

# Laryngopharyngeal Reflux in Obstructive Sleep Apnea-Hypopnea Syndrome: An Updated Meta-Analysis

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**Abstract:** Laryngopharyngeal reflux (LPR) is a common disorder in patients with obstructive sleep apnea-hypopnea syndrome (OSAHS). This meta-analysis was carried out to evaluate the LPR prevalence in individuals with OSAHS and to analyze the correlation of LPR positivity with the clinical features of patients with OSAHS. A detailed review of the English and Chinese literature on the occurrence of LPR in patients with OSAHS was performed by employing online search tools such as PubMed, EMBASE, Web of Science, VIP, CNKI, WanFang, etc. Two researchers analyzed the studies for quality according to the STROBE standard checklist. The acquired data were analyzed using Stata 11.0 and R 3.6.1 software. The effect size was estimated and calculated using weighted mean difference (WMD) and correlation coefficients. Moreover, a combined analysis was performed by employing either a random- or fixed-effects model. Ultimately, 27 studies met our inclusion criteria. Our study revealed that the LPR prevalence in OSAHS patients was 49%. We carried out subgroup analyses as per OSAHS severity, ethnicity, and body mass index (BMI). The results suggested that the probability of LPR in European and American patients with OSAHS was higher, and the prevalence of LPR was higher in obese individuals and patients with severe OSAHS. Moreover, apnea-hypopnea index (AHI) and BMI were higher in LPR-positive OSAHS patients than in LPR-negative OSAHS patients, but no significant variation in age was observed in the two groups. Moreover, the reflux symptom index (RSI) scores and the reflux finding score (RFS) exhibited a positive correlation with AHI. The current literature shows a higher incidence of LPR in individuals with OSAHS (49%). The severity of AHI in individuals with OSAHS is associated with the presence of LPR. Patients with OSAHS accompanied by LPR showed higher BMI and AHI as compared to those patients with LPR-negative OSAHS.

**Keywords:** LPR, obstructive sleep apnea-hypopnea syndrome, meta-analysis, correlation, reflux symptom index score, reflux finding score

## Introduction

Laryngopharyngeal reflux (LPR) is a highly prevalent clinical condition that affects nearly 10% of the US population, showing an upward trend in published papers in recent years.<sup>1</sup> LPR is a disease of the pharynx characterized by morning hoarseness, nocturnal cough, sore throat, excessive mucus in the pharynx, and pharyngeal foreign body sensation. It is recognized as a clinical disorder that differs from the classic gastroesophageal reflux disease (GERD).<sup>2</sup> Furthermore, LPR occurs mainly in the upper respiratory tract, mainly in the hypopharynx and larynx region, whereas GERD is due to gastric and duodenal reflux into the esophagus, resulting in acid reflux and heartburn.<sup>3,4</sup>

OSAHS is reported to be a commonly occurring sleep-breathing disorder, with about 3–7% of general adults suffering from it.<sup>5</sup> The pathogenesis of this disease is unclear, and clinical manifestations are mostly snoring during sleep, disrupted sleep architecture, increased nocturia, daytime sleepiness, memory loss, and neuropsychiatric symptoms.<sup>6</sup> Its

pathophysiology is characterized by the collapse of the upper airway structures resulting in partial or complete obstruction of airflow and decreased oxygen saturation during sleep.<sup>7</sup> Several studies on LPR in patients with OSAHS have been published in the last few years. Many authors consider LPR to be common comorbidity in patients with OSAHS, and it may be closely linked with the severity of the disease. Payne et al<sup>8</sup> evaluated the inflammatory manifestations in the pharynx of patients with OSAHS by fiberoptic laryngoscopy and the reflux finding scale (RFS) and found that 90% of OSAHS patients had features consistent with LPR, and a positive association was observed between apnea-hypopnea index (AHI) and RFS scores in OSAHS patients. During the pathophysiological process, OSAHS and LPR influence and promote each other, forming a vicious circle. However, common factors contributing to both diseases may involve other risk factors, including elevated body mass index (BMI), alcohol consumption, and smoking.

The relationship between LPR and OSAHS remains controversial as of this date. Iannella et al<sup>9</sup> had reported in a study that there was no association between the severity of OSAHS and the degree of salivary pepsin reflux. However, Gouveia et al<sup>10</sup> revealed a significant correlation between RSI scores and AHI ( $r=0.37$ ,  $P=0.0078$ ) and also concluded LPR symptoms may be related to the presence and severity of OSAHS. Furthermore, Magliulo et al<sup>11</sup> conducted a meta-analysis in 2018 to evaluate the LPR prevalence in patients suffering from OSAHS and the variations in clinical characteristics between individuals that are LPR positive and negative.

However, the incidence of LPR may vary between different OSAHS subgroups, while the latest research work has reported the link between LPR and OSAHS. The conclusions reached by Magliulo et al<sup>11</sup> remain to be further validated by observational studies. Therefore, it is essential to perform a meta-analysis by utilizing all existing studies to quantitatively assess the relationship between the occurrence of LPR and OSAHS. In this study, the pathogenesis of LPR in OSAHS patients and the correlation between the two diseases have been analyzed and discussed. Meanwhile, an updated meta-analysis has been conducted to evaluate the prevalence of LPR in patients suffering from OSAHS and associate their characteristics.

## Methods and Materials

### Method Used for Literature Search

Our meta-analysis was registered at the prospective register of systematic reviews (PROSPERO, the website is <https://www.crd.yorl.ac.uk/PROSPERO/>, and the ID is CRD4202235462). A computer search of PubMed, EMBASE, Web of Science, VIP, CNKI, and WanFang was performed to comprehensively collect literature on the onset of LPR in patients with OSAHS, and the search time frame was set between the database running time and August 1, 2022. The keywords and subject terms used included “laryngopharyngeal reflux” or “LPR” and “Obstructive Sleep Apnea-Hypopnea Syndrome” or “Obstructive Sleep Apnea” or “Obstructive Sleep Apnea Syndrome” or “OSA” or “OSAHS” or “OSAS.”

### Inclusion and Exclusion Criteria

The criteria for eligibility are stated below:

1. Case-control, cohort, Randomized controlled trial, or cross-sectional study.
2. Diagnostic criteria for LPR: RSI questionnaire score  $\geq 13$  and/or RFS score  $\geq 7$  or diagnosed by 24-hour oropharyngeal Dx-pH probe system.<sup>12,13</sup> The Ryan score is generated automatically by the system, which is a composite score, and the calculations of which are based entirely on the given pH thresholds of upright and supine positions. Scores more than 9.41 in the upright position and/or 6.80 in the supine position were considered indicative of LPR.<sup>14</sup>
3. Subjects fulfilled the diagnostic criteria for OSAHS as per polysomnography (PSG) (adults: AHI  $\geq 5$ /h; children: AHI  $\geq 1$ /h). OSAHS severity was described by means of traditional definitions (AHI  $< 5$ , normal; AHI 5–14, mild OSAHS; AHI 15–29, moderate OSAHS; and AHI  $\geq 30$ , severe OSAHS).<sup>15</sup>

The criteria of exclusion are stated below:

1. Editorials, reviews, letters, other sorts of literature reviews, or case reports.
2. Unable to extract enough information from the original article or contact the corresponding author for more information.
3. Studies that were not conducted in humans.
4. Studies included patients with OSAHS with a history of chronic airway disease, cerebrovascular disease, chronic cardiac failure, endocrine disease, and malignancies.
5. LPR has not been categorized as a different disorder from gastroesophageal reflux. Publications on gastroesophageal reflux disease (GERD) in individuals with OSAHS were not considered for this study.
6. Research reporting controls with AHI  $\geq 5$  events/h in adults and AHI  $\geq 1$  events/h in children.
7. Overlapping studies and data from the research conducted by the same authors.

## Literature Screening

Based on the above literature screening criteria, two researchers independently searched relevant articles from the above-mentioned databases and read their titles and abstracts, screened potentially eligible articles and obtained their full text, then read the full text in detail and evaluated again, and if the two researchers disagreed on the inclusion or exclusion of articles, a third researcher would analyze the disagreement and consult the data to determine whether to include or exclude. The PRISMA flow diagram below (Figure 1) summarizes the results of the article selection processes.

## Data Extraction and Management

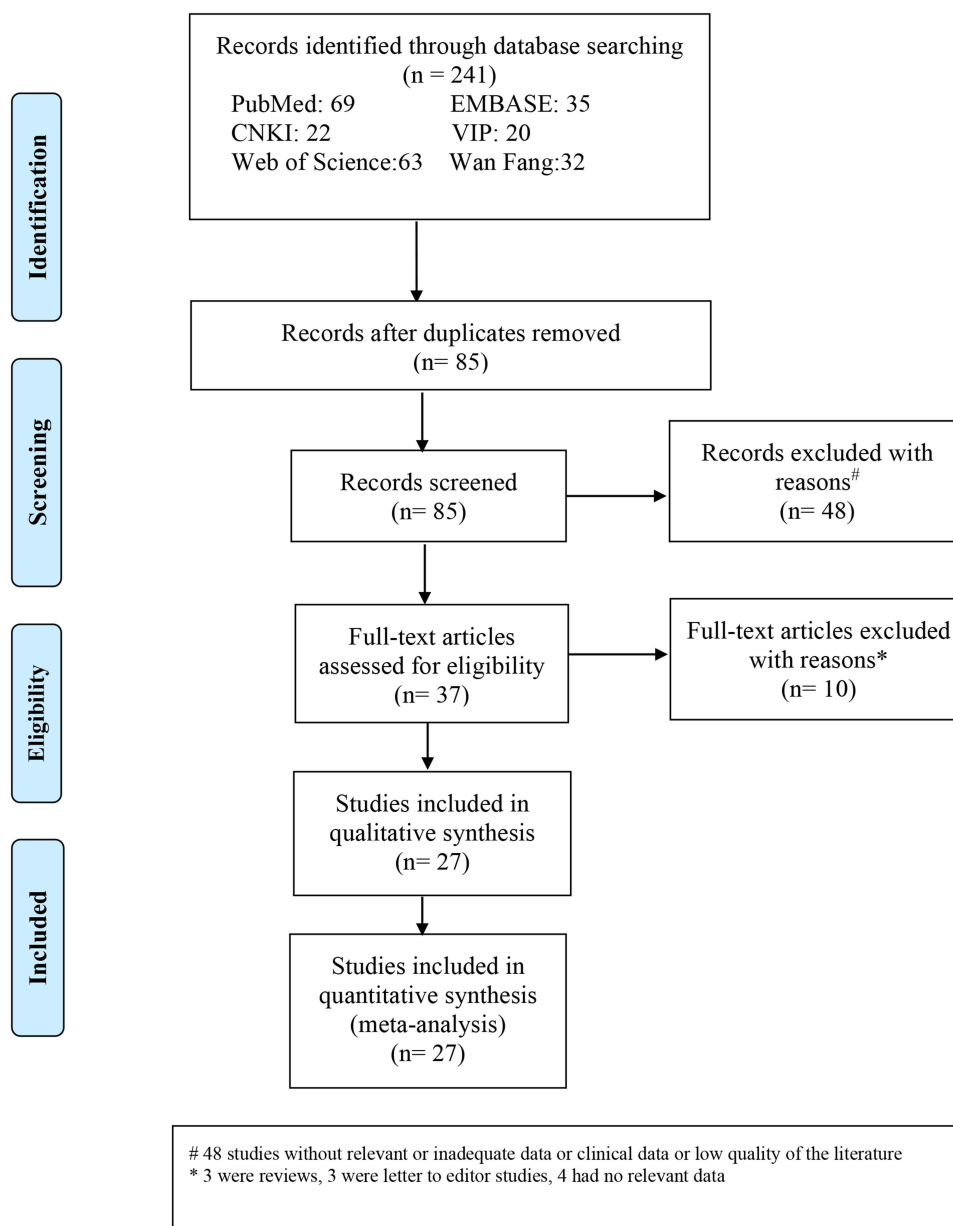
The quality of the selected research papers was assessed independently by two researchers utilizing the STROBE standard checklist.<sup>16</sup> The minimum and maximum scores on this list were between 0 and 44, respectively, and the studies that achieved no less than 16 scores were selected to proceed with meta-analysis.<sup>17</sup> The data extraction and evaluation from the literature were done independently by two other researchers, and the following information was achieved: 1. Basic information about the article: country, publication date, and first author; 2. Prevalence and incidence of LPR-positive patients with OSAHS; 3. Baseline characteristics of the study population: age, BMI, AHI, and lowest oxygen saturation comparison data; 4. OSAHS measurements and their types. 5. Study quality. If the included literature lacked the necessary content, the researchers contacted the article author no less than twice by phone or email, and they were requested to provide the missing data.

## Statistical Analysis

R (version 3.6.1) and Stata software (version 11.0) were used to summarize and examine the extracted data. We normalized and expressed the continuous variables as the WMD with a 95% confidence interval (95% CI). The current meta-analysis used Spearman's CORs to examine the associations between RSI/ reflux finding score (RFI) score and AHI score in patients with OSAHS. According to the standard error, which is generally dependent on the importance of the rank COR, the dependence of Spearman's product-moment COR on the sampling distribution is not indicated. Therefore, the Fisher transformation was used to compare each COR, and an investigation was subsequently conducted with the transformed values as the input before converting them back to CORs. Cohen's criteria were used to examine the measured effect size (small,  $\leq 0.3$ ; moderate,  $0.3-0.5$ ; and large,  $> 0.5$ ).<sup>18</sup> Moreover, Pearson's COR was employed to study the correlation between the AHI score and RSI/RFI score. In accordance with the above description, several studies have reported a method for converting Pearson's to Spearman's COR using the following formula:

$$r = 2 \sin \left( r_s \frac{\pi}{6} \right)$$

Where  $r$  and  $r_s$  represent Pearson's and Spearman's CORs, respectively,<sup>19</sup> Cochran's Q and chi-square tests were used to examine data heterogeneity. The  $I^2$  statistic was used to detect heterogeneity (25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively;  $I^2 < 50\%$  and  $I^2 \geq 50\%$  indicated low and high heterogeneity among studies, respectively). In the case of zero heterogeneity among studies, we employed fixed- and random-effects models.



**Figure 1** Flow diagram indicating the literature selection process and results based on the preferred reporting items for the meta-analysis.

Descriptive analysis, subgroup analysis, and meta-regression were employed to investigate the source of heterogeneity. The overall population was categorized according to disease severity, ethnicity, and BMI in order to conduct subgroup analyses. One study at a time was removed for the sensitivity analysis, which was conducted to explore how each study impacted the combined effect size. Begg's, Egger's tests, and linear regression were carried out to evaluate publication bias.

## Results

### Publications Retrieved and Included in the Study

Overall, 241 related research articles were collected from the databases. Out of which 228 duplicated studies were excluded by filtering the abstracts and titles, leaving 48 articles. We downloaded these 48 articles and thoroughly reviewed the complete text; 14 papers were discarded following a review of the inclusion and exclusion criteria. These papers were excluded for the following reasons: four publications were review articles, two were letters to the editor, four did not include a control group of

healthy people, two lacked relevant data, and two were animal experiments. Finally, 27 articles were considered for the meta-analysis, as shown in Figure 1. We identified 26 studies<sup>8,9,20–43</sup> involving LPR incidence in OSAHS patients, as shown in Table 1. Ten articles<sup>9,22,24,26,29,33,36,39,42,43</sup> compared the clinical characteristics of patients with LPR-positive OSAHS and LPR-negative OSAHS (Table 2). Six studies<sup>10,25,27–29,36</sup> provided Spearman's or Pearson's CORs between RSI score and AHI score. Four studies<sup>8,25,27,28</sup> provided Spearman's or Pearson's CORs between RSI and AHI scores. Figure 1 represents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for selecting and screening articles from the literature. Tables 1–3 present the fundamental data of the included studies.

## Prevalence of LPR Among Patients with OSAHS

The meta-analysis on the prevalence of LPR in individuals with obstructive sleep apnea included 26 studies (Table 1). A total of 2419 patients in total were involved, out of which 973 were LPR positive and 1446 were LPR negative. In these meta-analyses, the overall incidence of LPR-positive among OSAHS patients was calculated to be 49% (95% CI = 0.40–0.58,  $P < 0.001$ ,  $I^2 = 96.1\%$ ) (Figure 2).

## Subgroup Analysis

Subgroup analysis according to ethnicity showed that the overall incidence of LPR-positive OSAHS patients was 59% in the Caucasian population (95% CI = 0.42–0.77,  $P < 0.001$ ,  $I^2 = 94.2\%$ ); in the Latin Americans, the overall incidence of

**Table 1** Characteristics of Included Studies

Author	Year	Country	Ethnicity	Age(year)	Total Sample size	Patients With LPR	Prevalence of LPR	Measurement and Type
Altintas A <sup>36</sup>	2017	Turkey	Caucasian	46.7±12.9	62	25	0.403	PSG I
CampanholoMAT <sup>26</sup>	2022	Brazil	Latino	50.2±13.3	270	54	0.2	PSG I
Caparroz F <sup>22</sup>	2019	Brazil	Latino	49.3±11.3	67	40	0.597	PSG I
Elhennawi DM <sup>34</sup>	2016	Egypt	Caucasian	46.4±11.8	62	34	0.55	PSG I
Erdem D <sup>20</sup>	2018	Turkey	Caucasian	50.5±11.0	34	29	0.853	PSG I
Eryilmaz A <sup>30</sup>	2012	Turkey	Caucasian	49.6±10.9	28	25	0.893	PSG I
Gouveia CJ <sup>10</sup>	2019	America	Caucasian	46.3±15.4	33	–	–	PSG I
Iannella G <sup>9</sup>	2019	Italy	Caucasian	50.9±10.5	75	24	0.320	PSG I
Ji P <sup>29</sup>	2022	China	Asian	41.0±9.7	109	49	44.95	PSG I
Kim Sj <sup>35</sup>	2017	Korea	Asian	42.3±11.8	73	24	0.33	PSG I
Laohasiriwong S <sup>31</sup>	2013	Thailand	Asian	50.2±15.2	93	30	0.32	PSG I
Lee JS <sup>37</sup>	2017	Korea	Asian	42.3±11.8	88	44	0.500	PSG I
Payne RJ <sup>8</sup>	2006	Canada	Caucasian	43.9±8.8	29	26	0.900	PSG I
Pilakasiri A <sup>21</sup>	2018	Thailand	Asian	–	51	29	0.568	PSG I
Qing C <sup>39</sup>	2019	China	Asian	47.2±8.5	88	31	0.352	PSG I
Qu Y <sup>33</sup>	2015	China	Asian	46.0±2.0	36	23	0.639	PSG I
Rodrigues MM <sup>38</sup>	2014	Brazil	Latino	44.57±12.97	343	105	0.306	PSG I
Tamin S <sup>28</sup>	2022	Indonesia	Asian	43.38±8.76	32	28	0.875	PSG I
Tang X <sup>25</sup>	2021	China	Asian	42.98±10.21	64	33	0.516	PSG I
Wang G <sup>40</sup>	2018	China	Asian	47.6±14.4	92	18	0.196	PSG I
Wang L <sup>23</sup>	2020	China	Asian	50.6±13.6	40	6	0.150	PSG I
Wang XY <sup>42</sup>	2008	China	Asian	44.0±7.6	19	6	0.316	PSG I
Wu SE <sup>41</sup>	2018	China	Asian	43.2±6.7	54	15	0.278	PSG I
Xavier SD <sup>32</sup>	2013	Brazil	Latino	50.6±10.7	78	65	0.840	PSG I
Yang XP <sup>27</sup>	2022	China	Asian	37.8±5.5	284	69	0.193	PSG I
Yue R <sup>24</sup>	2020	China	Asian	36.44±10.38	45	33	0.733	PSG I
Zhang CQ <sup>43</sup>	2022	China	Asian	39.55±11.29	203	108	0.532	PSG I

**Abbreviations:** LPR, laryngopharyngeal reflux; PSG, polysomnography.

**Table 2** Participants' Characteristics of Included Studies

Author	AHI(Mean± SD)		BMI(Mean± SD)		Age(Mean± SD)		LSO <sub>2</sub> (Mean± SD)	
	LPR-	LPR+	LPR-	LPR+	LPR-	LPR+	LPR-	LPR+
Altintas A <sup>36</sup>	16.51±22.69	15.56±21	28.56±3.17	30.42±6.44	45.12±13.25	45.12±13.25		
Campanholo MAT <sup>26</sup>	35.5±18.15	33.3±17.3	30.6±5.7	29.5±7.2	56.05±13	58.3±12.95		
Caparroz F <sup>22</sup>	34.8±10.3	45.9±15.8	30±3.3	32.9±5.2			75.2±7.4	72.1±10.6
Iannella G <sup>9</sup>	24.18±9.43	28.75±13.01	27.7±3.77	34.4±4.94	50.2±15.3	51.5±14.8		
Ji P <sup>29</sup>	38.9±26.8	57.6±22.9			40.1±11.2	42.5±11.8	74.1±15.1	69.5±16.3
Qing C <sup>39</sup>	33.28±4.84	37.15±5.06					81.92±4.68	77.14±4.2
Qu Y <sup>33</sup>	23.36±11.15	33.8±33.43	26.31±2.7	28.03±3.52	49.23±8.64	46.22±10.49	82.67±1.94	79.26±1.74
Wang XY <sup>42</sup>	52.8±17.5	62.8±34.7			45.2±6.5	42±9.4	73.2±12.6	69.5±14.1
Yue R <sup>24</sup>	44.94±22.14	61.23±31.39	29.36±2.33	28.43±2.93	35.92±10.13	38.79±10.03		
Zhang CQ <sup>43</sup>	44.63±24.75	44.6±27.31	28.07±5.06	29.5±4.5				

**Abbreviations:** AHI, apnea-hypopnea index; BMI, body mass index; LPR, Laryngopharyngeal reflux; LSO<sub>2</sub>: Lowest oxygen saturation.

**Table 3** Correlation Coefficients (Cor-values) of Included Studies

Author	Year	N	Cor of AHI	Cor of AHI
			Versus RSI	Versus RFI
Gouveia CJ <sup>10</sup>	2019	33	0.37	
Tang X <sup>25</sup>	2021	64	0.54	0.776
Yang XP <sup>27</sup>	2022	284	0.26	0.318
Ji P <sup>29</sup>	2022	109	0.331	
Altintas A <sup>36</sup>	2017	62	0.338	
Tamin S <sup>28</sup>	2022	32	0.15	-0.115
Payne RJ <sup>8</sup>	2006	29		0.57

**Abbreviations:** AHI, apnea-hypopnea index; RSI, reflux symptom index; RFI, reflux finding score.

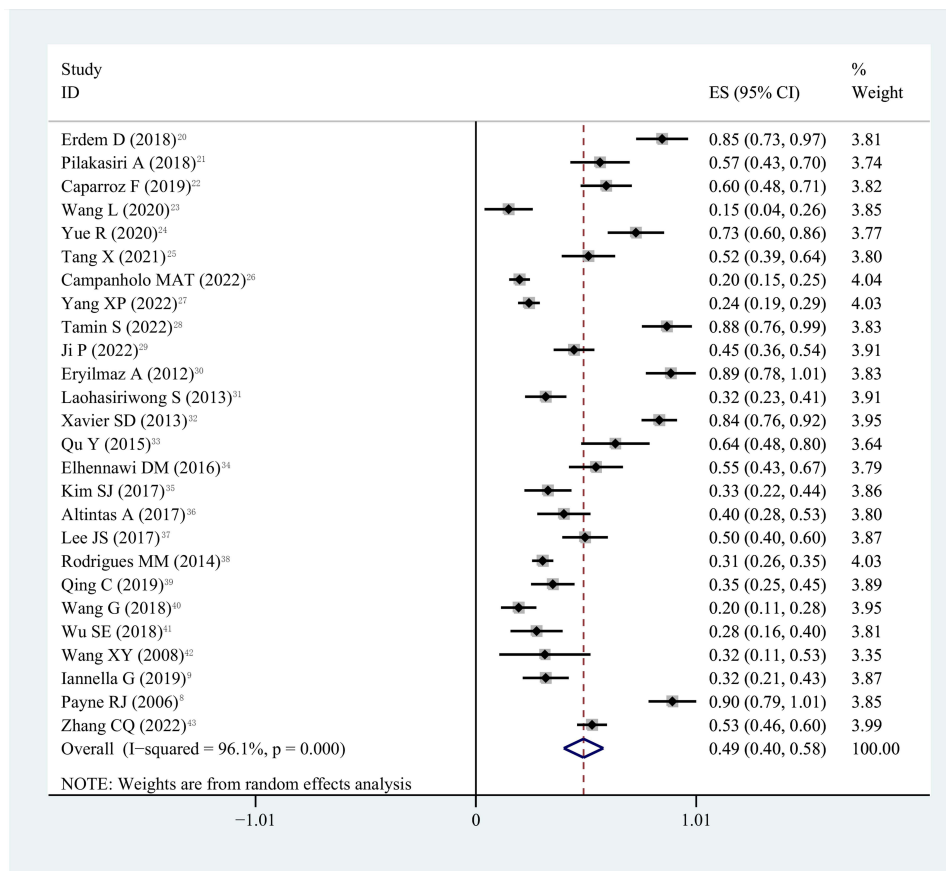
LPR-positive OSAHS patients was 56% (95% CI = 0.31–0.82, P < 0.001, I<sup>2</sup> = 98.7%); while, in the Asians, it was 43% (95% CI = 0.33–0.53, P < 0.001, I<sup>2</sup> = 93.0%). In subgroup analysis according to BMI, the overall incidence of LPR-positivity in individuals with OSAHS was 59% with a mean BMI ≥ 30 (95% CI = 0.43–0.75, P < 0.001, I<sup>2</sup> = 97.4%) and 41% in those with a mean BMI < 30 (95% CI = 0.32–0.51, P < 0.001, I<sup>2</sup> = 93.4%). In subgroup analysis according to a mean AHI, the overall incidence of LPR-positivity among individuals with OSAHS was 55% in those with a mean AHI ≥ 30 (95% CI = 0.41–0.70, P < 0.001, I<sup>2</sup> = 96.7%) and 44% in those with a mean AHI < 30 (95% CI = 0.31–0.57, P < 0.001, I<sup>2</sup> = 96.5%). ([Supplementary Table 1](#)).

### Age Variations Between Patients with Negative LPR and Positive LPR

Eight studies provided data on the age of patients that were LPR negative and those with positive laryngeal reflux, and the results suggested that there was no variation in age between the LPR+ and LPR- groups (WMD = -0.80, 95% CI = -2.77–1.17, P = 0.425, I<sup>2</sup> = 0.0%). ([Supplementary Table 2](#)). ([Supplementary Figure 1](#)).

### Differences in BMI Between Patients with Negative LPR and Positive LPR

Eight studies provided data on the BMI of patients that were LPR negative and LPR positive, and the results suggested that individuals in the LPR- group had a lower BMI in comparison to those in the LPR+ group (WMD = -1.61, 95% CI = -3.10–0.12, P = 0.034, I<sup>2</sup> = 81.5%). ([Supplementary Table 2](#)). ([Supplementary Figure 2](#)).



**Figure 2** Prevalence of laryngopharyngeal reflux in OSAHS patients based on a random effects model.

## AHI Variations Between Patients with Negative LPR and Patients with Positive LPR

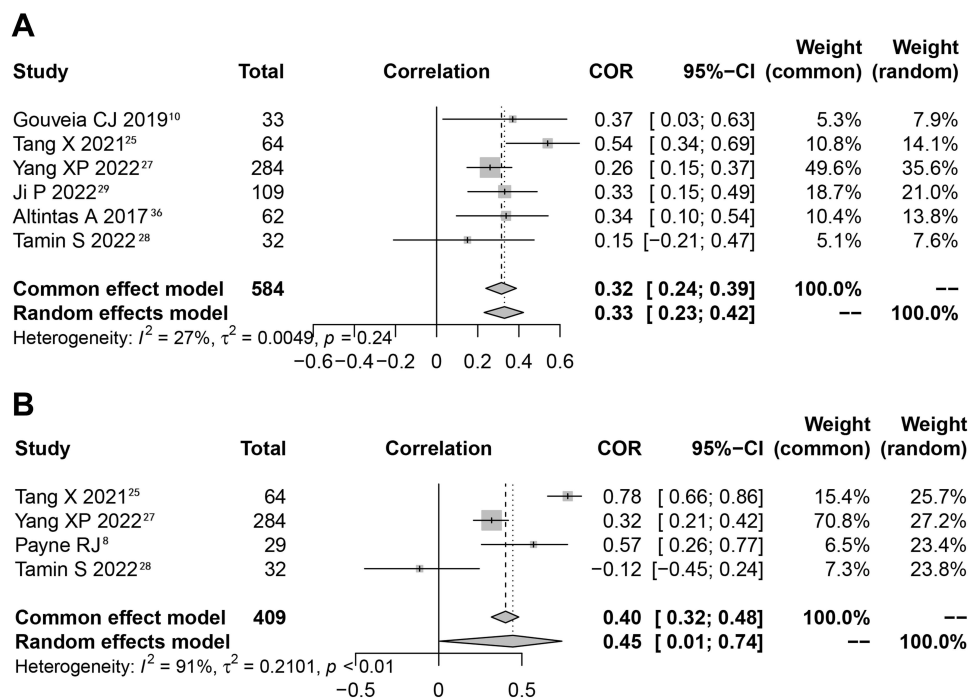
Ten studies provided AHI data between individuals with negative LPR and individuals with positive LPR, and the results suggested that individuals in the LPR- group had a lower AHI index than the LPR+ group (WMD =  $-5.61$ , 95% CI =  $-9.51$ -  $-1.70$ ,  $P = 0.005$ ,  $I^2 = 65.1\%$ ). ([Supplementary Table 2](#)). ([Supplementary Figure 3](#)).

## Differences in Minimum Oxygen Saturation Between Negative LPR and Positive LPR Patients

Five studies provided data on minimum oxygen saturation in patients with negative laryngeal reflux versus those with positive laryngeal reflux, and the findings indicated that individuals in the LPR- group had higher minimum oxygen saturation than those in the LPR+ group (WMD =  $3.82$ , 95% CI =  $2.81$ - $4.83$ ,  $P = 0.007$ ,  $I^2 = 0\%$ ). ([Supplementary Table 2](#)). ([Supplementary Figure 4](#)).

## Meta-Analysis of Correlation Between RSI Score, RFS Score, and AHI Score

Six studies reported Pearson's or Spearman's CORs for the association between RSI scores and AHI scores. AHI score is an important criterion for evaluating OSAHS, and it directly correlates with OSAHS severity. We conducted a meta-analysis on RSI scores and AHI scores in patients with OSAHS using the "meta" R package. The analysis revealed an effect size for the RSI score and AHI score of  $0.32$  (95% CI =  $0.24$ - $0.39$ ,  $P < 0.001$ ,  $I^2 = 27\%$ ) ([Figure 3A](#)). Three studies reported Pearson's or Spearman's CORs for the association between RFS and AHI scores in patients with OSAHS. The analysis revealed an effect size for RFS and AHI scores of  $0.45$  (95% CI =  $0.01$ - $0.74$ ,  $P = 0.047$ ,  $I^2 = 91\%$ ) ([Figure 3B](#)).



**Figure 3** Funnel plot of effect sizes measured as correlations RSI score, RFS score and AHI. (A) RSI score; (B) RFS score.

## Meta-Regression and Sensitivity Analysis

A combined analysis of the incidence of LPR in all OSAHS patients exhibited a high degree of heterogeneity ( $I^2=96.1\%$ ,  $P<0.001$ ). Hence, a meta-regression analysis was performed to identify the source of the high heterogeneity. Meta-regression analysis showed that the P values for the ethnicity, AHI, and BMI were 0.090, 0.195, and 0.054, respectively, indicating that the factors such as race, AHI, and BMI did not have a significant effect on heterogeneity. In sensitivity analyses, each of the 26 studies was removed one by one in turn, and the remaining studies were subjected to meta-analysis, and the results were compared with the results before the previous exclusion, which showed that the item-by-item removal of each study had no significant effect on the combined results. The [Figure 4](#) summarized the sensitivity analysis for meta-analysis of incidence. Less literature was included for meta-inclusion of the remaining continuous variables, and meta-regression and subgroup analyses were not performed.

## Publication Bias

In the meta-analysis regarding the incidence of laryngeal reflux, publication bias was not suggested in our combined analysis based on Egger's ( $P = 0.058$ ) and Begg's ( $P = 0.053$ ). ([Figure 5](#)). In the meta-analysis on the comparison of age in patients with OSAHS (negative and positive laryngeal reflux), publication bias was not significant in this combined analysis based on Egger's ( $P = 0.067$ ) and Begg's ( $P = 0.083$ ). In the meta-analysis on the comparison of BMI in patients with OSAHS (negative and positive laryngeal reflux), publication bias was not significant in this combined analysis according to Egger's ( $P = 0.321$ ) and Begg's ( $P = 0.386$ ). In the meta-analysis on the comparison of AHI in patients with OSAHS (negative and positive laryngeal reflux), publication bias was not significant in this combined analysis according to Egger's ( $P = 0.530$ ) and Begg's ( $P = 0.788$ ). In the meta-analysis on the comparison of minimum oxygen saturation in patients with OSAHS (negative and positive laryngeal reflux), publication bias was not significant in this combined analysis according to Egger's ( $P=0.488$ ) and Begg's ( $P = 0.462$ ). In the meta-analysis regarding the correlation between the RSI score and AHI index, the symmetry of the funnel plot according to linear regression analysis ( $t = 1.53$ ,  $P = 0.224$ ) suggested that the publication bias was not significant in this study.



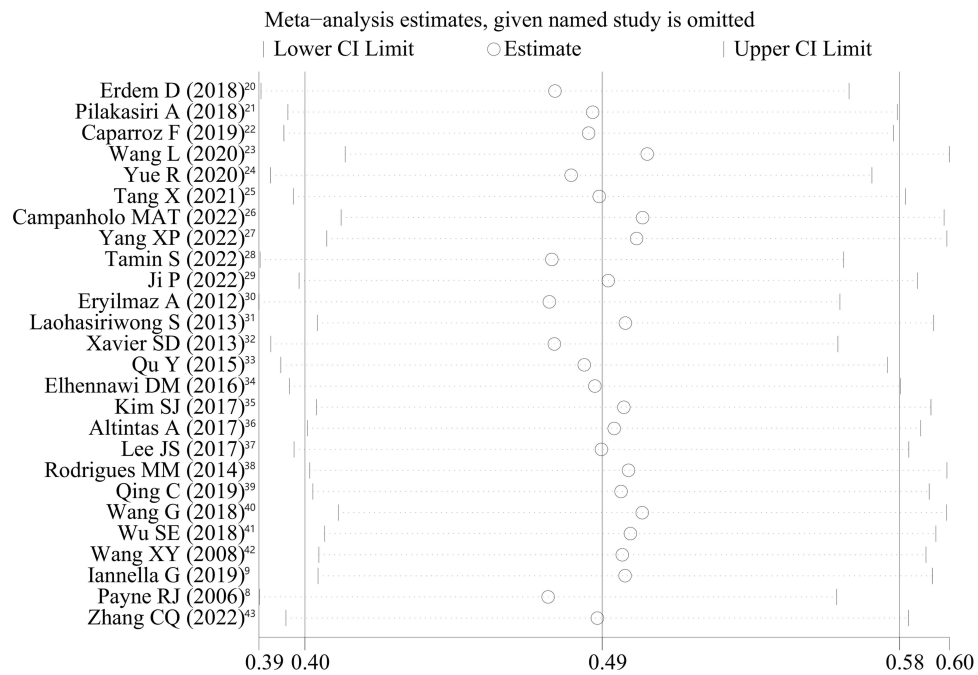


Figure 4 Sensitivity analysis of studies on prevalence of laryngopharyngeal reflux in OSAHS patients in meta-analysis.

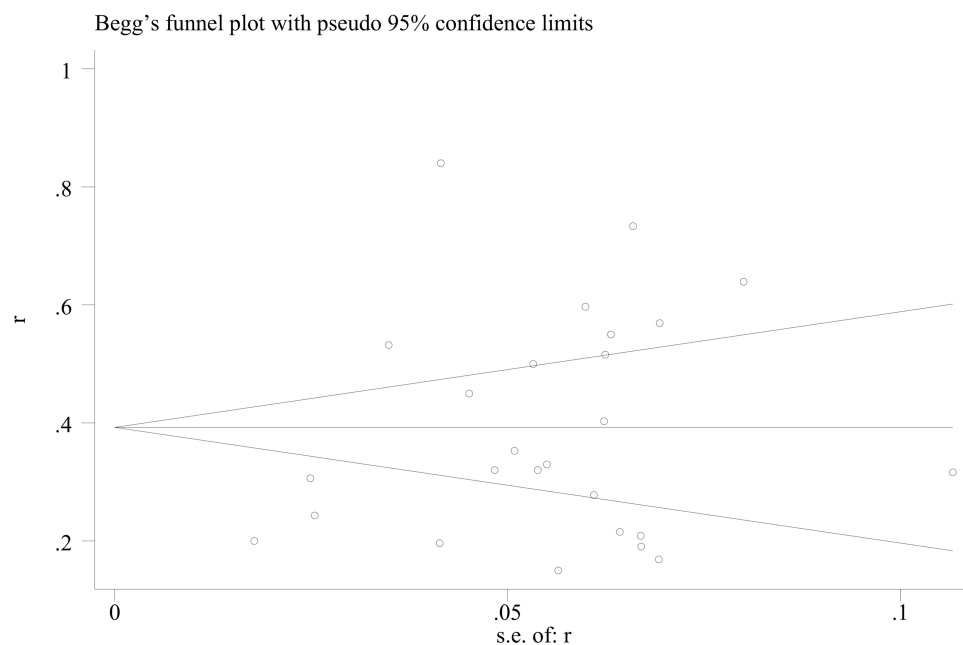


Figure 5 Funnel plots were employed to assess the publication bias among the included studies examining prevalence of laryngopharyngeal reflux of OSAHS patients.

## Discussion

In 1995, Janson et al<sup>44</sup> observed that patients with reflux symptoms were more likely to experience daytime sleepiness or fatigue in a large epidemiological survey of 2202 individuals, and this suggested that there may be a high co-morbidity between reflux and OSAHS. Early studies did not distinguish between typical GERD and disease resulting from reflux of gastric contents beyond the upper esophagus. As research progressed, the general term for the set of signs and symptoms due to reflux of gastric contents above the upper esophageal sphincter became known as LPR and was considered

a separate disease from gastroesophageal reflux disease (GERD).<sup>45</sup> All included studies in this study confirmed the high rate of LPR in patients with OSAHS. Caparroz et al<sup>22</sup> found a 59.7% LPR prevalence in patients with OSAHS using the RSI and RSF questionnaires. These results were confirmed by our meta-analysis, which showed a 49% incidence of LPR in patients with OSAHS. The high co-morbidity of OSAHS and LPR may be due to the presence of common risk factors such as alcohol consumption, smoking, obesity, and a high-fat diet. Furthermore, subgroup analysis suggested that the positivity rate of LPR was slightly higher in OSAHS patients with a mean AHI greater than 30; high-level of LPR positivity rate was observed in European and American OSAHS patients than in Asian and Latin American populations; similarly, it was higher in obese OSAHS patients. This suggests that OSAHS, obesity, and LPR exist in a vicious circle that affects each other. Secondly, the geographical and dietary habits differ between different ethnic groups, leading to a different prevalence of LPR in OSAHS patients. Europeans and Americans are likely to consume more high-fat foods than Asians, which leads to a higher prevalence of LPR. We further analyzed the age difference between LPR+ and LPR- patients, and the findings revealed no variation in age between the two groups, suggesting that age may not be an influencing factor for LPR. Lechien et al<sup>46</sup> showed a higher probability of LPR in the elderly, which was associated with the relaxation of the upper esophageal sphincter. The studies we included did not have articles specifically evaluating the LPR profile of elderly OSAHS. Therefore, it was not possible to confirm the effect of age on pharyngeal reflux in patients with OSAHS.

The relationship between OSAHS severity and the incidence of LPR has always been controversial, and no substantial evidence is found in the literature for its confirmation. Lee et al<sup>37</sup> studied 88 patients with OSAHS to analyze this point, and they reached a conclusion that OSAHS severity was independent of the severity of the clinical parameters associated with LPR. However, the findings of Elhennawi et al<sup>34</sup> were observed to be different in this regard. They studied a group of 62 OSAHS patients and observed that the mean reflux symptom index was greater than 13 scores in all patients with severe OSAHS. In addition, they noticed a considerably higher incidence of nocturnal LPR in patients with severe OSA in comparison to patients with mild OSA. Wang et al<sup>23</sup> illustrated that severe OSAHS condition led to lower mean nocturnal pharyngeal pH, and CPAP treatment was effective in reducing LPR episodes. AHI and minimum oxygen saturation are important indicators for evaluating the severity of OSAHS. We compared AHI and minimum oxygen saturation in LPR+ and LPR- OSAHS patients and combined these two indices for analysis. The results suggested that LPR+ patients had higher AHI and lower minimum oxygen saturation as compared to LPR- patients; meanwhile, the RSI index and AHI were weakly correlated with  $r = 0.32$ , whereas RFI was moderately correlated to AHI ( $r = 0.45$ ). All these results suggest that OSAHS patients with LPR may be under a more severe condition. The original cause of this phenomenon may be as follows: firstly, pharyngeal reflux not only affects the mucosal damage of the upper airway but also causes inflammatory edema in the pharynx and aggravates the obstruction of the upper airway, it also affects the lower airway and pulmonary function, and every time pharyngeal reflux occurs, the inhalation of acidic reflux can directly stimulate the nerve endings of the tracheal mucosa and cause spasm of the trachea;<sup>47</sup> on the other hand, the reflux acidic material stimulates chemoreceptors in the lower esophagus, and the chemoreceptors cause a vagal reflex that further aggravates the spasm of the airway. Trace amounts of inhaled acidic reflux stimulate the secretion of inflammatory substances from the tracheal mucosa, and these inflammatory substances can directly induce airway hyperresponsiveness.<sup>48</sup> Some scholars believe that micro-inhalation of acidic reflux further destroys the active substances on the airway and alveolar surface, which will further lead to alveolar atrophy and pulmonary atelectasis.<sup>49</sup> This vicious cycle caused by pharyngeal reflux directly causes increased nocturnal microarousals and breath-holding in patients with OSAHS, further aggravating the severity of OSAHS. Steward et al<sup>50</sup> treated 27 patients with co-morbid OSAHS and LPR with pantoprazole for up to 3 months and compared the patients' post-treatment and pre-treatment assessments of daytime sleepiness and reflux symptom assessment, roommate evaluation of their snoring, and sleep disorder degree index, and found that daytime sleepiness, reflux symptoms, and AHI were significantly improved in patients treated with acid suppression. Therefore, we hypothesize that frequent episodes of pharyngeal reflux may exacerbate the severity of OSAHS.

Another factor to consider that is related to both diseases, LPR and OSAHS, is the BMI of the patients, as OSAHS patients usually have a higher BMI. Our study revealed that the BMI of LPR+ patients was higher as compared to LPR- patients, suggesting that OSAHS patients with a high BMI may have a greater probability of having LPR. This result is

consistent with a previous meta-analysis.<sup>11</sup> Rodrigues et al<sup>38</sup> evaluated LPR-related clinical indicators in 105 OSAHS patients (39 obese and 66 non-obese) and found that LPR-related clinical indicators were higher in obese OSAHS patients. Xavier et al<sup>32</sup> also indicated that 89% of OSAHS patients had signs and symptoms of LPR, and obese OSA patients had a higher probability of LPR. The increase in intra-abdominal pressure is mainly caused by obesity, a mechanism that has significant pathophysiological implications in LPR and OSAHS. In OSAHS, obesity leads to increased respiratory effort, decreased thoracic range of motion, increased negative intrathoracic pressure, slowed esophageal clearance of reflux, and increased incidence of reflux episodes.<sup>51</sup> However, obesity is not the sole causative factor of LPR. Other factors such as age, gender, psychiatric factors, environmental factors, diet, smoking, and alcohol consumption can also cause LPR. We believe that further in-depth studies on this topic are essential to elucidate the role of BMI in the pathogenesis of LPR in patients with or without OSA.

In general, heterogeneity of results in meta-analyses is linked to several factors, such as the quality of included studies, population characteristics, and experimental methods. In our study, most of the results of the combined analyses were highly heterogeneous. To explore potential sources of heterogeneity, we performed subgroup analyses and meta-regression analyses with the largest inclusion sample with regards to the prevalence of LPR. Meta-regression analyses revealed no heterogeneity in terms of race, disease severity, and weight. Regardless of the meta-regression results, we still performed subgroup analyses by race, disease severity, and weight. However, no obvious sources of heterogeneity were found. Some unknown confounding factors may increase the heterogeneity of the meta-analysis and decrease its reliability.

Nevertheless, this meta-analysis has several strengths. This study indicates that OSAHS patients have a higher probability of developing LPR in combination and that clinicians should also consider patients' pharyngeal reflux when assessing OSAHS disease, as treatment of pharyngeal reflux may help control OSAHS disease; this is the largest meta-analysis of the relevant literature, and subgroup analysis was performed to present more reliable conclusions. Furthermore, newly published studies in Chinese were also included in this meta-analysis. Although a previous meta-analysis reported the relationship between LPR and OSAHS, this study included more literature, and the conclusions were different from that. Moreover, only the research papers of medium to high quality were considered for this study, which makes this meta-analysis more reliable.

However, there are still some potential limitations of this study. The dietary diversity and mental-emotional factors of the population may also cause LPR and may be one of the sources of heterogeneity, which can lead to statistical errors. Furthermore, due to the lack of a validated longitudinal cohort study in this study, we were unable to infer a causal relationship between OSAHS and LPR. There could be reciprocal or interdependent effects between LPR and OSAHS.

## Conclusion

Laryngopharyngeal reflux is a common symptom in patients with OSAHS. The overall incidence of positive LPR in patients with OSAHS was calculated to be 49% in this meta-analysis; OSAHS patients with LPR have higher AHI and BMI scores, and RSI and RFI scores for LPR are positively associated with AHI. Finally, more detailed study plans are needed in the future to determine the correlation between LPR and the risk of OSAHS.

## Data Sharing Statement

The original contributions presented in this meta-analysis are included in the article, further inquiries and R code can be directed to the corresponding authors.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests in this work.

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