No |
| Zhan et al\(^{72}\) | Stillbirth | SA; ELISA | 1 CS; 1 CCS | 3008 | 28 | OR | 2.53 (0.79 to 8.13) | 0.118 | 0.61 | 0 | 0.79 | No |
| Zhan et al\(^{72}\) | Low birth weight | NA | 7 CS or CCS | 10 121 | NA | OR | 1.35 (0.88 to 2.08) | NA | 0.16 | 72 | NA | Unclear |
| Zhan et al\(^{72}\) | Premature delivery | NA | 8 CS or CCS | 12 356 | NA | OR | 1.35 (0.86 to 2.12) | NA | 0.18 | 70 | NA | Unclear |
| Ophthalmic diseases | Wang et al\(^{65}\) | Diabetic retinopathy | S; H | 7 CS | 1815 | 406 | RR | 1.32 (0.97 to 1.80) | 0.058 | 0.04 | 55 | 0.27 | No |
| Zeng et al\(^{11}\) | Open-angle glaucoma | H; IgG; \(^{13}\)C-UBT | 19 CCS | 1580 | 695 | RR | 2.08 (1.42 to 3.04) | NA | <0.001 | 63.6 | 0.36 | No |

Continued
## Table 1 Continued

| Included meta-analyses | Outcomes | HP detection method | Number of studies | Number of participants | Number of cases | Type of metric | Relative risk (95% CI) | P value \(^a\) | P value \(^b\) | \(I^2\) (%) | P value \(^c\) | Whether exist publication bias |
|------------------------|----------|---------------------|-------------------|-----------------------|----------------|---------------|----------------------|-----------|-----------|-----------|-----------|-----------------------------|
| **Thyroid disease**    |          |                     |                   |                       |                |               |                      |           |           |           |           |                             |
| Hou et al\(^d\)        | Autoimmune thyroid diseases | ELISA; WB; UBT; SA | 15 CCS            | 3046                  | 2408           | OR            | 2.25 (1.72 to 2.93) | 0         | 0.00      | 61.6      | 0.68      | No                                         |
| Hou et al\(^d\)        | Grave's disease | ELISA; SA; UBT | 5 CCS            | 917                   | 498            | OR            | 2.78 (1.68 to 4.61) | 0         | 0.07      | 53.4      | 1.51      | No                                         |
| Hou et al\(^d\)        | Hashimoto's thyroiditis | ELISA; SA; UBT; NR | 8 CCS           | 1594                  | 872            | OR            | 2.16 (1.44 to 3.23) | 0         | 0.00      | 68.2      | 0.51      | No                                         |
| **Haematological disorders** |          |                     |                   |                       |                |               |                      |           |           |           |           |                             |
| Hudak et al\(^d\)      | Iron deficiency anaemia | R; H; \(^14\)C-UBT; \(^13\)C-UBT; IgG; SA; IgA; gastroscopy | 11 CSS; 3 CCS | 15 905               | NA             | OR            | 1.72 (1.23 to 2.42) | NA        | 0.00      | 61.5      | 0.38      | No                                         |
| Hudak et al\(^d\)      | Iron deficiency | 30 CSS            | 23 921           | NA                    | OR            | 1.33 (1.15 to 1.54) | NA        | 0.01      | 41.1      | 0.49      | No                                         |
| Hudak et al\(^d\)      | Anaemia   | 23 CSS            | 11 622           | NA                    | OR            | 1.15 (1.00 to 1.32) | NA        | 0.01      | NA        | 0.81      | No                                         |
| **Other outcomes**     |          |                     |                   |                       |                |               |                      |           |           |           |           |                             |
| Nweneke and Prentice\(^d\) | Circulating ghrelin levels | UBT; ELISA; S; H; culture; R; PCR | 7 CS; 11 CSS | 956                  | 1288           | SMD           | −0.42 (−0.57 to −0.27) | <0.00001 | 0.00      | 59        | 0.12      | No                                         |
| Xiong et al\(^d\)      | Henoch-Schonlein purpura | R; UBT; IgG; H. pylori antigen | 10 CCS           | 1309                  | 500            | OR            | 3.46 (2.68 to 4.47) | 0         | 0.06      | 46        | 0.03      | Yes                                        |
| Su et al\(^d\)         | Migraine | \(^13\)C-UBT; ELISA; biopsy | 5 CCS or CSS | 903                  | 355            | OR            | 1.92 (1.05 to 3.51) | 0.033     | 0.00      | 77.4      | 0.08      | Yes                                        |
| Li et al\(^d\)         | Recurrent aphthous stomatitis | PCR; UBT | 7 CCS | 510                   | 154            | OR            | 1.85 (1.24 to 2.74) | 0.002     | 0.21      | 28.5      | 0.49      | No                                         |
| Taye et al\(^d\)       | Atopy    | H; IgG; ELISA; UBT; SA; IgA | 2 CS; 3 CCS; 11 CCS | 10 968               | NA             | OR            | 0.82 (0.73 to 0.91) | <0.01     | 0.66      | 0         | 0.85      | No                                         |
| Hwang et al\(^d\)      | Chronic tonsilsitis | R; PCR; culture; CLO | 6 OS | 436                   | NA             | OR            | 1.99 (0.91 to 4.37) | 0.09      | 0.06      | 53.6      | 0.42      | No                                         |
| Gu et al\(^d\)         | Chonic ucaria | ELISA; UBT; S; H; IgG | 16 CCS           | 2200                  | 984            | OR            | 1.66 (1.12 to 2.45) | 0.022     | <0.0001   | 66        | 0.01      | Yes                                        |
| Yao et al\(^d\)        | Multiple sclerosis | ELISA; WB; CIA | 9 CCS | 2806                  | 782            | OR            | 0.73 (0.56 to 0.96) | 0         | 0.05      | 48        | 0.07      | Yes                                        |
| Dou et al\(^d\)        | Hailosis  | H; BUT; culture; PCR; Gram stain; ELISA; SA; endoscopy; CLO | 6 CCS;1 CSS | 2312                 | 467            | OR            | 4.03 (1.41 to 11.5) | 0.009     | <0.0001   | 89        | 0.05      | Yes                                        |
| Jørgensen et al\(^d\)  | Rosacea  | NA                  | 14 OS            | 2455                  | 1268           | OR            | 1.74 (1.03 to 2.93) | 0.039     | 0.00      | 85.6      | 0.09      | Yes                                        |
| Chen et al\(^d\)       | Sipgren's syndrome | Biopsy; ELISA; IgG | 9 CCS           | 2018                  | 1054           | OR            | 1.19 (1.01 to 1.41) | 0.033     | 0.86      | 0         | 0.77      | No                                         |
| Yong et al\(^d\)       | Psoriasis | IgG; ELISA; UBT; SA | 4 CCS; 3 PCS; 2 CCS | 15 46               | 728            | OR            | 1.58 (1.02 to 2.46) | 0.041     | 0.00      | 64        | 0.03      | Yes                                        |
| Yong et al\(^d\)       | Systemic sclerosis | IgG; ELISA; IgM; \(^14\)C-UBT; R | 7 CSS; 1 PCS | 14 46                 | 749            | OR            | 2.11 (1.62 to 2.76) | 0.00      | 0.33      | 13        | 0.84      | No                                         |

\(^a\) p value of significance level.  
\(^b\) p value of Q test.  
\(^c\) The publication bias was assessed using funnel plot.  
\(^d\) prevalence or incidence unless otherwise specified.
methods, were used to determine *H. pylori* positivity. A range of 2–79 study estimates were pooled per meta-analysis, and the median of the study estimate was 10. Among the 1239 individual studies, 274 (22%) were cross-sectional studies, 748 (60%) were case–control studies, 124 (10%) were cohort studies and 93 (8%) were mentioned as observational studies. Furthermore, 1 meta-analysis did not present the number of participants, and 12 meta-analyses did not present the number of cases. Among the meta-analyses that indicated the number of cases or participants, the median number of cases was 1032 (28–96 753) and the median number of participants was 3826 (222–377 976). A total of 76 meta-analyses included more than 1000 participants, 34 meta-analyses included more than 1000 cases and 11 meta-analyses included less than 300 cases. The 60 included articles were published from 2003 to 2019, 77% were published between 2014 and 2019, and the number of publication increased yearly before 2016 (figure 2). Various health outcomes associated with *H. pylori* infection included cancer outcomes (n=12), cardiovascular and cerebrovascular diseases (n=8), respiratory disorders (n=3), endocrine disease (n=10), urological disease (n=2), digestive disorders (n=18), neurocognitive disorders (n=5), pregnancy-related disorders (n=9), ophthalmic diseases (n=2), thyroid disease (n=3), haematological disorders (n=3) and other outcomes (n=13) (figure 3). A total of 23 articles conducted subgroup meta-analysis based on different study region (table 2). *H. pylori* infection was most harmful to Asians, followed by Europeans.

**Summary effect size**

Table 1 shows the summary effects of the included meta-analysis. Of the 88 outcomes, 74 (84%) had nominal significance (p<0.05). Of these outcomes, 61 (82%) were harmful associations enumerated as follows: 8 (67%) meta-analyses in cancer outcomes, 6 (75%) in cardiovascular and cerebrovascular diseases, 2 (67%) in respiratory disorders, 6 (60%) in endocrine diseases, 1 (50%) in urological diseases, 12 (67%) in digestive disorders, 4 (80%) in neurocognitive disorders, 6 (67%) in pregnancy-related disorders, 2 (17%) in ophthalmic diseases, 3 (100%) in thyroid diseases, 3 (100%) in haematological disorders and 9 (69%) in other outcomes. These associations had significant pooled estimates (p<0.05). Thus, *H. pylori* infection was associated with an increased risk of disease and harmful to human health (table 3). By contrast, 13 (15%) evidence from meta-analyses were beneficial associations enumerated as follows: 1 (33%) meta-analyses in respiratory disorders, 2 (15%) in cancer outcomes, 1 (10%) endocrine disease, 1 (50%) urological disease, 5 (28%) digestive disorders and 3 (23%) in other outcomes. These associations had significant pooled estimates (p<0.05), indicating that *H. pylori* infection was related to a decreased risk of some diseases. These findings could be beneficial to human health in some situations (table 3).

**Heterogeneity and publication bias of the included studies**

All of the included meta-analyses presented the results of heterogeneity between studies (table 1). In particular, 24 (27%) outcomes of meta-analyses showed no heterogeneity between studies (p≥0.1 of Q test), whereas 64 (73%) exhibited significant heterogeneity (p<0.1 of Q test). Moreover, 32 (57%) of 64 meta-analyses showed moderate to high heterogeneity (I²=50%–75%), and 24 (43%) showed high heterogeneity (I²>75%). Among 88 meta-analyses, 68 (77%) demonstrated no statistical evidence on publication bias according to Egger’s, whereas 20% of the meta-analyses presented publication bias (p<0.1 of Egger’s test). Only 2 (2%) meta-analyses did not report publication bias.

**Summary of the methodological quality of the included meta-analyses**

The methodological qualities of the 60 included articles were assessed using AMSTAR 2, and the results are shown in table 4. A total of 52 (87%) meta-analyses did not report a predefined explicit statement or protocol; only 8 (13%) meta-analyses were conducted using a comprehensive literature search strategy, and 24 (40%) meta-analyses did not report publication bias.
| Study region                  | Increase risk of                          | Decrease risk of                        | No association with                          |
|------------------------------|------------------------------------------|-----------------------------------------|---------------------------------------------|
| Europe                       | Cholangiocarcinoma, colorectal cancer, diabetes mellitus, diabetic nephropathy, alcoholic cirrhosis, Parkinson's disease  | Barrett's oesophagus  | Arrhythmia, asthma, biliary lithiasis, migraine, recurrent aphthous stomatitis, chronic urticaria  |
| America                      | Colorectal cancer, biliary lithiasis, chronic urticaria  | Barrett's oesophagus, asthma  | Arrhythmia, diabetes mellitus, alcoholic cirrhosis, recurrent aphthous stomatitis  |
| East (Asia, China)           | Cholangiocarcinoma, colorectal cancer, colon neoplasia, arrhythmia, diabetes mellitus, diabetic nephropathy, biliary lithiasis, ammonia levels in cirrhotic patients, chronic cholecystitis and cholelithiasis, Parkinson's disease, open-angle glaucoma, Henoch-Schonlein purpura, migraine, chronic urticaria  | Oesophageal squamous cell carcinoma, Barrett's oesophagus, asthma  | Myocardial infarction, COPD, biliary lithiasis, peptic ulcer disease, alcoholic cirrhosis, recurrent aphthous stomatitis, multiple sclerosis  |
| West                         | Colon neoplasia, myocardial infarction, COPD, peptic ulcer disease, open-angle glaucoma  | Oesophageal adenocarcinoma, asthma, multiple sclerosis  | Oesophageal squamous cell carcinoma, ammonia levels in cirrhotic patients  |
| Africa                       | Arrhythmia  |  | Barrett's oesophagus, diabetes mellitus, peptic ulcer disease  |
| Australia                    |                                              | Barrett's oesophagus  |  |
| Oceania                      |                                              |                                              | Biliary lithiasis  |

COPD, chronic obstructive pulmonary disease.

not perform a duplicate selection. Twelve (20%) meta-analyses did not conduct a duplicate data extraction, 53 (88%) meta-analyses provided a list of excluded studies but did not justify the exclusions, 6 (10%) meta-analyses did not provide a list of excluded studies, 50 (83%) meta-analyses partially described the included studies and 22 (37%) meta-analyses did not assess the risk of bias in the included studies. Furthermore, none of the meta-analyses reported the details of funding sources for the included studies, and 28 (47%) meta-analyses did not report potential sources of conflicts of interest. Overall, 85 (97%) methodological qualities of the included meta-analyses were categorised as ‘critically low’, and only 3 (3%) methodological qualities of the included meta-analyses were assessed as low quality (figure 4).

Evidence classification of the outcomes

The evidence quality of every outcome was assessed using the GRADE system (table 5). None of the evidence quality for any outcome was rated ‘high’. Most of the qualities of evidence were downgraded by the potential risk of bias and serious heterogeneity. A total of 32 (36%) evidence qualities of outcomes were rated ‘low’, 49 (56%) evidence were rated ‘very low’ and only 7 (8%) evidence were rated ‘moderate’ (figure 5). Table 5 shows the results of evidence quality from 88 outcomes.

Harmful outcomes associated with *H. pylori infection*

Our confidence level in the following was moderate: *H. pylori* infection is associated with an increased risk of chronic cholecystitis and cholelithiasis, gestational diabetes mellitus, systemic sclerosis and gastric cancer, and increased serum triglyceride level. Our confidence level in the following was low: *H. pylori* infection is associated with an increased risk of HCC, biliary lithiasis, PUD, duodenal ulcer, chronic hepatitis C, non-alcoholic fatty liver disease, diabetic neuropathy, Parkinson’s disease, hyperemesis gravidarum, fetal growth restriction, spontaneous abortion, birth defect, open-angle glaucoma, autoimmune thyroid diseases, Grave’s disease, Hashimoto’s thyroiditis, Henoch-Schonlein purpura, diabetic nephropathy, gastric ulcer, alcoholic cirrhosis Europeans, and Sjogren’s syndrome; ammonia levels decrease in patients with cirrhosis. Our confidence level in the following was very low: *H. pylori* infection is associated with an increased risk of lung cancer, cholangiocarcinoma, colorectal cancer, colon neoplasia, chronic tonsillitis, ischaemic heart disease, MI, coronary heart disease, arrhythmia, chronic bronchitis, metabolic syndrome, diabetes mellitus, type 2 diabetes mellitus, chronic atrophic gastritis, dyspepsia, chronic hepatitis

| Table 2 | Association between *H. pylori* infection and diverse diseases based on study region |
|---------|-----------------------------------------------------------------------------------|
| Study region | Increase risk of | Decrease risk of | No association with |
| Europe | Cholangiocarcinoma, colorectal cancer, diabetes mellitus, diabetic nephropathy, alcoholic cirrhosis, Parkinson's disease | Barrett's oesophagus | Arrhythmia, asthma, biliary lithiasis, migraine, recurrent aphthous stomatitis, chronic urticaria |
| America | Colorectal cancer, biliary lithiasis, chronic urticaria | Barrett's oesophagus, asthma | Arrhythmia, diabetes mellitus, alcoholic cirrhosis, recurrent aphthous stomatitis |
| East (Asia, China) | Cholangiocarcinoma, colorectal cancer, colon neoplasia, arrhythmia, diabetes mellitus, diabetic nephropathy, biliary lithiasis, ammonia levels in cirrhotic patients, chronic cholecystitis and cholelithiasis, Parkinson's disease, open-angle glaucoma, Henoch-Schonlein purpura, migraine, chronic urticaria | Oesophageal squamous cell carcinoma, Barrett's oesophagus, asthma | Myocardial infarction, COPD, biliary lithiasis, peptic ulcer disease, alcoholic cirrhosis, recurrent aphthous stomatitis, multiple sclerosis |
| West | Colon neoplasia, myocardial infarction, COPD, peptic ulcer disease, open-angle glaucoma | Oesophageal adenocarcinoma, asthma, multiple sclerosis | Oesophageal squamous cell carcinoma, ammonia levels in cirrhotic patients |
| Africa | Arrhythmia |  | Barrett's oesophagus, diabetes mellitus, peptic ulcer disease |
| Australia |  | Barrett's oesophagus |  |
| Oceania |  | Biliary lithiasis |  |

COPD, chronic obstructive pulmonary disease.
Table 3 Results of evidence quality for all outcomes classified by GRADE

| Level of evidence | Outcomes                                                                 | Increased risk of | Increase | Decreased risk of | Reduce | No association with |
|------------------|--------------------------------------------------------------------------|-------------------|----------|-------------------|--------|--------------------|
| High             | Chronic cholecystitis and cholelithiasis, gestational diabetes mellitus, gastric cancer, and systemic sclerosis | Triglyceride level |         | Infammatoty bowel disease |        | Stillbirth         |
| Moderate         | Hepatocellular carcinoma, biliary lithiasis, peptic ulcer disease, chronic hepatitis C, non-alcoholic fatty liver disease, diabetic neuropathy, Parkinson’s disease, hyperemesis gravidarum, fetal growth restriction, spontaneous abortion, birth defect, open-angle glaucoma, autoimmune thyroid diseases, Grave’s disease, Hashimoto’s thyroiditis, Henoch-Schonlein purpura, colorectal adenomatous polyp, Sjogren’s syndrome, duodenal ulcer, laryngeal carcinoma, chronic obstructive pulmonary disease, diabetic nephropathy, stillbirth | Ammonia levels in patients with cirrhosis |         | Oesophageal adenocarcinoma in the overall population, eosinophilic oesophagitis, oesophageal eosinophilia, atopy |        | Diabetic ischemic heart disease, fasting blood glucose and diabetic ischaemic heart disease |
| Low              | Hepatocellular carcinoma, biliary lithiasis, peptic ulcer disease, chronic hepatitis C, non-alcoholic fatty liver disease, diabetic neuropathy, Parkinson’s disease, hyperemesis gravidarum, fetal growth restriction, spontaneous abortion, birth defect, open-angle glaucoma, autoimmune thyroid diseases, Grave’s disease, Hashimoto’s thyroiditis, Henoch-Schonlein purpura, colorectal adenomatous polyp, Sjogren’s syndrome, duodenal ulcer, laryngeal carcinoma, chronic obstructive pulmonary disease, diabetic nephropathy, stillbirth, gastric ulcer, alcoholic cirrhosis in European, cerebral ischaemia | Ammonia levels in patients with cirrhosis |         | Oesophageal adenocarcinoma in the overall population, eosinophilic oesophagitis, oesophageal eosinophilia, atopy |        | Diabetic ischemic heart disease, fasting blood glucose and diabetic ischaemic heart disease |
| Very low         | Lung cancer, cholangiocarcinoma, chronic tonsillitis, colorectal cancer, colon neoplasia, ischaemic heart disease, myocardial infarction, coronary heart disease, atrial fibrillation, chronic bronchitis, metabolic syndrome, diabetes mellitus, type 2 diabetes mellitus, chronic atrophic gastritis, dyspepsia, chronic hepatitis B, ischaemic stroke, dementia, pre-eclampsia, iron deficiency anaemia, body mass index, hematostatic model assessment of insulin resistance, oesophageal squamous cell carcinoma in Eastern populations, Barrett’s esophagus, asthma, end-stage renal disease in adult, multiple sclerosis and gastro-oesophageal reflux disease | Carotid intima thickness, body mass index, hematostatic model assessment of insulin resistance, oesophageal squamous cell carcinoma in Eastern populations, Barrett’s esophagus, asthma, end-stage renal disease in adult, multiple sclerosis and gastro-oesophageal reflux disease |         | High-density lipoprotein cholesterol, circulating ghrelin levels, Oesophagogastric adenocarcinoma, pancreatic cancer, systolic blood pressure, atherosclerosis, type 1 diabetes mellitus, alcoholic cirrhosis in all populations, low birth weight, premature delivery, and diabetic retinopathy |        |                            |

B, ischaemic stroke, dementia, pre-eclampsia, iron deficiency anaemia, iron deficiency, anaemia, migraine, recurrent aphthous stomatitis, chronic urticaria, halitosis, rosacea, and psoriasis; an increase in the following parameters is observed: carotid intima thickness, body mass index, and hematostatic model assessment of insulin resistance.

Beneficial outcomes associated with *H. pylori* infection

Our confidence level in the following was moderate: *H. pylori* infection is associated with a decreased risk of irritable bowel syndrome. Our confidence level in the following was low: *H. pylori* infection is associated with a decreased risk of oesophageal adenocarcinoma in the overall population, colorectal adenomatous polyp, eosinophilic oesophagitis, oesophageal eosinophilia and atopy. Our confidence level in the following was very low: *H. pylori* infection is associated with a decreased risk of oesophageal squamous cell carcinoma in Eastern populations, Barrett’s oesophagus, asthma, end-stage renal disease in adults, multiple sclerosis and gastro-oesophageal reflux disease; decreasing high-density lipoprotein cholesterol and circulating ghrelin levels are also observed.

**DISCUSSION**

**Principal findings and possible explanations**

This umbrella review summarised the current existing evidence from meta-analyses on the associations between *H. pylori* infection and diverse health outcomes. In this umbrella review, 60 publications of interest were systematically reviewed. The role of *H. pylori* infection was explored in relation to a wide range of diseases (74 in
| AMSTAR 2 checklist | Overall assessment quality |
|--------------------|---------------------------|
| Included meta-analyses | No. 1 | No. 2 | No. 3 | No. 4 | No. 5 | No. 6 | No. 7 | No. 8 | No. 9 | No. 10 | No. 11 | No. 12 | No. 13 | No. 14 | No. 15 | No. 16 |
| Xuan et al | Yes | No | Yes | Yes | Yes | No | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Mounika | Yes | No | Yes | Partial yes | No | No | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | No | No | No | Critically low |
| Xie et al | Yes | No | Yes | No | Yes | Yes | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Wang et al | Yes | No | Yes | Partial yes | Yes | Yes | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Xiao et al | Yes | No | Yes | Partial yes | Yes | Yes | Partial yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Dong and Hao | Yes | No | Yes | Partial yes | No | No | Partial yes | Partial yes | Yes | No | No | No | Yes | Yes | No | Yes | No | Critically low |
| Zhou et al | Yes | No | Yes | Partial yes | No | Yes | Partial yes | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Liu | Yes | No | Yes | Partial yes | Yes | No | Partial yes | Partial yes | No | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Li et al | Yes | No | Yes | Partial yes | No | Yes | Partial yes | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Ma et al | Yes | No | Yes | Partial yes | No | No | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Liu et al | Yes | No | Yes | No | Yes | Yes | Partial yes | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Eröss et al | Yes | Yes | Yes | Partial yes | Yes | Yes | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Pasceri et al | Yes | No | Yes | Partial yes | Yes | Yes | Partial yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Liu et al | Yes | No | Yes | Partial yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Chen et al | Yes | No | Yes | Partial yes | No | No | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Saburi et al | Yes | No | Yes | Partial yes | No | No | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Yan et al | Yes | No | Yes | Yes | Yes | Yes | Partial yes | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Dong et al | Yes | No | No | Yes | No | Yes | Partial yes | Partial yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Wang et al | Yes | No | Yes | Partial yes | No | No | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Chen et al | Yes | No | Yes | No | Yes | Yes | Partial yes | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Upala et al | Yes | Yes | Yes | Partial yes | No | Yes | No | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Li et al | Yes | No | Yes | No | No | Partial yes | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Wang et al | Yes | No | Yes | Partial yes | Yes | No | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Wijarnpreecha et al | Yes | No | Yes | Partial yes | Yes | Yes | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Cremonini et al | Yes | No | Yes | Partial yes | Yes | Yes | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Weck and Brenner | Yes | No | No | No | No | Partial yes | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Zhou et al | Yes | No | Yes | Yes | Yes | Yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Shiota et al | Yes | No | Yes | Partial yes | No | No | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Jiang et al | Yes | No | Yes | Partial yes | Yes | Yes | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Ford et al | Yes | No | Yes | Partial yes | No | Yes | Partial yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Feng et al | Yes | No | Yes | Partial yes | No | No | Partial yes | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Wu et al | Yes | No | Yes | Partial yes | No | Yes | Partial yes | Partial yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Wang et al | Yes | No | Yes | Yes | Yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Included meta-analyses       | No. 1 | No. 2 | No. 3 | No. 4 | No. 5 | No. 6 | No. 7 | No. 8 | No. 9 | No. 10 | No. 11 | No. 12 | No. 13 | No. 14 | No. 15 | No. 16 | Overall assessment quality |
|-----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|---------------------------|
| Wang et al*                | Yes   | No    | Yes   | Yes   | Yes   | No    | Partial yes | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Wijarnpreecha et al*       | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | No   | Critically low             |
| Cen et al                  | Yes   | No    | Yes   | Partial yes | Yes   | Yes   | Partial yes | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Shah et al                 | Yes   | No    | Yes   | No    | Yes   | Yes   | Partial yes | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Wang et al                 | Yes   | No    | No    | Partial yes | Yes   | Yes   | No    | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Wang et al                 | Yes   | No    | Yes   | No    | Partial yes | Yes   | Yes   | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Yu et al                   | Yes   | No    | Yes   | No    | Yes   | Yes   | Partial yes | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Shindler-Itskovitch et al*| Yes   | No    | Yes   | Partial yes | No    | Yes   | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Shen et al                 | Yes   | No    | Yes   | Partial yes | Yes   | Yes   | Partial yes | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Ng et al                   | Yes   | No    | Yes   | Partial yes | Yes   | Yes   | Yes   | Partial yes | No    | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Zhan et al                 | Yes   | No    | Yes   | Partial yes | Yes   | Yes   | Partial yes | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Zeng et al                 | Yes   | No    | Yes   | No    | Yes   | Partial yes | No    | Yes   | Partial yes | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | No   | Critically low             |
| Nweneke and Prentice*      | Yes   | No    | Yes   | Partial yes | No    | No    | Yes   | Partial yes | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Xiong et al                | Yes   | Yes   | Yes   | Partial yes | Yes   | Yes   | Partial yes | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Su et al                   | Yes   | No    | Yes   | Partial yes | Yes   | Yes   | Yes   | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Li et al                   | Yes   | No    | No    | Yes   | No    | No    | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Taye et al                 | Yes   | No    | Yes   | Partial yes | Yes   | Yes   | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Low                      |
| Hwang et al                | Yes   | No    | No    | Partial yes | Yes   | No    | Partial yes | Partial yes | No    | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Gu et al                   | Yes   | No    | Yes   | Partial yes | Yes   | Yes   | Partial yes | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Yao et al                  | Yes   | No    | Yes   | Partial yes | Yes   | Yes   | Partial yes | Partial yes | No    | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Dou et al                  | Yes   | No    | Yes   | Partial yes | Yes   | Yes   | Partial yes | No    | No    | No    | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Jørgensen et al            | Yes   | No    | No    | Partial yes | Yes   | No    | Partial yes | Partial yes | No    | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Hou et al                  | Yes   | No    | Yes   | Partial yes | No    | No    | Partial yes | Partial yes | No    | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Critically low             |
| Hudaik et al               | Yes   | Yes   | Yes   | Partial yes | No    | Yes   | Partial yes | Partial yes | Yes   | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | No   | Critically low             |
| Chen et al                 | Yes   | Yes   | Yes   | Partial yes | Yes   | Yes   | Partial yes | Partial yes | No    | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | Yes   | No   | Critically low             |
| Yong et al                 | Yes   | Yes   | Yes   | Partial yes | Yes   | No    | Yes   | Partial yes | No    | No    | Yes   | Yes   | No    | Yes   | No    | Yes   | Yes   | Critically low             |
| Yong et al                 | Yes   | Yes   | Yes   | Partial yes | Yes   | Yes   | Partial yes | No    | No    | No    | Yes   | No    | Yes   | No    | Yes   | No    | No   | Critically low             |

AMSTAR 2 checklists: No. 1: Did the research questions and inclusion criteria for the review include the components of PIO? No. 2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? No. 3: Did the review authors explain their selection of the study designs for inclusion in the review? No. 4: If the review authors use a comprehensive literature search strategy? No. 5: Did the review authors perform study selection in duplicate? No. 6: Did the review authors perform data extraction in duplicate? No. 7: Did the review authors provide a list of excluded studies and justify the exclusions? No. 8: Did the review authors list the included studies in adequate detail? No. 9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? No. 10: Did the review authors report on the sources of funding for the studies included in the review? No. 11: Did the meta-analyses performed, did the review authors use appropriate methods for statistical combination of results? No. 12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? No. 13: Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review? No. 14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? No. 15: If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? No. 16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?
under pressure to comply with the hypothesis during H. pylori infection. Researchers believed in the association between infection and diseases might not be even published. If researchers strongly were probably more easily published than negative results. A smaller fraction was finally published. Positive results proportion of associations were recorded, and an even smaller fraction was found in thousands of individuals. However, only a small number of associations between H. pylori infection and diverse health outcomes were recorded. Inflated or false positives. Some of them had serious heterogeneity between studies. H. pylori infection could not be obtained because all of the meta-analyses did not present this aspect.

A large proportion (84%) of the health outcomes was associated with H. pylori infection. However, most of them (64%) had serious heterogeneity between studies. The potential heterogeneity might be due to possible confounding factors (e.g. different H. pylori measurement methods, alcohol consumption, smoking, sex, study region, different nationalities and time of follow-up). Substantial heterogeneity affected the results of meta-analyses, indicating that some associations between H. pylori infection and diverse health outcomes might be inflated or false positives. In addition, some of them (20%) had a notable publication bias, revealing that some negative results were not reported. In practice, associations between H. pylori infection and diseases might be found in thousands of individuals. However, only a small proportion of associations were recorded, and an even smaller fraction was finally published. Positive results were probably more easily published than negative results that might not be even published. If researchers strongly believed in the association between H. pylori infection and the risk of developing diseases, their work might be under pressure to comply with the hypothesis during publication. These requirements could cause publication biases in the results. Our result showed that 97% of the meta-analyses had ‘critically low’ methodological quality (figure 4). Evidence was downgraded by serious heterogeneity, potential bias and low method quality. Hence, none of the outcomes had high-quality evidence after evaluation based on the evidence classification criteria. Based on this metric, moderate-quality evidence only existed in six health outcomes, suggesting that H. pylori infection was probably associated with an increased risk of hypertriglyceridemia, chronic cholecystitis and cholelithiasis, gestational diabetes mellitus, gastric cancer and systemic sclerosis and a decreased risk of irritable bowel syndrome. Among these risks, the outcome of triglyceride level exhibited moderate heterogeneity ($I^2=71\%$), demonstrating that this association should be cautiously interpreted. This umbrella review shows there is no association between H. pylori infection and risk of stillbirth.

**Strengths and limitations of the umbrella review**

Our umbrella review has several great strengths. An umbrella review systematically searches, collects and assesses the strength and credibility of the evidence derived from various systematic reviews and meta-analyses on any clinical health outcomes related to a particular exposure. Studies have also revealed the strengths and significance of umbrella reviews in detail. Considering that the associations between H. pylori infection and diverse health outcomes have not been systematically and comprehensively assessed, this umbrella review comprehensively evaluated the methodological quality of meta-analyses and assessed the evidence quality of outcomes from the published meta-analyses of observational studies. The quality of the included studies in meta-analyses affects the quality of the meta-analyses. When possible, we reanalysed the summary estimates and explored the heterogeneity and publication bias of the included meta-analyses by using a standardised method. In this umbrella review, seven databases were comprehensively and systematically searched using a standard search strategy to identify eligibility. An uptrend of studies on associations between H. pylori infection and various health outcomes was found, indicating that the associations of H. pylori infection and diseases were widely explored. However, meta-analyses investigated on associations between H. pylori infection and musculoskeletal disorders, and mucosa associated lymphoid tissue (MALT) lymphoma were not found in our scope.

We used AMSTAR 2, which is a standard methodological quality assessment approach, to assess the quality of the method used for meta-analyses. Since AMSTAR 2 was developed from AMSTAR in 2017, it has been considered a valid and reliable methodological quality assessment tool. The lengths of AMSTAR 2 have been described in other studies. This tool helped us identify the highest methodological quality of the meta-analyses of RCTs and also the meta-analyses of observational studies. Therefore, AMSTAR 2 is more practical and applicable
Table 5  Details of evidence quality for outcomes classified by GRADE

| Included meta-analyses | Association between H. pylori and* | Downgrade factors | Upgrade factors | GRADE class |
|------------------------|------------------------------------|-------------------|----------------|-------------|
| **Cancer outcomes**    |                                    |                   |                |             |
| Xuan et al[13]         | Hepatocellular carcinoma           | −1                | 0              | −1          | 2           | 1           | Low         |
| Mounika[44]            | Lung cancer                        | −1                | −2             | 0           | 0           | 1           | 1           | Very low    |
| Xie et al[18]          | ESCC in Eastern populations        | −1                | −1             | 0           | 0           | 0           | 0           | Very low    |
| Xie et al[18]          | EAC in the overall population      | −1                | 0              | 0           | 0           | 0           | 0           | Very low    |
| Wang et al[64]         | Colorectal adenomatous polyp       | −1                | 0              | 0           | 0           | 0           | 0           | Low         |
| Xiao et al[14]         | Cholangiocarcinoma                 | −1                | −1             | 0           | −1          | −1          | 2           | Very low    |
| Dong and Hao[15]       | Colorectal cancer                  | −1                | −1             | 0           | 0           | 0           | 0           | Very low    |
| Zhou et al[24]         | Laryngeal carcinoma                | −1                | −1             | 0           | 0           | 0           | 1           | Very low    |
| Liu[28]                | Colon neoplasia                    | −1                | −2             | 0           | 0           | 0           | 0           | Very low    |
| Li et al[23]           | Gastric cancer                     | −1                | 0              | 0           | 0           | 0           | 1           | Moderate    |
| Ma et al[82]           | Oesophagogastric junction adenocarcinoma | −1               | −2             | 0           | 0           | 0           | 0           | Very low    |
| Liu et al[61]          | Pancreatic cancer                  | −1                | −2             | 0           | 0           | 0           | 0           | Very low    |
| **Cardiovascular and cerebrovascular diseases** | | | | |
| Pasceri et al[47]      | Ischaemic heart disease            | −2                | −1             | 0           | 0           | 0           | 0           | Very low    |
| Pasceri et al[47]      | Cerebral ischaemia                 | −2                | 0              | 0           | 0           | 0           | 1           | Low         |
| Wang et al[49]         | Diabetic IHD                       | −1                | 0              | 0           | 0           | 0           | 0           | Low         |
| Liu et al[54]          | Myocardial infarction              | −1                | −2             | 0           | 0           | 0           | 0           | Very low    |
| Chen et al[58]         | Coronary heart disease             | −2                | −2             | 0           | 0           | 0           | 0           | Very low    |
| Ramezani-Binabaj et al[43] | Atherosclerosis                  | −2                | −1             | 0           | −1          | −1          | 0           | Very low    |
| Yan et al[64]          | Arrhythmia                         | −1                | −2             | 0           | 0           | 0           | 0           | Very low    |
| Dong et al[76]         | Carotid intima thickness           | −1                | −2             | 0           | 0           | 0           | 0           | Very low    |
| **Respiratory disorders** |                                   |                   |                |             |
| Wang et al[47]         | COPD                               | −1                | −1             | 0           | 0           | 0           | 1           | Very low    |
| Wang et al[47]         | Chronic bronchitis                 | −1                | −1             | 0           | 0           | 0           | 0           | Very low    |
| Chen et al[46]         | Asthma                             | −1                | −1             | 0           | 0           | 0           | 0           | Very low    |
| **Endocrine disease**  |                                     |                   |                |             |
| Upala et al[54]        | Metabolic syndrome                 | −1                | −1             | 0           | 0           | 0           | 0           | Very low    |
| Upala et al[54]        | Fasting blood glucose              | −1                | −1             | 0           | 0           | 0           | 1           | Very low    |
| Upala et al[54]        | HDL-C                              | −1                | −2             | 0           | 0           | 0           | 1           | Very low    |
| Upala et al[54]        | Triglyceride level                 | −1                | −1             | 0           | 0           | 0           | 2           | Moderate    |

Continued
| Included meta-analyses | Association between H. pylori and* | Downgrade factors | Upgrade factors | Plausible confounding would change the effect | GRADE class |
|------------------------|-----------------------------------|------------------|----------------|---------------------------------------------|-------------|
|                        |                                   | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | |
| Upala et al*           | Systolic blood pressure           | −1           | −2            | 0            | 0          | 0            | 1            | 1            | Very low    |
| Upala et al*           | Body mass index                   | −1           | −1            | 0            | 0          | 0            | 0            | 1            | Very low    |
| Upala et al*           | HOMA-IR                           | −1           | −2            | 0            | 0          | 0            | 0            | 0            | Very low    |
| Li et al*              | DM                                 | −1           | −2            | 0            | 0          | −1           | 0            | 1            | Very low    |
| Li et al*              | T2DM                               | −1           | −2            | 0            | 0          | −1           | 1            | 1            | Very low    |
| Li et al*              | T1DM                               | −1           | −2            | 0            | 0          | 0            | 0            | 1            | Very low    |
| Urological disease     |                                    |               |               |              |            |              |              |              |             |
| Wang*                  | Diabetic nephropathy              | −1           | 0             | 0            | 0          | 0            | 0            | 1            | Low         |
| Wijarnpreecha et al*   | ESRD in adult                     | −1           | −2            | 0            | 0          | 0            | 0            | 0            | Very low    |
| Digestive disorders    |                                    |               |               |              |            |              |              |              |             |
| Eriss et al*           | Barrett’s oesophagus              | −1           | −2            | 0            | 0          | −1           | 0            | 1            | Very low    |
| Li et al*              | Gastric ulcer                     | −1           | 0             | 0            | 0          | 0            | 0            | 1            | Low         |
| Li et al*              | Duodenal ulcer                    | −1           | −1            | 0            | 0          | 0            | 0            | 1            | Low         |
| Cremonini et al*       | GERD in population with HP- negative status | −1           | −1            | 0            | 0          | 0            | 0            | 1            | Very low    |
| Weck and Brenner*      | Chronic atrophic gastritis        | −1           | −2            | 0            | 0          | −1           | 2            | 1            | Very low    |
| Zhou et al*            | Biliary lithiasis                 | −1           | −1            | 0            | 0          | 0            | 1            | 1            | Low         |
| Shiota et al*          | Peptic ulcer disease              | −1           | 0             | 0            | 0          | 0            | 0            | 1            | Low         |
| Jiang et al*           | Ammonia levels in cirrhotic patients | −1           | 0             | 0            | 0          | 0            | 0            | 1            | Low         |
| Ford et al*            | Dyspepsia                          | −1           | −1            | 0            | 0          | 0            | 0            | 1            | Very low    |
| Feng et al*            | Alcoholic cirrhosis in all population | −1           | −2            | 0            | 0          | 0            | 0            | 1            | Very low    |
| Feng et al*            | Alcoholic cirrhosis in European    | −1           | 0             | 0            | −1         | 0            | 1            | 1            | Low         |
| Wu et al*              | Inflammatory bowel disease         | −1           | 0             | 0            | 0          | 0            | 1            | 1            | Moderate    |
| Wang et al*            | Chronic hepatitis C                | −1           | −1            | 0            | 0          | 0            | 1            | 1            | Low         |
| Wang et al*            | Chronic hepatitis B                | −1           | −2            | 0            | 0          | −1           | 1            | 1            | Very low    |
| Wijarnpreecha et al*   | NAFLD                              | −1           | 0             | 0            | 0          | 0            | 0            | 1            | Low         |
| Cen et al*             | Chronic cholecystitis and cholelithiasis | −1           | 0             | 0            | 0          | 0            | 1            | 1            | Moderate    |
| Shah et al*            | Eosinophilic oesophagitis          | 0            | −1            | 0            | 0          | 0            | 0            | 1            | Low         |
| Shah et al*            | Oesophageal eosinophilia           | 0            | −1            | 0            | 0          | 0            | 0            | 1            | Low         |
### Table 5 Continued

| Included meta-analyses | Association between H. pylori and* | Downgrade factors | Upgrade factors | Plausible confounding would change the effect | GRADE class |
|------------------------|-----------------------------------|-------------------|----------------|--------------------------------------------|-------------|
| **Neurocognitive disorders** | | | | | |
| Wang et al\(^{55}\) | Diabetic neuropathy | −1 | 0 | 0 | 0 | 0 | 0 | 1 | Low |
| Wang et al\(^{51}\) | Ischaemic stroke | −1 | −1 | 0 | 0 | −1 | 0 | 1 | Very low |
| Yu et al\(^{50}\) | Stroke | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Very low |
| Shinder-Itskovitch et al\(^{61}\) | Dementia | −1 | −2 | 0 | 0 | 0 | 0 | 1 | Very low |
| Shen et al\(^{59}\) | Parkinson’s disease | 0 | 0 | 0 | 0 | −1 | 0 | 1 | Low |
| **Pregnancy-related disorders** | | | | | |
| Ng et al\(^{45}\) | Hyperemesis gravidarum | −1 | 0 | 0 | 0 | 0 | 0 | 1 | Low |
| Zhan et al\(^{72}\) | Pre-eclampsia | −1 | −1 | 0 | 0 | −1 | 0 | 1 | Very low |
| Zhan et al\(^{73}\) | Fetal growth restriction | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Low |
| Zhan et al\(^{72}\) | Gestational DM | −1 | 0 | 0 | 0 | 0 | 0 | 1 | Moderate |
| Zhan et al\(^{72}\) | Spontaneous abortion | −1 | 0 | 0 | 0 | 0 | 0 | 1 | Low |
| Zhan et al\(^{72}\) | Birth defect | −1 | 0 | 0 | 0 | 0 | 0 | 1 | Low |
| Zhan et al\(^{72}\) | Stillbirth | −1 | 0 | 0 | 0 | 0 | 0 | 1 | Moderate |
| Zhan et al\(^{72}\) | Low birth weight | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Very low |
| Zhan et al\(^{72}\) | Premature delivery | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Very low |
| **Ophthalmic diseases** | | | | | |
| Wang et al\(^{55}\) | Diabetic retinopathy | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Very low |
| Zeng et al\(^{71}\) | Open-angle glaucoma | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Low |
| **Thyroid disease** | | | | | |
| Hou et al\(^{67}\) | Autoimmune thyroid diseases | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Low |
| Hou et al\(^{67}\) | Graves’s disease | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Low |
| Hou et al\(^{67}\) | Hashimoto’s thyroiditis | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Low |
| **Homeopathy disorders** | | | | | |
| Hudak et al\(^{76}\) | Iron deficiency anaemia | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Very low |
| Hudak et al\(^{76}\) | Iron deficiency | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Very low |
| Hudak et al\(^{76}\) | Anaemia | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Very low |
| **Other outcomes** | | | | | |
| Nweneka and Prentice\(^{48}\) | Circulating ghrelin levels | −1 | −1 | 0 | 0 | 0 | 0 | 1 | Very low |
| Xiong et al\(^{64}\) | Henoch-Schonlein purpura | −1 | 0 | 0 | 0 | −1 | 1 | 1 | Low |
| Su et al\(^{52}\) | Migraine | −1 | −1 | 0 | 0 | −1 | 0 | 1 | Very low |
Included meta-analyses & Association between H. pylori and* & Risk of bias & Inconsistency & Indirectness & Imprecision & Publication bias & Large effect & Plausible confounding would change the effect & GRADE class

| Reference | Disease | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding would change the effect | GRADE class |
|-----------|---------|--------------|---------------|--------------|-------------|-----------------|-------------|---------------------------------------------|-------------|
| Li et al| Recurrent aphthous stomatitis | -1 | 0 | 0 | -1 | 0 | 0 | 1 | Very low |
| Taye et al| Atopy | -1 | 0 | 0 | 0 | 0 | 0 | 1 | Low |
| Hwang et al| Chronic tonsillitis | -1 | -1 | 0 | 0 | 0 | 0 | 1 | Very low |
| Gu et al| Chronic urticaria | -1 | -1 | 0 | 0 | -1 | 0 | 1 | Very low |
| Yao et al| Multiple sclerosis | -1 | 0 | 0 | 0 | -1 | 0 | 1 | Very low |
| Dou et al| Halitosis | -1 | -2 | 0 | 0 | -1 | 0 | 1 | Very low |
| Jørgensen et al| Rosacea | -1 | -2 | 0 | 0 | 0 | 0 | 1 | Very low |
| Chen et al| Sjogren’s syndrome | -1 | 0 | 0 | 0 | 0 | 0 | 1 | Low |
| Yong et al| Psoriasis | -1 | -1 | 0 | 0 | -1 | 0 | 1 | Very low |
| Yong et al| Systemic sclerosis | -1 | 0 | 0 | 0 | 0 | 1 | 1 | Moderate |

Reference: -1 means downgrade one level; -2 means downgrade two levels; 1 means upgrade one level.

* prevalence or incidence unless otherwise specified.

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DM, diabetes mellitus; EAC, oesophageal adenocarcinoma; ESCC, oesophageal squamous cell carcinoma; ESRD, end-stage renal disease; GERD, gastro-oesophageal reflux disease; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HP, H. pylori; IHD, ischemic heart disease; NAFLD, non-alcoholic fatty liver disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
than AMSTAR. In this umbrella review, 95% of the methodological qualities of existing meta-analyses studying the associations between *H. pylori* infection and diverse health outcomes were critically low, suggesting that the results of the meta-analyses might be inconclusive, and further meta-analyses with high methodological quality should be conducted to verify such conclusions.

We also adopted the GRADE system criteria, which are credibility-assessment criteria, to assess the evidence quality of outcomes from meta-analyses. The certainty of evidence is important for the recommendation of guidelines, affecting a patient’s outcomes. GRADE re-evaluates the quality of evidence and rates the certainty evidence for clinical decision-makers and guideline developers. This system is also used worldwide. We downgraded the evidence level because all of the meta-analyses exhibited a potential risk of bias, but we upgraded the evidence level because the result of the included meta-analyses might be affected by various potential confounders, such as age, sex or smoking. Although conducting AMSTAR 2 and GRADE classification was relatively subjective, they were performed by two investigators independently, and the results were checked by another investigator. The inconsistencies were resolved via a discussion, and all discrepancies were arbitrated by another researcher, thereby greatly reducing the subjectivity.

In terms of the study weakness, this umbrella review focused on the existing and published systematic review and meta-analyses and only included publications in Chinese and English. Thus, we might have missed some studies on the associations between *H. pylori* infection and diverse health outcomes. The potential missing data in other languages might affect the evaluation results. In this umbrella review, only systematic reviews and meta-analyses were included. Evidence from individual observational studies involving undeveloped a meta-analysis was not in the scope of our discussion, such as MALT lymphoma. This situation might result in conclusion bias of association between *H. pylori* infection and human health. In addition, we could not obtain a clear exposure time because most of the meta-analyses did not present the length of time of *H. pylori* infection. Most of the meta-analyses had heterogeneity, but we did not re-explore the factors causing heterogeneity, such as population characteristics (eg, age, sex and nationality), study design and study region. Common flaws are evident among meta-analyses. The evidence quality of meta-analyses depends on the quality of original individual studies included in meta-analyses. However, this umbrella review did not assess the quality of the original individual studies included in the meta-analyses. We extracted the data for calculation from the included meta-analyses but not from the original individual studies, possibly affecting the conclusion of this umbrella review.

**Clinical implications and future research**

Clinicians have considered whether individuals should be tested for *H. pylori* or offered eradication therapy for *H. pylori* infection since multiple unfavourable influences on human health related to *H. pylori* infection have been found. Different suggestions on addressing *H. pylori* infection have been provided in different guidelines because of objective factors (eg, local drug resistance, economic level, and medical and health conditions). Several guidelines, including Asian guidelines, recommend screening in every individual, whereas other guidelines recommend no screening. The different recommendations regarding *H. pylori* detection and eradication in different guidelines may cause confusion among clinicians. The significance of our study mostly included the summary of the diseases associated with *H. pylori* and the clarification of evidence quality to guide clinical practice.

Our umbrella review found that 69% of outcomes were unfavourable influences on human health which should be paid attention to by clinicians, even though most of them were low-quality evidence. In terms of eradication therapy for *H. pylori* infection, the beneficial influence (*H. pylori* infection as a protect factor) on human health might be considered by clinicians. This umbrella review found that a decreased risk of 13 types of conditions (eg, inflammatory bowel disease, laryngeal and oesophageal carcinoma) was also found, even though *H. pylori* was associated with an increased risk of a large proportion of diseases. *H. pylori*–eradicating drugs have adverse effects, such as increased resistance of *H. pylori*. Therefore, for an individual who tests positive, whether *H. pylori* infection is a risk factor or a protective factor should be distinguished before he/she receives eradication therapy. Before deciding on administering eradication therapy, clinicians should weigh the advantages and disadvantages of eradicating *H. pylori* based on an individual's situation.

Future prospective studies on *H. pylori* infection and health outcomes should use time-varying exposure (*H. pylori* infection duration) and confounder information to better model the association between *H. pylori* infection and health outcomes. Data remain scarce, and a large heterogeneity exists in some associations of *H. pylori* infection.
*Helicobacter pylori* infection and diseases. Prospective studies should be carried out to better characterise these associations. In the absence of data from RCTs for *H. pylori* infection and risk of developing diseases, Mendelian randomisation analyses may be useful in determining whether an observed association is likely to be causal. Meta-analyses investigating associations between *H. pylori* infection and some diseases, such as autoimmune liver disease, have not been found in our scope. A meta-analysis may be conducted to confirm these conclusions in the future because of the possible inconsistent results in different individual studies.

CONCLUSION

This umbrella review systematically and comprehensively collected a large amount of existing evidence on the associations between *H. pylori* infection and diverse health outcomes from published meta-analyses to help clinical decision-makers, guideline developers and investigators evaluate these associations. Although 60 meta-analyses explored 88 unique outcomes, moderate evidence only existed in six outcomes with statistical significance. *H. pylori* infection may be associated with a decreased risk of irritable bowel syndrome and an increased risk of hypertriglyceridemia, chronic cholecystitis and cholelithiasis, gestational diabetes mellitus, gastric cancer and systemic sclerosis. Further prospective studies and large RCTs with a good assessment of associations between *H. pylori* infection and health outcomes should be conducted to draw a firm conclusion.

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