Is Helicobacter pylori Infection Associated with Celiac Disease? A Meta-analysis

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Cite this article as: Yue M, Chen Q, Zhou X, Li L, Lu C. Is *Helicobacter pylori* infection associated with Celiac disease? A meta-analysis. *Turk J Gastroenterol.* 2022;33(3):205-212.

ABSTRACT

Background: *Some studies have reported the correlation between Helicobacter pylori and celiac disease (CD), but the results lack consistency. This meta-analysis aimed to quantify the relationship between H. pylori and CD. In addition, the study also analyzed the impact of H. pylori on the symptoms and classification of CD.*

Methods: *Studies published up to September 1, 2020 on 3 databases – EMBASE, MEDICINE, and PubMed – were searched. The statistical data of articles which met the requirements were collated and extracted.*

Results: *Twenty-five papers and 141 355 participants were finally enrolled. The results showed that the H. pylori infection rate of CD patients was 0.57 times greater compared to controls (OR = 0.57, 95% CI [0.44, 0.75]), while statistical differences were also seen in the subgroups of children (OR = 0.53, 95% CI [0.33, 0.85]) and adults (OR = 0.63, 95% CI [0.49, 0.81]). Furthermore, patients having CD with H. pylori were more likely to have symptoms of abdominal pain, diarrhea, and distension (OR = 2.5, 95% CI [1.35, 4.62]) (OR = 1.56, 95% CI [1.09, 2.24]) (OR = 2.75, 95% CI [1.74, 4.35]). However, H. pylori has no effect on CD classification.*

Conclusion: *The study confirmed that there is a correlation between H. pylori and CD, but the causality cannot be clarified. A demonstration of a causal role of H. pylori in CD in future prospective studies could have important therapeutic implications.*

Keywords: *Celiac disease, Helicobacter pylori*

INTRODUCTION

Celiac disease (CD) is an inherited autoimmune disease that occurs in the small intestine.[1] Almost 99% of the patients have HLA DR3-DQ2 and/or DR4-DQ8, compared with approximately 40% of the general population.[2] Celiac disease is a chronic condition, and clinical manifestations can involve the intestinal and extra-intestinal areas, which is one of the reasons for widespread concern.[3] Celiac disease affects approximately 0.5-1% of the global population, with a female predominance accompanying the increase in morbidity, including a 2- to 4.5-fold increase over approximately 20-50 years in the Western countries.[1,4] Nevertheless, the pathogenesis is not well understood and the only treatment consists of the permanent exclusion of gluten from the food intake (gluten-free diet, GFD).[5] Microbiome,[6] vitamin D,[7] and environmental factors such as infant feeding practices[8] may contribute to the pathogenesis of CD. In recent years, more and more researches have reported that *Helicobacter pylori* may be related to the pathogenesis of CD.[9] *H. pylori* may lead to increased intraepithelial lymphocytes (IELs); this is defined as a type I celiac lesion, in line with the Marsh–Oberhuber classification.[10,11]

H. pylori is colonized in human gastric mucosa, which mainly causes stomach injury.[12] The global infection rate of *H. pylori* is as high as almost 50%, and it also occurs in childhood.[13] Numerous studies have demonstrated that *H. pylori* infection is related to gastroduodenal diseases, including lymphocytic gastritis.[12] However, whether *H. pylori is* related to duodenal intraepithelial lymphocytosis is still controversial. Moreover, it also remains unclear whether or not *H. pylori* infection affects the pathophysiological changes of CD such as the alteration of intestinal mucosa.

The main purpose of this study was to quantify the relationship between *H. pylori* and CD, including *H. pylori* alteration before and after GFD treatment. The secondary purpose was to quantify the relationship between *H. pylori* and CD-related symptoms, as well as the Marsh classification, through meta-analysis.

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Received: ***May 25, 2021*** *Accepted:* ***June 14, 2021*** *Available Online Date:* ***January 25, 2022***

DOI: ***10.5152/tjg.2022.21360***

MATERIALS AND METHODS

Data Selection

A systematic literature search was performed in 3 databases (PUBMED, EMBASE, and MEDICINE) up to September 1, 2020. The search was restricted to human studies and English language manuscripts. Both retrospective and prospective studies which met the requirements were included in this study. The following search terms were used to retrieve potential articles: (*(Helicobacter*) OR (Helicobacter pylori) OR (Helicobacter infection) OR (HP) OR (H. pylori)) AND ((Celiac disease) OR (Celiac disease) OR (gluten-sensitive enteropathy) OR (gluten-induced enteropathy)*).

The search was independently performed by 2 authors according to title and abstract, and the full text of the study was retrieved if it met the requirements. In addition, a third author would evaluate the disagreement.

Inclusion Criteria and Quality Assessment

The diagnosis of CD was based on the Marsh classification and anti-tissue transglutaminase.[14] The Marsh classification consists of 4 categories based on histological changes: (1) Marsh 0: normal; (2) Marsh I: IELs increased with a normal crypt/villi ratio; (3) Marsh II: IELs increased with crypt hyperplasia; and (4) Marsh III: Disappearance of fluff.[10] The diagnosis of *H. pylori* was confirmed on the basis of at least 1 positive result from the following tests: (1) $^{13}C/^{14}C$ urea breath test (UBT); (2) rapid urease test (RUT); (3) *H. pylori* culture; and (4) first serology test positive. In addition, sufficient data for calculation were needed for inclusion in the study.

Quality assessment and risk of bias were assessed through the STROBE checklist for the studies included.[15] In addition, the work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16]

Data Extraction

Three authors independently extracted relevant information from each included study according to a unified standard and then proceeded to cross-check the results. The data extracted included author, region or country, method of detection of *H. pylori*, and whether the patient was a child or an adult. In addition, dichotomous variable data of *H. pylori* infection rate in CD patients and controls, *H. pylori* infection rate in CD patients before and after treatment, symptom differences between *H. pylori*-positive and -negative CD patients, as well as Marsh classification differences in the *H. pylori*-positive and -negative CD patients, were obtained. When it was necessary to fill in missing data, the authors of the included studies were contacted by e-mail for additional information.

Statistical Analysis

The calculation data involved in this study were all dichotomous variables. The data for calculation were described by odds ratio (OR) and 95% CI. Heterogeneity between studies was assessed by Cochran's Q statistic and quantified with the I^2 statistic. The value of I^2 was used to evaluate the level of heterogeneity, assigning the categories as low (<50%) and high (≥50%).[17] In this study, when heterogeneity was low, the pooled estimates were obtained using the fixed-model (Mantel and Haenszel) method. On the contrary, the random-model (M-H heterology) method was chosen if heterogeneity was high.[18] This part of the analyses was carried out through Review Manager (Version 5.3, The Nordic Cochrane Centre, Rigshospitalet). Furthermore, publication bias was estimated by Begg's test, with a value of $P > .05$ suggesting no publication bias. We used sensitivity analysis to evaluate whether the meta-analysis results were stable and reliable. Moreover, meta-regression was used to look for potential sources of heterogeneity, by the Monte Carlo permutation test. The difference was that this part of the analyses was carried out through the application of STATA 15 (StataCorp., College Station, Tex, USA).

Main Points

- *This study aimed to quantify the relationship between Helicobacter pylori and CD by meta-analysis.*
- *The results showed that the H. pylori infection rate of CD patients was lower than that of controls.*
- *Patients having CD with H. pylori were more likely to have symptoms of abdominal pain, diarrhea, and distension.*

RESULTS

Basic Characteristics

A total of 1020 related articles were identified for screening, of which 25 papers were finally enrolled according to the inclusion criteria (Tables S1-S8). The flowchart describing the process of the study selection has been schematically outlined in Figure 1. The participants in 13 studies were children, and 12 articles referred to adults. In addition, the studies were mainly carried out in Europe and the Middle East. The papers retrieved were observational case-control studies or cross-sectional studies. Overall, 141 355 participants were enrolled in this study, and the definitions used for *H. pylori* and CD across various studies met the eligibility criteria.

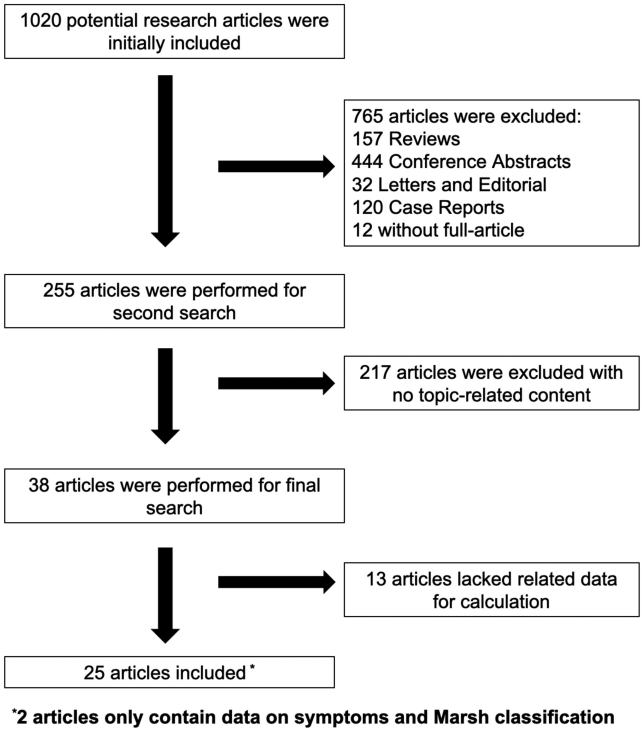

Figure 1. Flow chart for the process of identifying studies included in and excluded from the meta-analysis.

Comparison of Helicobacter pylori *Infection Between CD Patients and Controls*

The corresponding data have been listed in Table S1. Twenty-three papers reported *H. pylori* infection in CD, of which 12 reports concerned children. The total *H. pylori* infection rate of CD patients was 15.3%, while it was 10.6% in the controls. The total pooled results showed that *H. pylori* infection rate of CD patients was 0.57 times compared to controls, which showed statistical difference (OR = 0.57, 95% CI [0.44, 0.75]) (Figure 2). Subsequent subgroup analysis showed that *H. pylori* infection rate of CD patients was 0.63 times compared to controls in adults (OR = 0.63, 95% CI [0.49, 0.81]), while it was 0.53 in children (OR = 0.53, 95% CI [0.33, 0.85]). Both were statistically different (Figure 2).

In order to further quantify the relationship between *H. pylori* and CD, the study compared *H. pylori* infection rate in treated and non-treated CD patients. A total of 4 articles reported CD treatment (Table S2), and all treatment options involved a gluten-free diet. The result showed that although the *H. pylori* infection rate had decreased after treatment, there was still no statistical difference (OR = 1.29, 95% CI [0.81, 2.05]) (Figure 3).

Helicobacter pylori *Infection and Different Symptoms of CD Patients*

There were multiple articles reporting the relationship between *H. pylori* infection and 6 symptoms of CD patients including growth failure, inappetence, distension, abdominal pain, diarrhea, and vomiting. The main information has been listed in Tables S3-S8. According to the heterogeneity, the pooled estimates of abdominal pain and vomiting were obtained using the random-model method, while others chose the fixed-model method. We found that CD patients with *H. pylori* infection were more likely to have abdominal pain, diarrhea, and distension symptoms, which were 2.5, 1.56, and 2.75 times the odds respectively (OR = 2.5, 95% CI [1.35, 4.62]) (OR = 1.56, 95% CI [1.09, 2.24]) (OR = 2.75, 95% CI [1.74, 4.35]) (Figure 4). On the contrary, there was no statistical difference for the other symptoms (Figure 4).

Helicobacter pylori *Infection and Marsh Classification of CD Patients*

Four articles reported whether CD patients with or without *H. pylori* infection were more prone to conform to the Marsh III classification (Table S9). However, the result had no statistical difference (OR = 0.36, 95% CI [0.06, 2.07]) (Figure 5). Moreover, 4 more articles reported whether Marsh III CD patients with or without *H. pylori* infection were more likely to fall into the Marsh IIIc classification (Table S10). Again, there was no statistical difference (OR = 1.05, 95% CI [0.73, 1.51]) (Figure 5).

Publication Bias, Sensitivity Analysis, and Meta-Regression

Funnel plot analyses of studies assessing *H. pylori* infection on CD with its symptoms and Marsh classification revealed no significant publication bias, with the *P* values for Begg's test being 0.579, 0.117, 0.602, 0.174, 0.06, 0.851, 0.296, 0.734, and 0.806 respectively (Figure S1). Sensitivity analysis shows that although some meta results were fluctuant, the overall results were stable and reliable (Figure S2). In addition, the authors used meta-regression to look for possible sources of heterogeneity. The results showed that heterogeneity had nothing to do with region ($P > .751$), age ($P > .696$), and *H. pylori* detection method ($P > .788$).

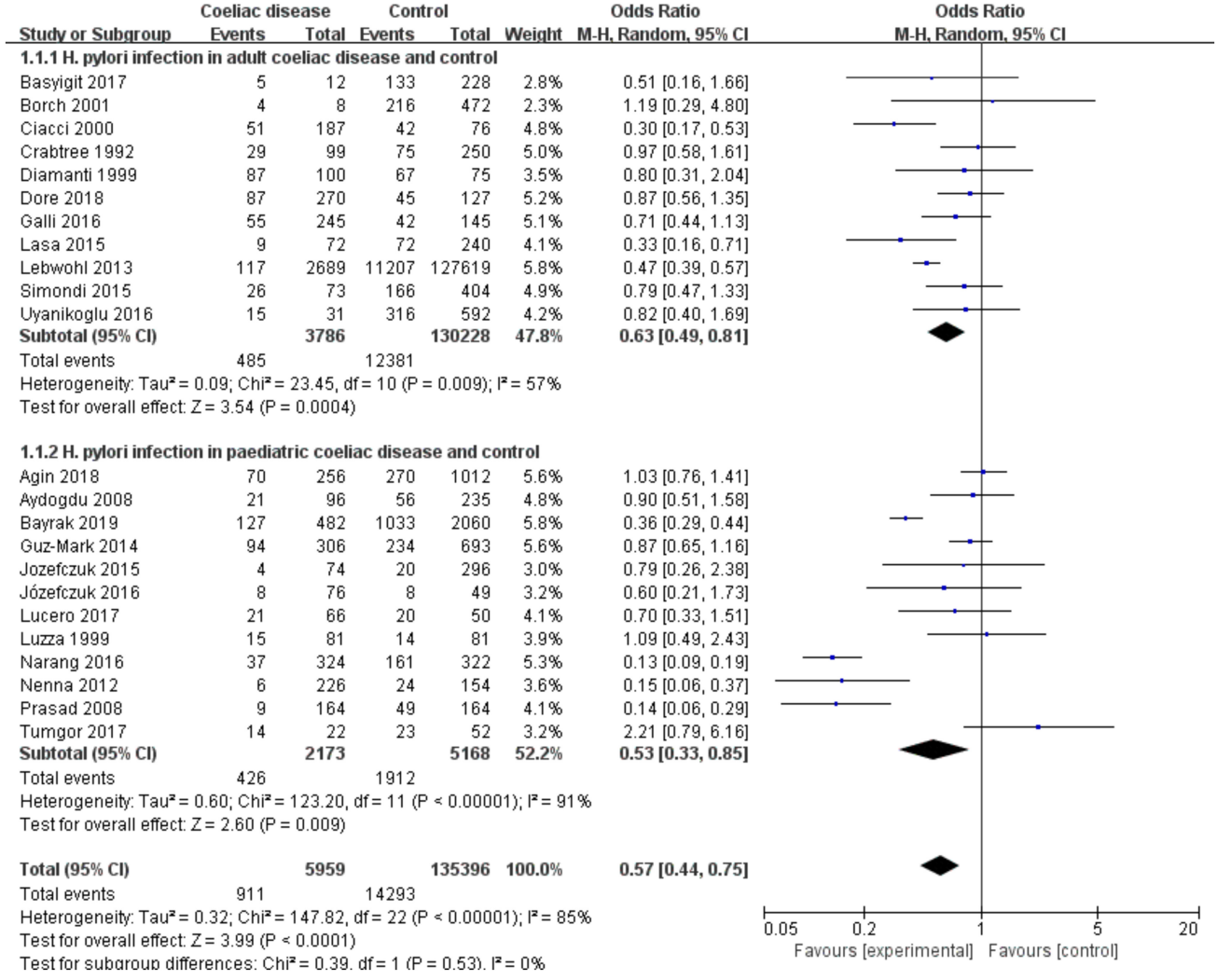

Figure 2. Summary estimates for the prevalence of *Helicobacter pylori* infection on CD patients and controls. The total pooled results showed statistical difference (OR = 0.57, 95% CI [0.44, 0.75]). Subsequent subgroup of adults and children also showed statistical difference (OR = 0.63, 95% CI [0.49, 0.81]) (OR = 0.53, 95% CI [0.33, 0.85]). However, the existence of heterogeneity suggested that there was certain variability in the study. CD, celiac disease; OR, odds ratio.

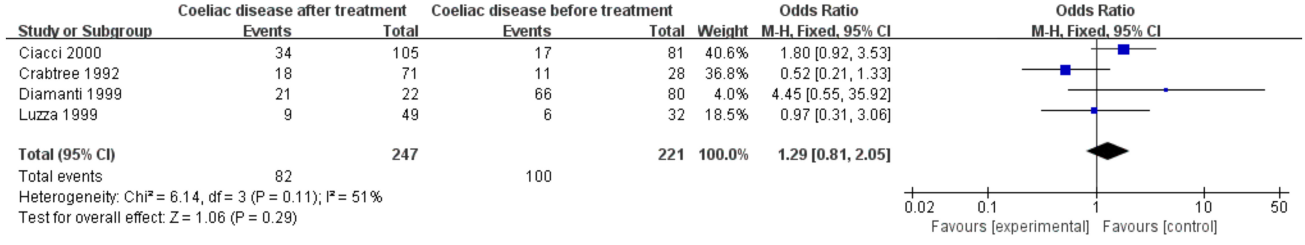

Figure 3. Summary estimates (I^2 value of > 50%) showed that there was still no statistical difference after CD treatment (OR = 1.29, 95% CI [0.81, 2.05]). CD, celiac disease; OR, odds ratio.

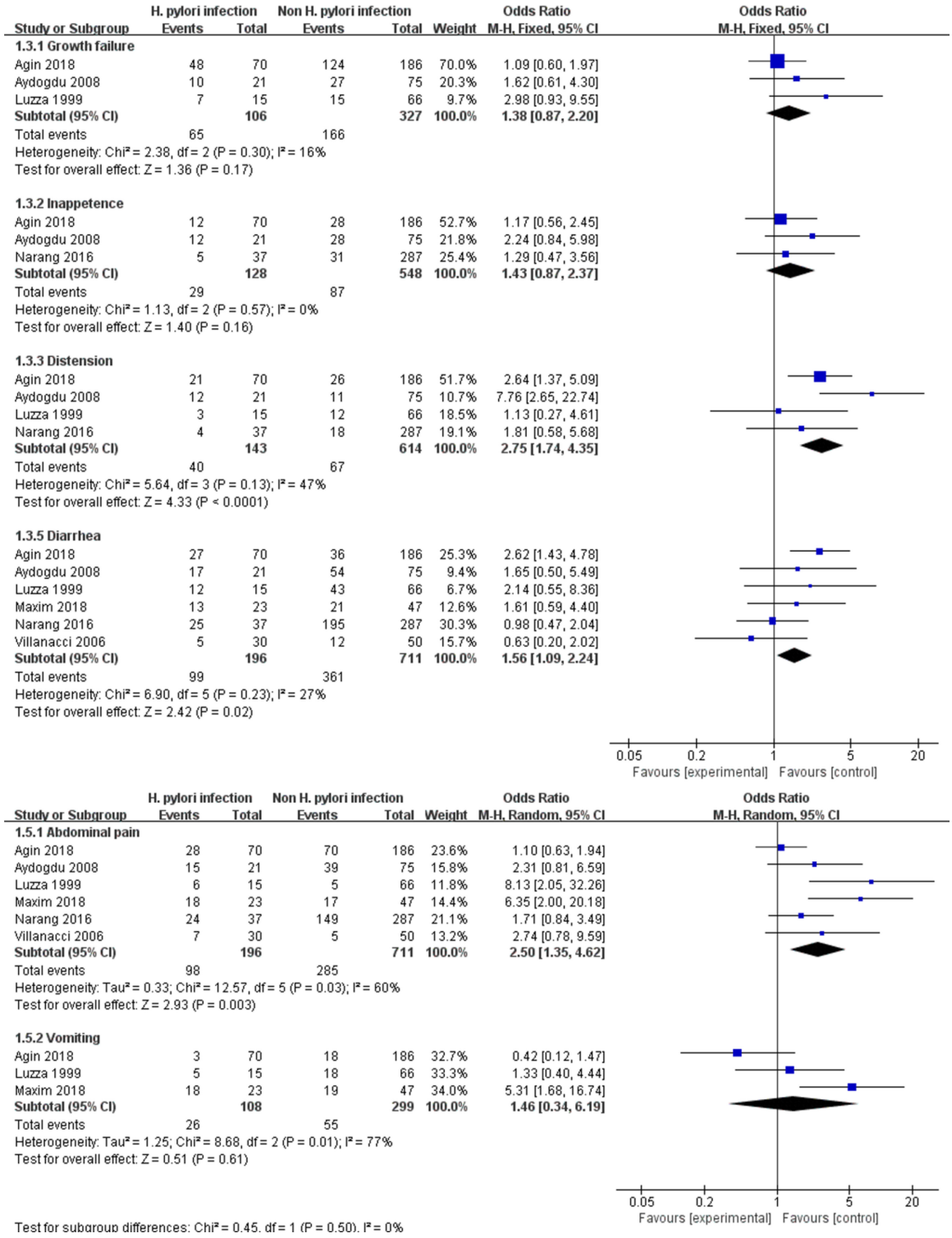

Figure 4. Summary estimates for the prevalence of CD symptoms with or without *Helicobacter pylori* infection. Abdominal pain, diarrhea, and distension symptoms showed statistical difference between the 2 groups. The I^2 value of > 50% of the groups for abdominal pain and vomiting indicated a high variability. CD, celiac disease.

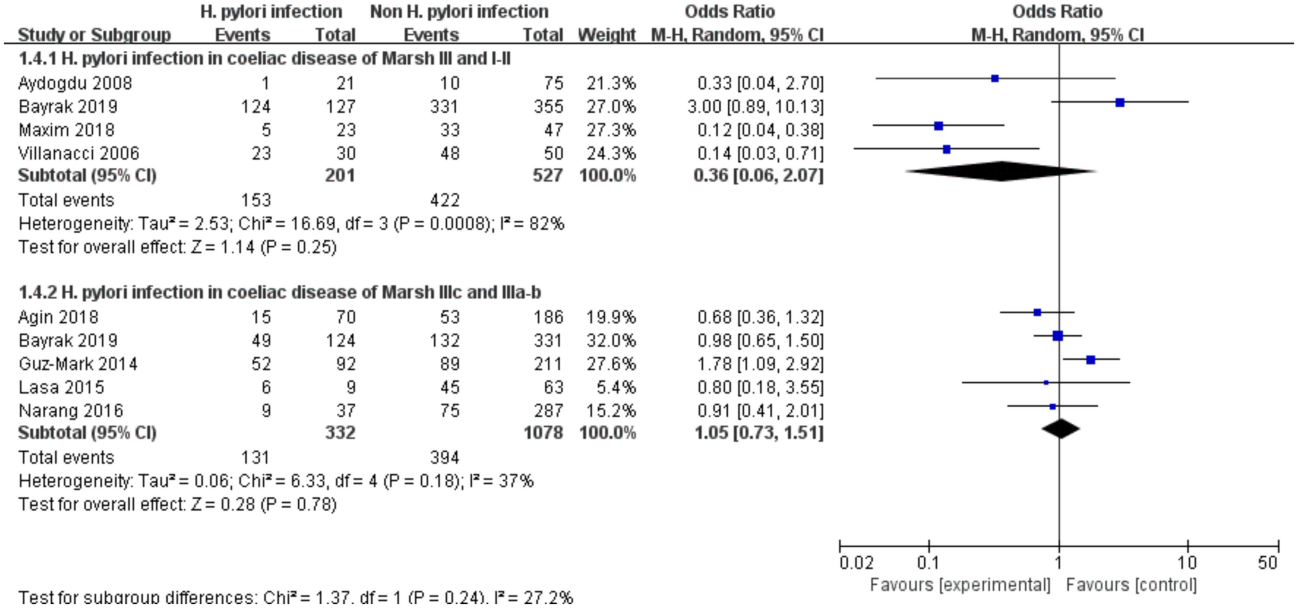

Figure 5. Summary estimates for the prevalence of CD Marsh classification with or without *Helicobacter pylori* infection. The results showed no statistical difference. CD, celiac disease.

DISCUSSION

This meta-analysis of 25 published studies demonstrated that *H. pylori* infection was lower in CD patients, suggesting that *H. pylori* infection may be a protective factor. However, the comparison of the results before and after CD treatment did not further support this hypothesis. *H. pylori* also did not affect the Marsh classification of CD. In addition, CD patients with *H. pylori* infection were more likely to have symptoms of abdominal pain, diarrhea, and distension.

The pathogenesis of CD is closely related to *H. pylori* infection, which may be closely related to the pathogenesis of these 2 entities. Epidemiologically, the incidence of CD is higher in developed countries, while the incidence of *H. pylori* is indeed lower. In terms of pathogenesis, the most well-known theory is the "hygiene hypothesis" postulate. Lebwohl et al. elaborated on this hypothesis.[19] The core point was Th1/Th2 immune unbalance under the complex interactions of *H. pylori* infection and CD. A previous study revealed that in CD patients, the downregulation of T-regulatory lymphocyte-mediated cellular responses in the intestinal wall were also diminished or lost, which indicated that T-regulatory lymphocytes may be closely related to the pathogenesis of CD.[20] Meanwhile, animal experiments confirmed that T-regulatory lymphocytes recruited by *H. pylori* play a role in immune response.[21,22] Therefore, individuals with *H. pylori* infection may affect immune responses to gluten by recruiting gastric T-regulatory cells.[19]

In addition, gut microbiome composition may be causative in the pathogenesis of CD.[2] Petersen et al.[23] reported that some bacteria express may potentially trigger a host immune response by mimicking gliadin. The gut microbiome can affect the immune system through the release of anti-inflammatory peptides or cytokines.[24] Specific to intestinal bacteria, *Bifidobacterium*, with anti-inflammatory agents, had a reduced diversity in one study[25] and the expression of *B. fragilis*, that causes increased intestinal permeability and degradation, was higher in another study.[26] Similarly, *E. coli* and *Staphylococcus* species also change by affecting intestinal permeability or producing toxins and metabolites.[27,28] *H. pylori* is also closely related to the gut microbiome. The alterative of relative abundance of *Bacteroidaceae* and *Enterobacteriaceae* caused by *H. pylori* was prevalent and alterative at the class, order, family, and genus levels was also observed.[29] From a different perspective, through modification of gastric pH or pepsin, *H. pylori* may affect ingested gluten and then reduce the immunogenicity.[13] It can be said that *H. pylori* makes a "secondary hit" in the development of CD.

In the study, the authors found that *H. pylori* can aggravate the symptoms of abdominal pain, diarrhea, and

distension, which may indicate that *H. pylori* itself can also cause these symptoms. Many previous studies have reported that *H. pylori* infection can cause recurrent abdominal pain.[30] Other articles have later reported that *H. pylori* seroconverting children had increased diarrhea days and diarrhea episodes[31] and that the infection can aggravate diarrhea caused by other bacterial infections including *Vibrio cholerae, Shigella,* or *Salmonella typhi*.[32] As is well-known, *H. pylori* itself can cause *H. pylori*-related dyspepsia, resulting in abdominal distension.[33] Therefore, while *H. pylori* plays against the development of CD, the opposite can also aggravate some symptoms. Although the result was innovative, it is important to highlight that this study still had shortcomings. The main shortcoming was the lack of prospective controlled studies in this article. The results of this study can only prove that the 2 do have a correlation rather than a causal relationship. If further data can confirm that the statistical difference disappears after *H. pylori* eradication or CD treatment, they can provide evidence of a causal relationship between the two. Unfortunately, since only 4 articles were selected, the results of this study did not confirm the change in *H. pylori* infection after CD treatment. Secondly, the heterogeneity of some results in this study may bias the results. Although we excluded some sources of heterogeneity through meta-regression analysis, there were still some potential factors that could not be excluded, including race, dietary habit, and whether there has been a history of *H. pylori* eradication. However, since the current articles did not have significant clinical heterogeneity, we believe that it was appropriate to analyze the pooled results.

In conclusion, this study confirmed that there is a correlation between *H. pylori* and CD. However, the causality cannot be clarified and requires more prospective studies to confirm. The gut microbiota and immune unbalance provide plausible mechanisms for disease progression in CD. In addition, *H. pylori* infection may aggravate some symptoms of CD. Future studies should focus more on prospective studies to determine whether there is a change in correlation after *H. pylori* eradication or CD treatment.

Ethics Committee Approval: The study was approved by the medical ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept – C.L., M.Y.; Design – C.L.; Supervision – Q.C.; Resources – X.Z., Q.C.; Materials – L.L.; Data Collection and/or Processing – M.Y., Q.C.; Analysis and/or Interpretation – L.L.; Literature Search – X.Z.; Writing Manuscript – M.Y.; Critical Review – C.L.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The study was funded by National Natural Science Foundation of China (81970498) and Zhejiang Medical and Health Science and Technology Plan Project (No. 2018KY387).

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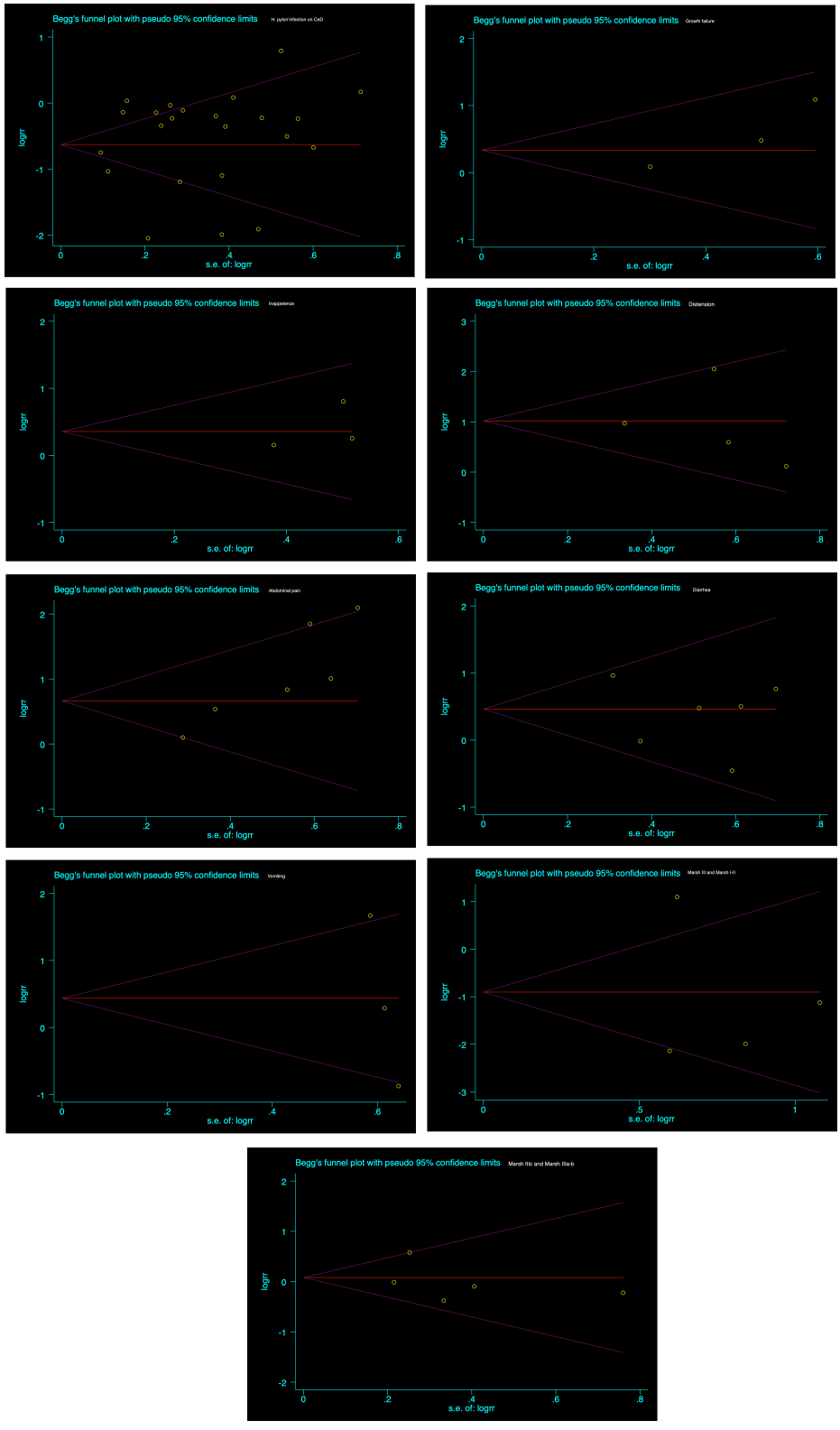
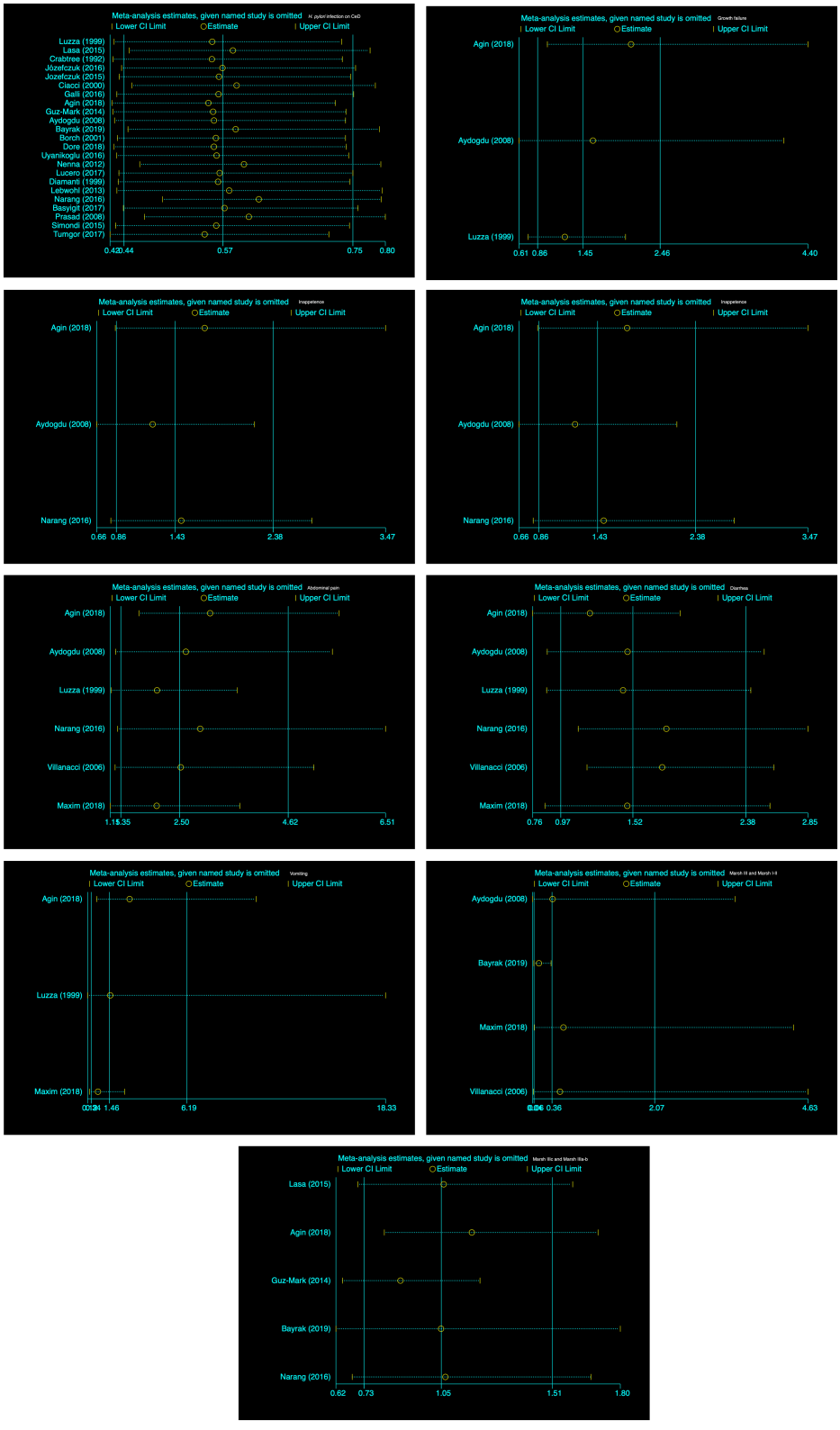


Supplementary Figure 1. Funnel plot analyses of studies assessing H. pylori infection on CD with its symptoms and Marsh classification.



Supplementary Figure 2. Sensitivity analysis of studies assessing H. pylori infection on CD.

Supplementary Table 1. Comparison of *Helicobacter pylori* Infection Between CD Patients and Controls

Author	Year	Regions	CD with HP+	CD with HP–	Control with HP+	Control with HP–
Luzza[1]	1999	Italy	15	66	14	67
Lasa[2]	2015	Argentina	9	63	72	168
Crabtree[3]	1992	United Kingdom	29	70	75	175
Józefczuk[4]	2016	Poland	8	68	8	41
Józefczuk[5]	2015	Poland	4	70	20	276
Ciacci[6]	2000	Italy	51	136	42	34
Galli[7]	2016	Italy	55	190	42	103
Agin[8]	2018	Turkey	70	186	270	742
Guz-Mark[9]	2014	Israel	94	212	234	459
Aydogdu[10]	2008	Turkey	21	75	56	179
Bayrak[11]	2019	Turkey	127	355	1033	1027
Borch[12]	2001	Sweden	4	4	216	256
Dore[13]	2018	Italy	87	183	45	82
Uyanikoglu[14]	2016	Turkey	15	16	316	276
Nenna[15]	2012	Italy	6	220	24	130
Lucero[16]	2017	Chile	21	45	20	30
Diamanti[17]	1999	Argentina	87	13	67	8
Lebwohl[18]	2013	United States	117	2572	11 207	116 412
Narang[19]	2016	India	37	287	161	161
Basyigit[20]	2017	Turkey	5	7	133	95
Prasad[21]	2008	India	9	155	49	115
Simondi[22]	2015	Italy	26	47	166	238
Tumgor[23]	2017	Turkey	14	8	23	29

CD, celiac disease; HP, *Helicobacter pylori.*

Supplementary Table 2. Comparison of *Helicobacter pylori* Infection in Treated and Non-treated CD Patients

Author	Year	Regions	T-CD with HP+	T-CD with HP–	NT-CD with HP+	NT-CD with HP–
Luzza[2]	1999	Italy	9	40	6	26
Crabtree[3]	1992	United Kingdom	18	53	11	17
Ciacci[6]	2000	Italy	34	71	17	65
Diamanti[17]	1999	Argentina	21	1	66	14

CD, celiac disease; T-CD, treated celiac disease; NT-CD, non-treated celiac disease; HP, *Helicobacter pylori*.

Supplementary Table 3. *Helicobacter pylori* Infection and Growth Failure in CD Patients

Author	Year	Regions	GF with HP+	Non-GF with HP+	GF with HP–	Non-GF with HP–
Agin[8]	2018	Turkey	48	22	124	62
Aydogdu[10]	2008	Turkey	10	11	27	48
Luzza[1]	1999	Italy	7	8	15	51

GF, growth failure; CD: celiac disease; HP, *Helicobacter pylori*.

Supplementary Table 4. *Helicobacter pylori* Infection and Inappetence in CD Patients

Author	Year	Regions	Inappetence with HP+	Non-Inappetence with HP+	Inappetence with HP–	Non-Inappetence with HP–
Agin[8]	2018	Turkey	12	58	28	158
Aydogdu[10]	2008	Turkey	12	9	28	47
Narang[19]	2016	India	5	32	31	256

CD, celiac disease; HP, *Helicobacter pylori*.

Supplementary Table 5. *Helicobacter pylori* Infection and Vomiting in CD Patients

Author	Year	Regions	Vomiting with HP+	Non-vomiting with HP+	Vomiting with HP–	Non-vomiting with HP–
Agin[8]	2018	Turkey	3	67	18	168
Maxim[24]	2018	Rumania	18	5	19	28
Luzza[1]	1999	Italy	5	10	18	48

CD, celiac disease; HP, *Helicobacter pylori*.

Supplementary Table 6. *Helicobacter pylori* Infection and Distension in CD Patients

Author	Year	Regions	Distension with HP+	Non-distension with HP+	Distension with HP–	Non-distension with HP–
Agin[8]	2018	Turkey	21	49	26	160
Aydogdu[10]	2008	Turkey	12	9	11	64
Luzza[1]	1999	Italy	3	12	12	54
Narang[19]	2016	India	4	33	18	269

CD, celiac disease; HP, *Helicobacter pylori*.

Supplementary Table 7. *Helicobacter pylori* Infection and Abdominal Pain in CD Patients

Author	Year	Regions	AP with HP+	Non-AP with HP+	AP with HP–	Non-AP with HP–
Agin[8]	2018	Turkey	28	42	70	116
Aydogdu[10]	2008	Turkey	15	6	39	36
Luzza[1]	1999	Italy	6	9	5	61
Narang[19]	2016	India	24	13	149	138
Villanacci[25]	2006	Switzerland	7	23	5	45
Maxim[24]	2018	Romania	18	5	17	30

CD, celiac disease; AP, abdominal pain; HP, *Helicobacter pylori*.

Supplementary Table 8. *Helicobacter pylori* Infection and Diarrhea in CD Patients

Author	Year	Regions	Diarrhea with HP+	Non-diarrhea with HP+	Diarrhea with HP–	Non-diarrhea with HP–
Agin[8]	2018	Turkey	27	43	36	150
Aydogdu[10]	2008	Turkey	17	4	54	21
Luzza[1]	1999	Italy	12	3	43	23
Narang[19]	2016	India	25	12	195	92
Villanacci[25]	2006	Switzerland	5	25	12	38
Maxim[24]	2018	Romania	13	10	21	26

CD, celiac disease; HP, *Helicobacter pylori*.

Supplementary Table 9. Comparison of *Helicobacter pylori* Infection in Marsh III and Marsh I-II CD Patients

Author	Year	Regions	Marsh III with HP+	Marsh I-II with HP+	Marsh III with HP–	Marsh I-II with HP–
Aydogdu[10]	2008	Turkey	1	20	10	65
Bayrak[11]	2019	Turkey	124	3	331	24
Maxim[24]	2018	Romania	5	18	33	14
Villanacci[25]	2006	Switzerland	23	7	48	2

CD, celiac disease; HP, *Helicobacter pylori*.

Supplementary Table 10. Comparison of *Helicobacter pylori* Infection in Marsh III and Marsh I-II CD Patients

Author	Year	Regions	Marsh IIIc with HP+	Marsh IIIa-b with HP+	Marsh IIIc with HP–	Marsh IIIa-b with HP–
Lasa[2]	2015	Argentina	6	3	45	18
Agin[8]	2018	Turkey	15	55	53	133
Guz-Mark[9]	2014	Israel	52	40	89	122
Bayrak[11]	2019	Turkey	49	75	132	199
Narang[19]	2016	India	9	28	75	212

CD, celiac disease; HP, *Helicobacter pylori*.

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