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Association Between *Helicobacter pylori* Exposure and Decreased Odds of Eosinophilic Esophagitis—a Systematic Review and Meta-analysis

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Abstract

Background & Aims: Previous or current infection with *Helicobacter pylori* (exposure) has been reported to protect against eosinophilic esophagitis (EoE), perhaps due to *H pylori*-induced immunomodulation. However, findings vary. We performed a systematic review and meta-analysis of comparative studies to more clearly define the association between *H pylori* exposure and EoE.

Methods: We searched 4 large databases to identify comparative clinical studies that included sufficient detail to determine the odds or risk of EoE (primary outcome) or esophageal eosinophilia (secondary outcome) among individuals exposed to *H pylori* (exposed) vs individuals who were tested and found to be unexposed. Estimates were pooled using a random-effects model. Meta-regression and sensitivity analyses were planned a priori. Studies were evaluated for quality, risk of bias, publication bias, and heterogeneity.

Results: We analyzed 11 observational studies comprising data on 377,795 individuals worldwide. *H pylori* exposure vs non-exposure was associated with a 37% reduction in odds of

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Author Contributions

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EoE (odds ratio [OR], 0.63; 95% CI, 0.51–0.78) and a 38% reduction in odds of esophageal eosinophilia (OR, 0.62; 95% CI, 0.52–0.76). Fewer prospective studies found a significant association between *H pylori* exposure and EoE ($P=.06$) than retrospective studies. Effect estimates were not affected by study location, whether the studies were performed in pediatric or adult populations, time period (before vs after 2007), or prevalence of *H pylori* in the study population.

Conclusions: In a comprehensive meta-analysis, we found evidence for a significant association between *H pylori* exposure and reduced odds of EoE. Studies are needed to determine the mechanisms of this association.

Keywords

bacteria; digestive system; allergy; immune system diseases

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, often times progressive, immune- and allergen-mediated condition defined by a threshold level of mucosal eosinophilic infiltration (15 eosinophils per high-power field (Eos/hpf)) in the esophagus along with symptoms of esophageal dysfunction, such as dysphagia or food impaction. While the first cases of EoE were described over a half-century ago^{1,2}, formal recognition of EoE as a disease entity only occurred in the mid-1990s. Over the past several decades, substantial progress has been made in our understanding of the pathophysiology of EoE; however, less is understood about predisposing and protective determinants for the disease. Indeed, both the incidence and prevalence of EoE are rapidly increasing and there is no disputing that the rate well exceeds that attributable merely to increased case-finding and detection bias.^{3–5} The rate of increase over a short period of time strongly implicates environmental factors and gene-environment interactions, as opposed to genetic factors alone. Thus, now more than ever, investigation into disease determinants is needed, particularly those which are modifiable.

Helicobacter pylori remains the most common chronic bacterial infection worldwide, with marked regional and ethnic variations in prevalence. The formal discovery of *H pylori* in the 1980s and the subsequent discovery that *H pylori* causes gastric adenocarcinoma in a small minority of infected individuals, led to eradication campaigns in some areas where gastric cancer is endemic. Eradication efforts coupled with industrialization, improved sanitation, and water conditions heralded a decreasing prevalence of *H pylori*, which corresponds temporally and geographically to a rising incidence of EoE and other immune-mediated diseases.^{3,6–10} Accumulating experimental and epidemiologic data generally support an inverse relationship between *H pylori* and inflammatory bowel disease (IBD), asthma, and food allergy.^{12–15} *H pylori* infection often occurs in early childhood and this early immunoregulation and enhanced immunotolerance may plausibly protect against the later development of aberrant Th2-mediated immune responses driving immune-mediated diseases in a susceptible host.^{13,15–20} Unfortunately, direct experimental evidence clarifying the role, if any, of *H pylori* on the development of EoE is lacking. However, indirect evidence from observational studies variably supports an inverse relationship between *H pylori* and EoE. Most recently, a prospective, multicenter case-control study by Molina-

Infante and colleagues found a statistically nonsignificant inverse association between *H pylori* infection and EoE, thus calling into question the relationship.²²

Our primary objective was to systematically review the literature for comparative studies detailing the risk of EoE in *H pylori*-exposed compared to non-exposed individuals. Because of anticipated differences in case definition over time, we also secondarily evaluated studies which included patients with esophageal eosinophilia (EE) in the absence of a formal diagnosis of EoE per se.

METHODS:

The current study follows the methodology stipulated in the Cochrane Handbook²⁴, the PRISMA guidelines²⁵, and MOOSE guidelines.²⁶

Data Sources and Searches

We systematically searched four databases—PubMed, EMBASE, CINAHL, and Web of Science—for relevant literature in conjunction with a certified biomedical librarian at Vanderbilt University (initial search: October 19, 2018). No restrictions were applied based on language, publication date, or peer-reviewed publication type, although we acknowledge that the ability to critically appraise the quality of abstracts and conference abstracts, for example, is limited. Key words searched included: “*helicobacter pylori*”, “*campylobacter pylori*”, “*helicobacter infections*”, “*eosinophilic esophagitis*”, “*esophageal eosinophilia*”. The full search strings for each database can be found in the Supplemental material. We also hand-searched references from included studies, as well as relevant review articles and published abstracts.

Inclusion/Exclusion Criteria

All clinical trials (randomized or nonrandomized), cohort (prospective, retrospective), case-control, and cross-sectional studies were considered eligible if they met the following additional criteria: (1) clear definition for eosinophilic esophagitis or esophageal eosinophilia (even if study-specific); (2) comparative study design with distinct comparison between patients with EoE or EE and patients without EoE or EE who had undergone endoscopic evaluation and esophageal biopsies; (3) *H pylori* testing in both case and comparator groups, along with test results; (4) clear description of demographic details including pediatric versus adult populations; (5) sufficient detail to calculate effect estimates.

Data Extraction

Eligibility assessment and data extraction were carried out independently by S.C.S. and A.T. with discrepancies resolved by a third investigator, N.N. A data collection form was designed by S.C.S. and included the following elements: first author’s last name; publication date; study design; country of origin; study time period; number of patients; study demographics (age, sex, pediatric/adult/both, smoking history, racial/ethnic background); study setting (community-based, hospital-based, multicenter, single-center) and study-specific inclusion/exclusion criteria; *H pylori* related details (number infected; current vs. former vs. never infection; diagnostic method (e.g. histology, rapid urease test, stool antigen

test, etc.); duration of infection; treatment details including antibiotic regimen and eradication success or failure); EoE and EE-related details (age of diagnosis, criteria for diagnosis, clinical symptoms, esophageal findings, presence of other atopic diseases, proton-pump inhibitor (PPI) use and timing of use related to diagnosis, other EoE therapy and response to therapy); endoscopy-related details (indication, number of biopsies, location of biopsies; gross findings) and histologic findings including Eos/hpf. Data extraction was performed in duplicate by S.C.S and A.T.

Primary exposure and outcomes

The primary exposure was *H pylori* infection (documented as current, former, or current versus former not specified). The primary outcome was EoE. EE was analyzed as a secondary outcome. Study-specific definitions of *H pylori* exposure, EoE diagnosis, and EE diagnosis were recorded as noted above. Abidance to the strict definition of EoE as 15 Eos/hpf on esophageal mucosal biopsies along with esophageal symptoms was documented separately. As detailed below, separate analyses were performed to analyze only those studies adhering to the currently accepted definition of EoE, understanding that there remains controversy regarding the positioning of PPI-responsive EE (PPI-REE).²⁷

Quality and Risk of Bias Assessment

Quality assessment was performed independently by S.C.S and A.T. using the Newcastle-Ottawa Scale (NOS)²⁸ for nonrandomized studies and the Cochrane Risk of Bias tool for randomized trials (although there were no studies fitting the latter category). Discrepancies were resolved by consensus with N.N. For the NOS, studies scored as ≥ 7 (of maximum score 9) were considered high-quality, consistent with the literature.²⁸ Separate NOS rubrics were used for case-control, cohort, and cross-sectional studies (modified NOS cohort rubric).²⁹

Qualitative Synthesis and Quantitative Statistical Analysis

Details of each study were summarized. The overall prevalence of *H pylori* in the study population was recorded. No studies identified reported relative risk. The odds of EoE (primary outcome) or EoE/EE in *H pylori* exposed versus non-exposed was calculated and reported as odds ratios (ORs) for each individual study. Individual study ORs were combined into a pooled OR (pOR) by using a random effects model. Egger test³⁰ and a funnel plot were used to assess publication bias for the primary outcome. Heterogeneity was estimated with chi-squared and I^2 test statistics. The chi-squared test suggests heterogeneity between studies when the P-value is less than 0.15. We further used I^2 cut-offs of <30%, 30–59%, 60–75%, and >75% to for low, moderate, substantial, and considerable heterogeneity, respectively.³¹ Based on the availability of appropriate studies and data, the follow meta-regression analyses were planned *a priori* to adjust for: study type (cohort versus case-control studies, and prospective versus retrospective studies), study geography (based on literature suggesting geographic differences in the association between *H pylori* and other esophageal symptoms, namely GERD²³), time period (pre-2007 versus post-2007), pediatric only versus adult only populations, prevalence of *H pylori* (low prevalence, defined as <20% versus moderate-high prevalence, defined as $\geq 20\%$), former versus current *H pylori* infection, PPI therapy versus no PPI therapy, serologic response to *H pylori* specific

virulence factors (e.g. VacA, CagA), and duration of *H pylori* infection prior to EoE diagnosis (or matched time point in comparator group).

All analyses were performed with RevMan 5.1 (Review Manager Version 5.1, Copenhagen, Denmark) and Comprehensive MetaAnalysis (version 2.0; Biostat, Englewood, NJ).

RESULTS

After removal of duplicates, our search yielded 291 results: EMBASE (123), Web of Science (97), PubMed (64), CINAHL (7). A total of 259 articles were excluded for irrelevance based on title and abstract screening. The full texts of the remaining 32 articles were reviewed for eligibility, along with full reference lists. Only one relevant abstract was identified, but these same data were subsequently published as full text and thus only the latter was included³²; no brief reports or other alternate publication types were identified. From 32 full-text articles reviewed, 21 were excluded for the reasons detailed in the flow diagram (Figure 1). One additional article was identified from search of reference lists and the full text was reviewed; however, this study was excluded because of lack of *H pylori* testing in the comparator group.³³ Thus, a total of 11 articles were eligible for analyses.

Characteristics of included studies (Table 1)

All included studies were observational; no interventional studies were identified. Two studies were cohort^{34,35}, 3 studies were cross-sectional^{36–38}, and 6 studies were case-control^{22,32,39–42}. Only one study encompassed a time period prior to 2000 (1989–2000)³⁵; otherwise, all studies included data from 2000 onwards when explicitly stated. One cross-sectional³⁸ and one case-control study⁴² included East Asian populations, while four studies were from the US, two from Sweden, one each from Germany and Australia, and one multicenter study that included centers from Spain, Italy, France, and Colombia.²²

Four studies were population-based, including 2 from a nationwide pathology database.^{32,36,38,40} We confirmed that the Dellon et al.³² and Sonnenberg et al.⁴⁰ studies were conducted using the same pathology database; the different names in the respective publications (Caris Life Sciences and Mirica Life Sciences) reflect the change in ownership. Because it is impossible to determine the degree of overlap between the two study populations, we performed a sensitivity analysis removing the Dellon et al. study, since the study time period (2008–2010) was included within the Sonnenberg et al. study (2008–2015).

Additional details of the included study populations are detailed in Table 1.

H pylori-related details

The overall prevalence of *H pylori* in the pooled study population (i.e. all tested individuals) from cohort and cross-sectional studies was 8.9% (N=5534/62,035), and ranged from a low of 7.0% in the individual studies by Dellon et al. (US)³² to a high of 71.8% in the study by Ma, et al. (China).³⁸ *H pylori* prevalence was 7.0% (N=179/2543) versus 9.0% (N=5355/59492) in EoE cases versus non EoE comparators. Current versus former *H pylori* infection was not readily discernible in the studies, as variable methods of testing for *H*

pylori were used and the testing modality with respect to EoE or EE diagnosis was not consistently explicitly stated (thus precluding meta-regression according to current versus former infection). Other details that were not available in any study included duration of *H pylori* infection prior to EoE/EE diagnosis or matched time point in controls and *H pylori*-specific virulence factors (e.g. CagA, VacA). Studies variably reported eradication therapy for *H pylori* and no studies reported eradication success or failure, nor the effect of *H pylori* therapy on EoE/EE diagnosis or related outcomes. Thus, meta-regression and subanalyses for these categories were not possible.

Eosinophilic Esophagitis and Esophageal Eosinophilia-related details

Nine of the 11 studies defined EoE as ≥ 15 Eos/hpf (one study >20 Eos/hpf) and esophageal symptoms (see Table 1). Acid-suppressive therapy with PPI was variably reported, and only one study stated failure of PPI therapy.³⁹ One study's protocol explicitly stated that biopsies were obtained with patients off of PPI therapy for 2 weeks prior to endoscopy.³⁴ Details regarding other EoE therapy were not consistently provided in studies, but these data were abstracted whenever available (Table 2). Endoscopic protocols, when described, were also variable in terms of the number and location of biopsies (Table 2).

***H pylori* status and Risk of Eosinophilic Esophagitis (primary outcome) or Esophageal Eosinophilia (secondary outcome)**

H pylori exposure was associated with a 37% lower odds of EoE (OR 0.63, 95% CI: 0.51–0.78), based on 8 studies (Figure 2). Although 9 of the 11 studies explicitly defined EoE as ≥ 15 Eos/hpf (one study >20 Eos/hpf) and esophageal symptoms, Sealock et al. reported *H pylori* information only according to EE status; thus, only 8 of 11 studies were included in the analysis of *H pylori* and risk of EoE according to a strict definition. Removing this study from the primary analysis did not alter the effect estimate. Based on meta-regression, there was no significant difference in effect estimates between cohort studies and case-control studies (Supplemental Figure 4a, $P=0.63$). The magnitude and direction of the protective effect estimate of *H pylori* exposure was unchanged (OR 0.62, 95% CI: 0.52–0.76) when we included the three studies^{36–38} that reported risk of EE only, as opposed to EoE by strict diagnostic criteria (Figure 3).

Notably, performing sensitivity analyses by removing the Dellon et al. study from both the primary and secondary analyses (as well as meta-regression analyses where appropriate) did not significantly affect the outcomes, other than slightly increasing the magnitude of protective benefit. *H pylori* exposure was associated with a 43% lower odds of EoE (OR 0.57, 95% CI: 0.40–0.80) or a 42% (OR 0.58, 95% CI: 0.44–0.76) lower odds of EoE/EE compared to non-exposed individuals. (Supplemental Figures 1 and 2).

Additional analyses (meta-regression analyses)

Meta-regression analyses revealed that study geography (US-based studies versus non-US studies, $P=0.26$), pediatric only versus adult population ($P=0.93$), time period of patient recruitment (pre-2007 versus post-2007, $P=0.18$), and *H pylori* prevalence of the study population (low versus moderate-high prevalence, $P=0.58$) did not influence the effect estimates (see Supplemental Figures 4b–4e); that is, the magnitude of the protective effect of

H pylori exposure on subsequent odds of EoE (or EoE/EE) was stable in each meta-regression analysis. Meta-regression analysis was also performed to adjust for studies done prospectively versus retrospectively. A statistically nonsignificant trend was seen in the effect estimates between these study types, with prospective studies less likely to show a significant association between *H pylori* exposure and EoE ($P=0.06$) (Figure 4). As noted above, data were either not available or there were too few studies to perform additional subanalyses. For example, while there were two studies performed in East Asian populations, meta-regression for Eastern versus Western geography could not be performed since one was a cross-sectional study³⁸ and the other a case-control study.⁴²

Publication bias and heterogeneity

A funnel plot was generated to assess for publication bias. The symmetric distribution of this plot suggested no publication bias (Supplemental Figure 3). Egger's test confirmed no publication bias ($P\text{-value}=0.77$). Statistical tests of heterogeneity demonstrated moderate heterogeneity for our primary outcome analysis ($I^2 = 57.9\%$, chi-squared test $P=0.02$) and substantial heterogeneity for the secondary outcome analysis ($I^2 = 69.3\%$, chi-squared test $P<0.001$). Removing the Dellon et al. study from the analyses improved the heterogeneity estimates for the secondary analysis ($I^2 = 50.6\%$), which was downgraded from substantial to moderate heterogeneity, but did not substantially affect the primary analysis estimate ($I^2 = 58.5\%$).

Risk of Bias Assessment according to the Newcastle Ottawa Scale (NOS)

All case-control and cross-sectional studies were rated as high-quality. The two cohort studies^{34,35} were rated fair-quality, mainly driven by insufficient data for adequate assessment of the comparability parameter. (Supplemental Table 1a and 1b) Removing these two studies and performing a sensitivity analysis limited to only high-quality studies based on NOS score ≥ 6 did not alter our findings. (Supplemental Figure 5).

DISCUSSION

In this meta-analysis of nearly 378,000 people tested for *H pylori*, we found that *H pylori* exposure was associated with a lower likelihood of EoE (and EoE/EE). The directionality of association was consistently observed across pediatric only versus adult populations, US versus non-US geography, low versus moderate-high *H pylori* prevalence areas, and time period of patient recruitment. Notably, the magnitude and directionality of the protective association between *H pylori* and EoE was preserved independent of cohort versus case-control study design, although there was a trend towards prospective studies being less likely to demonstrate this association. We acknowledge heterogeneity with respect to some definitions, *H pylori* testing modality, treatment details, and endoscopic protocols; however, these would expectedly result in nondifferential misclassification and bias towards a null association between *H pylori* and EoE.

EoE represents a major health burden both in terms of patient morbidity and cost to the healthcare system, with a recent population-based analysis estimating that EoE accounts for \$1.4 billion of healthcare spending annually.⁴³ Rates of EoE, among other immune-mediated

diseases, continue to escalate not only in Western industrialized countries but also in geographic locations such as East Asia and countries with recently developed economies, where the disease was previously nonexistent.³ The sharp trajectory suggests that a relatively abrupt change in environmental exposures is most responsible for the observed trend, as opposed to a shift in genetic predisposition; this is further supported by twin and familial studies showing that shared environmental exposures more so than genetic factors explain the heritability of EoE.⁴⁴ Elucidating environmental protective and predisposing determinants potentially offers mechanistic clues that, ideally, can be leveraged for prevention and treatment. Substantive epidemiologic data, including the present comprehensive analysis, and indirect evidence in experimental models of other immune- and allergic-mediated disease implicate *H pylori* as a protective factor. *H pylori* has co-evolved with humans for over 100,000 years^{45,46} and some protective benefit is evolutionarily expected. Two separate population-based analyses from the US⁴⁷ and the Netherlands⁴⁸ place the time period for the change in environmental exposure about 40–50 years ago, which corresponds to decreasing *H pylori* rates as a result of active eradication efforts and industrialization. Operating under the ‘hygiene hypothesis’, factors such as improved socioeconomic status, sanitation efforts, cleaner water sources, and industrialization are cited as leading factors underlying the rise in immune-mediated and allergic diseases, with *H pylori* argued to be merely a surrogate of these factors. While certainly contributory, these factors are unlikely to fully account for the inverse association between *H pylori* and EoE, as this association was preserved among Western industrialized countries, post-2007, and irrespective of baseline *H pylori* prevalence in our study, even after performing a sensitivity analysis removing the Dellon et al. study to account for the potential of overlapping cases with the Sonnenberg et al. study. However, our conclusions do differ from the recent prospective, multicenter case-control study by Molina-Infante and colleagues, which found a null association between *H pylori* and EoE (OR 0.97, 95% CI: 0.73–1.30) based on 808 patients. As the first prospective case-control study on this topic, their study had other strengths in addition to the prospective study design and multicenter recruitment, such as inclusion of only patients with EoE who were naïve to therapy (e.g. PPI), a standardized endoscopic and biopsy protocol, and testing for *H pylori* off PPI therapy. That said, it is plausible that bias might at least partially account for the null findings, as control patients were selected based on esophageal symptoms, and many also more commonly had esophageal pathology, such as reflux esophagitis. This is relevant because *H pylori* has been inversely associated with GERD and presence and severity of erosive esophagitis.^{49,50} Ultimately, it remains inconclusive as to whether infection with *H pylori* itself biologically protects against EoE. Our meta-analysis findings that support a protective benefit of *H pylori* exposure against EoE and thus oppose the findings of the only prospective case-control study highlight the need not only for additional large, prospective investigations, but also for investigations to define mechanisms underlying these observations.

Indeed, experimental data support the protective immunoregulatory phenotype of *H pylori*.^{13,16–20} This protection occurs through *H pylori*-induced alterations in signaling pathways that are similarly implicated in IBD, asthma, and allergy, such as attenuation of inflammatory Th1 and Th17 signaling pathways with or without upregulation of Th2 or T-regulatory pathways.^{13,17,20} Preliminary data further implicate specific *H pylori* proteins,

including CagA, VacA and gamma-glutamyl transpeptidase.^{15,51–54} Unfortunately, no included studies specifically reported serologic responses to *H pylori* specific proteins. Timing of *H pylori* exposure might also be an important mediator of protection. At least in experimental models of allergy, neonatal *H pylori* exposure conferred the highest immunotolerance.^{17,55} No studies commented on the duration of *H pylori* infection, so we were unable to evaluate the impact of timing of *H pylori* exposure and magnitude of protection against EoE. We do acknowledge that temporal relationship cannot be definitively established from our study. That said, primary *H pylori* infection most often occurs during early childhood, particularly in endemic areas, with incidence rates of infection as an adult estimated to be <1% per year.^{56–58} While adjustment for studies with pediatric only versus adult only populations did not alter our effect estimate significantly, insufficient power is a consideration since only two studies were performed exclusively in pediatric populations (0.3% of our study population, N=1008/377,975). A prospective study detailing timing of *H pylori* infection and cumulative exposure on risk of subsequent EoE, while the ideal study, is of course logistically limited by time, resources, and the rarity of EoE as an outcome (and potentially an even rarer outcome with *H pylori* exposure).

The present study has several strengths, including a large sample size across multiple geographies, comprehensive search strategy, and several relevant meta-regression analyses and sensitivity analyses, with consistent results overall and moderate heterogeneity. By including only patients who had undergone *H pylori* testing, we limited indication bias. Apart from inherent limitations of meta-analyses, our study has the following additional limitations. The lack of information on medication, and specifically PPI use at the time of endoscopy is a potential confounder for the two studies that reported data based on a US population-based pathology database^{32,40}. Between 2008–2015, the time period of enrollment for these studies, many US practitioners prescribed PPIs, which could suppress detection of *H pylori*⁵⁹, as first-line therapy for suspected EoE and which potentially could also increase the falsely negative diagnoses of EoE. Differences in biopsy protocol might also contribute to differences in sensitivity of *H pylori* detection and false negative diagnoses. Secondly, we were unable to account for potential confounders including socioeconomic status and early life exposures, although we would expect any unmeasured confounders to bias towards a null association between *H pylori* and EoE. Interestingly, we did not see a difference in our effect estimates between low and moderate-high prevalence *H pylori* populations, populations which presumably would have different environmental exposures. Of note, several studies found a very low prevalence of *H pylori* overall, which was universally lower in patients with versus without EoE (or EE) (Table 1). The two population-based studies from a large US pathology database reported an overall *H pylori* prevalence of approximately 7%, which is significantly lower than estimates for the US based on a recent comprehensive meta-analysis of global *H pylori* prevalence (pooled prevalence for general US population 35.6%, 95% CI: 30.0% – 41.1%).¹¹ The reasons for this discrepancy are unclear, but might reflect the combination of lack of data on PPI use, variability in biopsy protocol and sensitivity of *H pylori* detection, perhaps on the background of decreasing *H pylori* prevalence, as has been described for developed countries.^{22,60–62} Thirdly, we are unable to determine the effect of active versus former infection or the effect of *H pylori* treatment on risk of EoE (which relates to the timing of

infection and duration of cumulative *H pylori* exposure). Nine of the included studies did not specifically state if *H pylori* eradication therapy had been previously prescribed, but three of these studies did include *H pylori* serologic analysis, which would detect previous *H pylori* exposure and thus potentially a more immunotolerant phenotype and lower risk of EoE.

In conclusion, by performing a meta-analysis of 11 observational studies, we found that *H pylori* might be associated with decreased odds of EoE, an observation which was preserved across geographies, *H pylori* prevalence, pediatric versus adult populations, patient recruitment time period and primary study design. The limitations we have noted are difficult to overcome with observational study designs, particularly those constructed retrospectively. While robust prospective trials are ideal, these are logistically limited. Studies in experimental models of EoE would further clarify the putative role of *H pylori* in EoE pathophysiology by defining mechanisms active in the early phase of disease and protective pathways that, in the future, might be leveraged for clinical benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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none

Abbreviations:

CI	confidence interval
Eos	eosinophils
EoE	eosinophilic esophagitis
EE	esophageal eosinophilia
GERD	gastroesophageal reflux disease
Hp	high power field
H pylori	Helicobacter pylori
IBD	inflammatory bowel disease
NOS	Newcastle-Ottawa Scale
OR	odds ratio
PPI	proton-pump inhibitor
US	United States

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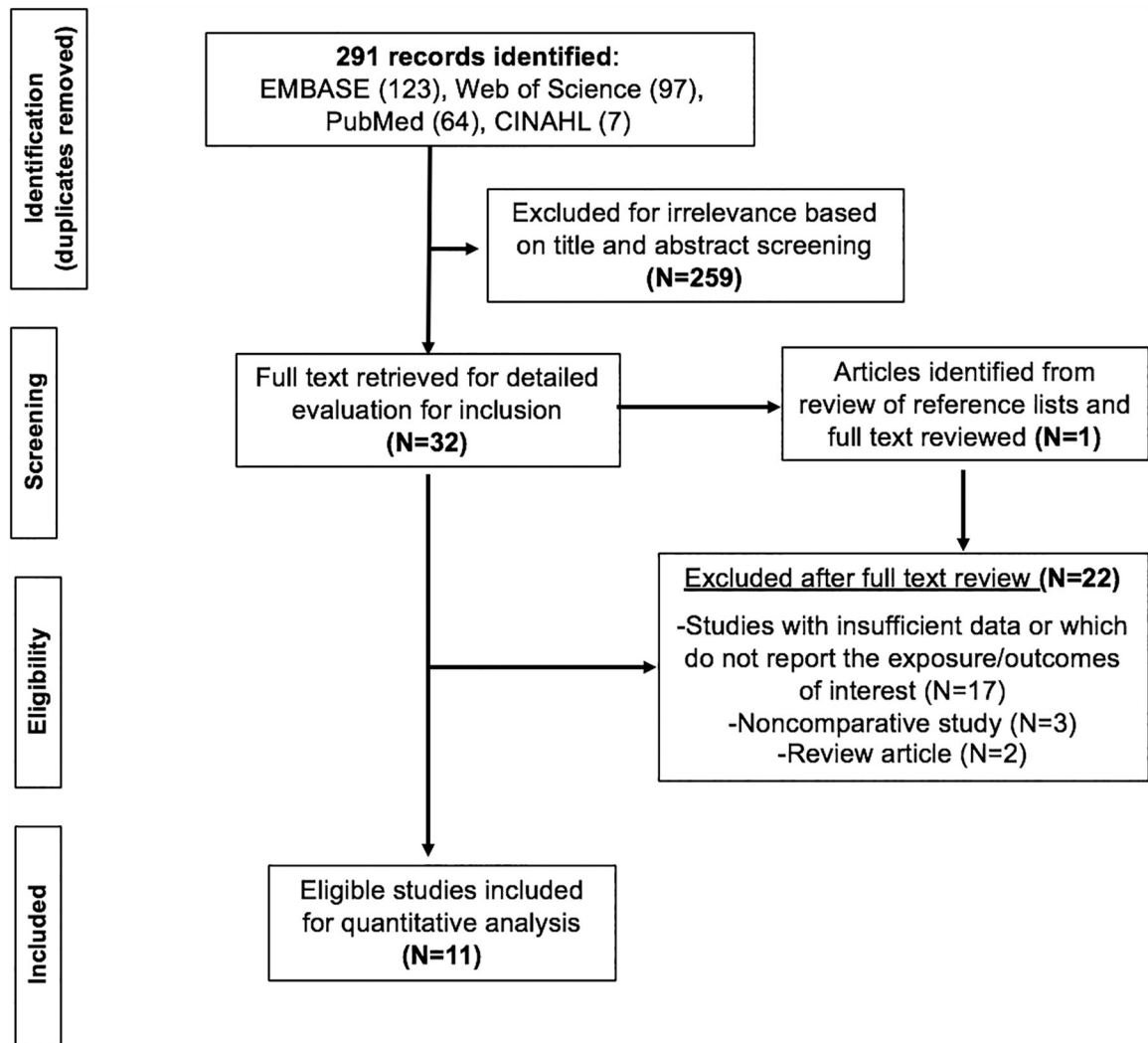


Figure 1:
PRISMA diagram of study selection

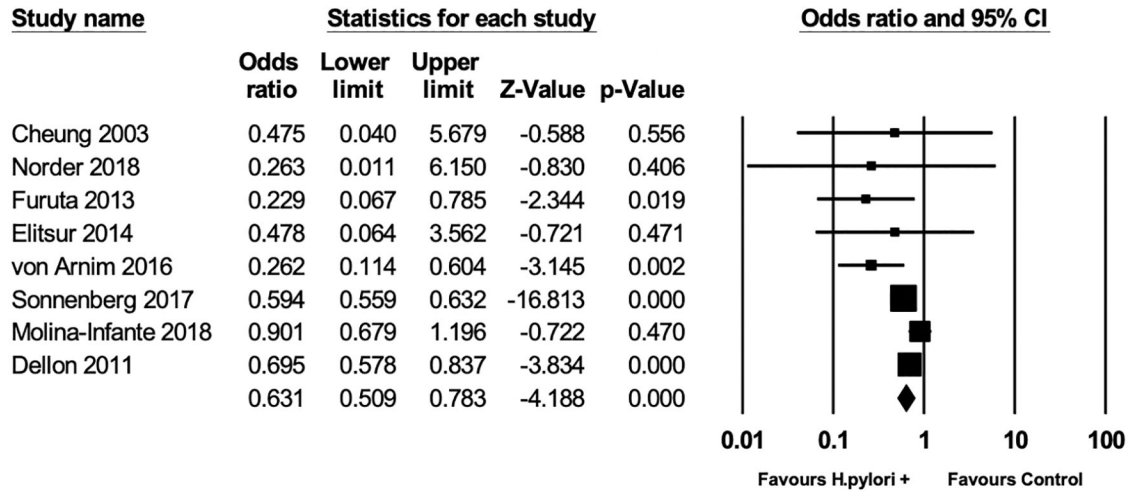


Figure 2:
Odds of eosinophilic esophagitis in *H pylori* exposed versus non-exposed individuals

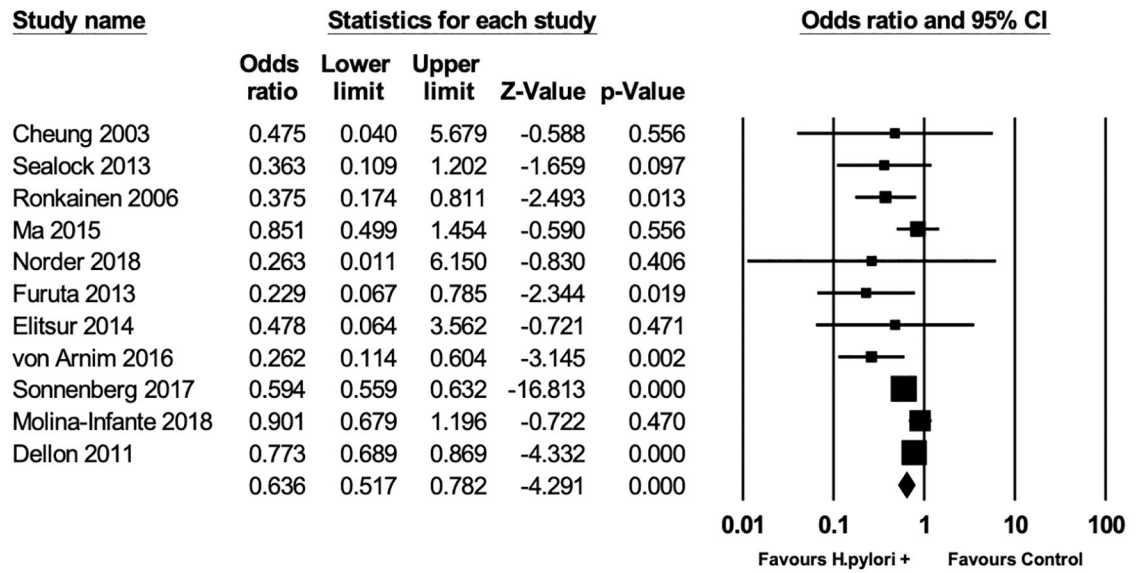


Figure 3:
 Odds of eosinophilic esophagitis or esophageal eosinophilia in *H pylori* exposed versus non-exposed individuals, pooled odds ratio

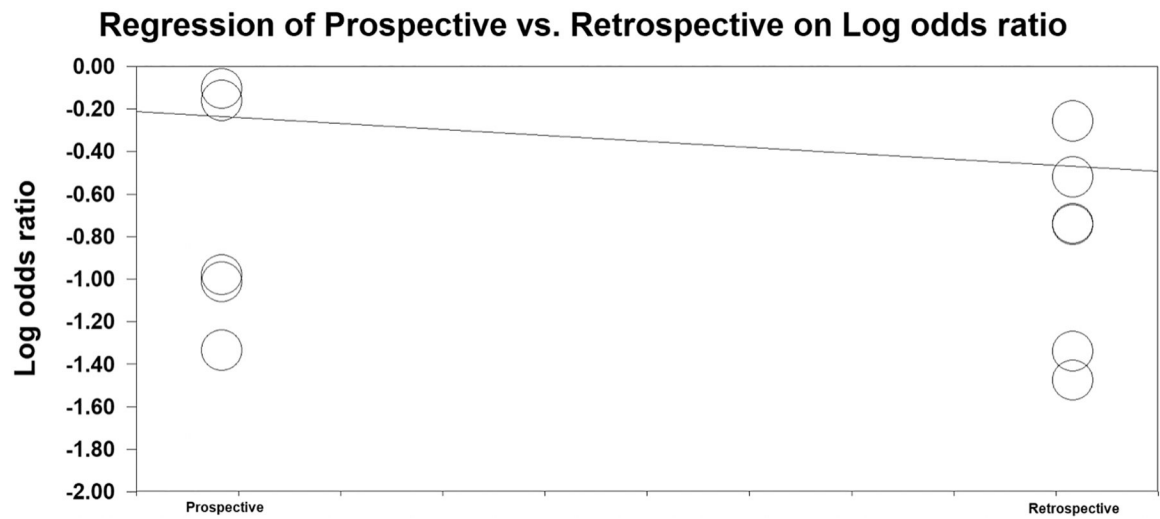


Figure 4: Meta-regression analysis showing the difference in effect estimates between prospective and retrospective study designs, with prospective studies less likely to show an association between *H pylori* exposure and eosinophilic esophagitis

Table 1:

Study Characteristics, Diagnostic Terminology, and Endoscopic Protocols

Author, Year	Study Design	Country or Region	Study Period	Definition of Cases	Definition of Comparators	Endoscopic Protocol	EoE Therapy ^a	Primary Study Objective
<u>CROSS-SECTIONAL AND COHORT STUDIES</u>								
<i>Cheung, 2003</i>	Retrospective cohort; Single-Center	Melbourne, Australia	1989–2000	EoE: dysphagia and >20 Eos/hpf	Dysphagia and 5 Eos/hpf	All had biopsies of lower esophagus, gastric body, antrum, and the third part of the duodenum. Most had biopsies from upper and middle esophagus as well	Unknown	To characterize EoE by comparison with those who presented with dysphagia, but had little or no eosinophilic infiltration in the esophagus
<i>Norder, 2018</i>	Prospective cohort; Single-Center	Sweden	2009–2014	EoE: history of esophageal dysfunction and 15 Eos/hpf	GERD: typical symptoms, had endoscopic and/or histopathologic esophagitis and <15 Eos/hpf	Diagnostic biopsies, and 2 bacterial samples 2cm above the Z-line, biopsies repeated at the proximal esophagus 5 cm below the upper esophageal sphincter, as well as brush samples and two biopsies from the buccal mucosa	2 weeks off of PPI prior to biopsies	To compare the microbiome of the esophagus in subjects with GERD and EoE
<i>Ronkainen, 2006</i>	Prospective; Cross-Sectional; Single-Center	Sweden	1998	EE: >0 Eos/hpf	0 Eos/hpf	At least two biopsy samples were taken from the following locations in the esophagus: 2 cm above the Z-line, at the Z-line, and any abnormal areas	Unknown	To assess the prevalence of EoE and the presence of eosinophils in the distal esophagus, and determine the association with upper GI symptoms
<i>Sealock, 2013</i>	Prospective; Cross-Sectional; Single-Center	United States	Not stated	EE: >15 Eos/hpf; EoE (definite): EE + esophageal symptoms + acid suppression meds EoE (probable): EE + either esophageal symptoms OR acid suppression meds	15 eos/hpf	1 esophageal 2–3 cm above the normal SCJ, and biopsies from suspected Barrett’s esophagus and multiple gastric biopsies	Variable	To determine the prevalence and risk factors of EE with or without EoE
<i>Ma, 2015</i>	Prospective; Cross-sectional (Population-based)	China	Not stated	EE: >0–15 Eos/hpf	0 Eos/hpf	At least 4 esophageal biopsies from 0.5cm above the Z-line and any abnormal areas	Unknown	To describe features of esophageal eosinophilia and eosinophilic esophagitis in a representative sample of adults in Shanghai, China
<u>CASE-CONTROL STUDIES</u>								

Author, Year	Study Design	Country or Region	Study Period	Definition of Cases	Definition of Comparators	Endoscopic Protocol	EoE Therapy ^a	Primary Study Objective
<i>De/lon, 2011</i>	Retrospective; Case-control; Multicenter (pathology database)	United States	2008–2010	EE: 15 Eos/hpf; EoE: EE + clinical suspicion for EoE and no reflux or BE	<15 Eos/hpf	Esophageal and gastric biopsies	Unknown	To investigate the association between EE and <i>H. pylori</i> infection
<i>Furuta, 2013</i>	Retrospective, Case-Control; Single center	Japan	2010–2011	EoE: history of EoE (defined by esophageal dysfunction and 15 Eos/hpf)	Age and gender matched, normal patients, without history of EoE, presenting for annual check-up.	Not stated	Unknown	To investigate the effect of <i>H. pylori</i> infection on EoE and eosinophilic gastroenteritis in Japanese patients
<i>Elitsur, 2014</i>	Retrospective, (nested) case-control; Single center	United States	2007–2012	EoE: 15 Eos/hpf (presence of esophageal symptoms not specifically stated)	<15 Eos/hpf	Esophageal biopsies (distal – 3; mid – 3 when EoE was suspected); stomach (antrum – 4 for histology, two for rapid urease test, body – 2); 2 from the duodenal bulb, and 2 from the 2nd part of duodenum	All had failed PPI therapy	To investigate the association between <i>H. pylori</i> infection and EoE in children
<i>von Arnim, 2016</i>	Retrospective, Case-Control; Single Center	Germany	Not stated	EoE: >15 Eos/hpf + Esophageal symptoms	Normal controls: age and sex matched controls without EoE, presenting to the ER 2009–2010.	2 biopsies from distal (3–5 cm above GEJ) and 2 from the proximal esophagus	Unknown	To assess if <i>H. pylori</i> infection is associated with a reduced risk of developing EoE
<i>Sommenberg 2017</i>	Retrospective, Case-Control; Multicenter (pathology database)	United States	2008–2015	3 definitions, variable certainty: 1 >15 Eos/hpf + dysphagia 2 >15 Eos/hpf + dysphagia, and exclusion of GERD/reflux esophagitis, BE, eosinophilic gastroenteritis, IBD, or other etiologies for eosinophilia 3 >50 Eos/hpf and exclusion of other causes listed in #2	No histologic abnormalities	Esophageal and gastric biopsies	Unknown	To investigate the influence of <i>H. pylori</i> on the ethnic variation of esophageal eosinophilia
<i>Molina-Infante, 2018</i>	Prospective, Case-Control; Multicenter	Spain, Italy, France, Colombia	2014–2017	EoE: Esophageal symptoms and 15 Eos/hpf	Esophageal symptoms and <5 Eos/hpf (age-, sex-, matched)	6 biopsies each from distal and proximal esophagus	Naïve	To determine the association of <i>H. pylori</i> and EoE

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Abbreviations: BE, Barrett's esophagus; ER, emergency room; Eos, eosinophils; EoE, eosinophilic esophagitis; EE, esophageal eosinophilia; EGD, esophagogastroduodenoscopy; GEJ, gastroesophageal junction; GERD, gastroesophageal reflux disease; hpf, high-power field; IBD, inflammatory bowel disease; PPI, proton-pump inhibitor

^aAcid suppression, topical steroids, other if listed

Table 2: *H. pylori* prevalence in patients with eosinophilic esophagitis or eosinophilic esophagitis versus comparator group

Author, Year	Study Population, N	Age; Pediatric vs. Adult vs. Both	Cases, N ^a	Comparator, N	Cases, N(%)	Comp., N (%)	Overall, N(%)	Cases, N(%)	Comp., N (%)	Overall, N(%)	H. pylori-negative Comp., N (%)	Overall, N(%)	Naïve to H. pylori therapy (yes, no, unknown)	Method(s) of H. pylori diagnosis	Current vs. Former Infection
CROSS-SECTIONAL AND COHORT STUDIES															
Cheung, 2003	42	Pediatric	21	21	1/21 (4.8%)	2/21 (9.5%)	3/42 (7.1%)	20/21 (9.5%)	19/21 (90.5%)	39/42 (92.9%)	19/21 (90.5%)	39/42 (92.9%)	Unknown	Unknown	Unknown
Nordr, 2018	21 ^f	Adult	9	14	0/9 (0.0%)	2/14 (14.3%)	2/23 (8.7%)	9/9 (88.9%)	12/14 (85.7%)	20/23 (87.0%)	12/14 (85.7%)	20/23 (87.0%)	Unknown	A Campylobacter-like organism (CLO) test (rapid urease test for CLOs, Ballard Medical Products, Draper, UT) was performed on gastric biopsy samples.	Unknown
Ronkainen, 2006	1000	Adult	EE: 48	952	8/48 (1.7%)	331/952 (34.8%)	339/1000 (33.9%)	40/48 (83.3%)	621/952 (65.2%)	661/1000 (66.1%)	621/952 (65.2%)	661/1000 (66.1%)	Unknown	Histology of gastric biopsy with the Warthin-Starry silver stain as well as culture.	Unknown
DeJong, 2011	165017	Both (Majority adult; 2.1% <18yo)	EE: 2,5767	56301	326/5767 (5.7%)	4048/56301 (7.2%)	4374/62068 (7.0%)	5441/5767 (94.3%)	52253/56301 (92.8%)	57694/62068 (93.0%)	52253/56301 (92.8%)	57694/62068 (93.0%)	Unknown	Histologic antibody staining (gastric biopsy) with concomitant chronic and/or active inflammation in the gastric mucosa	Unknown
Seaton, 2013	1357 ^b	Adult	EE: 33 ^c	1324	3/31 (9.7%)	285/1250 (22.8%)	288/1281 (22.5%)	28/31 (90.3%)	965/1250 (77.2%)	993/1281 (77.5%)	965/1250 (77.2%)	993/1281 (77.5%)	Variable	Histological diagnosis (gastric biopsies), or if review of the medical record showed a previous positive biopsy, presence of serum antibodies, or	Unknown

Author, Year	Study Population, N	Age; Pediatric vs. Adult vs. Both	Cases, N [EoE, unless stated as EE]	Comparator, N	Cases, N(%)	H. pylori-positive		H. pylori-negative		Naive to H. pylori therapy (yes, no, unknown)	Method(s) of H. pylori diagnosis	Current vs. Former Infection
					Overall, N(%)	Comp., N (%)	Cases, N(%)	Comp., N (%)	Overall, N(%)			
Ma, 2015	1021	Adult	EE: 67	954	733/1021 (71.8%)	687/954 (72.0%)	46/67 (68.7%)	21/67 (31.3%)	288/1021 (28.2%)	Unknown	treatment received Serum H. pylori antibodies were determined using IgG enzyme linked immunosorbent assay (ELISA)	Unknown
CASE-CONTROL STUDIES												
Furuta, 2013	160	Not stated	18	54	34/72 (47.2%)	30/54 (55.6%)	4/18 (22.2%)	14/18 (77.7%)	38/72 (52.8%)	Unknown	Serum anti-H. pylori antibody were measured using EIA	Unknown
Elitsur, 2014	966	Pediatric	62	904	31/966 (3.2%)	30/904 (3.3%)	1/62 (1.6%)	61/62 (98.4%)	935/966 (96.8%)	Unknown	Diagnosed with positivity of both histology (H&E and Giemsa staining), and rapid urease test (CLO).	Unknown
von Arnim, 2016	174	Adult	58	116	52/174 (29.9%)	44/116 (37.9%)	8/58 (13.8%)	50/58 (86.2%)	122/174 (70.1%)	Variable ^d	H. Pylori serology	Both
Sonnenberg, 2017	596479	Both	25969 ^e	284552	21839/310521 (7.0%)	20683/284552 (7.3%)	1156/25969 (4.5%)	24813/25969 (95.5%)	288682/310521 (93.0%)	Unknown	Histologic H. pylori staining as well as signs of chronic and/or active inflammation in gastric mucosa	Unknown
Molina-Infante, 2018	808	Both	404	404	312/808 (38%)	161/404 (39.9%)	151/404 (37.4%)	253/404 (62.6%)	496/808 (62%)	Yes	13C-urea breath test (UBT), monoclonal stool antigen test, or rapid urease test or histology collected by endoscopy	Unknown

^a See definitions in Table 1 for each study

^b 76 subjects not tested for *H. pylori*, thus denominator for calculations is 1281

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^c Case defined by EE. Number of *H. pylori* positive patients could not be determined for EoE (probable or definite).

^d 8 total *H. pylori* positive subjects included 5 subjects with prior infection and eradication.

^e Includes all patients with at least dysphagia and 15 Eos/hpf (of these, 11,915 and 6,708 patients met the stricter criteria for group 2 and group 3 categorization as defined in Table 1)

^f 4 subjects did not have *H. pylori* testing, thus denominator for calculations is 23