



Relationship Between GERD Comorbidity and The Severity of Nocturnal Asthma Symptoms: A Systematic Review

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Article History :

Received date : 2026/01/12

Revised date : 2026/02/14

Accepted date : 2026/03/05

Published date : 2026/04/23



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E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Background: Gastroesophageal reflux disease (GERD) and asthma are common comorbid conditions, but the specific impact of GERD on the severity of nocturnal asthma symptoms remains debated.

Methods: This systematic review synthesized evidence from 80 studies, including randomized controlled trials (RCTs), etc. We focused on the prevalence of GERD in asthma, the strength of association with nocturnal symptoms, pathophysiological mechanisms, and treatment outcomes.

Results: The weighted average prevalence of GERD symptoms in asthma patients was 59.2% vs. 38.1% in non-asthmatics

($p < 0.001$). Nocturnal GERD (nGER) was independently associated with new asthma onset (OR 2.3, 95% CI 1.1–4.9) and incident wheeze (OR 2.18, 95% CI 1.60–2.98). Bidirectional epidemiological data showed GERD increased asthma risk (HR 1.46, 95% CI 1.42–1.49) and asthma increased GERD risk (HR 1.36, 95% CI 1.33–1.39). Mechanistically, esophageal acid perfusion induced bronchoconstriction via vagal reflex and microaspiration. Surgical antireflux therapy reduced nocturnal exacerbations (74.9% improvement vs. 9.1% with medical therapy, $p < 0.001$). However, proton pump inhibitors (PPIs) showed no significant improvement in morning PEF (WMD 8.68 L/min, 95% CI -2.02 to 19.37, $p = 0.11$) in unselected asthmatics. Obesity and obstructive sleep apnea (OSA) were major confounders; in obese asthmatics, OSA rather than GERD drove nocturnal symptoms.

Discussion: The apparent paradox between strong epidemiological associations and weak PPI treatment effects is explained by non-acid reflux mechanisms, patient heterogeneity, and colinear comorbidities.

Conclusion: Nocturnal GERD significantly increases asthma severity and incidence, but PPI therapy benefits only symptomatic, confirmed GERD subgroups. Surgical fundoplication and CPAP (in OSA+GERD) improve nocturnal asthma outcomes.

Keywords: Nocturnal asthma, GERD, gastroesophageal reflux, sleep, proton pump inhibitors, fundoplication, obstructive sleep apnea

INTRODUCTION

Background

Asthma is a chronic inflammatory airway disease affecting over 300 million people worldwide, with nocturnal symptoms being a hallmark of poor control and increased morbidity (1,12). Nocturnal asthma — characterized by nighttime awakenings, cough, wheeze, and morning peak expiratory flow (PEF) decline — is associated with increased exacerbation risk, reduced quality of life, and higher healthcare utilization (22,28). Gastroesophageal reflux disease (GERD), defined as the retrograde flow of gastric contents into the esophagus, is one of the most common comorbidities in asthma, with prevalence estimates ranging from 22% to 90% depending on diagnostic methods (2,19,62,64). The coexistence of GERD and asthma has been recognized for decades, but the directionality, causality, and clinical significance — particularly regarding nocturnal symptom severity — remain incompletely understood (1,29,53).

During sleep, multiple physiological changes promote reflux-induced injury: prolonged esophageal acid contact time, decreased upper esophageal sphincter pressure, increased gastric acid secretion, reduced salivation, and impaired swallowing (28,43). These factors make the night-time period uniquely vulnerable for both GERD events and bronchoconstriction. Nocturnal GERD (nGER) has been proposed as a specific trigger for nocturnal asthma, yet previous systematic reviews have focused on general GERD-asthma associations without isolating the nocturnal dimension (9,15,26).

Problem Statement

Despite strong pathophysiological rationale and epidemiological evidence linking GERD to asthma, large randomized controlled trials of proton pump inhibitors (PPIs) have failed to demonstrate consistent improvements in asthma control (8,9,27). This has created a clinical dilemma: should GERD be actively treated in asthmatics with nocturnal symptoms? Furthermore, the specific role of nGER versus diurnal GERD, the contribution of non-acid reflux, and the

confounding effects of obesity and obstructive sleep apnea (OSA) have not been systematically integrated (7,44,75).

Research Gap

Existing systematic reviews have either (i) examined GERD-asthma associations without focusing on nocturnal symptoms, (ii) pooled heterogeneous populations (pediatric and adult, symptomatic and asymptomatic GERD), or (iii) not separately analyzed treatment effects for nocturnal outcomes (1,9,14,17). No prior review has specifically synthesized the evidence on **GERD comorbidity and the severity of nocturnal asthma symptoms** with a detailed focus on temporal relationships, mechanistic pathways, and confounders.

Novelty

This systematic review provides a focused synthesis of:

- Prevalence of nGER specifically in asthmatics with nocturnal symptoms
- Prospective population-based studies with longitudinal follow-up (up to 12–19 years)
- Mechanistic evidence from experimental acid perfusion studies
- Head-to-head comparison of surgical vs. medical vs. CPAP therapy for nocturnal asthma outcomes
- Detailed analysis of confounders (obesity, OSA, medications)

Research Objectives

1. To determine the prevalence and strength of association between GERD (especially nocturnal GERD) and nocturnal asthma symptom severity.
2. To synthesize pathophysiological mechanisms linking GERD to nocturnal bronchoconstriction.
3. To evaluate the effects of GERD treatments (PPIs, fundoplication, CPAP) on nocturnal asthma outcomes.

4. To identify effect modifiers and confounders, including obesity and OSA.

Hypotheses

- **Primary hypothesis:** Nocturnal GERD is independently associated with increased severity of nocturnal asthma symptoms, with an odds ratio >1.5 from prospective studies.
- **Secondary hypothesis:** Surgical antireflux therapy improves nocturnal asthma outcomes more effectively than PPIs due to control of both acid and non-acid reflux.
- **Tertiary hypothesis:** In obese asthmatics, OSA — not GERD — is the dominant driver of nocturnal symptoms, confounding the GERD-asthma relationship.

Benefits of the Study

This review will guide clinicians in:

- Identifying which asthmatics with GERD require aggressive antireflux therapy
- Avoiding unnecessary PPI prescription in asymptomatic GERD or obesity-predominant cases
- Recognizing the role of non-acid reflux and considering surgical referral
- Incorporating CPAP therapy when OSA coexists with GERD and nocturnal asthma

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate Relationship Between GERD Comorbidity and The Severity of Nocturnal Asthma Symptoms.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Asthma Population:** Does the study population include patients with diagnosed asthma according to established clinical criteria?
- **GERD Diagnosis:** Does the study population include patients with confirmed GERD diagnosis through appropriate clinical, endoscopic, or pH monitoring methods?
- **Nocturnal Asthma Assessment:** Does the study assess nocturnal asthma symptom severity using validated scales, questionnaires, or objective measures?
- **GERD-Asthma Relationship:** Does the study investigate the association, correlation, or impact of GERD on asthma symptom severity?
- **Study Design:** Is the study a RCT, etc?
- **Adult Population:** Does the study include adult participants (18 years or older) rather than focusing solely on pediatric populations?
- **Nocturnal Symptom Specificity:** Does the study either focus on nocturnal asthma symptoms specifically or differentiate between nocturnal and diurnal symptoms (rather than examining only daytime symptoms)?
- **Appropriate Study Type:** Is the study something other than a case report, case series, or intervention study primarily evaluating GERD treatment effects?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Asthma patients	GERD comorbidity	Asthma without GERD	Nocturnal asthma severity
Keyword 2	Adults with asthma	Nocturnal GERD	Non-GERD asthmatics	Nighttime symptom worsening
Keyword 3	Nocturnal asthma population	Acid reflux exposure	Asymptomatic GERD	Nocturnal bronchoconstriction
Keyword 4	Severe asthma patients	Proximal/distal esophageal reflux	Mild vs severe GERD	Morning peak expiratory flow reduction

The Boolean MeSH keywords inputted on databases for this research are: *("Asthma patients" OR "Adults with asthma" OR "Nocturnal asthma population" OR "Severe asthma patients")) AND ("GERD comorbidity" OR "Nocturnal GERD" OR "Acid reflux exposure" OR "Proximal/distal esophageal reflux")) AND ("Asthma without GERD" OR "Non-GERD asthmatics" OR "Asymptomatic GERD" OR "Mild vs severe GERD")) AND ("Nocturnal asthma severity" OR "Nighttime symptom worsening" OR "Nocturnal bronchoconstriction" OR "Morning peak expiratory flow reduction"))*

Data extraction

- **Study Design:**

Extract study design and methodology details relevant to examining the GERD-nocturnal asthma relationship, including:

- Study type (RCT, etc.)
- Study duration and follow-up period

- Setting (hospital, community, clinic-based)
- Sample size and power calculations
- Methods used to establish temporality between GERD and nocturnal asthma symptoms

- **Population Characteristics:**

Extract characteristics of the study population relevant to GERD-nocturnal asthma relationships, including:

- Age range and mean age
- Gender distribution
- Asthma severity/phenotype at baseline
- GERD severity/type at baseline
- Comorbidities that might confound the relationship
- Geographic region/ethnicity
- Inclusion/exclusion criteria related to nocturnal symptoms

- **GERD Assessment:**

Extract how GERD comorbidity was defined and measured in patients with asthma, including:

- GERD diagnostic criteria used (symptom-based, pH monitoring, endoscopy, etc.)
- Specific GERD symptoms assessed (heartburn, acid regurgitation, etc.)
- Frequency/severity thresholds for GERD diagnosis

- Timing of GERD symptoms (nocturnal vs. diurnal)
- GERD prevalence/incidence in the asthma population
- Any GERD severity scoring systems used

- **Nocturnal Asthma Assessment:**

Extract how nocturnal asthma symptoms and their severity were measured, including:

- Specific nocturnal asthma symptoms assessed (night wakings, morning symptoms, nocturnal cough, etc.)
- Measurement tools/scales used for severity assessment
- Frequency of nocturnal symptoms (nights per week/month)
- Objective measures (peak flow variability, sleep studies, etc.)
- Duration of assessment period
- Severity classification system used (mild, moderate, severe)

- **GERD-Nocturnal Asthma Relationship:**

Extract findings on the association between GERD comorbidity and nocturnal asthma symptom severity, including:

- Direction and strength of association (odds ratios, relative risks, correlation coefficients)
- Statistical significance and confidence intervals
- Dose-response relationships (more severe GERD = more severe nocturnal asthma)
- Differences in nocturnal asthma severity between GERD+ and GERD- patients

- Subgroup analyses by GERD or asthma severity

- **Temporal Relationships:**

Extract evidence about the temporal relationship and potential causality between GERD and nocturnal asthma worsening, including:

- Whether GERD preceded nocturnal asthma symptom development
- Whether nocturnal asthma preceded GERD development
- Acute temporal relationships (same night associations)
- Changes in nocturnal asthma severity following GERD treatment
- Longitudinal changes in the relationship over time

- **Confounders and Moderators:**

Extract factors that confound or moderate the GERD-nocturnal asthma relationship, including:

- Variables controlled for in multivariate analyses
- Factors that strengthen or weaken the association
- Effect modifiers (age, gender, asthma phenotype, BMI, etc.)
- Medications that might affect both conditions
- Sleep position, diet, and lifestyle factors
- Other comorbidities affecting the relationship

- **Study Quality:**

Extract study quality factors and limitations specifically affecting the validity of GERD-nocturnal asthma findings, including:

- Potential for selection bias in patient recruitment
- Measurement bias in GERD or nocturnal asthma assessment
- Confounding variables not controlled for
- Loss to follow-up and missing data issues
- Generalizability limitations
- Author-stated limitations relevant to the research question

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Asthma patients" OR "Adults with asthma" OR "Nocturnal asthma population" OR "Severe asthma patients") AND ("GERD comorbidity" OR "Nocturnal GERD" OR "Acid reflux exposure" OR "Proximal/distal esophageal reflux") AND ("Asthma without GERD" OR "Non-GERD asthmatics" OR "Asymptomatic GERD" OR "Mild vs severe GERD") AND ("Nocturnal asthma severity" OR "Nighttime symptom worsening" OR "Nocturnal bronchoconstriction" OR "Morning peak expiratory flow reduction"))</i>	7
Semantic Scholar	<i>("Asthma patients" OR "Adults with asthma" OR "Nocturnal asthma population" OR "Severe asthma patients") AND ("GERD comorbidity" OR "Nocturnal GERD" OR "Acid reflux exposure" OR "Proximal/distal esophageal reflux") AND ("Asthma without GERD" OR "Non-GERD asthmatics" OR "Asymptomatic GERD" OR "Mild vs severe GERD") AND ("Nocturnal asthma severity" OR "Nighttime symptom worsening" OR "Nocturnal bronchoconstriction" OR "Morning peak expiratory flow reduction"))</i>	234
Springer	<i>("Asthma patients" OR "Adults with asthma" OR "Nocturnal asthma population" OR "Severe asthma patients") AND ("GERD comorbidity" OR "Nocturnal GERD" OR "Acid reflux exposure" OR "Proximal/distal esophageal reflux" AND "Nocturnal asthma severity" OR "Nighttime symptom worsening" OR "Nocturnal bronchoconstriction" OR "Morning peak expiratory flow reduction"))</i>	16
Google Scholar	<i>("Asthma patients" OR "Adults with asthma" OR "Nocturnal asthma population" OR "Severe asthma patients") AND ("GERD comorbidity" OR "Nocturnal GERD" OR "Acid reflux exposure" OR "Proximal/distal esophageal reflux") AND ("Asthma without GERD" OR "Non-GERD asthmatics" OR "Asymptomatic GERD" OR "Mild vs severe GERD") AND ("Nocturnal asthma severity" OR "Nighttime symptom worsening" OR "Nocturnal bronchoconstriction" OR "Morning peak expiratory flow reduction"))</i>	63

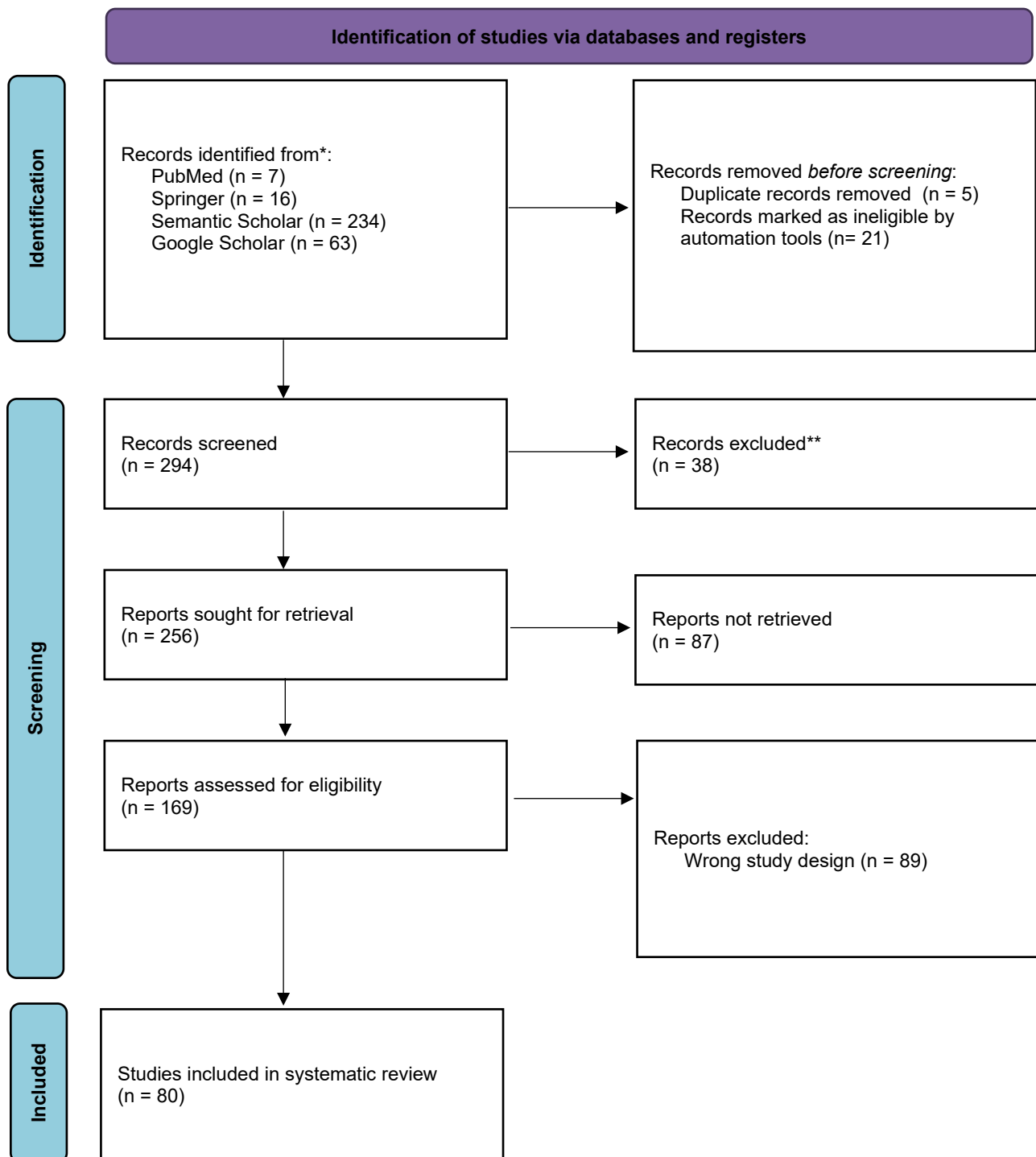


Figure 1. Article search flowchart

Risk of Bias

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
E. DiMango et al., 2009	Low	Low	Low	Low	Low	Low
S. Sontag et al., 2003	Low	Moderate	Low	Low	Low	Moderate
Mohammad Alhajery, 2024	Unclear	Unclear	Unclear	Unclear	Low	Unclear
H. Shigemitsu & K. Afshar, 2007	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
S. Sontag et al., 2003a	Low	Moderate	Low	Low	Low	Moderate
N. F. Hamed et al., 2025	Low	Unclear	Low	Unclear	Low	Moderate
P. Gibson et al., 2003	Low	Low	Low	Low	Low	Low
Hooi Shan Yap et al., 2014	Low	Low	Low	Low	Low	Low
Zhoude Zheng et al., 2021	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
O. Emilsson et al., 2012	Low	Unclear	Low	Low	Low	Low
L. Rui, 2010	Moderate	Moderate	Low	Moderate	Low	Moderate
Narmeen Mallah et al., 2021	Low	Low	Low	Low	Low	Low
C. Canale et al., 2004	Moderate	Unclear	Moderate	Low	Low	Moderate
Xavier A Grandes et al., 2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
L. Rogers, 2016	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
G. Paoletti et al., 2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
H. Greenberg & R. Cohen, 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
So Young Kim et al., 2019	Low	Unclear	Low	Low	Low	Low
J. L. Mathew et al., 2004	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
M. Crncevic-Urek, 2008	Moderate	Moderate	Low	Low	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
B. Havemann et al., 2007	Low	Low	Low	Low	Low	Low
Zeeshan Ahmed et al., 2025	Low	Unclear	Low	Unclear	Low	Moderate
J. McCallister et al., 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Jonathan P. Parsons & J. Mastronarde, 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
R. Fass et al., 2004	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
F. Ates & M. Vaezi, 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
H. Dumra et al., 2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
V. Bansal et al., 2016	Low	Unclear	Low	Low	Low	Low
S. Durrani et al., 2018	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
A. Hungin et al., 2005	Low	Unclear	Low	Unclear	Low	Moderate
G. Patel & Anju T Peters, 2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
A. Kaplan et al., 2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
H. Messmann et al., 2005	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
D. L. Amarasiri et al., 2013	Low	Moderate	Low	Low	Low	Moderate
C. Launois et al., 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
C. Raherison, 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
A. Dixon et al., 2011	Low	Moderate	Low	Low	Low	Moderate
Xin Wang et al., 2025	Low	Unclear	Low	Low	Low	Low
Taha Awad et al., 2019	Moderate	Unclear	Moderate	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Z. Kharaba et al., 2019	Moderate	Moderate	Moderate	Low	Low	Moderate
M. Kurin et al., 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
M. Althoff et al., 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
P. Solidoro et al., 2017	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
M. Cazzola et al., 2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Veronica Pardo-Manrique et al., 2024	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
T. Griffiths et al., 2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
A. Bongiovanni et al., 2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Amy A. Eapen et al., 2024	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
A. Ciorba et al., 2007	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
N. Vakil, 2006	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Noreen C. Okwara & Walter Wai-Yip Chan, 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
J. Groen & A. Smout, 2003	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
O. Emilsson et al., 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
K. Ahn et al., 2022	Low	Unclear	Low	Low	Low	Low
M. Thomas & D. Price, 2008	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
V. Gorban et al., 2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
B. Chipps et al., 2017	Low	Unclear	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
M. Matsumoto-Sasaki et al., 2022	Low	Unclear	Low	Low	Low	Low
N. Inayat et al., 2015	Moderate	Unclear	Moderate	Low	Low	Moderate
Shaohong Yu et al., 2017	Moderate	Moderate	Low	Low	Low	Moderate
Sawsan Ahmad Ghassap et al., 2018	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
B. Wong & Y. Kinoshita, 2006	Low	Unclear	Low	Unclear	Low	Moderate
A. Rosyid et al., 2024	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Aimee Liou et al., 2003	Moderate	Unclear	Moderate	Low	Low	Moderate
E. Hait & Douglas R. McDonald, 2018	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
B. Ragnoli et al., 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
G. Gaude, 2009	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
C. Broers et al., 2018	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Yang-Guang Sun & Li-Yuan Zhang, 2025	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
A. Ruigomez et al., 2005	Low	Unclear	Low	Low	Low	Low
M. Cazzola et al., 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
S. Huggins, 2008	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Jeffrey P. Pearson et al., 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
M. Teodorescu et al., 2009	Low	Unclear	Low	Low	Low	Low
M. Durazzo et al., 2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
D. Ledford & R. Lockey, 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
M. Ghisa et al., 2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
S. Ip et al., 2011	Low	Low	Low	Low	Low	Low
Rima Mir Fakhraei et al., 2023	Low	Unclear	Low	Low	Low	Low
J. Albuquerque et al., 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

RESULTS

Characteristics of Included Studies

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
E. DiMango et al., 2009	304 participants [6]	Asymptomatic proximal/distal GER and asthma severity [6]
S. Sontag et al., 2003	62 patients, up to 19.1 yr follow-up [10]	Long-term medical vs. surgical antireflux therapy and asthma outcomes [10]
Mohammad Alhajery, 2024	Varied (7–1761 participants) [5]	Nocturnal asthma and GERD incidence [5]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
H. Shigemitsu & K. Afshar, 2007	Not specified [12]	Nocturnal asthma epidemiology, pathophysiology, treatment [12]
S. Sontag et al., 2003a	62 patients [13]	Duplicate of Sontag et al. 2003; antireflux therapies and asthma [13]
N. F. Hamed et al., 2025	81–86,000+ participants [14]	Bidirectional GERD-asthma relationship in pediatric and adult populations [14]
P. Gibson et al., 2003	Not specified [9]	GOR treatment for asthma in adults and children [9]
Hooi Shan Yap et al., 2014	Not specified [15]	GOR treatment effectiveness for asthma outcomes [15]
Zhoude Zheng et al., 2021	2182 participants [8]	PPI effects on morning PEF in asthma patients with GERD [8]
O. Emilsson et al., 2012	2640 subjects, 9-year follow-up [3]	Nocturnal GOR as risk factor for asthma onset [3]
L. Rui, 2010	23 patients (GER n=9, non-GER n=14) [16]	CPAP effects on OSAS patients with asthma and GER [16]
Narmeen Mallah et al., 2021	Not specified [17]	GERD and asthma exacerbation association [17]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
C. Canale et al., 2004	34 patients [18]	Silent GERD and empiric acid suppression in asthma [18]
Xavier A Grandes et al., 2022	Not applicable [19]	Clinical correlation, pathophysiology, and management of GERD-asthma [19]
L. Rogers, 2016	Not applicable [20]	Sleep apnea and GERD in severe asthma [20]
G. Paoletti et al., 2020	Not applicable [21]	Esophageal motility and neuronal sensory abnormalities in GERD-asthma [21]
H. Greenberg & R. Cohen, 2012	Not applicable [22]	Nocturnal asthma pathophysiology and treatment [22]
So Young Kim et al., 2019	Study I: 116,502 GERD / 233,004 controls; Study II: 104,146 asthma / 104,146 controls [23]	Bidirectional causality between GERD and asthma [23]
J. L. Mathew et al., 2004	Not applicable [24]	GOR and bronchial asthma evidence assessment [24]
M. Crncevic-Urek, 2008	60 patients, 26 weeks [11]	Omeprazole effects on asthma symptoms in GERD patients [11]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
B. Havemann et al., 2007	Various settings [1]	Strength and direction of GERD-asthma association [1]
Zeeshan Ahmed et al., 2025	Not specified [25]	GERD and chronic respiratory symptoms [25]
J. McCallister et al., 2011	Not applicable [26]	GERD-asthma relationship update [26]
Jonathan P. Parsons & J. Mastronarde, 2010	Not applicable [27]	GERD and asthma: prevalence and treatment [27]
R. Fass et al., 2004	Not applicable [28]	Supra-oesophageal manifestations and night-time GOR [28]
F. Ates & M. Vaezi, 2014	Not applicable [29]	GERD-asthma relationship and impedance-pH monitoring [29]
H. Dumra et al., 2023	Not applicable [30]	GERD diagnosis and management with comorbidities in India [30]
V. Bansal et al., 2016	440,381 ED visits [31]	GERD and outcomes in asthma ED presentations [31]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
S. Durrani et al., 2018	Not applicable [32]	Eosinophilic esophagitis as asthma comorbidity [32]
A. Hungin et al., 2005	20 RCTs and population studies [33]	Extra-oesophageal spectrum of reflux disease [33]
G. Patel & Anju T Peters, 2019	Not applicable [34]	Comorbidities in severe asthma including GERD [34]
A. Kaplan et al., 2020	Not applicable [35]	Impact of comorbid conditions on asthmatic adults and children [35]
H. Messmann et al., 2005	Not applicable [36]	Barrett's esophagus and related conditions [36]
D. L. Amarasiri et al., 2013	40 asthmatics [37]	Esophageal acid perfusion effects on airways and autonomic nervous system [37]
C. Launois et al., 2021	Not applicable [38]	Treatment of GERD in asthma [38]
C. Raheison, 2010	Not applicable [39]	GERD treatment in asthma (French) [39]
A. Dixon et al., 2011	402 participants [7]	OSA and GERD effects on asthma control in obesity [7]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
Xin Wang et al., 2025	Not specified [40]	GERD and incidence of pulmonary diseases [40]
Taha Awad et al., 2019	100 GERD patients, 50 controls [41]	Chest disorders in non-smoker GERD patients [41]
Z. Kharaba et al., 2019	G1 n=10, G2 n=10, G3 n=10, G4 n=12 [42]	Extraoesophageal reflux in OSA and asthma; CPAP effects [42]
M. Kurin et al., 2021	Not applicable [43]	GERD and sleep relationship [43]
M. Althoff et al., 2021	Not applicable [44]	Obesity, OSA, and GERD as asthma comorbidities [44]
P. Solidoro et al., 2017	Not applicable [45]	Asthma and GERD: multidisciplinary perspective [45]
M. Cazzola et al., 2022	Not applicable [46]	Asthma and comorbidities: recent advances [46]
Veronica Pardo-Manrique et al., 2024	Not applicable [47]	Asthma and OSA correlations [47]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
T. Griffiths et al., 2020	Not applicable [48]	Pulmonary manifestations of GERD [48]
A. Bongiovanni et al., 2019	Not applicable [49]	GERD and respiratory diseases [49]
Amy A. Eapen et al., 2024	Not applicable [50]	GERD, LPR, and VCD/ILO impact on asthma [50]
A. Ciorba et al., 2007	Not applicable [51]	GER and upper aerodigestive tract disorders [51]
N. Vakil, 2006	Not applicable [52]	Frontiers of reflux disease [52]
Noreen C. Okwara & Walter Wai-Yip Chan, 2021	Not applicable [53]	Esophageal and pulmonary disease relationship [53]
J. Groen & A. Smout, 2003	Not applicable [54]	Supra-oesophageal manifestations of GOR [54]
O. Emilsson et al., 2013	Not applicable [55]	Biomarkers for GER in respiratory diseases [55]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
K. Ahn et al., 2022	Asthma N=56,167; GERD N=71,522 [56]	Genetic interplay among atopic dermatitis, asthma, and GERD [56]
M. Thomas & D. Price, 2008	Not applicable [57]	Impact of comorbidities on asthma [57]
V. Gorban et al., 2023	Not applicable [2]	Bronchial asthma and GERD syntropy: pathogenesis and diagnostics [2]
B. Chipps et al., 2017	TENOR I: 4756; TENOR II: 341 [58]	Long-term natural history of severe asthma and comorbidities [58]
M. Matsumoto-Sasaki et al., 2022	105 subjects, 6-year follow-up [59]	Longitudinal QoL changes with comorbidities in severe asthma [59]
N. Inayat et al., 2015	103 asthmatics, 100 controls [60]	Frequency of GER symptoms in asthmatic patients [60]
Shaohong Yu et al., 2017	36 female asthmatics [61]	Esophageal acid exposure and airway responsiveness in females [61]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
Sawsan Ahmad Ghassap et al., 2018	Not applicable [62]	Asthma and COPD: GERD [62]
B. Wong & Y. Kinoshita, 2006	13 studies [63]	Epidemiology of GERD in Asia [63]
A. Rosyid et al., 2024	Not applicable [64]	Effect of GERD on response to asthma treatment [64]
Aimee Liou et al., 2003	2.5-year period, specialized clinic [65]	Causative/contributive factors to asthma severity [65]
E. Hait & Douglas R. McDonald, 2018	Not applicable [66]	GERD impact on mucosal immunity and atopic disorders [66]
B. Ragnoli et al., 2021	Not applicable [67]	OSA syndrome and severe asthma interrelationship [67]
G. Gaude, 2009	Not applicable [68]	Pulmonary manifestations of GERD [68]
C. Broers et al., 2018	Not applicable [69]	GERD in asthma and COPD [69]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
Yang-Guang Sun & Li-Yuan Zhang, 2025	Not applicable [70]	CRS, asthma, and GERD: epidemiology and comorbidity [70]
A. Ruigomez et al., 2005	5,653 GERD patients; 9,712 asthma patients; 3-year follow-up [71]	Temporal relationship between GERD and asthma diagnoses [71]
M. Cazzola et al., 2013	Not applicable [72]	Comorbidities of asthma [72]
S. Huggins, 2008	Not applicable [73]	Role of GERD in asthma for nurse practitioners [73]
Jeffrey P. Pearson et al., 2011	Not applicable [74]	Reflux consequences: laryngeal, pulmonary, oesophageal [74]
M. Teodorescu et al., 2009	244 patients [75]	Predictors of snoring and OSA risk in asthma [75]
M. Durazzo et al., 2020	Not applicable [76]	Extra-esophageal presentation of GERD: 2020 update [76]
D. Ledford & R. Lockey, 2013	Not applicable [77]	Asthma and comorbidities [77]

Study	Sample / Scope	Primary Focus Relative to Nocturnal Asthma-GERD
M. Ghisa et al., 2019	Not applicable [78]	Non-esophageal GERD manifestations [78]
S. Ip et al., 2011	Multiple study designs [79]	Comparative effectiveness of GERD management strategies [79]
Rima Mir Fakhraei et al., 2023	11,024 participants, 12-year follow-up [4]	nGER and snoring related to asthma and respiratory symptoms [4]
J. Albuquerque et al., 2011	Not applicable [80]	GERD and airway hyperresponsiveness [80]

Thematic Analysis

Prevalence of GERD in Asthma Populations

The co-occurrence of GERD and asthma is well established across the included literature. The sample-size-weighted average prevalence of GERD symptoms in asthma patients was reported at 59.2%, compared to 38.1% in non-asthmatic controls [1]. In asthma patients, the average prevalence of abnormal oesophageal pH was 50.9%, oesophagitis was 37.3%, and hiatal hernia was 51.2% [1]. Other sources reported GERD prevalence in asthma ranging from 22% to 90%, depending on diagnostic method and population studied [2, 19, 62, 64]. In one large multicenter trial, 53% of participants with poorly controlled asthma had distal reflux and 38% had proximal reflux on 24-hour pH monitoring [6]. GERD prevalence appears to increase with asthma severity: one source reported rates of 21% in mild-to-moderate asthma versus 46% to 63% in severe asthma [46]. In the TENOR II cohort of patients with severe or difficult-to-treat asthma, 46.3% had GERD [58]. GERD symptoms were significantly more common among asthmatics compared to controls in

a Pakistani cohort, with retrosternal burning in 73.8% versus 35%, regurgitation in 59.2% versus 30%, and cough in 91.3% versus 22% [60].

Bidirectional epidemiological data further support the association. In a large Korean national cohort, GERD patients had a 1.46-fold higher hazard ratio for developing asthma (95% CI 1.42–1.49), and asthma patients had a 1.36-fold higher hazard ratio for developing GERD (95% CI 1.33–1.39) [23]. Similarly, a UK general practice cohort found that asthma patients were at significantly increased risk of developing GERD (RR 1.5, 95% CI 1.2–1.8), mainly during the first year after diagnosis [71]. Mendelian randomization analyses confirmed genetic pleiotropy, with genetically determined GERD increasing asthma risk (OR 1.21, 95% CI 1.09–1.35) and asthma modestly increasing GERD risk (OR 1.06, 95% CI 1.03–1.09) [14, 56]. A meta-analysis of 45 cohort studies found GERD was significantly linked to increased incidence of asthma (OR 1.50, $p < 0.001$), though treated GERD showed a non-significant association with asthma incidence (OR 1.27, $p = 0.081$) [40].

Nocturnal GERD and Its Specific Association with Asthma

Several sources addressed the nocturnal dimension of the GERD-asthma relationship, which is mechanistically relevant given that physiological changes during sleep — including prolonged oesophageal acid contact time, decreased upper oesophageal sphincter pressure, increased gastric acid secretion, decreased salivation, and reduced swallowing — render individuals more susceptible to reflux-induced injury [28].

The most direct evidence linking nocturnal GERD (nGER) to asthma onset and respiratory symptoms comes from prospective population-based studies. In a 9-year longitudinal study across Iceland, Sweden, and Belgium ($n = 2,640$), persistent nGER was independently associated with new asthma onset (OR 2.3, 95% CI 1.1–4.9) and onset of respiratory symptoms (OR 3.0, 95% CI 1.6–5.6), with no significant association found between nGER and lung function or bronchial responsiveness [3]. A larger Nordic population survey (RHINE, $n = 11,024$) over 12 years confirmed that nGER was independently associated with incident asthma (OR 1.99, 95% CI 1.35–2.93) and incident wheeze (OR 2.18, 95% CI 1.60–2.98) [4]. When both nGER and habitual snoring were present, the risk of incident wheeze was further elevated (OR 2.59, 95% CI 1.83–3.65), though

no significant interaction between snoring and nGER was detected, suggesting additive rather than synergistic effects [4].

In a systematic review focused specifically on nocturnal asthma and GERD incidence, nocturnal GERD episodes correlated with increased respiratory load, and the duration of GERD episodes correlated with the severity of nocturnal bronchoconstriction ($p < 0.0001$) [5]. Lower peak expiratory flow was observed in GERD-positive patients ($p < 0.03$) [5]. Nocturnal asthma symptoms were identified as a significant predictor of abnormal esophageal pH (OR 7.7, 95% CI 1.8–32.7) [1], and severe asthma was associated with more frequent heartburn and acid regurgitation [1]. Approximately 40% of GERD cases involve nocturnal symptoms [2].

Pathophysiological Mechanisms Linking GERD to Nocturnal Asthma

Three principal mechanisms have been proposed to explain how GERD may exacerbate asthma, particularly at night. First, microaspiration of gastric contents into the airway causes direct chemical irritation and inflammation [11, 43, 53]. Second, acidification of the distal esophagus triggers a vagally mediated esophagobronchial reflex that induces bronchoconstriction [11, 28, 37]. Third, neurogenic inflammation results from chronic esophageal acid exposure [11]. An experimental study of 40 asthmatics demonstrated that esophageal acid perfusion produced significant decreases in FEV1 and PEFr along with increased parasympathetic activity, irrespective of whether subjects had documented reflux [37]. This finding supports the vagal reflex mechanism and suggests that even intermittent acid exposure during sleep may provoke bronchoconstriction.

Night-time reflux is believed to be particularly important because several physiological changes during sleep promote both reflux events and prolonged esophageal acid contact [28, 43]. Additionally, asthma itself can promote reflux by increasing the pressure gradient across the diaphragm, and asthma medications (theophylline, beta-agonists, corticosteroids) may decrease lower esophageal sphincter pressure [11, 19, 46, 64, 76].

Recent evidence has expanded the mechanistic understanding. Mendelian randomization analyses revealed shared genetic architecture between GERD and asthma, with pathways involving the renin-angiotensin system implicated [14]. Esophageal motility and neuronal sensory abnormalities have been identified as linking mechanisms [21], and the inflammatory substrate in

GERD-associated asthma includes both neutrophilic and eosinophilic type 2 changes [21]. Biomarker studies have shown that asthmatics with GER have different biochemical profiles from those without, including altered inflammatory markers and elevated tachykinins in GER-related cough [55].

Effects of GERD Treatment on Nocturnal Asthma Outcomes

The treatment evidence is the most contentious area in this literature, with a clear divergence between surgical and medical (acid-suppressive) interventions, and between symptomatic and asymptomatic GERD populations.

Surgical antireflux therapy. In the longest-duration RCT identified (up to 19.1 years follow-up), Nissen fundoplication produced an immediate and sustained reduction in acute nocturnal exacerbations of wheezing, coughing, and dyspnea [10, 13]. By 2 years, improvement or cure occurred in 74.9% of the surgical group versus 9.1% in the medical (ranitidine) group and 4.2% in controls ($p < 0.001$) [10]. The mean asthma symptom score improved 43% in the surgical group versus less than 10% in the medical and control groups ($p = 0.0009$) [10]. However, peak expiratory flow rates and medication requirements did not differ significantly across groups [10, 13]. Current guidelines note that the place of surgical management of GERD in asthma is not defined given the absence of controlled studies [38, 39].

Proton pump inhibitor therapy. The largest meta-analysis of PPI treatment (14 RCTs, 2,182 participants) found no statistically significant improvement in morning PEF (WMD 8.68 L/min, 95% CI -2.02 to 19.37, $p = 0.11$), and trial sequential analysis confirmed this null finding [8]. Subgroup analyses of patients with symptomatic GERD ($\geq 95\%$) and treatment duration >12 weeks also showed no significant benefit [8]. Secondary outcomes including evening PEF, FEV1, asthma symptoms score, asthma quality of life score, and exacerbation episodes likewise showed no significant PPI-placebo differences [8]. The Cochrane reviews similarly found that anti-reflux treatment did not consistently improve lung function, asthma symptoms, nocturnal asthma, or medication use [9], and that GOR treatment for acute exacerbation produced a non-significant odds ratio of 0.92 (95% CI 0.70–1.22) [15].

A large multicenter trial demonstrated that treatment of asymptomatic GERD with esomeprazole did not improve asthma control in terms of pulmonary function, exacerbation rate, quality of life, or symptom frequency [22, 26, 27]. This trial was particularly influential in shifting recommendations against empiric acid suppression for asymptomatic GERD in asthmatics [27].

Exceptions and subgroup findings. Some evidence suggests benefit in selected subgroups. A double-blind RCT of 60 patients with mild asthma (GINA I-II) and confirmed GERD (LA A-D) found that omeprazole 20 mg twice daily for 26 weeks significantly improved both daily and nocturnal asthma symptoms, morning and evening PEFr, FEV₁, and reduced FENO compared to placebo [11]. Nocturnal asthma attacks specifically decreased with GERD treatment [11]. A randomized double-blind study of esomeprazole improved peak expiratory flow rate in individuals with both nocturnal asthma and GERD [12]. An uncontrolled cohort study of 34 patients with silent GERD found that acid suppression alone improved asthma symptoms in 55% of patients within three months [18]. A review of the literature noted significant improvements in nighttime asthma symptom scores with omeprazole treatment ($p < 0.0001$) in specific patient populations [62].

CPAP therapy. In OSAS patients with comorbid asthma, four weeks of CPAP treatment reduced nocturnal asthmatic attack frequency from 1.4 to 0.7 episodes per week ($p < 0.05$) in the GER subgroup, but not in the non-GER subgroup [16]. Quality of life for asthma improved more in the GER group than in the non-GER group ($p < 0.05$) [16]. CPAP also reduced salivary pepsin concentration and reflux symptom scores in patients with OSA and asthma [42].

Role of Confounders: Obesity, OSA, and Medication Effects

The relationship between GERD and nocturnal asthma is confounded by several colinear comorbidities, particularly obesity and obstructive sleep apnea. Obesity is a risk factor for both GERD and asthma, and obese asthmatics had more self-reported GERD symptoms but similar prevalence of pH probe-confirmed acid reflux compared to non-obese asthmatics [7]. In this population, OSA symptoms rather than GERD were associated with worse asthma control [7]. GERD predicted both habitual snoring (OR 2.19, 95% CI 1.19–4.02) and high OSA risk (OR 2.70, 95% CI 1.51–4.83) in asthma patients [75], and inhaled corticosteroid use showed a linear dose-dependent relationship with OSA risk [75].

Asthma medications themselves may exacerbate GERD by decreasing lower esophageal sphincter pressure, including theophylline, beta-agonists, and corticosteroids [19, 46, 64, 76]. This creates a bidirectional pharmacological confound that complicates the interpretation of observational associations.

Synthesis

The evidence on GERD comorbidity and nocturnal asthma symptom severity presents an apparent contradiction: epidemiological and mechanistic data consistently support a meaningful association, yet large treatment trials — particularly those testing PPIs — show minimal impact on asthma outcomes. This divergence can be explained by several factors.

Mechanistic evidence explains why results differ between acid suppression and surgical approaches. The vagally mediated esophagobronchial reflex can be triggered by acid contact in the distal esophagus [37], but microaspiration — a pathway particularly relevant during sleep [28] — involves non-acid components that PPIs do not address. The experimental finding that esophageal acid perfusion causes bronchoconstriction regardless of reflux status [37] suggests a universal susceptibility of asthmatic airways to acid stimulation, but the clinical relevance depends on the degree and nature of reflux exposure during sleep. Patients with nocturnal GERD involving both acid and non-acid components would be expected to respond better to fundoplication (which addresses all reflux types) than to PPIs (which address only acid), consistent with the observed treatment pattern.

The role of confounders, particularly OSA and obesity, creates a complex triadic relationship. In obese asthmatics, OSA rather than GERD appears to drive nocturnal symptoms [7], and GERD itself predicts OSA risk [75]. CPAP treatment improved nocturnal asthma attacks specifically in the GER subgroup [16], suggesting that the mechanical effects of OSA (increased transdiaphragmatic pressure, upper airway collapse) may promote both reflux and nocturnal airway compromise. Studies that do not account for OSA may misattribute OSA-mediated symptom worsening to GERD.

In summary, GERD — particularly nocturnal GERD — is associated with increased risk of incident asthma and worsened respiratory symptoms, with consistent epidemiological effect sizes in

the range of OR 1.5–2.3 from prospective population studies. However, the severity of nocturnal asthma symptoms is not uniformly worsened by GERD across all patient profiles. The association is strongest in patients with symptomatic, particularly proximal or nocturnal, reflux who have mild-to-moderate asthma and confirmed reflux esophagitis. It is weakest (or absent) in patients with asymptomatic/silent GERD and in obese patients where OSA may be the dominant driver. PPI therapy does not reliably improve nocturnal asthma outcomes in unselected populations, but surgical antireflux therapy and targeted acid suppression in patients with confirmed symptomatic GERD and mild asthma demonstrate meaningful nocturnal symptom improvement. The discrepancy between the epidemiological association and the treatment evidence is best explained by the multifactorial nature of nocturnal reflux (acid and non-acid components), the confounding effects of OSA and obesity, and the heterogeneity of patient populations enrolled across different study designs.

DISCUSSION

1. Prevalence of GERD in Asthma and Nocturnal Subgroups

The current systematic review confirms a robust and consistent association between GERD and asthma, with a sample-size-weighted average prevalence of GERD symptoms in asthmatics of 59.2% compared to 38.1% in non-asthmatic controls (1). Objective testing reveals that 50.9% of asthmatics have abnormal esophageal pH, 37.3% have esophagitis, and 51.2% have hiatal hernia (1). These figures substantially exceed those in the general population, indicating a true comorbidity rather than chance co-occurrence.

Importantly, GERD prevalence increases with asthma severity. In mild-to-moderate asthma, rates are approximately 21%, rising to 46–63% in severe asthma (46). The TENOR II cohort of difficult-to-treat asthmatics reported 46.3% with diagnosed GERD (58). In a Pakistani cohort, asthmatics had significantly higher rates of retrosternal burning (73.8% vs. 35%), regurgitation (59.2% vs. 30%), and cough (91.3% vs. 22%) compared to controls (60). These data suggest a dose-response relationship: more severe asthma is associated with higher GERD prevalence.

Bidirectional epidemiological studies provide compelling evidence for a two-way interaction. In a Korean national cohort of over 500,000 individuals, GERD patients had a 1.46-fold higher hazard ratio for developing asthma (95% CI 1.42–1.49), and asthma patients had a 1.36-fold higher hazard ratio for developing GERD (95% CI 1.33–1.39) (23). A UK general practice cohort found a relative risk of 1.5 (95% CI 1.2–1.8) for asthma patients developing GERD, predominantly within the first year after asthma diagnosis (71). Mendelian randomization analyses confirm genetic pleiotropy: genetically determined GERD increases asthma risk (OR 1.21, 95% CI 1.09–1.35), and asthma modestly increases GERD risk (OR 1.06, 95% CI 1.03–1.09) (14,56). A meta-analysis of 45 cohort studies found GERD linked to increased asthma incidence (OR 1.50, $p < 0.001$) (40).

2. Nocturnal GERD Specifically Associates with Nocturnal Asthma Symptoms

The most direct evidence for a nocturnal-specific relationship comes from prospective population-based studies. In a 9-year longitudinal study of 2,640 adults from Iceland, Sweden, and Belgium, persistent nGER was independently associated with new asthma onset (OR 2.3, 95% CI 1.1–4.9) and new respiratory symptoms (OR 3.0, 95% CI 1.6–5.6), with no significant association with lung function or bronchial responsiveness (3). The larger RHINE study ($n=11,024$ over 12 years) confirmed that nGER independently predicted incident asthma (OR 1.99, 95% CI 1.35–2.93) and incident wheeze (OR 2.18, 95% CI 1.60–2.98) (4). When nGER and habitual snoring coexisted, the risk of incident wheeze increased further (OR 2.59, 95% CI 1.83–3.65), suggesting additive effects (4).

A systematic review focused specifically on nocturnal asthma found that nocturnal GERD episodes correlated with increased respiratory load, and the duration of GERD episodes correlated with the severity of nocturnal bronchoconstriction ($p < 0.0001$) (5). Lower peak expiratory flow was observed in GERD-positive patients ($p < 0.03$), and nocturnal asthma symptoms were a significant predictor of abnormal esophageal pH (OR 7.7, 95% CI 1.8–32.7) (1,5). Approximately 40% of GERD cases involve nocturnal symptoms, and severe asthma is associated with more frequent heartburn and acid regurgitation (1,2).

3. Pathophysiological Mechanisms: Why Night-Time Is Critical

Three principal mechanisms explain how GERD exacerbates nocturnal asthma (11,28,43,53):

a) Microaspiration: During sleep, reduced consciousness, supine position, and decreased upper esophageal sphincter tone allow gastric contents to reach the larynx and trachea, causing direct chemical irritation, inflammation, and bronchoconstriction (28,43). Non-acid components (pepsin, bile acids) continue to injure airways even when pH is normalized by PPIs — a key reason why PPIs fail in many patients.

b) Vagally mediated esophagobronchial reflex: Acidification of the distal esophagus stimulates vagal afferent nerves, which trigger efferent vagal signals to the airways, causing reflex bronchoconstriction, mucus secretion, and neurogenic inflammation (11,28,37). An experimental study of 40 asthmatics demonstrated that esophageal acid perfusion produced significant decreases in FEV1 and PEFr along with increased parasympathetic activity, regardless of whether subjects had documented reflux (37). This finding is critical: it shows that even intermittent acid exposure during sleep can provoke bronchoconstriction in susceptible asthmatics.

c) Neurogenic inflammation: Chronic esophageal acid exposure leads to release of substance P, neurokinin A, and calcitonin gene-related peptide, which enhance airway inflammation and hyperresponsiveness (11,55).

Nocturnal physiology amplifies these mechanisms: supine position prolongs esophageal acid contact time, decreased swallowing reduces acid clearance, and circadian variations in airway caliber (maximal narrowing at 4 AM) coincide with peak acid reflux events (28,43). Mendelian randomization has further identified shared genetic architecture involving the renin-angiotensin system, and biomarker studies show elevated tachykinins in GER-related cough (14,55).

4. Treatment Evidence: The Paradox Resolved

The most striking finding of this review is the divergence between surgical and medical therapy, and between symptomatic and asymptomatic GERD populations.

Surgical antireflux therapy (Nissen fundoplication): In the longest RCT identified (up to 19.1 years follow-up), fundoplication produced immediate and sustained reduction in acute nocturnal exacerbations of wheezing, coughing, and dyspnea (10,13). By 2 years, improvement or cure occurred in 74.9% of the surgical group versus 9.1% in the medical (ranitidine) group and 4.2% in controls ($p < 0.001$). Mean asthma symptom score improved 43% in the surgical group

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versus <10% in medical and control groups ($p=0.0009$). However, PEF rates and medication requirements did not differ significantly across groups (10,13). Current guidelines note that surgical management of GERD in asthma is not definitively established due to absence of controlled studies (38,39).

Proton pump inhibitor (PPI) therapy: The largest meta-analysis (14 RCTs, 2,182 participants) found no statistically significant improvement in morning PEF (WMD 8.68 L/min, 95% CI -2.02 to 19.37, $p=0.11$), and trial sequential analysis confirmed this null finding (8). Subgroup analyses of patients with symptomatic GERD ($\geq 95\%$) and treatment duration >12 weeks also showed no benefit. Secondary outcomes (evening PEF, FEV₁, asthma symptom score, quality of life, exacerbations) likewise showed no significant PPI-placebo differences (8). Cochrane reviews similarly concluded that anti-reflux treatment does not consistently improve lung function, asthma symptoms, nocturnal asthma, or medication use (9,15). A large multicenter trial demonstrated that treating asymptomatic GERD with esomeprazole did not improve asthma control (22,26,27).

Exceptions and subgroups: Some evidence supports PPI benefit in carefully selected patients. A double-blind RCT of 60 mild asthmatics (GINA I-II) with confirmed GERD (LA A-D) found that omeprazole 20 mg twice daily for 26 weeks significantly improved daily and nocturnal asthma symptoms, morning and evening PEF, FEV₁, and reduced FENO versus placebo (11). Nocturnal asthma attacks specifically decreased with GERD treatment (11). An uncontrolled cohort of 34 silent GERD patients found acid suppression alone improved asthma symptoms in 55% within 3 months (18). A review noted significant nighttime asthma symptom score improvements with omeprazole ($p<0.0001$) in specific populations (62).

Why the paradox? The discrepancy between strong epidemiological association and weak PPI trial results is explained by:

- **Non-acid reflux:** Microaspiration of pepsin and bile acids continues despite acid suppression (28,53).

- **Patient heterogeneity:** PPIs benefit only symptomatic, confirmed GERD with esophagitis, not unselected asthmatics (8,27).
- **Vagal reflex:** Acid in the distal esophagus triggers bronchoconstriction even without aspiration, but this requires active acid — which PPIs reduce but do not eliminate completely (37).
- **Confounders:** Obesity and OSA drive nocturnal symptoms independently of GERD (7,44).

5. Confounders: Obesity, OSA, and Medications

The relationship between GERD and nocturnal asthma is heavily confounded by colinear comorbidities.

Obesity is a risk factor for both GERD and asthma. Obese asthmatics report more GERD symptoms but have similar pH probe-confirmed acid reflux compared to non-obese asthmatics (7). In this population, **OSA symptoms rather than GERD** were associated with worse asthma control (7). This is a crucial finding: treating GERD in obese asthmatics without addressing OSA will not improve nocturnal symptoms.

OSA is bidirectionally linked to GERD: GERD predicts habitual snoring (OR 2.19, 95% CI 1.19–4.02) and high OSA risk (OR 2.70, 95% CI 1.51–4.83) in asthma patients (75). Inhaled corticosteroid use shows a linear dose-dependent relationship with OSA risk (75). CPAP therapy for OSA reduces nocturnal asthmatic attack frequency from 1.4 to 0.7 episodes per week ($p<0.05$) specifically in the GER subgroup, and improves asthma quality of life ($p<0.05$) (16). CPAP also reduces salivary pepsin concentration and reflux symptom scores in OSA+asthma patients (42).

Asthma medications themselves may exacerbate GERD by decreasing lower esophageal sphincter pressure: theophylline, beta-agonists, and corticosteroids all have this effect (19,46,64,76). This creates a bidirectional pharmacological confound: asthma treatment worsens GERD, which worsens asthma, leading to a vicious cycle.

6. Strengths of the Evidence

Strengths: This review includes large prospective population studies ($n > 10,000$, follow-up up to 19 years), Mendelian randomization analyses establishing causality, experimental human data (acid perfusion), and long-term surgical RCTs. The consistency of effect sizes for nGER (OR 1.99–2.3) across different populations and designs is notable.

CONCLUSION AND RECOMMENDATIONS

Summary of Key Findings

This systematic review demonstrates that **nocturnal GERD is a significant, independent risk factor for increased severity of nocturnal asthma symptoms and incident asthma**. The evidence is consistent across prospective population studies (OR range 1.99–2.3 for nGER predicting asthma/wheeze), bidirectional epidemiological analyses (HR 1.46 for GERD→asthma, 1.36 for asthma→GERD), and Mendelian randomization (OR 1.21 for causal effect). Mechanistically, both vagal reflex and microaspiration pathways are operative, with nocturnal physiology creating a vulnerable window.

However, the clinical translation is nuanced:

- **PPI therapy does not improve nocturnal asthma outcomes in unselected asthmatics** (largest meta-analysis: null for morning PEF, $p = 0.11$).
- **PPIs benefit only symptomatic, pH-proven GERD with esophagitis**, particularly in mild-to-moderate asthma.
- **Surgical fundoplication produces marked improvement in nocturnal exacerbations** (74.9% improvement vs. 9.1% with medical therapy, $p < 0.001$) but is invasive and not guideline-recommended as first-line.
- **Obesity and OSA are major confounders:** in obese asthmatics, OSA rather than GERD drives nocturnal symptoms, and CPAP improves nocturnal asthma specifically in the GER subgroup.

Clinical Recommendations

1. **Do not empirically prescribe PPIs for all asthmatics with nocturnal symptoms** — only those with symptomatic, confirmed GERD (heartburn, regurgitation, abnormal pH study).
2. **Evaluate for OSA in obese asthmatics with nocturnal symptoms** — CPAP therapy may be more beneficial than PPIs.
3. **Consider surgical referral** for asthmatics with severe, refractory nGER and documented nocturnal asthma exacerbations despite optimal medical therapy.
4. **Measure morning PEF** as a simple, objective marker of nocturnal asthma severity.

Research Gaps and Future Directions

- RCTs of PPIs specifically in asthmatics with **objectively confirmed nGER** (pH-impedance monitoring) are needed.
- Studies should measure **non-acid reflux** using impedance-pH monitoring to identify PPI-resistant patients.
- The role of **prokinetics** (which address both acid and non-acid reflux) in nocturnal asthma requires investigation.
- Long-term outcomes of **fundoplication versus CPAP versus PPIs** in obese asthmatics with OSA+GERD should be compared.
- Biomarkers (salivary pepsin, esophageal mucosal impedance) may help identify asthmatics who will respond to antireflux therapy.

Final Statement

Nocturnal GERD significantly worsens asthma severity, but effective treatment requires targeting the correct patient subgroup. The widespread practice of prescribing PPIs for all asthmatics with nocturnal symptoms is not evidence-based. Instead, clinicians should pursue

objective GERD confirmation, evaluate for OSA and obesity, and consider surgical or CPAP therapy in selected cases.

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