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META-ANALYSIS

Xu et al: LPR and CRS in adults

Association of laryngopharyngeal reflux with chronic rhinosinusitis prevalence in adults: A systematic review and meta-analysis

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ABSTRACT

Laryngopharyngeal reflux (LPR) has been implicated in the pathogenesis of chronic rhinosinusitis (CRS), but the evidence from individual studies remains inconsistent. This meta-analysis aims to clarify the association between LPR and CRS in adults. We systematically searched PubMed, Embase, Web of Science, CNKI, and Wanfang for observational studies that evaluate the relationship between LPR and CRS in adult populations. Heterogeneity among studies was assessed using the Cochrane Q test and the I^2 statistic. Odds ratios (ORs) and 95% confidence intervals (CIs) were pooled using a random-effects model to account for heterogeneity. A total of eight cross-sectional studies involving 3,456 participants were included in the analysis. The results indicated a significant association between LPR and a higher prevalence of CRS in adults (OR = 4.77, 95% CI 2.51 to 9.07; $p < 0.001$; $I^2 = 63\%$). Sensitivity analysis restricted to high-quality studies (Newcastle-Ottawa Scale score ≥ 7) produced similar results with no observed heterogeneity (OR = 5.98, 95% CI 3.60 to 9.92; $I^2 = 0\%$). Exploratory subgroup analyses suggested a stronger association in studies with smaller sample sizes and when both LPR and CRS were diagnosed using objective methods. No significant evidence of publication bias was detected through Egger's test ($p = 0.35$); however, this analysis was underpowered and should be interpreted cautiously in the context of the small-study effect. In conclusion, LPR may be associated with an increased prevalence of CRS in adults, especially when both conditions are diagnosed using objective criteria. Further prospective studies are needed to confirm this association and explore the underlying mechanisms.

Keywords: Laryngopharyngeal reflux, chronic rhinosinusitis, association, meta-analysis.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common and often debilitating inflammatory disorder of the nasal and paranasal sinuses that persists for at least 12 weeks (1-3). It affects approximately 5–15% of the adult population worldwide and imposes a substantial burden on quality of life, daily functioning, and health care costs (4, 5). Patients experience persistent nasal obstruction, rhinorrhea, facial pain or pressure, and impaired olfaction, which collectively reduce productivity and well-being (1). Although established risk factors for CRS include allergic rhinitis, asthma, smoking, occupational exposures, and anatomical variations, the precise etiology remains incompletely understood in many cases (6). Identifying additional and potentially modifiable factors related to CRS is therefore crucial for improving prevention, early detection, and treatment outcomes.

Laryngopharyngeal reflux (LPR) refers to the retrograde flow of gastric or duodenal contents into the larynx, pharynx, and upper airway structures (7). Unlike typical gastroesophageal reflux disease (GERD), LPR often occurs in the upright position and may present without heartburn or regurgitation (8). LPR can be diagnosed by symptom-based tools such as the reflux symptom index (RSI), endoscopic findings including the reflux finding score (RFS), or objective methods such as 24-hour pH or impedance–pH monitoring and detection of pepsin in upper airway secretions (9, 10). The prevalence of LPR in adults is estimated to range between 10% and 30%, depending on the diagnostic approach and population studied (11). Biologically, refluxed gastric acid, pepsin, and bile salts may injure sinonasal mucosa, disrupt mucociliary clearance, and promote chronic inflammation, which may contribute to the development or persistence of CRS (12, 13). Over the past two decades, several observational studies have investigated the relationship between LPR and CRS, but their findings have been inconsistent, likely due to variations in study design, populations, diagnostic methods, and analytic adjustments (14-21). To address these uncertainties, we performed a systematic review and meta-analysis of observational studies to quantitatively assess the association between LPR and CRS in adults and to explore potential sources of heterogeneity across studies.

MATERIAL AND METHODS

This study followed the PRISMA 2020 (22, 23) and Cochrane Handbook guidelines (24) for conducting systematic reviews and meta-analyses, covering study design, data collection, statistical methods, and interpretation of results. The protocol of the meta-analysis has been registered at PROSPERO with the identifier: CRD420251156445.

Database search

To identify studies pertinent to this meta-analysis, we searched PubMed, Embase, Web of Science, Wanfang, and China National Knowledge Infrastructure (CNKI) databases using an extensive array of search terms, which involved the combined terms of (1) "laryngopharyngeal reflux" OR "LPR" OR "gastro-pharyngeal reflux" OR "gastropharyngeal reflux" OR "GPR" OR "extraesophageal reflux" OR "extra-oesophageal reflux" OR "supraesophageal reflux"; and (2) "chronic rhinosinusitis" OR "chronic sinusitis" OR "sinusitis" OR "CRS". The search was restricted to studies on human subjects and included only full-length articles published in English or Chinese in peer-reviewed journals. We also manually checked the references of related original and review articles to find additional relevant studies. The search covered all records from database inception up to August 12, 2025. The full search strategy for each database is shown in **Supplemental File 1**. Grey-literature sources were not included because they rarely provide standardized diagnostic definitions for LPR or CRS or sufficient extractable data, and they often did not undergo peer-review. Including grey literature could reduce methodological consistency and affect the reliability of the results.

Study eligible criteria

We applied the PICOS framework to define the inclusion criteria:

P (patients): Adults (≥18 years) from any clinical or community setting.

I (exposure): LPR diagnosed according to the criteria used among the original studies, using recognized symptoms, clinical, endoscopic, or instrumental methods.

C (comparison): Participants without LPR.

O (outcome): Prevalence of CRS in participants with LPR compared with those without LPR. The diagnosis of CRS was also consistent with the criteria used in the original studies.

S (study design): Observational studies, including cohort studies, case-control studies, and cross-sectional studies that report comparative data between LPR and non-LPR groups.

We excluded studies conducted exclusively in children (< 18 years), those including only patients with LPR or only patients with CRS, interventional RCTs without data on the LPR–CRS association, reviews, meta-analyses, case series, case reports, editorials, studies lacking clear definitions of LPR or CRS, reports without a comparison group or with insufficient data to estimate or convert effect measures to data of outcome, duplicate or overlapping cohorts (retaining only the most comprehensive or recent report), and laboratory, animal, or in-vitro studies.

Study quality evaluation

Two authors independently performed the literature search, study selection, quality assessment, and data extraction. Disagreements were resolved by discussion with the corresponding author. Study quality was assessed using a modified version of the Newcastle–Ottawa Scale (NOS) adapted for cross-sectional studies (25), as applied in prior meta-analyses (26, 27). The rubric covered selection (4 items), comparability (2 items), and outcome (3 items), with a maximum of 9 points. Details of the specific items and scoring criteria are provided in **Supplemental File 2**. Studies scoring ≥7 were considered high quality.

Data collection

The data collected for analysis included the study details (author, year, study country, and design), participant characteristics (sample size, mean age, and sex distribution), methods for the diagnosis of LPR and number of patients with LPR, methods for the diagnosis of CRS and number of patients with CRS, and covariates adjusted when the association LPR and CRS was analyzed.

Statistical analysis

The association between LPR and the prevalence of CRS in adults was summarized as odds ratio (OR) and corresponding 95% confidence interval (CI) (24). ORs and

standard errors were directly extracted or calculated from 95% CIs or p values, then log-transformed to stabilize variance and normalize the data (24). If multiple ORs were reported from different models, we used the one with the most complete adjustment. Heterogeneity was assessed using the Cochrane Q test and I^2 statistic (28), with a *p* value < 0.10 suggesting significant heterogeneity and I^2 values of < 25%, 25–75%, and > 75% indicating low, moderate, and high heterogeneity. A random-effects model was used to pool the data, accounting for potential influence of heterogeneity between studies (24). The primary analyses applied the DerSimonian–Laird (DL) method. Given the small number of included studies (k = 8), we also fitted the restricted maximum likelihood (REML) random-effects model with Hartung–Knapp–Sidik–Jonkman adjustment (HKSJ) in a sensitivity analysis, which offers more reliable confidence intervals in small-sample meta-analyses (24). The REML–HKSJ estimate closely matched the DL result and was considered the more conservative uncertainty framework, with DL presented mainly for comparability with prior studies. Besides I^2, τ^2 and 95% prediction interval (PI) are also calculated (24). Sensitivity analyses were performed by removing one study at a time. For the primary outcome, predefined subgroup analyses were conducted based on the study country (Western vs. Asian countries), sample size of each study, mean ages, proportions of men, methods for the diagnosis of LPR (self-report based on symptoms vs. objectively evaluated), methods for the diagnosis of CRS (symptom only vs. with objective evidence), and analytic models (univariate vs. multivariate). Publication bias was assessed using funnel plots and visual inspection for asymmetry, along with Egger's test (29). All analyses were performed using RevMan (Version 5.3; Cochrane Collaboration, Oxford, UK) and Stata (Version 17.0; Stata Corporation, College Station, TX, USA).

RESULTS

Study inclusion

The study selection process is shown in **Figure 1**. We first identified 451 records from the five databases. After removing 121 duplicates, 330 articles were screened by title and abstract. Of these, 309 were excluded for not meeting the aims of the meta-analysis. The full texts of the remaining 21 articles were reviewed by two independent authors, and 13 were excluded for various reasons as outlined in **Figure 1**. In the end, eight studies were included in the quantitative analysis (14-21).

Summary of study characteristics

Table 1 summarizes the characteristics of the eight studies included in this meta-analysis. All studies employed a cross-sectional design and were published between 1999 and 2025, conducted across the United States, Germany, China, and Sweden. The study populations varied and included otolaryngology patients with or without CRS, community-dwelling adults, and random population samples. The total sample size ranged from 40 to 1,878 participants per study, with a total of 3,456 patients included in the meta-analysis. The mean age of participants, where reported, ranged from 36.9 to 58.0 years, and the proportion of men ranged from 40.0% to 58.7%. LPR was diagnosed by diverse methods, including 24-hour triple-sensor pH monitoring (14-16), self-reported symptoms (17, 20), pepsin detection in nasal secretions or tissues combined with RSI (18, 19), and RSI/RFS criteria (21). CRS was identified using European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guideline-based definitions (19-21) or clinical history plus CT or revision surgery confirmation (14-16, 18), while the study by Pasic 2007 used symptom-based self-report (17). Most studies provided unadjusted data, with only one study (20) reporting adjusted estimates for potential confounders such as age, sex, BMI, educational level, smoking, and asthma. Study quality was assessed using the NOS (**Table 2**). NOS total scores ranged from 6 to 8, indicating moderate to high methodological quality. Most studies scored well on selection and comparability domains but lacked adjustment for confounders other than age and sex (14-19, 21).

Association between LPR and CRS

The pooled results of eight studies (14-21) showed that overall, LPR was significantly associated with a higher prevalence of CRS in adults (OR: 4.77, 95% CI: 2.51 to 9.07, $p < 0.001$; **Figure 2A**) with moderate heterogeneity (p for Cochrane Q test = 0.009, $I^2 = 63\%$, $\tau^2 = 0.43$, 95% PI: 1.13 to 20.07). In addition, the sensitivity analysis using REML random-effects model with Hartung–Knapp adjustment showed consistent results (OR: 4.59, 95% CI: 2.44 to 8.65, $p < 0.001$; $I^2 = 55.6\%$; **Supplemental Figure 1**). Sensitivity analyses were performed by removing one dataset at a time, and the results remained stable (OR: 4.11 to 5.98, p all < 0.05). Specifically, sensitivity analysis limited to studies of high quality (NOS ≥ 7) showed consistent results but no significant heterogeneity (OR: 5.98, 95% CI: 3.60 to 9.92, $p < 0.001$; $I^2 = 0\%$, **Figure 2B**). Subgroup analyses indicated that the results were consistent in studies from

Western and Asian countries (OR: 3.96 vs. 6.40, *p* for subgroup difference = 0.39; **Figure 3A**). Subgroup analysis according to sample size showed that studies with <100 participants reported a markedly larger association (OR: 10.16) than those with ≥100 participants (OR: 2.82), with a significant subgroup difference (p = 0.009), suggesting the possibility of small-study effects (**Figure 3B**).The association was not significantly different between patients with mean age < or ≥ 45 years (OR: 7.03 vs. 3.34, *p* for subgroup difference = 0.16; **Figure 4A**), or of the proportion of men < or ≥ 53% (OR: 4.84 vs. 5.01, *p* for subgroup difference = 0.96; **Figure 4B**). A stronger association between LPR and CRS was observed in studies with LPR diagnosed involving objective evaluation as compared to those with self-reported symptoms only (OR: 6.25 vs. 2.33, *p* for subgroup difference = 0.01; **Figure 5A**), and in studies with CRS diagnosed involving objective evidence as compared to those based on symptoms only (OR: 5.98 vs. 2.07, *p* for subgroup difference < 0.001; **Figure 5B**). The association was not significantly different between studies with univariate and multivariate analysis (OR: 4.90 vs. 4.60, *p* for subgroup difference = 0.94; **Figure 5C**).

Publication bias

Funnel plots did not show clear asymmetry, and Egger's test did not detect statistical evidence of small-study effects (p = 0.35; **Figure 6**). However, because only eight studies were included, both visual inspection and Egger's regression have low statistical power, and the absence of detected asymmetry should be interpreted with caution

DISCUSSION

This meta-analysis provides the most up-to-date quantitative synthesis of the association between LPR and CRS in adults. By pooling data from eight observational studies including 3,456 participants, we demonstrated that LPR is associated with a markedly increased prevalence of CRS. This relationship persisted in sensitivity analyses restricted to high-quality studies and across most subgroups, highlighting the robustness of the finding. Importantly, the strength of the association was greater when both LPR and CRS were diagnosed using objective criteria, suggesting that methodological rigor and adequate power enhance the reliability of observed associations.

Two recent field-level contributions help contextualize the present findings. First, a 2024 systematic review and meta-analysis by Aldajani et al. (30) examined a broad construct of 'reflux diseases,' pooling studies of both GERD and LPR together and reporting a significant overall association with CRS, as well as higher pH values and greater pepsin detection among CRS patients. Their work suggested that reflux—when defined broadly—may be relevant to CRS pathophysiology, but the heterogeneous exposure definitions (GERD, LPR, or combinations), variability in diagnostic tools, and inclusion of therapeutic studies limited the ability to isolate the specific contribution of LPR (30). Second, a Mendelian-randomization analysis by Chen et al. (2024) showed that genetically predicted GERD increases the risk of CRS, supporting a potential causal role for esophageal reflux disease in CRS (31). However, MR instruments for LPR do not currently exist, and GERD and LPR are biologically related yet clinically distinct phenotypes (31). Against this background, the present study provides a focused synthesis restricted to LPR, using standardized prevalence-odds estimates and objective CRS definitions. By isolating LPR as the exposure of interest, our analysis helps clarify its specific association with CRS beyond GERD-based evidence and broader reflux constructs.

The mechanisms by which LPR may contribute to the pathogenesis of CRS are biologically plausible and supported by experimental and clinical evidence (32). Refluxed gastric contents, particularly acid, pepsin, and bile salts, can reach the nasopharynx and paranasal sinuses (7, 33). These agents have been shown to disrupt epithelial barrier integrity, impair mucociliary clearance, induce pro-inflammatory cytokine production, and activate immune pathways in sinonasal mucosa (34, 35). Pepsin, in particular, remains enzymatically active even at neutral pH and has been detected in nasal secretions and mucosal tissues of CRS patients with LPR, suggesting ongoing mucosal injury (36). Furthermore, reflux-induced edema and inflammation may alter sinonasal drainage pathways, promoting chronic stasis and susceptibility to infection (37). Although the cross-sectional nature of most included studies limits the ability to confirm causality, these pathophysiological links provide a coherent explanation for the observed association.

The subgroup analyses provide additional insights into the potential impact of study characteristics on the observed relationship. The finding that objective diagnostic methods for LPR, such as pH monitoring or pepsin detection, were associated with higher effect estimates compared with symptom-based diagnosis underscores the

importance of accurate exposure measurement. Symptom-based assessments of LPR can be subjective and prone to misclassification, which may bias associations toward the null. Similarly, the stronger association in studies that diagnosed CRS with objective evidence, such as endoscopy or computed tomography, compared with symptom-only diagnosis, highlights that rigorous case definition enhances the ability to detect true relationships. These observations suggest that future research should adopt standardized, validated, and objective diagnostic criteria for both LPR and CRS to minimize heterogeneity and improve comparability across studies. Interestingly, studies with smaller sample sizes (< 100) yielded much larger effect estimates than larger studies. Rather than reflecting greater stability, this pattern is more consistent with potential small-study effects—where smaller studies with more variable methodology or selective reporting tend to show exaggerated associations. This underscores the need for cautious interpretation and highlights the importance of adequately powered studies in future research. The lack of significant differences in the association across subgroups defined by mean participant age, sex distribution, or adjustment for confounders suggests that the relationship between LPR and CRS may be relatively consistent across demographic strata and is not entirely explained by basic confounding factors such as age and sex. However, residual confounding by other variables, including allergic sensitization, smoking, or comorbid conditions such as asthma and gastroesophageal reflux disease, cannot be excluded. Most included studies were cross-sectional and unadjusted or adjusted for only a limited set of covariates, which restricts the ability to account for these factors. This limitation should be taken into consideration when interpreting the results. The sensitivity analysis restricted to studies with higher methodological quality (NOS ≥ 7) not only confirmed the overall finding but also eliminated between-study heterogeneity, strengthening confidence in the association. This suggests that some of the heterogeneity observed in the main analysis likely originated from methodological differences such as diagnostic definitions, participant selection, and control of confounding. These findings highlight the importance of rigorous study design and reporting in future research to enhance evidence quality.

The present meta-analysis has several notable strengths. First, it represents the most comprehensive and updated synthesis of the literature, including studies from both Western and Asian countries and incorporating recent research up to 2025. Second, we applied a prespecified protocol and followed PRISMA 2020 and Cochrane

guidelines to ensure methodological transparency. To enhance robustness given the small number of studies, we supplemented the DerSimonian–Laird analysis with an REML–HKSJ model, which produced effect estimates with overlapping confidence intervals and thus supported the stability of the primary findings. However, the wide prediction interval underscores uncertainty regarding the magnitude of the association across different populations. In addition, because the number of eligible studies was limited, our multiple dichotomized subgroup analyses should be interpreted cautiously. A meta-regression would have been methodologically preferable but was not feasible due to the small number of studies and lack of individual participant data. Finally, multiple sensitivity and subgroup analyses were conducted, and the consistent direction of results across these analyses enhances the robustness of the findings.

Nevertheless, several limitations warrant cautious interpretation. The primary limitation is the cross-sectional design of all included studies, which precludes inference of temporal or causal relationships between LPR and CRS. It remains unclear whether LPR contributes to the initiation of CRS or whether CRS may itself exacerbate LPR through nasal obstruction and increased negative intrathoracic pressure (38). Prospective cohort studies or interventional studies targeting LPR would be valuable to clarify causality. Second, heterogeneity in diagnostic criteria for both LPR and CRS across studies may have introduced misclassification and affected effect estimates. Although subgroup analyses based on diagnostic methods shed light on this issue, the lack of uniform gold-standard definitions limits the comparability of existing studies. On the other hand, although differentiating CRS phenotypes (CRSwNP vs. CRSsNP) is clinically important, the majority of included studies did not provide separate effect estimates for these subgroups, preventing phenotype-specific meta-analysis. Future studies with consistent stratification are needed to clarify whether the association between LPR and CRS differs by polyp status. Third, most studies lacked comprehensive adjustment for potential confounders beyond age and sex, raising the possibility of residual confounding. Fourth, the relatively small number of available studies limited the power to explore more nuanced subgroup effects, such as the influence of comorbid allergic rhinitis, asthma, or gastroesophageal reflux disease. Moreover, data from longitudinal or intervention trials were not available, and as such, the clinical significance of reducing LPR for the prevention or management of CRS remains uncertain. Finally, although neither the funnel plot nor Egger's test indicated statistical evidence of publication bias, the

power of these methods is very limited when fewer than ten studies are available. Moreover, the pattern observed in the sample-size subgroup—where smaller studies reported larger effect estimates—suggests the possibility of small-study effects, which may arise from selective reporting, methodological variability, or chance. These considerations reinforce the need for cautious interpretation.

From a clinical perspective, these findings suggest that clinicians should be aware of the potential link between LPR and CRS, particularly in patients with persistent or refractory CRS. Because all included studies were cross-sectional, the pooled effect represents differences in the prevalence odds of CRS rather than incidence or risk. Therefore, the findings indicate an association, not a temporal or causal relationship. Furthermore, as almost all studies reported unadjusted ORs, the results should not be interpreted as independent of confounding factors. The observed associations may partly reflect shared risk factors or residual confounding. Future research should focus on prospective longitudinal studies to determine whether LPR precedes CRS onset and whether effective control of LPR reduces the risk or severity of CRS. Standardization of diagnostic definitions and use of objective methods for both LPR and CRS will be crucial to improve comparability and reduce heterogeneity. Additionally, mechanistic studies exploring the role of pepsin and other reflux components in sinonasal mucosal inflammation could provide further biological insights. Randomized controlled trials (RCTs) of anti-reflux interventions in patients with CRS who have objectively confirmed LPR would be particularly informative in establishing causality and assessing potential therapeutic benefits. For example, a clinical trial in 2018 by Anzić et al. demonstrated that 8 weeks of omeprazole 20 mg once daily significantly reduced both LPR and CRS symptom and endoscopic scores compared with placebo, although most patients had residual disease at the end of treatment (39). Future trials could build on this by testing higher or guideline-recommended PPI doses and longer treatment durations, evaluating combined medical and lifestyle anti-reflux interventions, or comparing pharmacologic therapy with alternatives such as alginate formulations or surgical reflux control. These studies should also use standardized CRS outcomes—such as validated symptom scores, endoscopic grading, and imaging-based assessments—and include long-term follow-up to determine whether controlling LPR reduces CRS recurrence, improves quality of life, and lessens the need for surgical management.

CONCLUSION

In summary, this meta-analysis suggests that adults with LPR have higher prevalence odds of CRS compared with those without LPR. Given the cross-sectional and predominantly unadjusted nature of the included evidence, the findings should be interpreted as associational rather than causal. Prospective, well-controlled studies are needed to determine temporality and clarify whether addressing LPR influences CRS outcomes.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included studies

Study	Country	Design	Participants characteristics	No. of participants	Mean age (years)	Men (%)	Methods for the diagnosis of LPR	No. of patients with LPR	Methods for the diagnosis of the CRS	No. of patients with CRS	Variables adjusted
Ulualp 1999	USA	CS	Patients with otolaryngologic symptoms and findings; and healthy controls	101	46.6	53.5	24-hour triple-sensor pH monitoring	43	Symptoms + CT staging + prior treatment failure	18	None
DelGaudio 2005	USA	CS	Adults with refractory CRS after ESS vs. controls (successful ESS and non-CRS)	68	47.6	47.1	24-hour triple-sensor pH monitoring (nasopharynx, UES, esophagus)	35	History of ESS + persistent symptoms + endoscopic inflammation (EPOS-like criteria)	38	None

Jecker 2006	Germany	CS	Patients with recurrent CRS after surgery and healthy volunteers	40	36.9	52.5	24-hour triple-sensor pH monitoring	13	History + CT + revision surgery confirmation	20	None
Pasic 2007	USA	CS	Community-dwelling adults (≥18 years) recruited from public venues (hospitals, expos, colleges)	1878	48.5	40.0	Symptom-based (self-reported LPR symptoms)	849	Symptom-based (self-reported nasal congestion/drainage, sinus pain, or medication use)	1333	None
Wang 2017	China	CS	49 CRS patients (23 CRSwNP, 26 CRSsNP) and 9 normal controls from	58	39.0	53.4	Pepsin A detection in nasal secretions/tissues (ELISA/Wes	35	EPOS 2012 criteria (symptoms + endoscopy + CT)	49	None

			otolaryngology department				tern blot) + RSI questionnaire				
Li 2017	China	CS	Patients undergoing nasal surgery: CRSwNP, CRSsNP, and controls with anatomical abnormalities	46	43.7	58.7	Pepsin detection in nasal tissue by immunohisto chemistry	25	Clinical diagnosis + CT (Lund-Mackay score) + pathological confirmation	35	None
Bergqvist 2023	Sweden	CS	Random population sample aged 50-64 years	1111	58.0	50.0	Self-reported LPR symptoms	109	EPOS criteria	58	Age, sex, BMI, educational level, smoking, and asthma
Shen 2025	China	CS	Hospitalized CRS patients and healthy	154	41.2	57.1	RSI >13 and/or RFS >7;	55	EPOS 2020 criteria	104	None

			volunteers from physical examination				pepsin >75 ng/ml in nasal secretion (ELISA)				

Abbreviations: CS: Cross-sectional study; ESS: Endoscopic sinus surgery; UES: Upper esophageal sphincter; CT: Computed tomography; EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps; CRS: Chronic rhinosinusitis; CRSwNP: Chronic rhinosinusitis with nasal polyps; CRSsNP: Chronic rhinosinusitis without nasal polyps; LPR: Laryngopharyngeal reflux; RSI: Reflux symptom index; RFS: Reflux finding score; ELISA: Enzyme-linked immunosorbent assay; BMI: Body mass index.

Table 2. Study quality evaluation via the Newcastle-Ottawa Scale

Studies	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for age and sex	Control for other confounders	Exposure ascertainment	Same methods for events ascertainment	Non-response rates	Total
Ulualp 1999	1	1	1	1	0	0	1	1	1	7
DelGaudio 2005	1	1	1	1	0	0	1	1	1	7
Jecker 2006	1	1	1	1	0	0	1	1	1	7
Pasic 2007	1	1	1	1	0	0	0	1	1	6
Wang 2017	1	1	1	1	0	0	1	1	1	7
Li 2017	1	1	1	1	0	0	1	1	1	7
Bergqvist 2023	1	1	1	1	1	1	0	1	1	8
Shen 2025	1	1	1	1	0	0	1	1	1	7

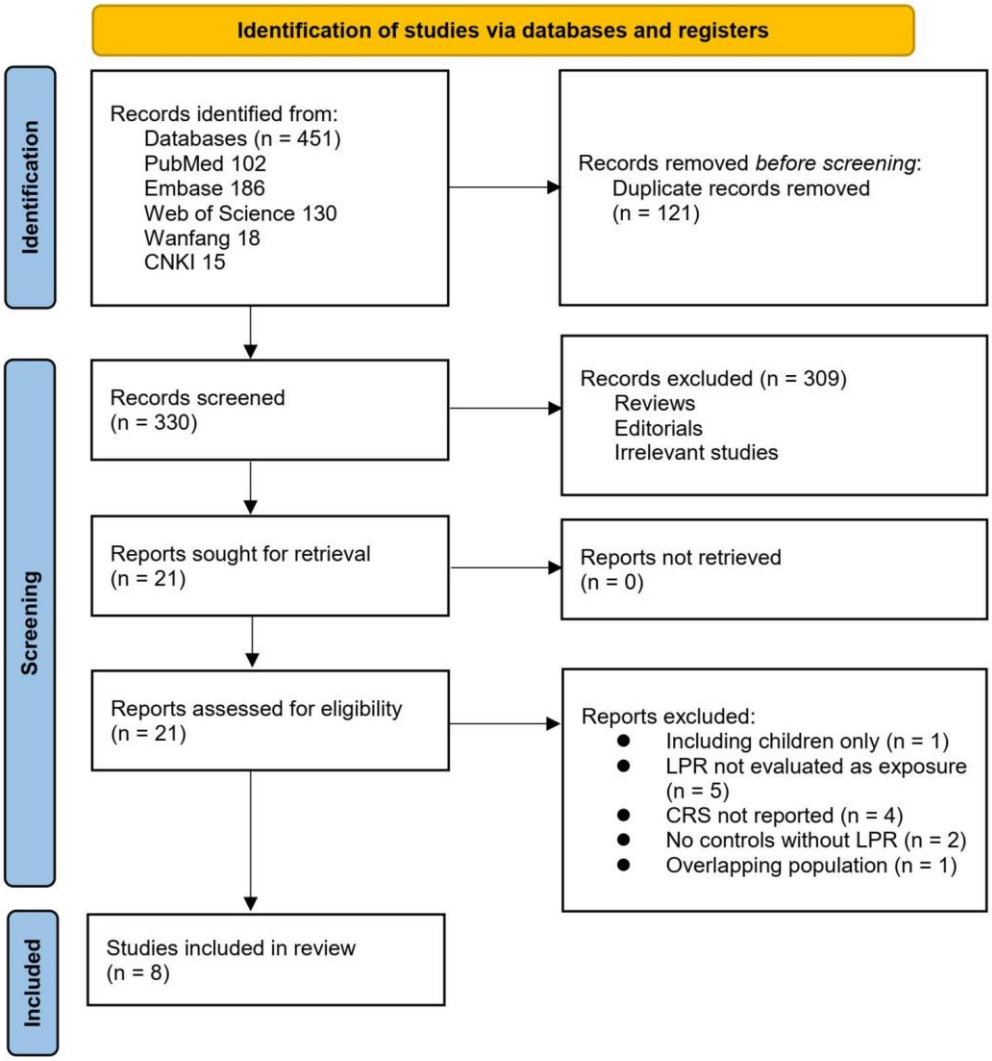


Figure 1. Flowchart of database search and study inclusion.

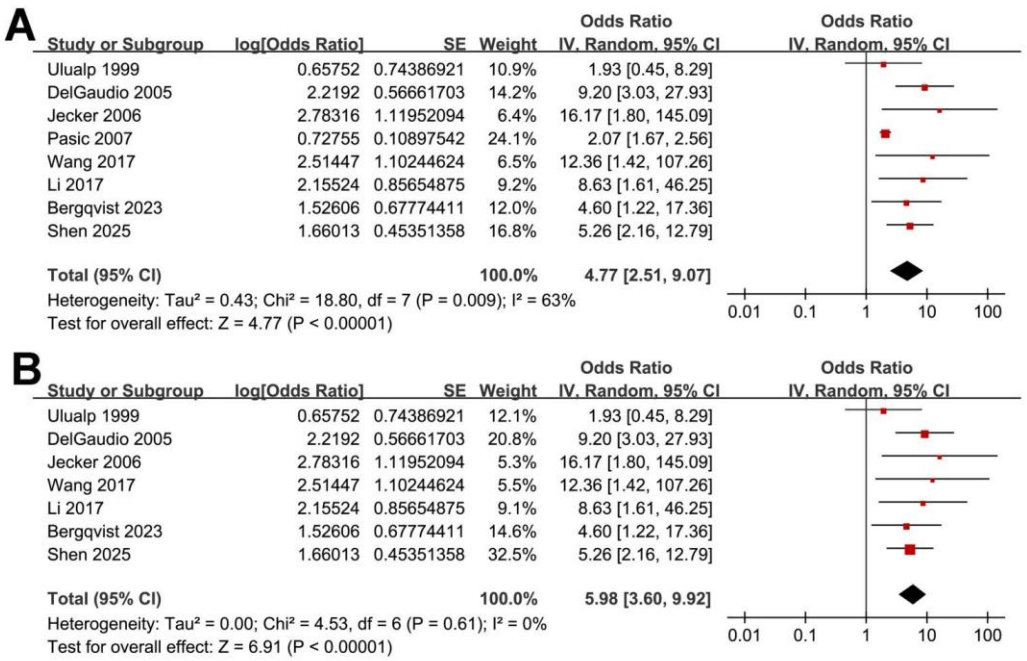


Figure 2. Association between LPR and CRS in adults—forest plots. (A) Primary random-effects meta-analysis including all eight eligible cross-sectional studies (total n = 3,456), showing a significant association between LPR and higher CRS prevalence (pooled OR = 4.77, 95% CI 2.51–9.07) with moderate between-study heterogeneity ($\tau^2 = 0.43$; $I^2 = 63\%$; Cochran Q $p = 0.009$). **(B)** Sensitivity analysis restricted to high-quality studies (modified Newcastle–Ottawa Scale [NOS] ≥ 7), yielding a comparable but more precise estimate (pooled OR = 5.98, 95% CI 3.60–9.92) and no detectable heterogeneity ($\tau^2 = 0.00$; $I^2 = 0\%$; Cochran Q $p = 0.61$). For each study, squares represent study-specific odds ratios (ORs) and are sized proportional to inverse-variance weight; horizontal lines indicate 95% confidence intervals (CIs). Diamonds denote pooled effects from an inverse-variance random-effects model (DerSimonian–Laird). The vertical line marks no association (OR = 1), and the x-axis is on a logarithmic scale (OR > 1 indicates higher CRS prevalence among participants with LPR). Abbreviations: LPR: Laryngopharyngeal reflux; CRS: Chronic rhinosinusitis; OR: Odds ratio; CI: Confidence interval; Q: Cochran's Q; NOS: Newcastle–Ottawa Scale.

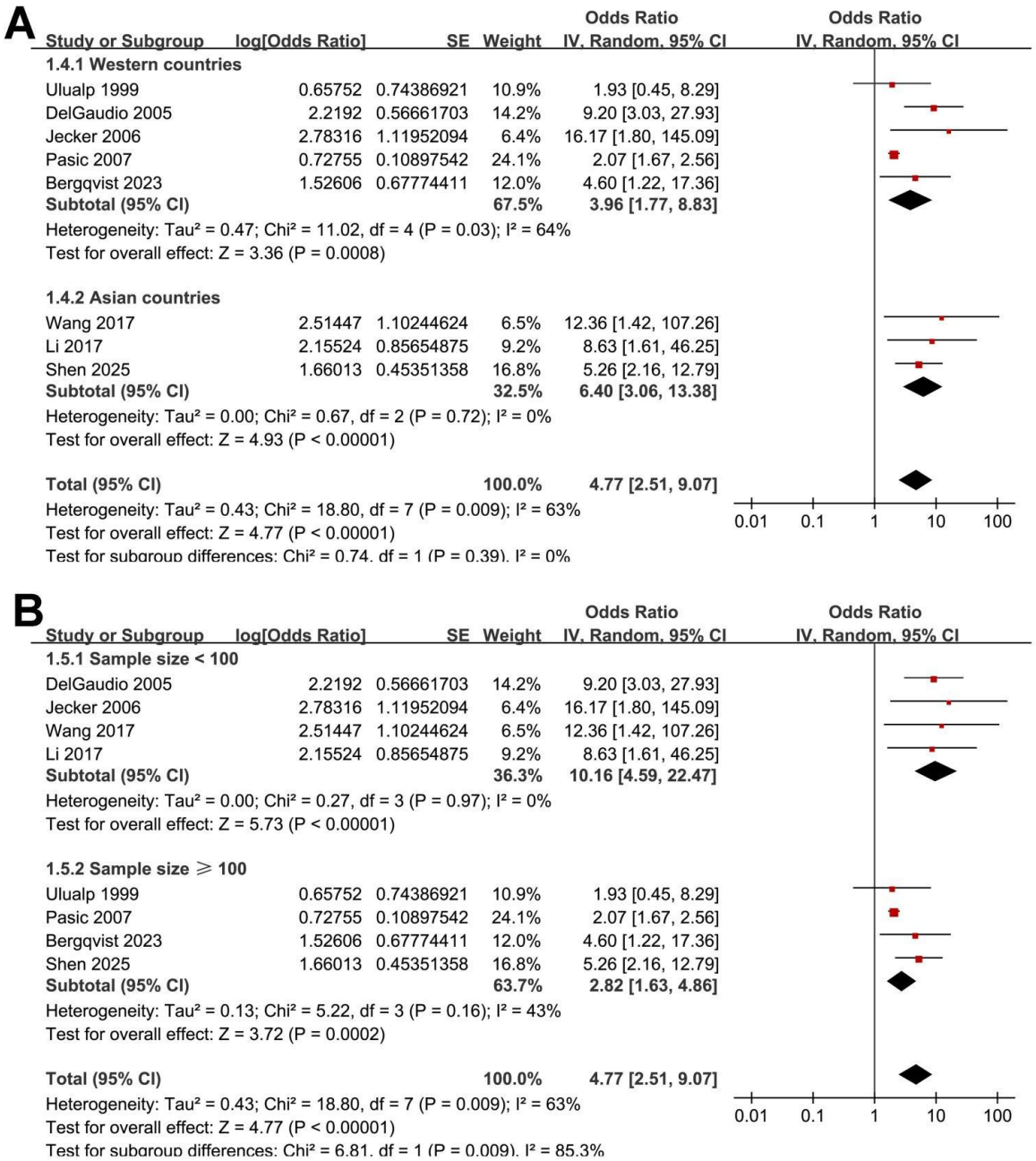


Figure 3. Subgroup forest plots for the association between LPR and CRS in adults. (A) Subgroup analysis by study region (Western vs Asian countries). Pooled odds ratios (ORs) were OR = 3.96 (95% CI 1.77–8.83) for Western studies and OR = 6.40 (95% CI 3.06–13.38) for Asian studies, with no statistically significant between-subgroup difference (test for subgroup differences $p = 0.39$). **(B)** Subgroup analysis by study sample size (<100 vs ≥100 participants). Smaller studies reported a larger pooled association (OR = 10.16, 95% CI 4.59–22.47) than larger studies (OR = 2.82, 95% CI 1.63–4.86), with a significant between-subgroup difference ($p = 0.009$),

consistent with possible small-study effects. Squares represent study-specific ORs (size proportional to inverse-variance weight) with horizontal lines indicating 95% confidence intervals; diamonds indicate pooled effects within each subgroup and overall. The vertical line denotes no association (OR = 1), and the x-axis is logarithmic. Abbreviations: LPR: laryngopharyngeal reflux; CRS: chronic rhinosinusitis; OR: odds ratio; CI: confidence interval.

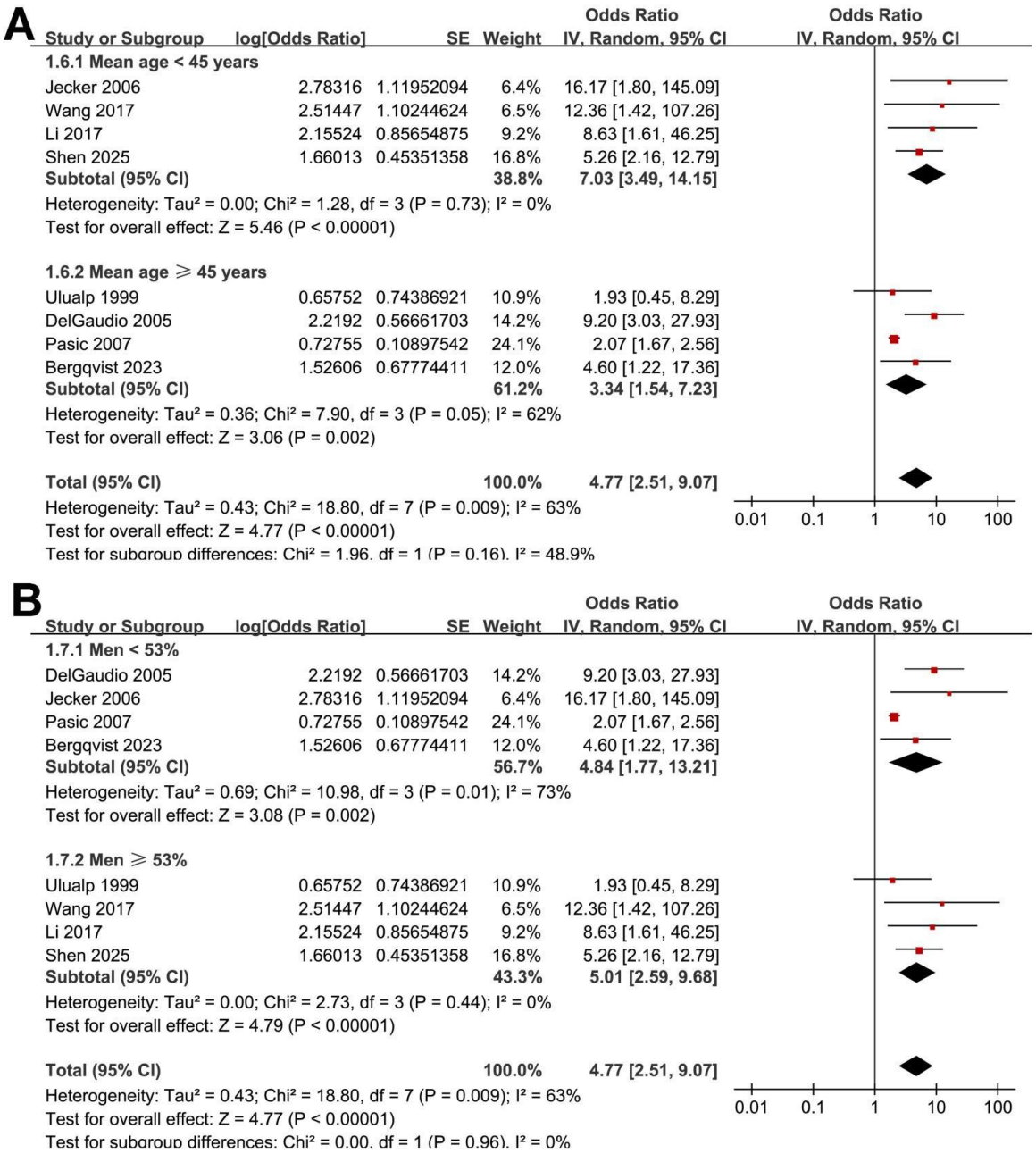


Figure 4. Subgroup forest plots for the association between LPR and CRS in adults. (A) Stratified by mean age (<45 vs ≥45 years): pooled OR = 7.03 (95% CI 3.49–14.15) vs 3.34 (95% CI 1.54–7.23); p for subgroup difference = 0.16. **(B)** Stratified by proportion of men (<53% vs ≥53%): pooled OR = 4.84 (95% CI 1.77–13.21) vs 5.01 (95% CI 2.59–9.68); p for subgroup difference = 0.96. Squares indicate study-specific ORs and diamonds pooled effects; x-axis is logarithmic with OR = 1 as the null. Abbreviations: LPR: laryngopharyngeal reflux; CRS: chronic rhinosinusitis; OR: odds ratio; CI: confidence interval.

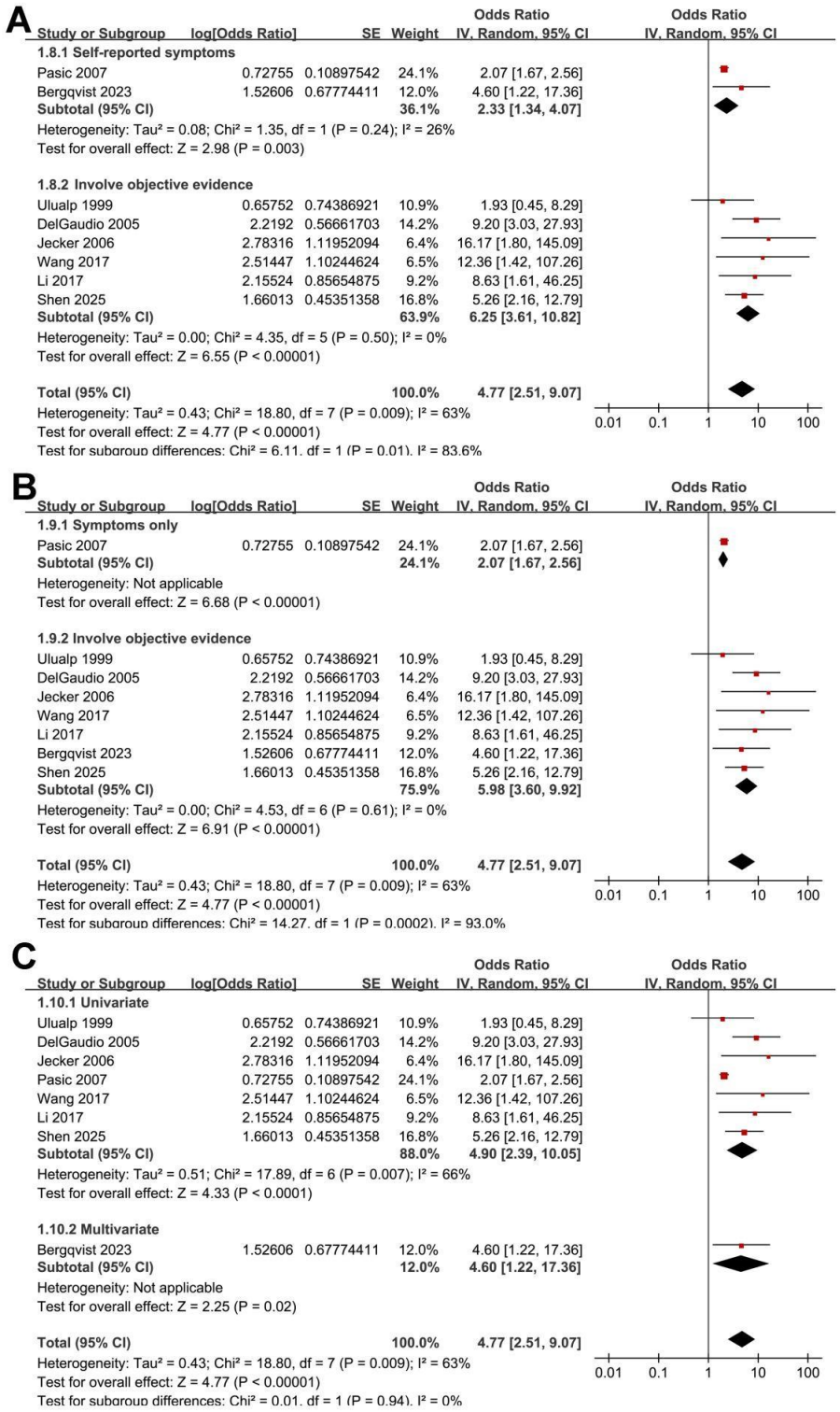


Figure 5. Subgroup forest plots for the association between LPR and CRS in adults by diagnostic approach and analysis model. (A) Stratified by LPR ascertainment: studies using self-reported symptoms vs studies using objective evaluation; pooled OR = 2.33 (95% CI 1.34–4.07) vs 6.25 (95% CI 3.61–10.82), *p* for subgroup difference = 0.01. **(B)** Stratified by CRS definition: symptoms only vs

objective evidence; pooled OR = 2.07 (95% CI 1.67–2.56) vs 5.98 (95% CI 3.60–9.92), *p* for subgroup difference < 0.001. **(C)** Stratified by analytic model: univariate vs multivariate estimates; pooled OR = 4.90 (95% CI 2.39–10.05) vs 4.60 (95% CI 1.22–17.36), p for subgroup difference = 0.94. Squares indicate study-specific ORs with 95% CIs; diamonds indicate pooled effects; the x-axis is logarithmic with OR = 1 as the null. Abbreviations: LPR: laryngopharyngeal reflux; CRS: chronic rhinosinusitis; OR: odds ratio; CI: confidence interval.

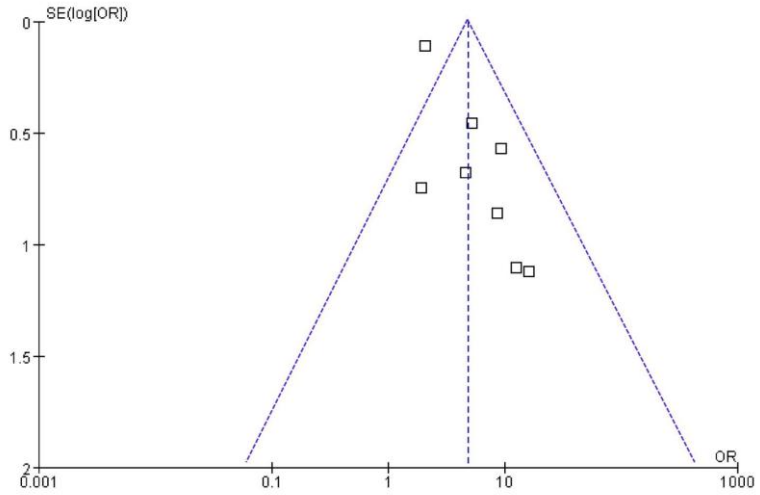


Figure 6. Funnel plot assessing publication bias and small-study effects in the meta-analysis of the association between LPR and CRS. The plot showed no clear asymmetry, and Egger's test did not detect small-study effects ($p = 0.35$). Because only eight studies were included, visual and statistical assessments are underpowered and should be interpreted cautiously. Abbreviations: LPR: laryngopharyngeal reflux; CRS: chronic rhinosinusitis.

SUPPLEMENTAL DATA

Supplemental file 1. Detailed search strategy for each database

PubMed

("Laryngopharyngeal Reflux"[Mesh] OR "laryngopharyngeal reflux"[tiab] OR "laryngo-pharyngeal reflux"[tiab] OR "laryngopharyngeal reflux disease"[tiab] OR LPR[tiab] OR "extraesophageal reflux"[tiab] OR "extra-oesophageal reflux"[tiab] OR "supraesophageal reflux"[tiab]) AND ("Sinusitis"[Mesh] OR rhinosinusitis[tiab] OR "chronic rhinosinusitis"[tiab] OR CRS[tiab] OR (sinusitis[tiab] AND chronic[tiab]))

Embase

('laryngopharyngeal reflux'/exp OR 'laryngopharyngeal reflux':ti,ab,kw OR 'laryngo-pharyngeal reflux':ti,ab,kw OR 'laryngopharyngeal reflux disease':ti,ab,kw OR LPR:ti,ab,kw OR 'extraesophageal reflux':ti,ab,kw OR 'extra-oesophageal reflux':ti,ab,kw OR 'supraesophageal reflux':ti,ab,kw) AND ('chronic rhinosinusitis'/exp OR 'rhinosinusitis'/exp OR 'sinusitis'/exp OR 'chronic rhinosinusitis':ti,ab,kw OR rhinosinusitis:ti,ab,kw OR CRS:ti,ab,kw OR (sinusitis:ti,ab,kw AND chronic:ti,ab,kw))

Web of Science

TS=("laryngopharyngeal reflux" OR "laryngo-pharyngeal reflux" OR "laryngopharyngeal reflux disease" OR LPR OR "extraesophageal reflux" OR "extra-oesophageal reflux" OR "supraesophageal reflux") AND TS=("chronic rhinosinusitis" OR rhinosinusitis OR CRS OR (sinusitis NEAR/3 chronic))

Wanfang

主题 = (“咽喉反流” OR “咽-喉反流” OR “咽喉反流病” OR LPR OR “食管外反流” OR “食管外返流” OR “上食管反流”) AND 主题 = (“慢性鼻窦炎” OR “慢性鼻-窦炎” OR “鼻-窦炎” OR “鼻窦炎” OR CRS OR (“鼻窦炎” AND “慢性”))

CNKI (China National Knowledge Infrastructure)

主题 = (“咽喉反流” OR “咽-喉反流” OR “咽喉反流病” OR LPR OR “食管外反流” OR “食管外返流” OR “上食管反流”) AND 主题 = (“慢性鼻窦炎” OR “慢性鼻-窦炎” OR “鼻-窦炎” OR “鼻窦炎” OR CRS OR (“鼻窦炎” AND “慢性”))

Supplemental file 2. Newcastle-Ottawa Scale adapted for cross-sectional studies

Selection: (Maximum 5 stars)

1) Representativeness of the sample:

a) Truly representative of the average in the target population. * (all subjects or random sampling)

b) Somewhat representative of the average in the target population. * (non- random sampling)

c) Selected group of users.

d) No description of the sampling strategy.

2) Sample size:

a) Justified and satisfactory. *

b) Not justified.

3) Non-respondents:

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *

b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.

c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor):

a) Validated measurement tool. **

b) Non-validated measurement tool, but the tool is available or described.*

c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

a) The study controls for the most important factor (select one). *

b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:

a) Independent blind assessment. **

b) Record linkage. **

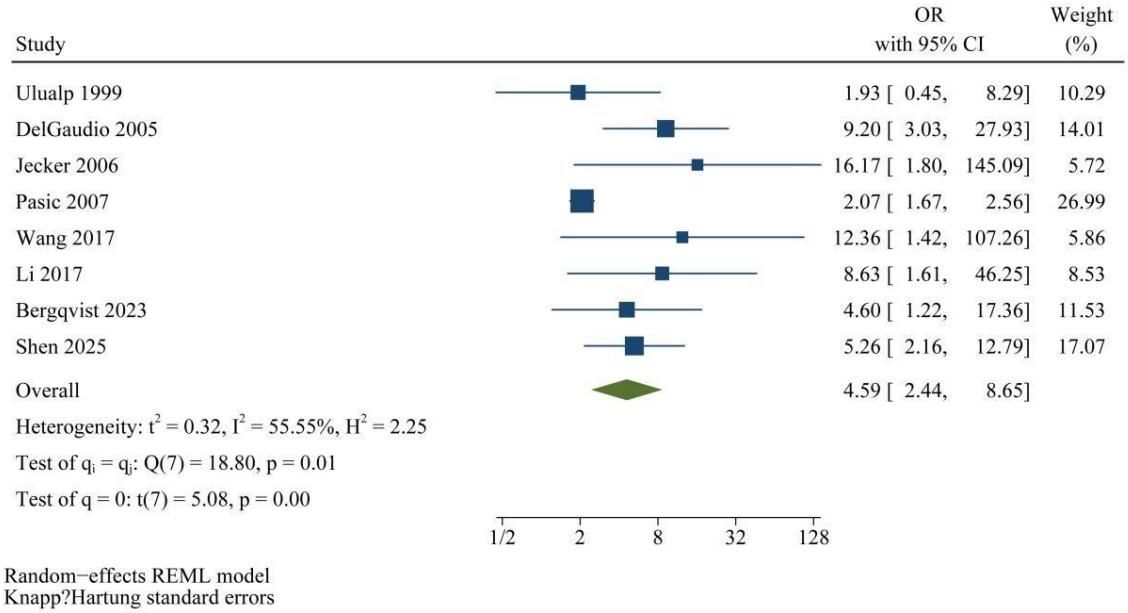
c) Self report. *

d) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *

b) The statistical test is not appropriate, not described or incomplete.



Supplemental figure 1. Sensitivity analysis of the association between LPR and CRS using a random-effects REML model with Hartung–Knapp adjustment. The pooled estimate remained significant and consistent with the primary analysis (OR = 4.59, 95% CI 2.44–8.65; $p < 0.001$; $I^2 = 55.6\%$). Abbreviations: LPR: laryngopharyngeal reflux; CRS: chronic rhinosinusitis; REML: restricted maximum likelihood; OR: odds ratio; CI: confidence interval.