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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 eligible 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 (I^2=50%–75%) and 24 had high heterogeneity (I^2>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 hypertriglyceridemia, chronic cholecystitis and cholelithiasis, gestational diabetes mellitus, gastric cancer and systemic sclerosis.

Trial registration CRD42019124680.

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.

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[14] and myocardial infarction (MI) nearly 2-fold.[15] Subsequently, with further research on *H. pylori* infection, it may be beneficial to health

in some conditions by decreasing the risk of diseases (e.g. asthma,[16] inflammatory bowel disease[17] and oesophageal cancer).[18] 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 reanalysed. 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 I^2 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), I^2, Egger's test or publication bias, the 2×2 table data from studies included in those meta-analyses were extracted for reanalysis.

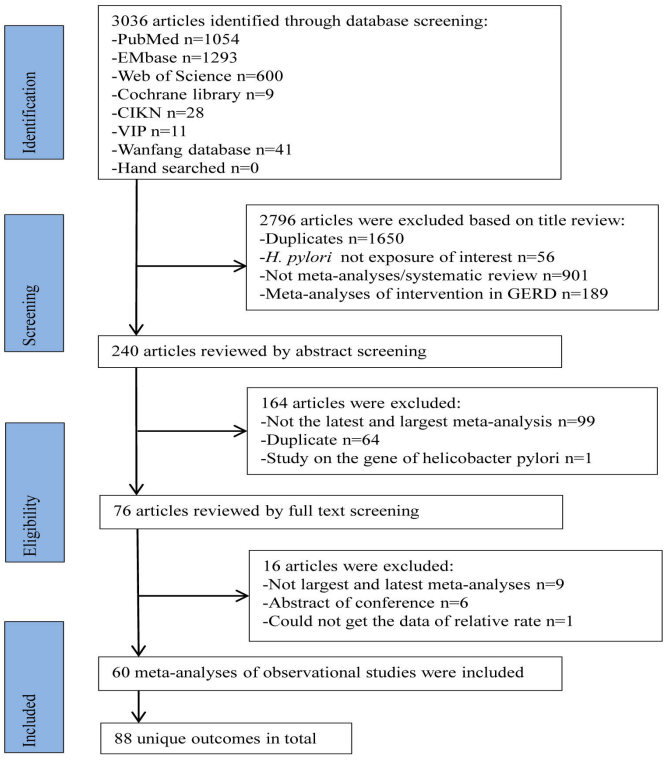

Figure 1 Flowchart of study selection process for umbrella review.

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),[19] 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.[19–21] 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.[22 23] 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 confouding 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 GRADE[22 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.[22 23] 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.[24 25] Publication bias was estimated by using Egger's test.[26] The overall effects of pooled meta-analysis, heterogeneity was considered significant at p value <0.1. Publication bias was cnsidered 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 articles[9–18 27–76] of observational studies were finally selected, covering 88 unique outcomes (figure 1). Fifty-four meta-analyses[10–17 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

Table 1 Description of 60 meta-analyses of H. pylori infection and prevalence or incidence of diseases included in umbrella review

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[†]	I^2 (%)	P value[‡]	Whether exist publication bias
Cancer outcomes												
Xuan *et al*[13]	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[44]	Lung cancer	ELISA	5 CCS;1 PNCCS; 1 PCS	17 951	16 244	OR	2.29 (1.34 to 3.91)	0.032	<0.01	83.9	NA	No[§]
Xie *et al*[18]	ESCC in Eastern populations	S; H; R; His $^{+}$; HpSe $^{+}$	16 OS	7665	1961	OR	0.66 (0.43 to 0.89)	NA	<0.01	74.5	0.42	No
Xie *et al*[18]	EAC in the overall population	S; H; U; His $^{+}$; HpSe $^{+}$	15 OS	6035	1330	OR	0.59 (0.51 to 0.68)	NA	0.13	29.9	0.37	No
Wang *et al*[58]	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*[14]	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[75]	Colorectal cancer	IgG; UBT; CagA	21 CCS; 2 CSS	182 561	24 295	OR	1.42 (1.38 to 1.46)	0	<0.01	71	0.74	No
Zhou *et al*[74]	Laryngeal carcinoma	ELISA; H; PCR	11 CCS	1030	418	OR	2.87 (1.7 to 4.84)	0	0.00	67.1	0.62	No
Liu[28]	Colon neoplasia	IgG; IgA; UBT; H; CaA	24 CCS; 7 CSS; 2 NCCS	25 897	12 145	OR	1.63 (1.39 to 1.90)	0	<0.01	80	0.14	No
Li *et al*[12]	Gastric cancer	WB; Chip; ELISA; neutralisation assay; EIA	10 CCS	1094	664	OR	2.78 (1.98 to 3.89)	0	0.23	22.8	0.1	No
Ma *et al*[42]	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*[41]	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*[47]	Ischaemic heart disease	CagA	3 PCS	2140	966	OR	1.26 (1.05 to 1.51)	<0.00001	0.01	53	NA	No[§]
Pasceri *et al*[47]	Cerebral ischaemia	CagA	4 RCCS	1103	446	OR	2.43 (1.89 to 3.13)	<0.00001	0.43	0	NA	No[§]
Wang *et al*[55]	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*[15]	Myocardial infarction	NA	19 CSS; 7 PCS	21 960	11 156	OR	1.73 (1.37 to 2.17)	0	0.00	87.9	0.71	No
Chen *et al*[48]	Coronary heart disease	NA	12 CSS; 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*[43]	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*[65]	Arrhythmia	IgG; ^{13}C-UBT; UBT	7 CCS	2014	1032	OR	1.80 (1.08 to 2.99)	0.024	<0.001	80	0.28	No
Dong *et al*[76]	Carotid intima thickness	NA	9 CCS	1370	694	SMD	0.80 (0.69 to 0.92)	<0.01	0.00	89.7	NA	No[§]
Respiratory disorders												
Wang *et al*[57]	COPD	S; ^{14}C-UBT	9 CCS	9465	3192	OR	2.25 (1.73 to 2.92)	0	0.00	75.5	0.27	No
Wang *et al*[57]	Chronic bronchitis	S; ^{14}C-UBT	5 CCS	5674	1824	OR	1.57 (1.33 to 1.86)	0	0.04	58.2	0.51	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[*]	P value[†]	I^2 (%)	P value[‡]	Whether exist publication bias
Chen *et al*[16]	Asthma	SA; ELISA; IgG; ^{13}C-UBT	8 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	7905	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	7596	NA	MD	8.12 (3.05 to 13.2)	NA	0.04	71	0.92	No
Upala *et al*[54]	Systolic blood pressure	UBT; biopsy; culture	5 CSS; 1 CS	7172	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 0.58)	NA	<0.01	57	0.92	No
Upala *et al*[54]	HOMA-IR	UBT; biopsy	7 CSS; 3 CS	7935	NA	MD	0.38 (0.03 to 0.73)	NA	0.03	85	0.92	No
Li *et al*[39]	DM	^{13}C-UBT; R; ^{14}C-UBT; SA; biopsy; culture; H	8 CSS; 68 CCS; 3 PCS	57 397	28 542	OR	1.69 (1.47 to 1.95)	0	<0.00001	86	0	Yes
Li *et al*[39]	T2 DM	^{13}C-UBT; R; ^{14}C-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	^{13}C-UBT; R; ^{14}C-UBT; biopsy; H	1 PCS; 11 CCS	3175	969	OR	1.23 (0.77 to 1.96)	0.499	<0.00001	82	0.46	No
Urological disease												
Wang *et al*[56]	Diabetic nephropathy	^{13}C-UBT; ELISA; H	6 CCS	636	211	OR	1.6 (1.1 to 2.33)	0.018	0.44	0	0.98	No
Wijarnpreecha *et al*[62]	ESRD in adult	A; H; R; UBT; SA; culture	33 CSS	NA	NA	RR	0.71 (0.55 to 0.94)	NA	<0.00001	79	NA	No[§]
Digestive disorders												
Erőss *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*[12]	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*[12]	Duodenal ulcer	WB; Chip; ELISA; neutralisation assay; EIA	17 CCS	2359	1333	OR	2.06 (1.50 to 2.84)	0	0.01	51.3	0.63	No
Cremonini *et al*[30]	GERD in population with HP-negative status	R; S; biopsy; H; UBT; Gram stain; culture; H&E; Giemsa stain	14 CCS	2010	1683	OR	1.34 (1.15 to 1.55)	0	<0.001	NA	NA	No[§]
Weck and Brenner[11]	Chronic atrophic gastritis	NA	34 OS	7726	5048	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	1333	432	OR	2.59 (1.21 to 5.55)	0.014	<0.0001	69.5	0.18	No
Shiota *et al*[10]	Peptic ulcer disease	PCR	42 CCS	4601	2524	OR	1.25 (1.09 to 1.44)	0.002	0.39	4.6	0.78	No
Jiang *et al*[37]	Ammonia levels in cirrhotic patients	^{14}C-UBT; R; H; culture; IgG	6 OS	396	632	SMD	0.34 (0.21 to 0.47)	NA	0.12	42.1	0.11	No
Ford *et al*[9]	Dyspepsia	NA	13 CSS	25 305	9010	OR	1.18 (1.04 to 1.33)	NA	<0.001	63	0.3	No
Feng *et al*[33]	Alcoholic cirrhosis in all population	R; UBT; H; ELISA	8 CCS	14 226	10053	OR	0.82 (0.35 to 1.91)	0.648	0.00	84.5	0.67	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[*]	P value[†]	I^2 (%)	P value[‡]	Whether exist publication bias
Feng *et al*[33]	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*[59]	Chronic hepatitis B	S	15 CCS	5129	2845	OR	3.17 (2.38 to 4.22)	0	0.00	77.9	0.02	Yes
Wijarnpreecha *et al*[63]	NAFLD	EIA; IgG; ^{14}C-UBT; H; S; SA	5 CSS; 1 CCS	38594	NA	OR	1.21 (1.07 to 1.37)	0.002	0.08	49	NA	No[§]
Cen *et al*[27]	Chronic cholecystitis and cholelithiasis	H; PCR; culture	18 CCS	1544	NA	OR	3.02 (1.90 to 4.82)	NA	0.21	20.1	0.43	No
Shah *et al*[49]	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*[49]	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	520	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*[70]	Stroke	S	6 CS; 4 CCS	166041	1769	OR	0.96 (0.78 to 1.14)	NA	0.03	48	0.68	No
Shindler-Itskovitch *et al*[51]	Dementia	Biopsy; IgG; IgA; R; H; CagA	1 CS; 6 CCS	86606	NA	OR	1.71 (1.17 to 2.49)	0.01	<0.001	76.1	0.33	No
Shen *et al*[50]	Parkinson's disease	ELISA; PCR; ^{13}C-UBT; H; prescriptions for HP eradication drug	6 CCS; 2 CSS	28201	1101	OR	1.59 (1.37 to 1.85)	0	0.55	0	0.02	Yes
Pregnancy-related disorders												
Ng *et al*[45]	Hyperemesis gravidarum	Biopsy; H; ELISA; IgG; CagA; EIA; ^{13}C-UBT; SA	33 CCS; 4 CSS; 1 CS	10289	NA	OR	1.35 (1.16 to 1.54)	<0.01	0.06	28	0.76	No
Zhan *et al*[72]	Pre-eclampsia	ELISA; CLIA; Heli-Blot assay; SA; UBT; WB	3 CS; 12 CCS; 1 CSS	10402	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	6009	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; CLIA	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	10121	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	12356	NA	OR	1.35 (0.86 to 2.12)	NA	0.18	70	NA	Unclear
Ophthalmic diseases												
Wang *et al*[55]	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*[71]	Open-angle glaucoma	H; IgG; ^{13}C-UBT	18 CCS	1580	695	OR	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[*]	P value[†]	I^2 (%)	P value[‡]	Whether exist publication bias
Thyroid disease												
Hou *et al*[67]	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*[67]	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*[67]	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*[35]	Iron deficiency anaemia	R; H; ^{13}C-UBT; ^{14}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*[35]	Iron deficiency		30 CSS	23 521	NA	OR	1.33 (1.15 to 1.54)	NA	0.01	41.1	0.49	No
Hudak *et al*[35]	Anaemia		23 CSS	11 622	NA	OR	1.15 (1.00 to 1.32)	NA	0.01	NA	0.81	No
Other outcomes												
Nweneka and Prentice[46]	Circulating ghrelin levels	UBT; ELISA; S; H; culture; R; PCR	7 CS; 11 CSS; 6 CCS	956	1288	SMD	−0.42 (−0.57 to −0.27)	<0.00001	0.00	59	0.12	No
Xiong *et al*[64]	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*[52]	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*[40]	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*[53]	Atopy	H; IgG; ELISA; UBT; SA; IgA	2 CS; 3 CCS; 11 CSS	10 968	NA	OR	0.82 (0.73 to 0.91)	<0.01	0.66	0	0.85	No
Hwang *et al*[36]	Chronic tonsillitis	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*[34]	Chronic urticaria	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*[66]	Multiple sclerosis	ELISA; WB; CIA IF	9 CCS	2806	782	OR	0.73 (0.56 to 0.96)	0	0.05	48	0.07	yes
Dou *et al*[31]	Halitosis	R; 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*[38]	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*[29]	Sjogren'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*[68]	Psoriasis	IgG; ELISA; UBT; SA	4 CSS; 3 PCS; 2 CCS	1546	728	OR	1.58 (1.02 to 2.46)	0.041	0.00	64	0.03	Yes
Yong *et al*[69]	Systemic sclerosis	IgG; ELISA; IgM; ^{13}C-UBT; R	7 CSS; 1 PCS	1446	749	OR	2.11 (1.62 to 2.76)	0.00	0.33	13	0.84	No

[*]p value of significance level.
†p value of Q test.
‡p value for Egger's test.
§The publication bias was assessed using funnel plot.
¶ prevalence or incidence unless otherwise specified.
A, antibody; CagA, cytotoxin-associated gene A; CCS, case–control study; CI, confidence intervals; CLIA, chemiluminescent immunoassay; CLO, *Campylobacter*-like organism test; COPD, chronic obstructive pulmonary disease; CS, cohort study; CSS, cross-sectional study; DM, diabetes mellitus; EAC, oesophageal adenocarcinoma; EIA, enzyme immunoassay; ESCC, oesophageal squamous cell carcinoma; ESRD, end-stage renal disease; GERD, gastro-oesophageal reflux disease; H, histology; HDL-C, high-density lipoprotein cholesterol; H&E, Hematoxylin and eosin stain; His +, positive histological examination of tissue samples; HOMA-IR, homeostatic model assessment of insulin resistance; HP, *H. pylori*; HpSe [+], seropositivity for antibodies to whole cell; IF, immunofluorescence; IHD, ischaemic heart disease; MD, mean difference; NA, not applicable; NAFLD, non-alcoholic fatty liver disease; NCCS, nested case-control study; NR, not reported; OS, observational study; PCR, polymerase chain reaction; PCS, prospective cohort study; PNCS, prospective nested cohort study; R, rapid urease test; RCCS, retrospective case–control study; RCSS, retrospective cross-sectional study; RR, relative rate; S, serology; SA, stool antigen; several, several methods; SMD, standard mean difference; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; U, rapid urease test; UBT, urea breath test; WB, western blot.

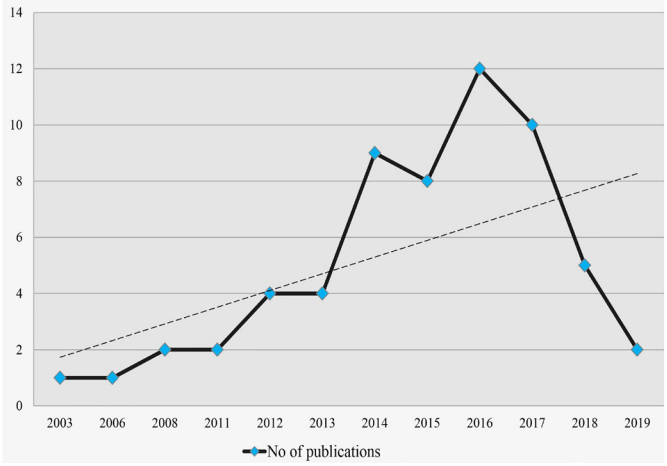

Figure 2 Number of publications per annum.

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[62] did not present the number of participants, and 12 meta-analyses[27 35 36 41 45 49 51 53 54 61–63 72] 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.

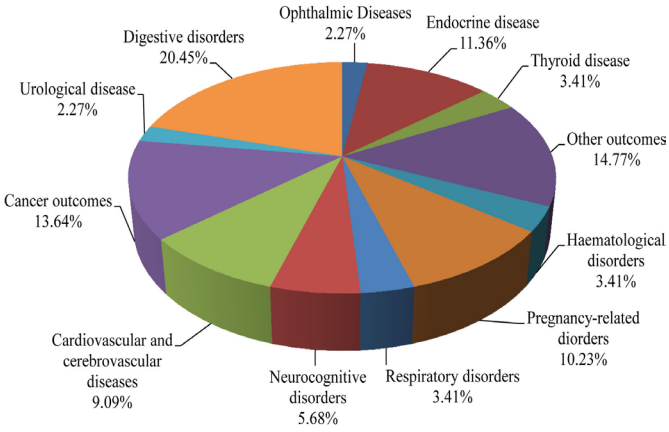

Figure 3 Map of 88 . *H. pylori*–related outcomes: percentage of outcomes per outcome category for all studies.

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, 1 (50%) 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 (I^2=50%–75%), and 24 (43%) showed high heterogeneity (I^2>75%). Among 88 meta-analyses, 68 (77%) demonstrated no statistical evidence on publication bias according to Egger's, whereas 18 (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

Table 2 Association between *H. pylori* infection and diverse diseases based on study region

Study region	Associations between *H. pylori* infection and outcomes		
	Increase risk of	Decrease risk of	No association with
Europe	Cholangiocarcinoma,[14] colorectal, cancer,[75] diabetes mellitus,[39] diabetic nephropathy,[56] alcoholic cirrhosis,[33] Parkinson's disease[50]	Barrett's oesophagus[32]	Arrhythmia,[65] asthma,[16] biliary lithiasis,[73] migraine,[52] recurrent aphthous stomatitis,[40] chronic urticaria[34]
America	Colorectal cancer,[75] biliary lithiasis,[73] chronic urticaria[34]	Barrett's oesophagus,[32] asthma,[16] asthma[16]	Arrhythmia,[65] diabetes mellitus,[39] alcoholic cirrhosis,[33] recurrent aphthous stomatitis[40]
East (Asia, China)	Cholangiocarcinoma,[14] colorectal cancer,[75] colon neoplasia,[28] arrhythmia,[65] diabetes mellitus,[39] diabetic nephropathy,[56] biliary lithiasis,[73] ammonia levels in cirrhotic patients,[37] chronic cholecystitis and cholelithiasis,[27] Parkinson's disease,[50] open-angle glaucoma,[71] Henoch-Schonlein purpura,[64] migraine,[52] chronic urticaria[34]	Oesophageal squamous cell carcinoma,[13] Barrett's oesophagus,[32] asthma[16]	Myocardial infarction,[15] COPD,[57] biliary lithiasis,[73] peptic ulcer disease,[10] alcoholic cirrhosis,[33] recurrent aphthous stomatitis,[40] multiple sclerosis[66]
West	Colon neoplasia,[28] myocardial infarction,[15] COPD,[57] peptic ulcer disease,[10] open-angle glaucoma[71]	Oesophageal adenocarcinoma,[13] asthma,[16] multiple sclerosis[66]	Oesophageal squamous cell carcinoma,[13] ammonia levels in cirrhotic patients[37]
Africa	Arrhythmia[65]		Barrett's oesophagus,[32] diabetes mellitus,[39] peptic ulcer disease[10]
Australia		Barrett's oesophagus[32]	
Oceania			Biliary lithiasis[73]

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,[27] gestational diabetes mellitus,[72] systemic sclerosis[69] and gastric cancer,[12] and increased serum triglyceride level.[54] Our confidence level in the following was low: *H. pylori* infection is associated with an increased risk of HCC,[13] biliary lithiasis,[73] PUD,[10] duodenal ulcer,[12]chronic hepatitis C,[60] non-alcoholic fatty liver disease,[63] diabetic neuropathy,[55] Parkinson's disease,[50] hyperemesis gravidarum,[45] fetal growth restriction,[72] spontaneous abortion,[72] birth defect,[72] open-angle glaucoma,[71] autoimmune thyroid diseases,[67] Grave's disease,[67] Hashimoto's thyroiditis,[67] Henoch-Schonlein purpura,[64] diabetic nephropathy,[56] gastric ulcer,[12] alcoholic cirrhosis Europeans,[33] and Sjogren's syndrome[29]; ammonia levels decrease in patients with cirrhosis.[37] Our confidence level in the following was very low: *H. pylori* infection is associated with an increased risk of lung cancer,[44] cholangiocarcinoma,[14] colorectal cancer[75], colon neoplasia,[28] chronic tonsillitis,[36] ischaemic heart disease,[47] MI,[15] coronary heart disease,[48] arrhythmia,[65] chronic bronchitis,[57] metabolic syndrome,[54] diabetes mellitus,[39] type 2 diabetes mellitus,[39] chronic atrophic gastritis,[11] dyspepsia,[9] chronic hepatitis

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	–		–		–
Moderate	Chronic cholecystitis and cholelithiasis,[27] gestational diabetes mellitus,[72] gastric cancer[12] and systemic sclerosis[69]	Triglyceride level[54]	Inflammatory bowel disease[17]	–	Stillbirth[72]
Low	Hepatocellular carcinoma,[13] biliary lithiasis,[73] peptic ulcer disease,[10] chronic hepatitis C,[60] non-alcoholic fatty liver disease,[63] diabetic neuropathy,[55] Parkinson's disease,[50] hyperemesis gravidarum,[45] fetal growth restriction,[72] spontaneous abortion,[72] birth defect,[72] open-angle glaucoma,[71] autoimmune thyroid diseases,[67] Grave's disease,[67] Hashimoto's thyroiditis,[67] Henoch-Schonlein purpura,[64] colorectal adenomatous polyp,[58] Sjogren's syndrome,[29] duodenal ulcer,[12] laryngeal carcinoma,[74] chronic obstructive pulmonary disease,[57] diabetic nephropathy,[56] gastric ulcer,[12] alcoholic cirrhosis in Europian,[33] cerebral ischaemia[47]	Ammonia levels in patients with cirrhosis[37]	Oesophageal adenocarcinoma in the overall population,[18] eosinophilic oesophagitis,[49] oesophageal eosinophilia,[49] atopy[53]	–	Diabetic ischemic heart disease, [55] fasting blood glucose[54] and diabetic ischaemic heart disease[56]
Very low	Lung cancer,[44] cholangiocarcinoma,[14] chronic tonsillitis,[36] colorectal cancer, colon neoplasia,[28] ischaemic heart disease,[47] myocardial infarction,[15] coronary heart disease,[48] arrhythmia,[65] chronic bronchitis,[57] metabolic syndrome,[54] diabetes mellitus,[39] type 2 diabetes mellitus,[39] chronic atrophic gastritis,[11] dyspepsia,[9] chronic hepatitis B,[59] ischaemic stroke,[61] dementia,[51] pre-eclampsia,[72] iron deficiency anaemia,[35] iron deficiency,[31] anaemia,[26] migraine,[52] recurrent aphthous stomatitis,[40] chronic urticaria,[34] halitosis,[31] rosacea[38] and psoriasis[68]	Carotid intima thickness,[76] body mass index[54] and homeostatic model assessment of insulin resistance[54]	Oesophageal squamous cell carcinoma in Eastern populations,[18] Barrett's oesophagus,[32] asthma,[16] end-stage renal disease in adult,[62] multiple sclerosis[66] and gastro-oesophageal reflux disease[30]	High-density lipoprotein cholesterol,[54] circulating ghrelin levels[46]	Oesophagogastric junction adenocarcinoma,[42] pancreatic cancer,[41] systolic blood prssure,[54] atherosclerosis,[43] type 1 diabetes mellitus,[39] alcoholic cirrhosis in all populations,[28] stroke,[70] low birth weight,[72] premature delivery[72] and diabetic retinopathy[70]

B,[59] ischaemic stroke,[61] dementia,[51] pre-eclampsia,[72] iron deficiency anaemia,[35] iron deficiency,[31] anaemia,[26] migraine,[52] recurrent aphthous stomatitis,[40] chronic urticaria,[34] halitosis,[31] rosacea,[38] laryngeal carcinoma,[74] cerebral ischaemia,[47] chronic obstructive pulmonary disease[57] and psoriasis[68]; an increase in the following parameters is observed: carotid intima thickness,[76] body mass index[54] and homeostatic model assessment of insulin resistance.[54]

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.[17] Our confidence level in the following was low: *H. pylori* infection is associated with a decreased risk of oesophageal adenocarcinoma in the overall population,[18] colorectal adenomatous polyp,[58] eosinophilic oesophagitis,[49] oesophageal eosinophilia[49] and atopy[53]. 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,[18] Barrett's oesophagus,[32] asthma,[16] end-stage renal disease in adults,[62] multiple sclerosis[66] and gastro-oesophageal reflux disease[30]; decreasing high-density lipoprotein cholesterol[54] and circulating ghrelin levels are also observed.[46]

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

Table 4 Detail of results for AMSTAR 2 assessing

Included meta-analyses	AMSTAR 2 checklist																Overall assessment quality
	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*[13]	Yes	No	Yes	Yes	Yes	Yes	No	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Mounika[44]	Yes	No	Yes	Partial yes	No	No	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Xie *et al*[18]	Yes	No	Yes	No	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Wang *et al*[58]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Xiao *et al*[14]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Dong and Hao[75]	Yes	No	Yes	Partial yes	No	No	Partial yes	Partial yes	No	No	No	No	Yes	Yes	Yes	No	Critically low
Zhou *et al*[74]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Liu[28]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Li *et al*[12]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Partial yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Ma *et al*[42]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Liu *et al*[41]	Yes	No	Yes	No	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Eröss *et al*[32]	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Pasceri *et al*[47]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Liu *et al*[15]	Yes	No	Yes	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Chen *et al*[48]	Yes	No	Yes	Partial yes	No	Yes	No	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Saburi *et al*[43]	Yes	No	Yes	Partial yes	No	No	Partial yes	Partial yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Critically low
Yan *et al*[65]	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Dong *et al*[76]	Yes	No	No	Yes	No	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Wang *et al*[57]	Yes	No	Yes	Partial yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Chen *et al*[16]	Yes	No	Yes	No	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Upala *et al*[54]	Yes	Yes	Yes	Partial yes	No	Yes	No	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Li *et al*[39]	Yes	No	Yes	Yes	No	No	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Wang *et al*[56]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Wijarnpreecha *et al*[62]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	No	No	Yes	No	Critically low
Cremonini *et al*[30]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Weck and Brenner[11]	Yes	No	No	No	No	No	Partial yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	Critically low
Zhou *et al*[73]	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Shiota *et al*[10]	Yes	No	Yes	Partial yes	Yes	No	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Jiang *et al*[37]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Ford *et al*[9]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Feng *et al*[33]	Yes	No	Yes	Partial yes	No	No	Partial yes	Partial yes	No	No	Yes	No	Yes	Yes	Yes	No	Critically low
Wu *et al*[17]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Partial yes	No	No	Yes	No	Yes	Yes	Yes	No	Critically low
Wang *et al*[60]	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low

Continued

Table 4 Continued

Included meta-analyses	AMSTAR 2 checklist																Overall assessment quality
	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	
Wang *et al*[59]	Yes	No	Yes	Yes	Yes	No	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Wijarnpreecha *et al*[63]	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Cen *et al*[27]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Shah *et al*[49]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Wang *et al*[55]	Yes	No	No	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Wang *et al*[61]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Yu *et al*[70]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Shindler-Itskovitch *et al*[51]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Shen *et al*[50]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Ng *et al*[45]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Zhan *et al*[72]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Zeng *et al*[71]	Yes	No	Yes	Partial yes	No	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Nweneka and Prentice[46]	Yes	No	Yes	Partial yes	No	No	Yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Xiong *et al*[64]	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Su *et al*[52]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Li *et al*[40]	Yes	No	Yes	No	Yes	No	Partial yes	Partial yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Taye *et al*[53]	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Hwang *et al*[36]	Yes	No	No	Partial yes	Yes	No	Partial yes	Partial yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Gu *et al*[34]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Yao *et al*[66]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Dou *et al*[31]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	No	Yes	Yes	No	No	Critically low
Jørgensen *et al*[38]	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Hou *et al*[67]	Yes	No	Yes	Partial yes	No	No	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Critically low
Hudak *et al*[35]	Yes	Yes	Yes	Partial yes	No	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Chen *et al*[29]	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Yong *et al*[68]	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Critically low
Yong *et al*[69]	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	No	Yes	No	Yes	No	Critically low

AMSTAR 2 checklists: No.1: Did the research questions and inclusion criteria for the review include the components of PICO? 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: Did 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 describe 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: If meta-analysis was 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?

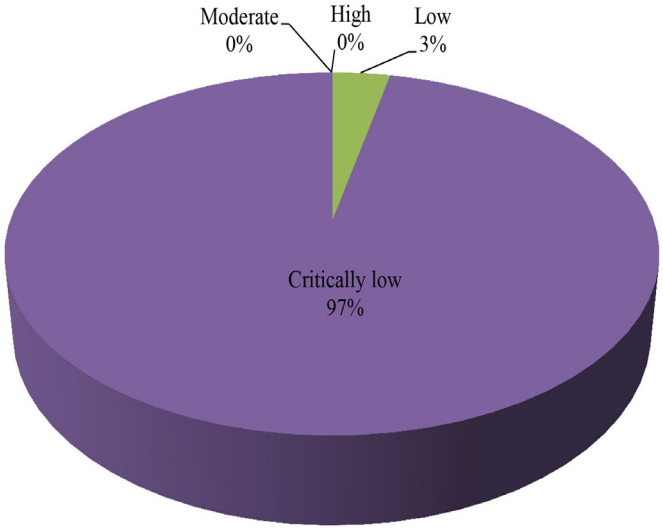

Figure 4 Map of results of AMSTAR 2: percentage of outcomes per outcome category for 88 meta-analyses.

total), including cancers, cardiovascular and cerebrovascular diseases, respiratory disorders, endocrine diseases, urological diseases, digestive disorders, neurocognitive disorders, pregnancy-related disorders, ophthalmic diseases, thyroid disease, haematological disorders and other outcomes (figure 3). *H. pylori* infection is likely more harmful in Asians by increasing the risk of 15 types of diseases (table 2). Through this umbrella review, an uptrend of research on the associations between *H. pylori* infection and health outcomes was found (figure 2). However, gaps in studies exploring the association between *H. pylori* infection and the musculoskeletal system diseases were identified as formal meta-analyses were not found. A clear reference exposure time of *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 reivew shows there is no association between *H.ylori* 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.[77] Studies have also revealed the strengths and significance of umbrella reviews in detail.[78–80] 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 limphoid 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.[19 81] The lengths of AMSTAR 2 have been described in other studies.[21 82 83] 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
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding would change the effect	
Cancer outcomes									
Xuan *et al*[13]	Hepatocellular carcinoma	–1	0	0	-1	–1	2	1	Low
Mounika[44]	Lung cancer	–1	–2	0	0	0	1	1	Very low
Xie *et al*[18]	ESCC in Eastern populations	–1	–1	0	0	0	0	1	Very low
Xie *et al*[18]	EAC in the overall population	–1	0	0	0	0	0	1	Low
Wang *et al*[58]	Colorectal adenomatous polyp	–1	0	0	0	0	0	1	Low
Xiao *et al*[14]	Cholangiocarcinoma	–1	–1	0	–1	–1	2	1	Very low
Dong and Hao[75]	Colorectal cancer	–1	–1	0	0	0	0	1	Very low
Zhou *et al*[74]	Laryngeal carcinoma	–1	–1	0	0	0	1	1	Low
Liu[28]	Colon neoplasia	–1	–2	0	0	0	0	1	Very low
Li *et al*[12]	Gastric cancer	–1	0	0	0	0	1	1	Moderate
Ma *et al*[42]	Oesophagogastric junction adenocarcinoma	–1	–2	0	0	0	0	1	Very low
Liu *et al*[41]	Pancreatic cancer	–1	–2	0	0	0	0	1	Very low
Cardiovascular and cerebrovascular diseases									
Pasceri *et al*[47]	Ischaemic heart disease	–2	–1	0	0	0	0	1	Very low
Pasceri *et al*[47]	Cerebral ischaemia	–2	0	0	0	0	1	1	Low
Wang *et al*[55]	Diabetic IHD	–1	0	0	0	0	0	1	Low
Liu *et al*[15]	Myocardial infarction	–1	–2	0	0	0	0	1	Very low
Chen *et al*[48]	Coronary heart disease	–2	–2	0	0	0	0	1	Very low
Ramezani-Binabaj *et al*[43]	Atherosclerosis	–2	–1	0	–1	–1	0	1	Very low
Yan *et al*[65]	Arrhythmia	–1	–2	0	0	0	0	1	Very low
Dong *et al*[76]	Carotid intima thickness	–1	–2	0	0	0	0	1	Very low
Respiratory disorders									
Wang *et al*[57]	COPD	–1	–1	0	0	0	1	1	Low
Wang *et al*[57]	Chronic bronchitis	–1	–1	0	0	0	0	1	Very low
Chen *et al*[16]	Asthma	–1	–1	0	0	0	0	1	Very low
Endocrine disease									
Upala *et al*[54]	Metabolic syndrome	–1	–1	0	0	0	0	1	Very low
Upala *et al*[54]	Fasting blood glucose	–1	–1	0	0	0	1	1	Low
Upala *et al*[54]	HDL-C	–1	–2	0	0	0	1	1	Very low
Upala *et al*[54]	Triglyceride level	–1	–1	0	0	0	2	1	Moderate

Continued

Table 5 Continued

Included meta-analyses	Association between H. pylori and*	Downgrade factors					Upgrade factors		GRADE class
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding would change the effect	
Upala *et al*[54]	Systolic blood pressure	–1	–2	0	0	0	1	1	Very low
Upala *et al*[54]	Body mass index	–1	–1	0	0	0	0	1	Very low
Upala *et al*[54]	HOMA-IR	–1	–2	0	0	0	0	1	Very low
Li *et al*[39]	DM	–1	–2	0	0	–1	0	1	Very low
Li *et al*[39]	T2DM	–1	–2	0	0	–1	1	1	Very low
Li *et al*[39]	T1DM	–1	–2	0	0	0	0	1	Very low
Urological disease									
Wang[56]	Diabetic nephropathy	–1	0	0	0	0	0	1	Low
Wijarnpreecha *et al*[62]	ESRD in adult	–1	–2	0	0	0	0	1	Very low
Digestive disorders									
Erőss *et al*[32]	Barrett's oesophagus	–1	–2	0	0	–1	0	1	Very low
Li *et al*[12]	Gastric ulcer	–1	0	0	0	0	0	1	Low
Li *et al*[12]	Duodenal ulcer	–1	–1	0	0	0	1	1	Low
Cremonini *et al*[30]	GERD in population with HP-negative status	–1	–1	0	0	0	0	1	Very low
Weck and Brenner[11]	Chronic atrophic gastritis	–1	–2	0	0	–1	2	1	Very low
Zhou *et al*[73]	Biliary lithiasis	–1	–1	0	0	0	1	1	Low
Shiota *et al*[10]	Peptic ulcer disease	–1	0	0	0	0	0	1	Low
Jiang *et al*[37]	Ammonia levels in cirrhotic patients	–1	0	0	0	0	0	1	Low
Ford *et al*[9]	Dyspepsia	–1	–1	0	0	0	0	1	Very low
Feng *et al*[33]	Alcoholic cirrhosis in all population	–1	–2	0	0	0	0	1	Very low
Feng *et al*[33]	Alcoholic cirrhosis in European	–1	0	0	–1	0	1	1	Low
Wu *et al*[17]	Inflammatory bowel disease	–1	0	0	0	0	1	1	Moderate
Wang *et al*[60]	Chronic hepatitis C	–1	–1	0	0	0	1	1	Low
Wang *et al*[59]	Chronic hepatitis B	–1	–2	0	0	–1	1	1	Very low
Wijarnpreecha *et al*[63]	NAFLD	–1	0	0	0	0	0	1	Low
Cen *et al*[27]	Chronic cholecystitis and cholelithiasis	–1	0	0	0	0	1	1	Moderate
Shah *et al*[49]	Eosinophilic oesophagitis	0	–1	0	0	0	0	1	Low
Shah *et al*[49]	Oesophageal eosinophilia	0	–1	0	0	0	0	1	Low

Continued

Table 5 Continued

Included meta-analyses	Association between H. pylori and*	Downgrade factors					Upgrade factors		GRADE class
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding would change the effect	
Neurocognitive disorders									
Wang *et al*[55]	Diabetic neuropathy	–1	0	0	0	0	0	1	Low
Wang *et al*[61]	Ischaemic stroke	–1	–1	0	0	–1	0	1	Very low
Yu *et al*[70]	Stroke	–1	–1	0	0	0	0	1	Very low
Shindler-Itskovitch *et al*[51]	Dementia	–1	–2	0	0	0	0	1	Very low
Shen *et al*[50]	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	1	1	Very low
Zhan *et al*[72]	Fetal growth restriction	–1	–1	0	0	0	1	1	Low
Zhan *et al*[72]	Gestational DM	–1	0	0	0	0	1	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	1	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	1	1	Low
Thyroid disease									
Hou *et al*[67]	Autoimmune thyroid diseases	–1	–1	0	0	0	1	1	Low
Hou *et al*[67]	Grave's disease	–1	–1	0	0	0	1	1	Low
Hou *et al*[67]	Hashimoto's thyroiditis	–1	–1	0	0	0	1	1	Low
Homeopathy disorders									
Hudak *et al*[35]	Iron deficiency anaemia	–1	–1	0	0	0	0	1	Very low
Hudak *et al*[35]	Iron deficiency	–1	–1	0	0	0	0	1	Very low
Hudak *et al*[35]	Anaemia	–1	–1	0	0	0	0	1	Very low
Other outcomes									
Nweneka and Prentice[46]	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

Continued

Table 5 Continued

Included meta-analyses	Association between H. pylori and*	Downgrade factors					Upgrade factors		GRADE class
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding would change the effect	
Li *et al*[40]	Recurrent aphthous stomatitis	–1	0	0	–1	0	0	1	Very low
Taye *et al*[53]	Atopy	–1	0	0	0	0	0	1	Low
Hwang *et al*[36]	Chronic tonsillitis	–1	–1	0	0	0	0	1	Very low
Gu *et al*[34]	Chronic urticaria	–1	–1	0	0	–1	0	1	Very low
Yao *et al*[66]	Multiple sclerosis	–1	0	0	0	-1	0	1	Very low
Dou *et al*[31]	Halitosis	–1	–2	0	0	–1	0	1	Very low
Jørgensen *et al*[38]	Rosacea	–1	–2	0	0	0	0	1	Very low
Chen *et al*[29]	Sjogren's syndrome	–1	0	0	0	0	0	1	Low
Yong *et al*[68]	Psoriasis	–1	–1	0	0	–1	0	1	Very low
Yong *et al*[69]	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, oesophgeal adenocarcinoma; ESCC, oesophageal squamous cell carcinoma; ESRD, end-stage renal disease; GERD, gastro-oesophageal reflux disease; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, hemeostatic 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.

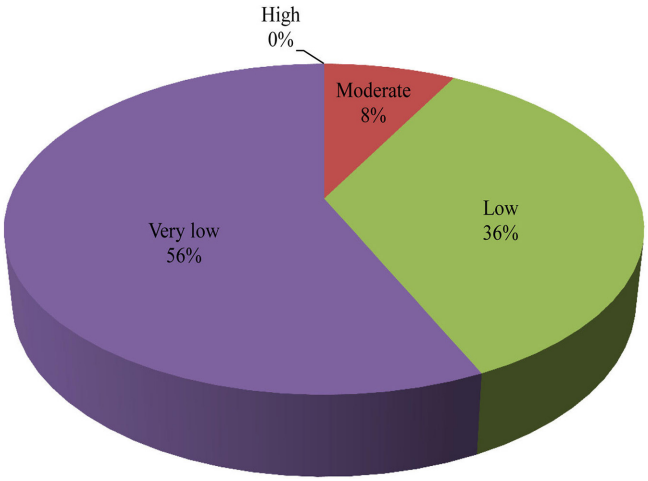

Figure 5 Map of results of GRADE: percentage of outcomes per outcome category for 88 evidence.

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.[84] GRADE re-evaluates the quality of evidence and rates the certainty evidence for clinical decision-makers and guideline developers.[22 84] 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.[85] 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.[86] 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.[87] 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 eradicating 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*.[88] 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 eradicating therapy. Before deciding on administering eradicating 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 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,[89 90] 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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