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META-ANALYSIS

Is there an association between *Helicobacter pylori* infection and irritable bowel syndrome? A meta-analysis

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is a prevalent and debilitating gastrointestinal condition. Research has reported persistent, low-grade mucosal inflammation and significant overlaps between patients with IBS and those with dyspepsia, suggesting a possible pathogenic role of *Helicobacter pylori* (*H. pylori*) in IBS. This study therefore aimed to provide the first systematic review and meta-analysis on the association between *H. pylori* infection and IBS.

AIM

To investigate the association between *H. pylori* infection and IBS.

METHODS

Using the keywords "*H. pylori* OR Helicobacter OR Helicobacter pylori OR infection" AND "irritable bowel syndrome OR IBS", a preliminary search of PubMed, Medline, Embase, Cochrane Database of Systematic Reviews, Web of Science, Google Scholar and WanFang databases yielded 2924 papers published in English between 1 January 1960 and 1 June 2018. Attempts were also made to search grey literature.

RESULTS

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A total of 13 clinical studies were systematically reviewed and nine studies were included in the final meta-analysis. Random-effects meta-analysis found a slight increased likelihood of *H. pylori* infection in patients with IBS, albeit this was not statistically significant (pooled odds ratio 1.47, 95% confidence interval: 0.90-2.40, $P = 0.123$). It must also be acknowledged that all of the available studies reported only crude odd ratios. *H. pylori* eradication therapy also does not appear to improve IBS symptoms. Although publication bias was not observed in the funnel plot, there was a high degree of heterogeneity amongst the studies included in the meta-analysis ($I2 = 87.38\%$).

CONCLUSION
Overall, current evidence does not support an association between IBS and *H. pylori* infection. Further rigorous and detailed studies with larger sample sizes and after *H. pylori* eradication therapy are warranted.

Key words: Irritable bowel syndrome; Functional; *Helicobacter pylori*; Infection; Meta-analysis

Core tip: This is the first systematic review to examine the association of *Helicobacter pylori* (*H. pylori*) infection and irritable bowel syndrome (IBS). 13 clinical studies were systematically reviewed and nine studies were included in the final meta-analysis. Random-effects meta-analysis suggests a tenuous association between the two (pooled odds ratio 1.47, 95% confidence interval: 0.90-2.40, $P = 0.123$). *H. pylori* eradication therapy also does not appear to improve IBS symptoms in the limited studies available. Further detailed trials with larger sample sizes and after *H. pylori* eradication therapy are necessary to elucidate the relationship between *H. pylori* infection and IBS pathogenesis.

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INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal (GI) disorders, characterized by chronic abdominal pain and a change in the frequency or form of stool[1]. It affects an estimated 10% to 15% of the global population[2] and carries a significant disease burden in terms of decreased productivity, increased healthcare costs and reduced health-related quality of life[3].

Despite the global prevalence of IBS, its pathophysiology remains unclear. Studies have reported disturbances in gut microbiota and persistent, subclinical systemic and mucosal inflammation in individuals with IBS[4]. Significant overlaps also exist between patients with IBS and those with dyspepsia[5], hinting at a possible pathogenic role of *Helicobacter pylori* (*H. pylori*) in IBS. *H. pylori* is a prevalent gram-negative bacterium that grows in the gut of more than half of the world's population, and it is even more common in developing countries[6]. The mode of transmission of *H. pylori* is unclear, but believed to be fecal-oral. *H. pylori*, especially strains that produce cytotoxin-associated gene A (CagA) protein, causes chronic inflammation in the stomach and duodenum, microbial dysbiosis[7] as well as elevated systemic inflammation[8]. *H. pylori* infection has been linked to several conditions, including dyspepsia and even hyperemesis gravidarum[9].

However, its role in the pathogenesis of IBS remains largely unknown. Some studies have highlighted increased rates of *H. pylori* infection in patients with IBS compared to healthy controls[10,11], while others have disputed this and found no association between *H. pylori* infection and IBS[12]. This association has been challenged as *H. pylori* is thought to affect mainly the upper GI trait instead of the lower GI tract. Some also contend that the association is merely fortuitous given the widespread prevalence of *H. pylori* infection globally[6]. This meta-analysis thus aimed to

investigate and better clarify the role of *H. pylori* in the pathogenesis of IBS. A better understanding of the pathogenesis of IBS has important clinical implications.

MATERIALS AND METHODS

Literature search was performed in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. By using the keywords "*H. pylori* OR *Helicobacter* OR *Helicobacter pylori* OR infection" AND "irritable bowel syndrome OR IBS", a preliminary search of PubMed, Medline, Embase, Cochrane Database of Systematic Reviews, Web of Science, Google Scholar and WanFang databases yielded 2924 papers published in English between 1 January 1960 and 1 June 2018. Attempts were made to search grey literature as well, using Google search engine and the Open System for Information on Grey Literature in Europe database. Title/abstract screening were performed independently by three researchers (Q.X.N., N.X.F. and W.R.L.) to identify articles of interest. For relevant abstracts, full articles were obtained, reviewed and also checked for references of interest. If necessary, the authors of the articles were contacted to provide additional data.

Full articles were obtained for all selected abstracts and reviewed by four researchers (Q.X.N., N.X.F, W.R.L. and Y.Q.K.) for inclusion. The inclusion criteria for this review were: (1) Published case-control or cross-sectional study; (2) patients with IBS; and (3) confirmed/laboratory testing for presence of *H. pylori* infection. Any disagreement was resolved by discussion and consensus amongst the three researchers. Each study was carefully reviewed and the primary outcome measure of interest was the proportion of *H. pylori* infection in patients with IBS compared to a control group. Odds ratio (OR) were calculated for each individual study, and estimates were pooled and where appropriate, 95% confidence intervals (95%CI) and P-values were calculated.

Heterogeneity amongst the different studies pooled was examined using the *I2* statistic and Cochran's *Q* test. Publication bias was assessed using a funnel plot and Egger test. All analyses were performed using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014) and STATA version 13.0 (2000; STATA Corp., College Station, TX, United States).

RESULTS

The literature search and abstraction process (and reasons for exclusion) was detailed in Figure 1. The key details of each study were extracted and summarized in Table 1[10-22]. A total of 13 studies were systematically reviewed. Four studies were excluded from the final meta-analysis as three did not have a control group while one did not detect *H. pylori* infection in either patients with IBS or healthy controls, hence no OR could be calculated.

As seen in Figure 2, the studies had an overall high degree of heterogeneity (*I2* = 87.38%), likely due to the different study designs and method of detection of *H. pylori* employed. Random-effects meta-analysis found that patients with IBS did not have a significantly increased likelihood of *H. pylori* infection, as the pooled OR was 1.47 (95%CI: 0.90-2.40, *P* = 0.123). Separate subgroup analyses and sensitivity analyses were likely underpowered and hence, were not conducted due to the small number of studies available. With regard to the possibility of publication bias, visual inspection of the funnel plot revealed a roughly symmetrical distribution of studies (Figure 3) and encouragingly, Egger test was not significant for publication bias (*P* = 0.189).

DISCUSSION

Overall, current evidence suggests that patients with IBS may have an increased likelihood of *H. pylori* infection, but this is not statistically significant (pooled OR 1.47, 95%CI: 0.90-2.40, *P* = 0.123). It must also be acknowledged that all of the available studies reported only crude odd ratios and did not adjust for potential confounders, further weakening any potential association between IBS and *H. pylori* infection. To the best of our knowledge, this review is the first to examine the association between IBS and *H. pylori* infection. The current meta-analysis is therefore a novel and significant contribution to current literature.

It is well demonstrated that *H. pylori* infection leads to chronic inflammation and is involved in the etiopathogenesis of atrophic gastritis, intestinal metaplasia and peptic

Table 1 Characteristics of all studies included in this meta-analysis (arranged alphabetically by first author's last name)

First author, Year	Study design	Study sample (*n*)	Country	Diagnosis of IBS	Method of *H. pylori* detection	Odds ratio (95%CI)	Conclusions
Abdelrazak *et al*[10], 2015	Case control	550	Egypt	Rome III criteria	Stool antigen test or ^{13}C-urea breath test positive	8.56 (4.06, 18.05)	Significantly higher rate of *H. pylori* detection in pediatric patients with IBS compared to healthy controls
Agreus *et al*[13], 1995	Case control	150	Sweden	More than 2 of the following symptoms (feeling of incomplete defecation, mucous stools, abdominal distension, abdominal pain or discomfort on defecation or relieved by defecation) and diarrhoea/constipation/or alternating diarrhoea and constipation and abdominal discomfort	Serum IgG by ELISA	0.56 (0.25, 1.25)	No association between *H. pylori* seropositivity and dyspepsia or IBS
Corsetti *et al*[14], 2004	Case control	309	Belgium	Rome II criteria	Gastric biopsy specimens	0.74 (0.36, 1.51)	The prevalence of *H. pylori* infection did not differ between patients with functional dyspepsia alone and patients with functional dyspepsia and IBS
El-Badry *et al*[15], 2018	Cross sectional	115	Egypt	Rome III criteria	*H. pylori* stool coproantigen	NA	*H. pylori* was detected in 55.7% of patients with IBS
Gerards *et al*[16], 2001	Case control	46	Germany	Not specified	^{13}C-urea breath test	0.96 (0.24, 3.87)	Rectal distension produced abdominal pain only in patients with IBS and who were *H. pylori* infected. *H. pylori* may contribute to visceral hypersensitivity
Hasan *et al*[17], 2017	Cross sectional	184	Iraq	Based on clinical and ultrasonography results	Serum IgG by ELISA	0.54 (0.278, 1.03)	Rate of *H. pylori* infection similar between patients with IBS and healthy controls
Locke *et al*[18], 2000	Cross sectional	148	United States	Abdominal pain with at least two of six Manning criteria symptoms	Serum IgG by ELISA and CagA IgG	7.22 (2.91, 17.9)	After adjusting for age, CagA-positivity but not *H. pylori* seropositivity was associated with IBS
Malinen *et al*[12], 2005	Case control	49	Finland	Rome II criteria	Real-time PCR analysis of fecal samples	NA	*H. pylori* was not detected in any of the control or test subjects. PCR assay may lack sensitivity

McDonald *et al*[19], 2017	Cross sectional	112	Peru	Rome III criteria	Endoscopy specimens	NA	*H. pylori* infection was detected in 58 (57.4%) of patients with IBS
Su *et al*[20], 2000	Cross sectional	69	Taiwan	Rome I criteria	^{13}C-urea breath test and endoscopy specimens	NA	*H. pylori* infection was detected in 33 (47.8%) of patients with IBS
Xiong *et al*[21], 2016	Case control	502	China	Rome III criteria	Not specified (presumably seropositivity)	0.96 (0.77, 1.19)	The prevalence of *H. pylori* infection in patients with IBS-D was similar to the general population and eradication therapy did not improve symptoms
Yakoob *et al*[22], 2012	Case control	330	Pakistan	Rome III criteria	Gastric biopsy specimens	1.76 (1.12, 2.75)	*H. pylori* infection was common in patients with IBS-D, and was associated with predominantly cagAs1-positive strains
Yang *et al*[11], 2017	Case control	670	China	Rome III criteria	Positive for rapid urease test and ^{14}C-urea breath test	1.62 (1.19, 2.20)	The rate of *H. pylori* infection was significantly higher in patients with IBS-D than healthy controls, however, eradication of *H. pylori* did not improve symptoms

H. pylori: *Helicobacter pylori*; CagA: Cytotoxin-associated gene A; ELISA: Enzyme-linked immunosorbent assay; IBS: Irritable bowel syndrome; IBS-D: Irritable bowel syndrome associated with diarrhea; NA: Not available.

ulcers[23]. Patients with IBS have been found to have increased lamina propria immune cells in the colonic mucosa[24] and significantly reduced levels of oleoylethanolamide (a fatty acid amide with anti-inflammatory properties) when compared to healthy controls[25]. These are suggestive of chronic, subclinical inflammation at the microscopic level[26]. Increased infiltration of mucosal mast cells have also been reported in the GI tract of patients with IBS when compared to healthy controls[27]. In considering the possible pathogenic mechanisms of *H. pylori* in relation to IBS, *H. pylori* infection has been associated with elevated inflammatory markers[8], increased mast cell activation[28] and gastric mucosal and neural remodeling[29]. Vacuolating cytotoxin A[30] and the neutrophil-activating protein[28] of *H. pylori* are both potent mast cell stimulators. Although a definite and consistent pattern of immune dysregulation has yet to be established in patients with IBS, increased mast cell activation and immune activity in the gut may correlate with symptoms of visceral hypersensitivity[31].

Furthermore, in a study utilizing the rectal barostat to elicit abdominal symptoms in patients with IBS, positive results were seen almost exclusively in *H. pylori*-positive patients with IBS, suggesting a potential role of *H. pylori* in stimulating visceral hypersensitivity[16]. Preclinical and clinical studies have often reported a link between increased intestinal mucosal inflammation and changes in sensory-motor function[32,33]. As such, *H. pylori* infection may result in gastric dysmotility and neuroplastic changes in the afferent neural pathways, giving rise to visceral hypersensitivity and prototypical IBS symptoms.

On the other hand, contrary findings have also been reported. A study on patients with functional dyspepsia found no association between *H. pylori* infection and increased pain perception of gastric distension[34]. Studies that investigated the effect of *H. pylori* eradication therapy on IBS symptoms also found no significant differences at follow-up[11,21]. However, the relationship is difficult to analyse as it may be confounded by the fact that *H. pylori* is eradicated with antibiotics, which is also associated with a significantly increased risk of developing IBS[35] and may also aggravate IBS symptoms[36].

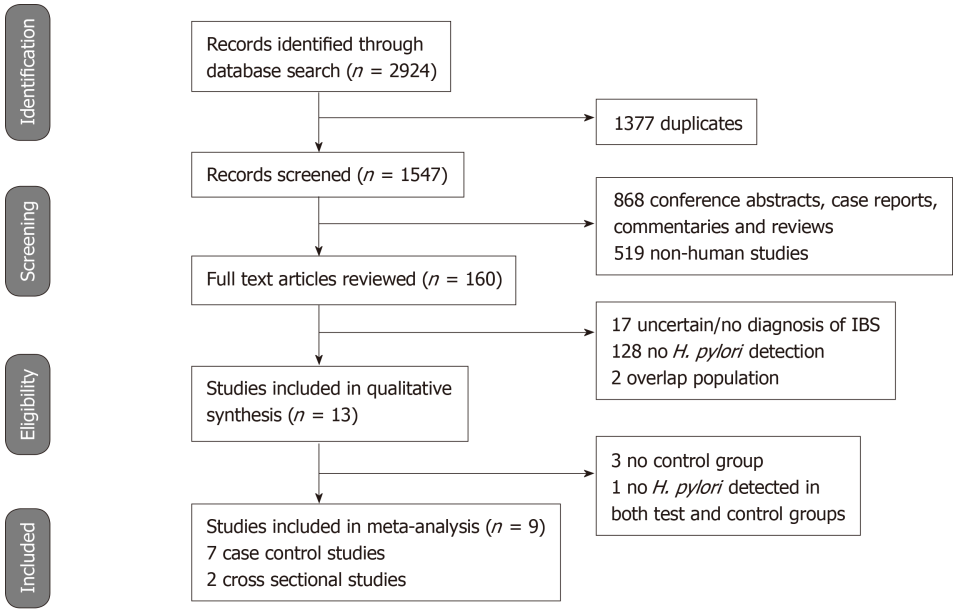

Figure 1 Meta-analysis of observational studies flowchart showing the studies identified during the literature search and abstraction process.*H. pylori*: *Helicobacter pylori*; IBS: Irritable bowel syndrome.

A fundamental understanding of the pathogenesis of IBS is still lacking. Additionally, psychological factors such as stress, depression and anxiety are known to contribute to the pathogenesis[37]. Our study investigated another potential contributory factor. Patients with IBS may have an increased likelihood of *H. pylori* infection albeit this is not statistically significant. The role of *H. pylori* eradication therapy is also unclear as it does not appear to improve IBS symptoms in the limited studies available.

Other limitations of current evidence that must be discussed include the fact that some of the available studies[13,18] used a self-report symptom questionnaire in the diagnosis of IBS. There is a known wide variability in the definition of constipation and diarrhoea[38], and the subjectivity and inter-study variability in the diagnosis of IBS could further affect the reliability of current findings. Also, some of the studies[13,18] included in the meta-analysis did not investigate study participants for organic disease that may contribute to IBS-like symptoms. Limited studies also performed CagA testing. In one study[18], CagA antibody positivity but not *H. pylori* seropositivity was found to be significantly associated with IBS. Future studies should examine the effect of CagA positivity as the CagA toxin is an important *H. pylori* virulence factor associated with a greater inflammatory response[39]. There was also a significant degree of heterogeneity amongst the various studies included in the meta-analysis ($I2$ = 87.38%). This could stem from the subjectivity and different definitions used in the diagnosis of IBS as previously discussed, as well as the differing tests used to detect *H. pylori* infection, *e.g.*, serum IgG antibodies, urea breath test and stool antigen assay. Moreover, the commonly-used serologic test is unable to distinguish between current and previous *H. pylori* infection as it remains positive for years, even after *H. pylori* eradication therapy[40]. Although some studies carefully selected only individuals who have no history of previous *H. pylori* eradication therapy[16], it was less clear in other studies. The duration of *H. pylori* infection may also affect our analysis as study subjects with more longstanding infection may have greater mucosal inflammation and more significant GI symptoms.

Last but not least, the influence of *H. pylori* on the composition of distal gut microbiota is an important area that deserves further study. Microbial dysbiosis is a known hallmark of IBS[41]. However, it is unclear how *H. pylori*, which is thought to affect mainly the upper GI tract, may affect the lower GI tract[42].

In conclusion, current evidence does not support an association between IBS and *H. pylori* infection. Patients with IBS may have a slight increased likelihood of *H. pylori* infection albeit this is not statistically significant. This relationship is complicated by admittedly problematic study designs and potential confounding factors. The role of *H. pylori* eradication therapy also remains unclear as it does not appear to improve IBS symptoms. Further rigorous and detailed studies with larger sample sizes, carefully selected subjects, and after *H. pylori* eradication therapy are warranted. The influence of *H. pylori* on gut microbiota should also be investigated.

Test for heterogeneity

Q	63.39
df	8
Significance level	$P < 0.0001$
I^2 (inconsistency)	87.38%
95%CI for I^2	78.14-92.71

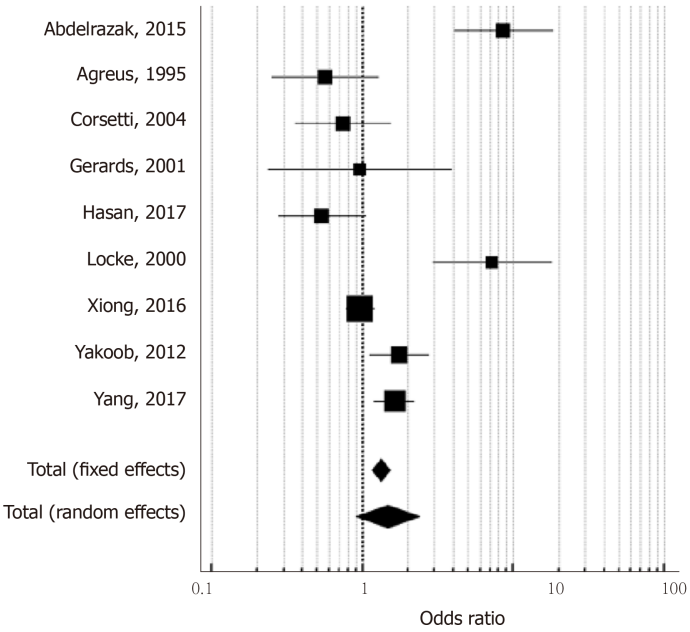

Figure 2 Forest plot showing the odds ratios and 95% confidence intervals of studies on the likelihood of *Helicobacter pylori* infection in patients with irritable bowel syndrome.

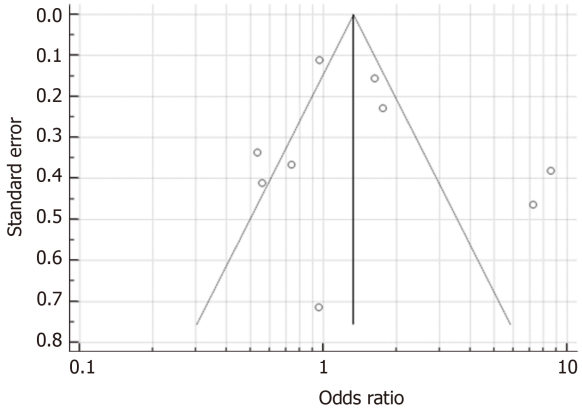

Figure 3 Funnel plot (with pseudo 95% confidence intervals) to assess publication bias. Egger test for publication bias = 1.28, 95% confidence interval: 0.80-3.36, $P = 0.189$.

ARTICLE HIGHLIGHTS

Research background

Helicobacter pylori (*H. pylori*) is a prevalent gram-negative bacterium found in the human gut. *H. pylori* infection has been linked to several conditions, including dyspepsia and even hyperemesis gravidarum. However, its role in the pathogenesis of irritable bowel syndrome (IBS) remains largely unknown.

Research motivation

An improved understanding of the pathogenic mechanisms of IBS may lead to more effective therapeutics.

Research objectives

To investigate the association between *H. pylori* infection and IBS.

Research methods

A comprehensive search of PubMed, Medline, Embase, Cochrane Database of Systematic Reviews, Web of Science, Google Scholar and WanFang databases was performed using the keywords "H. pylori OR Helicobacter OR Helicobacter pylori OR infection" AND "irritable bowel syndrome OR IBS".

Research results
A total of 13 clinical studies were systematically reviewed and nine studies were included in the final meta-analysis. Random-effects meta-analysis found a slight increased likelihood of *H. pylori* infection in patients with IBS, albeit this was not statistically significant (pooled odds ratio 1.47, 95% confidence interval: 0.90-2.40, $P = 0.123$). *H. pylori* eradication therapy also does not appear to improve IBS symptoms in the limited studies available.

Research conclusions
Current evidence does not support an association between IBS and *H. pylori* infection. This relationship is complicated by admittedly problematic study designs and potential confounding factors. *H. pylori* is eradicated with antibiotics, which is also associated with a significantly increased risk of developing IBS and may also aggravate IBS symptoms.

Research perspectives
Further rigorous and detailed trials with larger sample sizes, carefully selected subjects, and after *H. pylori* eradication therapy are warranted. The influence of *H. pylori* on gut microbiota also remains unknown and should be investigated.

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