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Association Between *Helicobacter Pylori* Infection and Periodontal and Gastric Diseases: A Meta-Analysis

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ABSTRACT

Background: *Helicobacter pylori* (Hp) infection has been implicated in both gastric and extra-gastric diseases, including periodontitis.
Methods: This meta-analysis investigated the association between *Helicobacter pylori* (Hp) infection and periodontitis by systematically reviewing eight studies. The analysis was conducted using the R package "meta," employing both fixed effects and random effects models. The level of heterogeneity among the studies was assessed using the I-squared statistic and tau values. Publication bias was evaluated through funnel plots, Begg's rank correlation, and Egger's regression tests to ensure the robustness of the findings.
Results: The meta-analysis included a total of 6061 observations, with 1404 cases of periodontitis. The fixed effects model produced an odds ratio (OR) of 2.3392 (95% confidence interval [CI]: 2.0207-2.7078), and the random effects model yielded a similar OR of 2.3220 (95% CI: 2.0050-2.6892). The I-squared statistic indicated low to moderate heterogeneity among the studies. Subgroup analyses demonstrated consistent associations across different Hp diagnostic methods.
Conclusion: Hp infection is significantly associated with an increased risk of periodontitis, highlighting its role in both gastric and oral health.

Introduction

Hp is a well-recognized pathogen that has been extensively studied for its role in various gastrointestinal diseases, particularly chronic atrophic gastritis and peptic ulcers. Recent research has expanded the understanding of Hp beyond the gastric environment, revealing its potential involvement in extra-gastric diseases, including periodontal disease. For instance, Li J et al.,[1] explored the biogenesis and biological functions of Hp outer membrane vesicles, highlighting the pathogen's complex interaction with host tissues beyond the stomach. Additionally, studies like those conducted by Bohatu S et al.,[2] have proposed mechanisms by which Hp might contribute to the pathogenesis of periodontal diseases, suggesting a systemic impact of this infection.

The possible link between Hp infection and periodontitis has sparked interest in the scientific community, prompting further investigation into whether periodontal therapy combined with Hp eradication could be more effective than either treatment alone. For example, Rahat M et al.,[3] reviewed the potential benefits of adjunctive eradication therapy in periodontal treatment, underscoring the need for integrated therapeutic approaches. Moreover, research by Li R et al.,[4] has examined the association between Hp genotypes and periodontitis, providing valuable insights into the pathogen's role in oral health.

Given these emerging connections, it is crucial to systematically evaluate the evidence linking Hp infection to periodontal disease and chronic atrophic gastritis. This meta-analysis aims to synthesize the existing literature on the association between periodontitis and Hp infection, contributing to the broader understanding of the pathogen's impact

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on oral and gastric health. By integrating data from various studies, this analysis will provide a comprehensive overview of the relationship between these conditions, thereby informing future research and clinical practice.

Materials and methods

Search strategies

The search strategy involved querying the MEDLINE and EMBASE databases using a combination of relevant terms, including "*Helicobacter pylori*," "Hp," "periodontal disease," "periodontitis," "gastric ulcer," "atrophic," "atrophy," "chronic," "gastritis," "pepsinogen," "incidence," "cohort," "follow-up," "long term," "prospective," and "retrospective." The search targeted English-language articles published between January 1995 and July 2024. For inclusion, studies on periodontitis required a minimum sample size of 100, while those on chronic atrophic gastritis required a minimum sample size of 1000. Eligible study designs included case-control, cross-sectional, RCT, and cohort studies.

Data extraction

Data extraction was conducted in a systematic manner. Initially, all authors provided their input on the items and variables to be extracted from the selected articles. A checklist was then developed, covering details such as the author's name, publication year, study country, study type, age of participants, sample size, method of Hp diagnosis, and sampling location. Two authors independently performed the data extraction, with discrepancies resolved by consulting a third reviewer. The extracted data included the first author, year of publication, study population characteristics (country, population type, sample size, age), follow-up details, Hp infection status at baseline, and incidence rates of periodontitis and chronic atrophic gastritis.

Quality assessment

The quality assessment of the included studies was conducted using the NHLBI's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Each study was evaluated based on 14 criteria, including the clarity of the research question, specification of the study population, participation rate, and whether the exposure and outcome measures were clearly defined and reliably implemented. Most studies demonstrated clear research objectives, well-defined populations, and consistent application of exposure measures. However, some studies lacked a thorough sample size justification and did not consistently blind outcome assessors to exposure status. Additionally, loss to follow-up was a concern in several studies. Overall, the studies were rated as Good, Fair, or Poor based on their adherence to these quality criteria, with particular attention given to the robustness of their methodologies and the handling of potential confounding variables.

Statistical analysis

The meta-analysis on the association between periodontal disease and *Helicobacter pylori* infection was conducted using the R package "meta".[5] Both fixed effects and random effects models were employed, depending on the level of heterogeneity among the studies. The Mantel-Haenszel method was used, with inverse variance weighting for study contributions and restricted maximum-likelihood estimation for the random effects model parameters. Heterogeneity was assessed using the I-squared statistic and tau values, indicating low to moderate levels of heterogeneity. Subgroup analyses and tests for publication bias, including funnel plot analysis, Begg's rank correlation,[6] Egger's regression,[7] Galbraith plot, and Baujat plot, were also performed to ensure the robustness of the findings.

Results

Characteristics of eligible studies

The meta-analysis included a total of eight studies on periodontal disease and Hp infection, comprising both case-control and cross-sectional designs, which investigated the association between periodontal disease and Hp infection. These studies were conducted across various countries, including Saudi Arabia, India, the USA, Brazil, China, and Iraq, reflecting a diverse geographical distribution. The studies varied significantly in terms of sample size and patient demographics. The smallest study was conducted by Al Asqah et al.,[8] in Saudi Arabia, including 101 patients with a mean age of 40.77 years. In contrast, the largest study was by Dye et al.,[9] in the USA, which was a cross-sectional design with 4474 participants, though the age of the participants was not reported. Other studies, such as those by Nisha et al.,[10] in India and Almashhadany et al.,[11] in Iraq, included 500 and 280 patients, respectively. The diagnostic methods for detecting Hp varied across the studies. Most studies, including those by Al Asqah et al.,[8] Anand et al.,[12] and Al-Refai et al.,[13] used the Rapid Urease Test (RUT). Some studies, like the one by Souto et al.,[14] in Brazil, utilized Polymerase Chain Reaction (PCR), while Yang et al.,[15] in China employed both RUT and PCR methods. Dye et al.,[9] uniquely used ELISA for detecting Hp antibodies (Table 1).

The included studies on chronic atrophic gastritis and Hp infection exhibit a diverse range of characteristics. The study by Valle et al.,[16] from Finland, designed as a cohort study, involved 2848 patients aged between 16 and 55 years. The Hp infection was diagnosed using the Giemsa stain method. In contrast, the study by Ozasa et al.,[17] conducted in Japan followed a case-control design and included 2320 patients. Hp infection in this study was detected using the Pirikaplate G Helicobacter enzyme immunoassay. Klinkenberg-Knol et al.,[18] conducted a cohort study in the Netherlands, involving 1352 patients with a mean age of 63 years. The Hp infection in this study was identified using the Steiner silver stain method. Lastly, the study by Lundell et al.,[19] from Sweden, designed as a randomized controlled trial (RCT), included 1134 patients. This study utilized both the Steiner silver staining and an immunohistochemical technique for detecting Hp infection (Table 2).

Table 1 – The characteristics of included studies on periodontal disease and Hp infection.

Study	Year	Country	Design	Hp diagnostic method	No. of patients	Age of patients
Al Asqah M et al.	2009	Saudi Arabia	Case-control	RUT	101	40.77±14.15
Anand et al.	2014	India	Case-control	RUT	134	41±11.7
Dye et al.	2002	USA	Cross-sectional	ELISA	4474	N/A
Nisha et al.	2016	India	Cross-sectional	RUT	500	N/A
Souto et al.	2008	Brazil	Cross-sectional	PCR	225	39.3
Yang et al.	2016	China	Case-Control	RUT & PCR	212	57.2 (25 - 95)
Al-Refai et al.	2002	Saudi Arabia	Case-Control	RUT	135	36.37 (21-65)
Almashhadany et al.	2022	Iraq	Cross-sectional	RUT	280	51.7

NHLBI's quality assessment

In terms of quality assessment using the NHLBI's Quality Assessment Tool, the studies received a range of evaluations. Four studies (by Anand et al.,[12] Dye et al.,[9] Nisha et al.,[10] and Yang et al.,[15]) were rated as "Good." These studies were recognized for their clear research objectives, well-defined study populations, and consistent implementation of exposure measures. However, some limitations were noted, such as the absence of sample size justification and the lack of repeated exposure assessments over time. The remaining studies, including those by Al Asqah et al.,[8] Souto et al.,[14] Al-Refai et al.,[13] and Almashhadany et al.,[11] were rated as "Fair." These studies generally had well-defined objectives and reliable exposure measures but were marked down due to the absence of key details such as participation rates, adjustments for potential confounding variables, and incomplete blinding of outcome assessors (Table 3).

The quality assessment of the included studies on chronic atrophic gastritis and Hp infection, conducted using the NHLBI's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, reveals variability in the methodological rigor across the studies. All four studies (Valle et al.,[16] Ozasa et al.,[17] Klinkenberg-Knol et al.,[18] and Lundell et al.,[19]) clearly stated their research questions and objectives, and defined their study populations comprehensively. The quality assessment categorized Klinkenberg-Knol et al.,[18] as a "Good" quality study, while the other three studies were rated as "Fair," indicating areas where methodological improvements could have strengthened the reliability of their findings (Table 4).

Risk of bias

The risk of bias analysis on periodontal disease (Figure 1A) reveals that the majority of the studies have unclear risks of bias in several key domains, including allocation concealment, blinding of participants and personnel, and outcome assessment. Most studies have low risk of bias in terms of selective reporting and incomplete outcome data, but overall, the studies are rated as having an unclear risk of bias due to inconsistencies in blinding and random sequence generation.

The risk of bias assessment on chronic atrophic gastritis indicates that Lundell et al.,[19] demonstrated the most robust methodology, with "Low" risk of bias across all domains. In contrast, Valle et al.,[16] Ozasa et al.,[17] and Klinkenberg-Knol et al.,[18] had "Unclear" ratings overall due to uncertainties in several domains, particularly in blinding and allocation concealment.

Meta analysis on periodontal disease and Hp infection

This meta-analysis investigates the association between periodontitis and Hp infection. The study utilized the R package "meta" for conducting the meta-analysis, employing two statistical models: fixed effects and random effects. The choice of model depends on the level of heterogeneity among the studies, with low heterogeneity favoring a fixed effects model and high heterogeneity suggesting a random effects model. The analysis pooled data from 8 studies with a total of 6061 observations and 1404 events (i.e., instances of periodontitis in individuals with Hpinfection). Both the common effect model and the random effects model yielded similar results, indicating that individuals with Hpinfection have a significantly increased risk of developing periodontitis. The fixed effects model reported an OR of 2.3392 (95% confidence interval: 2.0207-2.7078), while the random effects model yielded an OR of 2.3220 (95% CI: 2.0050-2.6892). Quantification of heterogeneity using the I-squared statistic and tau values revealed low to moderate levels of heterogeneity among the studies, further supporting the use of both models. The results were obtained through a Mantel-Haenszel method meta-analysis, utilizing inverse variance weighting for study contributions and restricted maximum-likelihood estimation for the random effects model's parameters (Figure 2).

Table 2 – The characteristics of included studies on chronic atrophic gastritis and Hp infection.

Study	Year	Country	Design	Hp diagnostic method	No. of patients	Age of patients
Valle et al.	1996	Finland	Cohort study	Giemsa stain	2848	35 (16-55)
Ozasa et al.	1999	Japan	Case-Control	Pirikaplate G Helicobacter enzyme immunoassay	2320	N/A
Klinkenberg-Knol et al.	2000	Netherlands	Cohort study	Steiner silver stain	1352	63
Lundell et al.	2006	Sweden	RCT	Steiner silver staining & Immunohistochemical technique	1134	N/A

Table 3 – Quality assessment of included studies with NHLBI's quality assessment tool for observational cohort and cross-sectional studies.

Study	Al Asqah M et al., 2009	Anand et al., 2006	Dye et al., 2002	Nisha et al., 2016	Souto et al., 2008	Yang et al., 2016	Al-Refai et al., 2002	Almashhadany et al., 2022
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	NR	Yes	NR	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	No	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?	No	Yes	Yes	Yes	Yes	Yes	Yes	No
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	NR	CD	No	CD
13. Was loss to follow-up after baseline 20% or less?	NA	NA	NA	NR	NR	NR	NR	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Quality Assessment	Fair	Good	Good	Good	Fair	Good	Fair	Fair

Table 4 – Quality assessment of included studies on chronic atrophic gastritis and Hp infection with NHLBI's quality assessment tool for observational cohort and cross-sectional studies.

Study	Valle et al., 1996	Ozasa et al., 1999	Klinkenberg-Knol et al., 2000	Lundell et al., 2006
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	No	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?	Yes	Yes	Yes	No
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	Yes	Yes	Yes	Yes
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	No	CD	Yes	Yes
13. Was loss to follow-up after baseline 20% or less?	No	No	Yes	No
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	Yes	Yes	No
Quality Assessment	Fair	Fair	Good	Fair

The funnel plot analysis shows that the x-axis limits are between 0.801 and 7.207, and the y-axis limits are between 0.549 and 0, indicating that the funnel plot generally presents an inverted funnel shape (Figure 3). The Trim and Fill analysis shown as Figure 4 results indicate that after adding two studies to adjust for funnel plot asymmetry, the number of studies increased to k = 10, with a total of 6387 observations and 1635 events. The random effects model estimated an OR of 2.2480 with a 95% CI of [1.9474; 2.5949], and the z-score was 11.06 with a *P*-value < .0001. The analysis also reported heterogeneity measures, including $tau^2 < 0.0001$, tau = 0.0006, $I^2 = 10.3\%$, and H = 1.06. The test of heterogeneity showed Q = 10.03 with 9 degrees of freedom (d.f.) and a *P*-value of .3482. In the linear regression test of funnel plot asymmetry, the t-statistic was 1.50 with df = 6 and a *P*-value of .1838, while in the rank correlation test, the z-score was 1.36 with a *P*-value of .1735. The sample estimates included bias = 0.8081, se.bias = 0.5380, intercept = 0.6992, and se.intercept = 0.1140.

The results of the Begg and Egger analyses, depicted in Supplementary Figures 1 and 2 respectively, provide an assessment of publication bias within the studies. The Begg analysis, using the rank correlation test of funnel plot asymmetry, yielded a z-value of 1.36 with a *P*-value of .1735, indicating no statistically significant evidence of publication bias. The sample estimates show a Kendall's S statistic (ks) of 11.0000 with a standard error (se.ks) of 8.0829, further supporting the lack of significant asymmetry in the funnel plot.

Similarly, the Egger analysis, which employs a linear regression approach to detect funnel plot asymmetry, returned a t-value of 1.50 with 6 degrees of freedom and a *P*-value of .1838. This suggests that the null hypothesis of no small-study effects (and hence no publication bias) cannot be rejected. The bias estimate is 0.8081 with a standard error of 0.5380, while the intercept is estimated at 0.6992 with a standard error of 0.1140. The multiplicative residual heterogeneity variance (tau^2) is 0.6947, indicating some variability among

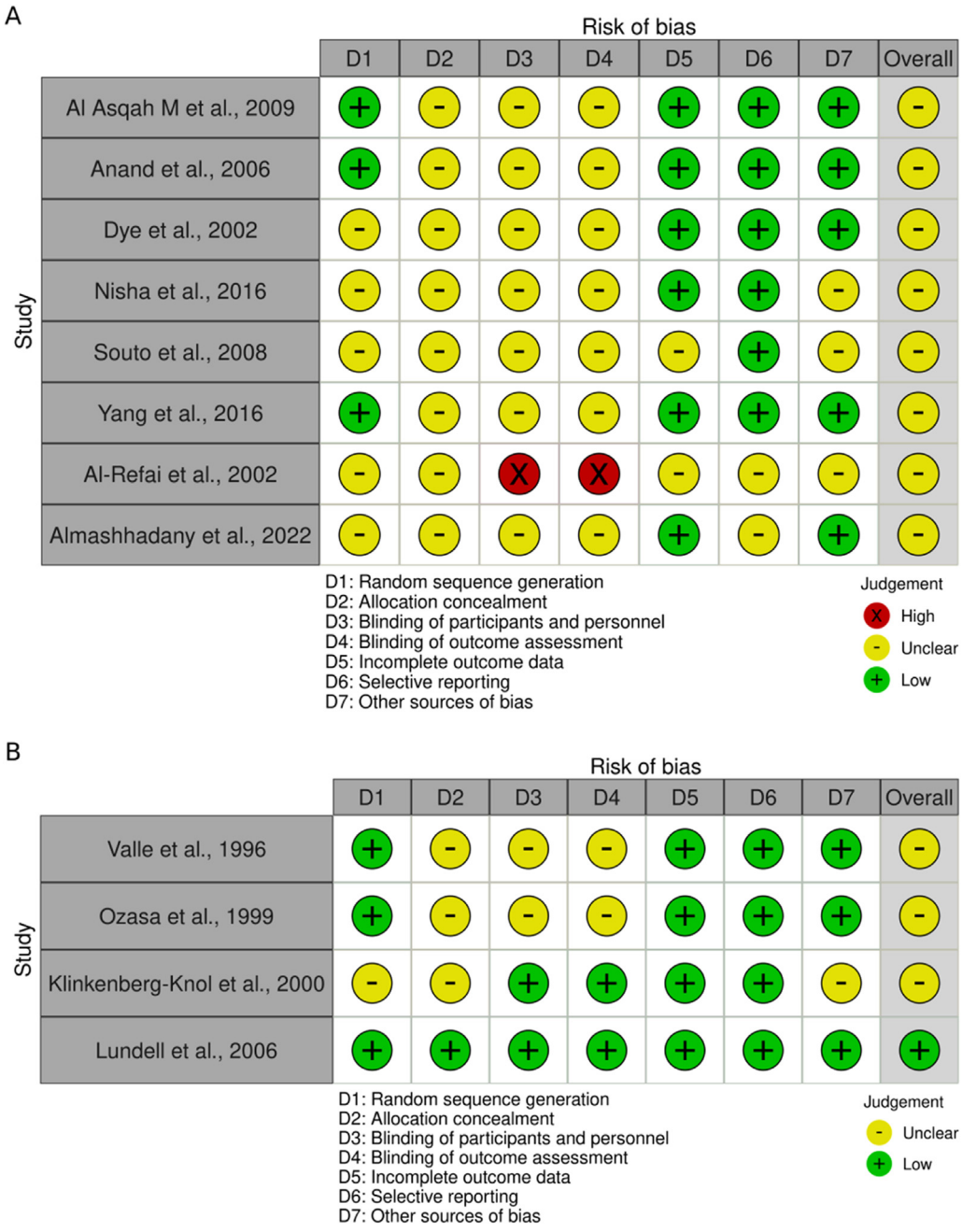

Fig. 1 – A, The risk of bias analysis of the meta-analysis on periodontal disease and Hp infection. B, The risk of bias analysis of the meta-analysis on chronic atrophic gastritis and Hp infection. The bias situation of these two meta-analyses was to assess the risk of bias in 7 aspects, "Low" meant low risk of bias, "High" meant high risk of bias, and "Unclear" means it was unclear whether there was a risk of bias. The seven aspects of the assessment were: D1: Random sequence generation, D2: Allocation concealment, D3: Blinding of participants and personnel, D4: Blinding of outcome assessment, D5: Incomplete outcome data, D6: Selective reporting, D7: Other sources of bias.

the study effects, though it does not appear to influence the overall assessment of publication bias significantly. Overall, both Begg and Egger tests suggest that there is no substantial evidence of publication bias in the included studies.

The Galbraith analysis shown as Supplementary Figure 3 conducted using the R meta package, reveals a distribution pattern where all included studies are positioned within the central two regions of the plot. Notably, the study by Dye et al.,[9] stands out by occupying the top of the third interval from the top of the plot, indicating a higher level of effect relative to its precision compared to other studies. This position suggests that Dye et al.,[9] might be contributing more variance to the meta-analysis than other studies, which are more closely clustered together. The relative dispersion of Dye et al.,[9] from the other studies highlights its unique influence within the overall analysis.

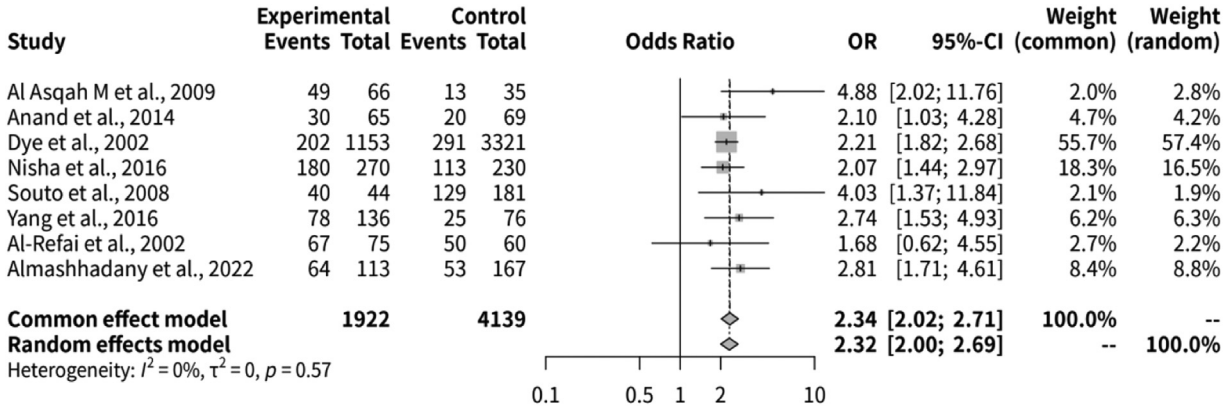

Fig. 2 – Forest plot of the meta-analysis on periodontal disease and *Helicobacter pylori* infection. The midpoint of the horizontal line represented the ratio (OR) of the number of Helicobacter pylori sero-positive patients with periodontitis to the number of patients with periodontitis alone, and the horizontal line represented its confidence interval. All OR in the figure were > 1, indicating that patients infected with H. pylori were likely to be susceptible to periodontitis.

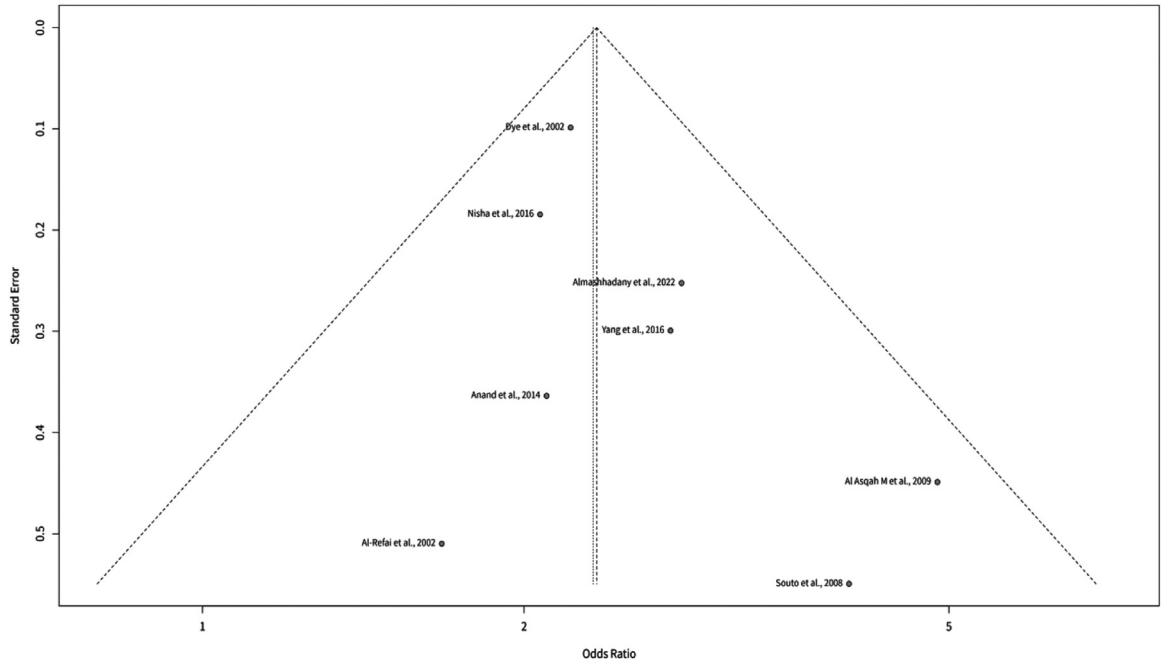

Fig. 3 – Funnel plot analysis of publication bias. The dots represented specific studies of the included literature. The horizontal axis represented the effect size, odds ratio (OR) of a single study. The vertical axis represented the standard error. The vertical bar represented the combined effect size and was an estimate of the total effect size for all studies. The two diagonal lines represented the 95% confidence interval (CI) of the combined effect size with different standard errors. The smaller the variation and the higher the accuracy, the dot would fall on the top of the inverted funnel.

The Baujat analysis shown as Figure 5 further complements this observation, with the study by Dye et al.,[9] located at the extreme upper left corner of the plot. This position indicates that this study has both high leverage and a substantial residual, signifying its significant contribution to the heterogeneity and overall influence in the meta-analysis. In contrast, Al Asqah M et al.,[8] is positioned on the far right of the plot, suggesting that while it has a strong influence, it does so with less heterogeneity compared to Dye et al.[9] The majority of the other studies are clustered in the lower-left corner of the Baujat plot, indicating lower leverage and residuals, meaning they contribute less individually to the heterogeneity and overall effect size in the meta-analysis. This clustering further underscores the distinct positions of Dye et al.,[9] and Al Asqah M et al.,[8] in the context of their respective impacts on the meta-analytic findings.

The meta-analysis results shown as Figure 6 provide subgroup-specific estimates of the OR, 95% CI, and associated statistics for different subgroups. The ORs range from 2.2117 to 4.0310, with corresponding 95% CIs indicating a moderate

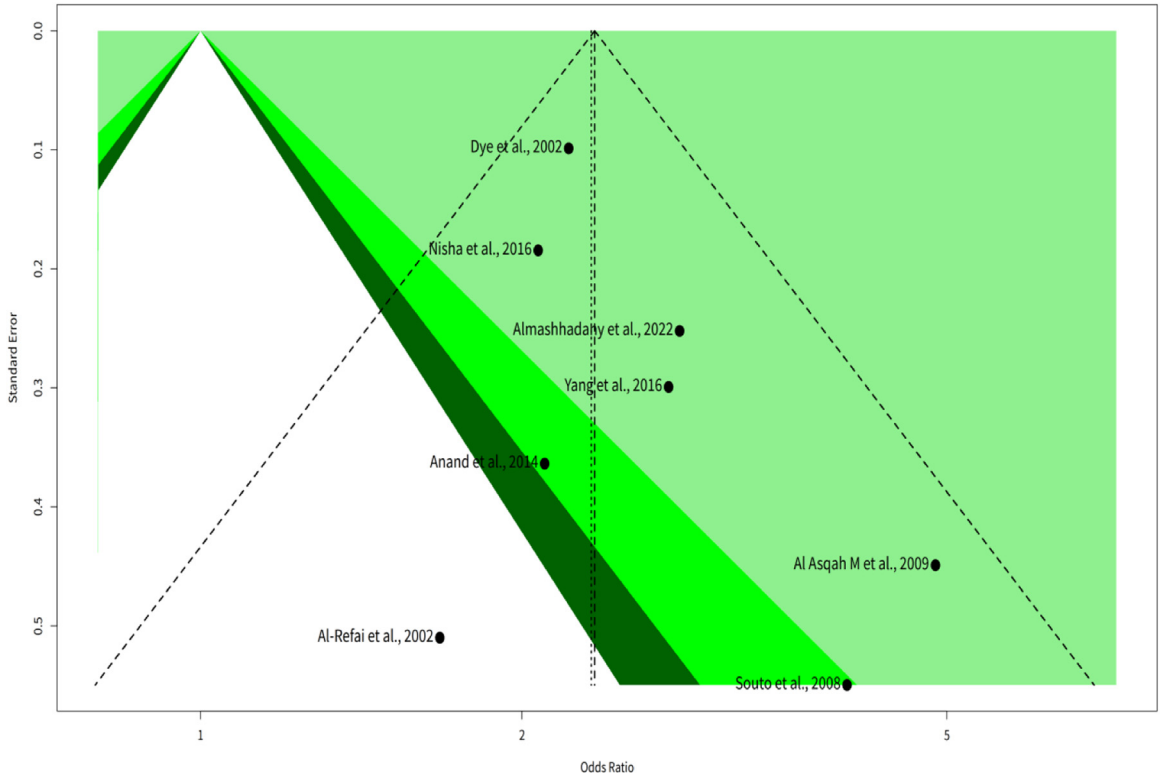

Fig. 4 – Trim and fill analysis adjusting for funnel plot asymmetry. This figure evaluated the effect of publication bias on the combined effect size by pruning and populating extreme or missing studies in the funnel plot. Pruning was the removal of extreme or low weight studies. Patch was to supplement the missing parts and estimate the number of missing studies by an iterative method.

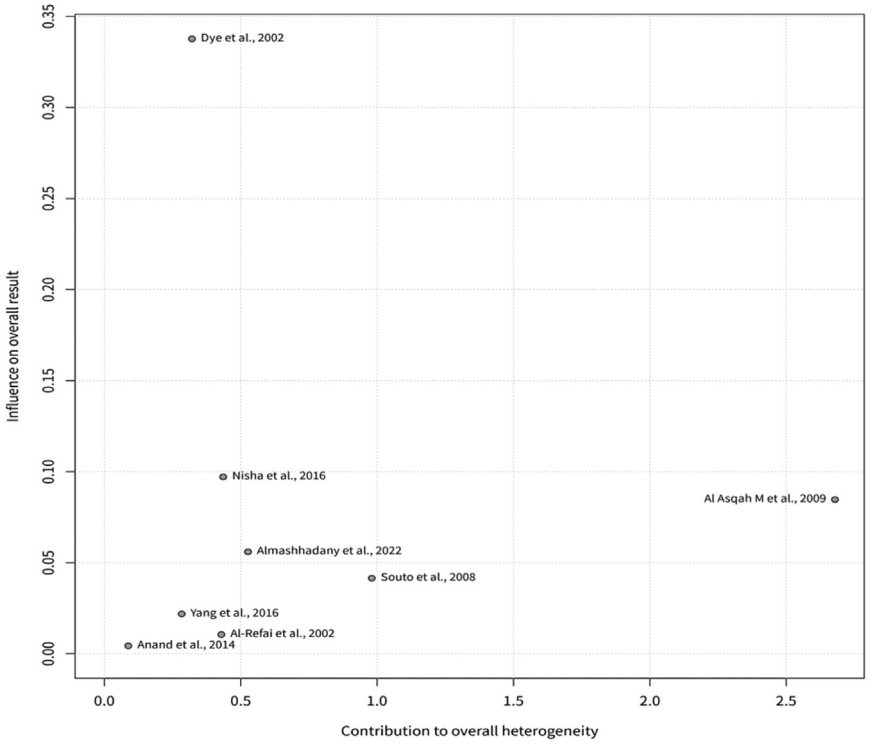

Fig. 5 – Baujat plot highlighting study influence and heterogeneity. The X-axis was the contribution of each subject to the overall heterogeneity, and the greater the value, the greater the heterogeneity. The Y-axis represented the squared variance with or without this study for the population standardization.

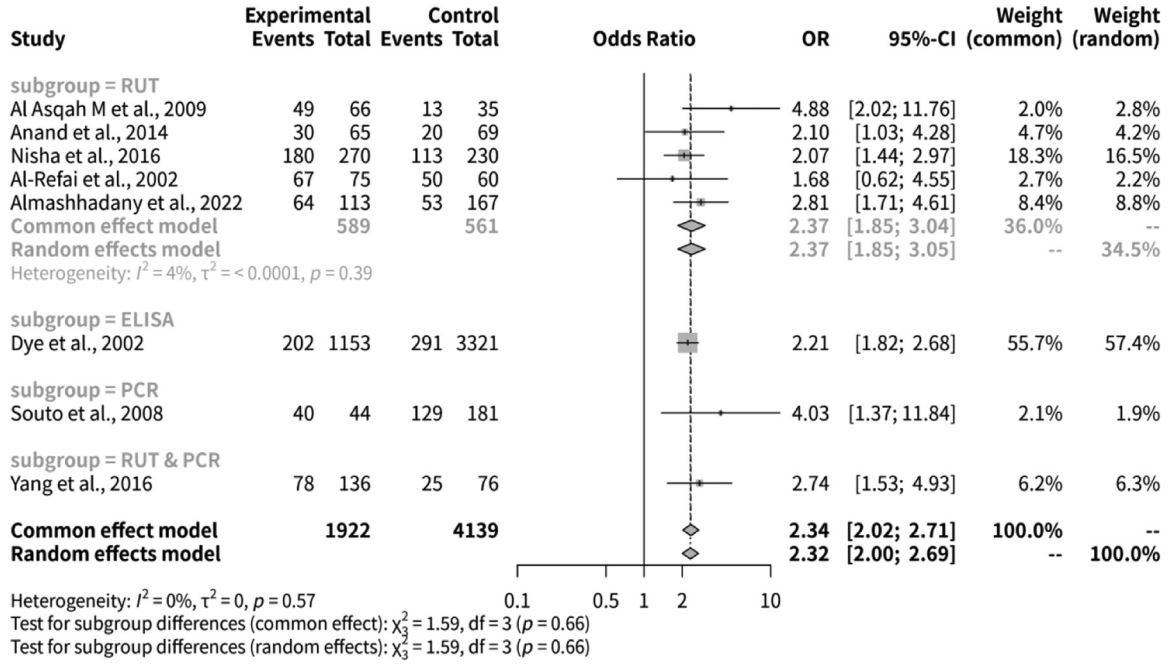

Fig. 6 – Subgroup analysis of the meta-analysis on periodontal disease and *Helicobacter pylori* infection based on Hp diagnostic method. The subgroup "RUT" had an OR of 2.3702 (95%-CI: 1.8474; 3.0409) with 5 studies and 3.6% I2 value. When combining the subgroups "RUT" and "PCR", the OR is 2.7434 (95%-CI: 1.5255; 4.9339). The test for subgroup differences showed that there are no significant differences between these subgroups (Q = 1.59, d.f. = 3, P-value = .6625), and the heterogeneity (Q = 5.73, d.f. = 7, P-value = .5710).

level of heterogeneity within each subgroup. The common effect model results show that the subgroup "RUT" has an OR of 2.3702 (95%-CI: 1.8474; 3.0409) with 5 studies and 3.6% I^2 value, indicating some heterogeneity. When combining the subgroups "RUT" and "PCR", the OR is 2.7434 (95%-CI: 1.5255; 4.9339). The test for subgroup differences shows that there are no significant differences between these subgroups (Q = 1.59, d.f. = 3, P-value = .6625). The I2 value, which measures the percentage of total variation across studies that is due to heterogeneity rather than chance, ranged from 0% to 67.6%. The test for heterogeneity (Q = 5.73, d.f. = 7, P-value = .5710) suggests that there is little to no heterogeneity among the studies.

Meta analysis on chronic atrophic gastritis and Hp infection

This meta-analysis shown as Figure 7 examines the association between chronic atrophic gastritis and *Helicobacter pylori* infection, pooling data from four studies with a total of 7654 observations. Two meta-analytical models were used: the fixed effects model and the random effects model. The heterogeneity between studies was evaluated using the I-squared statistic, which indicates a moderate level of inconsistency (55.6%, with a tau^2 value of 0.1532), suggesting that the random effects model is more suitable for this analysis. The results from both models show a significant association between chronic atrophic gastritis and Hp infection, with OR ranging from 4.6798 to 4.8543, and P-values < .0001 in both cases. Further tests of heterogeneity using the Q-statistic also support this conclusion, although the P-value is marginally significant (P = .0801). The meta-analytical method used includes the Mantel-Haenszel method for estimating the OR, inverse variance weighting, restricted maximum-likelihood estimation for tau^2, and a continuity correction of 0.5 to handle studies with zero cell frequencies. The funnel plot depicted in Supplementary Figure 4 exhibits an inverted funnel appearance, which is indicative of the relationship between study size and effect size in meta-analysis. This symmetrical, upside-down funnel pattern suggests that there is no apparent bias in the studies included in the analysis.

Discussion

Hp has been extensively studied for its role in the development of various gastric conditions, particularly chronic atrophic gastritis. The current research further reinforces the association between Hp infection and an increased risk of chronic atrophic gastritis. Studies have consistently demonstrated the pathogenic mechanisms by which Hp contributes to gastric mucosal damage and the progression to atrophic gastritis. For instance, Zhao et al.,[20] found that Hp infection significantly alters the composition and function of the gastric microbiota, which may contribute to the pathogenesis of non-atrophic and atrophic gastritis. Furthermore, Xie et al.,[21] revealed that Hp-induced expression of angiopoietin-like 4 facilitates bacterial colonization and exacerbates gastritis, highlighting a key factor in the progression of chronic atrophic conditions. This aligns with the findings of Wei et al.,[22] who demonstrated that Hp disrupts gastric mucosal

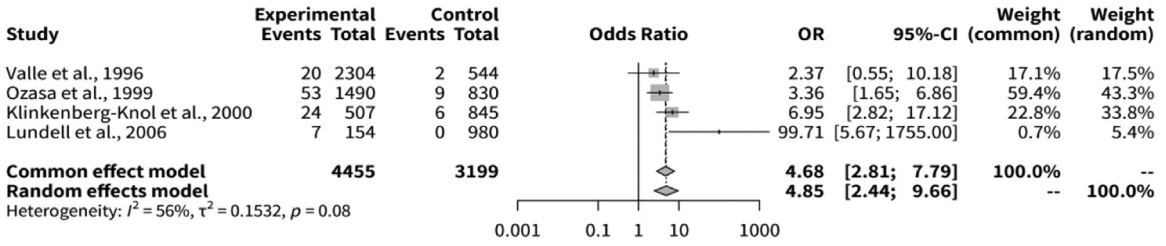

Fig. 7 – Forest plot of the meta-analysis on chronic atrophic gastritis and *Helicobacter pylori* infection. The association between chronic atrophic gastritis and helicobacter pylori infection indicated a moderate level of inconsistency (55.6%, with a tau2 value of 0.1532) with OR ranging from 4.6798 to 4.8543, and *P*-values <.0001 in both cases. The *P*-value of further tests of heterogeneity using the Q-statistic was *P* = .0801.

homeostasis by stimulating macrophages to secrete CCL3, further elucidating its role in the pathogenesis of atrophic changes in the gastric mucosa. Kishikawa et al.,[23] provided additional clinical insights by identifying specific characteristics of patients with Hp-induced atrophic gastritis, underscoring the significant impact of the infection on gastric health. Collectively, these studies reinforce the critical link between Hp infection and the development of chronic atrophic gastritis, emphasizing the need for targeted interventions to mitigate this risk. Our study's findings contribute to this body of evidence by confirming that Hp infection markedly increases the risk of chronic atrophic gastritis.

The association between Hp infection and periodontitis has been increasingly recognized in recent studies, emphasizing the potential bidirectional relationship between oral and gastric health. Zhang et al.,[24] discussed the presence of Hp in the oral cavity, highlighting its potential survival strategies that may contribute to oral diseases like periodontitis. This aligns with the findings of Sekar et al.,[25] who quantified Hp and its oncoproteins in the oral cavity, demonstrating a significant presence of the bacterium in individuals with periodontitis.

Further supporting this connection, Sung et al.,[26] reported a correlation between periodontitis, Hp infection, and gastrointestinal tract cancer mortality, suggesting that the oral presence of Hp could influence systemic health outcomes. Additionally, Li et al.,[27] conducted a population-based study in Taiwan that revealed a higher risk of gastric Hp infection in patients with periodontitis, underscoring the interrelationship between these conditions.

Our meta-analysis consolidates these findings, demonstrating that individuals with Hp infection have a significantly increased risk of developing periodontitis. The pooled data from 8 studies showed a consistent association, with both the fixed effects and random effects models yielding similar odds ratios. This analysis provides robust evidence that highlights the importance of addressing Hp infection not only as a gastric pathogen but also as a contributor to periodontal disease.

While our meta-analysis provides significant insights into the association between Hp infection and the increased risk of periodontitis, several limitations must be acknowledged. First, the studies included in the meta-analysis exhibit some degree of heterogeneity, particularly in terms of population characteristics, diagnostic methods for Hp infection, and definitions of periodontitis. Although we employed both fixed effects and random effects models to account for this heterogeneity, it remains a potential source of bias. Second, the observational nature of the included studies limits the ability to establish causality. Confounding factors, such as variations in oral hygiene practices, dietary habits, and other socioeconomic determinants, may also have influenced the observed associations. Additionally, publication bias cannot be entirely ruled out, despite the results of the funnel plot, Begg's, and Egger's tests suggesting no substantial evidence of bias. Finally, the meta-analysis relies on the accuracy of the primary studies' data, and any misclassification of Hp status or periodontitis could affect the overall findings.

Conclusion

In conclusion, this meta-analysis reinforces the significant association between *Helicobacter pylori* infection and an increased risk of both chronic atrophic gastritis and periodontitis. Our findings highlight the dual role of Hp as a key pathogen in gastric as well as oral diseases, underscoring the interconnectedness of oral and systemic health. The consistent association observed across multiple studies emphasizes the need for comprehensive management strategies that address Hp infection not only to prevent or mitigate gastric conditions like chronic atrophic gastritis but also to reduce the risk of periodontitis. With the continuous enrichment of statistical methods of data in the future, the assessment of bias risk of meta-analysis will become more and more detailed, and the statistics of the results of this study will be clearer. At the same time, the classification statistics and data processing of different influencing factors will become more and more detailed. Future research should focus on longitudinal studies with standardized diagnostic criteria to further elucidate the causal pathways linking Hp infection to these conditions and to explore potential therapeutic interventions.

Conflict of interest

None disclosed.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics statement

The study was approved by the Peking University Health Science Center (BJ-HD-020).

Consent for publication

All authors have agreed to publish.

Consent to participate

Written consent to participate.

Author contributions statement

QHL and YZ were involved in the conception and design, or analysis and interpretation of the data; FXQ the drafting of the paper, revising it critically for intellectual content; YZ the final approval of the version to be published; and that all authors agree to be accountable for all aspects of the work.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.identj.2024.12.027.

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