

Association Between *Helicobacter pylori* Infection and Inflammatory Bowel Disease: A Meta-analysis and Systematic Review of the Literature

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Background: Epidemiologic data suggest a protective effect of *Helicobacter pylori* infection against the development of autoimmune disease. Laboratory data illustrate *H. pylori*'s ability to induce immune tolerance and limit inflammatory responses. Numerous observational studies have investigated the association between *H. pylori* infection and inflammatory bowel disease (IBD). Our aim was to perform a systematic review and meta-analysis of this association.

Methods: Medline, EMBASE, bibliographies, and meeting abstracts were searched by 2 independent reviewers. Of 369 abstracts reviewed, 30 promising articles were reviewed in detail. Twenty-three studies met our inclusion criteria (subject $N = 5903$). Meta-analysis was performed with the metan command in Stata 10.1.

Results: Overall, 27.1% of IBD patients had evidence of infection with *H. pylori* compared to 40.9% of patients in the control group. The estimated relative risk of *H. pylori* infection in IBD patients was 0.64 (95% confidence interval [CI]: 0.54–0.75). There was significant heterogeneity in the included studies that could not be accounted for by the method of IBD and *H. pylori* diagnosis, study location, or study population age.

Conclusions: These results suggest a protective benefit of *H. pylori* infection against the development of IBD. Heterogeneity among studies and the possibility of publication bias limit the certainty of this finding. Further studies investigating the effect of eradication of *H. pylori* on the development of IBD are warranted. Because environmental hygiene and intestinal microbiota may be strong confounders, further mechanistic studies in *H. pylori* mouse models are also necessary to further define the mechanism of this negative association.

(*Inflamm Bowel Dis* 2010;16:1077–1084)

Received for publication August 12, 2009; Accepted August 26, 2009.

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This article was published online on Sept. 16, 2009. An error was subsequently identified. This notice is included in the online and print versions to indicate that both have been corrected Oct. 7, 2009.

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DOI 10.1002/ibd.21116

Published online 16 September 2009 in Wiley InterScience (www.interscience.wiley.com).

Key Words: *Helicobacter pylori*, inflammatory bowel disease, Crohn's disease, ulcerative colitis

Inflammatory bowel disease (IBD) is a growing worldwide health burden.^{1,2} Specifically, many developing countries have seen a dramatic rise in the incidence of IBD since 1990.^{2–7} This rise may partially be accounted for by the implementation of improved diagnostic methods and heightened awareness of IBD.^{1,3} Furthermore, improved access to a cleaner environment and the resulting decreased incidence of common childhood infections may be contributing as well by altering one's susceptibility to certain diseases with an autoimmune component, such as IBD.^{8,9} Importantly, this suggests a possible protective benefit of microbial infection during childhood.

Helicobacter pylori has coexisted with the human race for over 50,000 years.^{10,11} It is an infection acquired early in childhood, and if not eliminated by antimicrobial therapy, is carried throughout life, producing symptoms in only a minority.^{12,13} Recent epidemiological data suggests a possible protective benefit of *H. pylori* colonization against the development of certain diseases with an autoimmune component, such as asthma.^{14,15} Furthermore, there is emerging laboratory evidence illustrating *H. pylori*'s role in the regulation of the immune system. Specifically, *H. pylori* has been associated with increased gastric mucosal expression of Foxp3 (a T-regulatory cell marker) and has shown the ability to skew the host immunologic tone away from inflammatory Th1/Th17 responses (Fig. 1).^{16–21} Finally, IBD is more prevalent in areas with lower rates of *H. pylori* colonization, such as in the United States.²² In fact, there is a steady rise in the incidence of IBD in *H. pylori* endemic regions that corresponds to the beginning of anti-*H. pylori* therapy for peptic ulcer disease.²

To further investigate the possible association between *H. pylori* infection and IBD, we conducted a systematic review and meta-analysis to estimate the relative risk of *H. pylori* infection in patients with and without IBD. Given the epidemiological and laboratory data previously cited, we hypothesized an inverse relationship between *H. pylori* infection and IBD.

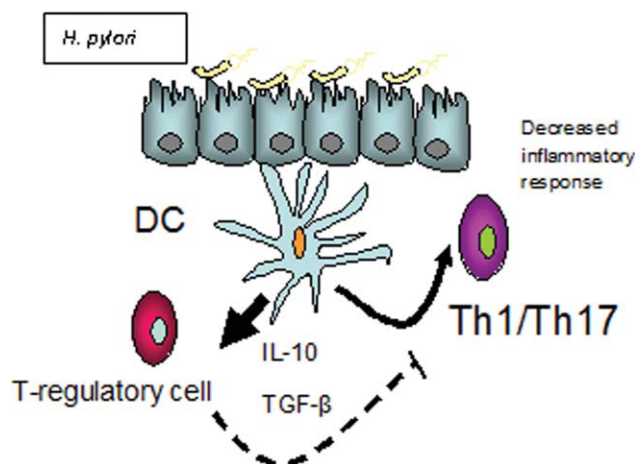


FIGURE 1. A proposed model of *H. pylori*'s effect on host immune regulation. *H. pylori*, through its interaction with dendritic cells (DC), is able to upregulate regulatory T-cells. This upregulation leads to decreased production of proinflammatory cytokines. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

MATERIALS AND METHODS

Search Strategy

This review was performed according to the standard guidelines for meta-analyses and systematic reviews of observational studies.²³ To find relevant articles for this review, we searched the following databases (from inception to March 2009): MEDLINE, EMBASE, Google Scholar, the Cochrane Central Register of Controlled Trials, ACP Journal Club, DARE, CMR, and HTA. The search strategy used free-text words and MeSH terms to increase the sensitivity of the search. The following search terms were used: "inflammatory bowel disease," "crohn's disease," "colitis, ulcerative," "IBD," "CD," "UC," "ulcerative colitis," "Crohn's," "*Helicobacter pylori*," "*H. pylori*," and "HP." Boolean operators (AND, OR, NOT) were used to narrow and widen the search results. The titles and abstracts from the search results were examined closely for potential inclusion in the study. Additionally, the references from selected articles were examined as a further search tool. We also consulted experts in the field to identify additional published and unpublished studies. Last, we searched the abstracts presented at Digestive Disease Week, United European Gastroenterology Week, and the American College of Gastroenterology Annual Scientific Meeting from 2003–2007.

Study Selection

For inclusion in the systematic review, a study had to meet the following criteria established by the study team: 1) *H. pylori* infection diagnosed by serology (IgG anti-

body), urea breath test (UBT), fecal antigen test (FAT), rapid urease test (RUT), or histology; 2) inclusion of a control group; 3) IBD and control groups were similar in age, sex, and from the same catchment area; 4) studies of human; and 5) data were reported that were sufficient to calculate *H. pylori* infection rates in both the IBD and control groups. Studies were excluded if they used data from a previously published study.

Data Extraction

To reduce reporting bias and error in data collection, 2 independent reviewers (J.L. and M.D.) extracted data from selected studies using standardized data extraction forms. These forms, created by the study team, included the: a) authors; b) title; c) year of publication; d) journal; e) study design; f) inclusion and exclusion criteria; g) method by which *H. pylori* infection was diagnosed; h) method by which IBD was diagnosed; i) number of patients with Crohn's disease (CD) and within this group, the number who were *H. pylori*-positive and -negative; j) number of patients with ulcerative colitis (UC) and within this group, the number who were *H. pylori* positive and negative; k) number of patients in the control group and within this group, the number of patients who were *H. pylori*-positive and -negative; l) reported previous use of antibiotics, and specifically antibiotics used to treat *H. pylori*, in the IBD and control groups; and m) reported previous use of immunosuppressive agents in the IBD group, specifically steroids, 5-aminosalicylates (5-ASAs), and tumor necrosis factor alpha (TNF- α) antibody medications. If needed, authors were contacted regarding specific questions relating to their study. The independent reviewers conferred after data extraction was complete, discrepancies were identified, and review of the relevant article led to consensus.

Statistical Analysis

The primary outcome of this analysis was the relative risk (RR) of *H. pylori* infection in IBD versus controls. RR was used to describe the ratio of the probability of the *H. pylori* infection occurring in IBD patients versus the controls. We calculated the RR with a 95% confidence interval (CI) based on a random-effects model as described by Mantel–Haenszel. Meta-analysis was performed with the metan command in Stata 10.1 (StataCorp, College Station, TX). Analysis with a funnel plot, Begg's test, and Egger's test were used to assess publication bias. Subgroup analyses were also performed. An I^2 statistic was used to measure the proportion of inconsistency in individual studies that could not be explained by chance.²⁴ Any heterogeneity identified would prompt subgroup analysis in an attempt to explain these findings.

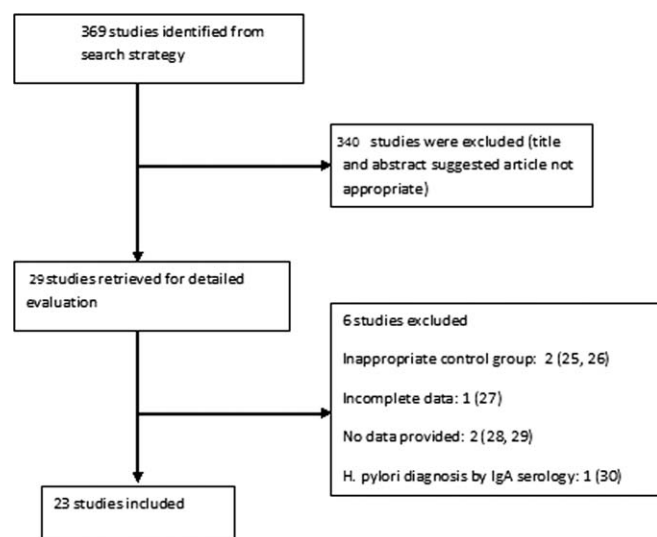


FIGURE 2. Flow diagram of studies identified in the systematic review.

Assessment of Study Quality

Each study chosen for review was carefully assessed for study quality by the study team. Study quality was assessed using the following criteria: 1) study design; 2) method of *H. pylori* diagnosis; 3) method of IBD diagnosis; 4) method of patient enrollment (consecutive versus selected); and 5) whether *H. pylori* infection rate was the primary or secondary outcome of the study.

RESULTS

Search Results

Our initial search strategy yielded 369 potential articles for inclusion. After detailed analysis of selected articles, 29 articles were reviewed in detail. Subsequently, 6 articles^{25–30} did not meet inclusion criteria. The reasons for exclusion included: 1 study included a control group from a different catchment area from the IBD group, and also differed significantly in mean age,²⁵ 1 study examined a control group with known *H. pylori* infection,²⁶ 1 study was published in abstract form only and the *H. pylori* infection rates in the control and IBD groups could not be calculated,²⁷ 2 studies did not provide data on *H. pylori*

TABLE 1. Characteristics of the Included Studies

Author	Year	Location	Single vs. Multicenter	n, Total	n, IBD (C/UC)	n, Control	Mean Age, IBD (CD/UC)	Mean Age, Control
el-Omar et al. (32)	1994	Poland	Single	210	110 (63/47)	100	38.7/47.3	NR
Mantzaris et al. (35)	1995	Greece	Single	210	90 (0/90)	120	NR	NR
Meining et al. (50)	1997	Germany	Multi	72	36 (36/0)	36	34.3	34.4
Oberhuber et al. (41)	1997	Germany	Single	275	82 (75/7)	193	NR	NR
Parente et al. (33)	1997	Italy	Single	432	216 (123/93)	216	38.6/39.9	NR
Wagtman et al. (31)	1997	Netherlands	Single	663	386 (386/0)	277	NR	NR
Duggan et al. (52)	1998	U.K.	Single	431	257 (87/170)	174	NR	NR
Corrado et al. (43)	1998	Italy	Single	90	30 (NR/NR)	60	12.2	7.3
D’Inca et al. (42)	1998	Italy	Single	151	108 (67/41)	43	40/37	38
Pearce et al. (34)	2000	U.K.	Single	133	93 (42/51)	40	42/46	43
Parente et al. (46)	2000	Italy	Single	361	220 (141/79)	141	NR	NR
Parlak et al. (37)	2001	Turkey	Single	188	111 (45/66)	77	37.2/41.9	37
Vare et al. (40)	2001	Finland	Single	349	279 (94/185)	70	43	NR
Feeney et al. (39)	2002	U.K.	Single	552	276 (139/137)	276	NR	NR
Furusu et al. (51)	2002	Japan	Single	75	50 (25/25)	25	NR	NR
Guslandi et al. (38)	2002	Italy	Single	90	60 (60/0)	30	NR	NR
Pascasio et al. (44)	2003	U.S.A.	Single	486	56 (56/0)	382	NR	NR
Piodi et al. (47)	2003	Italy	Single	144	72 (32/40)	72	48/49	NR
Triantafyllidis et al. (36)	2003	Greece	Single	243	116 (39/77)	127	42	44
Pronai et al. (48)	2004	Hungary	Single	333	133 (51/82)	200	34.2/38.4	36.3
Oliveira et al. (53)	2004	Brazil	Single	116	42 (0/42)	74	38.9	49.4
Oliveira et al. (49)	2006	Brazil	Single	117	43 (43/0)	74	40.9	49.4
Sladek et al. (45)	2007	Poland	Single	198	94 (50/44)	194	12.9	13.6

CD, Crohn’s disease; UC, ulcerative colitis; NR, not reported.

TABLE 2. Quality Assessment of the Included Studies

Author	H.P. ^a Diagnosis	IBD Diagnosis	Study Type	Patient Enrollment	Outcome
el-Omar et al. (32)	IgG	Chart review	Prospective	Random	Primary
Mantzaris et al. (35)	Histology/RUT	Not reported	Prospective	Consecutive	Primary
Meining et al. (50)	Histology	Histology	Prospective	Consecutive	Secondary
Oberhuber et al. (41)	Histology	Histology	Prospective	Consecutive	Secondary
Parente et al. (33)	IgG/histology	Chart review	Prospective	Consecutive	Primary
Wagtman et al. (31)	IgG	Chart review	Retrospective	Random	Primary
Duggan et al. (52)	IgG	Chart review	case-series	Consecutive	Primary
Corrado et al. (43)	IgG	Histology	Prospective	Consecutive	Secondary
D'Inca et al. (42)	Histology	Chart review	Prospective	Consecutive	Primary
Pearce et al. (34)	IgG/UBT	Radiology/histology	Prospective	Consecutive	Primary
Parente et al. (46)	UBT/histology	Chart review	Prospective	Consecutive	Primary
Parlak et al. (37)	Histology	Not reported	Prospective	Not reported	Primary
Vare et al. (40)	IgG	Chart review	Prospective	previous study	Primary
Feeney et al. (39)	IgG	Clinical criteria ^b	Case-series	Matched	Primary
Furusu et al. (51)	IgG/histology	Histology	Prospective	Not reported	Secondary
Guslandi et al. (38)	IgG	Not reported	Not reported	Not reported	Primary
Pascasio et al. (44)	Histology	Histology	Retrospective	Consecutive	Secondary
Piodi et al. (47)	UBT	Chart review	Prospective	Consecutive	Primary
Triantafyllidis et al. (36)	IgG	Chart review	Prospective	Not reported	Primary
Pronai et al. (48)	UBT	Histology	Prospective	Not reported	Primary
Oliveira et al. (53)	IgG/UBT	Histology	Prospective	Not reported	Primary
Oliveira et al. (49)	UBT	Histology	Prospective	Not reported	Primary
Sladek et al. (45)	Histology/RUT	Clinical/histology/serology	Not reported	Consecutive	Primary

^aH.P., *Helicobacter pylori*.

^bClinical criteria: authors state diagnoses were made according to "conventional clinical criteria."

infection rates,^{28,29} and 1 study used IgA serology as a diagnostic method for *H. pylori* infection.³⁰ Therefore, 23 studies^{31–53} with 5903 patients fulfilled the inclusion criteria for the review (Fig. 2).

Study Characteristics

The characteristics of the included studies are summarized in Tables 1 and 2. The results of each study are in Table 3. The largest study examining the relationship between *H. pylori* infection and incidence of IBD was conducted in the Netherlands by Wagtmans et al.³¹ The authors recovered frozen sera from 386 patients with known CD and 277 controls, and the sera was tested for the presence of IgG and IgA antibodies. Interestingly, the sera from the patients with Crohn's were recovered from frozen storage and in some instances had been there for 20 years. Unlike Halme et al,³⁰ which was excluded from our analysis, the authors provided data on the number of IgG-positive, IgA-positive, and IgG/IgA-positive patients. Therefore, we were able to exclude the IgA-positive patients in our analysis. Overall, 12.1% of IBD patients

were infected with *H. pylori*, while 35.4% of the control group were found to have *H. pylori* infection.

The earliest study examining *H. pylori* infection rates and IBD was published in 1994 by el-Omar et al.³² In this Polish study, el-Omar et al investigated 110 patients with IBD and 100 age- and sex-matched controls. *H. pylori* was diagnosed by the presence of IgG serologic antibodies. Prior to the study the authors studied serum samples from patients from their hospital with known *H. pylori* infection diagnosed by UBT and histology. By performing IgG antibody titers in these patients, they were able to show an IgG titer of 15 U/mL or above had a sensitivity and specificity of 96% and 84%, respectively, for *H. pylori* infection, thereby increasing the specificity of the serologic test. Therefore, they used this value as the cutoff for diagnosing *H. pylori* infection in the IBD and control groups. Overall, 22% of the IBD patients were positive for *H. pylori*, while 52% of the patients in the control group were *H. pylori*-positive. The authors, in a post-hoc analysis, did report a possible relationship between the lower prevalence of *H. pylori* infection in the IBD groups and current or previous use of sulfasalazine. This inverse relationship between

TABLE 3. Study Results

Author	% IBD Patients H.P. Positive (% CD/%UC)	% Controls H.P. Positive
el-Omar et al. (32)	21.8 (14.9/27.0)	52
Mantzaris et al. (35)	30.0 (NR/30.0)	52.5
Meining et al. (50)	8.3 (8.3/NR)	36.1
Oberhuber et al. (41)	30.5 (33.3/0.0)	35.2
Parente et al. (33)	48.1 (40.7/55.9)	58.8
Wagtman et al. (31)	12.2 (12.2/NR)	35.4
Duggan et al. (52)	34.2 (33.3/34.7)	36.2
Corrado et al. (43)	0.0 (NR/NR)	23.3
D'Inca et al. (42)	28.7 (28.4/29.3)	39.5
Pearce et al. (34)	17.2 (11.9/21.6)	25
Parente et al. (46)	38.2 (33.3/46.8)	50.3
Parlak et al. (37)	66.7 (62.2/69.7)	63.6
Vare et al. (40)	24.4 (12.9/29.7)	37.1
Feeney et al. (39)	0.05 (0.05/NR)	15.8
	13.9 (NR/13.9)	15.3
Furusu et al. (51)	29.4 (34.6/24.0)	52
Guslandi et al. (38)	15.0 (15.0/NR)	36.7
Pascasio et al. (44)	32.1 (32.1/NR)	46.1
Piodi et al. (47)	47.2 (53.1/42.5)	61.1
Triantafyllidis et al. (36)	34.5 (NR/NR)	55.1
Pronai et al. (48)	12.8 (13.7/12.2)	39
Oliveira et al. (53)	52.4 (NR/52.4)	51.4
Oliveira et al. (49)	51.2 (51.2/NR)	70.3
Sladek et al. (45)	9.6 (14.0/0.05)	38.5

NR, not reported; H.P., *Helicobacter pylori*.

previous or current sulfasalazine use and *H. pylori* infection was reported by 3 other included studies.^{33–35} One of these studies³⁵ was a letter to the editor (one of 3 letters to the editor included in our analysis).^{36,37} In this study, Mantzaris et al³⁵ reported *H. pylori* infection rates, based on histological analysis, of 30% in UC patients versus 53% in the control group (patients with irritable bowel syndrome). However, 7 of the included studies found no relationship between sulfasalazine use and incidence of *H. pylori* infection.^{36–42}

Three of the included studies examined the pediatric population exclusively.^{43–45} Among these is the only study conducted in North America. Pascasio et al⁴⁴ identified 56 cases of CD through retrospective analysis of 438 consecutive gastric biopsies with evidence of inflammation. In a secondary analysis, the authors examined each specimen for the presence of *H. pylori* and found that 32.1% of IBD patients were *H. pylori*-positive, while 34.0% of the specimens with no evidence of IBD had evidence for *H. pylori* infection.

Five of the included studies commented on previous *H. pylori* treatment.^{39,42,46–48} Of these, 4 studies excluded any patients who had been previously tested or treated for *H. pylori*.^{42,46–48} Parlak et al³⁷ excluded any patients who had ever received proton-pump inhibitors or antibiotics; therefore, one can assume these patients had never received treatment for *H. pylori*. Feeney et al,³⁹ in an attempt to assess different childhood risk factors for the development of IBD, included patients who had previously been treated for *H. pylori*. However, in a subgroup analysis, they could not account for the difference in *H. pylori* infection rates between the 2 groups based on previous *H. pylori* treatment. Two studies excluded any patients who had ever received certain antibiotics such as flagyl, ciprofloxacin, or clarithromycin, yet they did not specify previous treatment for *H. pylori*.^{36,38} Oliveira et al⁴⁹ and Sladek et al⁴⁵ excluded patients who received any antibiotics 3 months prior to *H. pylori* testing, yet the authors did not comment on antimicrobial exposure prior to this. Meining et al⁵⁰ excluded patients taking proton-pump inhibitors, antibiotics, or bismuth at the time of diagnosis, yet no mention of previous use was made.

Meta-Analysis of RR

Overall, a total of 27.1% of IBD patients had evidence of *H. pylori* infection, while 40.9% of patients in the control group were found to have *H. pylori* infection. The RR of *H. pylori* in IBD patients compared to controls was 0.64 (95% CI: 0.54–0.75) (Fig. 3). Subgroup analyses revealed a trend toward a greater effect for CD (RR: 0.60, 95% CI: 0.49–0.72) when compared to UC (RR: 0.75, 95% CI: 0.62–0.90). There was significant heterogeneity in the included studies ($I^2 = 75.8\%$). Furthermore, analysis of the funnel for publication bias suggested a possible bias against small studies demonstrating high RR (Fig. 4).

We conducted multiple subgroup analyses in an attempt to explain the observed heterogeneity. We divided the data based on the method of *H. pylori* diagnosis (serology versus UBT, FAT, RUT, or culture), method of IBD diagnosis (clinical versus pathological), study location (Eastern versus Western hemisphere), and study population age (pediatrics versus adult). None of these subgroup analyses were able to account for the observed heterogeneity. Subsequently, we separated the dataset into CD and UC and reperformed each of the aforementioned subgroup analyses. This analysis revealed a statistically significant reduction in the RR of *H. pylori* infection in CD patients diagnosed with *H. pylori* by nonserologic methods (RR: 0.71, 95% CI: 0.58–0.87; $I^2 = 54\%$)

DISCUSSION

Our systematic review of the literature has identified numerous studies examining the relationship between

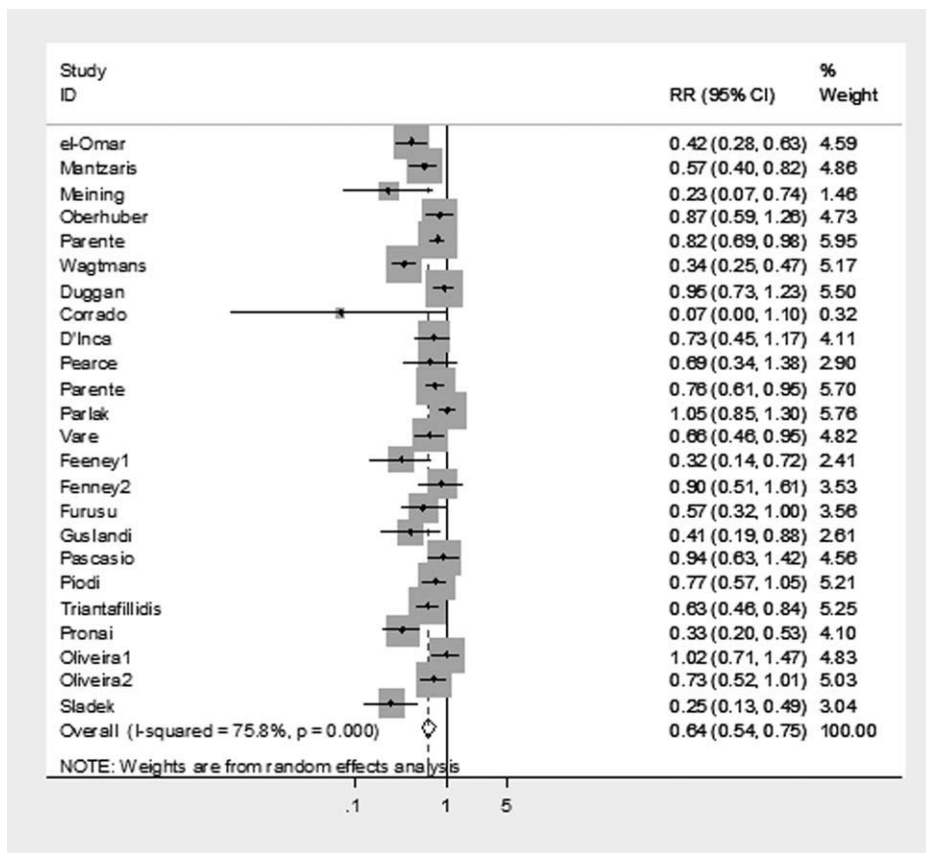


FIGURE 3. Forest plot of rate of *H. pylori* infection in patients with IBD versus controls.

H. pylori infection and IBD, the majority of which find a lower rate of *H. pylori* infection in IBD patients as compared to controls. Thirteen of the 23 studies found a statistically significant RR less than 1 for *H. pylori* infection in IBD patients versus controls, while none of the included studies found a statistically significant RR greater than 1. Our meta-analysis suggests a potential protective benefit of *H. pylori* infection against the development of IBD; however, significant heterogeneity and the possibility of publication bias limit our certainty in this association.

Mechanistic support for the association between the possible protective benefit of *H. pylori* infection against IBD is emerging. Rad et al²⁰ demonstrated that *H. pylori*-infected individuals expressed higher levels of Foxp3, a T-cell regulatory (Treg) marker, and that the depletion of Tregs resulted in a higher degree of gastric inflammation and reduced bacterial colonization. Furthermore, the importance of Tregs in the pathogenesis of IBD can be illustrated by the development of spontaneous colitis in mice deficient of IL-10, a key regulatory cytokine for Treg function.⁵⁴ It has also been shown that adoptive transfer of Tregs inhibits the development of experimental colitis in several models,^{55,56} suggesting that Tregs play an integral role in pre-

venting the development of colitis.⁵⁷ Further work attempting to define the possible role of Tregs on colitis is needed.

The data on the incidence of *H. pylori* infection and IBD found in the literature has several limitations. Most of the studies did not comment on the participants' previous

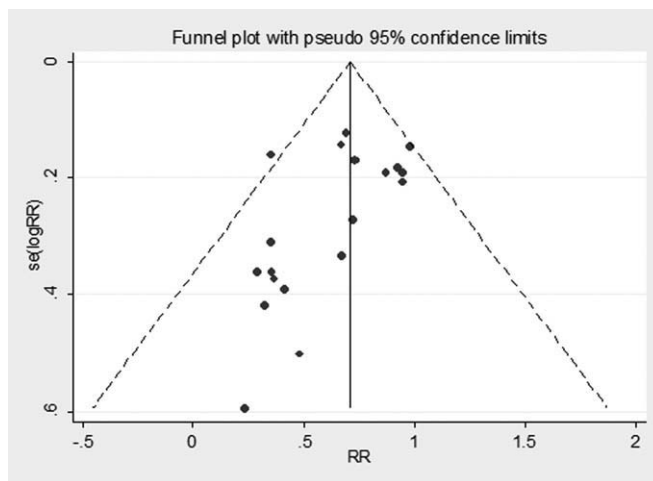


FIGURE 4. Funnel plot analysis.

history of treatment for *H. pylori* infection. It is therefore possible that study participants had been treated for *H. pylori* prior to entering the study, thereby producing a falsely low *H. pylori* infection rate. Additionally, our analysis included studies that used IgG serological antibodies as the diagnostic method for *H. pylori*. Given the high sensitivity and lower specificity of serologic testing, our results may include false-positives. Furthermore, many of the studies did not clearly identify the criteria for establishing an IBD diagnosis. Many studies referred to chart review and characteristic clinical and radiological findings associated with IBD as the standard for inclusion, yet few commented on personal review of the endoscopic findings or histology. Last, as with any study examining the association between 2 entities, causality cannot be inferred from the results.

Ideally, future studies should address these limitations. An ideal study examining the relationship between *H. pylori* infection and IBD would be conducted at the time of IBD diagnosis. After confirming the diagnosis of IBD through review of the endoscopic and histological findings, diagnostic testing for *H. pylori* with UBT, RUT, or histology would be initiated. In patients found to be *H. pylori*-positive, the presence or absence of *cagA*⁺ would be investigated, as the possible protective benefits of *H. pylori* against other autoimmune diseases come from *cagA*⁺ strains.^{15,58,59} The mechanism for the inverse association between *cagA*⁺ strains of *H. pylori* and the lower incidence of autoimmune disease has yet to be defined. Chen and Blaser⁵⁹ suggest the intense host responses to specifically *cagA*⁺ *H. pylori* strains may further alter T_H1- and T_H2-type immune responses with subsequent induction of immunoregulatory lymphocytes. Controls who are age- and sex-matched to the IBD group would be selected from the same area as the IBD group and tested for *H. pylori* by the same method. In both groups, a thorough history examining previous *H. pylori* treatment would be obtained.

In summary, our review suggests a possible protective benefit of *H. pylori* against the development of IBD. However, significant variation among the studies and the possibility of publication bias limit the certainty of this association. Therefore, further clinical studies investigating the effect of *H. pylori* eradication on the development of IBD are warranted. Because environmental hygiene and intestinal microbiota may be strong confounders, further mechanistic studies in *H. pylori* mouse models are also necessary to further define the mechanism of this negative association. If it is found that *H. pylori* does indeed protect against IBD, this will have profound effects not only on the way we approach *H. pylori* testing and treatment, but also the way we approach the treatment of IBD.

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