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Systematic Review

# The Relationship Between *Helicobacter pylori* and Inflammatory Bowel Disease

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**Abstract**

**Background:** *Helicobacter pylori* may have a protective effect against inflammatory bowel disease (IBD). We integrated epidemiological data to identify the correlation between IBD and *H. pylori*. Moreover, we analyzed whether IBD medication and classification affect *H. pylori*, and whether eradication of *H. pylori* leads to recurrence of IBD.

**Methods:** Articles published up to May 1, 2019, in three main databases including PubMed, MEDLINE and Embase, were searched. Study types included cross-sectional studies, retrospective studies and perspective studies, and data were combined and analyzed. Spearman correlation analysis and meta-analysis were performed after collecting and collating the relevant data. Sensitivity analysis and meta-regression were used to evaluate reliability and heterogeneity.

**Results:** Fifty-nine studies on IBD prevalence, 127 studies on *H. pylori* prevalence, and 23 studies for meta-analysis were included. IBD, ulcerative colitis (UC) and Crohn's disease (CD) were negatively correlated to *H. pylori* prevalence (all $P<0.001$). The meta-analysis results showed that compared to controls, the odds of having *H. pylori* infection were 0.44, 0.36, 0.54 for IBD, CD and UC, respectively (OR = 0.44, 95% CI = 0.34–0.59; OR = 0.36, 95% CI = 0.26-0.49; OR = 0.54, 95% CI = 0.4–0.72). Moreover, IBD patients were 1.41 times (OR = 1.41, 95% CI = 1.25–1.58) more likely to relapse after eradication of *H. pylori*. Finally, *H. pylori* infection was not related to IBD medication and classification.

**Conclusion:** *H. pylori* prevalence was negatively correlated to IBD and *H. pylori* had a protective effect against IBD. Furthermore, eradication of *H. pylori* can lead to recurrence of IBD.

**Keywords:** Crohn disease, *Helicobacter pylori*, Inflammatory bowel diseases, Ulcerative colitis

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## Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), comprises chronic gastrointestinal disorders characterized by dysregulated intestinal inflammation.[1,2] There are regional differences in the incidence of IBD, which is higher in developed countries, while lower in developing countries. However, the incidence in developing countries has also been rising in recent years.[3] The pathophysiology of IBD is unknown, which involves interactions with genetic susceptibility, environmental factors, immune dysregulation and imbalance of gut microbiota.[4-7]

Due to its ability to reflect the cellular immune response driven by continuous activity of the host immune system, many scholars have already paid attention to the correlation between IBD and *Helicobacter pylori*.[8] *H. pylori* is one of the most widespread chronic bacterial infections which can cause peptic ulcer, chronic gastritis, and gastric cancer.[9] It also seems to have a close relationship with extra-gastric diseases.[10] Potential protective effects of *H. pylori* on IBD have been provided in published data.[11,12] Rokkas et al reported a meta-analysis on *H. pylori* and IBD, although it had some shortcomings.[11] The *H. pylori* diagnosis was made by serologic testing in some studies, while serologic false-positive and false-negative rates are high.[13] As antibodies persist for a long time, serologic IgG test has less than 80% specificity for active *H. pylori* infection.[14] In addition, some studies have clearly included patients with dyspepsia, constipation and irritable bowel syndrome (IBS) as control groups. However, *H. pylori* infection is closely related to these diseases.[15,16] These two points affected the reliability of the entire meta-analysis to some extent. Furthermore, the meta-analysis of selected articles only analyzed a small number of individuals in a certain region, which did not reflect the IBD prevalence in high-risk areas of *H. pylori* worldwide. Epidemiological evidence can greatly increase the reliability of conclusions.

In this systematic review, studies which met the requirements were collected and used for systematic comparison. We firstly aimed to collect articles addressing the prevalence of IBD and *H. pylori* all over the world and clarifying the correlation. The second purpose was to conduct a meta-analysis to further verify the correlation by optimizing screening criteria. Furthermore, we tried

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to find the relationship between IBD medication and *H. pylori*, disease severity and *H. pylori*. Finally, we attempted to find out whether *H. pylori* eradication affects IBD recurrence. This study would provide a comprehensive view of the relationship between IBD and *H. pylori*.

## Materials and Methods

### *Data Sources and Study Selection*

The authors searched English-language papers published up to May 1, 2019, in three main databases including PubMed, MEDLINE and Embase. In addition, the following three screening schemes were used: 1) *((prevalence) OR (epidemiolog*)) AND ((IBD) OR (inflammatory bowel disease) OR (CD) OR (Crohn's disease) OR (UC) OR (ulcerative colitis))*, which was used to screen for IBD prevalence. 2) *((prevalence) OR (epidemiolog*)) AND ((Helicobacter pylori) OR (H. pylori) OR (HP))*. Based on the IBD prevalence, this scheme was used to screen for *H. pylori* prevalence. 3) *((IBD) OR (inflammatory bowel disease) OR (CD) OR (Crohn's disease) OR (UC) OR (ulcerative colitis)) AND ((Helicobacter pylori) OR (H. pylori) OR (HP))*, which was used to screen articles for meta-analysis.

Inclusion criteria for the correlation analysis were: 1) epidemiological data from Jan 1, 2000; 2) reports on adults; 3) reporting both IBD prevalence and *H. pylori* prevalence in an area; 4) the ability of combined and analyze the data. Inclusion criteria for the meta-analysis were: 1) data referring to the correction of *H. pylori* and IBD, 2) *H. pylori* was diagnosed by histology and/or UBT and/or RUT and/or bacterial culture, not serologic tests, 3) controls were healthy individuals, 4) reports on adults.

### *Data Extraction*

Two authors independently examined papers which may be available and a third author double-checked them. If there was ambiguity, another author evaluated the study again. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed.[17]

### *Statistical Analysis*

IBD (including CD and UC) prevalence (/$10^5$) and *H. pylori* prevalence (%) for each country or region were estimated by pooling the data. Statistical heterogeneity was evaluated by Cochran's Q-test and the $I^2$ statistic. In addition, the random effects model was used to calculate pooled results. Spearman correlation analysis was performed to demonstrate whether *H. pylori* was negatively correlated to IBD.

Odds ratios (ORs) with 95% CIs were used to describe the ratio of *H. pylori* occurring in IBD patients vs. controls, *H. pylori* occurring by IBD medication, *H. pylori* occurring by IBD classification and recurrence of IBD after *H. pylori* eradication. The Fixed-model method (if $I^2 \leq 50\%$, $P > 0.1$) or random-model method (if $I^2 > 50\%$, $P \leq 0.1$) was selected in the study.[18,19] In addition, standardized mean difference (SMD) was used to describe Crohn's disease activity index (CDAI) and C-reactive protein (CRP) pre- or post- *H. pylori* eradication.

Sensitivity analysis was done to evaluate the stability of the study. Meta-regression was used to look for sources of heterogeneity. All analyses were conducted using STATA 15.1 (StataCorp., College Station, Texas, USA) or SPSS 25.0 (IBM, Chicago, IL, USA).

## Results

### *Basic Characteristics*

Figure 1 presents the flowchart describing the process. A total of 17919 articles entered the screening list for IBD

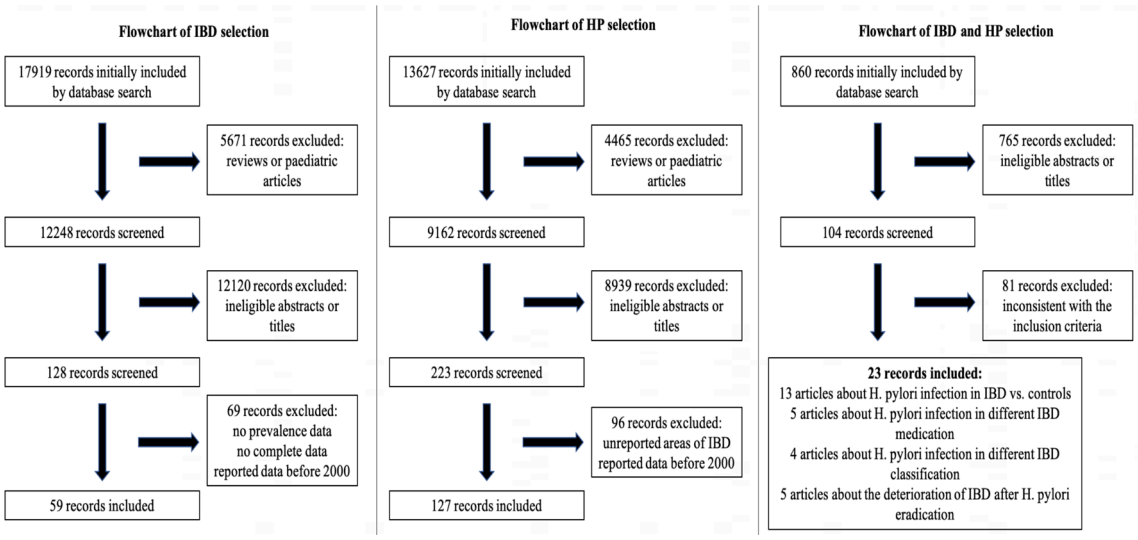


**Figure 1**. Flowchart Describing the Process of Study Selection

prevalence, 13 627 for *H. pylori* prevalence and 860 for meta-analysis. Finally, 59 articles for IBD prevalence (Supplementary file 1), 127 articles for *H. pylori* prevalence (Supplementary file 1) and 23 articles for meta-analysis were found eligible for our research (Supplementary file 2). We selected the prevalence data of the UK in the 1990s because of data limitations. Epidemiological data covered 6 continents and 33 countries or regions (Table 1).

### *Correlation Between IBD Prevalence and Helicobacter pylori Prevalence*

The main characteristics of IBD prevalence and *H. pylori* prevalence are presented in Table 1. The pooling data showed that in North America, Europe, and Oceania, which consist of developed countries, the IBD prevalence was high (378.8/$10^5$, 95% CI = 241.5–516/$10^5$; 372.6/$10^5$, 95% CI = 292.6–452.6/$10^5$; 308.6/$10^5$, 95% CI = 270.3–346.9/$10^5$, respectively), while the *H. pylori* prevalence was low (22.5%, 95% CI: = 20.4-24.7%; 36.9%, 95% CI = 32.7–41.2%; 32.9%, 95% CI = 19.4–46.4%, respectively) (Figure 2B). On the contrary, the IBD prevalence was low (37.6/105, 95% CI = 14.7–60.5/105; 50.6/105, 95% CI = 35.1–66.2/105; 31.6/105, 95% CI = 28.0–35.2/105, respectively), while the *H. pylori* prevalence was high (63.7%, 95% CI = 52.8–74.6%; 47.8%, 95% CI = 45.1-50.4%; 68.3%, 95% CI = 46.8–89.7%, respectively) in South America, Asia, and Africa, which are mostly developing countries (Figure 2B).

**Table 1.** Prevalence of IBD, CD, UC and *H. pylori* Since 2000 Across the World.

| Country/Region | No. of Reporting Studies (IBD/HP) | HP Prevalence Estimates, % (95% CI) | IBD Prevalence Estimates, (/$10^5$) (95% CI) | CD Prevalence Estimates, (/$10^5$) (95% CI) | UC Prevalence Estimates, (/$10^5$) (95% CI) |
|---|---|---|---|---|---|
| **North America (*n* = 11/14)** | | | | | |
| USA | 6/10 | 22.0 (19.6–24.4) | 450.2 (405.5–494.9) | 212.2 (164.7–259.7) | 238.1 (223.0–253.2) |
| Canada | 3/3 | 22.5 (9.7–35.2) | 468.4 (355.3–581.6) | 249.7 (225.8–273.5) | 213.2 (121.4–305.0) |
| Puerto Rico | 2/1 | 33.0 (29.0–37.0) | 31.5 (18.4–44.6) | 10.4 (1.5–19.2) | 17.9 (7.3–28.5) |
| **South America (*n* = 5/7)** | | | | | |
| Brazil | 4/5 | 64.4 (53.2–75.5) | 30.4 (3.6–57.2) | 11.8 (0–24.4) | 18 (3.8–32.3) |
| Chile | 1/2 | 61.7 (36.1–87.4) | 66.6 (65.5–67.8) | 20.8 (20.1–21.4) | 45.9 (44.9–46.8) |
| **Oceania (n = 4/7)** | | | | | |
| New Zealand | 2/2 | 26.5 (11–42.1) | 277.1 (215.2–339.1) | 142.1 (115.1–169.1) | 121.7 (75.5–167.8) |
| Australia | 2/5 | 35.4 (16.4–54.4) | 338.4 (325.8–351.1) | 183.2 (156.8–209.6) | 146.6 (126.5–166.7) |
| **Asia (*n* = 14/52)** | | | | | |
| Taiwan, China | 2/4 | 51.1 (40–62.1) | 10.2 (8.6–11.7) | 1.9 (1.6–2.2) | 8.3 (7.0–9.5) |
| Hong Kong, China | 1/3 | 41.1 (36.5–45.8) | 45.8 (44.0–47.6) | 17.5 (16.4–18.6) | 27.4 (26.0–28.8) |
| Japan | 1/9 | 30.2 (21.3–39.2) | 84.8 (53.2–116.4) | 21.2 (20.8–21.7) | 63.6 (62.8–64.4) |
| Korea | 1/21 | 54.8 (50.5–59.2) | 95.6 (94.7–96.5) | 29.6 (29.2–30.1) | 66.0 (65.2–66.7) |
| Malaysia | 3/4 | 37.4 (29.6–45.2) | 12.1 (1.2–23.1) | 3.8 (0.8–6.8) | 8.2 (0.2–12.2) |
| Sri Lanka | 2/1 | 70.2 (58.3–82.1) | 7.1 (5.9–8.3) | 1.7 (0.7–2.8) | 5.4 (4.8–5.9) |
| India | 1/2 | 64.7 (55.2–74.2) | — | — | 44.3 (26.2–62.4) |
| Israel | 1/4 | 54.2 (48.8–59.5) | 332.1 (326.3–338) | 162.6 (158.2–166.7) | 169.5 (165.3–173.7) |
| Turkey | 1/3 | 79.0 (73.9–84.1) | — | — | 4.8 (3.5–6.2) |
| Lebanon | 1/1 | 51.9 (46.3–57.5) | 159.2 (95.6–222.9) | 53.1 (16.8–89.9) | 106.2 (54.2–158.1) |
| **Europe (*n* =24/46)** | | | | | |
| UK* | 2/5 | 29.0 (14.1–43.9) | 340.8 (240.5–441.1) | 127.7 (97.7–157.7) | 208.9 (143.9–273.9) |
| Sweden | 2/2 | 13.3 (8.8–17.8) | 813.1 (497–1129.3) | 304.1 (88.6–519.6) | 439.5 (261.3–617.6) |
| Denmark | 2/5 | 19.5 (18.8–31.8) | 660.5 (238.3–1082.8) | 207.5 (97.0–318.1) | 453.1 (141.4–764.8) |
| Finland | 1/2 | 31.9 (0–70.2) | 595.0 (589.0–602.0) | — | — |
| Italy | 3/3 | 25.3 (18.9–31.8) | 202.0 (120.5–283.4) | 15 (0.1–30) | 83.5 (20.2–146.7) |
| Spain | 2/4 | 49.2 (40.9–57.4) | 374.5 (39.6–709.4) | 154.1 (80.6–227.5) | 219.3 (0–483.1) |
| Croatia | 3/2 | 44.2 (38.9–49.5) | 144.3 (70.6–218.1) | 53.3 (17.6–88.9) | 90.1 (55.1–125.0) |
| Switzerland | 2/1 | 18.9 (13.1–24.7) | 306.8 (108.5–505.2) | 100.7 (91.9–109.5) | 105.0 (96.0–125.0) |
| Portugal | 1/3 | 59.1 (33.9–84.3) | 146.0 (116.0–175.0) | 73.0 (58.0–87.0) | 71.0 (56.0–85.0) |
| German | 1/7 | 34.5 (28.5–40.4) | 744.0 (707.0–755.0) | 322.0 (302.0–346.0) | 412.0 (389.0–436.0) |
| Netherlands | 1/2 | 35.5 (28.2–42.7) | 444.2 (421.5–467.0) | 176.1 (161.7–190.4) | 231.4 (215.0–247.8) |
| France | 1/2 | 20.2 (15.4–25.0) | 276.3 (272.0–280.5) | 161.1 (157.9–164.4) | 104.0 (101.4–106.6) |
| Poland | 1/4 | 60.0 (42.3–77.6) | 157.0 (155.0–159.0) | 35.0 (33.0–36.0) | 112.1 (111.0–113.1) |
| Romania | 1/2 | 68.6 (60.2–76.9) | 3.9 (3.6–4.2) | 1.5 (1.3–1.7) | 2.4 (2.2–2.7) |
| Hungary | 1/2 | 27.5 (19.0–36.0) | 550.0 (540.0–546.0) | 200.0 (190.0–200.0) | 340.0 (330.0–340.0) |
| **Africa (*n* = 1/2)** | | | | | |
| Algeria | 1/2 | 68.3 (46.8–89.7) | 31.6 (28.0–35.2) | 19.0 (16.2–21.8) | 10.6 (8.5–12.7) |

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; HP, Helicobacter pylori; USA, United States of America; UK, United Kingdom.
*All data are from the 1990s.

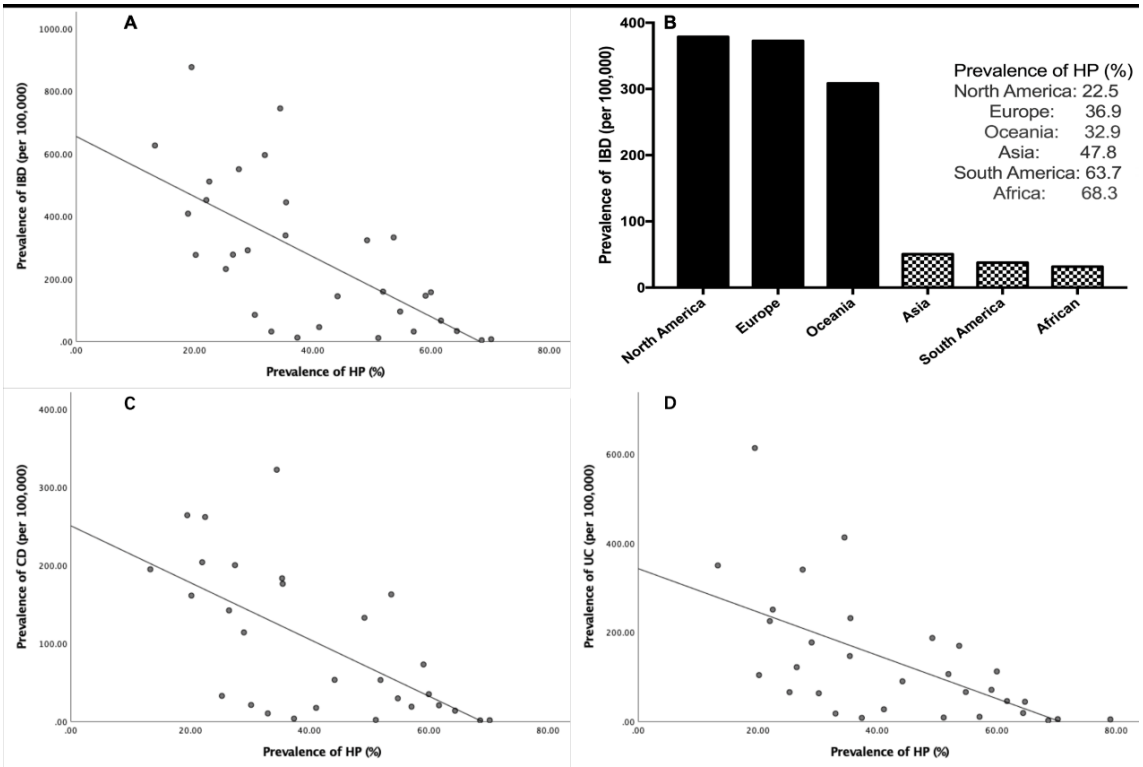


**Figure 2**. A, C, D) *H. pylori* prevalence was negatively correlated to IBD, CD, UC prevalence (coefficient= -0.679, $P<0.001$; coefficient=-0.616, $P<0.001$; coefficient = -0.666, $P<0.001$). B) A continent with more developed countries had higher IBD prevalence and lower *H. pylori* prevalence; while a continent with more developing countries had lower IBD prevalence and higher *H. pylori* prevalence.

Spearman correlation analysis showed that *H. pylori* prevalence was negatively correlated to IBD prevalence (coefficient = -0.679, $P<0.001$) (Figure 2A). In addition, *H. pylori* prevalence was negatively correlated to both CD prevalence (coefficient = -0.616, $P<0.001$) (Figure 2C) and UC prevalence (coefficient = -0.666, $P<0.001$) (Figure 2D).

*Helicobacter pylori* Prevalence in IBD Patients vs Controls

The main characteristics of included papers for meta-analysis are shown in Supplementary file 2. We found that IBD patients were 0.44 times (OR = 0.44, 95% CI = 0.34–0.59, $I^2 = 80.1\%$, $P<0.01$) more likely to have *H. pylori* infection compared to controls (Figure 3A). CD patients were 0.36 times (OR = 0.36, 95% CI = 0.26–0.49, $I^2 = 67.6\%$, $P<0.01$) more likely to have *H. pylori* infection compared to controls (Figure 3B). In addition, UC patients were 0.54 times (OR = 0.54, 95% CI = 0.4–0.72, $I^2 = 76.9\%$, $P<0.01$) more likely to have *H. pylori* infection compared to controls (Figure 3C). The *H. pylori* prevalence rates of IBD, CD, UC were all lower than the controls.

*Helicobacter pylori* Occurring in Different IBD Medications

Five articles described different *H. pylori* prevalence rates with different IBD medication. The drugs included sulfasalazine, mesalazine, corticosteroids and immunosuppressants. Sulfasalazine and mesalazine were put in the same class due to their similar pharmacological effects. Corticosteroids and immunosuppressants were classified into another class because of the effect of inhibiting the body's immune system. But, there was no difference in terms of *H. pylori* infection between the two classes (OR = 2.02, 95% CI = 1.0–4.09, $I^2 = 56.3\%$, $P = 0.057$) (Figure 4A).

*Helicobacter pylori* Occurring in Different IBD Classes

According to the collected data, we classified moderate and severe IBD condition into one class, while remission and mild cases were placed into another class. In two of four articles, the patients were diagnosed as CD, while the others were UC. We found that more serious disease condition was not associated with lower *H. pylori* infection (OR = 1.06, 95% CI = 0.66–1.71, $I^2 = 33.3\%$, $P = 0.213$) (Figure 4B). In subgroup analysis, neither CD (OR = 0.96, 95% CI = 0.48-1.92, $I^2 = 77.2\%$, P = 0.036) nor UC (OR = 1.17, 95% CI = 0.6–2.26, $I^2 = 0\%$, $P = 0.846$) affected *H. pylori* infection (Figure 4B).

Recurrence of IBD after *Helicobacter pylori* Eradication

A total of five articles were selected for this section. First of all, the *H. pylori* eradication plans chosen in the five articles were not consistent. Two articles used seven-day triple therapy, one article used fourteen-day triple therapy, one article used fourteen-day therapy without reporting the prescription, and one article used five- plus five-day sequential therapy. Three articles described the recurrence rate of IBD post-*H. pylori* eradication. IBD patients were 1.41 times (OR = 1.41, 95% CI = 1.25–1.58, $I^2 = 0\%$,

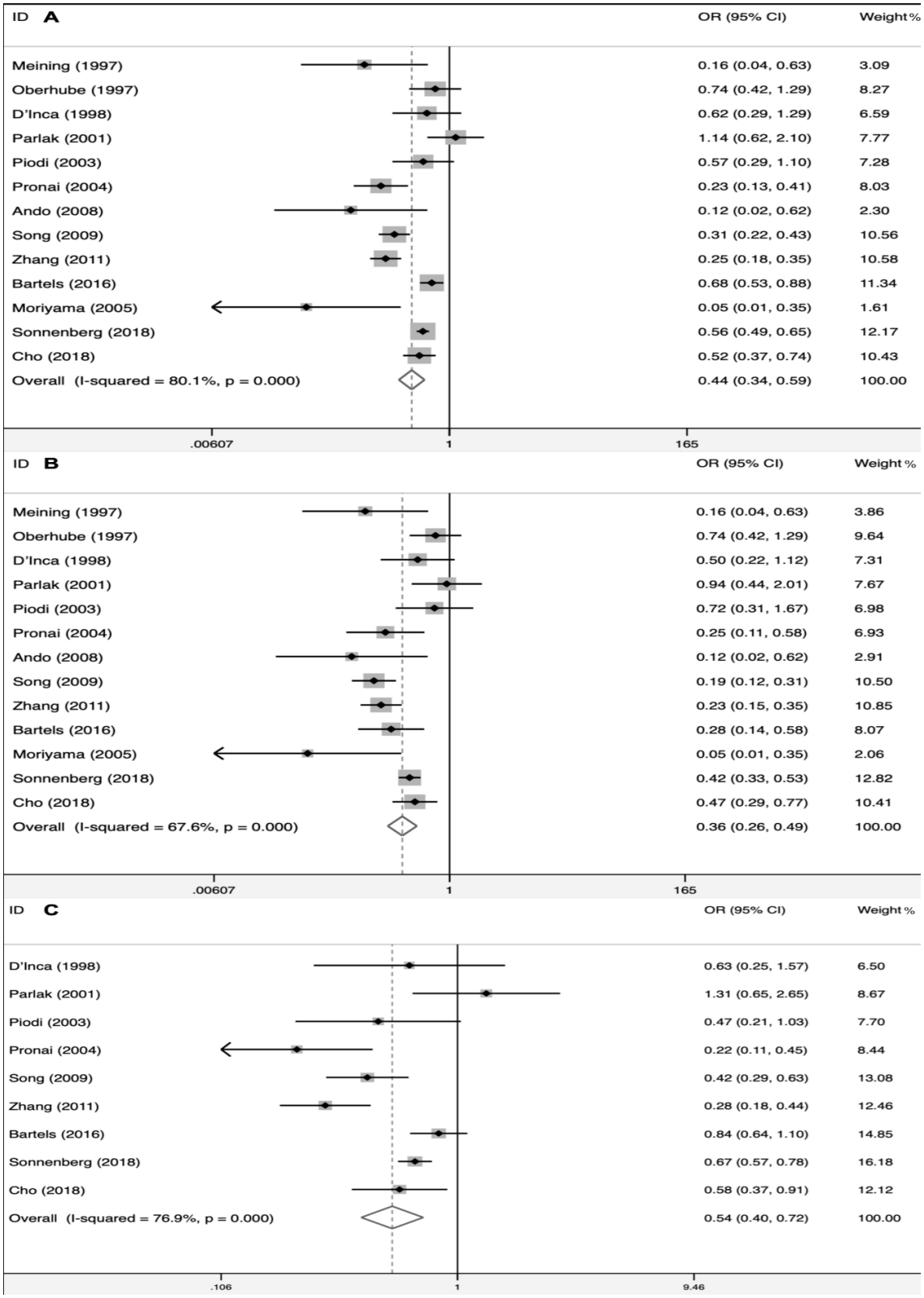


**Figure 3**. IBD, CD and UC patients were 0.44, 0.36, 0.54 times more likely to have *H. pylori* infection compared to controls, respectively (OR = 0.44, 95% CI = 0.34–0.59; OR = 0.36, 95% CI = 0.26–0.49; OR = 0.54, 95% CI = 0.4–0.72).

*P* = 0.728) more likely to relapse post-*H. pylori* eradication compared to those without *H. pylori* eradication (Figure 5), which showed that *H. pylori* eradication was a risk factor. When we removed a group of data with large weight, the results of the two external sets of data were not statistically significant (OR = 1.34, 95% CI = 0.75–2.38, $I^2$ = 0%, *P* = 0.434). In addition, post-*H. pylori* eradication, CRP (SMD = -0.05, 95% CI = -3.09–3.02, $I^2$ = 91.3%, *P* = 0.001) and CDAI (SMD = 0.06, 95% CI = -0.41–0.53, $I^2$ = 0%, *P* = 0.678) had no statistical difference.

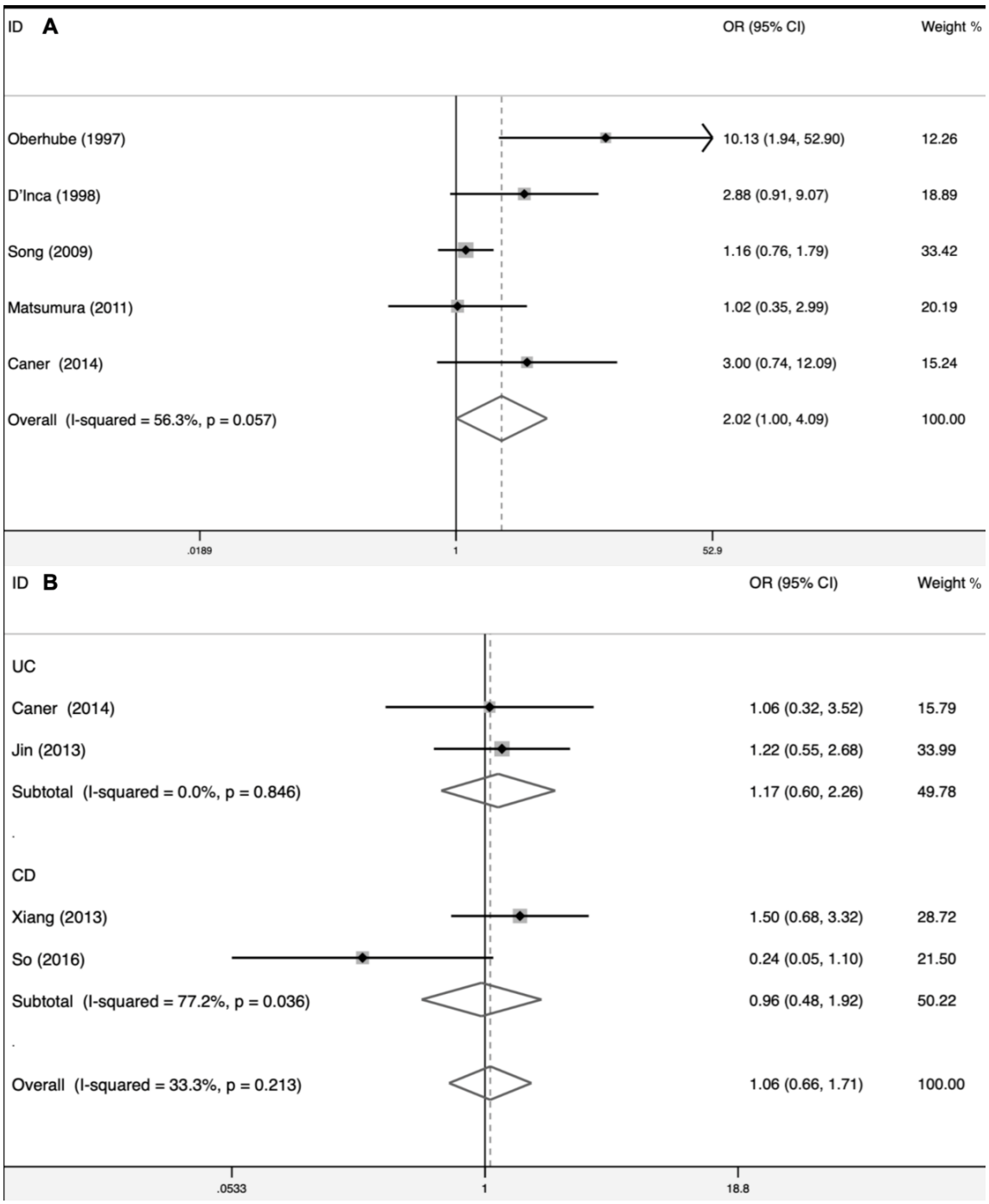


**Figure 4**. A) There was no difference in *H. pylori* prevalence rates between the two classes (OR = 2.02, 95% CI = 1.0–4.09). B) Serious disease condition of IBD, CD and UC did not have lower *H. pylori* infection (OR = 1.06, 95% CI = 0.66–1.71; OR=0.96, 95% CI = 0.48–1.92; OR = 1.17, 95% CI = 0.6–2.26).

### *Sensitivity Analysis and Meta-regression*

Some meta-analysis results had heterogeneity. Through some methods, we aimed to identify the reliability of the results and look for sources of heterogeneity. Sensitivity analysis demonstrated that the results were stable and reliable. No article showed bias in the analysis.

Meta-regression proved that study districts ($P = 0.817$), study time ($P = 0.987$), *H. pylori* test method ($P = 0.333$), multi-center or single-center study ($P = 0.872$), and number of individuals ($P = 0.981$) did not affect the results of meta-analysis on *H. pylori* prevalence in IBD patients. Also, CD and UC analysis did not find a heterogeneous source for study districts ($P = 0.922$, $P = 1.000$), study time ($P = 0.983$, $P = 0.998$), *H. pylori* test method ($P = 0.148$, $P = 0.759$), multi-center or single-center study ($P = 0.666$, $P = 0.943$), and number of individuals ($P = 0.889$, $P = 1.000$). Moreover, combined medication ($P = 0.869$), immunosuppressant ($P = 0.869$) and *H. pylori* test method ($P = 0.429$) were not factors affecting heterogeneity of *H. pylori* prevalence in IBD medication.

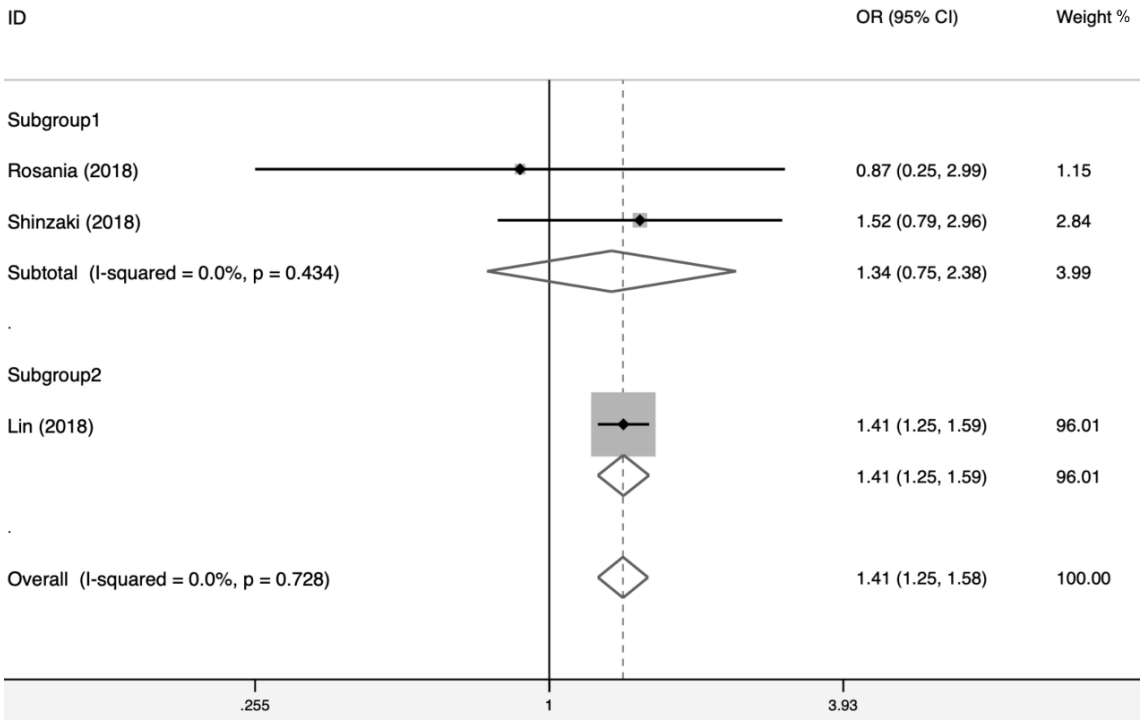


**Figure 5**. IBD patients were 1.41 times (OR=1.41, 95% CI=1.25–1.58) more likely to relapse after *H. pylori* eradication compared to those without *H. pylori* eradication.

## Discussion

Relevant preliminary studies data suggested a potential protective effect for *H. pylori* against IBD. The findings of this study demonstrated that *H. pylori* was negatively correlated to IBD through the collection of global epidemiological data. The meta-analysis was consistent with the conclusions that *H. pylori* was a key protective factor against IBD. Furthermore, post-*H. pylori* eradication, the recurrence of IBD was obviously worse, which provided strong evidence for *H. pylori* as a protective factor. Other results showed that *H. pylori* was not related to IBD medication and classification.

The potential mechanism of *H. pylori* in preventing IBD is still unknown. The influence of immune regulation is a universally recognized factor. Twenty years ago, D'Elios et al reported results indicating that *H. pylori*-specific T cell clones exhibited a Th2-like phenotype and produced IL-5 or IL-4 together with INF-α.[20] *In vitro*, it showed that *H. pylori* infection protects against DSS-induced colitis via decreasing Th17, balancing Th17/Treg responses and shifting macrophages to anti-inflammatory M2 phenotype.[21] Engler et al confirmed that the protective factor was dependent on the IL-18 signaling and NLRP3 inflammasome.[22] Other studies revealed that *H. pylori* has been associated with increased expression of Foxp3, which changes host immune response and diverts it away from the inflammatory Th1/Th17 pathway.[23,24]

The role of *H. pylori* DNA may be another important factor for protecting IBD. Luther et al conducted *in-vitro* research revealing that *H. pylori* DNA can down-regulate pro-inflammatory responses from dendritic cells (DCs) and attenuate DSS-induced colitis.[25] Meanwhile, another study found that the inhibitory effect of *H. pylori* genomic DNA is restricted to the TLR-9 signaling pathway in the pathogenesis of IBD.[26] Furthermore, CagA gene of *H. pylori* strains resulted in higher production of β-defensins. As is well-known, production of altered human defensin is associated with IBD pathogenesis.[27,28] Compared to mutant *H. pylori* strains, one study demonstrated that the Th2 cytokine response protecting against DSS-colitis was CagA dependent.[29]

It is established that the treatment of IBD patients with anti-TNF-α agents, immunosuppressant and/or corticosteroid increases the risk of infections.[30] However, there is very little direct evidence in *H. pylori* infection. Conlan et al found that imunosuppression by a corticosteroid failed to exacerbate *H. pylori* infection in an *in-vitro* model.[31] In a clinical study, similar results were found, showing that treatment of IBD patients with anti-TNF-α factors and immunosuppressants did not influence the prevalence of *H. pylori* infection.[32] Our meta-analysis results also confirmed that the use of immunosuppressive drugs did not affect *H. pylori* infection.

Intestinal microbiota may be another key factor.[33] In certain murine colitis models, many research findings indicate that a single symbiotic organism has the ability to induce colitis, which may have a relationship to human IBD.[33] It was shown that long-term *H. pylori* infection

can cause significant changes in the composition of the large intestine microbiota, which indicates that *H. pylori* may regulate the intestinal microflora, thereby affecting the occurrence of IBD.[34] In clinical applications, related articles demonstrated that probiotics and fecal microbiota transplantation were associated with a significant improvement in the treatment of IBD.[35,36] In this meta-analysis, we found that the recurrence rate of IBD was high after *H. pylori* eradication. Is this related to intestinal flora imbalance? One study observed that eradication of *H. pylori* alters gut microbiota, specifically *Lachnobacterium*, *B. adolescentis* and *Coriobacteriaceae*.[37] Martin-Nunez et al also demonstrated that infection and eradication of *H. pylori* with antibiotics cause alterations in gut microbiota.[38] Furthermore, one study indicated that exposure to antibiotics during pregnancy is associated with increased risk of very early onset IBD regardless of gastroenteritis.[39] Therefore, recurrence of IBD after *H. pylori* eradication may be related to gut microbiota imbalance.

This article has done a lot of work, but there were still some shortcomings. A large number of epidemiological data were collected and combined for correlation analysis, but it did not represent every country or region. For example, only one African country reported IBD prevalence. Studies of IBD prevalence basically included enough individuals to reflect the prevalence of the entire region, while such studies were not available for *H. pylori* prevalence. Although we statistically combined data, which did not fully reflect the overall *H. pylori* prevalence in the entire region. The final result may be affected by this factor. In addition, although the inclusion criteria were optimized, we excluded patients with functional dyspepsia in the control group. Several studies did not report whether there were such patients in the control group, which may have affected the results. Moreover, we ruled out some factors by meta-regression, but the included articles did not consider the effects of age, gender, lifestyle, smoking, etc. We lacked data for comprehensive analysis. The included articles for meta-analysis were mainly done in Europe and Asia, and data was lacking from other regions and developing countries. Although we found that IBD patients were 1.41 times more likely for recurrence after *H. pylori* eradication, one study had a large weight, which may have biased the results. Therefore, more randomized controlled studies are needed to improve the reliability of the results.

In conclusion, the epidemiological results and meta-analysis results of this study demonstrated that *H. pylori* infection is negatively correlated to IBD and *H. pylori* is a protective factor against IBD. In addition, *H. pylori* eradication might lead to the recurrence of IBD.

## Authors' Contribution

YZh and LW designed research. YZh and ZhZh searched papers. YL evaluated the disagreement. ZhZh conducted the statistical analysis. YZh wrote the paper and LW revised the paper.

## Conflict of Interest Disclosures

None.

## Ethical Statement

Not applicable.

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## Supplementary Materials

Supplementary file 1. Prevalence of IBD, CD, UC and H. pylori since 2000 all over the world.
Supplementary file 2. Included articles for analysis in this study.

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