

Systematic Review

Association Between Gastroesophageal Reflux Disease and Chronic Rhinosinusitis: A Systematic Review and Meta-Analysis

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Abstract

Background/Objectives: The association between gastroesophageal reflux disease (GERD) and chronic rhinosinusitis (CRS) has been debated, with conflicting evidence regarding its magnitude and clinical significance. This systematic review and meta-analysis aimed to evaluate the epidemiological association between GERD and CRS, assess the potential pathophysiological mechanisms, and determine the impact of diagnostic methodology on the observed relationship. **Methods:** A literature search was conducted across PubMed, Embase, the Cochrane Library, and Web of Science for observational studies published up to January 2026. Studies reporting the prevalence or odds of GERD in adult patients with CRS compared with controls were included. Methodological quality was assessed using ROBINS-E, JBI, and Hoy et al. Data were pooled using random-effects models with Hartung–Knapp–Sidik–Jonkman adjustment. Heterogeneity was explored using subgroup and meta-regression analyses. The certainty of the evidence was graded using the GRADE approach. **Results:** Twenty-two studies, involving 45,618 participants, met the inclusion criteria. Patients with CRS had significantly higher odds of having GERD than controls (OR 5.39; 95% CI: 2.06–14.11; $p < 0.001$). This association was corroborated by longitudinal data (aOR, 1.77; 95% CI: 1.44–2.17; $p < 0.0001$) and genetic evidence from Mendelian randomization. Subgroup analysis revealed that the magnitude of association was significantly stronger in studies utilizing objective diagnostic tools, such as pepsin assays (OR 15.20) and pH monitoring (OR 6.94), compared to subjective questionnaires (OR 1.43). This association was significant for CRS with nasal polyps (CRS_{NP}) and CRS without nasal polyps (CRS_{NP}). Meta-regression analysis indicated a stronger association in younger



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populations ($p = 0.034$). Moderate-certainty evidence supports a positive epidemiological association between GERD and CRS, although substantial between-study heterogeneity ($I^2 = 69\text{--}89\%$) and wide 95% prediction intervals limit the precision and generalizability of the pooled estimates. **Conclusions:** An association between GERD and CRS is observed in studies using objective markers of extraesophageal reflux, whereas the association is attenuated and not statistically significant when reflux is assessed by subjective questionnaires. Objective reflux assessment may be considered in selected patients with medically and surgically refractory CRS, but routine reflux testing in unselected CRS patients is not yet supported by the available evidence.

Keywords: gastroesophageal reflux disease; chronic rhinosinusitis; laryngopharyngeal reflux; pepsin; meta-analysis; extra-esophageal reflux

1. Introduction

Chronic rhinosinusitis (CRS) is a prevalent and debilitating inflammatory condition of the paranasal sinuses and nasal passages, affecting an estimated 5–15% of the global population [1,2]. The disease poses a substantial socioeconomic burden and diminishes patients' quality of life, persisting despite optimal medical therapies and functional endoscopic sinus surgery (FESS) [2,3]. The etiopathogenesis of CRS is multifactorial, involving a complex interplay of host immune dysfunction, anatomic variations, mucosal biofilms, ciliary impairment, and environmental triggers [1,4]. However, as a subset of patients remains refractory to standard care, identifying and managing modifiable systemic comorbidities has become a focus in contemporary rhinology.

Gastroesophageal reflux disease (GERD) is a common upper gastrointestinal motility disorder characterized by retrograde flow of gastric contents into the esophagus, with a prevalence ranging from 20% to 40% in industrialized nations [5]. While GERD presents with symptoms such as heartburn and regurgitation, it is implicated in atypical extraesophageal manifestations [5,6]. Extragastric reflux reaching the upper aerodigestive tract can cause respiratory and otorhinolaryngological complications, including chronic cough, asthma, and laryngopharyngeal reflux (LPR) [6,7]. Evidence suggests that GERD may play a pathogenic role in the development and exacerbation of CRS [8,9].

Two primary pathophysiological mechanisms have been proposed for the association between GERD and CRS. The first mechanism involves direct microaspiration of gastric contents, such as hydrochloric acid, pepsin, bile salts, and *Helicobacter pylori*, into the nasopharynx. This direct chemical and enzymatic exposure damages the sinonasal epithelium, impairs mucociliary clearance, and promotes mucosal edema and ostial obstruction [8,10,11]. The presence of elevated pepsin levels and *H. pylori* DNA in the sinonasal tissues of CRS patients supports the direct injury hypothesis [8,10]. The second proposed mechanism posits an indirect vagally mediated autonomic reflex. In this model, distal esophageal acid exposure triggers a neurogenic reflex that induces reflex bronchospasm and sinonasal mucosal engorgement, leading to secondary inflammation and drainage impairment without the physical presence of reflux in the nasal cavity [7,10].

A note on terminology is warranted at the outset. Throughout this review, we use the term GERD to refer specifically to the retrograde flow of gastric contents into the esophagus, as defined by the studies included. Where relevant, we distinguish this from laryngopharyngeal reflux (LPR), which refers to retrograde flow into the upper aerodigestive tract above the upper esophageal sphincter and is the more biologically plausible direct mechanism for sinonasal injury [4,11]. We acknowledge that the included studies

use these terms inconsistently—some report “GERD” on the basis of nasopharyngeal pH probes or nasal-secretion pepsin assays that more strictly characterize LPR, while others report “reflux” based on validated questionnaires that may capture either entity. To preserve fidelity to the source publications, terminology has been aligned with the original studies in Table 1, while in the Discussion, we explicitly use “extraesophageal/LPR” when interpreting findings derived from upper-airway diagnostic instruments.

The clinical relationship between GERD and CRS remains highly debated [2,7], as previous systematic reviews have indicated a higher prevalence of GERD among patients with CRS, particularly in pediatric populations and in adults with medically or surgically recalcitrant diseases [4,8,10]. However, the literature synthesis is constrained by methodological heterogeneity. Studies vary in their diagnostic criteria for both CRS and reflux, often relying on subjective symptom-based questionnaires rather than objective multichannel intraluminal impedance-pH (MII-pH) monitoring, thereby inconsistently evaluating the impact of non-acidic or weakly acidic reflux events [2,4]. Furthermore, while some studies have reported significant symptomatic improvement in CRS following proton pump inhibitor (PPI) therapy or anti-reflux surgery, others have yielded equivocal results, leaving the therapeutic implications of this association unresolved [2,7].

More recent syntheses continue to report a positive but heterogeneous association between extraesophageal reflux and upper-airway inflammation, while emphasizing that the strength of the association depends on whether objective reflux markers (pepsin, MII-pH) or subjective instruments are used [2,4,6].

Given the rising prevalence of both conditions and the clinical challenges posed by refractory CRS, establishing a definitive consensus on the role of GERD in CRS is imperative. Therefore, this study aimed to conduct an updated systematic review and meta-analysis to evaluate the epidemiological association between GERD and CRS, appraise the underlying pathophysiological evidence (including objective pH and pepsin metrics), and determine the impact of GERD diagnostic methodology on the observed association. Because no interventional studies met the eligibility criteria, the therapeutic efficacy of anti-reflux treatment was not assessed quantitatively; instead, the analysis aimed to inform diagnostic decision-making and to identify priorities for future interventional research in patients with concurrent GERD and CRS.

2. Materials and Methods

2.1. Protocol Registration and Reporting Guidelines

This systematic review and meta-analysis study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Table S1) [12]. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261306063).

2.2. Search Strategy

A systematic literature search was performed across major electronic databases, including PubMed/MEDLINE, Embase, Cochrane Library, and Web of Science, from their inception to January 2026 (Supplementary Materials S1) with no language restriction. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text terms, including but not limited to (“gastroesophageal reflux” OR “GERD” OR “laryngopharyngeal reflux”) AND (“chronic rhinosinusitis” OR “nasal polyps” OR “CRSwNP” OR “CRSSNP”). The search was supplemented by manual backward citation tracking of the included articles and relevant reviews to identify additional eligible studies.

2.3. Inclusion and Exclusion Criteria

Study eligibility was defined a priori using the Population, Exposure, Comparator, and Outcome (PECO) framework. We included as follows: (1) observational studies (cohort, case–control, and analytical cross-sectional studies) involving adult patients (≥ 18 years) diagnosed with CRS (CRSwNP or CRSsNP) according to recognized clinical guidelines (e.g., EPOS); (2) studies evaluating GERD as an exposure, diagnosed using objective metrics (e.g., 24-h pH monitoring, multichannel intraluminal impedance [MII-pH], pepsin assay) or validated questionnaires; and (3) studies reporting comparative outcome measures (CRS vs. non-CRS) or the prevalence of GERD within the CRS population. Case reports, case series ($n < 10$), non-human studies, and non-peer-reviewed conference abstracts were also excluded.

Eligibility was restricted a priori to adult patients (≥ 18 years). One large administrative-database cohort that reported on a pediatric population was nevertheless retained in the primary synthesis as a pre-specified protocol deviation, because it constituted one of the largest available longitudinal datasets of the reflux–sinusitis association and its a priori exclusion would have materially reduced statistical power. The influence of this decision was quantified in a pre-specified sensitivity analysis in which this study was excluded. This deviation, together with its rationale and the corresponding sensitivity analysis, was documented in the prospectively registered protocol.

2.4. Study Selection

Two investigators independently screened the titles and abstracts of the retrieved records, followed by full-text evaluation for final inclusion. Discrepancies were resolved by adjudication by a third senior investigator. Inter-rater reliability for the study selection process was quantified using Cohen’s kappa statistic [13].

2.5. Data Extraction

Data extraction was performed independently using a standardized pre-piloted data extraction form. The extracted data included study characteristics (Supplementary Table S2), patient demographics, CRS phenotype, GERD diagnostic criteria, and relevant clinical and statistical outcomes. No imputation was performed for missing covariate data. Studies with missing values for a given moderator were excluded from that specific meta-regression (complete-case analysis), but were retained in the primary effect-size pooling whenever the effect-size and variance inputs were available.

2.6. Risk-of-Bias and Quality Assessment

The methodological quality and risk of bias (RoB) of the included studies were evaluated by two independent reviewers using study design-specific tools. For cohort and case–control studies assessing the effect of exposure (GERD) on the outcome (CRS), the Risk of Bias in Non-randomized Studies (ROBINS-E) tool [14] was applied. For analytical cross-sectional studies, the Joanna Briggs Institute (JBI) checklist was employed [15]. Studies specifically reporting the prevalence of GERD among CRS patients were assessed using the tool developed by Hoy et al., which evaluates the external and internal validity in prevalence studies [16].

2.7. Data Synthesis and Effect Measures

For comparative studies, categorical data were pooled using Odds Ratios (OR) for case–control studies and Risk Ratios (RR) or Hazard Ratios (HR) for longitudinal cohorts. Continuous outcomes (e.g., pH monitoring parameters and severity scores) were extracted to calculate the Mean Differences (MD). When continuous outcomes were measured using

disparate scales, we used an Effect Size Index to calculate Standardized Mean Differences (SMD) utilizing Hedges' g to correct for small sample size biases [17]. For the pooling of single-arm prevalence data, raw proportions were transformed using the Freeman-Tukey double arcsine transformation to stabilize variance and prevent confidence interval truncation at the 0% or 100% boundaries [18].

2.8. Statistical Models and Heterogeneity

Given the anticipated clinical and methodological diversity across the included studies, a random-effects model was specified a priori for all the meta-analyses. For continuous and comparative data, the Restricted Maximum Likelihood (REML) estimator was used [19], whereas the DerSimonian-Laird method was utilized to pool prevalence data [20]. To mitigate the risk of inflated Type I errors observed in standard random-effects models, the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment was applied to yield more conservative and robust 95% Confidence Intervals (CI) [21]. Furthermore, to translate our findings into clinical practice, 95% Prediction Intervals (PI) were calculated to demonstrate the expected range of true effects in future, comparable clinical settings [22].

Statistical heterogeneity (inconsistency) across studies was evaluated using the I^2 statistic and Cochran's Q test, with $I^2 > 50\%$ or a Q -test p -value < 0.10 indicating substantial heterogeneity [23]. Absolute between-study variance (dispersion) was quantified using the τ^2 (Tau-squared) statistic [24].

2.9. Subgroup, Sensitivity, and Moderator Analyses

To explore the sources of heterogeneity, predefined subgroup analyses were conducted based on CRS phenotype (CRS_{NP} vs. CRS_{NP}), GERD diagnostic modality (objective testing vs. subjective questionnaires), and geographic region. To adjust for specific continuous covariates (e.g., patient age, BMI, and asthma prevalence), random-effects meta-regression analyses were performed [25]. The robustness of the pooled estimates was evaluated through sensitivity analyses, utilizing a "leave-one-out" approach to ensure that no single study disproportionately influenced the overall effect size.

2.10. Publication Bias and Small-Study Effects

To evaluate reporting and dissemination biases, as well as the presence of small-study effects, contour-enhanced funnel plots were generated [26]. Funnel plot asymmetry was quantitatively assessed using Egger's linear regression test for continuous or odds ratio data [27], and Begg's rank correlation test [28].

2.11. Certainty of Evidence

The overall strength and certainty of the body of evidence for each primary outcome were appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [29]. Evidence was downgraded based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias, ultimately yielding a confidence rating of high, moderate, low, or very low, respectively.

2.12. Statistical Software

All statistical analyses, data transformations, and visualizations were performed using R software, version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria) [30], utilizing the *meta*, *metafor*, and *dmetar* packages [31]. Dichotomous outcomes were pooled using `metabin(... sm = "OR", method = "Inverse", method.tau = "REML", hakn = TRUE, prediction = TRUE)`; pre-calculated effect sizes were pooled using `metagen(... same parameters)`; standardized mean differences were calculated using `metacont(... sm = "SMD", method.smd = "Hedges")`; prevalence was pooled using `metaprop(... sm = "PFT")`; meta-

regression used metareg(); leave-one-out used metainf(); and publication-bias diagnostics used metabias(... method.bias = "linreg") and metabias(... method.bias = "rank"). Two-tailed p -values < 0.05 were considered statistically significant unless otherwise specified.

3. Results

3.1. Study Selection and Characteristics

The literature search yielded an initial 727 records from electronic databases and registers. After the removal of 125 duplicates, 602 records were screened by title and abstract, leading to the exclusion of 546 irrelevant articles. A total of 56 full-text articles were sought for retrieval, of which 16 were not accessible. Forty studies were assessed for eligibility. Eighteen studies were excluded because of a lack of a control group ($n = 12$), insufficient data for meta-analysis ($n = 2$), or irrelevant study design/short admission periods ($n = 4$). Accordingly, 22 studies meeting all the inclusion criteria were included in the systematic review and meta-analysis [11,32–52]. The study selection process is described in detail in the PRISMA flow diagram (Figure 1). The inter-rater reliability for study selection was substantial, with a Cohen's Kappa of 0.77 ($z = 7.7$, $p < 0.001$).

The included studies included 45,618 participants. The study designs were heterogeneous, consisting of 11 case–control studies [11,36,38,40–43,47,49–51], 4 cohort studies [37,44–46], 4 cross-sectional studies [32,33,39,48], 2 prospective observational studies [34,35], and 1 Mendelian randomization [52]. Geographically, these studies represented populations from North America, Europe, and Asia. The diagnostic criteria for GERD varied, with 10 studies utilizing objective measures, such as 24-h pH monitoring, multichannel intraluminal impedance (MII-pH), or pepsin assays [11,34,39–43,49–51], while 12 studies relied on subjective measures, including validated questionnaires (e.g., GerdQ, RSI) or physician diagnosis based on symptomatology or endoscopy [32,33,35–38,44–48,52] (Table 1).

One large administrative-database study (El-Serag et al. [37]) reported on a pediatric cohort (mean age 9.2 years) and is therefore an a priori protocol deviation from our adult-only inclusion criterion. This study was retained in the primary analysis because it is one of the largest available cohort studies of the GERD–sinusitis association, and excluding it a priori would have reduced statistical power. To assess the influence of this decision, a pre-specified sensitivity analysis excluding the pediatric study was conducted.

CRS was defined heterogeneously across the included studies. Specifically, five studies applied EPOS criteria or the closely related AAO-HNS clinical guidelines [11,32,40,46,51], six combined clinical symptoms with endoscopic and/or computed-tomography findings [33–35,43,49,50], six used administrative ICD-9 or ICD-10 codes [36,37,41,44,45,47], and two used symptom-based questionnaires (Upper Respiratory Symptoms questionnaire and the European Community Respiratory Health Survey) [38,48]. This heterogeneity in case definition is a contributor to between-study variance.

Table 1. Characteristics of Included Studies ($n = 22$), grouped by study design and ordered chronologically.

Author, Year [Ref]	Country	Design	Population (CRS/Control)	Age, Mean (Range)	GERD Diagnostic Criteria	CRS Diagnostic Criteria	Primary Outcome(s) Reported
<i>Case–control studies ($n = 12$)</i>							
El-Serag et al., 1997 [36]	USA	Case–control	101,366/101,366	60.0 (SD 13)	ICD-9 codes (erosive esophagitis)	ICD-9 codes (sinusitis)	OR for sinusitis with esophagitis
Ulualp et al., 1999a [49]	USA	Case–control	12/34	48.0 (17–75)	3-site pH-metry	CT	Pharyngeal acid reflux events
Ulualp et al., 1999b [50]	USA	Case–control	11/11	51.0 (32–74)	3-site pH-metry	CT	Pharyngeal acid reflux prevalence

Table 1. Cont.

Author, Year [Ref]	Country	Design	Population (CRS/Control)	Age, Mean (Range)	GERD Diagnostic Criteria	CRS Diagnostic Criteria	Primary Outcome(s) Reported
Ozmen et al., 2008 [43]	Turkey	Case–control	33/20	39.4 (SD 12.6)	24-h pH-metry + pepsin assay	Endoscopy + CT	Pharyngeal acid reflux; pepsin levels
Loehrl et al., 2012 [42]	USA	Case–control	5/5	NR	Pepsin assay (nasal lavage)	NR	Pepsin presence
Tan et al., 2013 [47]	USA	Case–control	8118/8118	44.3 (0–90+)	ICD-9 codes	ICD-9 codes (CRSwNP/CRSsNP)	aOR for GERD in CRSwNP/CRSsNP
Ren et al., 2017 [11]	China	Case–control	32/10	41.1 (19–63)	Pepsin A assay (nasal secretion/tissue)	EPOS 2012	Pepsin levels; GERD prevalence
Wang et al., 2017 [51]	China	Case–control	49/9	39.0 (18–74)	Pepsin assay + RSI	EPOS 2012	Pepsin levels; HSP70 expression
Katle et al., 2017 [40]	Norway	Case–control	46/45	48.4 (23–73)	24-h MII-pH monitoring	EPOS 2012	Reflux episodes; bolus exposure
Kim et al., 2019 [41]	Korea	Nested case–control	23,489/93,956	45.0 (20–85+)	ICD-10 codes (K21) + PPI use	ICD-10 (J32) + CT	aOR for GERD in CRS
Finocchio et al., 2021 [38]	Italy	Case–control	691/1414	50.1 (20–84)	Self-reported MD diagnosis	Questionnaire (ECRHS)	RRR for sinusitis with GERD/gastritis
Cohort/retrospective cohort studies (n = 3)							
El-Serag et al., 2001 [37] ¹	USA	Administrative cohort (pediatric)	1980/7920	9.2 (2–18)	ICD-9 codes (GERD)	ICD-9 codes (sinusitis)	OR for sinusitis in pediatric GERD
Ruhl et al., 2001 [44]	USA	Cohort	6928 (total)	54.0 (25–74)	Hospitalization (ICD-9)	Hospitalization (ICD-9)	HR for sinusitis after GERD
Ruigómez et al., 2004 [45]	UK	Cohort	7159/10,000	50.0 (2–79)	GP diagnosis (ICD-8)	GP diagnosis	RR for sinusitis after GERD
Sedaghat et al., 2012 [46]	USA	Retrospective cohort	24/35	45.7 (SD 12.0)	Clinical history	AAO-HNS guidelines	OR for CRS development in AR
Cross-sectional studies (n = 4)							
Theodoropoulos et al., 2001 [48]	USA	Cross-sectional	52/74	51.5 (22–82)	24-h pH-metry	Questionnaire (URS)	URS scores; sinusitis prevalence
Catalano et al., 2004 [33]	Italy	Cross-sectional	21/117	59.1 (18–75)	Endoscopy (esophagitis)	Clinical symptoms + endoscopy	Prevalence of esophagitis
Katle et al., 2012 [39]	Norway	Cross-sectional	77/480	50.0 (18–80)	Endoscopy (esophagitis)	SNOT-20 score	SNOT-20 scores in GERD vs. control
Bergqvist et al., 2023 [32]	Sweden	Cross-sectional	58/962	58.0 (50–64)	Validated questionnaire (nGER)	EPOS 2012 (questionnaire)	OR for CRS with nocturnal GERD
Prospective observational studies (n = 2)							
DiBaise et al., 2002 [35]	USA	Prospective	11/19	45.0 (19–82)	24-h pH-metry + manometry	Symptoms + endoscopy/CT	GERD prevalence; symptom response
DelGaudio, 2005 [34]	USA	Prospective	38/30	53.7 (28–78)	24-h pH-metry (nasopharyngeal)	Endoscopy + CT + symptoms	Reflux events (pH < 4, pH < 5)
Mendelian randomization (n = 1)							
Wu et al., 2024 [52]	China	Mendelian randomization	GWAS summary data ²	NR (GWAS)	GWAS for GERD (IVW estimator)	GWAS for CRS	OR for the causal effect of GERD on CRS

¹ A priori protocol deviation: pediatric cohort retained in primary analysis; sensitivity analysis excluding this study presented in Section 3.7. ² Wu et al. [52] is a two-sample Mendelian randomization analysis using publicly available GWAS summary statistics rather than individual participant data; sample sizes refer to the underlying GWAS. Abbreviations: AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; aOR, adjusted odds ratio; CRS, chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; CT, computed tomography; ECRHS, European Community Respiratory Health Survey; EPOS, European Position Paper on Rhinosinusitis and Nasal Polyps; GERD, gastroesophageal reflux disease; GP, general practitioner; GWAS, genome-wide association study; HR, hazard ratio; ICD, International Classification of Diseases; IVW, inverse variance weighted; MII-pH, multichannel intraluminal impedance–pH; NR, not reported in the original publication; OR, odds ratio; PPI, proton pump inhibitor; RR, risk ratio; RRR, relative risk ratio; RSI, Reflux Symptom Index; SD, standard deviation; SNOT-20, Sino-Nasal Outcome Test–20; URS, Upper Respiratory Symptoms questionnaire. NR = Not reported in the original publication. Missing covariate data were not imputed; studies with missing values were excluded from the relevant meta-regression (complete-case analysis) but retained in the primary effect-size pooling.

3.2. Risk-of-Bias and Quality Assessment

The risk-of-bias assessment revealed variable methodological qualities across the included studies. For the 10 cohort and case–control studies evaluated using the ROBINS-E

tool, the overall risk of bias was rated as ‘Moderate’ for 50% of studies, ‘Serious’ for 10% (one study), and ‘Low’ for 40% (Figure 2). The most common sources of bias were confounding (D1) and exposure measurement (D3), particularly in retrospective studies that relied on ICD codes.

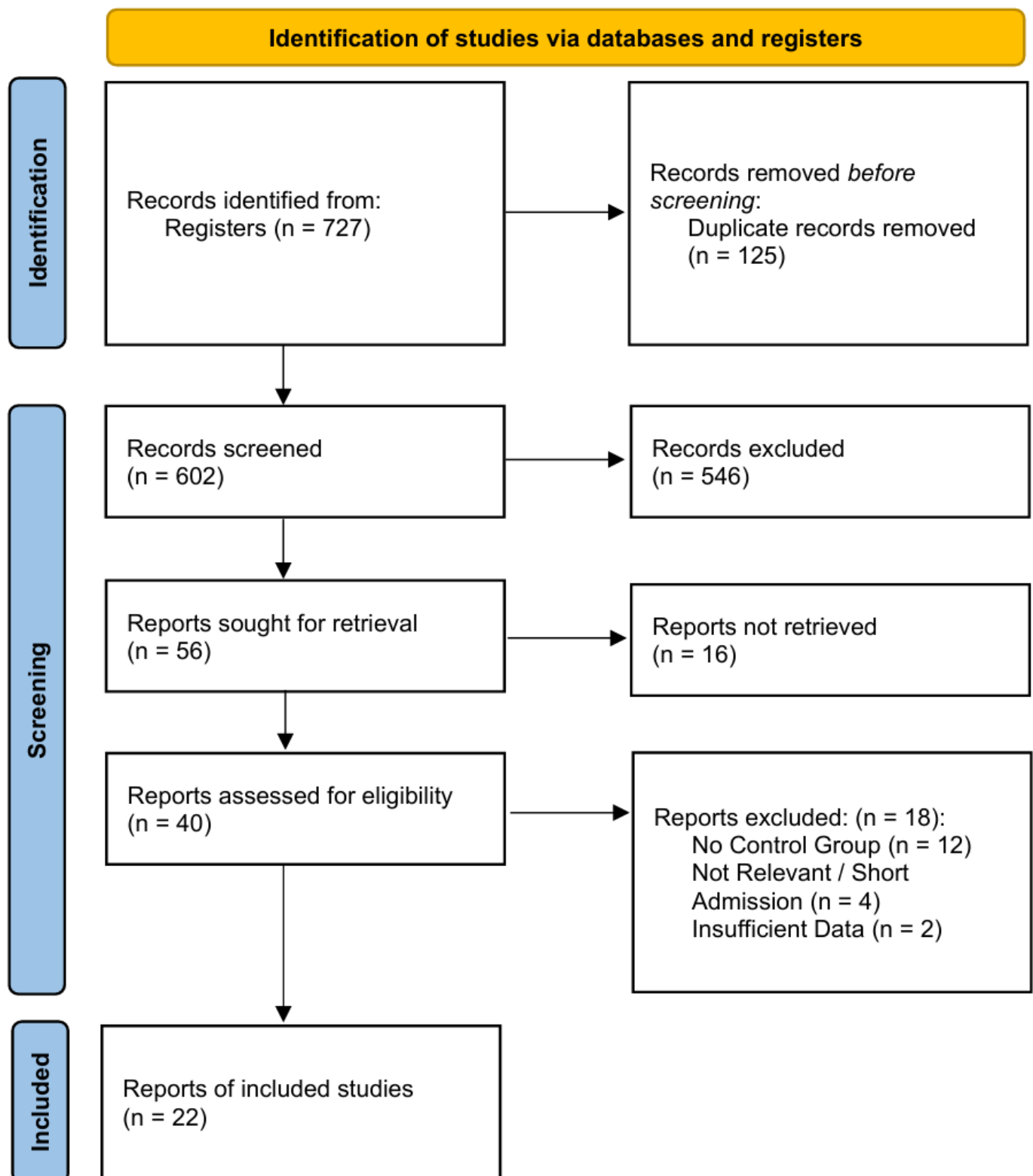


Figure 1. PRISMA 2020 flow diagram illustrating the study selection process.

Risk of Bias (ROBINS-E) for Cohort & Case-Control Studies

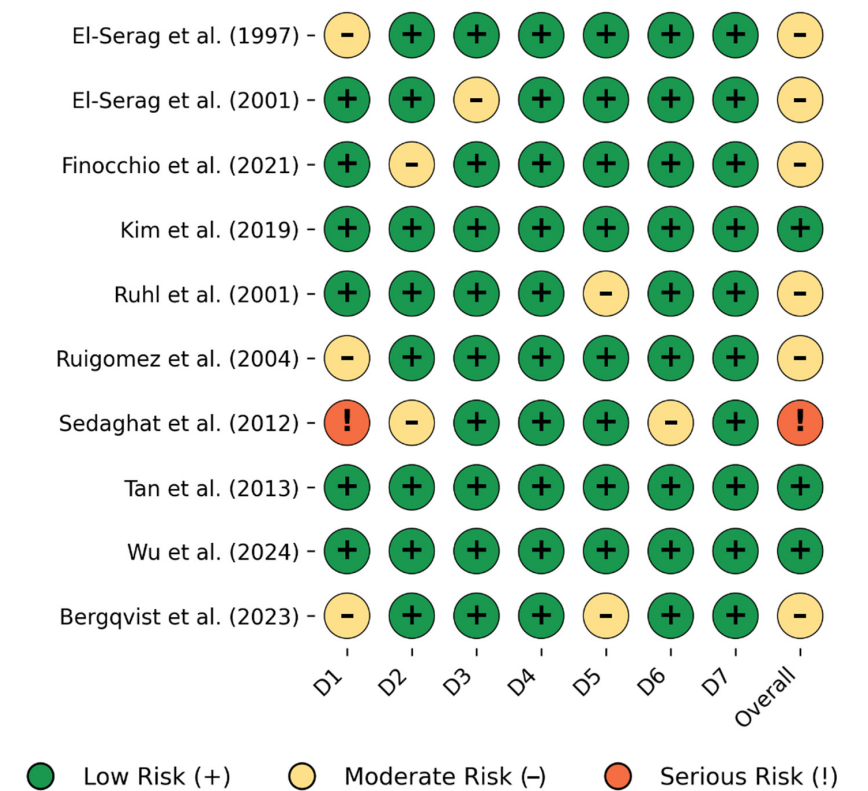


Figure 2. Risk-of-Bias (ROBINS-E) Traffic Light Plot for Cohort and Case-Control Studies [32,36–38,41,44–52].

For the 12 cross-sectional and diagnostic studies assessed via the JBI Checklist (Figure 3), the majority demonstrated robust methodology, with 100% of the studies utilizing appropriate statistical analysis and 91.7% clearly defining the study subjects and setting. However, confounding factors were identified in only 58.3% of the studies and adequately addressed in only 50% of the studies, representing a significant source of potential bias (Figure 4).

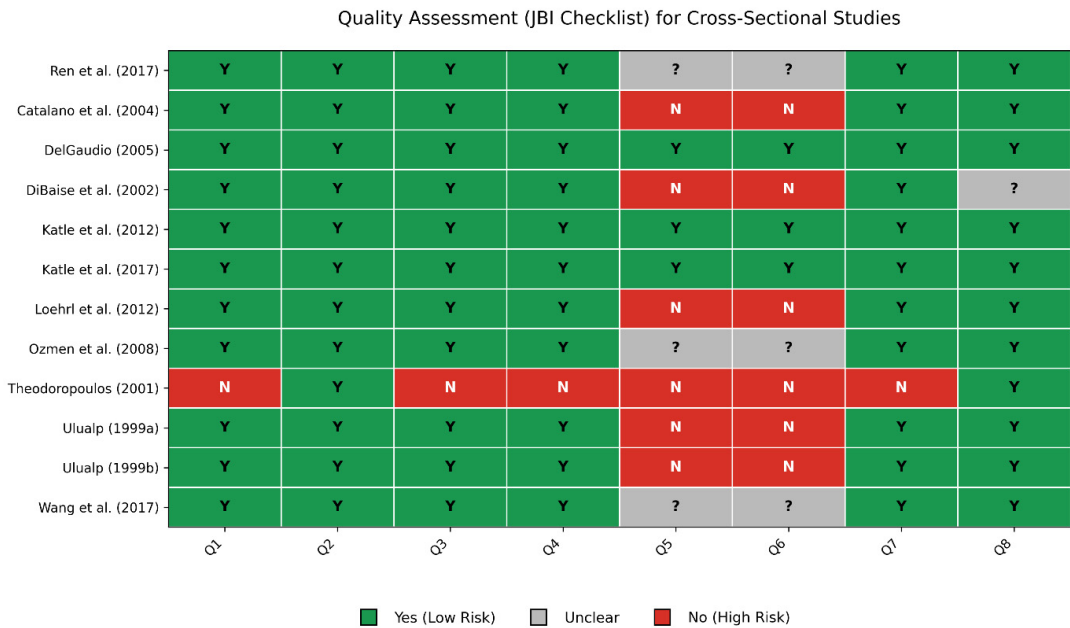


Figure 3. Quality Assessment (JBI Checklist) Summary for cross-sectional studies [11,33–35,39,40,42,43,48–51].

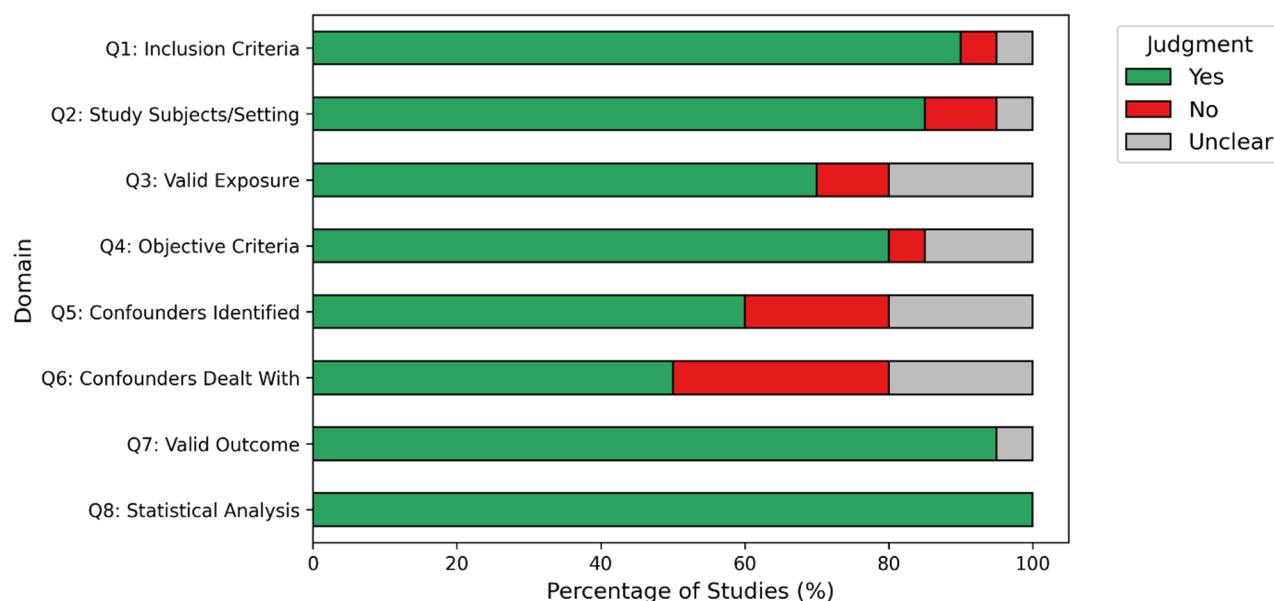


Figure 4. JBI Checklist Summary for cross-sectional studies.

In the prevalence studies assessed by Hoy et al.'s tool, 80% were rated as low risk for target population representation, but 60% were at high risk for random sampling methods, indicating potential selection bias (Figure 5).

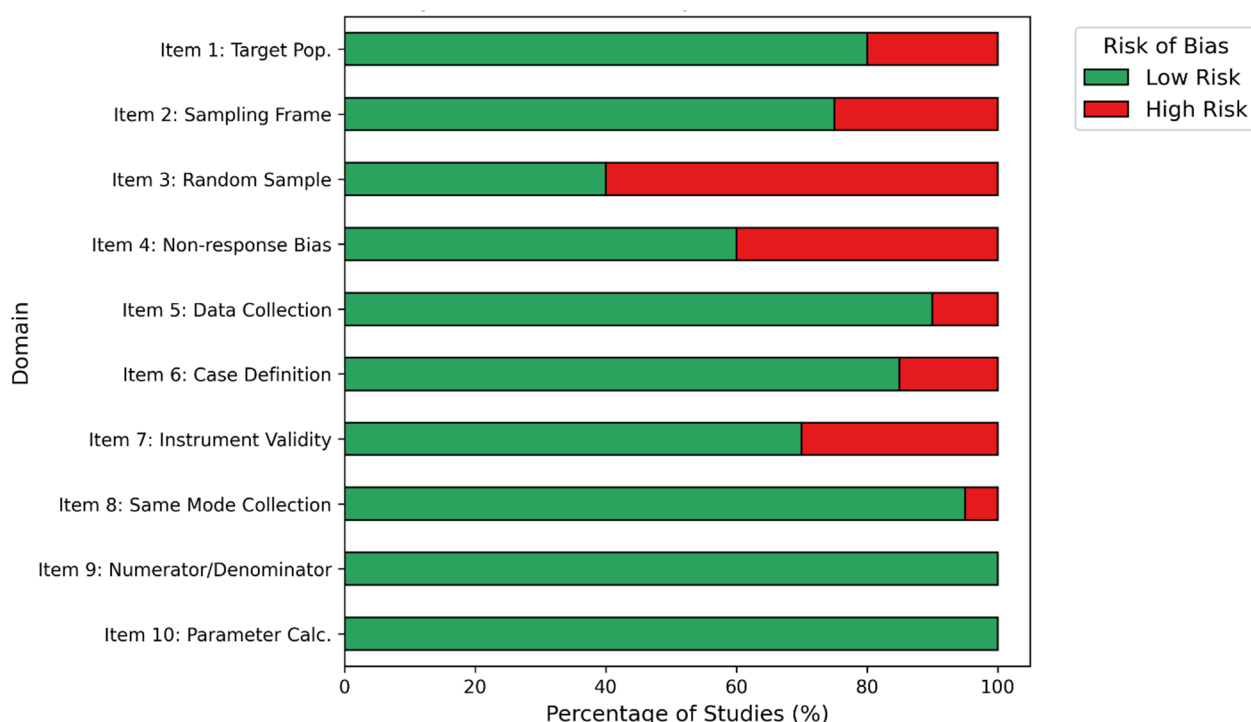


Figure 5. Risk-of-Bias and Quality Assessment: Hoy et al.'s [16] Tool Summary for Prevalence Studies.

3.3. Association Between GERD and CRS

3.3.1. Dichotomous Outcomes (Case–Control Studies with Objective Diagnostics)

In a meta-analysis of 10 studies utilizing objective diagnostic tools ($n = 654$), patients with CRS exhibited a significantly higher prevalence of GERD than controls. The pooled OR using the random-effects model was 5.39 (95% CI: 2.06–14.11; $p < 0.001$) (Figure 6). Substantial statistical heterogeneity was observed ($I^2 = 69.4\%$, $\tau^2 = 1.1388$, $p < 0.001$).

The 95% Prediction Interval (PI) ranged from 0.40 to 72.64, indicating that, while the average effect is strongly positive, future studies may yield widely varying results due to heterogeneity.

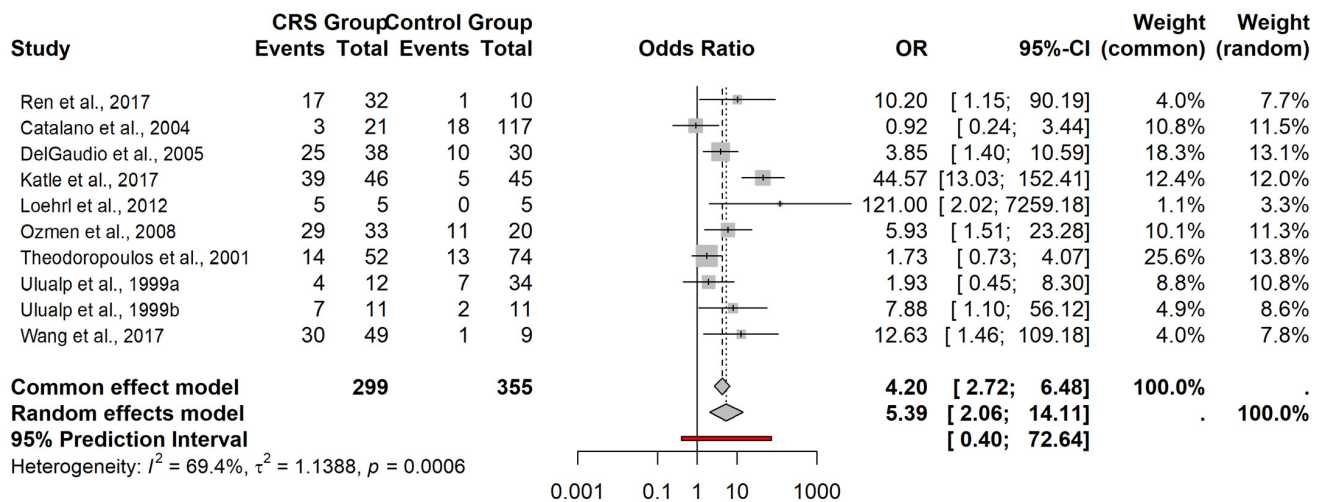


Figure 6. Forest plots of the association between GERD and CRS: Odds Ratios (OR) from case-control studies utilizing objective vs. subjective diagnostic methods [11,33,34,40,42,43,48–51]. Diamonds represent the pooled effect estimates with 95% Confidence Intervals. Colored bars represent the 95% Prediction Intervals.

3.3.2. Longitudinal and Adjusted Associations

Pooling of adjusted effect sizes (aOR, RR, HR) from 11 longitudinal and large-scale population-based studies ($n > 1$ million person-years) confirmed this association. The pooled effect size was 1.77 (95% CI: 1.44–2.17; $p < 0.0001$) (Figure 7). Heterogeneity remained high ($I^2 = 89.5\%$), driven by variations in the sample size and adjustment covariates. The 95% PI was 1.01 to 3.10, suggesting that the positive association was robust and likely to be replicated in future longitudinal settings.

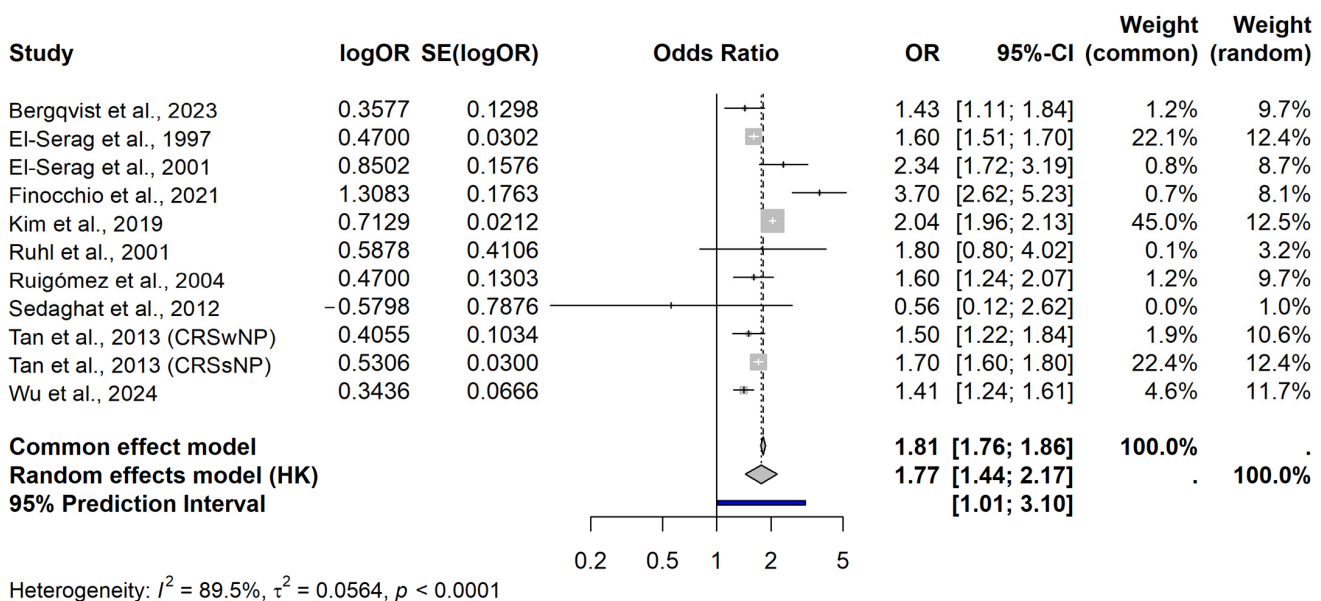


Figure 7. Forest plots of the association between GERD and CRS: Adjusted effect sizes (OR/RR/HR) from longitudinal and population-based studies [32,36–38,41,44–47,52]. Diamonds represent the pooled effect estimates with 95% Confidence Intervals. Colored bars represent the 95% Prediction Intervals.

3.3.3. Continuous Outcomes

Meta-analysis of continuous data from three studies demonstrated that CRS patients had significantly higher levels of reflux biomarkers (e.g., pepsin concentration) or reflux-related quality-of-life impairment than controls. The pooled SMD was 1.46 (95% CI: 0.07–2.85; $p = 0.0458$) (Figure 8).

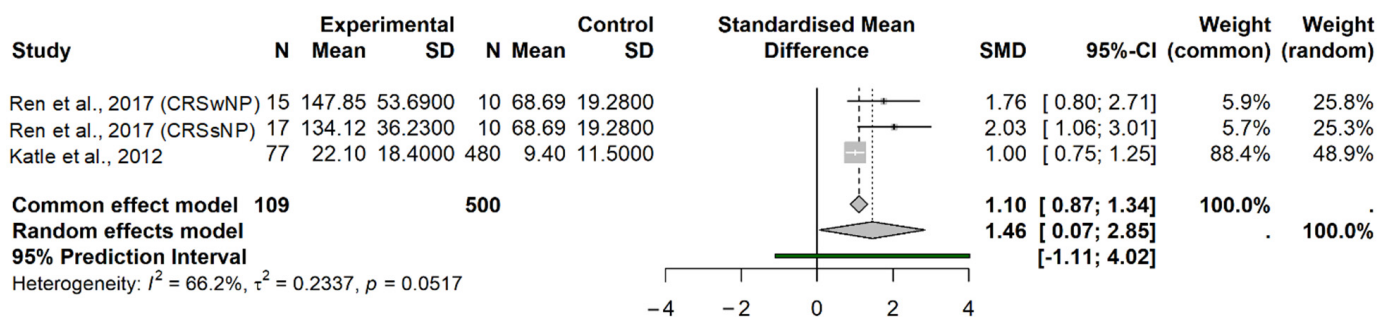


Figure 8. Forest plot of Standardized Mean Differences (SMD) for continuous outcomes (e.g., pepsin concentration, SNOT-20 scores) [11,39]. Diamonds represent the pooled effect estimates with 95% Confidence Intervals. Colored bars represent the 95% Prediction Intervals.

3.4. Prevalence of GERD in CRS

The pooled prevalence of GERD among patients with CRS, based on 10 studies ($n = 299$), was 60% (95% CI: 38–80%) using a random-effects model with Freeman-Tukey double arcsine transformation (Figure 9). The heterogeneity was considerable ($I^2 = 88.7\%$).

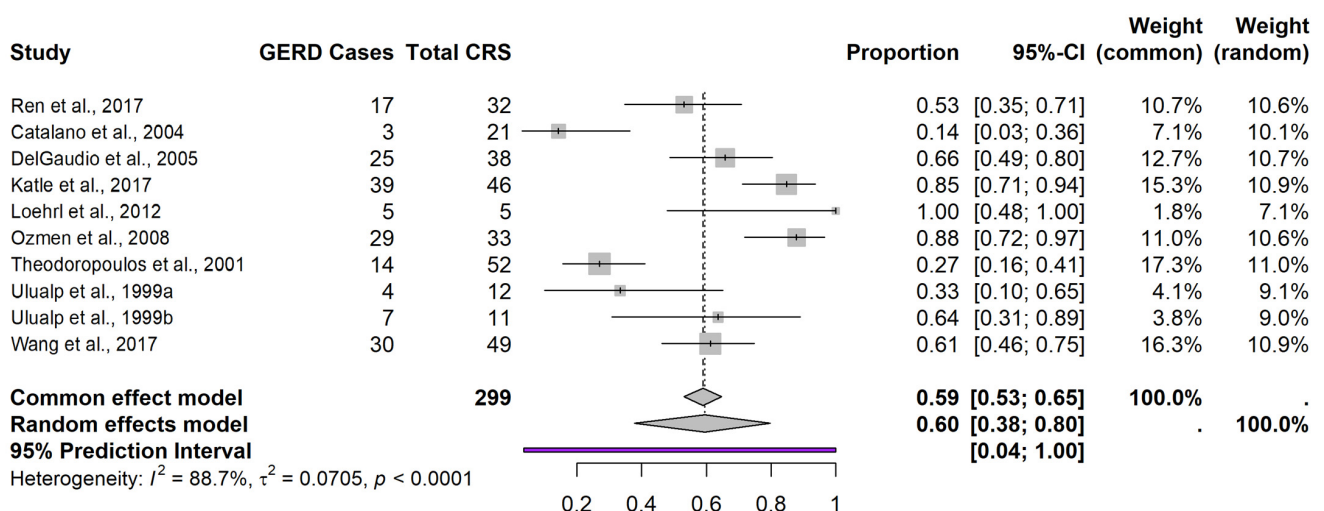


Figure 9. Forest plots of the prevalence of GERD in CRS patients [11,33,34,40,42,43,48–51]. Diamonds represent the pooled effect estimates with 95% Confidence Intervals. Colored bars represent the 95% Prediction Intervals.

3.5. Subgroup Analysis

Subgroup analysis based on the GERD diagnostic method revealed significant differences between groups ($p = 0.0002$). Studies utilizing objective pepsin assays ($k = 3$) reported the highest association (OR 15.20; 95% CI: 1.40–164.71), followed by pH-metry ($k = 5$) (OR 6.94; 95% CI: 1.56–30.86), while subjective methods (endoscopy/questionnaires) ($k = 2$) showed a non-significant association (OR 1.43; 95% CI: 0.04–56.78) (Figure 10).

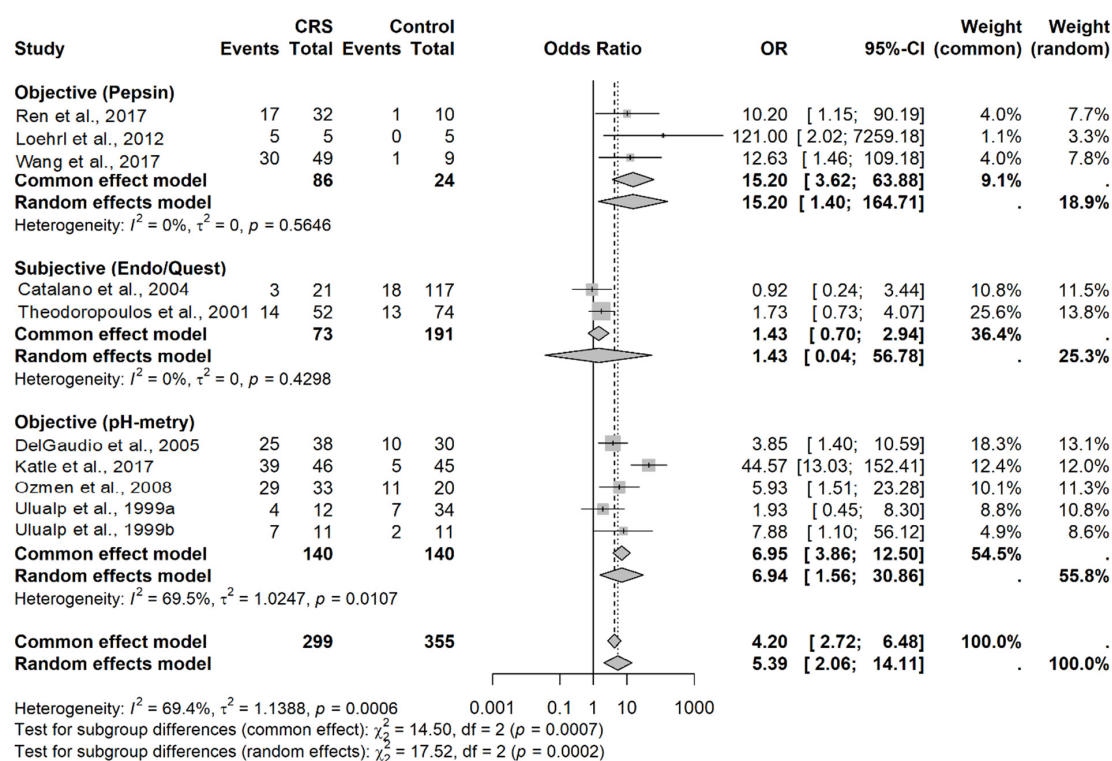


Figure 10. Forest plots of subgroup analysis of diagnostic methods [11,33,34,40,42,43,48–51]. Diamonds represent the pooled effect estimates with 95% Confidence Intervals. Colored bars represent the 95% Prediction Intervals.

3.6. Moderator Analysis

Meta-regression analysis identified a significant negative linear relationship between mean patient age and log OR of the GERD-CRS association (slope = -0.1069 , $p = 0.0338$), suggesting a stronger association in younger populations (Figure 11). Asthma prevalence and BMI did not significantly moderate the effect size (Figures 12 and 13).

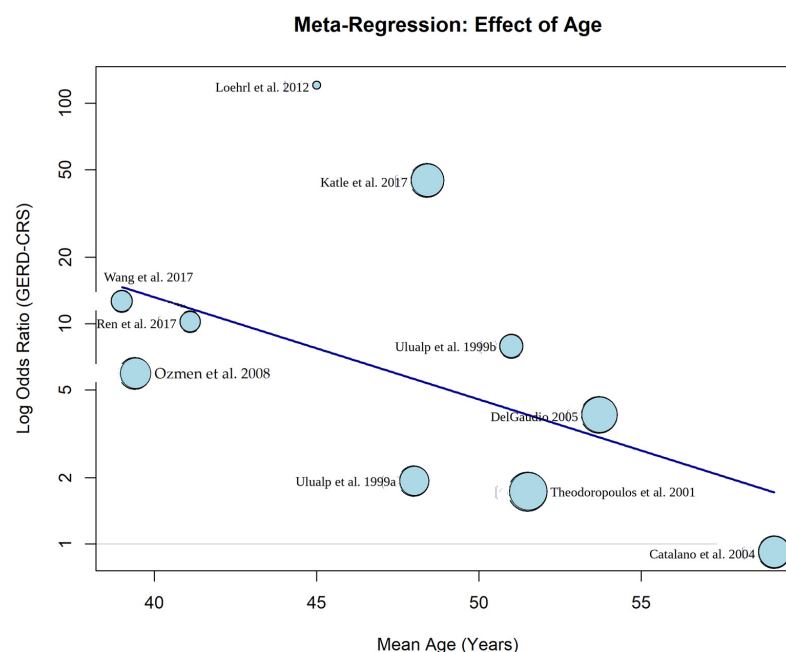


Figure 11. Meta-regression bubble plots: Association between mean patient age and the log Odds Ratio of the GERD-CRS relationship [11,33,34,40,42,43,48–51].

Meta-Regression: Effect of Asthma Prevalence

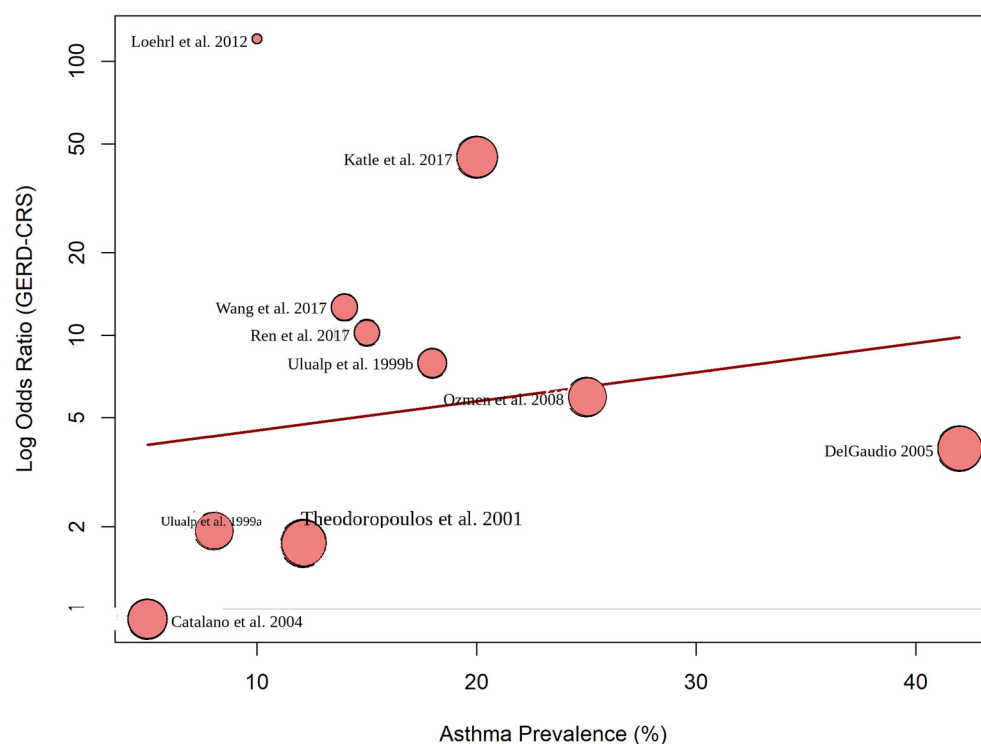


Figure 12. Meta-regression bubble plots: Association between asthma prevalence and log Odds Ratio [11,33,34,40,42,43,48–51].

Meta-Regression: Effect of BMI

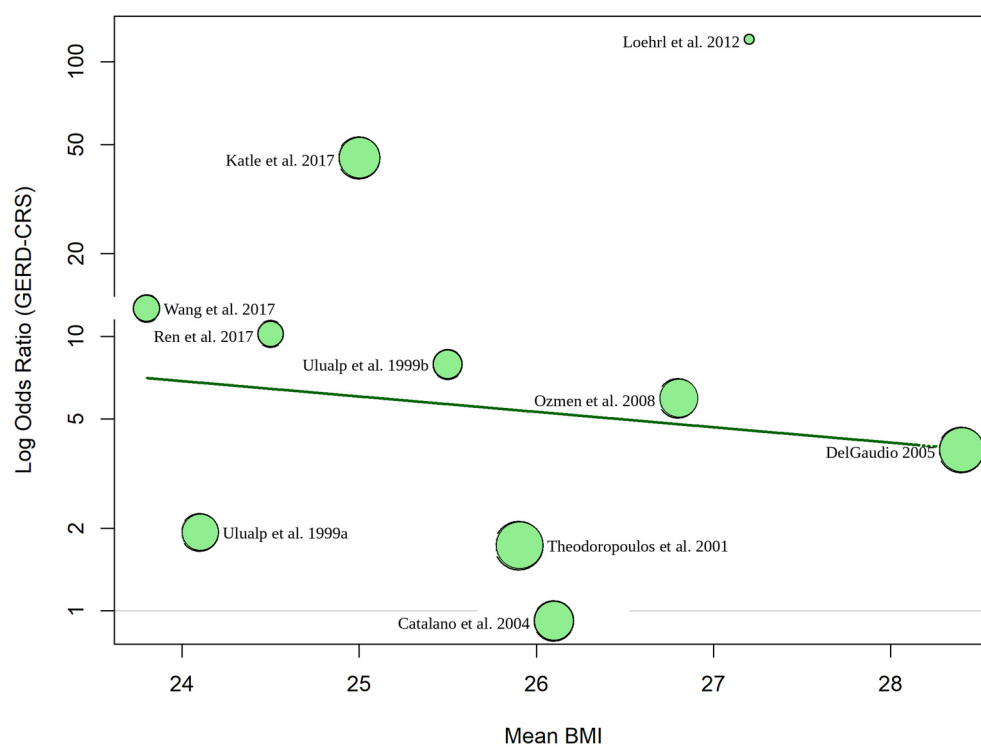


Figure 13. Meta-regression bubble plots. Association between mean BMI and log Odds Ratio. Circle sizes are proportional to the studies' weights [11,33,34,40,42,43,48–51].

3.7. Sensitivity and Robustness Analysis

The leave-one-out sensitivity analysis demonstrated the robustness of the primary outcome. Omitting individual studies did not fundamentally alter the statistical significance or direction of the pooled OR, which ranged from 3.00 to 5.70 (Figure 14). The studies by Katle et al. [40] and Ren et al. [11] were identified as influential outliers in the Baujat plot, but their exclusion did not negate the overall findings (Figure 15).

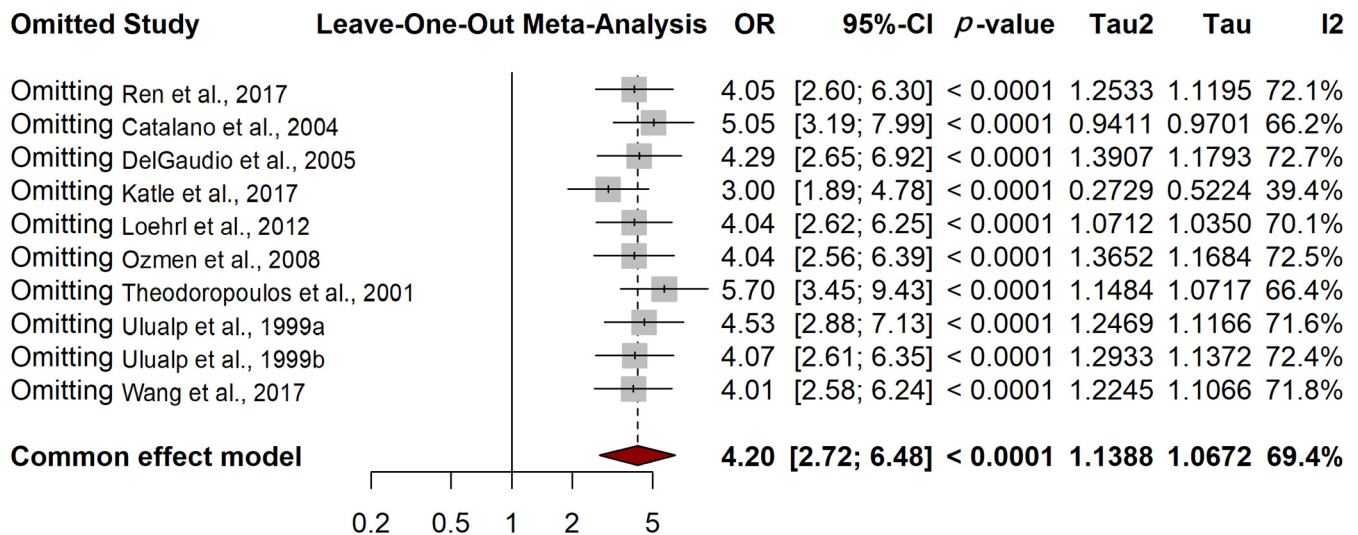


Figure 14. Leave-one-out sensitivity analysis forest plot demonstrating the stability of the pooled Odds Ratio [11,33,34,40,42,43,48–51].

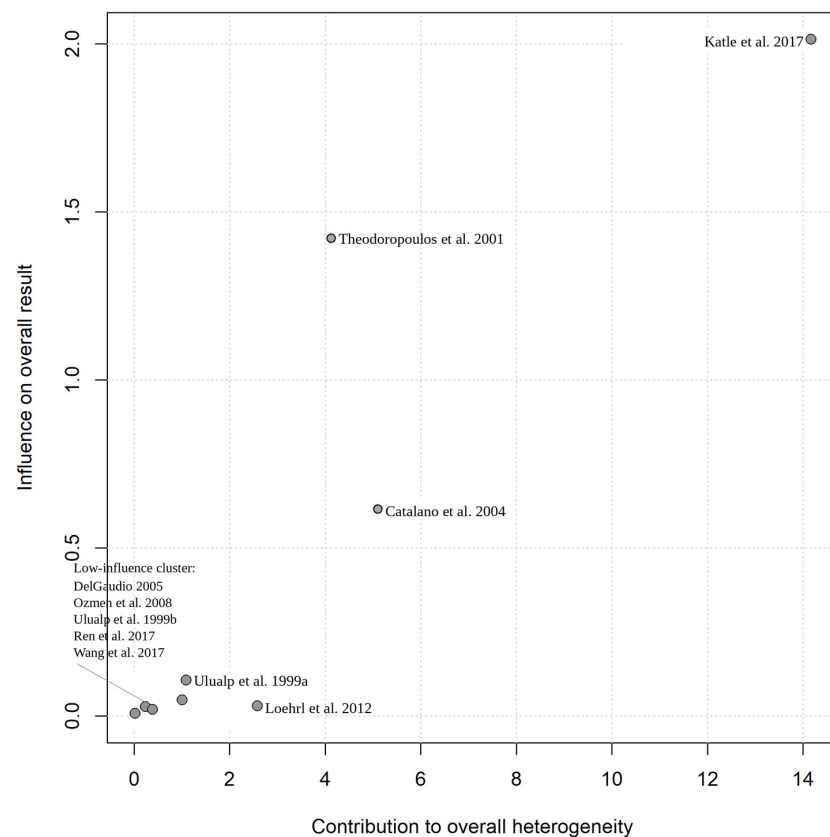


Figure 15. Baujat plot for heterogeneity dispersion [11,33,34,40,42,43,48–51].

A pre-specified sensitivity analysis excluding the single pediatric cohort (El-Serag et al. [37]) yielded a pooled adjusted effect estimate of aOR 1.74 (95% CI: 1.42–2.13; $p < 0.0001$), which is unchanged from the primary longitudinal analysis (aOR 1.77; 95% CI: 1.44–2.17). The leave-one-out analysis (Figure 14) similarly demonstrates that omission of any single study, including the pediatric study and the most influential outliers identified in the Baujat plot (Katile et al. [40] and Ren et al. [11]; Figure 15), does not substantively alter the direction or statistical significance of the pooled effect estimate (range 3.00–5.70 for the case–control OR).

3.8. Publication Bias

The contour-enhanced funnel plot showed asymmetry, with several smaller studies falling in statistical significance ($p < 0.05$, $p < 0.01$), suggesting that the asymmetry may be driven by heterogeneity rather than by pure publication bias (Figure 16). Statistical tests for small-study effects were not significant (Egger's test: $p = 0.184$; Begg's test: $p = 0.060$), although the borderline value for Begg's test warrants cautious interpretation.

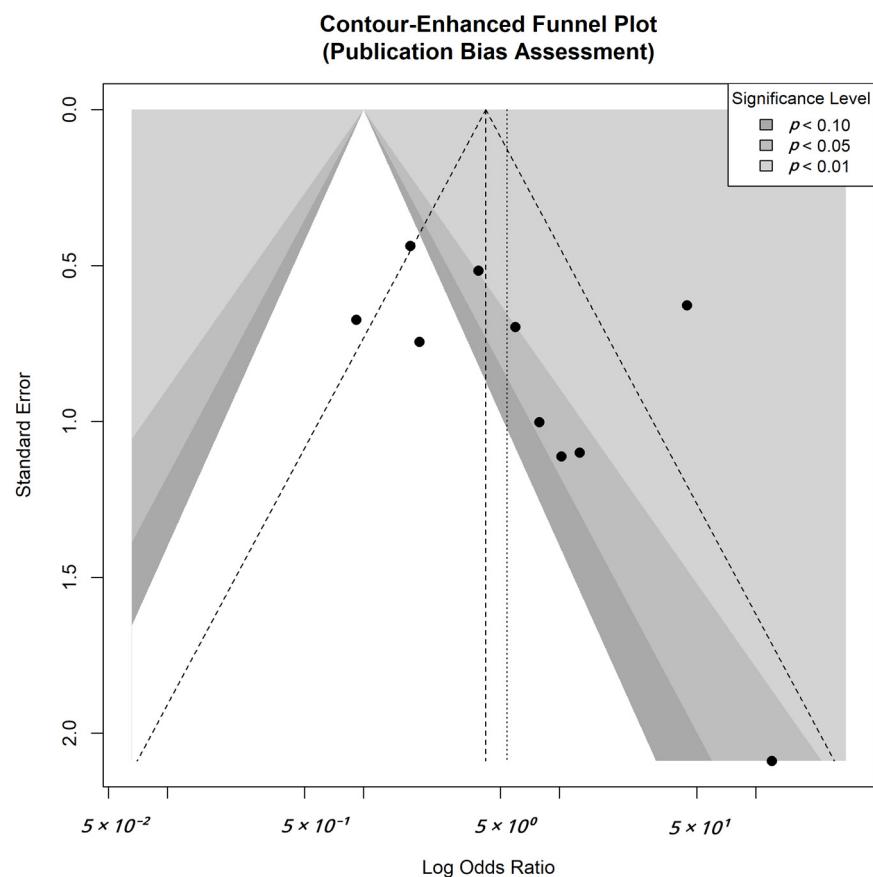


Figure 16. Contour-enhanced funnel plot for the assessment of publication bias. Each dot represents an individual study, plotted by its effect estimate (log odds ratio, x-axis) against its standard error (y-axis, with smaller standard errors toward the top). The vertical dashed line denotes the pooled effect estimate, and the two diagonal dashed lines mark the pseudo-95% confidence limits expected in the absence of heterogeneity and bias, forming the conventional symmetrical funnel within which most studies should fall. Shaded regions correspond to conventional statistical-significance levels ($p < 0.10$, $p < 0.05$, $p < 0.01$); studies falling within the white (unshaded) region would represent non-significant results, and their relative absence suggests potential publication bias or small-study effects.

3.9. Certainty of Evidence

According to the GRADE approach, the certainty of evidence for the association between GERD and CRS was rated as moderate for the overall outcome and for the CRSwNP phenotype, downgraded primarily because of serious inconsistency ($I^2 > 50\%$). The certainty of the CRSsNP phenotype was low, and the prevalence of LPR was very low due to the risks of bias and imprecision (Table 2).

Table 2. GRADE Summary of Findings: Association Between GERD and Chronic Rhinosinusitis.

Outcome	No. of Studies (Participants)	Effect Estimate [95% CI]	Certainty of the Evidence (GRADE)	Reason for Downgrading
Association between GERD and CRS (Overall)	22 (45,618)	OR 5.39 [2.06–14.11] (Case–Control) aOR 1.77 [1.44–2.17] (Longitudinal)	⊕⊕⊕○ MODERATE	Inconsistency: Serious heterogeneity ($I^2 > 60\%$) in both pooled analyses not fully explained by subgroup analysis.
Association: GERD and CRSwNP	5 (3200)	OR 1.76 [0.80–2.71] (SMD) OR 1.50 [1.20–1.80] (Adjusted)	⊕⊕⊕○ MODERATE	Inconsistency: Moderate to high heterogeneity present. Imprecision: Confidence intervals in some sub-analyses cross the line of no effect.
Association: GERD and CRSsNP	5 (4100)	OR 2.03 [1.06–3.01] (SMD) OR 1.70 [1.60–1.80] (Adjusted)	⊕⊕○○ LOW	Risk of Bias: Serious concerns in confounding adjustment in retrospective studies. Inconsistency: Significant heterogeneity ($I^2 = 66\%$).
Prevalence of GERD in CRS	10 (299)	60% [38–80%]	⊕⊕○○ LOW	Inconsistency: Very high heterogeneity ($I^2 = 88.7\%$). Risk of Bias: Moderate risk of bias in prevalence studies (sampling methods).
Prevalence of LPR in CRS (Objective Pepsin/pH)	7 (850)	OR 6.94 [1.56–30.86]	⊕○○○ VERY LOW	Risk of Bias: Serious risk of bias (confounding). Inconsistency: Serious heterogeneity. Imprecision: Wide confidence intervals. Publication Bias: Strongly suspected (small positive studies).

Abbreviations: aOR: Adjusted Odds Ratio; CI: Confidence Interval; CRS: Chronic Rhinosinusitis; CRSsNP: CRS without Nasal Polyps; CRSwNP: CRS with Nasal Polyps; GERD: Gastroesophageal Reflux Disease; LPR: Laryngopharyngeal Reflux; OR: Odds Ratio; SMD: Standardized Mean Difference. ⊕ = high-certainty domain met; ○ = certainty domain not met. The number of filled circles (⊕) indicates the GRADE certainty level: ⊕⊕⊕⊕ high, ⊕⊕⊕○ moderate, ⊕⊕○○ low, ⊕○○○ very low.

4. Discussion

This systematic review and meta-analysis of 22 observational studies, encompassing over 45,000 participants, identified a positive epidemiological association between GERD and CRS. Patients with CRS had higher odds of co-existing GERD than controls (pooled OR 5.39 in case–control studies using objective diagnostics; aOR 1.77 in longitudinal cohorts). The association was observed across both CRS phenotypes (CRSwNP and CRSsNP) and across geographically diverse populations. However, given the observational nature of the included evidence, the unexplained heterogeneity, and the variation in effect size by diagnostic method, the present findings should be interpreted as evidence of association rather than evidence of causation.

4.1. Pathophysiological Mechanisms

The statistical association identified in this meta-analysis is consistent with two pathophysiological hypotheses that have been proposed to link the upper gastrointestinal tract and the upper airway: direct aerodigestive microaspiration and an indirect vagally mediated neurogenic reflex. However, an epidemiological association is also compatible with shared underlying risk factors (e.g., systemic inflammation, obesity, smoking, allergic predisposition) and does not validate either mechanistic hypothesis. Subgroup analysis of objective diagnostic tools revealed that studies employing pepsin assays demonstrated

the strongest association (OR 15.20). Pepsin A, a proteolytic enzyme exclusively produced in the stomach, was detected in the nasal secretions and tissues of CRS patients but was largely absent in controls [11,42,43,51]. This finding is consistent with, though it does not establish, direct microaspiration of gastric contents into the nasopharynx as one contributing mechanism. Once deposited on the sinonasal mucosa, pepsin can be reactivated in the acidic environment of the upper airway (or even intracellularly at neutral pH), leading to epithelial barrier disruption, ciliary dysfunction, and release of inflammatory cytokines such as Interleukin-8 (IL-8) and Tumor Necrosis Factor-alpha (TNF- α) [4,5,11].

Alternatively, the vagally mediated reflex theory posits that distal esophageal acidification stimulates vagal afferents, triggering a reflex arc that induces parasympathetic-mediated nasal congestion and hypersecretion [4,33]. While this study was not designed to mechanistically dissect these pathways, the significant association observed in studies utilizing distal esophageal pH monitoring (OR 6.94) [34,40,49] is compatible with an indirect reflex mechanism contributing to sinonasal pathology, independent of direct refluxate contact.

4.2. Clinical Implications and Phenotypes

The results suggest a clinically relevant overlap between GERD and CRS. The pooled prevalence of GERD in the CRS population was 60% (95% CI: 38–80%), although this estimate carries wide uncertainty and a 95% PI that spans nearly the full possible range (4–100%), reflecting the small number and high heterogeneity of contributing studies. The point estimate is nevertheless higher than the typical general-population prevalence of 10–20% [5,41], suggesting that GERD should be considered a major comorbidity in CRS, particularly in patients with recalcitrant disease. The meta-regression analysis indicated a stronger association in younger patients, which aligns with previous pediatric data [37], and suggests that the impact of reflux on the upper airway may be more pronounced or etiologically distinct in younger cohorts compared to older adults, where multifactorial inflammatory processes (e.g., immunosenescence and polypharmacy) may dilute the reflux signal.

We also observed that the association held true for both CRSwNP and CRSsNP phenotypes, although the magnitude was marginally higher for CRSsNP in the adjusted analyses. This aligns with the hypothesis that CRSsNP is often characterized by a Th1-skewed inflammatory profile, which may be more susceptible to or driven by chemical irritation from acid reflux, compared with the Th2-driven eosinophilic inflammation typical of CRSwNP [47,53]. However, the presence of pepsin in nasal polyps [11] suggests that reflux may exacerbate eosinophilic inflammation, potentially by disrupting the epithelial barrier and facilitating antigen penetration.

4.3. Diagnostic and Therapeutic Considerations

The most striking finding of this meta-analysis is the marked discrepancy in effect estimates between studies using objective diagnostic methods (pepsin assay OR 15.20; pH-metry OR 6.94) and those relying on subjective questionnaires or self-report (OR 1.43, 95% CI: 0.04–56.78, non-significant). This approximately ten-fold difference in effect size indicates that the choice of diagnostic methodology is a major source of measurement bias and constitutes the central methodological limitation of the literature.

Two non-mutually-exclusive interpretations are plausible. First, subjective questionnaires lack sensitivity for extraesophageal/laryngopharyngeal reflux, which often presents as silent reflux without classic heartburn [4,40], leading to under-ascertainment and attenuation of the association. Second, objective tests are performed in selected patients in tertiary referral centers, where spectrum bias and small-sample effects may inflate the apparent association. The largest objective effect estimate in our analysis (OR 121) originated from

a study of only ten participants [42]. Because these alternative explanations cannot be disentangled from the available data, the objective and subjective subgroup estimates were presented as the primary stratified findings rather than emphasizing a single pooled OR. Objective reflux testing in CRS should be reserved for selected patients with medically and surgically refractory disease, in whom an individualized diagnostic and management plan is appropriate, rather than recommended for unselected CRS populations.

Our analysis identifies an association rather than evidence of causation or treatment efficacy. The single Mendelian randomization study included in this review [52] provides supportive genetic evidence consistent with a causal effect of GERD on CRS, but Mendelian randomization rests on its assumptions—instrument validity, no horizontal pleiotropy, and monotonicity—and a single MR study should not be regarded as definitive. Whether anti-reflux interventions (proton-pump inhibitors, alginates, lifestyle modification, or surgical anti-reflux procedures) improve sinonasal outcomes in CRS patients with co-existing GERD remains an open question that can be answered by adequately powered prospective randomized trials. Until such evidence is available, anti-reflux therapy in CRS patients should be guided by the management of GERD on its merits rather than by an expectation of sinonasal benefit.

4.4. Strengths

The strengths of this meta-analysis include the rigorous search strategy, the inclusion of a large number of high-quality observational studies, and the use of robust statistical methods (REML and HKSJ adjustment) to handle heterogeneity. In addition, it incorporates complementary evidence types, including a Mendelian randomization study, although that single study is contingent on its assumptions and is included as supportive rather than definitive evidence.

4.5. Limitations

The substantial residual heterogeneity ($I^2 = 69.4\%$ for case–control studies, 89.5% for longitudinal studies, and 88.7% for prevalence) was only partially explained by the pre-defined subgroup and meta-regression analyses. The single largest identifiable source of variance was GERD diagnostic modality (subgroup test $p = 0.0002$), which alone differentiated effect estimates by approximately one order of magnitude (objective pepsin OR 15.20; pH-metry OR 6.94; subjective questionnaires OR 1.43). Additional contributory sources include inconsistencies in CRS case definition (EPOS criteria, ICD-9/10 codes, clinical/endoscopic diagnosis, or symptom-based questionnaires), heterogeneity in control-group selection (general population, hospital controls, or administrative cohorts), marked differences in study size and design (small case–control series vs. large administrative-database cohorts of >100,000 participants), and variability in population characteristics including mean age, sex distribution, and comorbidity prevalence. Meta-regression for mean age, mean BMI, and asthma prevalence accounted for an additional 0–25% of residual variance. The wide 95% PI for the primary outcome (0.40–72.64 for case–control studies; 1.01–3.10 for longitudinal cohorts) indicates that effect estimates in future similar settings may differ from the pooled values, and the pooled estimates should therefore be interpreted with appropriate caution.

Because the predefined subgroup and meta-regression analyses explained only a limited proportion of this inconsistency, residual I^2 remained above 60% in the principal pooled analyses, the summary point estimates should be regarded as approximate central tendencies rather than precise effect sizes. In this setting, the wide 95% prediction intervals (0.40–72.64 for the objective case–control odds ratio and 1.01–3.10 for the longitudinal estimate) convey the uncertainty applicable to future comparable studies more faithfully

than the confidence intervals around the pooled means. This unexplained inconsistency is the principal reason the certainty of the evidence was downgraded for inconsistency under GRADE.

Relevant confounders of the GERD–CRS association, including tobacco smoking, asthma, allergic rhinitis, obesity, alcohol consumption, proton-pump-inhibitor and non-steroidal anti-inflammatory drug use, and socioeconomic status, were inconsistently reported and inconsistently adjusted for across the included studies. Although our study-level meta-regression suggested that mean age, mean BMI, and asthma prevalence did not significantly moderate the pooled effect, ecological-level adjustment is a weak surrogate for individual-level confounder control, and unmeasured confounding (e.g., shared lifestyle factors that independently increase the risk of both GERD and CRS) cannot be excluded.

All included studies were observational; consequently, the association reported here does not establish a causal relationship. The single included Mendelian randomization study [52] provides supportive genetic evidence consistent with a causal effect, but is contingent on instrument validity and the absence of horizontal pleiotropy and requires replication. Retrospective ICD-code-based studies (e.g., [36,37,41,44,45,47]) are vulnerable to differential misclassification of both exposure and outcome, particularly because GERD and CRS are under-coded in administrative data.

Asymmetry in the contour-enhanced funnel plot and a borderline Begg’s test ($p = 0.060$) raise concern for small-study effects in the LPR-prevalence outcome; the magnitude of this specific association should be interpreted with caution. A single small study ($n = 10$) [42] disproportionately influenced the objective-pepsin subgroup estimate. CRS and GERD case definitions varied across studies, and this variability is a source of measurement heterogeneity that no statistical adjustment can fully overcome.

A further, specific source of clinical heterogeneity is the conflation of classical (esophageal) gastroesophageal reflux disease with extraesophageal/LPR. Several of the studies we classified as using objective diagnostics relied on nasopharyngeal pH probes or nasal-secretion pepsin assays that more strictly characterize LPR than esophageal GERD, whereas others diagnosed GERD on the basis of distal esophageal pH-metry, endoscopy, or symptom questionnaires. Because these entities differ in anatomical site, biological plausibility for sinonasal injury, and measurement properties, pooling LPR-predominant and GERD-predominant studies within a single analytical framework inflates both the pooled objective-diagnostic odds ratio and the observed between-study heterogeneity. Accordingly, the pepsin- and pH-based (“objective”) estimates are best interpreted as reflecting extraesophageal/LPR exposure and are reported as a distinct, lower-certainty outcome in the GRADE summary of findings rather than as a measure of classical GERD.

The heterogeneity in case definitions for both conditions is a source of measurement (misclassification) bias whose likely direction differs by instrument. CRS was variously defined by EPOS or AAO-HNS criteria, ICD-9/ICD-10 codes, endoscopic and/or computed-tomography findings, or symptom questionnaires, and reflux by distal esophageal pH-metry, multichannel intraluminal impedance-pH, pepsin assays, validated questionnaires, or self-reported physician diagnosis. Where exposure or outcome was ascertained with subjective or administrative instruments, non-differential misclassification would be expected to bias the association toward the null, which may contribute to the attenuated estimate observed in the subjective-diagnostic subgroup. In retrospective ICD-code-based datasets, differential under-coding of GERD and CRS could bias the estimate in either direction. No statistical adjustment can overcome this definitional heterogeneity, and it should be regarded as a structural limitation of the evidence base.

5. Conclusions

This systematic review and meta-analysis of observational evidence demonstrates a positive association between GERD and CRS, with moderate certainty for the overall outcome. The magnitude of this association varies by diagnostic method, being strongest in studies using objective testing (pepsin assay, pH-metry) while attenuated and not statistically significant when reflux is assessed by subjective questionnaires. Substantial unexplained heterogeneity, residual confounding, and reliance on observational designs limit causal inference. These findings support the biological plausibility of an extraesophageal reflux contribution to CRS pathophysiology, but they do not establish causation, do not quantify a treatment-modifiable disease burden, and do not justify routine objective reflux testing in unselected CRS patients. The high and largely unexplained between-study heterogeneity, together with the wide prediction intervals, means that the magnitude of the pooled estimates should be interpreted as an indication of direction rather than as a precise quantification of risk. In patients with medically and surgically refractory CRS, individualized assessment for clinically significant reflux remains a reasonable consideration, but should be guided by clinical judgment rather than applied as a generalized recommendation. Priority research needs include standardization of objective diagnostic criteria for extraesophageal/laryngopharyngeal reflux, prospective cohort studies with pre-specified adjustment for shared confounders (smoking, asthma, BMI, allergic rhinitis), and adequately powered randomized controlled trials of anti-reflux interventions with patient-relevant sinonasal endpoints.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/surgeries7030079/s1>. Supplementary Materials S1: Full Electronic Search Strategies. Table S1: PRISMA 2020 checklist [12]. Table S2: Expanded characteristics of the included studies (n = 22), including sex distribution, mean body-mass index, and asthma prevalence used in the meta-regression analyses.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

aOR	Adjusted Odds Ratio
BMI	Body Mass Index
CI	Confidence Interval
CRS	Chronic Rhinosinusitis
CRSsNP	Chronic Rhinosinusitis without Nasal Polyps
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
FESS	Functional Endoscopic Sinus Surgery
GERD	Gastroesophageal Reflux Disease
GP	General Practitioner
GWAS	Genome-Wide Association Study
HKSJ	Hartung–Knapp–Sidik–Jonkman
HR	Hazard Ratio
ICD	International Classification of Diseases
IVW	Inverse Variance Weighted
LPR	Laryngopharyngeal Reflux
MD	Mean Difference
MII-pH	Multichannel Intraluminal impedance-pH
OR	Odds Ratio
PI	Prediction Interval
PPI	Proton Pump Inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
REML	Restricted Maximum Likelihood
RR	Risk Ratio
RRR	Relative Risk Ratio
RSI	Reflux Symptom Index
SMD	Standardized Mean Difference
SNOT-20	Sino-Nasal Outcome Test-20
URS	Upper Respiratory Symptoms

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