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A meta-analysis of the association between the presence of *Helicobacter pylori* and periodontal diseases

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Abstract

Background: The objective of this meta-analysis is to evaluate the association between the presence of *Helicobacter pylori* (*H pylori*) and periodontal disease (PD).

Methods: PubMed and EMBASE databases were searched to identify eligible articles published from inception up to April 2018. Further articles were retrieved through a manual search of recent reviews. Cross-sectional studies, case–control studies and cohort studies reporting the association between *H pylori* and PD were included. The pooled odds ratio (OR) and their 95% confidence interval (CI) were calculated.

Results: Four case-control studies and nine cross-sectional studies were included. A total of 6800 patients were included in this review. The odds for oral *H pylori* positivity was 2.31 times (95% CI: 1.99–2.68) greater than those without *H pylori*. Subgroup analyses involving different study locations, designs, and types of study population showed the similar results. The pooled OR for the gastric disease patients was the largest (3.50, 95% CI: 2.22–5.53, five articles). Stomach *H pylori* was also significantly associated with PD, with OR 2.90 (95% CI: 1.37–6.14, two articles).

Conclusions: This meta-analysis supports an association between *H pylori* and PD. More well-designed studies, especially prospective cohort studies are necessary to confirm these results.

Abbreviations: CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, *H pylori* = *Helicobacter pylori*, OR = odds ratio, PCR = polymerase chain reaction, PD = periodontal disease, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RUT = rapid urease test.

Keywords: *Helicobacter pylori*, meta-analysis, periodontal disease

1. Introduction

Periodontal disease (PD) is a group of inflammatory pathologies involving tooth supporting tissues, the structures that make up the periodontium.[1–3] PD mainly includes gingivitis and periodontitis. PD is one of the most prevalent oral diseases worldwide.[2] *Porphyromonas gingivalis*, *Actinobacillus actinomycetae*, and *Bacteroides furosae* have been reported as the major periodontal pathogens.[3,4]

Helicobacter pylori (*H pylori*) has cohabited with humans for at least 100,000 years,[5] which is one of the most common bacterial infections in humans. *H pylori* is a gram-negative bacteria which usually exists in the human stomach. *H pylori* has been designated as a Group 1 Carcinogen by the International Agency for Research on Cancer of the World Health Organization.[6,7] It has been suggested that *H pylori* may be transmitted orally and is detected in dental plaque and saliva.[8,9] There is a close relation between the infection of *H pylori* in the oral cavity and stomach.[9–11] A number of articles reported that *H pylori* was very common in oral cavity, including oral mucosa, and dental plaque.[8,9,12]

A number of studies focused on the association between the presence of oral or stomach *H pylori* (positivity) and PD. Some researchers reported that there was a positive association between them,[9,13,14] while some did not show any association.[15–17] Thus, whether *H pylori* is associated with PD remains controversial. No meta-analysis has yet been conducted to assess this association. Therefore, the aim of this study was examined the association

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Ethical approval: This study is a meta-analysis and does not involve patient and animal experiments so the ethical approval is not necessary.

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between oral or stomach *H pylori* and PD by combining all the eligible articles. This meta-analysis was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18] The PRISMA 2009 Checklist is reported in Appendix 1, http://links.lww.com/MD/D21.

2. Methods

2.1. Search strategies

The PubMed and EMBASE databases were searched to identify eligible articles published from inception up to April 2018. The search strategy was as follows: (periodontal disease OR periodontitis OR gingivitis) AND (*Helicobacter pylori* OR *H pylori* OR *h. pylori*). The search strategies were shown in Appendix 2, http://links.lww.com/MD/D21. We restricted our searches to human studies published in English. In addition, further articles were retrieved through a manual search of recent reviews.

2.2. Inclusion criteria

Two authors independently read the titles and abstracts of the articles. When there was any inconsistence between the two authors, a third author was consulted to reach a consensus. The inclusion criteria were as follows:

1. subjects: there were two groups: oral or stomach *H pylori* positivity group, and oral or stomach *H pylori* negativity group.

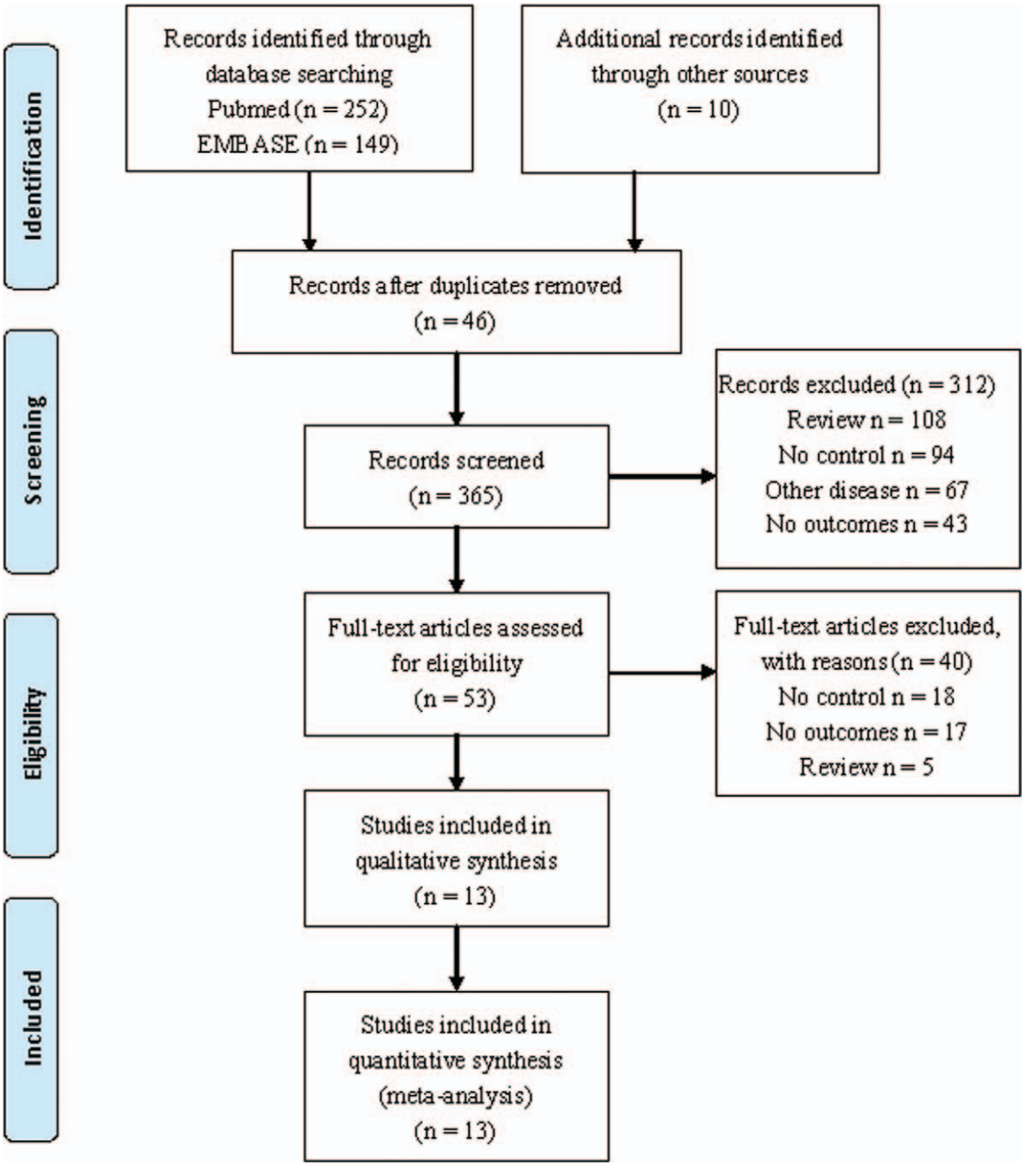

Figure 1. Flow chart of the search strategy.

Table 1

The characteristics of the eligible articles.

Author	Year	Country	Design	Source	Patients	Hp diagnostic method	Sample size	HP+ (%)	Male (%)	Mean age (range)	Smoking	Drinking	Index
Al Asqah M	2009	Saudi Arabia	Cross-sectional	Hospital	Gastric disease‡	RUT	101	65.3	55.4	40.8	0.0	NR	PD*
Anand PS	2006	India	Case-control	Hospital	Gastric disease‡	RUT	134	48.5	67.2	40 (15, 76)	40.3	22.4	PD
Dye BA	2002	USA	Cross-sectional	community	General population	ELISA	4474	25.8	50.7	NR (20, 60)	NR	NR	PD
Medina ML	2010	Argentina	Cross-sectional	Hospital	Gastric disease‡	PCR	98	18.4	39.8	43.7 (5, 78)	NR	NR	PD
Nisha KJ	2016	India	Cross-sectional	community	General population	RUT	500	54.0	47.8	NR (18, 60)	28.8	NR	PD
Riggio MP	1999	UK	Cross-sectional	Hospital	CP	PCR	73	39.7	46.6	45.1 (36, 60)	NR	NR	PD
Salehi MR	2013	Iran	Case-control	Hospital	CP	PCR	100	21.0	42.0	35.6 (NR)	NR	NR	PD*
Silva DG	2010	Brazil	Cross-sectional	Hospital	Gastric disease†	PCR	115	11.3	40.9	49.6 (NR)	0.0	NR	PD
Souto R	2008	Brazil	Cross-sectional	Hospital	CP	PCR	225	19.6	39.1	39.3 (NR)	NR	NR	PD
Sujatha S	2015	India	Cross-sectional	Hospital	Gastric disease‡	RUT	40	70.0	NR	45 (NR)	NR	NR	PD
Umeda M	2003	Japan	Cross-sectional	Hospital	PD	PCR	28	28.6	75.0	54.5 (NR)	NR	NR	PD
Valadan Tahbaz S	2017	Iran	Case-control	Hospital	CP	PCR	100	5.0	44.0	39.2 (16, 75)	10.0	5.0	PD*
Yang J	2016	China	Case-control	Hospital	PD	RUT, PCR	212	64.2	77.8	57.2 (25, 95)	0.0	5.7	PD

CP = chronic periodontitis, ELISA = enzyme-linked immunosorbent assay, PCR = polymerase chain reaction, PD = periodontal disease, RUT = rapid urease test.

* PD: only contained periodontitis.

† Complaints regarding the upper digestive tract, without systemic diseases.

‡ Dyspepsia.

Rapid urease test (RUT), polymerase chain reaction (PCR), or enzyme-linked immunosorbent assay (ELISA) to confirm the presence of *H pylori*.

2. outcomes: PD (including periodontitis and gingivitis). Each individual was tested whether to have PD. For the association of *H pylori* and PD, articles eligible for inclusion should report odds ratio (OR) or relative risk (RR) and their 95% confidence interval (CI), or data to calculate them.

3. study design: cross-sectional studies, case-control studies and cohort studies. The article which did not report the data about association of *H pylori* and PD was excluded.

2.3. Data extraction

The relevant data were independently extracted by two authors, and were further checked by a third author to reach a consensus when there was inconsistence. The following data were extracted: the first author, year of publication, country, research design, source of the patients, types of study population, *H pylori* diagnostic method, sample size, the number of patient with *H pylori*-positive and *H pylori*-negative, age, sex, smoking habits, alcohol consumption, and the outcomes. The outcomes mainly included PD, periodontitis, and gingivitis. There were two types of study population: gastric disease, and general population. Some articles enrolled the patients who had dyspepsia or complaints regarding the upper digestive tract (gastric disease). Some articles enrolled the general population with or without PD (general population).

2.4. Statistical analysis

A χ^2 test of homogeneity was conducted, and inconsistency index (I^2) statistics were calculated. If heterogeneity did not exist among articles, a fixed-effects model was performed. Otherwise, a random-effects model was performed. The association between oral *H pylori* or stomach *H pylori* and PD were analysed separately.

For pooled estimate of binary data, OR with its corresponding 95% CI were calculated. Subgroup analyses in terms of different study locations (developed countries and developing countries), designs (cross-sectional studies and case-control studies), and types of study population (gastric disease and general population)

Table 2

The meta-analysis results of oral *H pylori* and periodontal disease.

	Number of studies	Patients	HR (95% CI)	Heterogeneity (I^2, *P*)
All	13	6200	2.31 (1.99–2.68)	35.6%, .098
Country				
Developing	10	1625	2.47 (1.95–3.13)	45.9%, .055
Developed	3	4575	2.20 (1.82–2.66)	0.0%, .435
Design				
Cross-sectional	9	5654	2.37 (2.02–2.77)	34.0%, .146
Case-control	4	546	2.01 (1.35–2.99)	51.1%, .105
Patient type				
Gastric disease*	5	488	3.50 (2.22–5.53)	37.7%, .170
General population	8	5712	2.19 (1.99–2.68)	24.5%, .234

* Gastric disease: contained the patients with dyspepsia and those complaints regarding the upper digestive tract, without systemic diseases.

were performed. A two-sided P value $\leq .05$ was considered as statistical significance. Sensitivity analysis was performed using the leave-one-out approach. All analyses were performed using the STATA software (version 14.0).

3. Results

3.1. Characteristics of eligible studies

Figure 1 showed the article selection procedure. The search yielded 411 articles. After exclusion, a total of 13 eligible articles were included for analysis.[13–16,19–27]

Among these articles, three were conducted in developed countries (the USA,[13] the UK,[22] and Japan[26]), and others in developing countries. Four articles were case-control studies, and nine were cross-sectional studies. Eleven articles were performed in a hospital setting, while only two were performed in a community setting. The sample sizes of the selected studies ranged from 28 to 4474. A total of 6200 patients were included in this review. The proportion of the patients with *H pylori* positivity ranged from 5.0% to 70.0%, with a median of 28.6%. The characteristics of the selected studies were summarized in Table 1.

3.2. Meta-analysis of PD

There was no heterogeneity among the thirteen articles ($I^2 = 35.6\%$, $P = .098$), thus a fixed-effects model was performed. The combined OR was 2.31 (95% CI: 1.99–2.68; Table 2, Fig. 2), which indicated that the patients with *H pylori* positivity was positively associated with PD.

Subgroup analyses were performed to evaluate the association between oral *H pylori* and PD (Table 2). The pooled OR in developing countries was 2.47 (95% CI: 1.95–3.13), and that in developed countries was 2.20 (95% CI: 1.82–2.66). The summarized ORs for articles based on cross-sectional studies and case-control studies were 2.37 (95% CI: 2.02–2.77) and 2.01 (95% CI: 1.35–2.99), respectively. For the patients with gastric disease, the pooled OR was 3.50 (95% CI: 2.22–5.53). For general population, the pooled OR was 2.19 (95% CI: 1.99–2.68).

A sensitivity analysis was conducted to identify potential heterogeneity. Almost all pooled OR and 95% CI from the included articles were within the estimated ranges, expect the article conducted by Dye et al (Table 3).[13]

Two articles also reported the association between stomach *H pylori* and PD. The pooled OR was 2.90 (95% CI: 1.37–6.14; Fig. 3).

4. Discussion

H pylori is a gram-negative microaerophilic bacterium that colonizes gastrointestinal mucosa and is considered to be an influencing factor for many oral diseases. In this meta-analysis, risk of PD in the patients with oral *H pylori* positivity was 2.31 times higher than those with *H pylori* negativity. Although five eligible articles reported that there was no significant association between *H pylori* and PD,[15,16,21,22,26] the result indicated that high expression of *H pylori* positivity was associated with a higher prevalence of PD. The association between oral *H pylori* and PD may be related with the following mechanisms.

1. There is a close relation between *H pylori* positivity in the oral cavity and the stomach. Some researches indicated that *H*

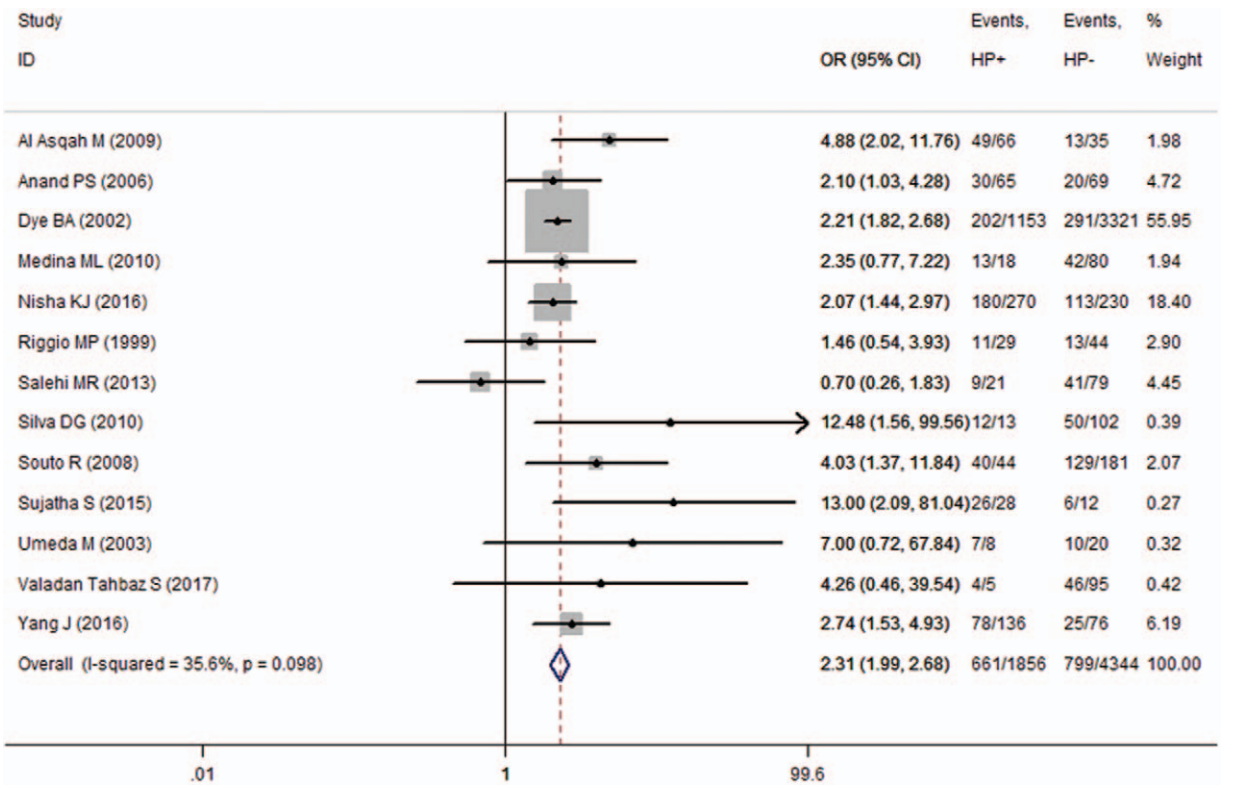

Figure 2. Forest plot evaluating the combined OR between oral *H pylori* and periodontal disease.

Table 3

The result of sensitivity analysis.

Study omitted	Coefficient	95% CI
Al Asqah M	2.36	(2.21–2.51)
Anand PS	2.45	(2.29–2.60)
Chaudhry S	2.43	(2.28–2.58)
Dye BA	2.75	(2.52–2.98)
Gülseren D	2.43	(2.28–2.58)
Hu Z	2.43	(2.28–2.58)
Liu Y	2.43	(2.28–2.58)
Medina ML	2.43	(2.28–2.58)
Nisha KJ	2.51	(2.34–2.67)
Riggio MP	2.45	(2.30–2.60)
Salehi MR	2.47	(2.32–2.62)
Silva DG	2.38	(2.23–2.53)
Souto R	2.40	(2.25–2.55)
Combined	2.43	(2.28–2.58)

pylori could transmit through oral-oral or fecal-oral routes.[28–30] The oral cavity is the first extra-gastric reservoir of *H pylori*.[9,11,31] The oral mucosa (especially the gingival sulcus) and dental plaque are places for bacterial colonization.[12] Based on the result of a meta-analysis, the prevalence of co-infection of gastric and dental plaque *H pylori* was 49.7%.[32]

2. Some experiment demonstrated that *H pylori* existed in the gingiva plaque, and might played a role in the development of PD.[27,33,34]

As gram-negative and anaerobic bacteria in biofilms went up, the inflammation of periodontium deteriorated and cytokines secretion increased.[33,34]

The pooled OR in the gastric disease patients was 3.50 (95% CI: 2.22–5.53), which was higher than that in general population, according to the results of subgroup analyses. Two articles also reported the association between stomach *H pylori* and PD. The combined OR was 2.90, which was higher than that in oral *H pylori* positivity (OR = 2.31). These results showed that gastric disease had a positive impact on PD. A meta-analysis reported that the prevalence of co-infection of gastric and dental plaque *H pylori* was 49.7%.[32] Bouziane et al performed a meta-analysis of randomized controlled trials, and reported that the adjunction of periodontal treatment to eradication therapy appeared to reduce gastric *H pylori* recurrence compared with eradication therapy alone.[35] This result provides some useful information for periodontists, that periodontists should ask the patients about history of gastric disease, and examine the oral and stomach *H pylori*. If the patient has symptoms of gastric disease, the periodontist should suggest relevant treatments to maintain the effect of periodontal therapy.

Some limitations should be addressed.

1. This meta-analysis only enrolled cross-sectional studies and case-control studies; therefore we could not confirm the association between *H pylori* and PD. Whether PD existed and then created an environment for *H pylori* or whether *H pylori* played a role in the onset and development of PD could not be differentiated. Therefore, prospective cohort studies should be performed to solve this question.
2. Lots of factors can have an effect on PD, such as age, sex, smoking, poorly controlled diabetes, possibly obesity, stress and osteopenia.[3,12] In order to understand whether *H pylori* was an independent predictor for PD, the above factors should be controlled. This meta-analysis was based on the unadjusted data, which did not control those factors. Therefore, our results may be confounded by other factors.
3. This meta-analysis did not consider the effects of other bacteria to PD. Some studies demonstrated that *P gingivalis*, *A actinomycetae*, and *B furosae* were associated with PD.[4,12,36]

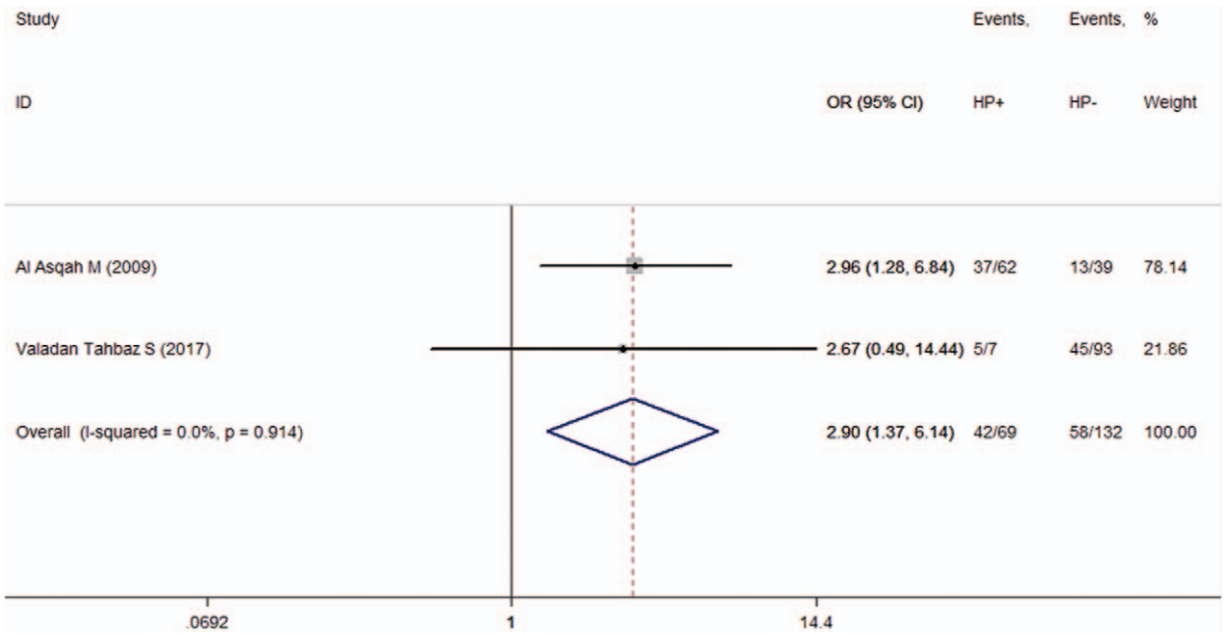

Figure 3. Forest plot evaluating the combined OR between stomach *H pylori* and periodontal disease.

5. Conclusions

In conclusion, this meta-analysis based on the eligible articles supports an association between *H* pylori positivity and PD. The pooled OR in the gastric disease patients was 3.50 (95% CI: 2.22–5.53), which was higher than that in general population. More well-designed studies, especially prospective cohort studies are necessary to confirm these results. The periodontists should ask the patients with PD about history of gastric disease, and examine the oral and stomach *H pylori*.

Author contributions

Conceptualization: Xin-lin Chen.
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Formal analysis: Yi-ming Chen, Hui-biao Li.
Funding acquisition: Xin-lin Chen.
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Project administration: Zheng Chen, Xin-lin Chen.
Resources: Zheng Chen, Yeming Lu.
Software: Hui-biao Li.
Writing – original draft: Zheng Chen, Jiarong Cai, Xin-lin Chen.
Writing – review & editing: Zhengyang Zhou.

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