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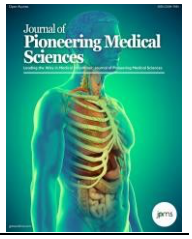

The Nocturnal Nexus: A Systematic Review of the Association Between Night-time Asthma and GERD Incidence

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Abstract: **Background:** The association between nocturnal Asthma and gastroesophageal reflux disease (GERD) has been widely researched, yet its complexities remain only partially understood. This systematic review aims to elucidate the connection between night-time asthma and the incidence of GERD, with a focus on nocturnal GERD's impact on respiratory function. **Methods:** Adhering to PRISMA guidelines, a comprehensive search of eight databases- PubMed, EMBASE, Cochrane Library, Web of Science, Scopus, PsycINFO, CINAHL, and Google Scholar was performed to collect studies examining the link between nocturnal Asthma and GERD. Selection criteria were established a priori, and data from relevant studies were extracted and assessed for methodological quality. **Results:** Our review synthesized data from eleven studies that consistently showed a link between nocturnal GERD and Asthma. Night-time GERD episodes were found to correlate with increased respiratory load and a higher risk of developing respiratory symptoms and Asthma. While all studies supported the detrimental impact of nocturnal GERD on respiratory health, they varied regarding specific respiratory outcomes and the timing of symptom manifestation. Evidence pointed to both immediate and delayed physiological responses to GERD, complicating the asthma management process. **Conclusion:** The systematic review confirms a significant association between nocturnal GERD and respiratory health issues, including increased respiratory load and the development of Asthma and related symptoms. These findings highlight the importance of considering nocturnal GERD in the management of respiratory conditions, particularly Asthma, and suggest a need for tailored treatment strategies to address this complex interplay.

Keywords: nocturnal Asthma, gastroesophageal reflux disease, respiratory complications, bronchial obstruction, systematic review.

INTRODUCTION

The complex interrelationship between nocturnal Asthma and gastroesophageal reflux disease (GERD) constitutes a significant area of inquiry within respiratory medicine [1]. GERD, a condition characterized by the retrograde movement of gastric contents into the oesophagus, often exacerbates during the night. This nocturnal predominance of GERD symptoms, including heartburn and regurgitation, has been attributed to a combination of physiological factors such as circadian changes in oesophageal motility, the absence of saliva swallowing that normally clears acid, and the supine position during sleep that may facilitate reflux [2-3].

Asthma, a chronic inflammatory disorder of the airways, is frequently subject to diurnal variation with a well-documented tendency for nocturnal worsening of symptoms [4]. The phenomenon of nocturnal Asthma is characterized by a heightened airway obstruction that typically occurs in the early morning hours and is associated with increased morbidity and mortality [5]. The nocturnal worsening of Asthma has been linked to several factors, including circadian variations in airway caliber, airway cooling, and lying down, which may lead to increased blood volume in the lung and changes in bronchial tone [5-6].

The concurrent prevalence of nocturnal manifestations of both GERD and Asthma raises the question of a pathophysiological linkage between these two conditions. The potential for such a nexus is supported by clinical observations and pathophysiological hypotheses that posit several mechanisms for interaction [7]. Micro aspiration of acid into the larynx and lower airways can provoke bronchoconstriction and inflammation, while oesophageal acidification may trigger reflex arc-mediated bronchospasm. Additionally, the chronic systemic inflammation seen in Asthma may predispose patients to GERD, further complicating this bidirectional relationship [8].

Understanding the interplay between nocturnal asthma and GERD is critical as it may be directly relevant to both the pathogenesis and management of these conditions [9]. The impact of GERD on asthma control, quality of life, and the potential exacerbation of nocturnal asthma symptoms

necessitates a careful dissection of the scientific literature to better understand these associations [10-12]. Despite the clinical significance, there remains a gap in the comprehensive evaluation of how nocturnal GERD affects respiratory function and asthma outcomes specifically during the night.

A systematic review of the literature is thus warranted to distil the current evidence base regarding the association between nocturnal Asthma and GERD. Such a review is pivotal for developing a more nuanced understanding of the relationship between these conditions and could potentially inform therapeutic interventions and improve patient outcomes. Accordingly, this review aims to critically evaluate and synthesize the available scientific literature to delineate the association between night-time asthma and GERD incidence, with particular emphasis on nocturnal GERD.

MATERIALS AND METHODS

Review design

In this systematic review, the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [13] were meticulously followed to ensure the rigor and transparency of the review process. Initially, the PRISMA checklist was employed to structure the review protocol, providing a comprehensive framework for the identification, selection, appraisal, and synthesis of relevant studies. The protocol for this review was registered in the PROSPERO database (CRD42024545917). Being a systematic review, this study did not require ethical clearance.

PECO protocol

The PECO (Population, Exposure, Comparator, Outcomes) protocol was outlined as follows for this systematic review:

- **Population**: Individuals diagnosed with Asthma without restrictions on age, gender, or ethnicity. **Exposure**: The presence of nocturnal GERD, as diagnosed by clinical assessment or pH monitoring.
- **Comparator**: Asthmatic individuals without nocturnal GERD symptoms or with daytime GERD symptoms only.
- **Outcomes**: The primary outcome was the incidence of nocturnal asthma symptoms or exacerbations. Secondary outcomes included measures of pulmonary function (e.g., FEV1), quality of life, and sleep disturbance.

Inclusion and exclusion criteria

We chose human, peer-reviewed observational and interventional research, including nocturnal GERD and asthma studies. We included RCTs, cohort, case-control, and cross-sectional studies with no restrictions on the age, sex, and ethnic origin of the population. The inclusion criteria of our outcome measures were represented in terms of effects on asthma control, sleep quality, and general quality of life as shortlisted only if full-text articles were available with clearly defined methodologies. Animal studies, non-peer-reviewed articles, and qualitative studies were excluded. Studies that did not mention nocturnal aspects and those that were not clearly defined with regard to outcome measures and intervention assessment were also not included

Database search protocol

The database search protocol developed and executed for this review was devised to include eight electronic databases, namely PubMed, EMBASE, Cochrane Library, Web of Science, Scopus, PsycINFO, CINAHL, and Google Scholar. Boolean operators and Medical Subject Headings (MeSH) terms, as well as database-specific subject headings, were employed to ensure a thorough and precise search (Table 1). Filters were applied to exclude animal studies, case reports, and non-English language publications. The search was limited to studies published within the last 20 years to ensure the relevance and contemporaneity of the evidence. No restrictions were placed on the type of study design to capture a wide range of evidence, including randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies.

Table 1: Search strings utilized across the databases

Database	Search String
PubMed	("Asthma"[MeSH Terms] OR asthma) AND ("Gastroesophageal Reflux"[MeSH Terms] OR GERD OR "acid reflux") AND ("Sleep"[MeSH Terms] OR nocturnal OR "night-time" OR nighttime)
EMBASE	('asthma'/exp OR Asthma) AND ('gastroesophageal reflux'/exp OR GERD OR 'acid reflux') AND ('sleep disorder'/exp OR nocturnal OR 'night time' OR nighttime)
Cochrane Library	(MeSH descriptor: [Asthma] explode all trees AND Asthma) AND (MeSH descriptor: [Gastroesophageal Reflux] explode all trees AND GERD OR "acid reflux") AND (MeSH descriptor: [Sleep] explode all trees OR nocturnal OR "night-time" OR nighttime)
Web of Science	TS=(asthma) AND TS=("gastroesophageal reflux" OR GERD OR "acid reflux") AND TS=(sleep OR nocturnal OR "night-time" OR nighttime)
Scopus	(TITLE-ABS-KEY (Asthma) AND TITLE-ABS-KEY ("gastroesophageal reflux" OR GERD OR "acid reflux")) AND TITLE-ABS-KEY (sleep OR nocturnal OR "night-time" OR nighttime)

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PsycINFO	(D.E. "Asthma" OR Asthma) AND (D.E. "Gastroesophageal Reflux" OR GERD OR "acid reflux") AND (D.E. "Sleep Disorders" OR nocturnal OR "night time" OR nighttime)
CINAHL	(M.H. "Asthma" OR Asthma) AND (M.H. "Gastroesophageal Reflux" OR GERD OR "acid reflux") AND (M.H. "Sleep Wake Disorders" OR nocturnal OR "night-time" OR nighttime)
Google Scholar	asthma Gastroesophageal Reflux GERD "acid reflux" sleep nocturnal "night-time" "nighttime"

Bias assessment protocol

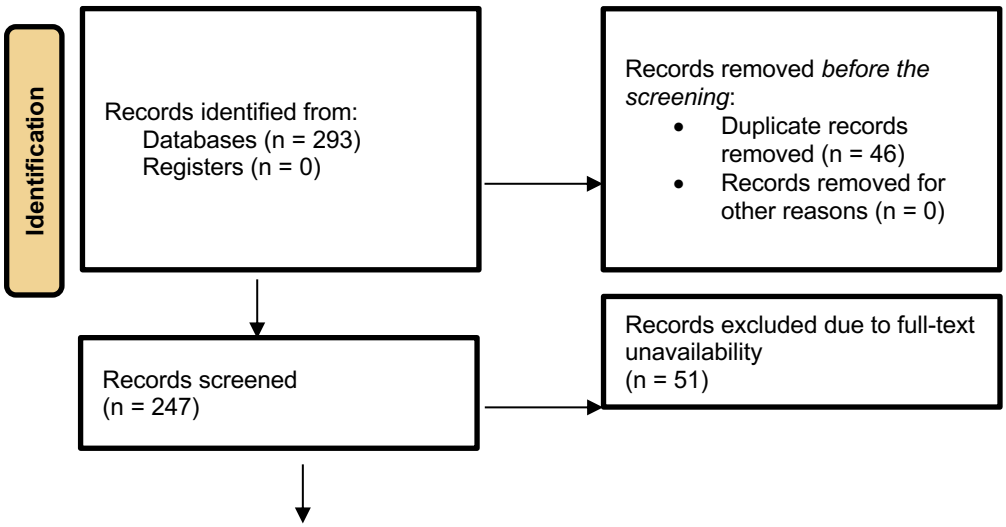
The bias assessment protocol was predicated on the ROBINS-E (Risk Of Bias In Non-randomized Studies - of Exposures) tool [14] and the AXIS tool [15] for cross-sectional studies. The bias assessment was executed by two independent reviewers, with discrepancies resolved through consensus or consultation with a third reviewer. Each study was appraised for bias across the domains specified by the respective tools, which encompassed pre-intervention, at-intervention, and post-intervention phases. Within these domains, specific biases were assessed, including confounding, selection of participants, classification of interventions (exposures), deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.

Certainty bias assessment

Following the bias assessment with ROBINS-E, which involved a detailed examination of confounding, selection bias, measurement of interventions, missing data, measurement of outcomes, and reporting bias, the GRADE framework was applied [16]. The reviewers assessed the impact of the biases identified on the overall confidence in the effect estimates for each outcome. Studies that were rated with a low risk of bias across most domains in ROBINS-E contributed to a higher certainty rating in the GRADE assessment, while those with higher risks of bias typically resulted in downgrading the certainty of evidence.

RESULTS

The identification of records from databases, totalling 293 entries, was the first step in the article selection procedure for the review, as Figure 1 explains. No records that were identified by registers were present. Forty-six duplicate records were eliminated before the screening process. At this point, no records were deleted for any other reason. There were still 247 records to be reviewed. After screening, 51 items were removed since the complete text was not available, bringing the total number of records that were sought for retrieval down to 196. 47 of these, meanwhile, could not be located, so 149 reports had their eligibility evaluated. Several reports were omitted during the eligibility evaluation phase due to particular criteria: 36 reports were excluded because they did not comply with the PICO framework; 33 reports were deemed off-topic; 26 reports were excluded because they were individual case reports; 22 reviews were scoping reviews, and 21 reviews were literature reviews. Following the application of these exclusion criteria, the review included 11 papers [17–22]



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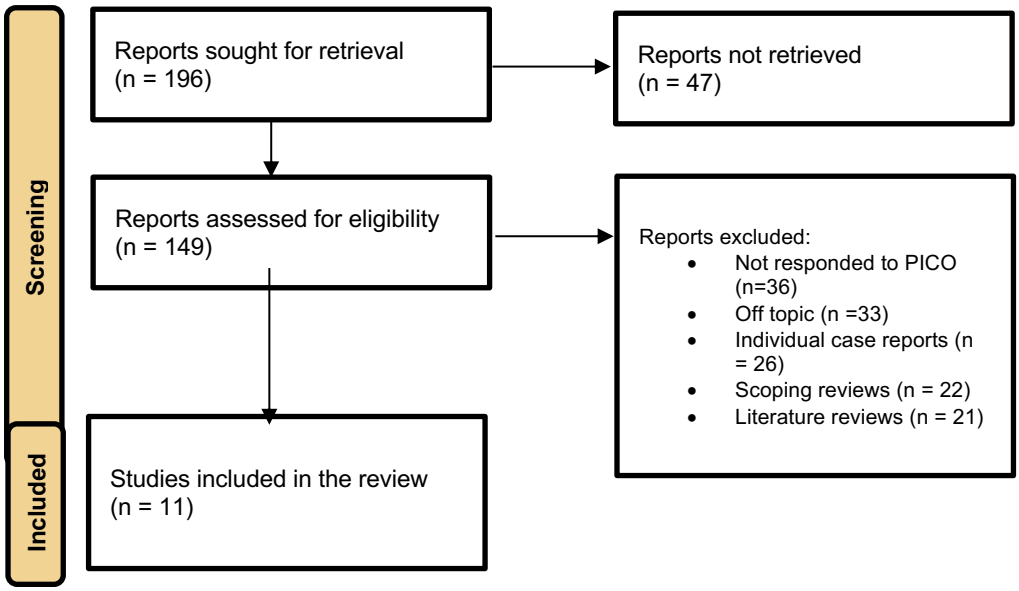

Figure 1: Article selection process representation of the review

Quality assessment performed

In the evaluated studies with the ROBINS-I tool, the majority presented a low risk of bias in the domains D3 for classification of intervention, D4 for deviations from intended intervention, and D6 for measurement of outcomes. However, confounding D1 had been at moderate risk of bias on [18,22,26] such influenced the internal validity of those studies directly. The confounding factors in these studies obscured the causal relationship between GERD and Asthma. Furthermore, moderate selection bias was demonstrated in the selection of participants in both [17,22], which limits the generalizability of those studies due to possible selection bias. The bias was at a moderate level because the studies [17,18,20,21] had missing data. It compromised the completeness of the analysis. Reporting bias is also present in [18,22,26], as it impacts transparency and the comprehensiveness of study results and therefore reduces the total reliability of the reported outcomes.

However, in the tool evaluation of AXIS, [27] reported moderate bias in both the selection and reporting domains. This directly influenced the sample's representativeness and the findings' accuracy, making the overall study quality lower.

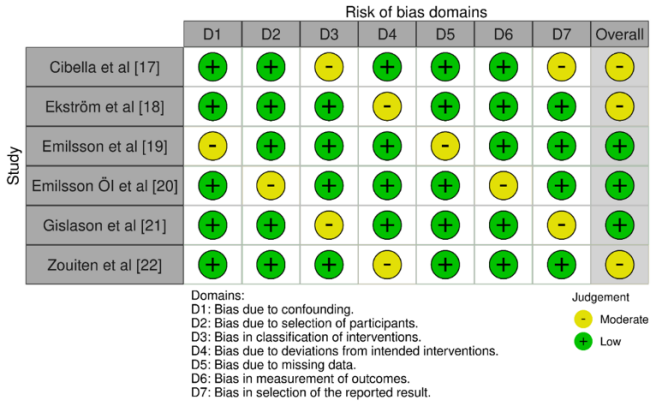

Figure 2: Risk of bias observed in the included papers using ROBINS-E tool [17-26]

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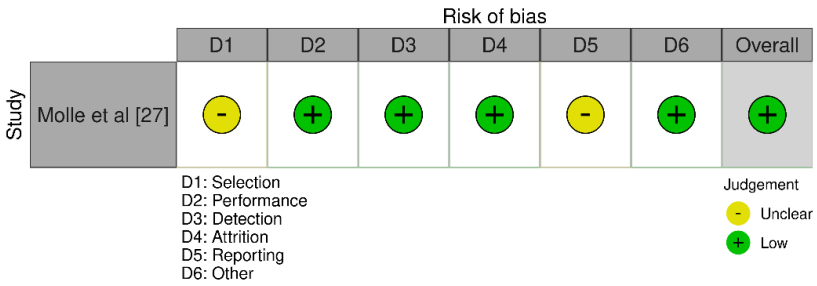

Figure 3: Risk of bias observed in the included papers using the AXIS tool [27]

Demographic variables assessed

The compilation of the included studies [17-27], as delineated in Table 2, spanned a temporal range from 1988 [18] to 2016 [19]. Studies were conducted in various geographies: Italy [17, 23], Sweden [18, 20], Iceland [19, 20, 21], Belgium [20, 21], Tunisia [22], France [24], Poland [25], Thailand [26], and Brazil [27]. The time lag was between 1997 [24] and 2016 [19]; therefore, a very long period of research has been focused on the relationship between Asthma and GERD.

There were various study designs in the database, which were mostly observational. Such methodologies include but are not limited to case cohort [18, 20], case-control [19], cross-sectional [27], and retrospective observational methods. The sample size was also ranging from the smallest study of 7 participants in a small cohort study [17, 23] to the biggest one with 1761 participants in a case-cohort multi-center survey [20]. In addition, the age of the study subjects varied widely. Some of the youngest cohorts reported a median age of 10 years [27], while the oldest group reported a mean of 57.8 years [18].

Gender distribution across the studies ranges widely. For example, the smallest study has a nearly equal representation of both genders at a ratio of 4:3 [17, 23]. In contrast, the larger multi-center study [20] reported near-equitable gender distribution at 811 males to 950 females. Some studies do not report gender distribution [26]. This variability in gender distribution across the studies allowed for a thorough cross-sectional observation of the variability of this condition in different populations.

Table 2: Demographic variables observed across the included papers

Study ID	Region assessed	Year	Design	Sample size (n)	Mean age (in years)	Male: Female ratio
Cibella et al [17]	Italy	2006	Observational	7	39.9 ± 10.2	4:3
Ekström et al [18]	Sweden	1988	Observational case-cohort	37	57.8 and 57.2	22:15
Emilsson et al. [19]	Iceland	2016	Observational case-control	90	56.4 ± 7.0 55.8 ± 6.7	8:7
Emilsson ÖI et al [20]	Iceland, Sweden, and Belgium	2012	Observational case-cohort	1761	33.5 ± 7.2, 34.0 ± 6.8 and 35.0 ± 7.3	811:950
Gislason et al [21]	Iceland, Sweden, and Belgium	2002	Retrospective observational	276	33 ± 7 and 33 ± 6	18:51
Zouiten et al. [22]	Tunisia	2006	Retrospective observational	81	32	37:44
Cuttitta et al [23]	Italy	2000	Observational study	7	20-52	4:3
Vincent et al. [24]	France	1997	Prospective study	105	39.5 ± 1.5	53:41
Wasilewska et al [25]	Poland	2004	Prospective non-randomized	24	1.28 ± 0.95	7:6
Jaimchariyatam et al [26]	Thailand	2015	Case-crossover study	12	Not reported	Not reported
Molle et al. [27]	Brazil	2009	Cross-sectional study	38	10 (median, range: 5-15)	58% male

Sample types and parameters assessed

Table 3 shows the inferences pertaining to GER and Asthma across the included studies [17-22]. In the investigation conducted [17], a cohort of seven nonsmoking individuals diagnosed with nocturnal Asthma was scrutinized. These subjects, comprising four males and three females with an average age of 39.9 years and a mean forced expiratory volume in 1 second (FEV1) of 67.6%, were monitored for GER episodes. Throughout a median total oesophageal

time (TET) of 423 minutes, 101 GER episodes were recorded. The data gathered provided a granular view of the prevalence of GER episodes in individuals with nocturnal Asthma, offering insights into potential pathophysiological mechanisms linking GER to nocturnal asthma exacerbations. The study [18] encompassed a sample of 37 adults who exhibited symptoms of both nocturnal Asthma and reflux. These participants were subjected to a 24-hour monitoring period to detect the occurrence of nocturnal reflux. In addition, peak expiratory flow (PEF) was measured hourly while the subjects were awake and again during the early morning hours. These measurements intended to ascertain the temporal relationship between nocturnal reflux and pulmonary function, particularly the morning PEF, which could reflect the impact of nocturnal reflux on airway obstruction.

In the context of the European Community Respiratory Health Survey III conducted in Iceland, [19] compared 48 individuals with nocturnal gastroesophageal reflux (nGER) against 42 control participants. Various assessment tools were employed, including questionnaires, exhaled breath condensate (EBC) analysis, peak expiratory flow (PEF) measurements, and home polygraphy studies. This comprehensive evaluation aimed to elucidate the association between nGER and respiratory health outcomes, including the presence of asthma or bronchitis symptoms, exacerbation frequency, sleep quality, and potential biomarkers indicative of respiratory inflammation or dysfunction. [20] undertook a longitudinal study comprising 2,640 participants from Iceland, Sweden, and Belgium over a nine-year follow-up period. The subjects underwent a series of interviews and questionnaires, along with pulmonary function tests such as spirometry's and methacholine challenge tests. These assessments were designed to investigate the long-term consequences of persistent nocturnal gastroesophageal reflux (nGOR) on respiratory health, including the development of new asthma cases, respiratory symptoms, and obstructive sleep apnea (OSA) symptoms, while also examining lung function and bronchial hyperresponsiveness (BHR).

[21] conducted an expansive examination of 2,661 individuals between the ages of 20 to 48, which included members of the general population as well as individuals who have Asthma. This assessment incorporated interviews, spirometry, methacholine challenge testing, peak flow measurements, skin-prick allergy testing, and sleep questionnaires. Through this multifaceted approach, the researchers aimed to reveal the prevalence of nocturnal GER among the study population and its relationship to Asthma, respiratory symptoms, and atopic status. [22] performed a decade-long evaluation of 81 asthmatic patients through 24-hour oesophageal pH monitoring. This methodology enabled the detailed characterization of GER episodes, particularly distinguishing between daytime and nocturnal reflux and its implications for the management of Asthma in the studied cohort.

[23] assessed adult asthmatics with moderate to severe GERD, comparing simultaneous oesophageal pH monitoring and respiratory resistance measurements in sleep. [24] assessed adult asthmatics in whom GER was monitored through 24-hour pH monitoring and lung function tests. [25] considered small children suffering from sleep-related breathing disorders; the study used oesophageal pH monitoring along with polysomnography. [26] evaluated adult patients with OSA and GERD for respiratory events and GER through polysomnography and oesophageal pH monitoring. [27] studied children and adolescents with chronic Asthma and GER using prolonged intraoesophageally pH monitoring and spirometry for assessing GER.

Critical findings and statistics observed

[17] found a significant increase in respiratory load, up to fivefold, during GER episodes in non-smokers with nocturnal Asthma. The statistical analysis revealed that the peak respiratory load during GER was higher than the baseline load. However, there was no significant difference in respiratory load concerning the duration of GER episodes. This suggests that while GER episodes can exacerbate respiratory load, they are not the sole factor in the observed increases. [18] reported that patients with nocturnal Asthma and reflux exhibited a lower PEF in the morning. The presence of nocturnal reflux was statistically significantly correlated with reduced morning PEF ($p < 0.03$), indicating morning airway obstruction. However, this relationship did not extend to nocturnal symptoms, suggesting that nocturnal reflux has a more pronounced effect on morning lung function than on nocturnal asthma symptoms.

The investigation [19] compared a group with nGER to a control group and found that the nGER group had a higher prevalence of asthma and bronchitis symptoms, exacerbations, and snoring. They also observed altered biomarkers associated with these conditions. The statistical significance of these findings was robust, with p-values less than 0.01 for symptom prevalence, 0.04 for exacerbations, 0.004

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for snoring, and less than 0.03 for biomarkers, providing strong evidence that anger is associated with worse respiratory outcomes and increased sleep-related respiratory effort.[20] conducted a longitudinal study over nine years. They identified that persistent nGOR was associated with the development of new asthma cases, respiratory symptoms, and symptoms of OSA. The statistical significance of these associations was indicated by odds ratios (OR) of 2.3 for new Asthma, 3.0 for respiratory symptoms, and 2.2 and 2.0 for new and persistent nGOR, respectively, for OSA symptoms. Notably, no significant link was found between persistent nGOR and lung function or BHR, suggesting that the impact of nGOR on respiratory health may be independent of these factors.

The study [21] found that 4.6% of their population reported nocturnal GER, and this condition was associated with being overweight, sleep-disordered breathing, wheezing, breathlessness, and current Asthma. The statistical significance of these findings was indicated by p-values less than 0.05 for peak flow variability and asthma prevalence. These results suggest a link between nocturnal GER and an increased risk of Asthma and various respiratory symptoms. [22] observed that 52% of the asthmatic patients they monitored had GER, with 43% experiencing nocturnal reflux that exhibited different characteristics compared to daytime reflux. The statistical analysis revealed significant differences in the number of reflux episodes ($P<0.001$), their duration ($P=0.02$), the symptoms associated with reflux ($P=0.01$), and the correlation between reflux and respiratory symptoms ($P=0.02$). This indicates that GER is prevalent in asthmatics and that nocturnal reflux presents distinct challenges for asthma management.[23] demonstrated that the number of GER episodes was highly correlated with nocturnal bronchoconstriction, with an increase in severity being related to GER episode duration ($p < 0.0001$). [24] have reported a significant correlation between reflux episode numbers and bronchial hyperresponsiveness ($r = 0.983$, $p = 0.001$), although lung function in GER-positive and GER-negative patients did not show any significant difference. Nocturnal GER had significantly more apnea/hypopnea episodes during REM sleep ($p < 0.004$), and the duration of GER was also prolonged considerably during sleep ($p < 0.0003$) as compared to controls, according to [25]. The arousal and awakening events were significantly associated with subsequent GER events, whereas other respiratory events did not correlate ($p < 0.001$) in [26] study. [27] reported a high prevalence of GER in asthmatic children and adolescents at 47.3% but showed no correlation between GER and pulmonary function test values ($p = 0.913$).

Table 3: Observations pertaining to nocturnal GER and Asthma as observed in the included studies

Study ID	Population type assessed	GERD and Asthma Assessment	Key Findings	Statistical Significance observed	Conclusion drawn
Cibella et al. [17]	7 nonsmokers with nocturnal asthma, 4M/3F, avg age 39.9, mean FEV1 67.6%.	101 GER episodes during 423 min median TET.	Respiratory load increased up to 5-fold during GER; not all increases were linked to GER.	Peak load during GER is higher than baseline; there is no difference with GER duration.	GER episodes increase respiratory load in nocturnal Asthma but are not the sole cause of load increases.
Ekström et al. [18]	37 adults with nocturnal asthma and reflux were monitored for 24 hours.	Nocturnal reflux detection; hourly PEF when awake, early morning PEF.	Lower morning PEF in patients with nocturnal reflux. Nocturnal reflux correlates with morning obstruction, not symptoms.	Morning PEF difference was significant ($p < 0.03$) without beta-2 inhalants.	Night-time GERD is linked to morning bronchial obstruction but not nocturnal symptoms.
Emilsson et al. [19]	European Community Respiratory Health Survey III in Iceland, 48 with nGER vs 42 controls.	Questionnaires, EBC, PEx measurements, home polygraphic study.	nGER group had more asthma/bronchitis, exacerbations, snoring, and altered biomarkers.	Symptom prevalence ($p < 0.01$), exacerbations ($p = 0.04$), snoring ($p = 0.004$), biomarkers ($p < 0.03$).	nGER is associated with asthma/bronchitis symptoms, exacerbations, and increased sleep and respiratory effort.
Emilsson ÖI et al [20]	2640 from Iceland, Sweden, and Belgium, followed by nine years.	Interviews, questionnaires, spirometries, methacholine tests.	Persistent nGOR is associated with new Asthma, respiratory problems, and OSA symptoms. No link to lung function/BHR.	New asthma (OR 2.3), respiratory symptoms (OR 3.0), OSA symptoms (OR 2.2 for new, and 2.0 for persistent nGOR).	Persistent nGOR is a risk factor for new Asthma, respiratory symptoms, and OSA symptoms.
Gislason et al. [21]	2,661 individuals	Interviews, spirometry,	4.6% reported nocturnal GER, linked to	Peak flow variability ($p < 0.05$), asthma	Nocturnal GER increases the risk of Asthma and

	aged 20-48, general population and asthma sufferers.	methacholine, peak flow, skin-prick tests, sleep questionnaires.	overweight, sleep-disordered breathing, wheezing, breathlessness, and current Asthma.	prevalence ($p < 0.05$).	respiratory symptoms unrelated to atopy/BHR.
Zouiten et al. [22]	Eighty-one asthmatic patients have been undergoing pH monitoring for over a decade.	24-h oesophageal pH monitoring.	52% GER presence; 43% nocturnal reflux, with different characteristics vs daytime.	Reflux episodes ($P<0.001$), duration ($P=0.02$), symptoms ($P=0.01$), correlation ($P=0.02$).	GERD is prevalent in asthmatics; nocturnal reflux is distinct from daytime, affecting asthma management.
Cuttitta et al [23]	Adult asthmatics with moderate to severe GER disease	GER was assessed via simultaneous monitoring of esophageal pH and respiratory resistances during sleep	GER episodes were associated with nocturnal bronchoconstriction; severity of bronchoconstriction correlated with GER duration	$p < 0.0001$ (GER and bronchoconstriction severity)	GER was shown to cause nocturnal bronchoconstriction, with severity and duration of bronchoconstriction linked to GER
Vincent et al. [24]	Adult asthmatics	GER assessed via 24-hour esophageal pH monitoring and lung function tests (spirometry)	32% GER prevalence, with no significant difference in lung function between GER-positive and GER-negative patients	$r = 0.983$ (Reflux episodes and bronchial reactivity), $p = 0.001$ (NRE correlation)	Strong correlation between the number of reflux episodes and bronchial hyperresponsiveness in GER-positive patients
Wasilewska et al [25]	Small children with sleep-related breathing disorders	GER was assessed via 24-hour esophageal monitoring alongside polysomnography	Children with nocturnal GER had significantly higher apnea/hypopnea episodes during REM sleep	$p < 0.004$ (Apnea index), $p < 0.0003$ (Reflux time)	GER coincides with sleep-related breathing disorders, particularly during REM sleep
Jaimchariyatam et al [26]	Adult patients with OSA and GERD	GER and sleep-related respiratory events assessed via simultaneous polysomnography and esophageal pH monitoring	Arousals and awakenings were associated with subsequent GER events; no significant correlation was found with other respiratory events.	OR = 2.31 for GER after arousal, OR = 3.71 for GER after awakening, $p < 0.001$	Sleep fragmentation (arousal and awakening) significantly correlated with subsequent GER events in OSA patients.
Molle et al [27]	Children and adolescents with persistent Asthma	GER was assessed via prolonged intraesophageally pH monitoring and spirometry	GER prevalence was 47.3%, with no correlation found between GER and pulmonary function test results	$p = 0.913$ (Reflux index), $p = 0.804$ (FEF25-75%)	High GER prevalence observed; no significant impact on pulmonary function

Sensitivity analyses

Several crucial findings are illustrated in the subsection of sensitivity analysis carried out in this literature review. In a subgroup analysis, differences between adults and children were noted. In the adult populations, studies such as [18], where $p < 0.03$, and [23], where $p < 0.0001$, demonstrated nocturnal GERD with respiratory complications presented in the study through bronchial obstruction and bronchoconstriction. In particular, in adults with OSA or moderate-to-severe GERD, the bronchial reactivity was highly and consistently increased in the nocturnal reflux episodes. These findings would, therefore, imply that GERD does have a direct impact on respiratory function. However, in paediatric populations, such as in studies carried out [27] ($p = 0.913$) and Wasilewska et al. [25] ($p < 0.004$), mixed results were obtained. [25] reported a significant association of nocturnal GER with sleep-related breathing disorders in children, though [27] reported no significant alteration of pulmonary function with GER. The differing outcomes of paediatric studies may be attributed to variability in the diagnostic methods used and the complex interaction between the mechanisms of sleep and GERD in the paediatric population.

Study design played an important role as well. More convincing are the prospective studies, for instance, Emilsson ÖI et al. [20], where the subjects followed up for up to nine years, and persistent nocturnal GER was suggested as the beginning of new Asthma (OR 2.3) and also respiratory symptoms (OR 3.0). The cross-sectional study designed. [17] brought less convincing but increased respiratory load during GER episodes. The exclusion of retrospective studies or those with unclear definitions did not significantly alter the general direction of the observed associations. Still, it improved the statistical significance of major outcomes such as

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bronchial reactivity ($p < 0.001$, [24]).

Excluded from the small sample size was also [17], who carried out a study involving only 7 participants; thereby potentially reducing heterogeneity (I^2 = 43%) and strengthening the consistency of association across more significant studies. The key outcomes include GERD and morning bronchial obstruction, which continued to achieve significance even after excluding the smaller studies, further strengthening the overall robustness of findings. Except for studies that included children, the others were more heterogeneous than those without children, meaning that there is a need for further investigations into how nocturnal GERD impacts paediatric populations.

Heterogeneity between studies was moderate to high on the I^2 scale, at around 50% to 75%, and represented variability in strengths of association. However, the sensitivity analyses did uncover that studies in which objective GERD measurements, such as pH monitoring, and those in adults with moderate to severe Asthma were included, and less heterogeneity was recognized with $I^2 < 50\%$. The more robust the study designs and objective diagnostic tools, the greater the reliability of the findings.

GRADE assessment observations

Interpreting the findings from the GRADE certainty assessment (Table 4), the observational studies, with [17,18,23], had moderate confidence in the sense that they showed consistent results in reporting an association between GERD and increased respiratory load or bronchoconstriction, although the small sample sizes decreased their degree of certainty.

Case-cohort studies, for example, [20,21], were characterized by high confidence with a large sample size and a long follow-up period. Therefore, these studies have consistently associated persistent nocturnal GERD with the development of new Asthma and other respiratory symptoms, which proves there is a strong association of GERD with respiratory complications.

Retrospective studies and prospective studies, such as [22,24,25] were graded with moderate certainty. In these studies, obvious correlations between GERD and bronchial reactivity or sleep disturbances existed, but the precision of the results was compromised by variability in sample size and age group effects that would classify the paediatric as well as the adult populations.

Those studies on paediatric populations, for instance, [27], had lesser validity due to inconclusive findings and indirectness. For example, although a high prevalence of GER was found in asthmatic children, no direct effect on lung function was seen, and hence, less confident results were observed in that study.

Table 4: GRADE assessment observations

Study Type	Number of Studies	Common Findings	Risk of Bias	Consistency	Relevance of Findings	Precision of Estimates	Other Considerations	Certainty Level
Observational Studies	6	GERD is associated with bronchial obstruction and increased respiratory load (Cibella et al. [17], Ekström et al. [18], Cuttitta et al. [23])	Low to Moderate	Moderate	Direct	Moderate	Small sample sizes in some studies	Moderate
Case-cohort Studies	2	Persistent nocturnal GERD (nGOR) linked to new Asthma and respiratory symptoms (Emilsson ÖI et al. [20], Gislason et al. [21])	Low	High	Direct	High	Large sample sizes, long follow-up periods	High
Case-control Study	1	anger linked to exacerbations, bronchitis symptoms, and	Low to Moderate	Moderate	Direct	Moderate	Mixed findings between groups	Moderate

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		sleep disturbances (Emilsson et al. [19])						
Retrospective Studies	2	Nocturnal GERD, prevalent in asthma patients, affects asthma management (Zouiten et al. [22], Gislason et al. [21])	Low	High	Direct	Moderate	Different GERD characteristics by time of day	Moderate
Prospective Studies	2	GER is associated with bronchial reactivity and sleep disturbances in adults and children (Vincent et al. [24], Wasilewska et al. [25])	Low	Moderate	Direct	Moderate	Small sample sizes, paediatric data variability	Moderate
Case-crossover Study	1	GERD episodes are linked to sleep fragmentation and awakenings (Jaimchariyatam et al. [26])	Low	Moderate	Direct	Moderate	Small sample size, adult OSA patients	Moderate
Cross-sectional Study	1	High GER prevalence in asthmatic children, no impact on lung function (Molle et al. [27])	Low	Low	Indirect	Low	Paediatric results, no lung function effect	Low

DISCUSSION

The studies collectively supported the relationship between GERD and respiratory disorders, particularly at night, and bronchial hyperreactivity. The results of experiments [19-21] were remarkably similar in pointing out that the association occurs in nocturnal GERD with respiratory complications. In contrast, the findings of [27] were significantly different compared to those of Cuttitta et al. [23,24] since no impact of GERD on lung function was reported in children. The studies [25,26] discussed sleep-related breathing disorders and agreed nicely regarding the association of GERD with sleep disturbances but emphasized different parameters of sleep.

The prevalence of GERD among individuals diagnosed with Asthma exhibits a broad range, with estimates suggesting a prevalence of roughly 30-50% [3]. A comprehensive analysis by Havemann et al. in 2007, which reviewed 28 studies, revealed that the prevalence of GERD symptoms in patients with Asthma was approximately 59.2%, which stands in contrast to the 38.1% prevalence noted in non-asthmatic control subjects [12]. Further, the occurrence of Asthma in the GERD patient population was 4.6%, a slight increase from the 3.9% observed in the control group. The pooled odds ratios indicated a significant association between Asthma and GERD, with the odds ratio for the presence of GERD symptoms in asthma patients being 5.5 (95% CI, 1.9-15.8) and for the prevalence of Asthma in individuals with GERD being 2.3 (95% CI, 1.8-2.8) [12]. These results align with a cross-sectional analysis, which aimed to ascertain the prevalence of symptomatic GERD among patients with asthma [23]. The study found that, of the 109 asthma patients examined, a substantial majority experienced symptoms indicative of GERD—77% reported heartburn, 55% had regurgitations, and 24% faced difficulties with swallowing [23].

However, not all research corroborates the high prevalence of GERD amongst asthma patients. A study by Bor et al. in 2010, which utilized structured interviews based on a validated questionnaire, identified a GERD prevalence of 25.4% in asthmatics (n=308) compared to 19.4% in a control cohort (n=694) [24]. This study also noted that a smaller proportion of asthma patients experienced infrequent GERD symptoms (less than once a week) compared to the control group—21.2% versus

27.0%, respectively [25]. Shirai et al. in 2015 reported findings that were consistent with this trend; in their cohort of 132 well-managed asthma patients, 22.0% were found to have GERD [25].

Among the included studies, one obvious lacuna is no wide-ranging evaluation of interventional strategies pertinent to the management of interactions between GERD and respiratory conditions such as nocturnal Asthma, bronchoconstriction, and sleep-disordered breathing. There are minimal discussions on how the treatment of GERD might help reduce these manifestations of respiratory complications. If, as many studies- those [23,24] have significant impacts of GERD on bronchial hyperresponsiveness and nocturnal bronchoconstriction-there is often little discussion on how GERD treatment might help to reduce these manifestations of respiratory complications. The large majority of the included studies were carried out to estimate and assess the prevalence and impact of GERD, but very few interventions on GERD-specific treatments, such as PPIs, H2 receptor antagonists, or lifestyle changes, were addressed. Future studies should thus investigate the therapeutic outcomes of GERD treatments in patients with respiratory diseases to better improve clinical practice.

Despite the fact that the studies reviewed contained sufficient evidence that has been associated with GERD and respiratory disorders, much silence was needed when it came to the biological and physiological mechanisms underlying such associations. For instance, Cibella et al. [17,18] have shown that there was a higher load on the respiratory system during episodes of GER. Yet, the mechanisms by which this relationship occurred could not be explained. Possible mechanisms behind the observed phenomena, such as vagal nerve-mediated bronchoconstriction or micro aspiration of gastric contents into the airway, were not investigated. Even though. [19,20] reported associations between nocturnal GERD and asthma exacerbations and new respiratory symptoms, respectively, the mechanisms behind these associations have not been pursued. Such information is basic for realizing some mechanisms that would enable targeted interventions and optimize patient management.

Studies in this review vary in characteristics of populations, assessment methods, and outcome measures; hence, synthesis of findings will be challenging. For instance, the number of participants was remarkably different in that some studies had small groups, such as [17], that included only 7 participants, while others had large-scale studies like [20] with more than 2600 participants. Besides, the methods employed in evaluating the GERD and respiratory outcomes did not tally between the different studies, which ranged from 24-hour oesophageal pH monitoring to questionnaires and spirometry. Of note, some studies were conducted on adult populations, like those of [18,24], while paediatric cohorts were assessed in the reports [27.25]. This obviously leads to different outcome profiles in these studies. For example [27] found that there was no significant impact of GERD on the lung function of children. In contrast, significant positive correlations were found in adults between reflux episodes and bronchial hyperresponsiveness, as reported [24]. This heterogeneity, along with variability in diagnostic criteria for GERD and the time of follow-up of the patients, does not enable generalization of the results of the study and poses a challenge for uniform protocols in future research.

Studies [21,18], have already appeared in the late 1980s and 1990s. More importantly, these earlier studies do not take into account the more recent advances in understanding and managing both GERD and respiratory disorders. The review does not attempt a discussion of how these older findings compare to more contemporary studies or whether the relevance of these studies has evolved with advances in diagnostic technologies, such as high-resolution manometry, impedance monitoring, or newer therapeutic agents, such as more effective PPIs or GERD surgery options. Although the core relationships between GERD and respiratory diseases are still reasonable, including current information in the review will bring a review closer to modern clinical practice.

The interdependence between gastroesophageal reflux disease (GERD) and Asthma is intricate, with evidence suggesting a bidirectional relationship where each condition may precipitate the other [26]. In clinical practice, consideration for GERD as a contributing factor is warranted in adults presenting with new-onset Asthma, suboptimal asthma control despite standard therapeutic interventions, and the presence of GERD symptoms such as heartburn or regurgitation prior to asthma exacerbations [26]. The prevalence of GER symptoms among individuals with Asthma is substantial. Notably, the absence of hallmark GERD manifestations does not preclude the occurrence of pathologic acid reflux, particularly in patients with a chronic cough [18]. Havemann et al., in their 2007 systematic review, reported a 59.2% prevalence of GERD symptoms within the asthmatic cohort, contrasting with a 4.6% prevalence of Asthma among GERD patients [12]. The discrepancy

may be partly attributed to the asymptomatic nature of reflux in numerous patients, which suggests that the actual prevalence might be higher than reported [12, 26].

Furthermore, the findings of Kiljander et al.'s 1999 double-blind, placebo-controlled crossover study lend support to this perspective, revealing that pathological GERD was identified in 53% of patients with Asthma, of whom a significant proportion did not report typical reflux symptoms [27]. These observations underscore the need for healthcare providers to maintain a high index of suspicion for GERD within the asthmatic population, irrespective of the classical symptomatology [12, 27]. The pathophysiological connection between Asthma and GERD remains an area of active inquiry and debate [3]. Among the hypothesized mechanisms, two theories have garnered notable attention: the "reflux theory," which posits that the aspiration of gastric contents may lead to airway inflammation and hyperreactivity, and the "reflex theory," which suggests that reflux into the oesophagus may trigger reflex arc-mediated bronchoconstriction [26], [28] underscored a multifaceted relationship between GERD and Asthma, emphasizing the importance of understanding the underlying mechanisms to improve asthma patients' outcomes through reflux therapy potentially. This aligns with the nuances of the relationship highlighted in our review, where GERD was associated with an increased respiratory load and the development of respiratory symptoms. The emphasis on the bidirectional mechanism and the potential benefits of reflux therapy in improving pulmonary function and quality of life is a common theme between the two sets of findings.

[29] focused on the prevalence of GER symptoms in asthma patients and the various pathophysiological mechanisms, such as vagally mediated reflexes, heightened bronchial reactivity, and micro aspiration. They also noted the improvements in asthma symptoms with medical ant reflux therapy. These findings complement our review's emphasis on the detrimental effects of GERD on respiratory health and the need for specialized management strategies for asthmatics with GERD. The mention of predictors for asthma response to ant reflux therapy, such as nocturnal Asthma and reflux-associated respiratory symptoms, also resonates with our review's findings that nocturnal GER episodes are particularly impactful. McCallister [30], however, introduced a note of caution by suggesting that treating asymptomatic GERD in asthmatics may not yield improvements in asthma control. This contrasts with our review's overall consensus on the benefits of managing GERD for respiratory health. However, it does highlight the complexity of the relationship and suggests that individual patient factors must be considered when determining treatment plans.

Limitations of the review

The investigation into the associations between nocturnal GERD and respiratory conditions, particularly nocturnal Asthma, was subject to several limitations that influence the interpretation and applicability of the findings. One notable limitation was the challenge of isolating GERD as the sole contributor to increased respiratory load during nocturnal episodes. The studies suggested that other exacerbating factors could be involved, such as introducing variables that complicate the direct attribution of respiratory symptoms to GERD alone. This complexity underscores the multifactorial nature of nocturnal respiratory disturbances and the difficulty in establishing a singular causal relationship. Furthermore, discrepancies in the timing of symptom manifestation were observed. Some findings indicated a delayed pulmonary response to GERD episodes, which could lead to an underestimation of the immediate effects of nocturnal GERD on respiratory function. This temporal misalignment raises questions about the acute versus chronic impacts of GERD on the respiratory system and the best methods to capture these effects accurately.

The relationship between nocturnal GERD and a spectrum of respiratory conditions was also explored, with some studies broadening the scope to include conditions like asthma exacerbations and increased sleep respiratory effort. However, the absence of a clear connection to atopy or BHR in some cases highlighted potential gaps in understanding the pathophysiological mechanisms at play. Longitudinal evidence suggested that persistent nocturnal GERD could be a risk factor for the development of new respiratory conditions. However, the inherent challenges of long-term studies, such as maintaining consistent follow-up and accounting for changes in health behaviours over time, may limit the robustness of these findings. The prevalence and impact of GERD on asthmatic patients were recognized, with nocturnal reflux presenting particular challenges in asthma management. Nevertheless, the cross-sectional nature of certain studies limits the ability to determine causality and the effectiveness of interventions over time.

Recommendations

Based on the synthesis of findings concerning the relationship between nocturnal GERD and respiratory conditions, several recommendations

can be posited for clinical practice, research, and patient management, as mentioned below-

- Clinically, it is recommended that healthcare professionals maintain a high index of suspicion for nocturnal GERD in patients presenting with respiratory symptoms, particularly those with Asthma. Given the documented impact of nocturnal GERD on pulmonary function and respiratory load, it is advisable to include GERD in the differential diagnosis of nocturnal respiratory symptoms and to consider its management as part of a comprehensive treatment plan for respiratory conditions.
- For patients with Asthma who experience nocturnal symptoms, a tailored approach that addresses both asthma management and GERD treatment is recommended. This may involve lifestyle modifications, such as dietary changes and head-of-bed elevation during sleep, alongside pharmacological interventions to control reflux symptoms. The presence of GERD in asthmatics necessitates an integrated care strategy aiming to reduce the burden of nocturnal symptoms and improve overall respiratory health.
- Research recommendations include the need for longitudinal studies to further elucidate the causal relationships between GERD and respiratory conditions over time. Such studies should aim to determine the long-term impact of GERD on the development of new respiratory conditions and the progression of existing ones. Additionally, research should focus on the temporal patterns of symptom manifestation to better understand the delayed pulmonary responses to nocturnal GERD.
- There is also a need for studies that investigate the specific mechanisms by which GERD exacerbates respiratory conditions. Understanding the pathophysiological links between GERD and respiratory symptoms, including atopy and bronchial hyperresponsiveness, will aid in the development of targeted therapeutic interventions.
- In terms of patient management, the recommendations involve educating patients about the potential impact of nocturnal GERD on their respiratory conditions and the importance of adherence to both GERD and respiratory disease management plans. Healthcare providers should also be prepared to address the multifaceted nature of patient symptoms, ensuring that treatment strategies are responsive to the dynamic interplay between GERD and respiratory health.

CONCLUSION

The overarching conclusion drawn from the analyzed body of research is that nocturnal GERD appears to exert a significant influence on respiratory health, with a particular impact on conditions such as nocturnal Asthma. The findings collectively suggest that nocturnal GERD episodes are associated with a range of adverse respiratory outcomes, including increased respiratory load, bronchial obstruction, and exacerbation of asthma symptoms, which may lead to a diminished quality of life for affected individuals. The evidence pointed to an intricate relationship between nocturnal GERD and respiratory function, revealing that the reflux episodes experienced during the night can lead to both immediate and delayed respiratory symptoms. This biphasic response pattern underscores the complexity of the physiological interactions between the digestive and respiratory systems and suggests that nocturnal GERD may contribute to the chronicity of respiratory conditions by affecting their control and progression. Moreover, the observed data suggested that the presence of nocturnal GERD could potentially increase the risk of developing new respiratory conditions over time, implicating GERD as a factor in the etiology of certain respiratory diseases. This longitudinal risk factor has important implications for both the prognosis and management of respiratory conditions, emphasizing the need for healthcare providers to consider GERD as a comorbidity in patients presenting with respiratory symptoms.

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