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Association between *Helicobacter pylori* infection and Sjögren syndrome

A meta-analysis

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Abstract

Background: *Helicobacter pylori* has been proved as a risk factor of many diseases. There are some researches trying to find connection between *H. pylori* and Sjögren syndrome (SS). However, the conclusions of these studies are controversial. We conducted this meta-analysis to evaluate the association between *H. pylori* and SS.

Methods: We searched PubMed and Embase databases for researches which include the data of *H. pylori* infection rate in SS and control groups. A fixed-effects model was used to analyze the risk odds ratio (OR) with 95% confidence intervals (CIs) according to the heterogeneity across the selected studies.

Results: Nine studies with 1958 participants including 619 patients with SS met the inclusion criteria. The total infection rate of *H. pylori* was 53.83% (1054/1958). We found that the patients with SS had a significantly higher *H. pylori* infection rate than control groups (OR = 1.19, 95% CI: 1.01–1.41, $P = .033$). Subgroup analysis demonstrated a significantly higher *H. pylori* infection rate in patients with primary SS than controls (OR = 1.24, 95% CI: 1.03–1.50, $P = .026$).

Conclusion: This meta-analysis is the 1st meta-analysis about the association between *H. pylori* and SS. The pooled data suggested a significantly higher *H. pylori* infection rate in patients with SS. More prospective or multicenter retrospective researches could be conducted in the future.

Abbreviations: 13C-UBT = 13C-urea breathe test, CIs = confidence intervals, ELISA = enzyme-linked immunosorbent assay, *H. pylori* = *Helicobacter pylori,* HSP60 = heat shock protein of 60 kDa, MALT = mucosa associated lymphoid tissue, OR = odds ratio, pSS = primary Sjögren syndrome, SS = Sjögren syndrome, sSS = secondary Sjögren syndrome.

Keywords: *Helicobacter pylori*, meta-analysis, sicca syndrome, Sjögren syndrome

1. Introduction

Helicobacter pylori is a widely prevalent bacterium, and its infection rate in population ranges from 28.3% to 98.6% in different areas over the world, which is especially higher in less developed countries.[1]*Helicobacter pylori* has been proved to be a risk factor of many diseases, including not only some gastrointestinal-related diseases like chronic atrophic gastritis,[2] gastric mucosa-associated lymphoid tissue (MALT) lymphoma,[3] peptic ulcer disease,[4] but also other systemic diseases like immune thrombocytopenic purpura,[5] and diabetes mellitus.[6] As a systemic autoimmune disease, Sjögren syndrome (SS) was reported to have a link with *H. pylori* infection by some researchers,[7–10] which characterized by lymphocytic infiltration and destruction of exocrine glands.[11] This phenomenon may result from bacterial induced autoimmune response, and *H. pylori* is one of commonly known infectious factors that trigger the autoimmune reactions. However, some studies found there were no significant differences of *H. pylori* infection rate between SS and control group.[12–16] Therefore, whether *H. pylori* infection is a risk factor of SS remains controversial.

We performed this meta-analysis to have a better understanding of whether the relation between *H. pylori* and SS existed. The association between the 2 diseases may be of great value for patients with SS with gastrointestinal diseases to receive more reasonable treatment.

2. Methods

2.1. Inclusion criteria

1. Study design is a case–control study.
2. Provision of raw data on *H. pylori* infection in SS group and control group.
3. *H. pylori* infection was confirmed with at least 1 positive result by either mucosal biopsy, enzyme-linked immunosorbent assay (ELISA) or ^{13}C-urea breathe test (^{13}C-UBT).
4. Studies written in English language.

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Table 1

Main characteristics of the studies included in this meta-analysis on *H. pylori* in SS and non-SS controls.

References	Year	Country or area	Method of detection	Specimen	*H. pylori* (+) in SS group	*H. pylori* (+) in control group	Diagnostic criteria of SS	Link with *H. pylori*
Showji et al[7]	1996	Japan	ELISA (*H. pylori* IgG)	Serum	5/7	10/24	Sjögren Disease Research Committee, of Japan,[31] 1978	+
Ferraccioli et al[15]	1996	Italy	Biopsy	Tissue	15/21 pSS	50/80	European SS classification criteria[32]	–
Collin et al[14]	1997	Finland	Biopsy	Tissue	10/32 pSS	25/64	California criteria[33]	–
Shogo et al[8]	1999	Japan	ELISA (*H. pylori* IgG)	Serum	105/139 pSS 65/82 sSS 40/57	112/198	Sjögren Disease Research Committee, of Japan,[31] 1978	+
Aragona et al[10]	1999	Italy	ELISA (*H. pylori* IgG)	Serum	38/53 pSS 27/34 sSS 11/19	21/43	European SS classification criteria,[32] 1993	+
Theander et al[13]	2001	Sweden	ELISA (*H. pylori* IgG)	Serum	73/142 pSS	200/576	European classification criteria,[32] 1993	–
Sorrentino et al[16]	2004	Italy	ELISA (*H. pylori* IgG)	Serum	31/54 pSS	93/150	European criteria,2002[34]	–
El Miedany et al[9]	2005	Egypt	ELISA (*H. pylori* IgG)	Serum	51/67 pSS 29/36 sSS 22/31	36/64	European criteria,[34] 2002	+
Ram et al[12]	2013	Latin America	ELISA (*H. pylori* IgG)	Serum	66/82	113/140	European criteria,[34] 2002	–

ELISA = enzyme-linked immunosorbent assay, *H. pylori* = *Helicobacter pylori*, pSS = primary Sjögren syndrome, SS = Sjögren syndrome, sSS = secondary Sjögren syndrome.

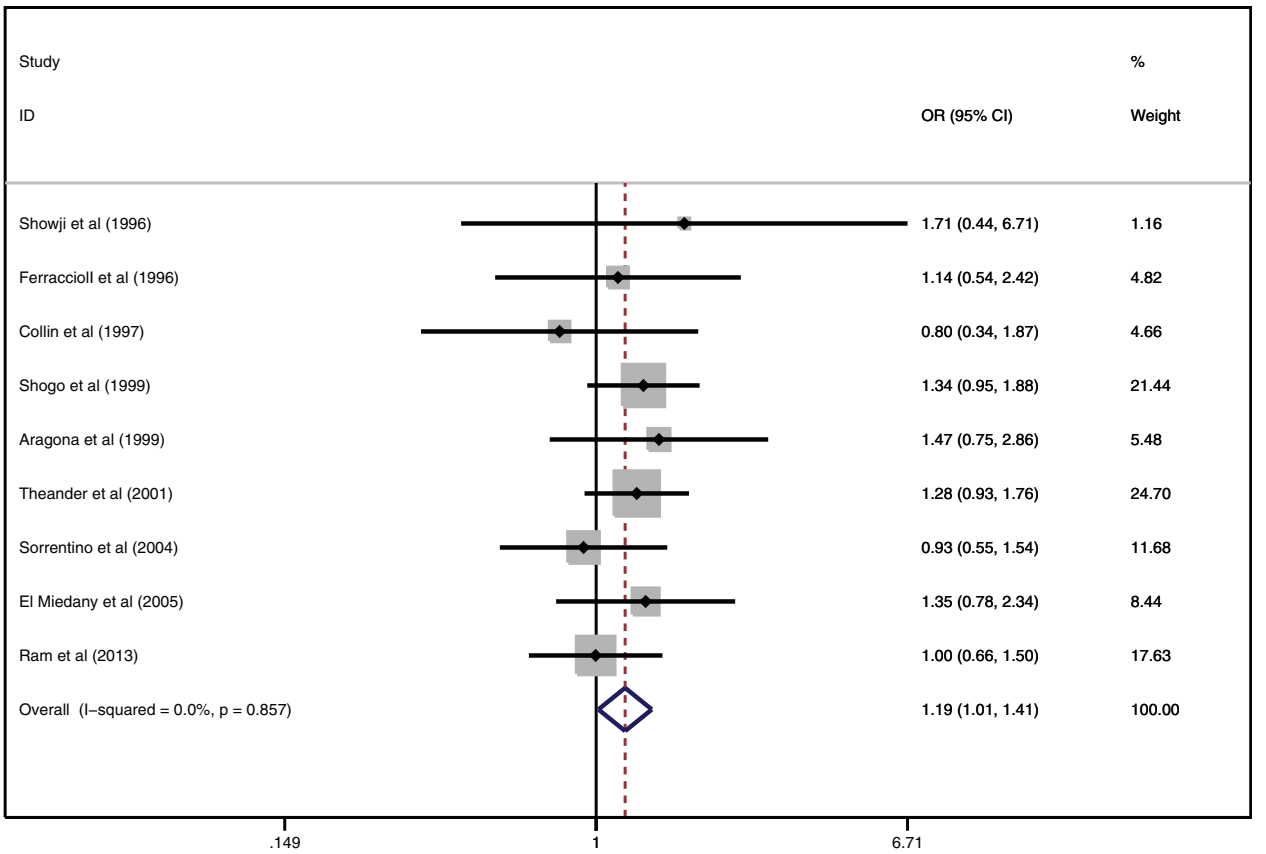

Figure 1. Forest plot about association between *Helicobacter pylori* infection and Sjögren syndrome.

2.2. Exclusion criteria

1. Case report or observational researches without control group.
2. The *H. pylori* infection raw data in SS group or in control group cannot be fully available.
3. Papers written by the same authors.
4. Animal studies only.
5. The participants in studies received *H. pylori* eradication treatment including H_2 blockers, proton pump inhibitors, or antibiotic drugs within 4 weeks.

2.3. Literature search

This meta-analysis was made by following the PRISMA guidelines. Two investigators (CQQ and XYZ) searched the PubMed and Embase databases from database inception to May 27, 2018 with a systemic literature search strategy. The keywords we used were included in supplementary data file, http://links.lww.com/MD/C677. The 2 authors performed the search and repeated several times in different medical science information centers affiliated to Nanjing Medical University at different times independently. The full texts of the relevant papers in English were reviewed by the 2 investigators. The reference lists of the relevant papers or systemic reviews previously published were also taken into consideration for additional search.

2.4. Data extraction

Data extraction was conducted by the 2 authors (CQQ and XYZ) independently. We reviewed and collected the information including the 1st author(s), year of publication, country or area of study, study design type, way of diagnosis, amount of study subjects, population of *H. pylori* infection in SS and control group from the selected studies. We only included 1 study if the same raw data were published in different studies. The raw data of ELISA would be collected if the study contained more than 1 detection method.

2.5. Statistical analysis

We used Chi-squared test and I^2 test to measure the heterogeneity among studies. There was no significant heterogeneity in this study when $P > .1$ and $I^2 < 50\%$. The Mantel–Haenszel fixed-effects model was applied to evaluate odds ratio (OR) and 95% confidence interval (CI) in this meta-analysis if heterogeneity was no significant, or a random-effect model was applied.[17] Publication bias was assessed by using funnel plots as a qualitative analysis, Egger linear regression test (Egger test) and Begg rank correlation test (Begg test) as quantitative analysis.[18,19] *P*-values $< .05$ of all tests in this article were statistically significant. We conducted statistical analysis with the STATA 12.0 (2000; STATA Corp, College Station, TX). No approval of ethics was needed because all studies included in this meta-analysis were published previously.

3. Results

3.1. Characteristics of the studies

We totally included 9 studies which met the criteria in this meta-analysis. Table 1 showed the characteristics of the studies we included. The process of literature search and identification are

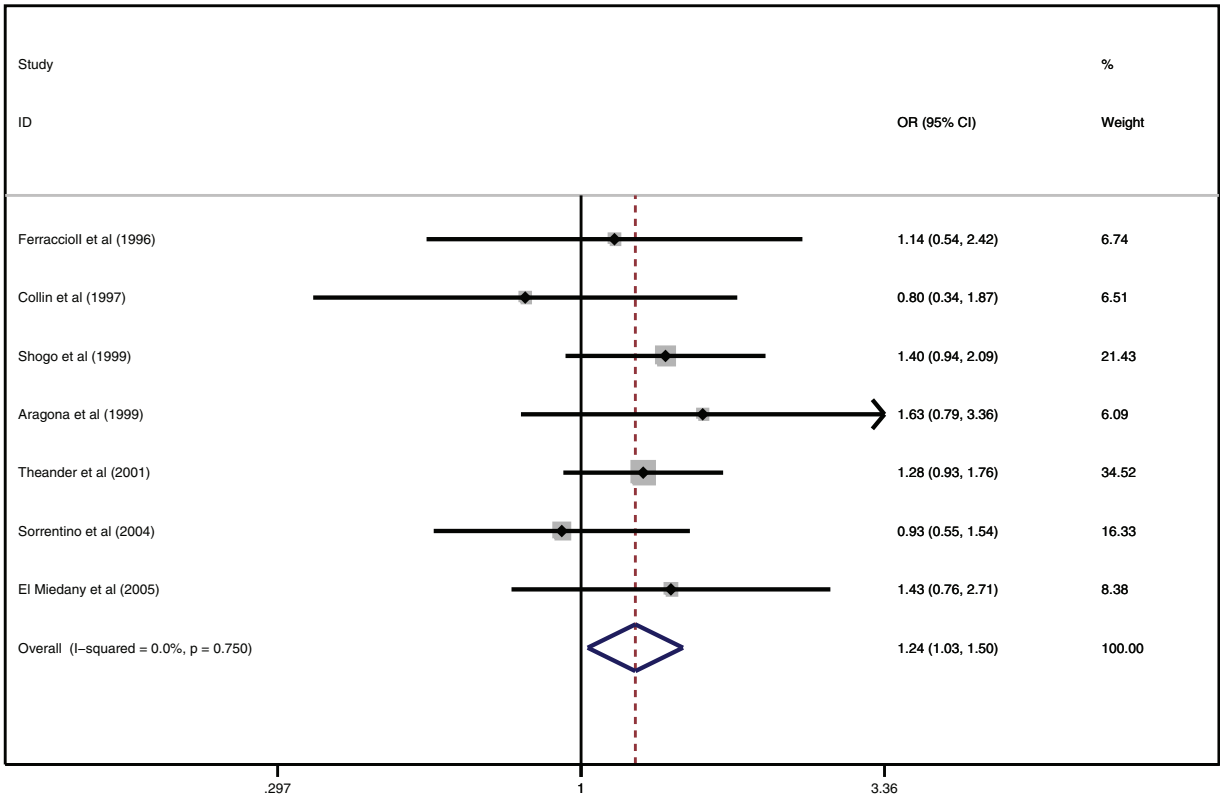

Figure 2. Meta-analysis of primary Sjögren syndrome groups of the selected studies.

shown in PRISMA Flow Diagram. There are 1958 participants including 619 patients with SS and 1339 control patients in these selected studies. The total prevalence rate of *H. pylori* was 53.83% (1054/1958), of which the SS group was 63.65% (394/614) and the control group was 49.29% (660/1339). About 68.89% (423/614) primary SS (pSS) and 17.43% (107/614) patients were reported in 7 studies. Two of the selected studies did not mention the type of patients with SS. The publication year of these studies ranged from 1996 to 2013. Participants from different countries or areas (5 from Europe, 2 from Japan, 1 from Latin America, and 1 from Egypt) were involved in the selected studies. Of the nine studies, 7 studies used ELISA as the confirmation way of *H. pylori* infection and the others used tissue biopsy. The positive correlation between *H. pylori* and SS was claimed to be found in 5 selected studies while no positive correlation was found in the other 4.

3.2. Subgroup analysis

We found a small but significantly higher *H. pylori* infection rate in patients with SS than that in controls from the forest plot (Fig. 1) of overall meta-analysis (OR 1.19, 95% CI 1.01–1.41, $P = .033 < .05$). Though the heterogeneity was low ($I^2 = 0$), subgroup analysis was made since there are 2 different types of SS (pSS and secondary SS). We excluded 2 literatures where the type of SS was unclear. The association still existed in patients with pSS according to the forest plot, in which OR was 1.24, 95% CI 1.03–1.50, $P = .026 < .05$ (Fig. 2). The patients with pSS had a more likely higher *H. pylori* infection rate than controls. However, no significant difference was found when comparing secondary SS (sSS) with controls after analysis of 3 literatures with mentioned sSS population (OR 1.24, 95% CI 0.87–1.76, $P = .238$) (Fig. 3) We also conducted a subgroup analysis according to the different detection ways of *H. pylori* infection. The patients with SS had a higher *H. pylori* infection rate than controls by using ELISA to confirm infection (OR 1.22, 95% CI 1.03–1.44, $P = .024$) (Fig. 4). The other 2 studies did not show significantly difference between SS and controls with tissues biopsy conformation.

3.3. Evaluation of publication bias

From the funnel plot, we found no publication bias (Fig. 5). Egger test and Begg test did not show any publication bias (Egger test: $P = .76 > .05$, 95% CI: −1.79 to −1.38 [Fig. 6]; Begg test: $z = 0.10 < 1.96$, $P = .917 > .05$ continuity corrected [Fig. 7]).

4. Discussion

We found a small but significant higher *H. pylori* infection in SS than controls from this meta-analysis. As we know, it was the 1st meta-analysis about the association between *H. pylori* and SS. Some assumptions were proposed to explain this association. Firstly, *H. pylori* infection has been proved to play an important role in the pathogenesis of many autoimmunity diseases, and similar mechanisms may also exist in SS. As antigens, *H. pylori* or other microbes induce immune response in human body. Some investigators found a heat shock protein of 60 kDa (HSP60) produced by *H. pylori* induced the activation of human lymphocytes by molecular mimicry as a component of *H. pylori* antigens, which could damage the immunologic tolerance of human body because of the protein's homology between human and microbes.[10,20] The significant higher prevalence rate of anti-HSP60 in patients with SS reported by Aragona et al[10] might demonstrate the role of HSP60 in the pathogenesis of SS. The correlation between *H. pylori* and SS may provide a new explanation of many interesting phenomena occurring in patients with SS clinically and histologically. It was reported that patients

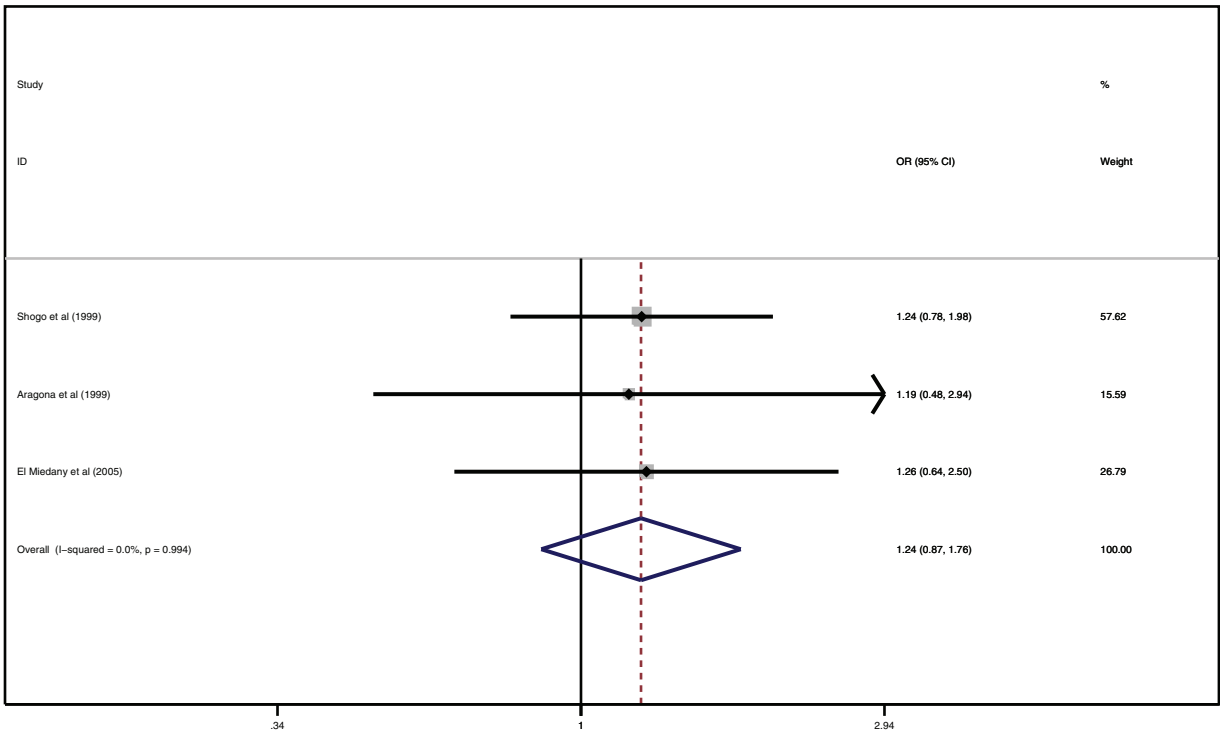

Figure 3. Meta-analysis of secondary Sjögren syndrome groups of the selected studies.

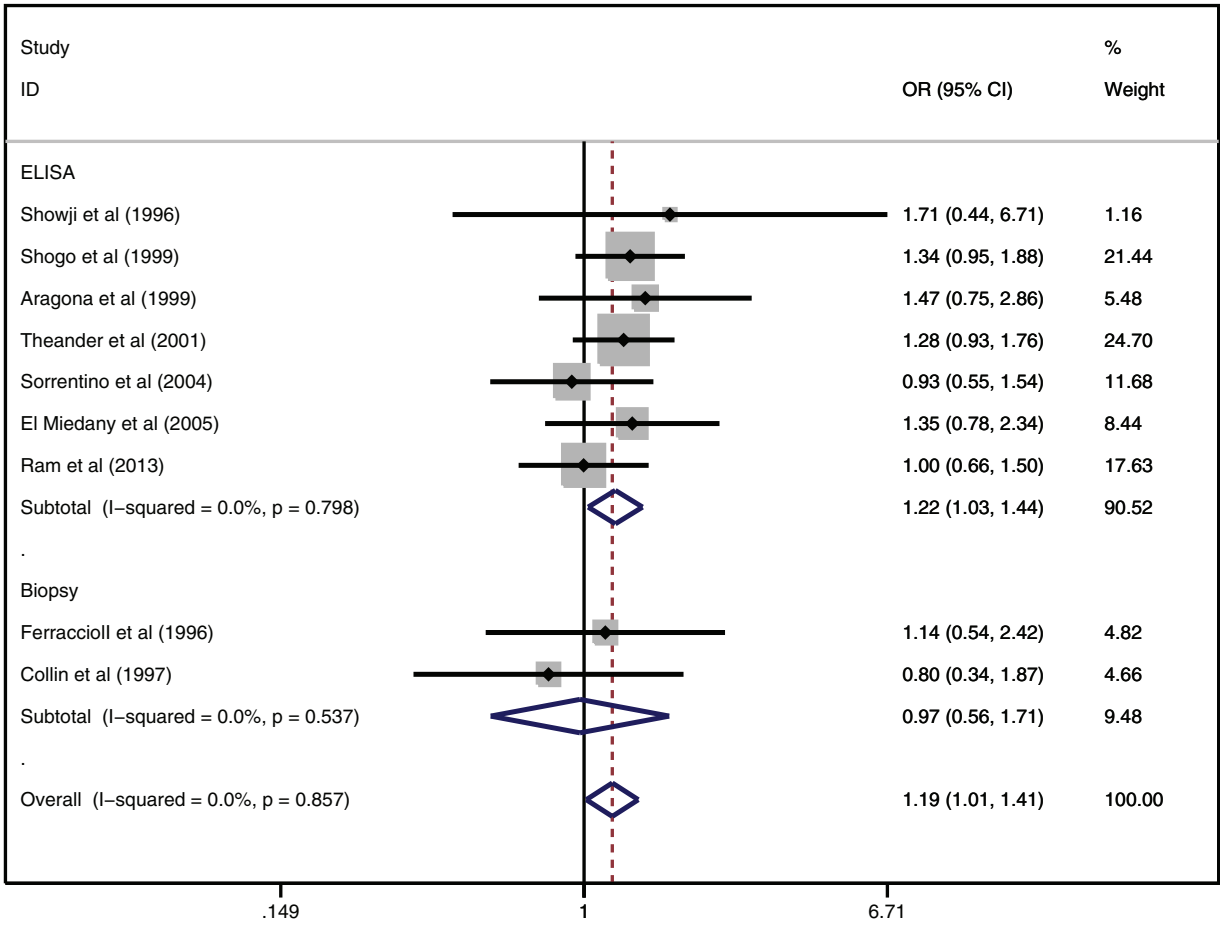

Figure 4. subgroup analysis according to the different detection ways of *Helicobacter pylori* infection.

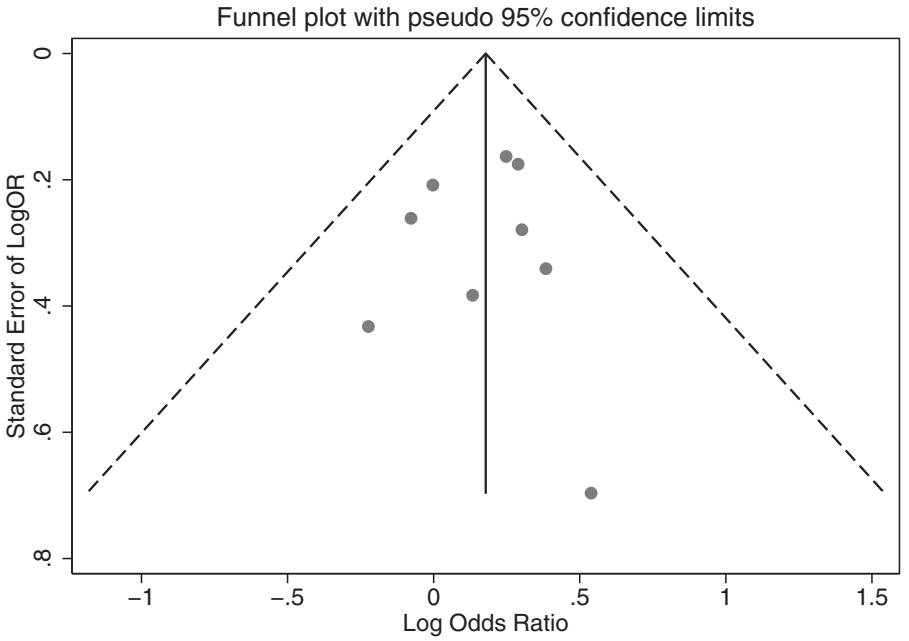

Figure 5. Funnel plot of publication bias.

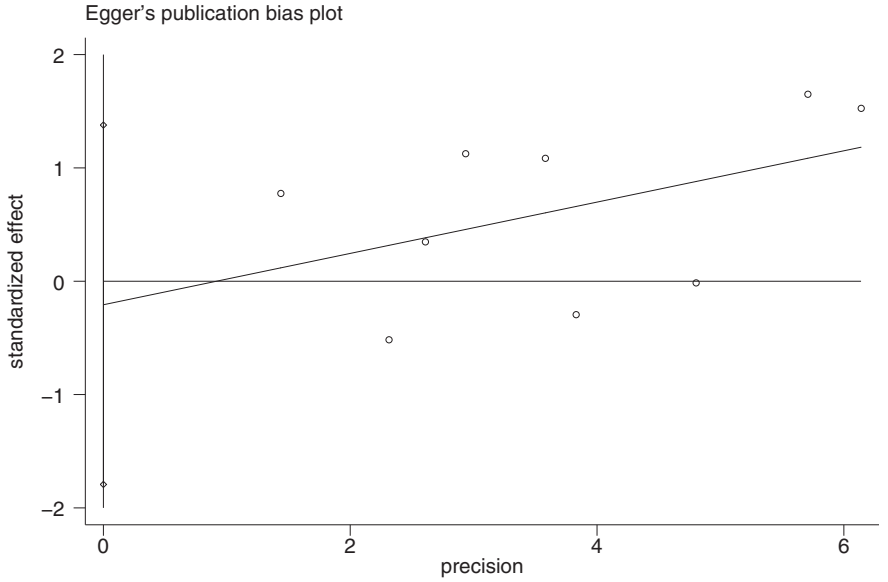

Figure 6. Publication bias with Egger test.

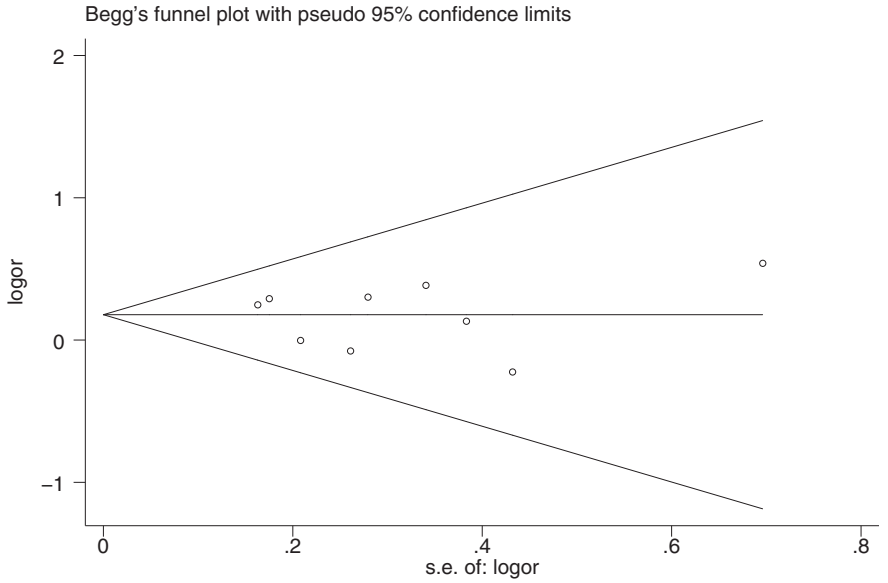

Figure 7. Publication bias with Begg test.

with SS have more possibilities of chronic gastritis,[21] which *H. pylori* infection has been widely considered as a main causative factor.[2] Moreover, the histologic manifestation of lymphocytic infiltration in gastric mucosa is similar to salivary glands in patients with SS.[22] Researchers tried most to explain the fact that patients with SS had a higher risk of development to lymphoma, and most of lymphoma following SS are MALT lymphoma.[23] As is well known, gastric MALT lymphoma is strongly correlated with *H. pylori* infection,[24] and eradication therapy will induce regression of the lymphoma.[25] Although the MALT lymphoma along with SS was mainly found in silvery glands[26] as a result of routine salivary glands biopsy for diagnosis according to the SS classification criteria,[27] regression of lymphoma was actually found after these patients with SS with gastric *H. pylori* infection received eradication therapy in some case reports.[28,29] Based on the results of our above study, it is likely that *H. pylori* infection would be a risk factor of SS-associated MALT lymphoma. *H. pylori* eradication might be effective as a prevention of lymphoma in patients with SS. More studies are needed to be conducted in this area.

4.1. Type of SS

In this meta-analysis, we found a significant higher *H. pylori* infection rate in patients with pSS than controls but nonsignificant in patients with sSS. Due to the lack of data or obfuscation of SS type, only three selected studies with 104 patients were included in sSS group analysis, while seven studies with 423

patients in pSS group. The unneglected gap of population may affect the meta-analysis results of sSS between pSS and sSS. Also, the components difference of primary diseases per se was possible to contribute to the different results though the association between these primary diseases (mainly other autoimmune diseases) and *H. pylori* are inconclusive.[20]

4.2. Ways of H. pylori testing

There were significant differences between SS group and controls by serologic test but such difference did not exist by tissue biopsy in our subgroup analysis. As only 2 studies were included, it was reasonable to believe that the difference was a result of small number of samples. Although serologic test was considered highly accurate and specific in the recent guidelines,[30] the ^{13}C-UBT was regarded as the best recommended noninvasive way to diagnose *H. pylori* infection in recent guidelines.[30] However, none of the studies included in this meta-analysis used ^{13}C-UBT to confirm *H. pylori* infection. Therefore, it is necessary to conduct studies by ^{13}C-UBT to compare results among different methods of detection.

4.3. Limitations of the study

Firstly, the number of selected studies or participants was relatively small. Secondly, the diagnostic criteria of SS varied in details because of unavoidable limitation of areas and times.[31–34] Thirdly, the control groups were selected differently across studies included. Fourthly, geographical and socioeconomic difference in *H. pylori* infection may have an impact on the results. Lastly, exclusion of non-English in the meta-analysis could lead to statistically bias.

5. Conclusion

This meta-analysis was the 1st meta-analysis about the association between *H. pylori* and SS. And the pooled data suggested a significantly higher *H. pylori* infection rate in patients with SS. More prospective or multicenter retrospective researches could be conducted in the future.

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