European Review for Medical and Pharmacological Sciences 2019; 23: 10509-10516

Correlation between *Helicobacter pylori* infection and Crohn's disease: a meta-analysis

W.-L. WANG[1], X.-J. XU[2]

[1]Department of Gastroenterology, Jiaxing Traditional Chinese Medicine Hospital, Jiaxing, China
[2]Department of Acupuncture, The Second Hospital of Jiaxing, The Second Affiliated Hospital of Jiaxing University, Jiaxing, China

Abstract. – OBJECTIVE: Researches on the potential correlation between Helicobacter pylori (Hp) infection and Crohn's disease (CD) are controversial. This study aims to clarify their correlation and provide a new theoretical basis for uncovering the pathogenesis of inflammatory bowel diseases (IBD).

MATERIALS AND METHODS: Relevant literature has been searched reporting the correlation between Hp infection and susceptibility to CD in Medline, PubMed, and Cochrane Collaboration database published from 1991 to 2019. Data of the eligible literatures were extracted and analyzed for the OR and the corresponding 95% CI using the Review Manager (RevMan) software.

RESULTS: A total of 20 pieces literature of involving 2055 cases of CD patients and 3442 cases of controls were enrolled. Hp infection rate in CD patients and controls was 30.6% and 42.7%, respectively. There was a significant difference in Hp infection rate between CD patients and controls [OR=0.42, 95% CI (0.33-0.54), $p<0.00001$], showing a negative correlation. Heterogeneity existed between the included studies.

CONCLUSIONS: Hp infection is a protective factor for CD. However, heterogeneity and publication bias may restrict the accuracy of the conclusions. It is necessary to further explore the potential influence of the Hp infection on CD.

Key Words:
Hp infection, CD, Meta-analysis.

Introduction

Crohn's disease (CD) is a chronic, non-specific inflammatory granulomatous gastrointestinal disease. The etiology and pathogenesis of CD are still unclear. It is generally believed that IBDs result from the interactions among environmental, genetic, infection and immune factors[1]. *Helicobacter pylori* (Hp) infection may play a vital role in the pathogenesis of CD.

Hp is a Gram-negative bacterium that is highly contagious planting in human gastric mucosa[2]. Long-term Hp infection is a crucial pathogenic factor for chronic gastritis, peptic ulcer, and gastric adenocarcinoma[3]. Currently, the relation between Hp infection and CD is still controversial. Rokkas et al[4] insist on a negative correlation between them, whereas some researches declare no correlation. This work analyzed relevant literatures to clarify the potential influence of Hp infection on CD.

Materials and Methods

Materials

Relevant literature has been searched reporting the correlation between Hp infection and susceptibility to CD in Medline, PubMed, and Cochrane Collaboration database published from 1991 to 2019. Keywords were used as follows: CD, Crohn's disease, Crohn disease, Crohn's, *Helicobacter pylori*, H. pylori and Hp. Citations in each literature were manually reviewed.

Inclusive criteria were as follows: (1) literatures reporting the correlation between Hp infection and CD; (2) literatures providing the case numbers of Hp-positive and Hp-negative CD patients and controls; (3) case-control or cohort studies; (4) the detection methods of Hp included: Hp-IgG antibody detection, urea breath test, fecal Hp antigen detection, fast urease test or histological examination. The diagnosis strategies for IBD included: questionnaires, tissue biopsy, imaging examinations, colonoscopy, etc.

Exclusive criteria were as follows: (1) unpublished full-text literatures or abstracts; (2) literatures lacked valid raw data; (3) reviews or repeated literatures.

Corresponding Author: Wenli Wang, MM; e-mail: gracewwl@163.com

Data Acquisition

Data were independently extracted using a unified data extraction table and analyzed by two researchers. The extracted data included first author, year of publication, research method, Hp detection method, diagnosis strategy of CD, case numbers of CD patients and controls, case number of Hp-positive subjects, and mean age of CD patients and controls. Any disagreement was discussed and solved by two researchers.

Statistical Analysis

Review Manager 5.3 software (London, UK) was used for data processing. CD patients were considered as case group and non-CD subjects were in control group. OR and corresponding 95% CI in case group and control group were calculated. Briefly, OR>1 indicated that Hp infection was the risk factor for CD; OR<1 indicated that Hp infection was the protective factor for CD; and OR=1 indicated no relation between Hp infection and CD. The heterogeneity test was conducted using Chi-square test and I^2 test with α=0.05. A fix-effects model was utilized when $I^2 \leq 50$; otherwise, a random-effects model was used. Subgroup analyses and sensitivity analysis were performed to identify the resource of heterogeneity. Publication bias was evaluated by depicting funnel plots.

Results

Baseline Characteristics of Enrolled Literatures

227 literatures were screened out by searching the keywords. After reviewing the titles, abstracts and full texts, 20 eligible case-control studies[2,5-23] were finally enrolled in this work (Figure 1). The

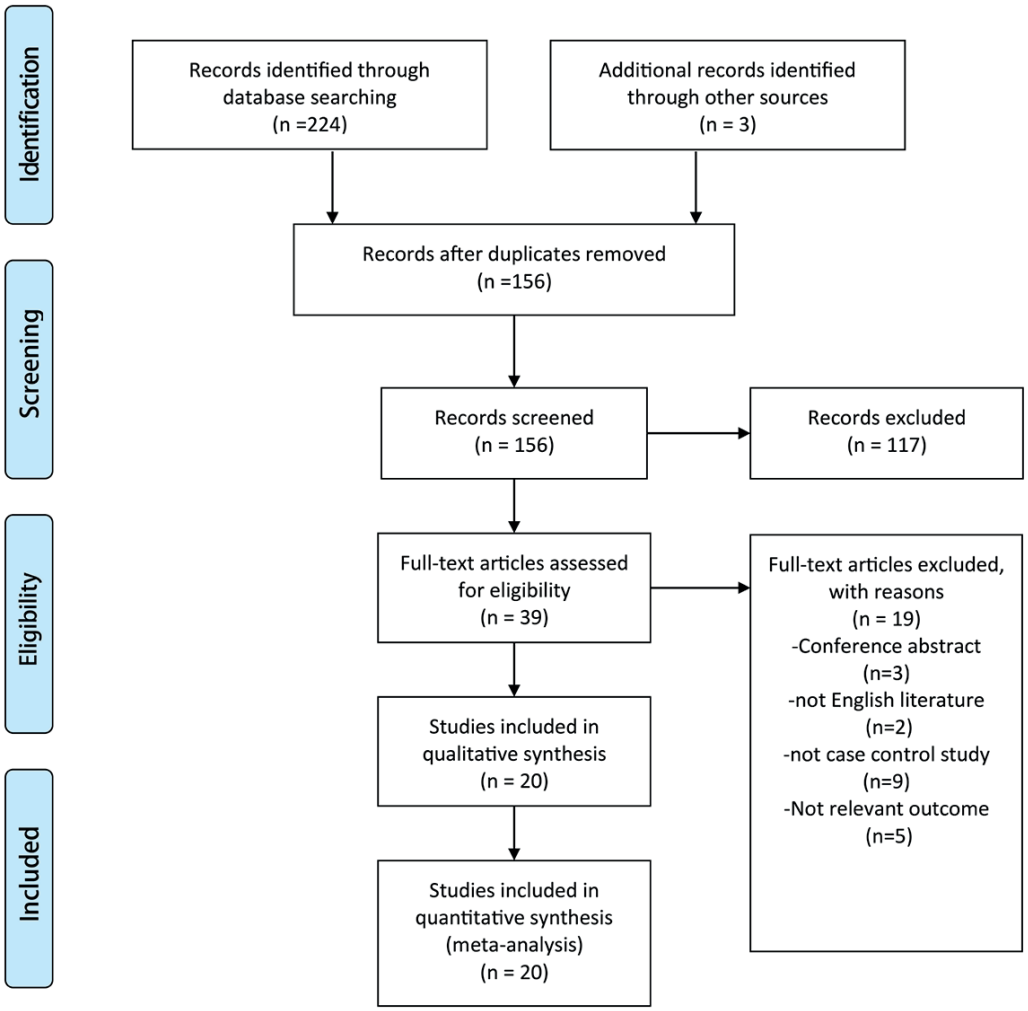

Figure 1. Flow diagram of the publication selection process.

Table I. Baseline characteristics of enrolled literatures

Included studies	Country	Mean age, CD	Mean age, Control	CD (n)	Control (n)	H.P. diagnosis	IBD diagnosis
Ando 2008	Japan	28.9	29.0	38	12	UBT	Not reported
Duggan 1998	Britain	NR	NR	87	174	IgG	Chart review
Farkas 2016 (1)	China	41	41	100	100	Histology/IgG	histology
Farkas 2016 (2)	Hungary	36	41	80	89	histology/IgG	histology
Furusu 2002	Japan	NR	NR	25	25	IgG/Histology	Histology
Garza-Gonzalez 2010	Mexico	50.5	51.6	21	75	IgG	NR
Guslandi 2002	Italy	NR	NR	60	30	IgG	NR
Kaakoush 2010	Australia	11.4	9.4	77	102	PCR	Endoscopic/ histologic
Magalhães-Cost 2014	Portugal	39	42	33	26	RUT	histology
Matsumura 2001	Japan	31.7	NR	90	525	IgG	Chart review
Oliveira 2006	Brazil	40.9	49.4	43	74	UBT	histology
Parente 1997	Italy	38.6	NR	123	216	IgG/Histology	Chart review
Parente 2000	Italy	NR	NR	141	141	UBT/histology	Chart review
Piodi 2003	Italy	48	NR	32	72	UBT	Chart review
Pronai 2004	Hungary	34.2	36.3	51	200	UBT	histology
Rosania 2012	German	41.5	41	90	254	IgG	Chart review
Song 2009	Korea	33.5	40.7	147	316	UBT	Chart review/ personal interview
Vare 2001	Finland	43	Nr	94	70	IgG	Chart review
Wagtmans 1997	Netherlands	NR	NR	386	277	IgG	Chart review
Xiang 2013	China	46.2	46.8	229	248	UBT/culture	Endoscopic/ histology
Zhang S 2011	China	31.0	36.0	104	416	UBT	Endoscopic/ histology

Note: The data of Farkas 2016 (1) and Farkas 2016 (2) were from the same study. This study was conducted in two areas: Asia and Eastern Europe. Farkas K, Chan H, Rutka M, Szepes Z, Nagy F, Tiszlavicz L, Nyári T, Tang W, Wong G, Tang R, Lo A, Cheung C, Wong S, Lui R, Molnár T, Ng SC. Gastroduodenal involvement in asymptomatic Crohn's disease patients in two areas of emerging disease: Asia and Eastern Europe. J Crohns.

baseline characteristics of enrolled literatures were depicted in Table I. A total of 5497 cases were enrolled, including 2055 cases of CD patients and 3442 cases of controls. All enrolled literatures recorded the detection methods of Hp infection and the results, including enzyme-linked immunosorbent assay (ELISA) method (8 literatures), DNA detection (1 literature), anti-IgG antibody detection and histological culture (2 literatures), ^{13}C-urea breath test (3 literatures), and fast urease test (6 literatures).

Hp Infection and CD

A total of 20 literatures involving 2055 cases of CD patients and 3442 cases of controls were enrolled. There were 450 (30.6%) Hp-positive CD patients and 1476 (42.9%) Hp-positive controls. After analysis using the random-effects model, it is indicated that Hp infection was negatively correlated to the incidence of CD [OR=0.41, 95% CI (0.32-0.53), p<0.0001] (Figure 2).

Heterogeneity existed between the included studies (I^2=64%, p<0.0001). Funnel plots were depicted using the random-effects model, showing an asymmetric shape and missing data. It is indicated that publication bias existed among the enrolled literatures, which may be related to the study heterogeneity (Figure 3). After removing the largest-weight work conducted by Xiang et al[22], pooled effects of the remaining researches still exerted significant difference [OR=0.42, 95% CI (0.32-0.55), p<0.0001] (Figure 4). In addition, pooled effects of the remaining were similar to the results after removing the least-weight work conducted by Ando et al[2] [OR=0.42, 95% CI (0.33-0.54), p<0.0001] (Figure 5). The above data suggested the robust conclusions we obtained.

Next, subgroup analyses based on the research countries were conducted. Heterogeneity still existed in developed countries (I^2=70%, p<0.0001) rather than in developing countries (I^2=27%, p=0.24). The pooled effects in developed [OR=0.43, 95%

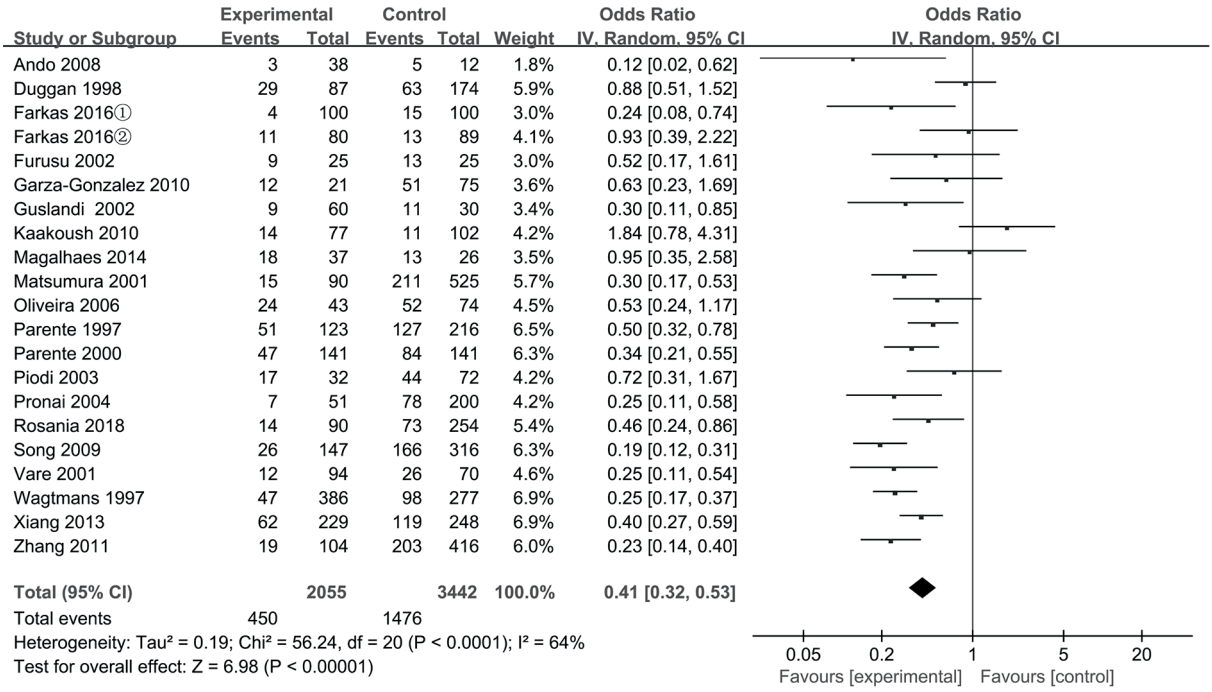

Figure 2. Forest map of the relationship between Hp infection and CD.

CI (0.32-0.59), $p<0.0001$] and developing countries [OR=0.36, 95% CI (0.26-0.52), $p<0.0001$] were listed in Figure 6. It is concluded that the Hp infection rate was negatively correlated to the incidence of CD in both developed and developing countries, which was much more pronounced in developing countries.

Discussion

This research enrolled 20 case-control studies to clarify the potential correlation between Hp infection and susceptibility to CD. Our data verified that Hp infection may be a protective factor for CD. Among the 20 eligible works, most of them

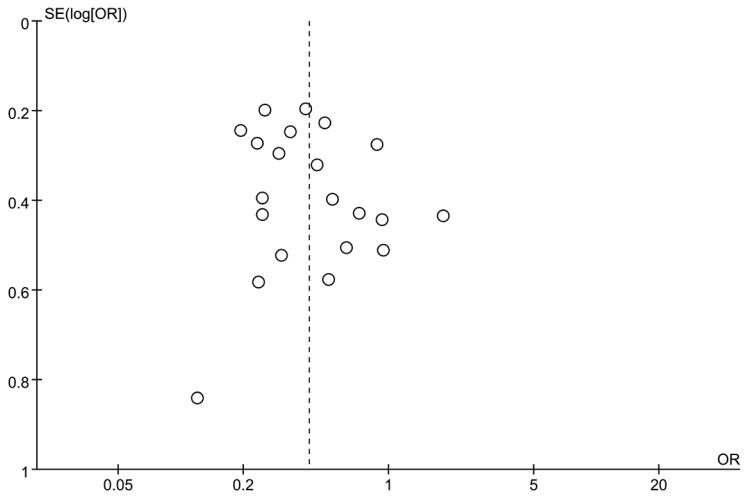

Figure 3. Funnel plots of the relationship between Hp infection and CD.

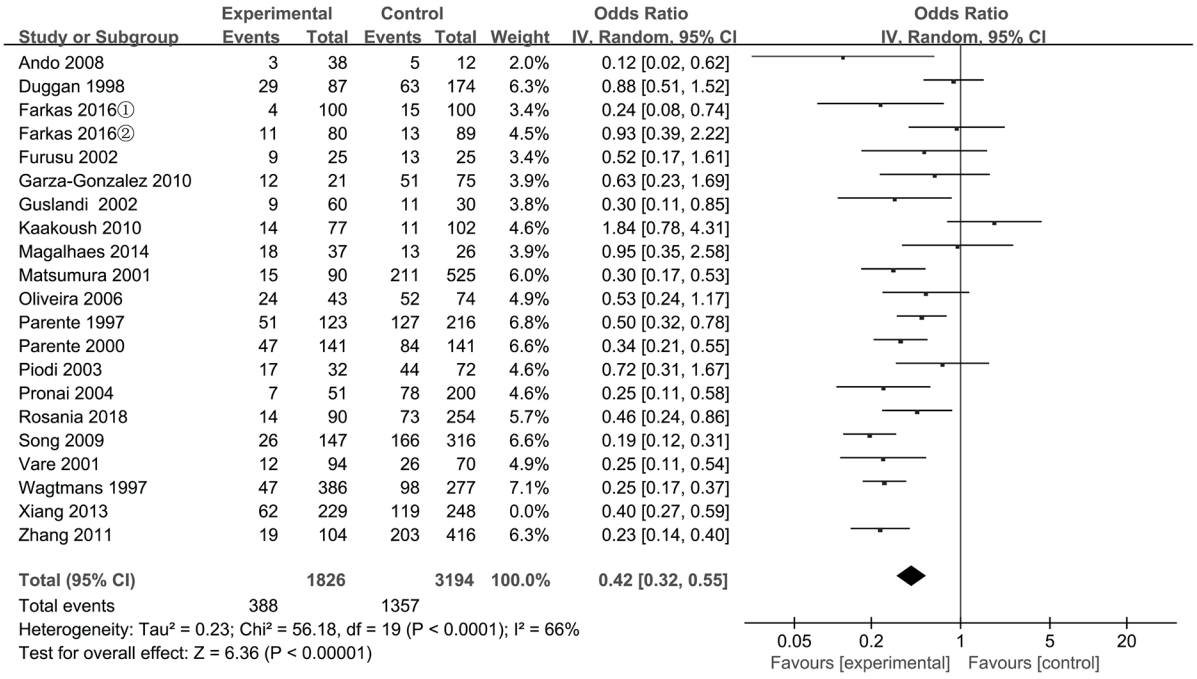

Figure 4. Sensitivity analysis on the relationship between Hp infection and CD.

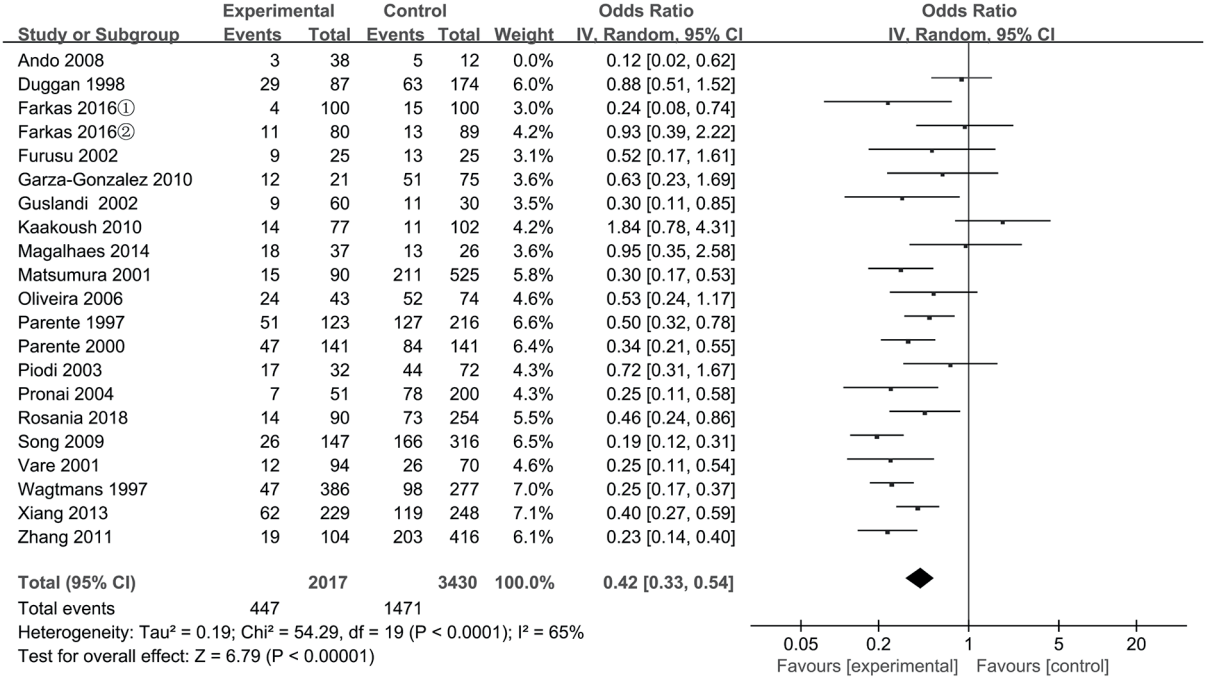

Figure 5. Sensitivity analysis on the relationship between Hp infection and CD.

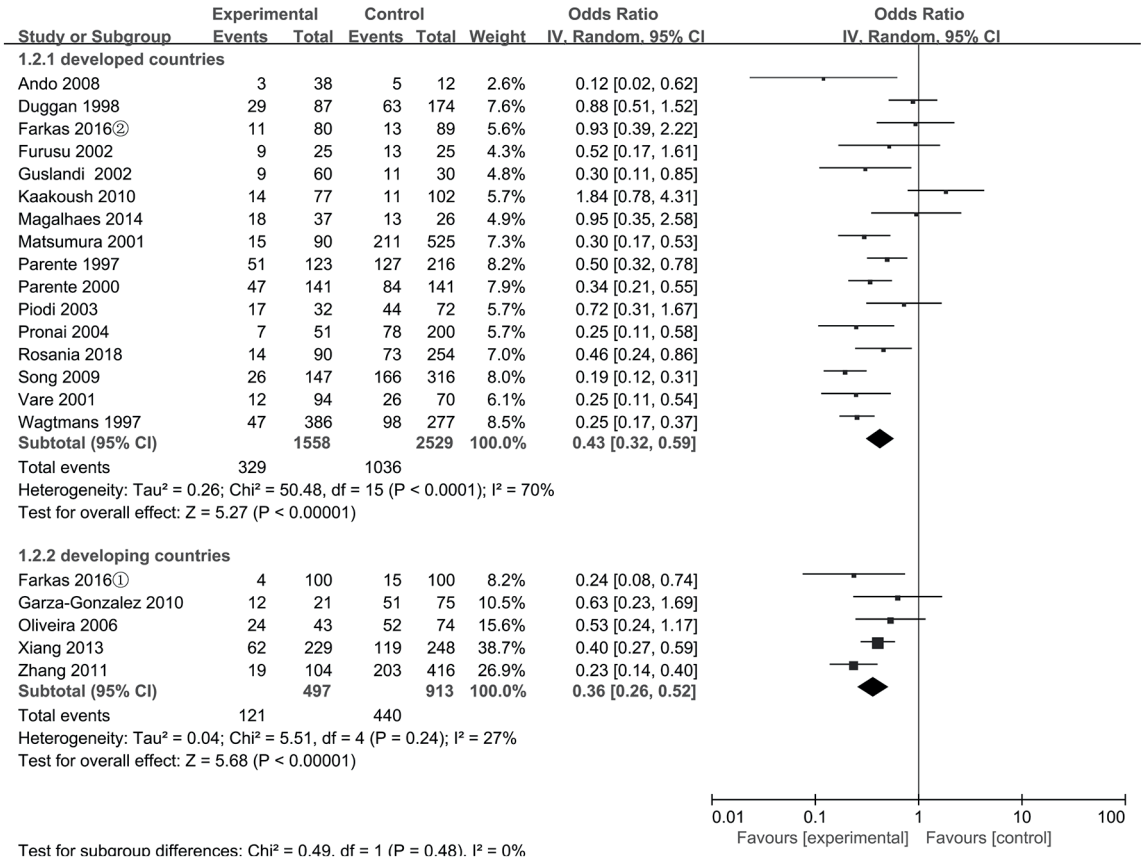

Figure 6. Subgroup analyses on the relationship between Hp infection and CD.

considered the lower rate of Hp infection in CD patients relative to controls. A negative relation between Hp infection and the incidence of CD was identified in 13/20 studies. None of them indicated that Hp infection is a risk factor for CD. A previous study conducted by Ando et al[2] pointed out that the decreased rate of Hp infection in CD patients is significantly pronounced than that of controls. Consistently, this meta-analysis obtained the same conclusion. Based on the research countries, subgroup analyses showed that Hp infection rate was negatively correlated to the incidence of CD in both developed and developing countries, which was much more pronounced in developing countries.

Mechanisms underlying the protective role of Hp infection on the pathogenesis of CD are unclear. It is generally believed that the immune response may be explained. By activating dendritic cells, Hp infection induces T cell expression and activates the immune response of Th1/Th17. Subsequently, the pro-inflammatory cytokines are inactivated and, in turn, the inflammatory response in intestinal mucosal is alleviated[24]. It is reported that Hp infection-induced lipopolysaccharide production could stimulate the production of defensins in Paneth cells. A large number of defensins contribute to kill or inhibit the pathogenic microorganisms, thus maintaining the intestinal mucosal antibacterial barrier function and immune balance[25].

Some limitations of this study should be pointed out. First of all, case-control studies presented a relatively low intensity of argumentation for disease etiology, which may restrict the clinical application. Secondly, the heterogeneity in the enrolled researches had a certain impact on the reliability of the final conclusion. There were many confounding factors among these works, including baseline characteristics (i.e., age, gender, ethnicity, living environment, matching the information of controls), Hp detection methods and pathological differences of CD (i.e., subtypes, disease location, and staging). In particular, most of the enrolled studies used serum anti-IgG antibody detection as the method for determining Hp

infection. This method was characterized as high sensitivity and low specificity, which may lead to false-positive results. Thirdly, potential publication bias may decrease the accuracy of our conclusions.

Conclusions

Hp infection is protective to the progression of CD. However, heterogeneity and publication bias may restrict the accuracy of the conclusions. It is necessary to further explore the potential influence of Hp infection on CD.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Zhang J, Chen SL, Li LB. Correlation between intestinal flora and serum inflammatory factors in patients with Crohn's disease. Eur Rev Med Pharmacol Sci 2017; 21: 4913-4917.
2) Ando T, Watanabe O, Ishiguro K, Maeda O, Ishikawa D, Minami M, Hasegawa M, Kondo S, Goto Y, Ohmiya N, Niwa Y, Goto H. Relationships between Helicobacter pylori infection status, endoscopic, histopathological findings, and cytokine production in the duodenum of Crohn's disease patients. J Gastroenterol Hepatol 2008; 23 Suppl 2: S193-S197.
3) Crowe SE. Helicobacter pylori infection. N Engl J Med 2019; 380: 1158-1165.
4) Rokkas T, Gisbert JP, Niv Y, O'Morain C. The association between Helicobacter pylori infection and inflammatory bowel disease based on meta-analysis. United European Gastroenterol J 2015; 3: 539-550.
5) Duggan AE, Usmani I, Neal KR, Logan RF. Appendicectomy, childhood hygiene, Helicobacter pylori status, and risk of inflammatory bowel disease: a case control study. Gut 1998; 43: 494-498.
6) Farkas K, Chan H, Rutka M, Szepes Z, Nagy F, Tiszlavicz L, Nyári T, Tang W, Wong G, Tang R, Lo A, Cheung C, Wong S, Lui R, Molnár T, Ng SC. Gastroduodenal involvement in asymptomatic Crohn's disease patients in two areas of emerging disease: Asia and Eastern Europe. J Crohns Colitis 2016; 10: 1401-1406.
7) Furusu H, Murase K, Nishida Y, Isomoto H, Takeshima F, Mizuta Y, Hewlett BR, Riddell RH, Kohno S. Accumulation of mast cells and macrophages in focal active gastritis of patients with Crohn's disease. Hepatogastroenterology 2002; 49: 639-643.
8) Garza-González E, Pérez-Pérez G, Mendoza-Ibarra SI, Flores-Gutiérrez JP, Bosques-Padilla FJ. Genetic risk factors for inflammatory bowel disease in a North-eastern Mexican population. Int J Immunogenet 2010; 37: 355-359.
9) Guslandi M, Fanti L, Testoni PA. Helicobacter pylori seroprevalence in Crohn's disease: lack of influence by pharmacological treatment. Hepatogastroenterology 2002; 49: 1296-1297.
10) Kaakoush NO, Holmes J, Octavia S, Man SM, Zhang L, Castaño-Rodríguez N, Day AS, Leach ST, Lemberg DA, Dutt S, Stormon M, O'Loughlin EV, Magoffin A, Mitchell H. Detection of Helicobacteraceae in intestinal biopsies of children with Crohn's disease. Helicobacter 2010; 15: 549-557.
11) Magalhães-Costa MH, Reis BR, Chagas VL, Nunes T, Souza HS, Zaltman C. Focal enhanced gastritis and macrophage microaggregates in the gastric mucosa: potential role in the differential diagnosis between Crohn's disease and ulcerative colitis. Arq Gastroenterol 2014; 51: 276-282.
12) Matsumura M, Matsui T, Hatakeyama S, Matake H, Uno H, Sakurai T, Yao T, Oishi T, Iwashita A, Fujioka T. Prevalence of Helicobacter pylori infection and correlation between severity of upper gastrointestinal lesions and H. pylori infection in Japanese patients with Crohn's disease. J Gastroenterol 2001; 36: 740-747.
13) Oliveira AG, Rocha GA, Rocha AM, Sanna M, Moura SB, Dani R, Marinho FP, Moreira LS, Ferrari Mde L, Castro LP, Queiroz DM. Isolation of Helicobacter pylori from the intestinal mucosa of patients with Crohn's disease. Helicobacter 2006; 11: 2-9.
14) Parente F, Cucino C, Bollani S, Imbesi V, Maconi G, Bonetto S, Vago L, Bianchi Porro G. Focal gastric inflammatory infiltrates in inflammatory bowel diseases: prevalence, immunohistochemical characteristics, and diagnostic role. Am J Gastroenterol 2000; 95: 705-711.
15) Parente F, Molteni P, Bollani S, Maconi G, Vago L, Duca PG, Rembacken B, Axon AT, Bianchi Porro G. Prevalence of Helicobacter pylori infection and related upper gastrointestinal lesions in patients with inflammatory bowel diseases. A cross-sectional study with matching. Scand J Gastroenterol 1997; 32: 1140-1146.
16) Piodi LP, Bardella M, Rocchia C, Cesana BM, Baldassarri A, Quatrini M. Possible protective effect of 5-aminosalicylic acid on Helicobacter pylori infection in patients with inflammatory bowel disease. J Clin Gastroenterol 2003; 36: 22-25.
17) Pronai L, Schandl L, Orosz Z, Magyar P, Tulassay Z. Lower prevalence of Helicobacter pylori infection in patients with inflammatory bowel disease but not with chronic obstructive pulmonary disease - antibiotic use in the history does not play a significant role. Helicobacter 2004; 9: 278-283.
18) Rosania R, Minenna MF, Giorgio F, Facciorusso A, De Francesco V, Hassan C, Panella C, Ierardi E. Probiotic multistrain treatment may eradicate Helicobacter pylori from the stomach of dyspeptics: a placebo-controlled pilot study. Inflamm Allergy Drug Targets 2012; 11: 244-249.

19) Song MJ, Park DI, Hwang SJ, Kim ER, Kim YH, Jang BI, Lee SH, Ji JS, Shin SJ. [The prevalence of Helicobacter pylori infection in Korean patients with inflammatory bowel disease, a multicenter study]. Korean J Gastroenterol 2009; 53: 341-347.

20) Vare PO, Heikius B, Silvennoinen JA, Karttunen R, Niemelä SE, Lehtola JK, Karttunen TJ. Seroprevalence of Helicobacter pylori infection in inflammatory bowel disease: is Helicobacter pylori infection a protective factor? Scand J Gastroenterol 2001; 36: 1295-1300.

21) Wagtmans MJ, Witte AM, Taylor DR, Biemond I, Veenendaal RA, Verspaget HW, Lamers CB, van Hogezand RA. Low seroprevalence of Helicobacter pylori antibodies in historical sera of patients with Crohn's disease. Scand J Gastroenterol 1997; 32: 712-718.

22) Xiang Z, Chen YP, Ye YF, Ma KF, Chen SH, Zheng L, Yang YD, Jin X. Helicobacter pylori and Crohn's disease: a retrospective single-center study from China. World J Gastroenterol 2013; 19: 4576-4581.

23) Zhang S, Zhong B, Chao K, Xiao Y, Cui Y, Gao X, Chen B, He Y, Hu P, Chen M, Mitchell HM. Role of Helicobacter species in Chinese patients with inflammatory bowel disease. J Clin Microbiol 2011; 49: 1987-1989.

24) Kao JY, Rathinavelu S, Eaton KA, Bai L, Zavros Y, Takami M, Pierzchala A, Merchant JL. Helicobacter pylori-secreted factors inhibit dendritic cell IL-12 secretion: a mechanism of ineffective host defense. Am J Physiol Gastrointest Liver Physiol 2006; 291: G73-G81.

25) Tanabe H, Sato T, Watari J, Maemoto A, Fujiya M, Kono T, Ashida T, Ayabe T, Kohgo Y. Functional role of metaplastic paneth cell defensins in Helicobacter pylori-infected stomach. Helicobacter 2008; 13: 370-379.