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REVIEW

Association between recurrent aphthous stomatitis and *Helicobacter pylori* infection: a meta-analysis

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Abstract
Objectives Several studies have shown the possible involvement of *Helicobacter pylori* infection in individuals with recurrent aphthous stomatitis (RAS), but the relationship remains controversial. This meta-analysis was performed to validate the association between RAS and *H. pylori* infection.
Materials and methods The PubMed database was searched up to January 25, 2013 to select studies on the prevalence of *H. pylori* infection between RAS patients and control subjects. Studies were included if they evaluated and clearly defined exposure to RAS, reported the incidence of *H. pylori* infection, or provided data for their estimation. For subgroup analyses, studies were separated by region, publication year, and source of controls to screen the potential factors against the results. Before meta-analysis, the studies were evaluated for publication bias and heterogeneity. Summary odds ratio (OR) estimates with 95 % confidence intervals (CIs) were calculated using the fixed-effects model.
Results Seven case-control studies containing 339 cases and 271 controls were eventually selected for analysis. A total of 100 (29.50 %) RAS patients had *H. pylori* infection, which was significantly greater than the 54 (19.93 %) non-RAS controls with *H. pylori* infection (OR=1.85, 95 % CI: 1.24–2.74, *P*=0.002). This result persisted in a hospital-based control subgroup (OR=2.72, 95 % CI: 1.57–4.72).
Conclusions Based on our meta-analysis, *H. pylori* infection is associated with an increased risk of RAS.
Clinical relevance The eradication of *H. pylori* in the stomach may promote relief of RAS symptoms and healing of oral ulcers, and even prevent the occurrence of RAS.

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Introduction

Recurrent aphthous stomatitis (RAS) is a common disease, characterized by symptoms of periodic painful solitary or multiple mucosal ulcerations. The prevalence of RAS varies from 5 % to 20 % in the general population, depending on the method and group studied [1].

Although RAS is the most common disease affecting the oral mucosa, the etiology and pathogenesis of RAS remain unknown; many factors are thought to be its risk factors, such as local, microbial, systemic, nutritional, immunological, and genetic factors [2–4]. Several studies have investigated the role of microorganisms including bacteria and viruses in the etiopathogenesis of recurrent aphthous ulcer (RAU) [5–7]. To date, no substantial data exists to establish a microbial etiology for RAS. Some studies have shown that *Helicobacter pylori* is associated with RAS [8–14]. *H. pylori* is a microaerophilic, gram-negative spiral bacterium that infects more than 50 % of human gastric mucosa [15]. It is clearly linked to the pathogenesis of chronic gastritis, peptic ulceration, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma [16–18]. In addition, *H. pylori* has been detected in the dental plaque and saliva of healthy persons with gastric disease [19, 20]. These data have suggested that the oral cavity may be an alternative reservoir for the organism. However, the role of *H. pylori* infection in the development of RAS remains controversial.

Considering the histological similarities between gastric and oral ulcers, it would be prudent to assume a possible involvement of this organism in the development of RAS. Therefore, to gain a better understanding, we performed a systematic review with meta-analysis of published case-

control studies investigating the association between *H. pylori* infection and the risk of RAS.

Materials and methods

Data sources

We identified studies by a systematic literature search of PubMed (inception through January 25, 2013) database by two study investigators (L.L. and G.H.Y.) independently for all relevant articles on the effect of RAS on the risk of *H. pylori* infection, with a combination of the following keywords: '*Helicobacter pylori*' OR '*H. pylori*' OR 'HP' AND 'recurrent aphthous stomatitis' OR 'recurrent aphthous ulcer'.

The title and abstract of studies identified in the search were reviewed to exclude any that were irrelevant. The full text of the remaining articles was examined to determine whether it contained information of interest. Moreover, for a closer examination to broaden the scope of our findings, we performed a manual search of references cited in the selected articles to screen any potentially relevant papers that were missed in the database search.

Inclusion criteria

To be included in our meta-analysis, articles had to contain the following criteria: (1) they must be case-control studies; (2) the exposure of interest was the presence of an oral ulcer; (3) the outcome of interest was the risk of *H. pylori* infection; (4) studies must have provided raw data dealing with *H. pylori* infection in both RAS and control groups; (5) RAS was defined using Scully and Porter's criteria or the occurrence of associated clinical symptoms, and the *H. pylori* infection was confirmed by at least one positive result from the following tests: ^{13}C urea breath test (^{13}C-UBT), enzyme-linked immunosorbent assay (ELISA), and polymerase chain reaction (PCR).

Exclusion criteria

We excluded studies reporting only standardized incidence ratios without control groups. We also excluded studies in which the raw data of *H. pylori* infection rates were not available for either the RAS patients or control subjects. Reviews and duplicated publications were also excluded. Studies in which the research participants had a history of drug use in the past month prior to the test or had serious systemic conditions were excluded as well.

After rigorous searching, we reviewed all papers in accordance with the criteria defined above for further analysis. The flow diagram summarizing study identification and selection is shown in Fig. 1.

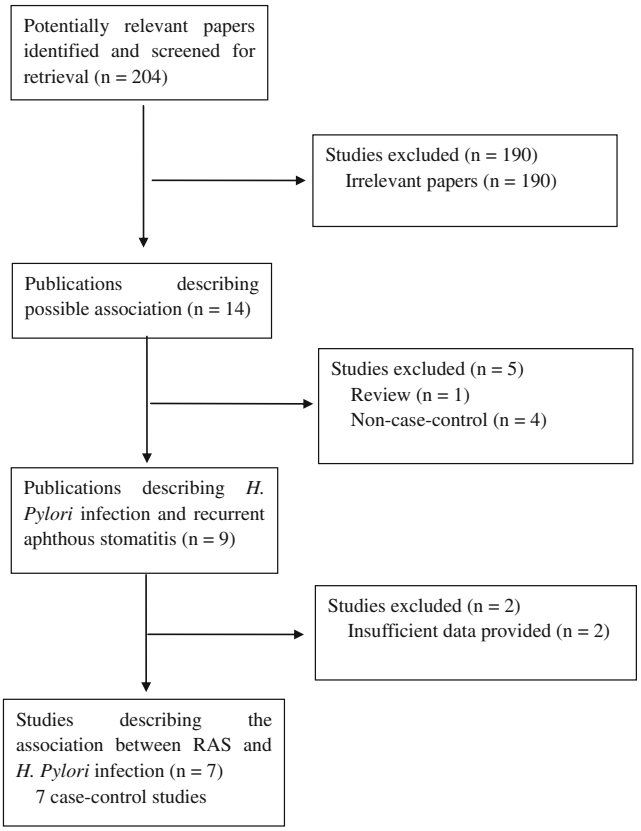

Fig. 1 Flow chart of literature searches for this meta-analysis of examining the association between *Helicobacter pylori* infection and recurrent aphthous stomatitis (RAS)

Quality of included studies

The Newcastle–Ottawa scale (NOS) was used to assess the study quality [21]. Three parameters were examined in the NOS: selection, comparability, and exposure (case-control studies) or outcome (cohort studies). The highest study quality was nine points with a maximum of four points for selection, two points for comparability, and three points for exposure/outcome in the NOS.

Data extraction

Data extraction was conducted independently by two reviewers (L.L. and G.H.Y.). For each study analyzed, the following data were collected: study design, first author, year of publication, country of the population studied, methods of *H. pylori* detection, total number of persons in each group (cases vs. controls), primary outcome reported, and the type of controls. The numbers of *H. pylori*-positive and -negative patients in the RAS group and the control group of each study were recorded, respectively. Data on the following confounding risk factors for the infection of *H. pylori* were extracted from each study: age, sex, region, and gastric disease history. Conflicts in data extraction were resolved by consensus, referring back to the original articles.

Statistical analysis

For the meta-analysis, we calculated pooled estimates for all the studies. For the subgroup analyses, we separated studies by region (Asia, South America, or Europe), publication period (1996–2000, 2001–2005, or 2006–2010), and source of controls (population-based or hospital-based). The odds ratio (OR) of RAS associated with the infection of *H. pylori* was evaluated for each study.

To evaluate whether the results of the studies were homogeneous, we used the Cochran's *Q*-test with a 0.10 level of significance and the I^2 test with values >50 % suggestive of significant heterogeneity [22].

The fixed- or random-effects model was used for meta-analysis according to the heterogeneity. If the result of the *Q*-test was $P>0.10$ and the I^2-test was $I^2<$ 50 %, ORs were pooled according to the fixed-effects model (Mantel–Haenszel); otherwise, the random-effects model (DerSimonian and Laird) was used [23, 24]. In the absence of heterogeneity, the fixed- and random-effects models provide similar results. When heterogeneity is found, the random-effects model is considered to be more appropriate, although both models may be biased [25].

We assessed publication bias using the Begg and Mazumdar adjusted rank correlation test [26] and the Egger regression asymmetry test [27].

All the reported *P* values were two-sided, and all analyses (expect for heterogeneity) were considered as significant when $P<0.05$. The significance of the pooled OR was determined by the *Z*-test.

Data manipulation and statistical analyses were carried out using STATA statistical software package version 12.0 (2000; STATA Corp., College Station, TX, USA) and Review Manager meta-analysis software version 5.2 (Cochrane Collaboration, Oxford, UK).

Results

Literature search

As shown in Fig. 1, the systematic literature review identified 204 relevant references. One hundred and ninety irrelevant papers were excluded after screening the titles. By reviewing the abstracts and full texts, five studies, including one review [28], were excluded because they did not have a case-control design [9–11, 29]. In the remaining nine publications, two studies were discarded due to insufficient data [12, 13]. Thus, a total of seven case-control studies published between 1996 and 2010 fulfilled our inclusion criteria and were included in the meta-analysis [14, 30–35].

Characteristics of included studies

The study characteristics are listed in detail in Table 1. Fritscher et al. [30] performed a case-control study of 105 children and adolescents originating from the Integrated Child and Adolescent Clinic of Faculty in Brazil using PCR to identify *H. pylori* infection. In 2002, Iamaroon et al. [31] conducted a case-control study on patients (age range, 12–36 years) and volunteers (age range, 13–40 years) from Thailand by using nested PCR to define *H. pylori* infection. Long et al. [14] carried out a case-control hospital-based study on patients older than 30 years old with a diagnosis of *H. pylori* infection by PCR from May 2006 to October 2007, in Nanfang Hospital, Guangzhou, China. Maleki et al. [32] performed a case-control study on Iranian subjects, disregarding age and gender, in dental and medical centers with a defined diagnosis of *H. pylori* infection using a urea breath test (UBT) from June 2006 to March 2007. Riggio et al. [33] detected *H. pylori* DNA by PCR in 11 % of RAS patients (age range, 22–63 years) and none of the control subjects (age range, 21–79 years) in the UK. Porter et al. [34] carried out a case-control study on London persons from June 1995 to December 1995 with a diagnosis of *H. pylori* infection by PCR. Victória et al. [35] used PCR to estimate *H. pylori* infection in persons exposed to oral ulcers who were recruited from the Oral Diagnosis Clinic in Brazil.

With respect to the country of publication, three studies were from Asia (Thailand and Iran were grouped with Asia according to similarities in racial traits), two were from South America, and two were from Europe. According to the publication period, two studies were published from 1996 to 2000, three were published from 2001 to 2005, and two were published from 2006 to 2010. The controls used in four studies were hospital-based, while those in the remaining three studies were population-based.

Quality of included studies

Table 1 depicts the methodological quality of all studies examined. The mean NOS score for all case-control studies was 7 (range, 6–7). Most studies adjusted the following confounders: age (6/7), sex (5/7), and gastric disease history (7/7).

Overall

Meta-analysis of all included studies assessing *H. pylori* infection showed that exposure to RAS was associated with a significant increase of 9.57 % in the incidence of *H. pylori* infection. Since there was no evidence of heterogeneity, we calculated the pooled estimates using the Mantel–Haenszel method for the fixed-effects model ($P=0.211$, $I^2=28.5$ %). The overall data available for our meta-analysis containing 610 patients showed a total *H. pylori* infection rate of 25.25 %

Table 1 Characteristics of studies on *H. pylori* infection in RAS cases and controls

First Author	Year	Country	Region	Study type	Method	Number of cases	Number of controls	Type of controls	Number of cases with HP (+)	Number of controls with HP (+)	Study quality		
											Selection	Comparability	Exposure or outcome
Fritscher	2004	Brazil	South America	C-C	PCR	53	52	Non-RAS patients (HB)	6	3	***	-	**
Iamaroon	2003	Thailand[a]	Asia	C-C	PCR	22	15	Healthy controls (PB)	2	3	***	*	**
Long	2007	China	Asia	C-C	PCR	82	74	Non-RAS patients (HB)	36	12	***	**	**
Maleki	2009	Iran[*]	Asia	C-C	UBT	43	44	Healthy controls (PB)	16	14	***	**	**
Riggio	2000	UK	Europe	C-C	PCR	28	13	Patients with normal oral mucosa (HB)	3	0	***	**	**
Porter	1997	England	Europe	C-C	PCR	75	25	Patients without oral lesions (HB)	23	6	***	**	**
Victória	2003	Brazil	South America	C-C	PCR	36	48	Healthy controls (PB)	14	16	***	**	**

C-C case-control, *PCR* polymerase chain reaction, *UBT* urea breath test, *HP Helicobacter pylori*, *HB* hospital-based, *PB* population-based

[a] Thailand and Iran were grouped in Asia according to similarities in racial traits

*One point in Newcastle-Ottawa csale (NOS) score for quality of included studies

**Two points in Newcastle-Ottawa csale (NOS) score for quality of included studies

***Three points in Newcastle-Ottawa csale (NOS) score for quality of included studies, (-) stand for zero point in Newcastle-Ottawa csale (NOS) score for quality of included studies

(154/610). The cumulative sample sizes of the RAS group and the control group were 339 and 271, respectively, of which 100 cases (29.50 %) and 54 controls (19.93 %) were *H. pylori*-positive, while 239 cases (70.5 %) and 217 (80.07 %) controls were *H. pylori*-negative. As shown in Fig. 2, the overall OR was 1.85 (95 % CI: 1.24–2.74) and the overall effect Z value was 0.002 ($P<0.05$), which indicated that *H. pylori* infection is associated with an increased risk of RAS.

Subgroup analysis

We further conducted subgroup analyses of all included studies based on region, publication period, and source of controls, respectively, to determine the influencing factors that may have impacted the overall results. However, when data were divided into subgroups, as shown in Table 2, the results of the *Q*-test were $P=0.03$, $I^2=71$ % in the Asian subgroup and $P=0.05$, $I^2=74$ % in the 2006 to 2010 subgroup; thus, the random-effect models were used in both of these subgroups. The subgroup meta-analysis based on region showed no significant associations among Asians, South Americans, and European. Likewise, there were no associations in different publication years. However, in studies with hospital-based controls, the presence of RAS consistently showed a greater rate of *H. pylori* infection (OR=2.72, 95%CI: 1.57–4.72), compared to those with population-based controls (OR=1.13, 95%CI: 0.62–2.05). Information extracted from the primary literature was not sufficient to perform subgroup analyses based on age, sex, or CagA status of *H. pylori*.

Bias diagnostics

Begg's test was created for assessment of possible publication bias (Fig. 3). The *P* values for the Begg's and Egger's tests were $P=1.00$ and $P=0.49$, respectively, both indicating the absence of heterogeneity and suggesting that the results of the present meta-analyses were relatively stable and that the publication bias might exert little influence on the overall results.

Discussion

In this study, we examined the potential association between RAS and *H. pylori* infection by performing a quantitative meta-analysis of published case-control studies. To the best of our knowledge, this is the first published meta-analysis to examine this association. After analyzing 610 patients, including 154 cases of *H. pylori* infection, we found that the rate of *H. pylori* infection was greater in RAS patients than in non-RAS patients after adjusting for confounding variables ($P=0.002$). This result implied

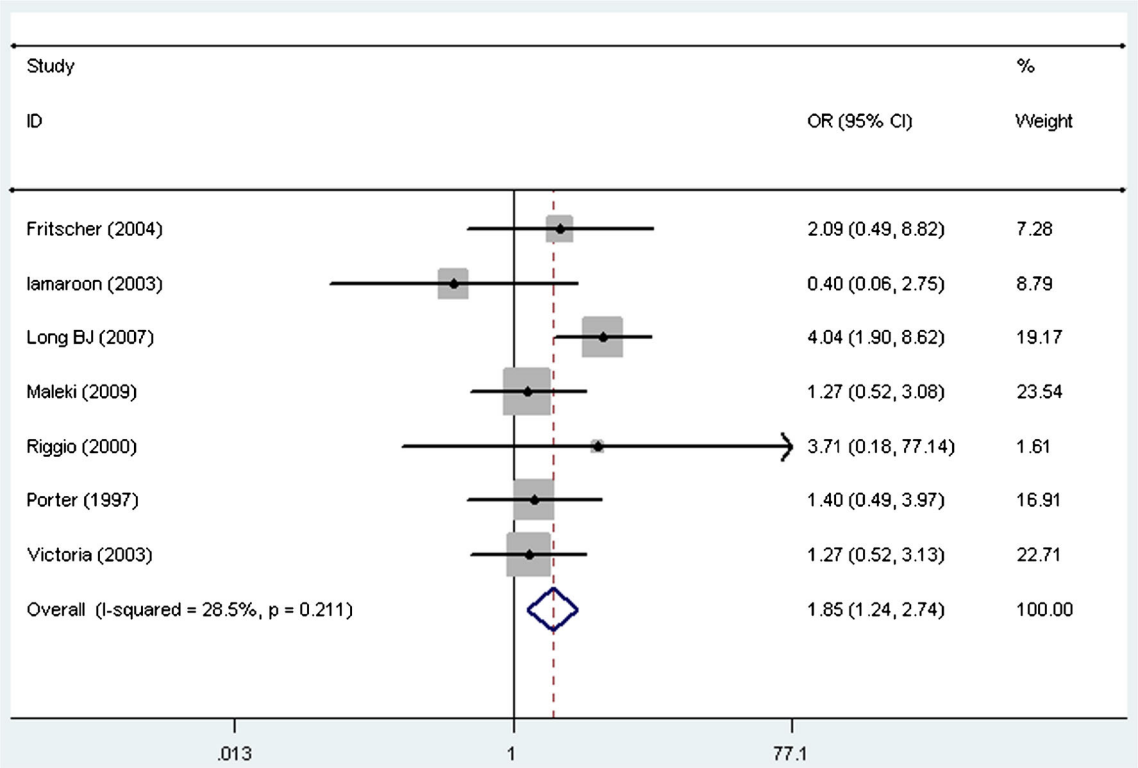

Fig. 2 Meta-analysis for the association between RAS and *Helicobacter pylori* infection

that *H. pylori* infection is associated with an increased risk of RAS.

Iamaroon et al. [31] found that 14 of 27 RAS specimens from patients with chronic gastritis were positive for *H. pylori* and that all RAS samples from patients with the absence of chronic gastritis were negative for *H. pylori*, which indicated a connection between *H. pylori* in RAS and chronic gastritis. Long et al. [14] observed that there was a greater incidence of chronic gastric disorders in patients with *H. pylori*-associated RAS than with non-*H. pylori*-associated RAS, suggesting that chronic gastric diseases are linked with the infection of *H. pylori* and that a relationship between RAS and chronic

Table 2 Subgroup analysis of the prevalence of *H. pylori* infection in RAS cases vs. controls

Subgroup	No. of studies	Cases with HP (+)	Controls with HP (+)	OR [95 % CI]	*P*	*Z*	Tests of heterogeneity			
							Q	*df*	*P*	I^2 (%)
Region										
Asia*	3	54/147	29/133	1.60 [0.51–5.08]	0.42	0.80	6.96	2	0.03	71
South America	2	20/89	19/100	1.47 [0.69–3.14]	0.32	1.00	0.32	1	0.57	0
Europe	2	26/103	6/38	1.60 [0.60–4.24]	0.34	0.95	0.36	1	0.55	0
Year										
1996–2000	2	26/103	6/38	1.60 [0.60–4.24]	0.34	0.95	0.36	1	0.55	0
2001–2005	3	22/111	22/115	1.23 [0.61–2.46]	0.56	0.58	1.81	2	0.40	0
2006–2010	2	52/125	26/118	2.32 [0.75–7.22]	0.15	1.45	3.80	1	0.05	74
Source of control										
Population-based	3	32/101	33/107	1.13 [0.62–2.05]	0.68	0.41	1.25	2	0.54	0
Hospital-based	4	68/238	21/164	2.72 [1.57–4.72]	0.0004	3.53	2.79	3	0.43	0
All studies	7	100/339	54/271	1.85 [1.24–2.74]	0.002	3.03	8.39	6	0.21	28.5

HP Helicobacter pylori, *OR* odds ratio, *CI* confidence interval, *df* degrees of freedom

*Thailand and Iran were grouped in Asia according to similarities in racial traits

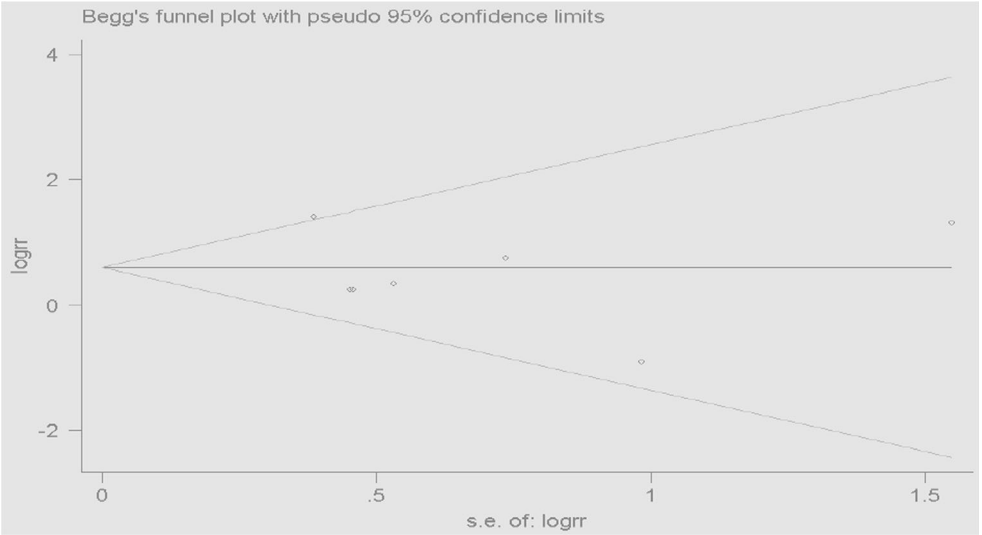

Fig. 3 Publication bias tests for the overall data (*H. pylori*-positive vs. *H. pylori*-negative)

gastric diseases exists. They also observed that anti-*H. pylori* using a three-medicine regimen could significantly relieve the symptoms of RAS and promoted the healing of RAS. However, determination of whether the eradication of *H. pylori* in the stomach would inhibit the recurrence of RAS as well as cure the disease eventually and whether the prevention of *H. pylori* survival in the oral cavity after oral ulcer healing requires further research [14]. Maleki et al. [32] pointed out that patients with *H. pylori*-associated RAS presented more severe symptoms than those with non-*H. pylori*-associated RAS, which indicated that *H. pylori* infection might aggravate the condition of oral ulcers. In addition, the severity and frequency of RAS decreased significantly after the eradication of *H. pylori* in the stomach.

Several reasons may explain these findings. First, histological similarities between peptic ulcers and aphthous lesions exist, and *H. pylori* plays a critical role in peptic ulcer disease. In view of the similar histological features between RAS and peptic ulcers, some investigations support the association between RAS and *H. pylori* infection [9, 10, 12–14]. The cellular immune system is involved in both of these diseases. *H. pylori* can produce heat shock proteins and several lymphocyte chemotactic factors, which cause neutrophilic infiltration and mucosal injury. Also, production of free radicals with cytotoxic effects and release of some cytokines, such as IL-8, are seen in both conditions [8]. Second, the acidic environment of the oral cavity and the warm temperature near 37 °C in dental plaque offers an ideal medium for the growth of *H. pylori.* Furthermore, results showing that *H. pylori* could be isolated from the oral cavity indicated that the oral cavity might be a second reservoir for *H. pylori*. Many studies have been published that support as well as contradict this theory. The presence of *H. pylori* in the dental plaque of patients both with and without stomach disorders has been investigated [13, 36–40]. Several studies supported that there was a significant association between the presence of *H. pylori* in the dental plaque and gastritis [37–39].The pathogenic bacteria could be found simultaneously in dental plaque and gastric mucosa, giving the evidence of the closely correlation between gastric infection and the presence of *H. pylori* in the mouth. Moreover, some studies [41–43] and a meta-analysis [44] demonstrated that periodontal treatment could improve the eradication rate of gastric *H. pylori*, which suggested that dental plaque was an important source of gastric *H. pylori* reinfection and the oral cavity might be a source of transmission or reinfection. Dental plaque control should be further performed in the treatment of gastric disease related with *H. pylori*. However, to date, the hypothesis that the oral cavity is a reservoir for *H. pylori* remains controversial. Third, there are epidemiological issues related to bacterial oral–fecal transmission [8]. As is well known, *H. pylori* colonizes in the gastric mucosa and can be excreted with the feces. Since the fecal–oral route appears to be particularly prevalent in developing countries [45], oral–fecal transmission may play a potential role in the development of RAS related to *H. pylori*.

Based on this meta-analysis, seven articles fulfilled the inclusion criteria. Only one study reached a significant level for a difference in *H. pylori* infection between the RAS and control groups; three of the studies showed no significant difference between the two groups; and the remaining three studies lacked evidence of any difference in prevalence between the two groups. This phenomenon may be due to the study population, the small sample size, or even the detection methods used.

Considering the potential effect of the interactions between *H. pylori* infection and genetic variation on the risk [46], we performed subgroup analyses stratified by regions. The level of *H. pylori* infection was not significantly different among Asians, South Americans, and Europeans, suggesting that regional factors exerted little influence on the overall results.

Then, we conducted subgroup analyses by separating the publication period and the source of controls, respectively, taking into account the potential effects of the confounding factors on the results. Similarly, no association was observed in the subgroup analysis based on the publication year. However, significant differences of *H. pylori* infection between hospital-based and population-based controls were evaluated. The level of *H. pylori* infection was greater in hospital-based controls, which was greater than the overall results (OR=2.72), implying that control subjects who came from the hospital might have a greater risk of *H. pylori* infection.

To better interpret the results, some limitations of this meta-analysis should be acknowledged. First, some inevitable bias may exist in the results as our meta-analysis only focused on papers published in the English language, missing some eligible studies that were unpublished or reported in other languages. Second, despite using a precise literature searching strategy to identify eligible studies, it is possible that a few studies meeting the inclusion criteria were not included. Third, sufficient information could not be extracted from the primary literature; thus, the interactions between *H. pylori* infection and other factors, such as age, gender, and nutritional status could not be considered in the analysis despite being potential confounders. Finally, the results must be interpreted with care because of the limited number and small sample sizes of each included study.

Conclusion

In summary, although modest limitations existed, the present meta-analysis showed a greater rate of *H. pylori* infection in RAS patients compared with control subjects. Future prospective studies assessing confounders and well-designed investigations with large sample sizes are needed to specifically test the effects of eradication of *H. pylori infection* on RAS.

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Conflict of interest The authors declare no conflict of interest.

References

1. Rennie JS, Reade PC, Hay KD, Scully C (1985) Recurrent aphthous stomatitis. Br Dent J 159(11):361–367
2. Ship JA, Chavez EM, Doerr PA, Henson BS, Sarmadi M (2000) Recurrent aphthous stomatitis. Quintessence Int 31(2):95–112
3. Scully C, Porter S (2008) Oral mucosal disease: recurrent aphthous stomatitis. Br J Oral and Maxillofac Surg 46(3):198–206
4. Jenerowicz D, Silny W, Dańczak-Pazdrowska A, Polańska A, Osmola-Mańkowska A, Olek-Hrab K (2012) Environmental factors and allergic diseases. Ann Agric Environ Med 19(3):475–481
5. Scully C, Porter S (1989) Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. J Oral Pathol Med 18(1):21–27
6. Scully C (1993) Are viruses associated with aphthae and oral vesiculo-erosive disorders? Br J Oral Maxillofac Surg 31(3):173–177
7. Cohen L (1978) Etiology, pathogenesis and classification of aphthous stomatitis and Behcet's syndrome. J Oral Pathol 7(6):347–352
8. Birek C, Grandhi R, McNeill K, Singer D, Ficarra G, Bowden G (1999) Detection of *Helicobacter pylori* in oral aphthous ulcers. J Oral Pathol Med 28(5):197–203
9. Karaca S, Seyhan M, Senol M, Harputluoglu MM, Ozcan A (2008) The effects of gastric *Helicobacter pylori* eradication on recurrent aphthous stomatitis. Int J Dermatol 47(6):615–617
10. Richter J, Grimmová M, Stiborová I, Král V, Jílek D (2003) Detection of *Helicobacter pylori* in the saliva of patients with recurrent aphthous stomatitis. Cas Lek Cesk 142(11):665–669
11. Shimoyama T, Horie N, Kato T, Kaneko T, Komiyama K (2000) *Helicobacter pylori* in oral ulcerations. J Oral Sci 42(42):225–229
12. Taş DA, Yakar T, Sakalli H, Serin E (2013) Impact of *Helicobacter pylori* on the clinical course of recurrent aphthous stomatitis. J Oral Pathol Med 42(1):89–94
13. Albanidou-Farmaki E, Giannoulis L, Markopoulos A, Fotiades S, Aggouridaki X, Farmakis K, Papanayotou P (2005) Outcome following treatment for *Helicobacter pylori* in patients with recurrent aphthous stomatitis. Oral Dis 11(1):22–26
14. Long BJ, Chen K, Wu BL, Duan JM (2007) Detection of *Helicobacter pylori* in oral cavity of patients with recurrent aphthous ulcer. J South Med Univ 27(4):477–478
15. Blaser MJ, Berg DE (2001) *Helicobacter pylori* genetic diversity and risk of human disease. J Clin Investig 107(7):767–773
16. Gong M, Ling SS, Lui SY, Yeoh KG, Ho B (2010) *Helicobacter pylori* γ-glutamyl transpeptidase is a pathogenic factor in the development of peptic ulcer disease. Gastroenterology 139(2):564–573
17. Wang Z, Yu Y, Yang W, Chen B, Li X (2013) Does *Helicobacter pylori* eradication really reduce the risk of gastric cancer at the population level? Gut 62(6):950
18. Nakamura S, Sugiyama T, Matsumoto T, Iijima K, Ono S, Tajika M, et al. (2012) Long-term clinical outcome of gastric MALT lymphoma after eradication of *Helicobacter pylori*: a multicentre cohort follow-up study of 420 patients in Japan. Clin Oral Invest 61(4): 507–513
19. Jia CL, Jiang GS, Li CH, Li CR (2009) Effect of dental plaque control on infection of *Helicobacter pylori* in gastric mucosa. J Periodontol 80(10):1606–1609
20. El-Mekki A, Kumar A, Alknawy B, Al-Ammari O, Moosa R, Quli S et al (2011) Comparison of enzyme immunoassays detecting *Helicobacter pylori* specific IgG in serum and saliva with endoscopic and biopsy findings in patients with dyspepsia. Indian J Med Microbiol 29(2):136–140
21. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting—Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283:2008–2012
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
23. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22(4): 719–748
24. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
25. Petitti DB (1994) Meta-analysis, decision analysis and cost-effectiveness analysis. In: Petitti DB (ed) Methods for quantitative synthesis in medicine, 2nd edn. New York, Oxford, pp 90–114

26. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50:1088–1101
27. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109): 629–634
28. Afghari P, Khazaei S, Kazemi S, Savabi O, Keshteli AH, Adibi P (2011) The role of *Helicobacter pylori* in the development of recurrent aphthous stomatitis: SEPAHAN systematic review no. 9. Dent Res J (Isfahan) 8(Suppl 1):S2–S8
29. Mansour-Ghanaei F, Asmar M, Bagherzadeh AH, Ekbataninezhad S (2005) *Helicobacter pylori* infection in oral lesions of patients with recurrent aphthous stomatitis. Med Sci Monit 11(12):CR576–CR579
30. Fritscher AMG, Cherubini K, Chies J, Dias ACO (2004) Association between *Helicobacter pylori* and recurrent aphthous stomatitis in children and adolescents. J Oral Pathol Med 33(3):129–132
31. Iamaroon A, Chaimano S, Linpisarn S, Pongsiriwet S, Phornphutkul K (2003) Detection of *Helicobacter pylori* in recurrent aphthous ulceration by nested PCR. J Oral Sci 45(2):107–110
32. Maleki Z, Sayyari AA, Alvavi K, Sayyari L, Baharvand M (2009) A study on the relationship between *Helicobacter pylori* and recurrent aphthous stomatitis using a urea breath test. J Contemp Dent Pract 10(1):9–16
33. Riggio MP, Lennon A, Wray D (2000) Detection of *Helicobacter pylori* DNA in recurrent aphthous stomatitis tissue by PCR. J Oral Pathol Med 29(10):507–513
34. Porter SR, Barker GR, Scully C, Macfarlane G, Bain L (1997) Serum IgG antibodies to *Helicobacter pylori* in patients with recurrent aphthous stomatitis and other oral disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 83(3):325–328
35. Victória JMN, Kalapothakis E, de Silva JFC, Gomez RS (2003) *Helicobacter pylori* DNA in recurrent aphthous stomatitis. J Oral Pathol Med 32(4):219–223
36. Navabi N, Aramon M, Mirzazadeh A (2011) Does the presence of the *Helicobacter pylori* in the dental plaque associate with its gastric infection? A meta-analysis and systematic review. Dent Res J 8(4):178–182
37. Al Asqah M, Al Hamoudi N, Anil S, Al Jebreen A, Al-Hamoudi WK (2009) Is the presence of *Helicobacter pylori* in the dental plaque of patients with chronic periodontitis a risk factor for gastric infection? Can J Gastroenterol 23(3):177–179
38. Eskandari A, Mahmoudpour A, Abolfazli N, Lafzi A (2010) Detection of *Helicobacter pylori* using PCR in dental plaque of patients with and without gastritis. Med Oral Patol Oral Cir Bucal 15(1):e28–e31
39. Assumpção MB, Martins LC, Melo Barbosa HP, Barile KA, de Almeida SS, Assumpção PP et al (2010) *Helicobacter pylori* in dental plaque and stomach of patients from Northern Brazil. World J Gastroenterol 16(24):3033–3039
40. Namiot Z, Namiot DB, Kemona A, Stasiewicz J (2004) Effect of antibacterial therapy and salivary secretion on the efficacy of *Helicobacter pylori* eradication in duodenal ulcer patients. Oral Surg Oral Med Oral Pathol Oral Radiol Enod 97(6):714–717
41. Song HY, Li Y (2013) Can eradication rate of gastric *Helicobacter pylori* be improved by killing oral *Helicobacter pylori*? World J Gastroenterol 19(39):6645–6650
42. Zarić S, Bojić B, Janković L, Dapčević B, Popović B, Čakić S et al (2009) Periodontal therapy improves gastric *Helicobacter pylori* eradication. J Dent Res 88(10):946–950
43. Jia CL, Jiang GS, Yang XX, Dou HQ, Li CR (2009) Effects on *Helicobacter pylori* reinfection in gastric mucosa by two oral plaque control methods. Hua Xi Kou Qiang Yi Xue Za Zhi 27(2):172–174
44. Bouziane A, Ahid S, Abouqal R, Ennibi O (2012) Effect of periodontal therapy on prevention of gastric *Helicobacter pylori* recurrence: a systematic review and meta-analysis. J Clin Periodontol 39(12):1166–1173
45. Li CF, Ha T, Ferguson DA, Chi DS, Zhao RG, Patel NR et al (1996) A newly developed PCR assay of *H. pylori* in gastric biopsy, saliva, and feces. Evidence of high prevalence of H. pylori in saliva supports oral transmission. Dig Dis Sci 41(11):2142–2149
46. Snaith A, El-Omar EM (2008) *Helicobacter pylori*: host genetics and disease outcomes. Expert Rev Gastroenterol Hepatol 2(4):577–585