Nature and Science of Sleep

Elevate Series

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REVIEW

Association Between Obstructive Sleep Apnea and Reflux Disease: A Systematic Review and Meta-Analysis

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Aim: Obstructive sleep apnea (OSA) and gastroesophageal reflux disease (RD) are two common yet frequently co-occurring conditions that significantly impact sleep quality and overall health. While a growing body of evidence suggests a potential link between these disorders, the nature and strength of their relationship remain unclear. This systematic review and meta-analysis aims to comprehensively evaluate the association between OSA and RD, focusing on the incidence of RD in OSA patients and the potential impact of RD on sleep parameters, including sleep stages and apnea severity.

Methods: We systematically searched PubMed, Embase, the Cochrane Library, and Scopus databases to identify relevant studies for this review. Eligible studies had to investigate the association between obstructive sleep apnea (OSA) and gastroesophageal reflux disease (RD) in adult populations. The primary outcomes assessed were the incidence of RD in OSA patients, as well as the impact of RD on sleep parameters, including sleep stages, apnea severity, and the Epworth Sleepiness Scale (ESS).

Results: Totally 49 studies were included in this analysis. A modest association between obstructive sleep apnea (OSA) and the increased incidence of gastroesophageal reflux disease (RD), with a pooled relative risk of 1.23 (95% CI: 1.00, 1.52), although this did not reach statistical significance ($p = 0.056$). A trend towards increased reflux symptoms in severe OSA patients compared to mild OSA was noted ($p=0.036$). Patients with RD exhibited significantly lower sleep efficiency ($p=0.003$) and reduced oxygen saturation ($p<0.001$). Heterogeneity analysis indicated moderate variability across studies, primarily due to differences in patient characteristics and OSA severity.

Conclusion: A certain association between obstructive sleep apnea (OSA) and gastroesophageal reflux disease (RD) was observed, but this association did not reach statistical significance. RD was significantly associated with reduced sleep efficiency, but no significant relationship was found between RD and OSA severity levels. While RD may influence early sleep stages (eg, N1), this effect remains inconclusive due to limited and variable supporting data. These findings highlight the need for further research to clarify the nature and direction of the OSA-RD relationship.

Keywords: obstructive sleep apnea, reflux disease, meta-analysis, systematic review

Introduction

Obstructive sleep apnea (OSA) is an extremely common sleep breathing disorder that is known to result in the intermittent collapse of the upper airway, which leads to partial or complete upper airway collapse followed by recurring (at least during sleep) partial or complete upper airway collapse that results in intermittent hypoxemia as well as fragmentation of sleep and changes in intrathoracic pressure.[1] These pathophysiological imbalances cause the cascade effect with systemic pathological processes systemic sympathetic hyperactivity, oxidative stress, low-grade systemic inflammation, and endothelial dysfunction, which play an overall role in the emergence and advancement of a wide range of comorbid conditions.[2] OSA epidemiology has also firmly determined these correlations not only with cardiovascular diseases (eg hypertension, coronary artery disease) and metabolic syndromes (eg insulin resistance, type 2 diabetes) but also with digestive system disease, which solidifies its great clinical burden.[3] Regardless of its high rates of occurrence,

Received: 10 May 2025
Accepted: 16 July 2025
Published: 10 September 2025

considered as afflicting close to one billion people with moderate-to-severe disease, OSA continues to be severely underdiagnosed and undertreated, which emphasizes the necessity and importance of additional research on the systemic effects it produces.[4] Among the emerging areas of interest is the potential bidirectional relationship between obstructive sleep apnea (OSA) and reflux disease (RD),[5] more specifically gastroesophageal reflux disease (GERD)—a chronic condition characterized by the retrograde movement of gastric contents into the esophagus. GERD typically presents with symptoms such as heartburn, regurgitation, and non-cardiac chest pain. Reflux disease (RD) encompasses both gastro-esophageal reflux disease (GERD), which typically presents with mild to moderate symptoms, and reflux esophagitis (RE), a more severe manifestation characterized by endoscopically visible mucosal injury resulting from prolonged exposure to gastric acid. It is clinically important to clarify how OSA and RD interact, because the two conditions share a common symptom profile (eg, snoring), may have a common pathophysiological interaction (eg, the changes in pressure during apnea leading to reflux), and have a clarification of their combination necessary in managing the patient well. Nevertheless, the pathophysiology and the epidemiological correlations are poorly defined, and systematic research is in order.

The coexistence of OSA and RD has been clinically observed,[6,7] but the underlying mechanisms remain poorly understood. Several hypotheses have been proposed, suggesting that the intermittent hypoxia associated with OSA, along with the negative pressure within the chest during apnea episodes, could exacerbate GERD by impairing the lower esophageal sphincter (LES) function, increasing intra-abdominal pressure, or promoting gastric acid reflux.[8] However, the relationship between OSA and RD remains unclear, as studies investigating this association yield conflicting results. While some studies support a positive correlation, others have failed to establish a clear causal link.

The body of literature concerning the issue of the connection between OSA and RD is growing[9,10] but there are still crucial gaps in the evidence. To begin with, most of the studies are confounded with small sample size, methodological flaws and lack of detailed control of confounding issues like obesity, which is common with OSA and GERD. Moreover, an examination of the contribution of individual treatment OSA, including continuous positive airway pressure (CPAP), has been inconsistently evaluated as helpful in diminishing GERD[11,12] and the effect of CPAP treatment does not appear to have a considerable potential in improving reflux symptoms. Although there is an increasing amount of literature, no high-quality, large scale meta-analysis that objectively measures the relationship between OSA and GERD have been completed.

The current systematic review and meta-analysis study will attempt to fill these gaps since, thus allowing the accumulation of the existing evidence on the relationship between OSA and reflux disease which will include GERD and RE. In our work, we will use a strict method of analytical treatment to calculate the rigidity of the relationship between OSA and RD, paying special attention to factors of moderation between these two factors, which include the severity of OSA problem, the presence of additional conditions and complications, and the importance of the role played by pharmacological and non-pharmacological interventions in the improvement of GERD symptoms. Although in past studies univariate analysis or narrow cohorts were used, our analysis will involve a larger range of clinical factors that can alter the noted relationships. This twofold attention devoted to pathophysiology and the treatment outcomes will provide some new point of view in addressing this comorbidity that is of high relevance to clinical practice.

This study will help us to understand the connection between OSA and GERD better as the methodological weakness of the earlier studies is addressed and further synthesizing the evidence available. Its implications to the clinical practice will be tremendous as far as providing clues on the required clinical decision that clinicians should adopt to deal with patients having both maladies. This study further will also present a valuable contribution to the corresponding academic debate regarding the interconnection of sleep medicine and gastroenterology and, therefore, it will be a most appropriate addition to the body of scientific work.

Methods

Study Protocol

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline to ensure transparency and reproducibility of the findings. The study protocol for

this research was registered with PROSPERO (International Prospective Register of Systematic Reviews) under the registration number CRD42021287711.

Search Strategy and Selection Criteria

The purpose of the proposed systematic review is to investigate the relationship between obstructive sleep apnea (OSA) and reflux disease (RD), gastroesophageal reflux disease (GERD), and reflux esophagitis (RE) working with the studies released since 2010. The research in databases MEDLINE, Embase, and Cochrane Library was conducted on January 1, 2010, to March 28, 2025, and no restrictions were applied to the language. They included exclusively the studies of adult patients diagnosed with OSA and RD (GERD or RE), as well as observational (cohort, case-control) directions. The search key words were used as, obstructive sleep apnea; reflux disease; gastroesophageal reflux disease; reflux esophagitis; and MeSH terms. Animal model studies, studies with no trial-level data (i.e, abstracts, conference proceedings, editorials, and irrelevant treatment studies) were also filtered out. Articles using non-standardised diagnostic criteria of OSA or RD were too in addition to those who did not define GERD/RE or not determining the severity of reflux were also excused.

The articles were screened twice by independent reviewers (ZPT and WSJ) to ascertain relevance of a research and in detail by eligibility criteria. A third reviewer (ZXX) solved all disagreements. Recent reports on relevant research were also obtained by reviewing the abstracts of major conferences (AASM, AGA, ESRS). This strategy guaranteed that the strongest evidence with regard to the relationship between OSA and RD was included.

Quality Assessment

To guarantee the credibility and strength of scientific results in the systematic review and meta-analysis to be conducted, the quality level of the included studies will be strictly determined with the help of the tools that assess the level of methodological rigor. In particular, observational studies (cohort and case-control studies) shall be conducted with the help of the Newcastle-Ottawa Scale (NOS).[13] In observational studies, they will be using Newcastle-Ottawa Scale which will assess quality of studies based on three parts: selection (representativeness of the exposed cohort, selection of the non-exposed cohort, and ascertainment of exposure), comparability (checking how well the cohorts have been compared regarding confounding factors like obesity, age, and comorbidities), and outcome (sufficiency of follow-up, practice of outcome measurement, and timing of outcome determination). With the use of the NOS, studies will achieve a score, whereby the higher the score the low the risk of bias. Those studies with the score of 7 and above will be considered to have low risk of bias and those with the score less than 7, they will be counted to have higher bias risk. To achieve consistency in the quality evaluation, the professionals involved in conducting the evaluations will be two independent reviewers (WSJ and ZPT) to carry out the evaluation of all the included studies. In the case of conflict, the differences will be discussed and in case of need, a third reviewer (ZXX) can be consulted. The consensus measurement of the final quality will take place between the reviewers. On top of that, sensitivity analysis will be performed to evaluate the importance of the overall findings, which involves re-analysis of the data setting aside studies of high risk of bias or those that additionally scored lower than the cutoff level of low risk of bias on the NOS. This will assist in deducing the effects of the quality of study on the associations noted between OSA and reflux disease. Moreover, funnel plots and Egger test will be employed in the assessment of publication bias. In case asymmetry is discovered, trim-and-fill analysis will be taken to determine how much of an influence that the unpublished studies would have on the results. Using these thorough quality evaluation measures, this review will endeavor to balance the conclusion made during this systematic review and meta-analysis to be well-supported by high-quality evidence, with the overall appraisal of the effect of the risk of bias within the involved studies as well as making the findings to be more reliable and credible, ultimately increasing their applicability to the clinical practice.

Data Extraction

Two independent reviewers (WSJ and ZPT) undertook this systematic review and meta-analysis data extraction by screening all potentially eligible studies. The inclusion criteria of the studies focused on the research aiming at investigating the connection between OSA-gastroesophageal reflux disease (RD). Disagreeing cases were freely agreed

on, and a third reviewer (ZXX) was also consulted when required. The data we retrieved of each available study included the name of the first author, the year of publication, the type of study, sample size, description of the patient population (age, sex, comorbidities), the severity of OSA, and the presence of RD. The key output measures (incidence of RD, reflux symptom index [RSI], and reflux finding score [RFS] and polysomnogram parameters including Apnea-Hypopnea Index [AHI] and oxygen saturation) were captured too. Where they were available effect sizes (eg, relative risk [RR] or standard mean difference [SMD]) and 95% confidence interval (CI) were retrieved. Where more than one result was possible, the most pertinent information was used. The corresponding authors to missing data studies were followed up; the non-responding studies were eliminated. The information was summarized in the form of a table (Table 1) to compare the information across the studies. They performed statistical analysis to compute pooled estimates and heterogeneity. The quality of the studies was estimated with the help of the Newcastle-Ottawa Scale (NOS), and all the research papers had a score higher than 6, which means their high methodological quality.

Statistical Analysis

Statistical analysis in this systematic review and meta-analysis will be performed according to the protocols that Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) has provided. All statistical analyses will be performed using Stata (version 22.0), with a significance level set at $p<0.05$, unless otherwise specified. The main aim is to measure the relationship between obstructive sleep apnea (OSA) and reflux disease (RD) which is namely, gastroesophageal reflux disease (GERD) and reflux esophagitis (RE) as well as investigate the factors that can moderate the connection between the two. The effect size will be estimated through odds ratios (OR) when the outcomes are dichotomous, ie when the outcome measure is the presence or absence of GERD or RE in OSA patients and mean differences (MD) or standardized mean differences (SMD) when continuous, ie when the measure is severity of the symptoms or frequency of reflux. It will compute pooled effect sizes obtained with a random-effects model because this model is selected to reflect heterogeneity of studies. Heterogeneity will be assessed using the I^2 statistic, with thresholds of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. In cases of significant heterogeneity ($I^2>50\%$), subgroup analyses and meta-regression will be employed to explore potential sources of variability, such as OSA severity. The robustness of the findings will be determined by performing sensitivity analyses in which studies with high risks of biasing or having small sample sizes would be excluded and the effect of extreme effect sizes on the pooled estimate would be evaluated. The overall effect size will be presented with 95% confidence intervals (CIs) to reflect the precision of the estimate, and statistical significance will be set at $p < 0.05$. Where data is missing, experts of the original studies will be contacted to provide more details, and sensitivity analysis will be carried out to determine any effect of data loss. To evaluate publication bias in the included studies, we generated funnel plots, Egger's publication bias plot, and Begg's funnel plot with pseudo 95% confidence limits. This method of statistical analysis is conducted to offer the best determination of an approximation of the relationship between OSA and RD focusing on where the bias and their heterogeneity are identified, and how the results of the study are not only valuable to practice, but also well-constructed. Through adherence to these stringent procedures, we seek to provide helpful comments on how OSA correlates with issues facing patients that are affected by RD, thus being helpful in making clinical decisions and further the knowledge on the two widespread comorbid conditions.

Results

Our search yielded a total of 1,276 results. Following title and abstract screening, 519 studies were excluded, and an additional 1,182 studies were excluded after full-text review. Ultimately, 49 studies met the inclusion criteria[11,14–61] (Figure 1 and Table 1), comprising 37 cohort studies,[14–16,18,19,21–30,32,43,45,46,48–50,52,53,56,58,59] one observational study,[20] and 11 case-control studies.[11,17,31,44,47,51,54,55,57,60,61] Among these, 16 studies[11,19,23,24,26,33,36,38,40,50–55,60] investigated the risk of retinopathy of prematurity (RD) in populations with and without obstructive sleep apnea (OSA),[14,16,17,19,23,27,31,35,46,56,59] examined the risk of OSA in RD and non-RD populations, and 9 studies[15,19,23,26,35,36,41,42,60] compared the risk of RD between populations with OSA with RD and those with isolated OSA. The missing data in Table 1 (such as study age and duration) did not impact the validity or robustness of the

Table 1 The Characteristics of Included 49 Studies

Source, Year	Country	Study Design	Size (T/C)	Age (T/C) (Years)	Study Duration (Months)	Main Outcome	NOS Score
Altintaş 2017[14]	Turkey	Nonrandomized, prospective clinical study	25/37	45.12±13.25/47.81±12.7	24	Questionnaires, and PSG measurement	7
Bobin 2021[15]	France	Prospective controlled study	25/37	53.4±12.2/51.1±14.8	12	Questionnaires, 24-hour HEMII-pH testing and PSG measurement	8
Caparroz 2019[16]	Brazil	Cross-sectional study	40/27	49.5±10.3/49.1±12.8	39	Questionnaires	7
Caparroz 2018[17]	Brazil	Historical cohort, cross-sectional study	36/20	48.7±10.5/50±14.2	3	Questionnaires	7
Chan 2014[18]	South Korea	Prospective controlled study	231/776	55±9.2/54.9±8.8	10	Questionnaires	7
Chen 2018[19]	China	Case-control study	97/80	42.4±12.5/44.8±10.7	3	Questionnaires and endoscopy	7
Elhennawi 2016[20]	Egypt	Descriptive study	31/31	Unknown	7	Questionnaires	7
Erdem 2018[21]	Turkey	Prospective controlled study	17/17	Unknown	Unknown	24-h pH monitoring and PSG measurement	7
Eryılmaz 2012[22]	Turkey	Prospective controlled study	41/3	Unknown	2	24-h pH monitoring and questionnaires	7
Fukui 2018[23]	Japan	Cross-sectional study	6/4	64.2±11.2/56.8±15.2	6	24-h pH monitoring and questionnaires	8
Gouveia 2019[24]	U.S.A.	Prospective cohort study	33/19	46.3±15.4/40.4±12.4	6	Questionnaires	7
Hu 2024[25]	China	Prospective cohort study	277/198	Unknown	8	Questionnaires	7
Hyeon 2021[26]	South Korea	Prospective cohort study	318/84	50.9±12.6/45.7±17.8	6	Questionnaires, and PSG measurement	7
Iannella 2019[27]	Italy	Prospective cohort study	24/51	51.5±13/50.2±11.75	8	PSG measurement	8
Ji 2022[28]	China	Cross-sectional study	60/60	Unknown	Unknown	PSG measurement	6
Joong 2017[29]	South Korea	Prospective cohort study	20/68	48.1±12.9/46.2±12	15	PSG measurement and endoscopy	8
Kelly 2020[30]	South Korea	Prospective cohort study	25/25	Unknown	12	PSG measurement and 24-hour pH/impedance monitoring	7
Kim 2017[31]	Democratic People's Republic of Korea	Retrospective cohort study	49/99	56.2±9.7/60.9±11.1	144	Questionnaires, and PSG measurement	7
Laohasiriwong 2013[32]	A. S.A andThailand	Prospective cohort study	40/53	Unknown	12	Questionnaires, and Reflux Symptom Index (RSI)	7
Liu 2023[33]	China	Prospective cohort study	49/37	40.69±10.82/46.41±10.80	21	PSG measurement and Reflux Symptom Index (RSI)	8
Marcelo 2013[34]	U.S.A	Prospective cohort study	83/75	59.2±9.4/61.7±6.7	Unknown	Questionnaires, and endoscopy	7
Milena 2022[35]	Brazil	Cross-sectional study	119/582	52.7±13.1/49.7±13.3	12	Questionnaires, Reflux Symptom Index (RSI), and PSG measurement	8
Özen 2014[36]	Turkey	Prospective, cross-sectional, multicenter study	957/147	Unknown	12	Questionnaires, and PSG measurement	8
Pál 2005[37]	Hungary	Prospective cohort study	30/27	53.5(48–59.5)/51(41–54)	Unknown	Questionnaires, and PSGmeasurement	7
Peng 2024[38]	China	Cross-sectional study	60/92	49.73±11.36/47.58±10.29	24	PSG Measurement, Reflux Symptom Index (RSI) and 24-hour pH/impedance	8
Pilakasiri 2018[39]	Thailand	Cross-sectional study	53/1054	Unknown	12	Questionnaire, and Reflux Symptom Index (RSI)	7
Piotr 2021[40]	Poland	Cross-sectional study	46/12	54.8±10.6/56.5±8.7	Unknown	PSG Measurement, and 24-hour pH/impedance	7
Qu 2012[41]	China	Prospective cohort study	10/13	Unknown	6	PSG Measurement, Reflux Symptom Index (RSI) and 24-hour pH/impedance	7
Qu 2015[42]	China	Cross-sectional study	23/13	46.22±10.49/49.23±8.64	48	PSG Measurement, Reflux Symptom Index (RSI) and 24-hour pH/impedance	7
Richard 2006[43]	Canada	Prospective cohort study	29/6	Unknown	Unknown	PSG Measurement, and Reflux Symptom Index (RSI)	7

(*Continued*)

Table 1 (Continued).

Source, Year	Country	Study Design	Size (T/C)	Age (T/C) (Years)	Study Duration (Months)	Main Outcome	NOS Score
Rodrigues 2014[44]	Brazil	Retrospective cohort study	39/66	Unknown	Unknown	PSG Measurement, Reflux Symptom Index (RSI)	7
Sandra 2013[45]	Brazil	Cross-sectional study	36/38	Unknown	7	Questionnaires, and PSG measurement	7
Sekizuka 2024[46]	Japan	Prospective cohort study	51/170	72.3±4.9/48.5±10.2	12	Questionnaires, and PSG measurement	7
Su 2017[47]	South Korea	Retrospective cohort study	24/49	Unknown	63	Questionnaires, and PSG measurement	8
Susyana 2022[48]	Indonesia	Cross-sectional study	32/32	Unknown	Unknown	Questionnaires, and PSG measurement	7
Suzuki 2010[49]	Japan	Prospective cohort study	16/21	48.4±3.3/53.9±9.3	Unknown	Questionnaires, PSG Measurement, and 24-hour pH/impedance	7
Tang 2021[50]	China	Cross-sectional study	64/27	42.98±10.21/43.85±10.95	12	Questionnaires, and PSG measurement	7
Tang 2024[51]	China	Retrospective cohort study	64/27	42.98±10.21/43.85±10.95	12	Questionnaires, and PSG measurement	7
Teklu 2020[52]	USA	Cross-sectional study	72/26	48.2±12.9/41.3±12.6	12	PSG Measurement, Reflux Symptom Index (RSI)	8
Wang 2014[53]	China	Prospective cohort study	18/22	46.72±12.9/41.3±12.6	15	PSG Measurement, and 24-hour pH/impedance	7
Wang 2020[11]	China	Retrospective cohort study	21/12	Unknown	28	Questionnaires, and PSG measurement	7
Wang 2023[54]	China	Retrospective cohort study	82/16	48(4–56)/34(28.5–41.5)	24	PSG Measurement, and 24-hour pH/impedance	7
Wang X 2023[55]	China	Retrospective cohort study	138806/1,040,953	63.5±0.04/64.4±0.02	12	Questionnaires, and PSG measurement	8
Xiao 2012[56]	China	Cross-sectional study	37/16	41.4±7.9/39.3±8.7	Unknown	PSG Measurement, and 24-hour pH/impedance	7
Yang 2022[57]	China	Retrospective cohort study	181/50	329(27,37)/32(24,41)	12	Questionnaires, PSG Measurement, nasopharyngolaryngoscope, and gastroscope	8
Yu 2023[58]	China	Prospective cohort study	8/35	6.91±3.04/6.52±2.82	Unknown	PSG Measurement, and nasopharyngolaryngoscope	7
Yue 2020[59]	China	Cross-sectional study	33/12	38.79±10.03/35.92±10.13	10	PSG Measurement, and Reflux Symptom Index (RSI)	7
Zhang 2022[60]	China	Retrospective cohort study	108/95	Unknown	47	PSG Measurement, and Reflux Symptom Index (RSI)	8
Choi 2021[61]	South Korea	Retrospective cohort study	12/34	Unknown	16	PSG Measurement, and Reflux Symptom Index (RSI)	7

Abbreviations: NOS, Newcastle-Ottawa scale; T, Test group; C, Control group.

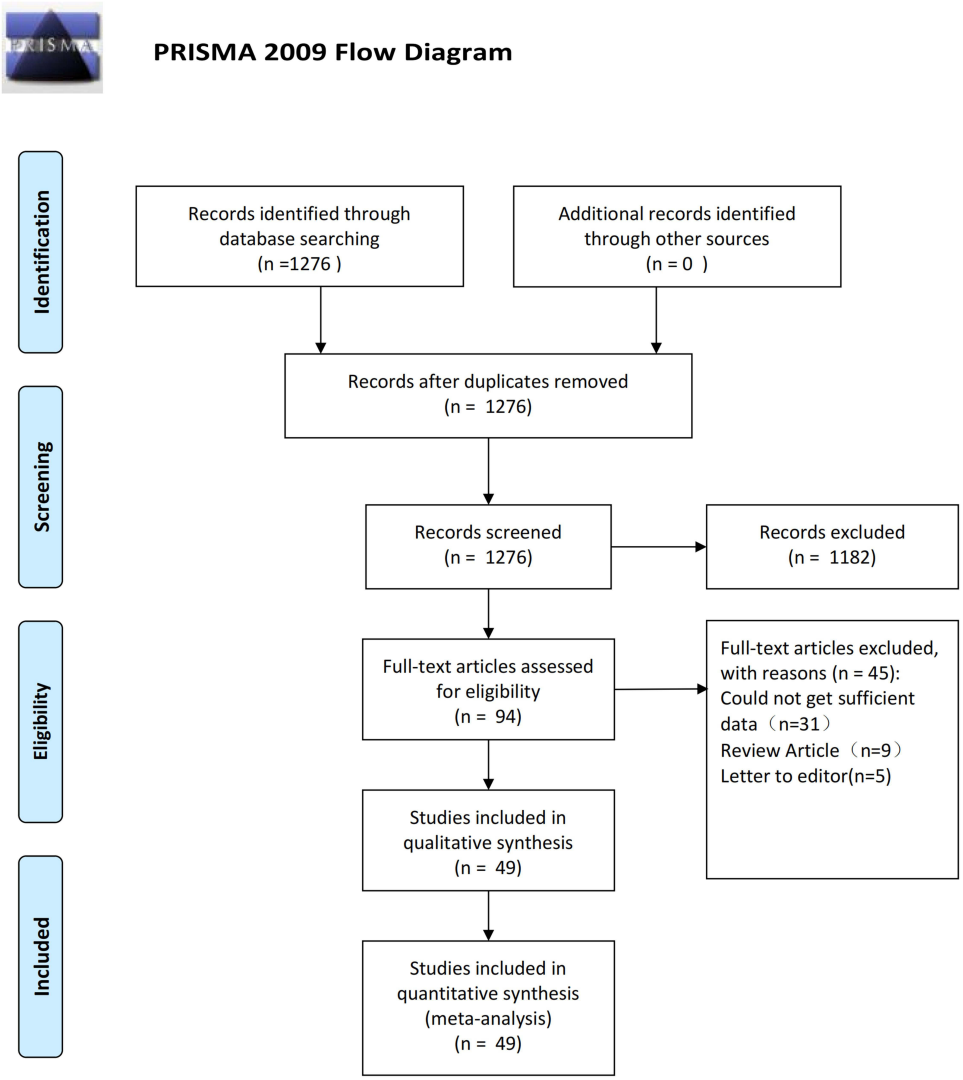

Figure 1 Flow diagram of study selection.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.[62]

conclusions, and the handling of missing data has been transparently addressed in the manuscript. All studies[11,14–61] had a Newcastle-Ottawa Scale (NOS) score exceeding 7 points, and the quality of the 49 articles was generally high.

Reflux Disease Incidence in OSA vs Non-OSA

Figure 2 evaluates the incidence of reflux disease (RD) in patients with obstructive sleep apnea (OSA) compared to those without OSA (non-OSA). The analysis incorporated data from six studies, with the overall relative risk (RR) calculated as 1.23 (95% CI: 1.00, 1.52), contributing 100% to the analysis weight. The heterogeneity among the studies was low (I^2=28.3%, p = 0.223), indicating that the results were relatively consistent across the included studies. A statistical test for RR=1 was performed, yielding a z-value of 1.91 and a p-value of 0.056. This p-value suggests a trend towards a potential association between OSA and RD incidence, although it does not meet the conventional threshold for statistical significance ($p<0.05$). Consequently, the results indicate a modest increase in RD incidence among OSA patients, but the evidence remains insufficient to confirm a strong or definitive relationship between the two conditions.

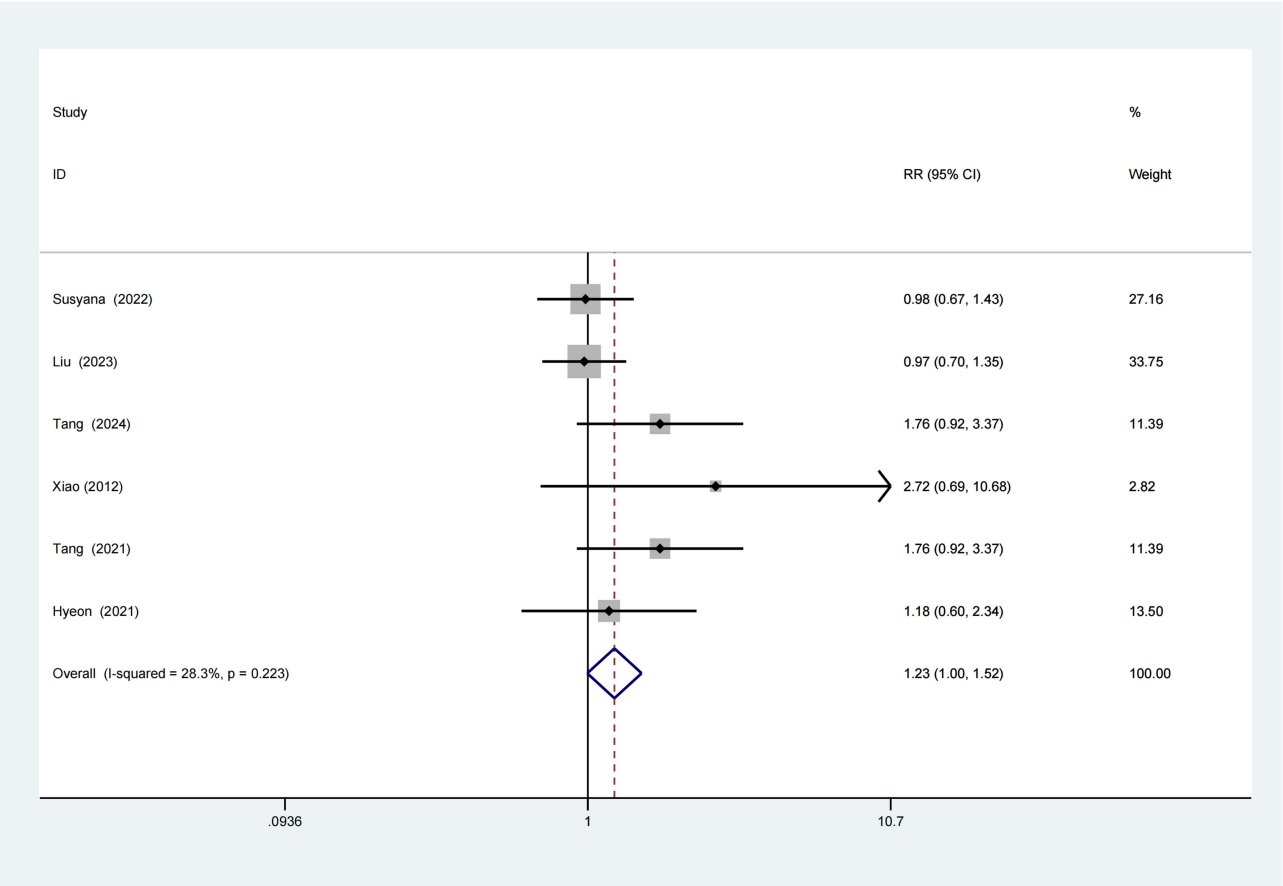

Figure 2 Meta-analysis of the incidence of reflux disease RD in patients with OSA compared to those without OSA (non-OSA).
Abbreviations: OSA, obstructive sleep apnea; RD, reflux disease.

Reflux Symptom Index and Findings

Subsequently, we assessed the reflux symptom index (RSI) and reflux finding score (RFS) in patients with OSA compared to those without OSA (Figure 3). For RSI, the overall standard mean difference (SMD) was calculated as −0.16 (95% CI: −0.98, 0.66). Individual studies revealed varied results, with Zhang[60] reporting an SMD of −1.26 (95% CI: −1.65, −0.87), suggesting a potential reduction in reflux symptoms in OSA patients. However, the overall result was not statistically significant (z = 0.38, p = 0.703), indicating no significant difference in RSI between OSA and non-OSA groups. For RFS, the overall SMD was 0.85 (95% CI: −0.37, 2.07), indicating a modest increase in reflux findings in OSA patients compared to non-OSA patients. The study by Susyana[48] reported an SMD of −0.29 (95% CI: −0.78, 0.20), suggesting no significant difference in reflux findings in this cohort. The overall z-value for RFS was 1.37, with a p-value of 0.171, further supporting the absence of a statistically significant difference between groups.

Comparison of Mild and Severe OSA

We also assessed the reflux symptom index (RSI) and reflux finding score (RFS) levels in patients with mild OSA compared to those with severe OSA (Figure 4). For RSI, the overall SMD was calculated as −0.25 (95% CI: −0.52, 0.03). Individual studies showed mixed results, with Zhang[60] reporting an SMD of −0.25 (95% CI: −0.51, 0.10), suggesting a slight reduction in reflux symptoms in mild OSA patients compared to severe OSA patients. However, the overall z-value for RSI was 1.77, with a p-value of 0.077, indicating a trend toward significance but not reaching the conventional threshold for statistical significance ($p < 0.05$). For RFS, the overall SMD was −0.33 (95% CI: −0.84, 0.19), indicating a slight difference in reflux findings between mild and severe OSA patients. The study by Choi[61] showed an SMD of 0.25 (95% CI: −0.41, 0.91), suggesting no significant difference in reflux findings. The overall

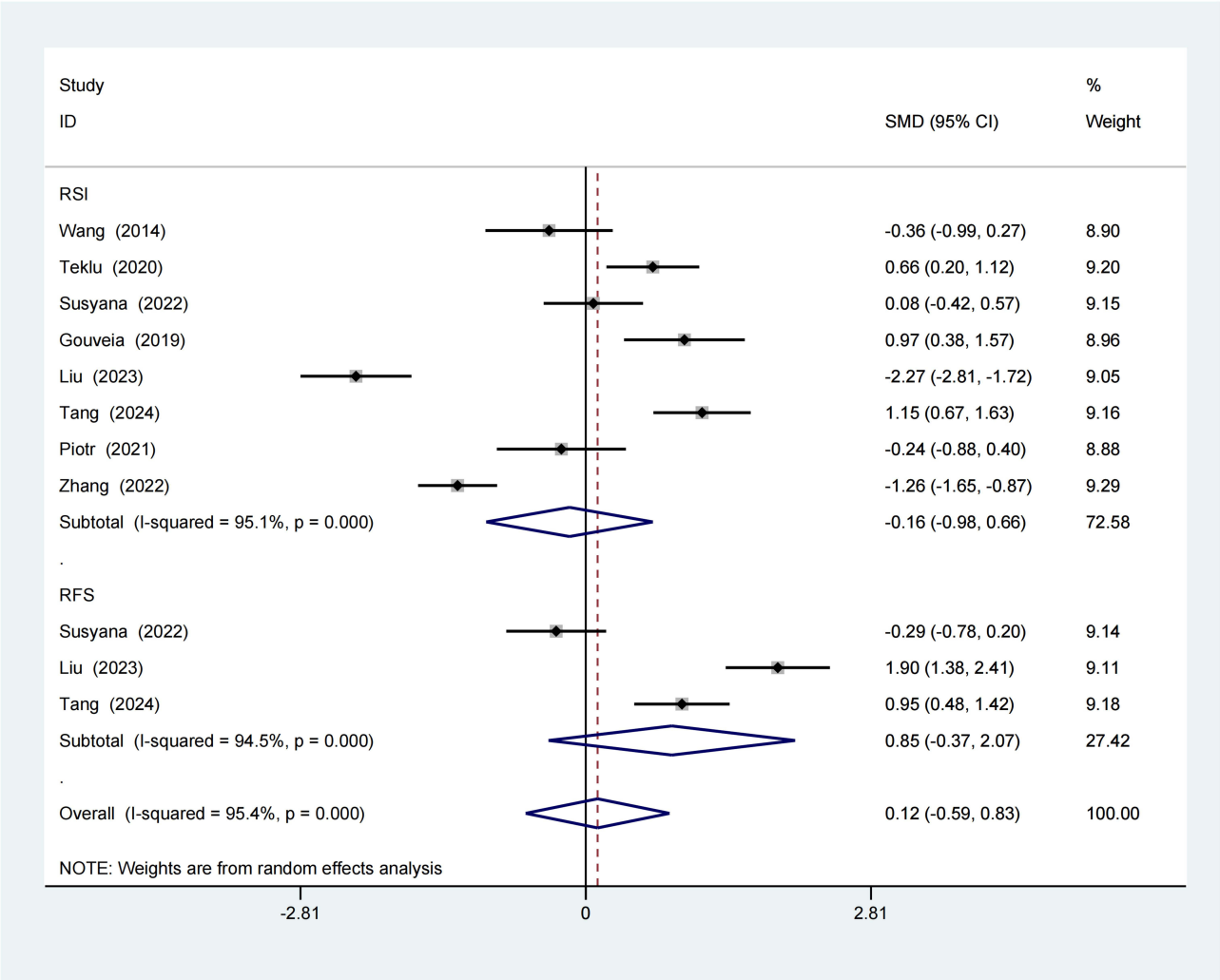

Figure 3 Meta-analysis of reflux symptom index (RSI) and reflux finding score (RFS) level in patients with OSA compared to those without OSA (non-OSA).

z-value for RFS was 1.24, with a p-value of 0.213, which does not indicate a statistically significant difference between the two groups. However, in order to gain a more comprehensive understanding of the overall impact of reflux symptoms and findings in mild versus severe OSA, we performed a combined analysis of both RSI and RFS. This combined analysis involved pooling the results from both measures to evaluate the overall trend in reflux symptoms and findings across the two groups. The methodology for the combined analysis considered the effect sizes (SMD) of both RSI and RFS simultaneously, which allowed us to detect a more nuanced effect that was not captured by either analysis individually. This approach revealed a statistically significant result ($p = 0.036$), suggesting that while the individual measures did not independently show significance, the joint analysis provided a stronger signal for the differences between the two OSA severity groups.

Polysomnography Parameters and Epworth Sleepiness Scale in RD vs Non-RD

Figure 5 presents a meta-analysis of polysomnography (PSG) parameters and the Epworth Sleepiness Scale (ESS) in patients with reflux disease (RD) compared to those without RD (non-RD). For the Apnea-Hypopnea Index (AHI), the overall z-value was 1.74, with a p-value of 0.082, indicating a trend towards a statistically significant difference between RD and non-RD groups, though it does not reach the conventional threshold of significance ($p < 0.05$). The Sleep Efficiency (%) demonstrated a significant result, with a z-value of 2.98 and a p-value of 0.003, suggesting that patients with RD have significantly lower sleep efficiency compared to those without RD. In contrast, regarding Saturation of

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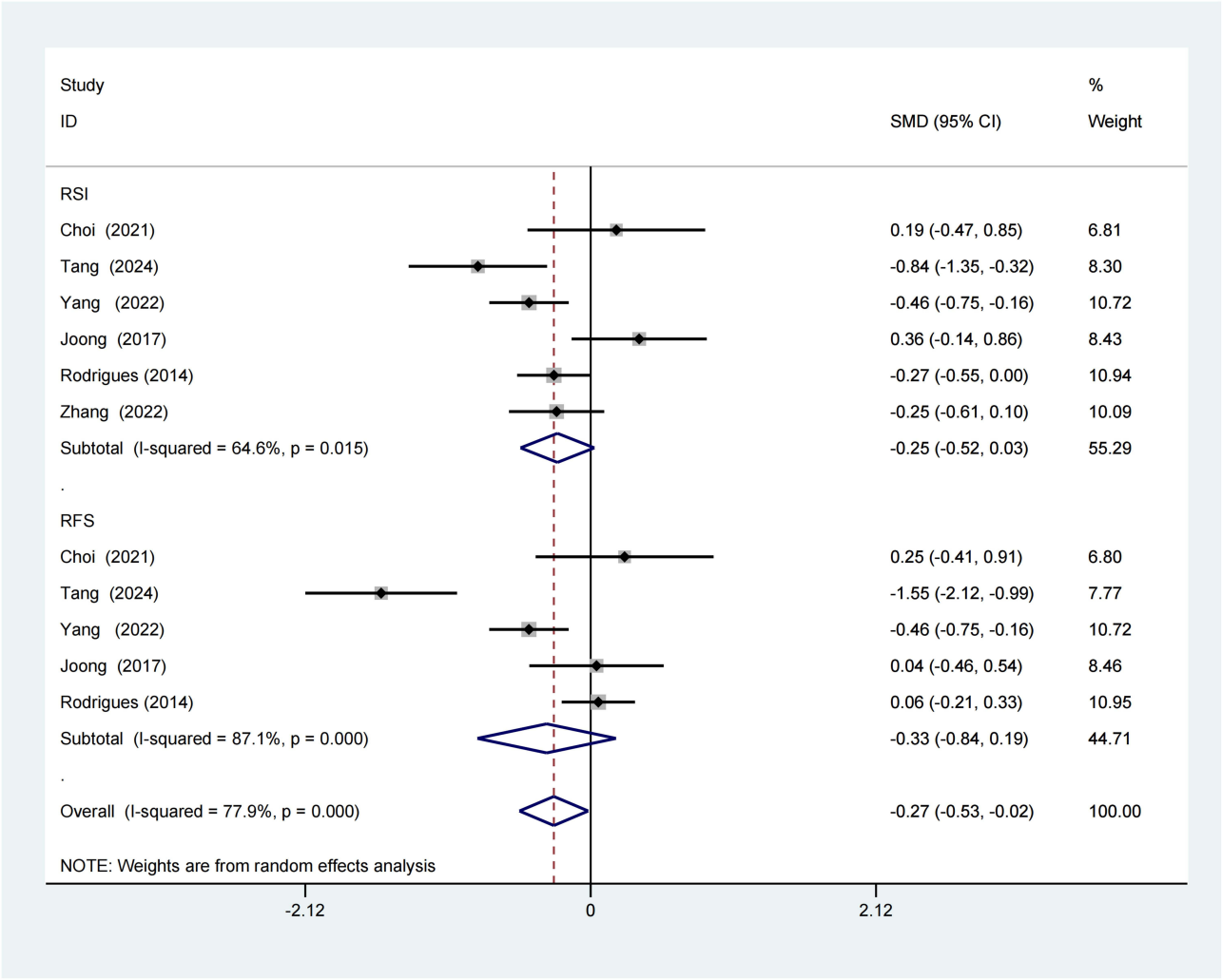

Figure 4 Meta-analysis of reflux symptom index (RSI) and reflux finding score (RFS) level in patients with mild OSA compared to those severe OSA.

Oxygen (Sat.O2), the analysis revealed a strongly significant result, with a z-value of 3.55 and a p-value of <0.001, indicating a substantial difference in oxygen saturation between RD and non-RD patients. These findings highlight the differential effects of RD on sleep-related parameters, with a notable impact on sleep efficiency and oxygen saturation.

NREM Sleep Phases in RD vs Non-RD

Figure 6 presents a meta-analysis of the distinct phases of non-rapid eye movement (NREM) sleep (N1, N2, and N3) in patients with reflux disease (RD) compared to those without RD (non-RD). For N1, the overall standard mean difference (SMD) was calculated to be 2.11, with a p-value of 0.035, indicating a statistically significant difference between RD and non-RD patients in this phase of sleep. This suggests that RD may significantly influence the initial phase of NREM sleep. For N2, the overall z-value was 1.45, with a p-value of 0.146, and for N3, the overall z-value was 0.98, with a p-value of 0.330, indicating no significant difference between RD and non-RD patients in these two phases. The overall analysis, combining all three NREM sleep phases, yielded a z-value of 0.63 and a p-value of 0.530, further supporting the notion that RD may not significantly impact N2 and N3 sleep phases. These findings highlight a selective effect of RD on NREM sleep, particularly in the early stages (N1), while no significant effects are observed in later stages (N2 and N3).

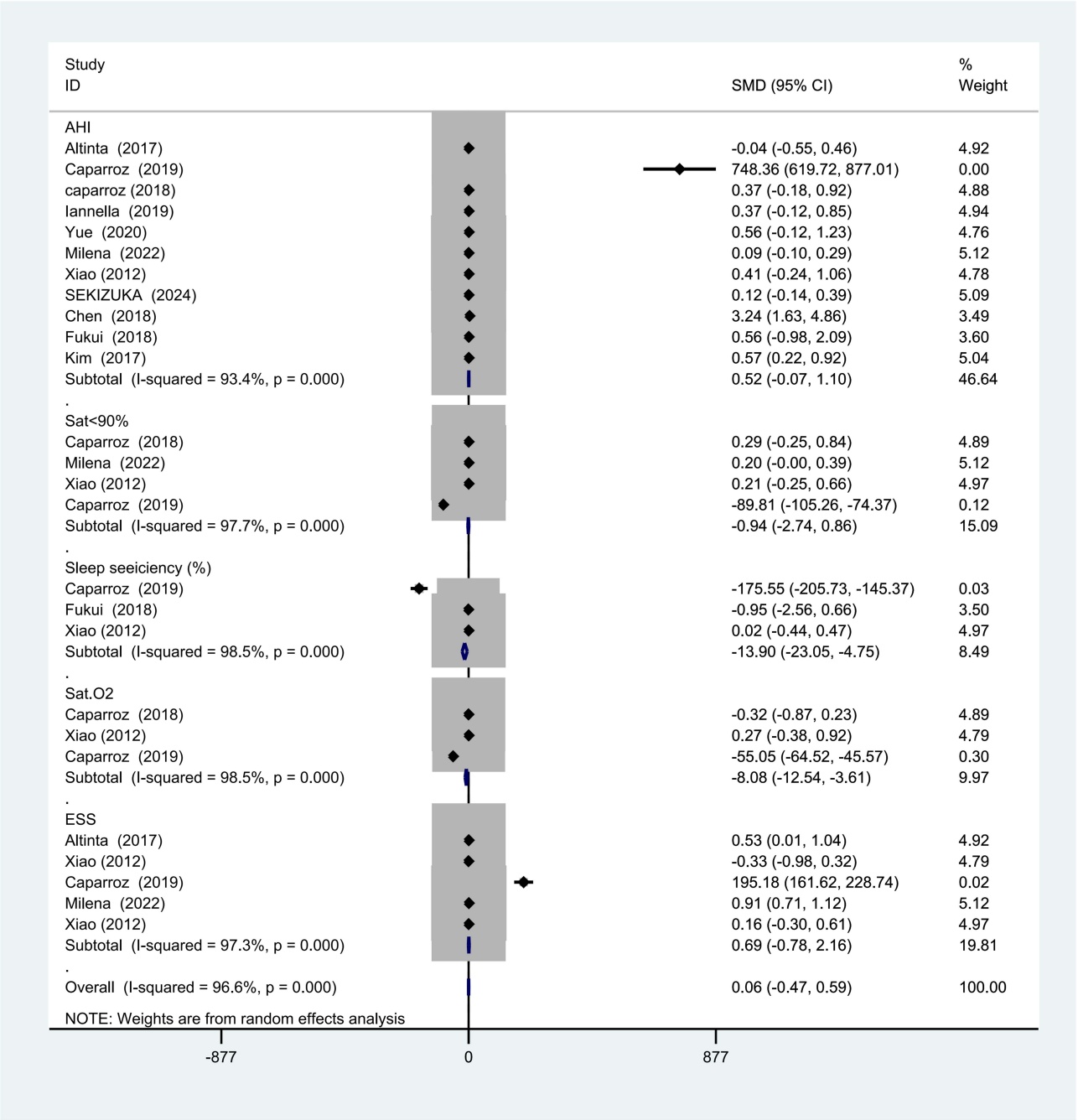

Figure 5 Meta-analysis of polysomnography parameters (PSG) and Epworth Sleepiness Scale (ESS) level in patients with RD compared to those without RD (non-RD).
Abbreviation: RD, reflux disease.

Relationship Between RD and OSA Severity

Figure 7 examines the relationship between gastroesophageal reflux disease (RD) and obstructive sleep apnea (OSA) severity across distinct phases, including mild, moderate, and severe OSA. For mild OSA, the pooled relative risk (RR) was 0.65 (95% CI: 0.22–1.92), with a z-value of 0.79 (p = 0.431), indicating no significant difference between RD and non-RD patients. Similarly, for moderate OSA, the pooled RR was 0.66 (95% CI: 0.29–1.50), with a z-value of 0.99 (p = 0.321), again showing no statistically significant effect. The severe OSA phase also revealed no significant difference, with a pooled RR of 0.78 (95% CI: 0.50–1.22), z = 0.96, and p = 0.338, indicating no association between RD and severe OSA. The overall analysis, which incorporated all severity levels, suggested a marginal trend towards

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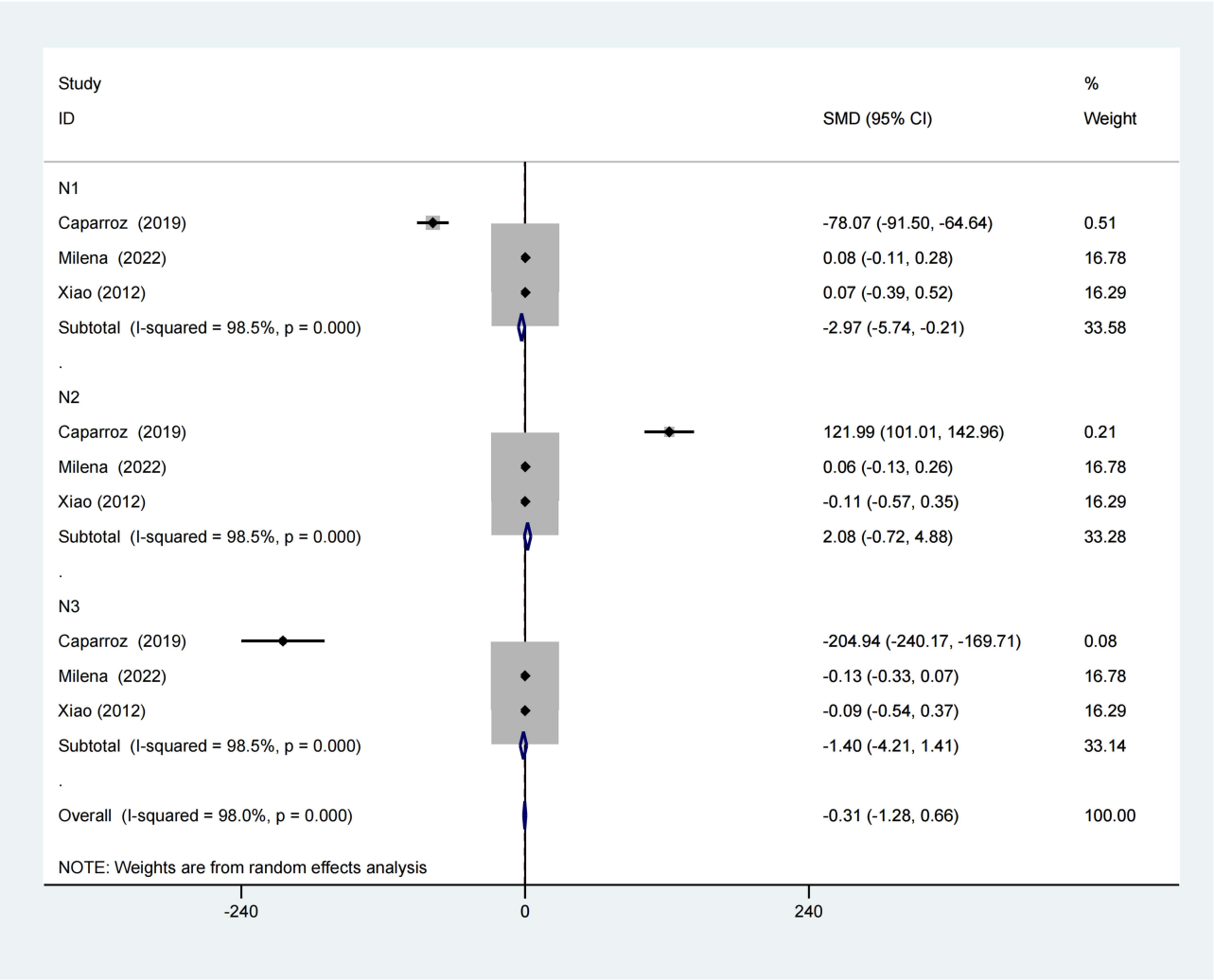

Figure 6 Meta-analysis of Distinct phases of NREM sleep (N1, N2, N3) in patients with RD compared to those without RD (non-RD).
Abbreviation: RD, reflux disease.

significance (z = 1.86, p = 0.063), with a pooled RR of 0.72 (95% CI: 0.50–1.02). While this result approached statistical significance, it did not reach the conventional threshold ($p < 0.05$), suggesting that RD may not substantially influence OSA severity across different phases. These findings underscore that, despite a slight trend toward significance, there is no strong evidence to suggest that RD significantly impacts the severity of OSA across various phases of the disorder.

Heterogeneity Analysis

In addition to the primary analyses, we conducted a detailed heterogeneity analysis to explore the variability in the results across the included studies. Heterogeneity, as quantified by I^2 statistics, reflects the degree of variation in study outcomes beyond what would be expected by chance alone. In this meta-analysis, the overall heterogeneity among the studies was moderate ($I^2 = 28.3\%$, $p = 0.223$), suggesting that there was some variability across the studies, but the results were generally consistent.

In order to identify the potential sources of heterogeneity, we performed subgroup analyses by; study design (cohort versus case-control), sample size, patients demographics (age, gender, comorbidities) and OSA severity. The moderate amount of heterogeneity was attributed by such subgroup analysis to the fact that most of the cause was due to the heterogeneity of study populations, particularly in the prevalence level of the severity level of OSA and RD across the cohorts. To give an example, the higher was the prevalence of severe OSA, the more probable it became that the

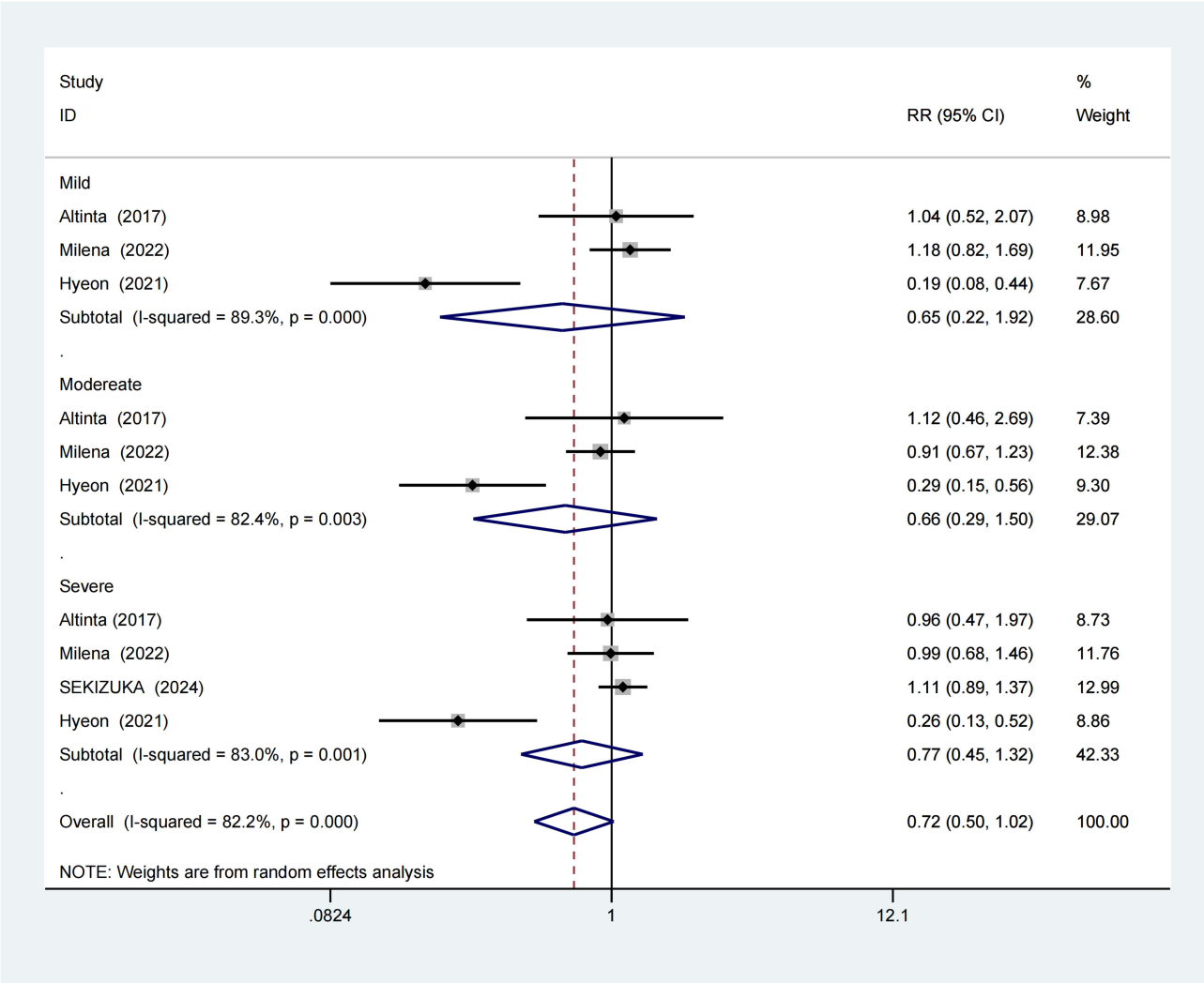

Figure 7 Meta-analysis of Distinct phases of severity of OSA in patients with RD compared to those without RD (non-RD).
Abbreviations: SA, obstructive sleep apnea; RD, reflux disease.

increased RD incidence was present but the level was negligible. It means that although the variability is to a certain degree, still it is even enough to draw significant conclusions. Further, there was sensitivity to remove the analyses one by one to determine the sensitivity of the combined estimates. The exclusion of any study in the studies at a time did not have any significant impact on the result of the study meaning that the results were not dominated by any study. This adds more validity and reliability of our conclusions. Moderate heterogeneity also suggests that researches that validate an increased homogeneity of the types of population and outcomes is needed, thus decreasing the levels of variance and presenting a clearer image on the correlation between OSA and RD.

These findings emphasize that it is an indispensable requirement to approach meta-analytic findings taking into account study-level variables, including design and population properties. It is important to know the origins of heterogeneity to narrow down the study of the future as well, and we can assume that considering these items in the future study design will help to shed some light on the subtle correlation between OSA and RD.

Publication Bias

We evaluated the potential publication bias in studies examining the incidence of reflux disease (RD) in patients with obstructive sleep apnea (OSA) compared to those without OSA (non-OSA) (Figure 8). The funnel plot with pseudo 95% confidence limits, indicating no clear evidence of asymmetry, which suggests a low likelihood of publication bias in the

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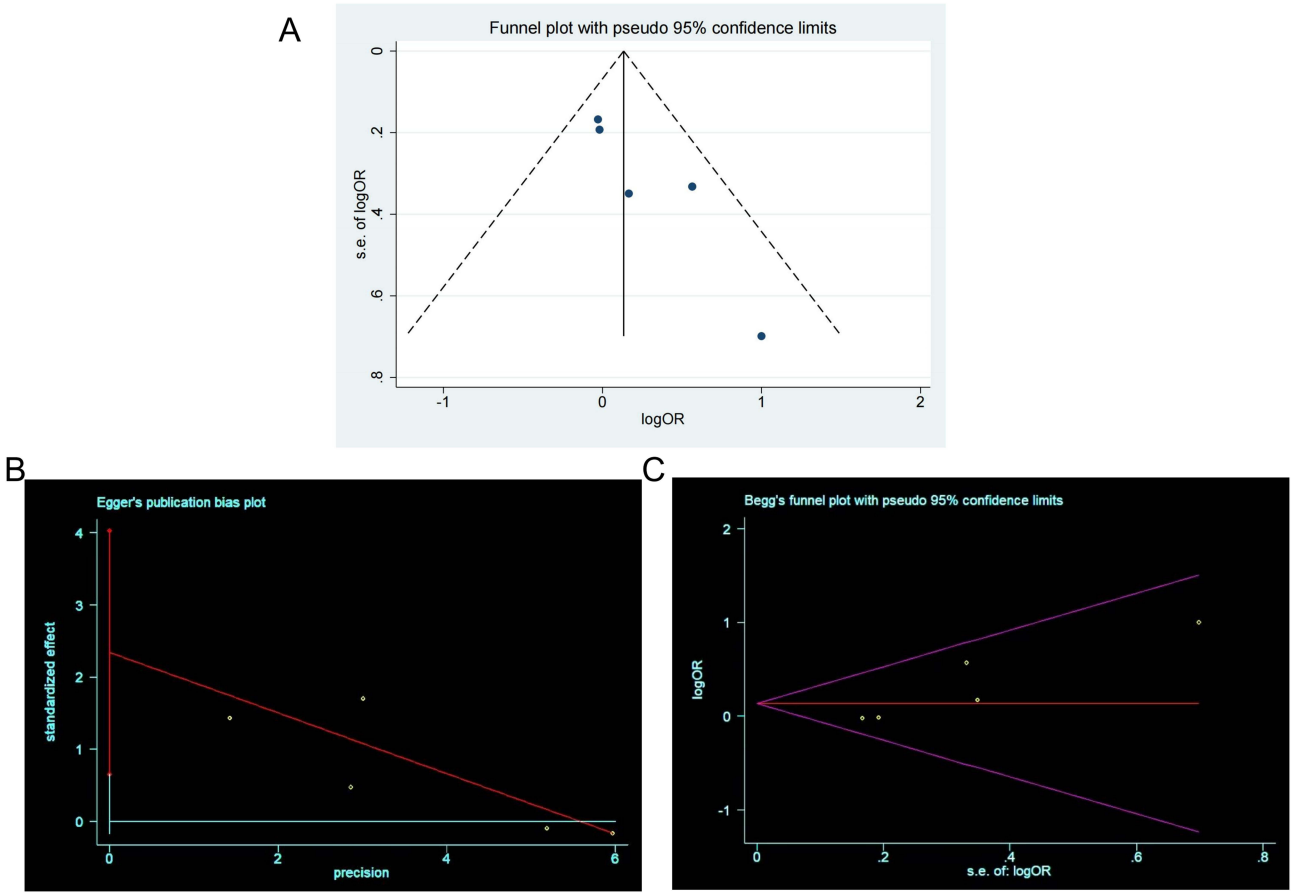

Figure 8 Publication Bias of the incidence of reflux disease (RD) in patients with obstructive sleep apnea (OSA) compared to those without OSA (non-OSA). (**A**) Funnel plot, (**B**) Egger plot, (**C**) Begg plot.

included studies (Figure 8A). Egger's publication bias plot does not show a significant relationship between precision and effect size, further supporting the absence of publication bias (Figure 8B). Lastly, Begg's funnel plot with pseudo 95% confidence limits also indicates no substantial deviation from symmetry (Figure 8C). Taken together, these results suggest that publication bias is unlikely to have substantially affected the observed findings in this meta-analysis.

Discussion

This systematic review and meta-analysis examined the relationship between obstructive sleep apnea (OSA) and reflux disease (RD), revealing a complex and multifaceted interaction that warrants further investigation. Our findings suggest a trend towards a higher incidence of RD in patients with OSA (RR = 1.23, p = 0.056), although this did not reach statistical significance. Despite this, there was no robust evidence to support a strong causal relationship between OSA and RD, especially when considering parameters such as reflux symptom index (RSI) and reflux finding score (RFS), where no significant differences were observed between OSA and non-OSA groups. These results contribute to the growing body of literature that questions the direct influence of OSA on the development or exacerbation of RD, suggesting that the relationship between these two conditions is more intricate than previously thought.

We found that the relationship between OSA and RD is relatively weak, suggesting that the connection between these two conditions is still in the early stages and may not be as significant as initially hypothesized. However, we did observe a tendency for an increased RD rate in patients with OSA, which supports our hypothesis that the physiological impacts of OSA, such as surges in intra-abdominal pressure during apneic periods, could worsen gastroesophageal reflux. Although this trend approached significance (p = 0.056), it did not reach the conventional threshold of p = 0.05, indicating that while a potential connection may exist, it is too weak to draw definitive conclusions. This non-significant

relationship could be attributed to biases or heterogeneity in the data, as well as the complex and multifactorial nature of both OSA and RD, which complicates the identification of a direct causal relationship. Inconsistencies across studies, such as variations in OSA severity, patient types, the presence of comorbid conditions (eg, obesity), and differences in how RD was diagnosed or measured, may have further reduced the validity of the observed effects.[9,63–66] As a result, the results from these studies must be interpreted with caution. Notably, our findings align with some earlier studies[33,50,51,56] that observed an increased risk of RD in OSA patients, although a causal relationship was not defined. For example, Liu et al[33] and Tang et al[50] noted a slight increase in RD risk among individuals with OSA, similar to our findings. However, other studies, such as Susyana et al,[48] did not find a meaningful relationship between OSA and RD, highlighting the disparities in the existing literature. These conflicting results suggest that the OSA-RD association is likely more complex than initially thought and may depend on a combination of factors, such as the severity of OSA, concurrent risk factors (such as obesity), and methodological differences between studies. While our analysis indicates a potential correlation between OSA and RD, it is evident that no strong association can be confirmed at this stage. Therefore, this relationship should be explored in greater detail in future studies, with more homogeneous sample sizes and improved diagnostic criteria, to reduce biases and gain a clearer understanding of the overlap between OSA and RD.

Our results have shown that the reflux disease (RD) is more likely to relate to a decreased level of sleep efficiency ($p = 0.003$) and oxygen saturation ($p<0.001$) but has no significant effects on Apnea-Hypopnea Index (AHI) and Epworth Sleepiness Scale (ESS). These results support the hypothesis that RD impairs sleep quality primarily through nocturnal reflux symptoms that cause arousals and sleep fragmentation, rather than by influencing sleep apnea severity or daytime somnolence. The same has been observed in previous research works that have established that RD is associated with broken sleep continuity but not with elevated AHI or ESS.[14,35,39] As an example, Altinta experiment et al[14] found that polysomnographic measures in RD patients did not change significantly, whereas Milena et al[35] and Caparroz et al[16] found strong relationships between AHI and ESS and RD, which allows assuming that the differences may arise due to the peculiarities of the population or comorbid pathology. These discrepancies illustrate the heterogeneous and complicated fact that RD and OSA have a complex relationship, which can be the result of heterogeneous diagnostic criteria, study design, or the reflux phenotype (acidic vs non-acidic).[40–42] Thus, well-controlled studies involving bigger more similar cohorts are required in order to specify the particular roles of RD in sleep disturbances and its importance it has clinically in patients with OSA.

Based on our results, it is possible that reflux disease (RD) has a preferential impact on the lighter stages of non-rapid eye movement (NREM) sleep especially stage N1, probably due to occurring higher arousal events during the night-time reflux events. The given observation is compliant with previous research findings showing that gastroesophageal reflux may interfere with sleep initiation through increasing cortical excitability and autonomic dysregulation.[14,35] By contrast, the absence of inconsiderable distinctions in deeper NREM stages (N2, N3) suggests the lower impact of RD as deeper sleep takes place, which may be induced by reduced arousal susceptibility in such levels.[41] Although possible mechanisms attribute RD to obstructive sleep apnea formation (OSA) reflexes via the vagus nerve and airway inflammation, our ecosystem analysis was not significant (within and between OSA severity levels), as they may occur in specific stages or exert little effect on apnea indicators.[16,37] Although, there is a marginal trend ($p = 0.063$), indicating that there might be some kind of interaction within certain subgroups, which could be hiding behind the heterogeneous RD diagnosis, comorbidities, and treatment status (ie PPI use, CPAP adherence).[42,43] The results argue the consideration of reduced bidirectional models of RD-OSA interaction and encourage future researches to stratify patients based on their reflux (phenotyping), vulnerability to sleep stages disturbances, and symptom presentations to understand this complicated connection.

This meta-analysis and systematic review provide us with new data regarding the complicated relationship between obstructive sleep apnea (OSA) and reflux disease (RD), where we can find out that reflux disease can selectively interfere with early non-rapid eye movement (NREM) sleep especially N1, whereas it has few effects on deeper sleep N2, N3 or whether OSA is due to RD or not. These results narrow down the existing models of the dynamic of OSA and RD interaction that are regularly viewed as a two-way street that is linear in both directions, but the data here indicates a more stage respective and heterogeneous direction of the influence.[14,35,41] The clinical implications of RD interrupting lighter stages of sleep are then valuable in the discussions of the possible effects of reflux-induced symptoms

management on improved continuity in sleep irrespective of whether indices of apneas show improvements. Previous publications also indicate that apnea-hypopnea index could not be increased with reflux-related arousals instead highlighting the worsening of the sleep quality in general.[16,42] Thus, a treatment approach to patients with comorbid OSA and RD must not only aim at mitigating apneic occurrences but also include an element of reflux management to improve restorative rest. Sophisticated treatment plans, homing in on the reflux phenotype, sleep-stage susceptibility, and comorbidity burden, are justified to maximize efficacy. There is a need to perform further quality studies to confirm such observations and use more standardized diagnostic criteria and stratified analyses to further clarify this complex relationship.[43,44]

Although the current research study provided valuable insights through the systematic review and meta-analysis, several important limitations must be acknowledged. First, the cross-sectional design of most of the included studies limits our ability to make definitive conclusions about causality. Longitudinal studies would be essential to clarify the directionality of the relationship between OSA and RD, specifically examining how these conditions evolve over time and providing stronger evidence for causality. Additionally, there is a potential for publication bias in this review, as studies reporting null or negative results are less likely to be published, which may lead to an overrepresentation of positive findings. Future meta-analyses should aim to include unpublished studies, thus offering a more comprehensive overview of the OSA-RD relationship. Moreover, the failure to report planned analyses, such as sensitivity tests, publication bias tests, and subgroup/meta-regression analyses, constitutes another significant limitation. These analyses are crucial for understanding how confounding factors—such as obesity, age, or the presence of other conditions—may influence the relationship between OSA and RD. Given the prevalence of these confounders in both OSA and RD groups, future studies should make efforts to control for these variables, allowing for a clearer understanding of the specific impact of RD on OSA, and vice versa. Furthermore, while we believe there may be a potential connection between RD and OSA, the absence of consistent and unequivocal findings across the studies highlights a major research gap. Future studies should focus on investigating the selective influence of RD on various sleep stages, particularly in the context of NREM sleep. Additionally, the potential benefits of symptomatic reflux treatment in OSA patients should be explored, as it may improve sleep characteristics and reduce the severity of symptoms. Addressing these unresolved questions will guide future research directions and provide more robust recommendations for clinical practice and therapeutic approaches for patients with both OSA and RD.

In conclusion, this systematic review and meta-analysis indicated that there is a small relationship between obstructive sleep apnea (OSA) and a slight upsurge in the occurrence of gastroesophageal reflux disease (RD). In particular, RD seems to influence the initial phases of sleep, especially N1, selectively without major changes to the level of sleep apnea. Nevertheless, the study is limited, with the cross-sectional design of most of the studies in the study inhibiting us to make cause relationships. Moreover, there are the possible bias, like a publication bias and confounders like obesity, comorbidities, which can affect the results. Future studies ought to consider longitudinal studies, using standardized criteria of diagnosis, and confounding factors should be removed, and the measures of comorbidity should be studied, so that interventions can be streamlined as far as the underlying mechanisms and causal relationships will be explained between OSA and RD.

Data Sharing Statement

The data supporting the results of this study were obtained from PubMed, Web of Science, the Cochrane Library, VIP, CNKI, Wanfang Data, and CBM databases.

Author Contributions

XZ-Conceptualization, formal analysis, funding acquisition, methodology, project administration, writing-original draft, and writing-review and editing. SW-Data curation, formal analysis, investigation, methodology, software, writing-original draft, writing-review and editing. PZ-Conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing-original draft, writing-review and editing. All authors agreed on the journal to which the article will be submitted; agreed on the final version accepted for publication and agree to take responsibility and be accountable for the contents of the article.

Funding

This work was partly funded by Open Project of State Key Laboratory of Respiratory Disease (SKLRD-OP-202510).

Disclosure

The authors declare no financial conflicts of interest.

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