

## Association between *Helicobacter pylori* infection and migraine: A meta-analysis

Jing Su, Xiao-Ying Zhou, Guo-Xin Zhang

Jing Su, Xiao-Ying Zhou, Guo-Xin Zhang, Department of Gastroenterology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China

Jing Su, Xiao-Ying Zhou, First Clinical Medical College of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China

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Correspondence to: Guo-Xin Zhang, Professor, Department of Gastroenterology, The First Affiliated Hospital of Nanjing Medical University, No. 300 of Guangzhou Road, Nanjing 210029, Jiangsu Province, China. [guoxinz@njmu.edu.cn](mailto:guoxinz@njmu.edu.cn)

Telephone: +86-25-83718836 Fax: +86-25-83674636

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### Abstract

**AIM:** To quantify the association between *Helicobacter pylori* (*H. pylori*) infection and migraine.

**METHODS:** A systematic literature search of PubMed and EMBASE was conducted from inception to December 2013. Studies that provided data dealing with *H. pylori* infection in patients with migraine, as well as healthy controls, were selected. Meta-analysis was carried out using the odds ratio (OR) with a fixed or random effects model, and a 95%CI for the OR was calculated. An unconditional logistic regression model was used to analyze potential parameters related to *H. pylori* prevalence. Subgroup analyses were conducted as methods of detection and evidence grade.

**RESULTS:** Five case-control studies published between 2000 and 2013 were finally identified, involving 903 patients, with a total *H. pylori* infection rate

of 39.31%. The prevalence of *H. pylori* infection was significantly greater in migraineurs than in controls (44.97% vs 33.26%, OR = 1.92, 95%CI: 1.05-3.51,  $P = 0.001$ ). A sensitivity test indicated that no single study dominated the combined results. Univariate regression analysis found that publication year, geographical distribution and evidence grade were relevant to the results and were the main reason for the heterogeneity. Subgroup analysis found a significantly greater infection rate of *H. pylori* in Asian patients with migraine, but no statistically significant infection rate in European patients. The ORs were 3.48 (95%CI: 2.09-5.81,  $P = 0.000$ ) and 1.19 (95%CI: 0.86-1.65,  $P = 0.288$ ), respectively.

**CONCLUSION:** The pooled data suggest a trend of more frequent *H. pylori* infections in patients with migraine.

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**Key words:** *Helicobacter pylori*; Migraine; Meta-analysis; Odds ratio; Subgroup analysis

**Core tip:** Recently, researchers have focused on the relationship between migraine and *Helicobacter pylori* (*H. pylori*) infection. Some studies have reported a strong positive correlation, and eradication of the bacterium resulted in a decrease in migraine attacks. Meanwhile, others have indicated totally negative results. In this meta-analysis, we found a trend of more frequent *H. pylori* infection in patients with migraine; thus, the eradication of this bacterium may reduce the clinical manifestations in migraineurs. Moreover, subgroup analysis found a significantly greater infection rate of *H. pylori* in patients with migraine in Asia compared with other countries.

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## INTRODUCTION

Migraine is one of the most common neurological disorders, and is characterized by attacks of severe headache, and autonomic and neurological symptoms. The prevalence of migraine in the general population ranges from 6% to 13%, and is more common in women. The two main types of migraine are migraine with aura, occurring in approximately 25% of patients with migraine, and migraine without aura, occurring in the remaining 75% of patients<sup>[1,2]</sup>. Migraine without aura seems to be caused by a combination of genetic and environmental factors, whereas migraine with aura is probably determined largely by genetic factors<sup>[3,4]</sup>.

*Helicobacter pylori* (*H. pylori*) is a Gram-negative organism that causes chronic active gastric inflammation. Infection is strongly associated with duodenal ulceration, gastric ulceration and gastric cancer<sup>[5]</sup>. The association between *H. pylori* infection and various extraintestinal pathologies, such as coronary heart disease, primary Raynaud's phenomenon, migraine, Alzheimer's disease and mild cognitive impairment, has recently been addressed. However, the results remain controversial<sup>[6]</sup>.

Recently, researchers have focused on the relationship between migraine and *H. pylori* infection. Some studies have reported a strong positive correlation, and eradication of the bacterium resulted in a decrease of migraine attacks. Meanwhile, others have indicated totally negative results. This meta-analysis was conducted to determine the prevalence of *H. pylori* infection in patients with migraine and healthy controls, as well as to establish whether *H. pylori* infection is a risk factor for migraine.

## MATERIALS AND METHODS

### Literature search

The PRISMA guidelines<sup>[7]</sup> for conducting meta-analysis were followed. Two investigators (Su J and Zhou XY) performed a systematic literature search of PubMed and Embase, from inception to December 2013, using the medical subject heading terms “(*Helicobacter pylori* or *H. pylori*) AND (migraine or headache)”. The two investigators worked independently, at different times and at different medical science information centers affiliated with Nanjing Medical University. The search was repeated several times. The last search was conducted on December 20, 2013. The relevant articles, texts, and reference lists were manually searched to broaden the scope of our findings. We evaluated the full texts of papers published in English, as well as the English abstracts of papers published in other languages.

### Inclusion criteria

The inclusion criteria as follows: (1) study design: pub-

lished case-control and cross-sectional studies; (2) studies that provided data dealing with *H. pylori* infection in patients with migraine as well as healthy controls; and (3) studies in which *H. pylori* infection was confirmed by the <sup>13</sup>C-urea breath test, mucosal biopsy, enzyme-linked immunoassay (ELISA), and/or polymerase chain reaction (PCR). At least one positive test was regarded as confirmation of infection.

### Exclusion criteria

The exclusion criteria as follows: (1) case reports and observational studies without control groups; (2) studies in which the *H. pylori* infection rate data were not available for either the study group or the control group; (3) subset of a published article by the same authors; and (4) studies in which research subjects had a history of drug use, including antibiotics, H2 blockers, or proton pump inhibitors, within 4 wk.

### Data extraction and appraisal of study quality

The two investigators who performed the literature search also performed the data extraction, working independently. The first authors, year and country of publication, study type, method of detection, and type of specimen identified were recorded for each included study. The numbers of *H. pylori*-positive and -negative patients in the groups with migraine were collected. When data from one study was reported in more than one manuscript, only one was selected for the meta-analysis, according to the following criteria (applied consecutively): (1) availability of adjusted odds ratio (OR) estimates for patients and controls; (2) longer follow-up period (applicable to nested case-control and cross-sectional analyses); and (3) larger sample size. When the relationship between *H. pylori* infection and migraine was reported in different articles referring to the same study, both were considered eligible, but only one was included in the meta-analysis. The Newcastle-Ottawa scale scoring system assessed the quality of the studies, which is used to assess nonrandomized trials<sup>[8]</sup>.

### Statistical analysis

In this study, the random effects model or fixed effects model was used for the meta-analysis, according to the heterogeneity between studies. The *Q*-test ( $P < 0.10$  was considered indicative of statistically significant heterogeneity) and the *I*<sup>2</sup> statistic (values of 25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively) were used to test heterogeneity. The fixed effects model was used when there was no significant heterogeneity ( $P < 50\%$ ); otherwise, the random effects model was used. *P* tests were used to calculate *P*-values. All the reported *P*-values were two-sided, and *P*-values less than 0.05 were regarded as statistically significant for all included studies<sup>[9]</sup>.

Calculation of dichotomous variables was carried out using the OR with the 95%CI as the summary statistic. The sensitivity test and meta-regression analysis (random

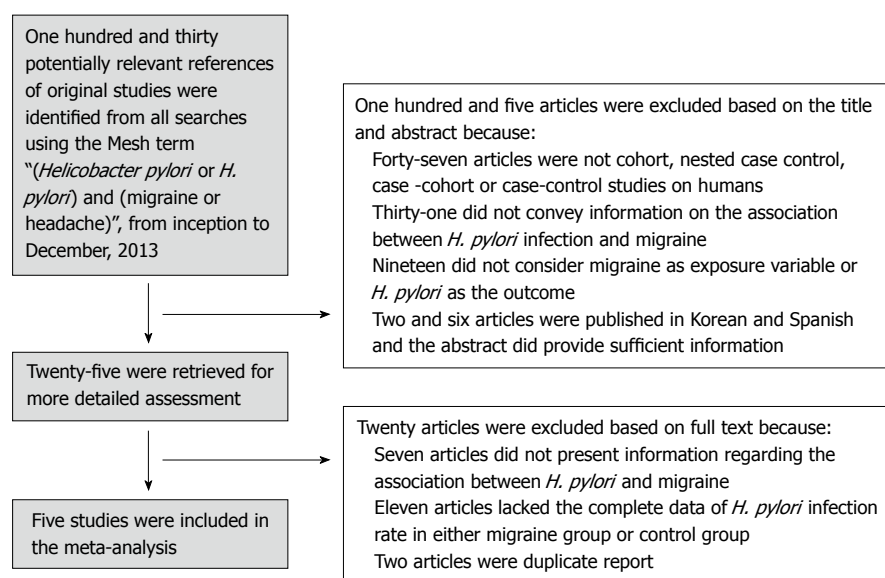


Figure 1 Flow diagram of the study selection process. *H. pylori*: *Helicobacter pylori*.

Table 1 Characteristics of studies on *Helicobacter pylori* infection in the migraine and control groups

Ref.	Year	Country	Method of detection	Specimen	Grade of reference	<i>H. pylori</i> (+) in migraineurs	<i>H. pylori</i> (+) in controls
Gasbarrini <i>et al</i> <sup>[1]</sup>	2000	Italy	<sup>13</sup> C-UBT	Breath	High	70/175	59/152
Pinessi <i>et al</i> <sup>[5]</sup>	2000	Italy	<sup>13</sup> C-UBT, ELISA	Breath, Serum	High	31/103	32/103
Tunca <i>et al</i> <sup>[20]</sup>	2004	Turkey	Biopsy	Tissue	High	40/70	20/60
Yiannopoulou <i>et al</i> <sup>[6]</sup>	2007	Greece	<sup>13</sup> C-UBT	Breath	Low	30/49	19/51
Hosseinzadeh <i>et al</i> <sup>[29]</sup>	2011	Iran	ELISA	Serum	Low	39/70	15/70

*H. pylori*: *Helicobacter pylori*; <sup>13</sup>C-UBT: <sup>13</sup>C urea breath test; ELISA: Enzyme-linked immunosorbent assay.

effects model) with the restricted maximum likelihood method were used to examine the impact of variables on heterogeneity between studies. Begg's test was used to evaluate the publication bias<sup>[10-11]</sup>. Analyses were performed using STATA statistical software, Version 12.0.

## RESULTS

### Description of studies

The two investigators agreed on the data extraction results. The strategy used for the study selection is displayed in Figure 1. Five studies published between 2000 and 2011 were eligible for the meta-analysis (Table 1). These studies involved 903 patients, with a total *H. pylori* infection rate of 39.31% (355/903). The cumulative sample size of the study group was 469, of which 210 were *H. pylori*-positive (44.97%). Of the total 436 controls, 145 (33.26%) were *H. pylori*-positive. Concerning the *H. pylori* detection methods, one study used ELISA (serum), two studies used the <sup>13</sup>C urea breath test, one study used a biopsy, and one study used both ELISA and the <sup>13</sup>C urea breath test.

All of the five included studies reported being approved by the Ethics Committees of their respective institutes and stated that informed consent was obtained

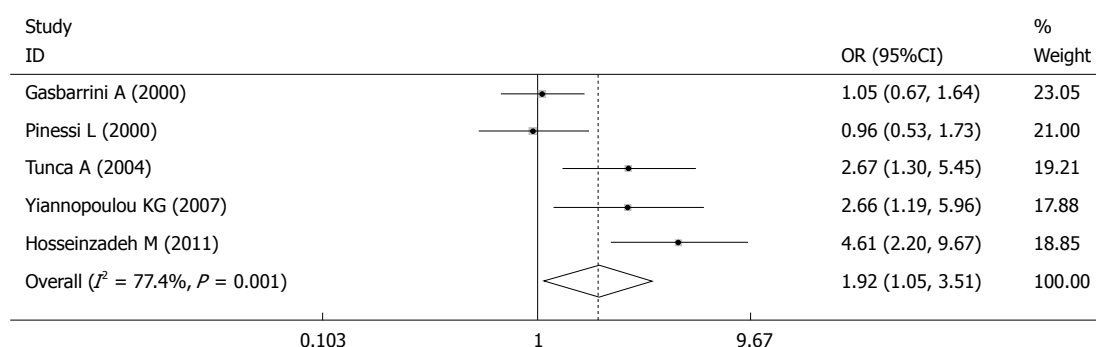
from all study participants before enrollment.

Overall, the prevalence of *H. pylori* infection was significantly greater in patients with migraine than in controls (44.97% *vs* 33.26%, OR = 1.92, 95%CI: 1.05-3.51, *P* = 0.001, *I*<sup>2</sup> = 77.4%) (Figure 2). A sensitivity test indicated that no single study dominated the combined results (Figure 3). Univariate regression analysis and subgroup analysis were performed to investigate the influencing factors that may have impacted the overall results.

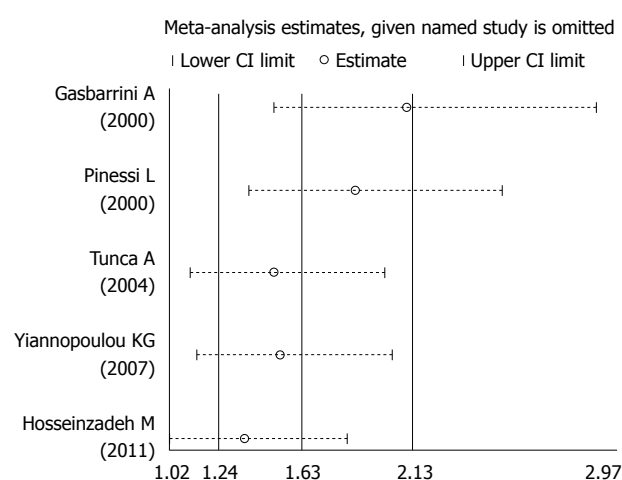
### Subgroup analysis of *H. pylori* infection prevalence

The meta-analysis results showed that the prevalence of *H. pylori* infection in patients with migraine was greater than that in controls, and the heterogeneity was high (*P* = 77.4%). Univariate regression analysis found that publication year, geographical distribution, and evidence grade were relevant (*P* = 0.028, *P* = 0.041, and *P* = 0.047, respectively). Subgroup analysis was performed to further investigate the above influencing factors, which may have impacted the overall results.

Stratification analysis by geographical region indicated that the levels of *H. pylori* infection among migraineurs were greater in Asia, but not statistically significant in Europe. The ORs were 3.48 (95%CI: 2.03-5.95) for the two studies conducted in Asia (*P* = 0.000), and 1.28 (95%CI:



**Figure 2** Meta-analysis of the prevalence of *Helicobacter pylori* infection in the migraine group compared with the control group. Weights are from random effects analysis.



**Figure 3** Sensitivity analysis of the five included studies.

0.76-2.17) for the three studies from Europe ( $P = 0.358$ ) (Figure 4A).

Subgroup analysis assessing the quality of evidence for each included study was performed, and each study was classified into low, moderate, or high quality. Two studies were included in the low quality group, and the pooled data indicated that the positive rate of *H. pylori* infection was greater in the migraine group than in the control group (OR = 3.60, 95%CI: 2.09-6.19,  $P = 0.000$ ). Three studies were included in the high quality group, and the positive rate of infection was similar between the migraine and control groups (OR = 1.23, 95%CI: 0.90-1.69,  $P = 0.190$ ) (Figure 4B).

Three studies published between 2000 and 2005 were included in our analysis. In these studies, the positive rate of infection was similar between the migraine and control groups (OR = 1.23, 95%CI: 0.90-1.69,  $P = 0.190$ ). In studies published after 2005, the pooled data indicated that the positive rate of *H. pylori* infection was greater in the migraine group than in the control group (OR = 3.60, 95%CI: 2.09-6.19,  $P = 0.000$ ) (Figure 4C).

### Publication bias

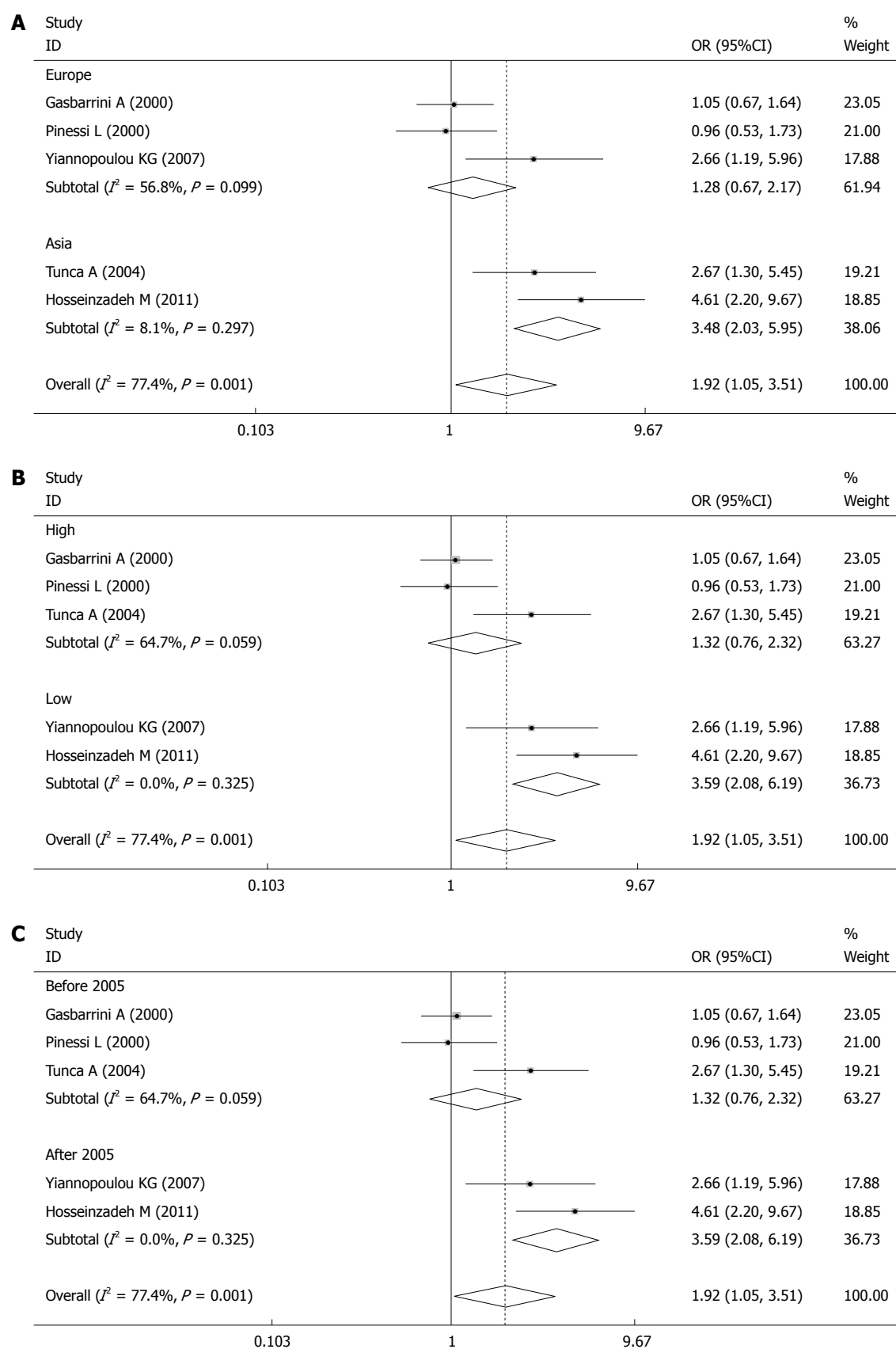
Funnel plot analysis did not show any evidence of publication bias (Begg's test;  $Z = 1.47$ ,  $P = 0.083$ , continuity corrected) (Figure 5).

## DISCUSSION

Our meta-analysis, which evaluated a total of five case-control studies, showed that *H. pylori* infection is indeed a risk factor for migraine. For articles published in recent years, however, the relationship between *H. pylori* infection and migraine remains controversial. There were probably three reasons why *H. pylori* infection was not found to be a risk factor for migraine in some studies. First, *H. pylori* infection can reduce food sensitivity. Food sensitivity is a well-known, but still unexplained, phenomenon for those with migraine<sup>[12-14]</sup>. Second, migraine is related with vasoactive substances (NO, serotonin, *etc.*)<sup>[15]</sup>. Researchers have found that there was no significant difference in plasma thiobarbituric acid-reactive substances and NO metabolites between patients with migraine infected with *H. pylori* and control subjects<sup>[16,17]</sup>. Third, the migraineurs who are included in most studies do not have a high incidence of *H. pylori* infection, since this bacterial infection appears to be age-related<sup>[18]</sup>. Therefore, the prevalence of *H. pylori* infection in patients with migraine may be less than or equal to that of healthy people.

However, many studies agree that *H. pylori* infection is associated with migraine. In our meta-analysis, five studies recruited patients who mainly suffered from migraine without aura because this subtype of migraine seems to be caused by a combination of genetic and environmental factors, whereas migraine with aura is probably determined largely, or exclusively, by genetic factors<sup>[3-4]</sup>.

The meta-analysis of five studies from across the globe indicated that *H. pylori* infection was greater in patients with migraine than in controls ( $P = 0.000$ ). Recently, it has been suggested that the probable pathogenic role of *H. pylori* chronic infection in migraine is based on the relationship between the host immune response against the bacterium and the chronic release of vasoactive substances<sup>[19]</sup>. The host inflammatory response to *H. pylori* is characterized by infiltration of neutrophils, monocytes and lymphocytes into the gastric mucosa. Recruitment and activation of immune cells in the underlying mucosa involves bacterium chemotaxins, epithelial derived chemotactic peptides (chemokines) such as IL-8 and GRO- $\alpha$ , and proinflammatory cytokines released by mononuclear phagocytes (*e.g.*, tumor necrosis factor-



**Figure 4 Forest graph of *Helicobacter pylori* infection.** Weights are from random effects analysis. A: Stratified by geographic distribution; B: Stratified by the quality of evidence for each included study; C: Stratified by the publication year.



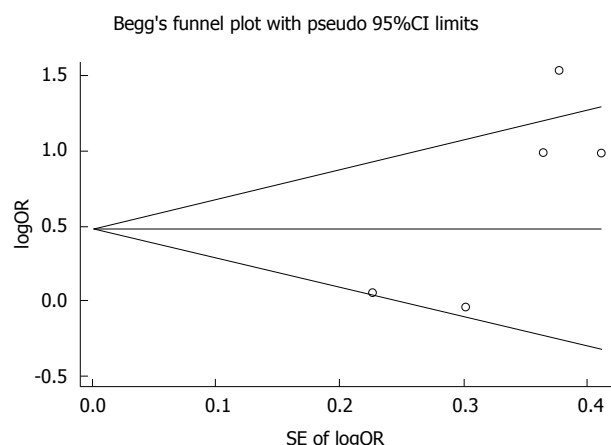


Figure 5 Funnel plot to detect publication bias.

alpha, IL-1 and IL-8) as part of nonspecific immunity<sup>[20-22]</sup>. The multiplicity and large quantity of vasoactive substances produced may induce a hyperreactivity of cerebral vessels to various well-known trigger factors, such as psychological or physical stress, peculiar foods, female hormones, and others, which are capable of determining the clinical manifestation of the disease<sup>[23-26]</sup>.

Other studies have provided evidence that migraine has a gastrointestinal origin and is related to *H. pylori* infection to a certain extent. Salmon found that children with recurrent abdominal pain had a high risk of developing migraine and that recurrent abdominal pain was an early expression of migraine in children<sup>[27]</sup>. Moreover, Mavromichalis *et al*<sup>[28]</sup> conducted a study showing that 29 of the 31 patients with migraine had an associated gastrointestinal disorder. *H. pylori* colonization was found in seven of the children. These findings suggested that upper gastrointestinal mucosal inflammation may play an important role in the pathogenesis not only of recurrent abdominal pain, but also of migraine. Other researchers have found a correlation between migraine and digestive disorders in adults. They found that approximately 75.7% of patients who had migraines also suffered from digestive disorders [reflux (47.1%), gastric ulcers (17.1%), and gastritis (4.3%)], and the prevalence of *H. pylori* infection was 38.6%<sup>[29]</sup>. The explanation of this phenomenon is that gastrointestinal neuroendocrine cells can synthesize and secrete 5-hydroxytryptamine, substance P, and vasoactive intestinal polypeptides. When *H. pylori* infects a cell, inflammation stimulates the cell to secrete these substances and causes a central nervous system disorder by the brain-gut axis, which indirectly proves why most patients have migraine attacks that are associated with gastrointestinal symptoms<sup>[30]</sup>.

There are other reasons for why the prevalence of *H. pylori* infection is greater in migraineurs than in controls. *H. pylori* spreads through the fecal-oral route<sup>[31]</sup> and 60% of patients with migraine have a family history<sup>[3]</sup>; therefore, bacterial transmission among relatives is an important factor. Except for the above reasons, some individual factors, such as human leukocyte antigen type or other

unknown factors, may make an individual more susceptible to the supposed vasospastic triggers induced by *H. pylori*<sup>[32,33]</sup>.

Recently, certain studies suggested that *H. pylori* eradication treatment may provide pain relief. Gasbarrini *et al*<sup>[1]</sup> studied 225 patients and *H. pylori* was detected in 40% of the patients by the <sup>13</sup>C-urea breath test. With eradication of the bacterium, it was demonstrated that during follow-up for 6 mo, the frequency, density and duration of migraine attacks reduced significantly. Faraji *et al*<sup>[34]</sup> conducted a similar randomized, double blind, controlled trial of 64 migraineurs and suggested that *H. pylori* treatment was significant in the management of migraine headaches among Iranian patients.

For results showing significant heterogeneity ( $I^2 > 50\%$ ), we used the random effects model for the meta-analysis. Meanwhile, the influence analysis indicated that no single study dominated the combined results. The high heterogeneity may be derived from the differences of areas, detection methods and study quality. Based on our subgroup results, the reported prevalence of *H. pylori* infection ranges widely between nations. In developing countries, such as Asia, the infection rate is significantly greater than that in developed countries. The lower prevalence of *H. pylori* infection in industrialized nations is attributed to the higher standards of hygiene and socioeconomics. Meanwhile, it has been suggested that ethnicity and place of birth may also play a role in susceptibility to *H. pylori* infection<sup>[35]</sup>. Furthermore, our subgroup analysis found that the levels of *H. pylori* infection among patients with migraine were greater in Asia, but not statistically different in Europe. This fact might result from a significantly greater prevalence of *H. pylori* cagA-positive strains in Asian countries<sup>[36]</sup>. It has been shown that cagA-positive strains cause greater release of cytokines by gastric epithelial cells<sup>[37]</sup>. The high persistent inflammatory response to cagA-positive strains of the bacterium induces a hyperreactivity of cerebral vessels to various well-known trigger factors, such as psychological or physical stress, peculiar foods, female hormones and others that are related to migraine<sup>[1]</sup>. The *H. pylori* infection rate reported in cases was slightly greater in the years after 2005 than in the 2000-2005 period. This difference is mainly explained by the fact that the enrolled articles from 2000-2005 are mostly from developed countries, where the *H. pylori* infection rate is decreasing<sup>[38,39]</sup>.

After the completion of our study, a recent review paper also indicated that the eradication of *H. pylori* seems to be efficient in patients suffering from migraine<sup>[40]</sup>. In conclusion, our updated and cumulative meta-analysis of five studies suggests a trend of more frequent *H. pylori* infection in patients with migraine. Patients with migraine should have their *H. pylori* infection treated, since bacterial eradication has been shown to reduce the clinical manifestations of migraine. Considering the obvious heterogeneity, more studies including larger sample sizes should be done in the future to further clarify the association between *H. pylori* infection and migraine.

## Study limitations

First, the selection of the controls varied between studies. Second, the *H. pylori* infection was diagnosed by different methods and strategies among the studies, with some relying on a single detection method, while others used more than one method. These variations may have produced different positive rates of *H. pylori* infection because of advances in each of the technologies, thus influencing the cumulative positive rates. Third, the papers included in the present meta-analysis were limited to those published and listed on PubMed up to December 2013; therefore, it is possible that some relevant published studies, which may have met the inclusion criteria, were missed. These overlooked studies may have corrected some inherent biases caused by the study design. Finally, the fact that the data were derived from the abstracts of papers not written in English might contribute to the selection bias.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

*Helicobacter pylori* (*H. pylori*) is a Gram-negative organism, and its infection is associated with some extraintestinal pathologies, such as coronary heart disease, primary Raynaud's phenomenon and migraine. However, the relationship between infection and the above diseases remains controversial.

### Research frontiers

Many researchers have focused on the relationship between migraine and *H. pylori* infection. Some studies have reported a strong positive correlation, but others have indicated totally negative results. This meta-analysis was performed to quantify the association between *H. pylori* infection and migraine.

### Innovations and breakthroughs

This meta-analysis was conducted to determine the prevalence of *H. pylori* infection in patients with migraine and healthy controls, and to demonstrate whether *H. pylori* infection is a risk factor for migraine. Meanwhile, factors including publication year, geographical distribution and evidence grade were also analyzed. From our data, authors found a trend of more frequent *H. pylori* infection in patients with migraine.

### Applications

The results suggested that people with migraine may have a higher prevalence of *H. pylori* infection than healthy people. For migraineurs infected with *H. pylori*, the eradication of this bacterium may reduce their clinical manifestations.

### Terminology

Migraine is a primary episodic headache disorder characterized by various combinations of neurological, gastrointestinal, and autonomic changes. Migraineurs are people who are diagnosed with migraine.

### Peer review

This is an interesting and timely study, which tackles an important clinical issue. The authors conducted this meta-analysis to determine the prevalence of *H. pylori* infection in patients with migraine and healthy controls, as well as to demonstrate whether *H. pylori* infection is a risk factor for migraine. The results are interesting and suggest that a trend of increased prevalence of *H. pylori* infection was found in patients with migraine. However, more studies including larger samples sizes should be done in the future to further clarify the association between *H. pylori* infection and migraine.

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