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Gastroesophageal reflux disease and asthma exacerbation: A systematic review and meta-analysis

Narmeen Mallah[1,2,3,4] | Julia May Turner[1] | Francisco-Javier González-Barcala[5,6,7] | Bahi Takkouche[1,2,3]

[1]Department of Preventive Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain

[2]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBER-ESP), Madrid, Spain

[3]Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain

[4]Methodology and Statistics Unit, Galicia Sur Health Research Institute (IISGS), Vigo, Spain

[5]Department of Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain

[6]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBER-ES), Madrid, Spain

[7]Department of Respiratory Medicine, University Hospital of Santiago de Compostela (CHUS), Santiago de Compostela, Spain

Correspondence
Francisco-Javier González-Barcala, Department of Respiratory Medicine, University Hospital of Santiago de Compostela (CHUS), Santiago de Compostela, Spain.
Email: franciscojavier.gonzalez.barcala@usc.es

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Abstract

Background: Gastroesophageal reflux disease (GORD) is highly prevalent and often coexists with asthma exacerbation. Divergent findings about the association between the two diseases were reported. We conducted a systematic review and meta-analysis to determine whether there exists an association between GORD and asthma.

Methods: We searched MEDLINE, EMBASE, and other databases and then performed a manual search, to identify eligible studies. Pooled odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using fixed- and random-effect models. We evaluated the quality of included studies, explored heterogeneity between studies, undertook subgroup analyses, assessed publication bias, and performed sensitivity analyses.

Results: We identified 32 eligible studies, conducted in 14 countries and including a total of 1,612,361 patients of all ages. Overall, GORD shows a weak association with asthma exacerbation (OR = 1.27; 95% CI 1.18–1.35). This association was observed in cohort, case-control, and cross-sectional designs and in European as well as non-European populations. Subgroup analyses show that GORD is associated with frequent asthma exacerbations (≥3 exacerbations, OR = 1.59; 95% CI 1.13–2.24) and with exacerbations needing oral corticosteroid therapy (OR = 1.24; 95% CI 1.09–1.41). GORD pediatric patients are at higher odds of asthma exacerbation than adults. We did not detect any evidence of publication bias and the association between GORD and asthma exacerbation held in all undertaken sensitivity analyses.

Conclusions: Gastroesophageal reflux disease and asthma exacerbation are weakly associated.

KEYWORDS
asthma exacerbation, gastroesophageal reflux disease, meta-analysis

1 | INTRODUCTION

Asthma exacerbations—also known as attacks or flare-ups—consist of aggravated respiratory symptoms together with decreased lung function, in the worst cases leading to death.[1] Exacerbation is associated with but distinct from asthma severity, as even patients with mild asthma or few symptoms can suffer life-threatening exacerbations.[1]

The US National Institutes of Health define asthma exacerbation as "a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome," and the events considered indicative of this occurrence include asthma-related emergency department visits, hospitalization, and death.[2] The economic and societal burden of these events is considerable. Data collected as part of the 2019 National Health Interview Survey showed that 44.3% of children and 40.4% of adults with current asthma in the US experienced at least one attack in the previous year.[3] In 2018, the rate of asthma-related emergency department visits in the United States was 105 per 10,000 children and 35 per 10,000 adults, and the respective rates of hospitalization were 10 and 4 per 10,000.[4] In Europe, 0.6% of all hospital admissions and 0.4% of inpatient bed days are due to asthma exacerbations, but the rates differ up to tenfold between European countries.[5] Patients with moderate or severe persistent asthma who suffer exacerbations generate more than twice the asthma-related healthcare cost as those who do not exacerbate.[6] Indirect costs, such as losses incurred owing to missed workdays, further increase the economic burden.[5] Moreover, increasing exacerbation severity and frequency translate to lower quality of life.[7]

For all these reasons, reducing future risk of exacerbations constitutes a key objective of asthma management,[1] and one component of this goal focuses on controlling asthma-related comorbidities.[8] Gastroesophageal reflux disease (GORD) is one such comorbid condition, for which patients can receive medical or surgical treatment. Like asthma, GORD has a high worldwide prevalence, estimated at 14% in a recent systematic review, though this figure varies considerably between geographical regions.[9] Havemann and colleagues found that in asthma patients, the prevalence of GORD symptoms and that of abnormal esophageal pH were 59% and 51%, respectively.[10] Though GORD and asthma appear to be linked, the literature is inconclusive on the mechanism and even on the direction of causality.[11] Similarly, the relationship between GORD and asthma exacerbation remains unclear: While some studies that examine this relationship report a significant positive association, with up to 400% increased likelihood of frequent exacerbation in patients with GORD compared with those without,[12] others inversely report a negative association,[13] and the rest have found no association between GORD and asthma exacerbation.[14]

In view of this conflicting evidence, we propose a meta-analysis of the association between GORD antecedents and the occurrence of asthma exacerbation.

Key Message

This meta-analysis summarizes the association between gastroesophageal reflux disease (GORD) and asthma exacerbation, two highly prevalent diseases that often coexist, but no concise evidence about their association is available in the literature. Our findings show that patients with GORD have 27% increased odds of suffering asthma exacerbations compared with asthma patients without GORD and that the association is more pronounced in patients with pediatric age.

2 | STUDY DESIGN AND METHODS

2.1 | Protocol and registration

PRISMA guidelines were followed for the presentation of this meta-analysis. The study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identification number CRD42020214585.

2.2 | Outcome

The outcome of this meta-analysis was asthma exacerbation. It was defined as: deterioration in asthma requiring hospitalization, emergency department or outpatient visit, and/or corticosteroid prescription (or increased corticosteroid dose).

2.3 | Search strategy

Pertinent studies were identified by searching MEDLINE, EMBASE, Conference Proceedings Citation Index-Science, the five regional bibliographic databases of the World Health Organization, and the Open Access Thesis and Dissertations, from inception to July 2021. The search was not restricted by language, date, study design, or any other factor. For MEDLINE, we used two syntaxes: (asthma) and ((gastro-oesophageal reflux) OR (GORD) OR (GERD) OR (reflux) OR (gastrooesophageal reflux)) and ((exacerbation) or (worsening) or (attack)); and "gastroesophageal reflux" [MeSH Terms] AND "asthma" [MeSH Terms] AND (exacerbation OR worsening OR attack). This search strategy was adapted for each database. The search was completed by reviewing the reference lists of all the eligible articles and relevant reviews. The reviews we examined are listed in Appendix S1.

2.4 | Study selection

Two researchers (JMT and NM) independently screened the titles and abstracts to select potentially eligible studies for a full-text review. All

disagreements were resolved by consensus or by consulting a third researcher (BT). We included human studies that reported an odds ratio (OR), incidence rate ratio (IRR), or relative risk (RR) of the association between GORD and asthma exacerbation, together with the corresponding 95% confidence interval (CI), or that provided sufficient raw data for their calculation. Where more than one article existed for the same study or population, we included the most recent and complete version.[15,16] We contacted authors to inquire about missing details.[17]

2.5 | Data extraction and quality assessment

The same two researchers (JMT and NM) extracted the first author's name and publication year; country; study design; sample size; number of exacerbated patients; patient age and sex; effect measure with 95% CI; adjustment, restriction and matching variables; and outcome definition. In all cases, we recorded the effect measure adjusted for the highest number of variables.

JMT and NM then assessed the quality of the studies included in this meta-analysis, using the Newcastle-Ottawa Scale (NOS) for cohort studies, based on 8 criteria, and the version of the same scale adapted for cross-sectional studies.[18,19] The detailed quality assessment protocol is available in Appendix S2.

2.6 | Statistical analysis

Odds ratio and RR were considered as measures of effect in this study. ORs were deemed unbiased estimates of RR.[20] We weighted the study-specific measures of effect by the inverse of their variance to obtain a pooled global OR, using fixed- and random-effect models. Where studies reported effect measures for different subgroups of patients, we pooled the results to obtain a general OR. We checked for heterogeneity using DerSimonian and Laird's Q test and quantified it using R_i, the proportion of total variance due to between-study variance.[21] R_i values below 0.4, between 0.4 and 0.75, and above 0.75 were considered to represent low, moderate, and high heterogeneity, respectively. We adopted the fixed effects OR for low or no heterogeneity; otherwise, we used the random-effects OR. Subsequently, we stratified the analysis by study design, quality score, age category, exposure and outcome ascertainment, geographical location, definition of asthma exacerbation, and exacerbation frequency.

2.7 | Publication bias

We checked for publication bias visually using funnel plot and then formally using Egger's test and trim-and-fill analysis.[22,23]

2.8 | Sensitivity analysis

As studies included in this meta-analysis had cohort and cross-sectional designs, we undertook a sensitivity analysis assuming that the latter are the least likely to be published in case of a null association (OR = 1). We therefore re-estimated the summary OR assuming the following extreme scenario: (1) the included cross-sectional studies represent only half of the studies that have ever been conducted on GORD and asthma exacerbation, (2) the unpublished cross-sectional studies found an OR of 1, and (3) the prevalence of asthma exacerbation in those unpublished studies was the same as the average prevalence obtained from the published studies.

All analyses were performed with the software HEpiMA version 2.1.3[24] and STATA version 12 (Stata Corp).

3 | RESULTS

3.1 | General study characteristics

Figure 1 represents the study selection strategy. Our search returned 1161 publications, of which 27 articles encompassing 32 studies met the eligibility criteria of our meta-analysis (Figure 2 and Table 1). The list of included studies and observations regarding certain articles are available in Appendix S1.

Of the 32 included studies, 21 had a cohort design (four prospective and 17 retrospective), 10 were cross-sectional, and the remaining case-control studies. In total, they enrolled 1,612,361 patients, more than 250,000 of whom experienced asthma exacerbation. The studies covered five continents and 14 countries. Sixteen studies were undertaken in adults (N = 386,824) while eight involved pediatric patients (N = 344,408). Five studies included patients of all ages or did not specify the age category, and three other studies used a mixed population of adults and adolescents. Half of the studies were conducted in Europe (N = 16, of which six were UK studies) and nearly a third were carried out in the United States (N = 9).

3.2 | Association of GORD with asthma exacerbation

Overall, GORD shows a weak association with asthma exacerbation (OR = 1.27, 95% CI 1.18–1.35) (Figure 2 and Table 2). A weak positive association was observed throughout the different subgroups. A substantial amount of heterogeneity exists between all studies (R_i = 0.96) and in most subgroups (Table 2).

The association between GORD and asthma exacerbation is stronger in pediatric asthma patients (OR = 1.32, 95% CI 1.21–1.44) than in adults (OR = 1.26, 95% CI 1.07–1.48) (Table 2).

The association between GORD and asthma exacerbation was observed in all geographical location subgroups with no meaningful difference in the pooled OR estimates between them. Six of the 16 European studies were carried out in the UK, and the odds of asthma exacerbation were slightly higher for European non-British populations (N = 10; OR = 1.40, 95% CI 1.27–1.54) than those for the British population (OR = 1.21, 95% CI 1.07–1.37) (Table 2).

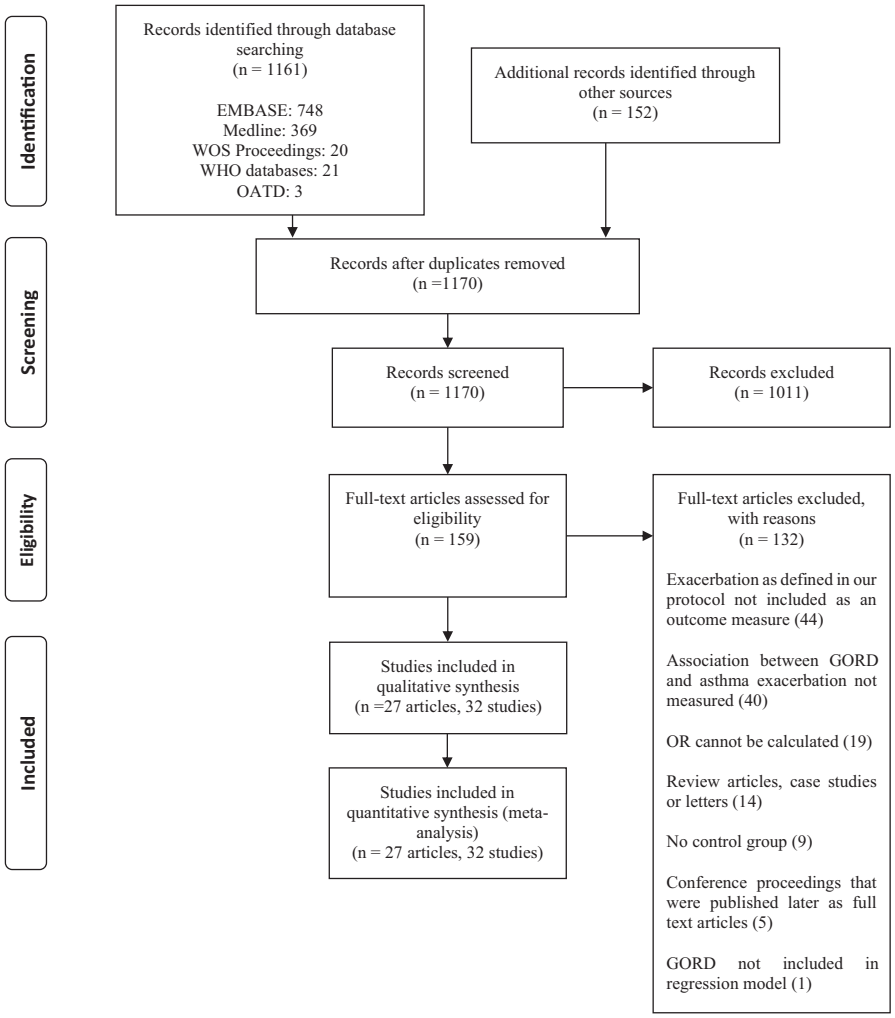

FIGURE 1 Flow diagram of study selection for the meta-analysis about GORD and asthma exacerbation

The increased likelihood of exacerbation in patients with GORD was observed in cohort studies (OR = 1.27, 95% CI 1.18–1.38) as well as in cross-sectional studies (OR = 1.21, 95% CI 1.16–1.26) with no notable differences between the pooled estimates from the two design subgroups (Table 2). Stratifying the cohort studies into prospective and retrospective cohorts showed a stronger association between GORD and asthma exacerbation in retrospective cohort studies (OR = 1.30, 95% CI 1.21–1.40) than in prospective cohort studies (OR = 1.19, 95% CI 0.83–1.70) (Table 2).

Regarding the definition of asthma exacerbation, 60% of studies used a concomitant definition that included any of the three indicators considered for our meta-analysis (hospitalization for asthma, emergency department/outpatient visit for asthma, and oral corticosteroid use for asthma), while the remaining 40% included only one or two of these indicators. The association of GORD with exacerbation was similar in studies that used a concomitant definition of exacerbation and in studies that restricted exacerbation to the need of oral corticosteroid therapy. Furthermore, GORD was also found to be non-significantly associated with hospitalization for asthma exacerbation (OR = 1.18, 95% CI 0.89–1.57) (Table 2).

Asthma exacerbation was reported as a dichotomous outcome (e.g., occurrence of at least one asthma exacerbation in the past year, yes/no) in more than half of the studies ($N = 17$) included in the meta-analysis. In addition, the measured frequency of exacerbations differed between studies, with some examining the association of GORD with ≥1 asthma exacerbations, and others recording the occurrence of ≥2, ≥3, or ≥4 exacerbations. When we stratified these 17 studies according to exacerbation frequency, we observed a stronger association between GORD and asthma exacerbation for studies reporting ≥3 or ≥4 exacerbations (OR = 1.59, 95% CI 1.13–2.24) than for studies reporting ≥1 or ≥2 exacerbations (OR = 1.17, 95% CI 1.13–1.21) (Table 2).

3.3 | Methodological assessment

The quality appraisal of included studies is provided in detail in Appendix S2. Based on the total quality score, more than half of the studies (18 out of 32) were classified as high-quality studies. The association of GORD with asthma exacerbation was observed in low (OR = 1.37, 95% CI 1.24–1.52) as well as in high-quality studies (OR = 1.21, 95% CI 1.09–1.34) (Table 2). No meaningful differences were found between pooled estimates from high-quality studies and the global OR pooled from all studies (Table 2).

In most of the included studies ($N = 25$), exposure was ascertained through medical records or medical examination. Stratifying the studies according to the source of exposure data revealed a far more

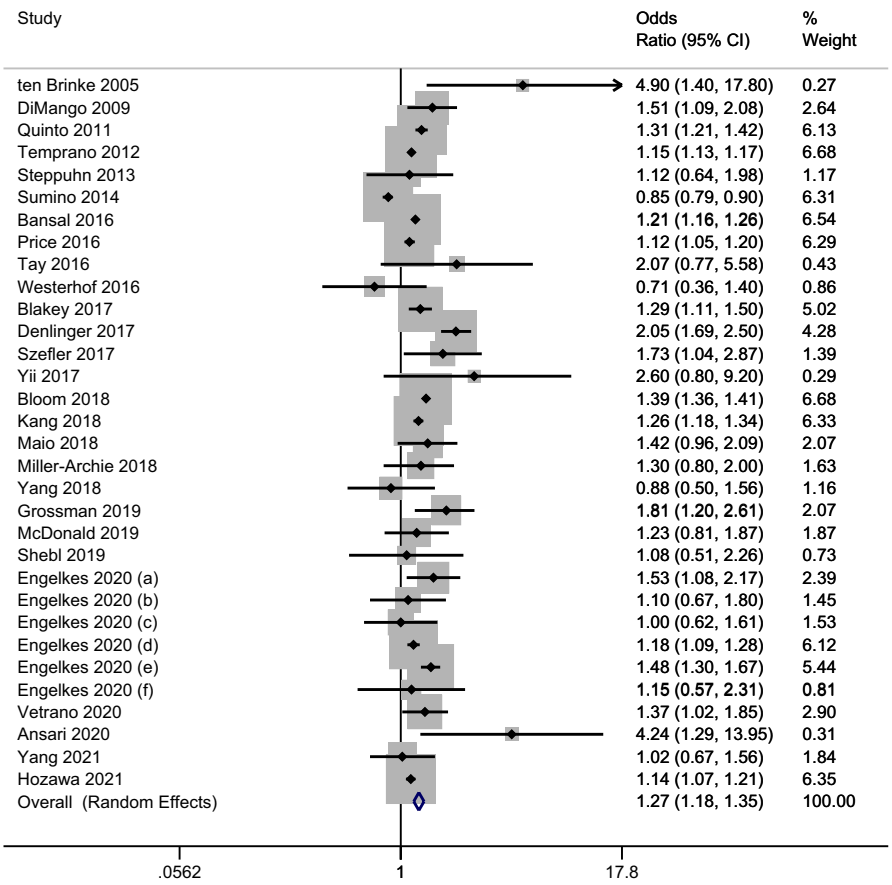

FIGURE 2 Forest plot of studies on GORD and asthma exacerbation

substantial association between GORD and asthma exacerbation in the remaining seven studies, which used self-reporting (OR = 1.75, 95% CI 1.52–2.01 vs. OR = 1.22, 95% CI 1.13–1.32) (Table 2).

Similarly, the investigators of 78% of the studies determined asthma exacerbation through medical records and examination while the remaining 22% relied on self-reporting or did not specify the method of outcome ascertainment. The association between GORD and asthma exacerbation was observed in both subgroups of studies but with stronger magnitude in studies that relied on self-reporting or did not specify how they determined exacerbations (OR = 1.75, 95% CI 1.52–2.01 vs. OR = 1.22, 95% CI 1.13–1.32) (Table 2).

Twelve of the 32 included studies fully controlled for age and sex in addition to asthma treatment, tobacco smoking, or obesity. Higher pooled ORs were obtained from studies that controlled for those variables (OR = 1.34, 95% CI 1.24–1.45) than from those with incomplete adjustment (OR = 1.22, 95% CI 1.13–1.32) (Table 2).

3.4 | Publication bias

The funnel plot of studies included in the meta-analysis was slightly skewed (Figure 3), but Egger's test did not provide evidence of publication bias (p-value = .784). Moreover, though the trim-and-fill analysis suggested the addition of two studies, the corrected OR was the same as that estimated for all studies, thus confirming further the absence of evidence of publication bias.

3.5 | Sensitivity analyses

Two studies included in this meta-analysis were carried out in very specific populations: pregnant women,[25] and individuals exposed to environmental agents from 9/11 events.[26] The re-estimated summary OR after exclusion of these two studies was the same as that obtained from all studies (OR = 1.27; 95% CI 1.18–1.36).

A third study reported an OR that was far higher than those reported in the remaining studies.[12] Excluding this outlier from the analysis did not alter our results (OR = 1.26; 95% CI 1.18–1.35).

Nine studies included in the meta-analysis measured asthma exacerbation in severe, difficult, or problematic asthma patients. The re-estimated pooled OR after their exclusion did not notably change the summary estimate from all studies (OR = 1.25; 95% CI 1.16–1.35).

The association between GORD and asthma exacerbation was maintained after the re-estimation of the summary OR under the extreme assumptions related to cross-sectional design (OR = 1.21; 95% CI 1.14, 1.29).

4 | DISCUSSION

The association between GORD and asthma occurrence has been assessed by several reports before the last decade. However, the association between GORD and asthma exacerbation has only been recently addressed. Most of the studies eligible for this

TABLE 1 Main characteristics of studies included in the meta-analysis about GORD and asthma exacerbation

Author, Year	Country	Participant characteristics		Study size	Number of patients with exacerbation	Risk ratio (95% CI)	Adjustment, restriction, or matching variables	Outcome definition
		Age (years)	Sex (%)					
Cohort studies								
Hozawa et al., 2021	Japan	Mean (SD): Non-exacerbation group: 43.6 (12.8) Exacerbation group: 44.3 (12.4)	F: 58.6% M: 41.4%	42,685	5844	1.14 (1.07–1.21)	Age, sex, comorbidities, frequency of pulmonary tests, asthma treatment	OCS use/ED visit
Vetrano et al., 2020	Italy	Mean (SD): 61.0 (16.2)	F: 63.0 M: 37.0	284	214	1.37 (1.02–1.85)	Age, asthma severity	OCS use
Engelkes et al., 2020 (a)	Netherlands	Mean (range): 10.2 (5.0–17.9)	F: 41.8 M: 58.2	31,705	871	1.53 (1.08–2.17)	Age, sex, comorbidities, history of exacerbations	Hospitalization/ED or outpatient visit/OCS use
Engelkes et al., 2020 (b)	Italy	Mean (range): 14.8 (6.6–17.9)	F: 39 M: 61	4267	855	1.10 (0.67–1.80)	Age, sex, comorbidities, history of exacerbations	Hospitalization/ED or outpatient visit/OCS use
Engelkes et al., 2020 (c)	Italy	Mean (range): 7.2 (5.0–14.0)	F: 36.1 M: 63.9	8264	727	1.00 (0.62–1.61)	Age, sex, comorbidities, history of exacerbations	Hospitalization/ED or outpatient visit/OCS use
Engelkes et al., 2020 (d)	United Kingdom	Mean (range): 10.9 (5.0–17.9)	F: 41.5 M: 58.5	124,554	12,638	1.18 (1.09–1.28)	Age, sex, comorbidities, history of exacerbations	Hospitalization/ED or outpatient visit/OCS use
Engelkes et al., 2020 (e)	Spain	Mean (range): 8.9 (5.0–17.9)	F: 40.2 M: 59.8	30,749	8968	1.48 (1.30–1.67)	Age, sex, comorbidities, history of exacerbations	Hospitalization/ED or outpatient visit/OCS use
Engelkes et al., 2020 (f)	Denmark	Mean (range): 9.3 (5.0–17.9)	F: 37.4 M: 62.6	12,521	756	1.15 (0.57–2.31)	Age, sex, comorbidities, history of exacerbations	Hospitalization/ED or outpatient visit/OCS use
Grossman et al., 2019	United States	Mean (SD): 36 (12)	F: 63.9 M: 36.1	1840	Not reported	1.81 (1.20–2.61)	Age, sex, FEV1, race, history of exacerbations	OCS use
Shebl et al., 2019	Egypt	*With exacerbation*: Mean (SD): 29.95 (4.39) *Without exacerbation*: Mean (SD): 30.71 (3.86)	F: 100 M: 0.0	308	77	1.08 (0.51–2.26)	Sex, adherence to asthma treatment	Hospitalization/ED or outpatient visit/OCS use
McDonald et al., 2019	Australia, New Zealand, Singapore	*Severe asthma*: Mean (SD): 54.8 (14.9) *Non-severe asthma*: Mean (SD): 56.0 (16.9)	F: 58.3 M: 41.7	354	209	1.23 (0.81–1.87)	Age, sex, obesity	Hospitalization/ED or outpatient visit/OCS use

(Continues)

TABLE 1 (Continued)

Author, Year	Country	Participant characteristics		Study size	Number of patients with exacerbation	Risk ratio (95% CI)	Adjustment, restriction, or matching variables	Outcome definition
		Age (years)	Sex (%)					
Bloom et al., 2018	United Kingdom	All ages included	F: 54.5 M: 45.5	424,326	173,150	1.39 (1.36–1.41)	Age, sex, socioeconomic status, smoking status, BMI, comorbidities	Hospitalization/ED or outpatient visit/OCS use
Miller-Archie et al., 2018	United States	All patients ≥18	F: 41.9 M: 58.1	5152	138	1.3 (0.8–2)	Age, sex, race/ethnicity, education, smoking status, comorbidities, environmental exposure.	Hospitalization
Kang et al., 2018	South Korea	All patients ≥20	F: 65.9 M: 34.2	22,130	9115	1.26 (1.18–1.34)	Age, sex, comorbidities, history of exacerbations, adherence to asthma treatment	Hospitalization/ED or outpatient visit/OCS use
Yii et al., 2017	Singapore	Mean (SD): 56 (18)	F: 53.7 M: 46.3	177	18	2.6 (0.8–9.2)	Asthma severity	Hospitalization/ED or outpatient visit/OCS use
Blakey et al., 2017	United Kingdom	Mean (SD): 45 (18)	F: 57 M: 43	118,981	12,736[a]	1.29 (1.11–1.50)	Age, sex, BMI, smoking status, comorbidities, NSAIDs, % predicted PEF; blood eosinophils, respiratory medications, acute OCS courses, primary care consultation, ED admissions.	Hospitalization/ED or outpatient visit/OCS use
Denlinger et al., 2017	United States	All patients ≥6 years	F: 59.2 M: 40.8	1908	173	2.05 (1.69–2.5)	Age, sex, race, smoking status, clinical center, income, medication adherence, BMI, comorbidities, bronchodilator reversibility, blood eosinophils, IgE levels.	Hospitalization/ED or outpatient visit/OCS use
Price et al., 2016	United Kingdom	Mean (SD): 48.8 (17.4)	F: 65.9 M: 34.1	130,547	8429	1.12 (1.05–1.20)	Not reported	Hospitalization/ED or outpatient visit/OCS use
Sumino et al., 2014	United States	Mean (SD): 53.2 (14.4)	F: 18.1 M: 81.9	25,975	9824[b]	0.85 (0.79–0.90)	Sex, race, follow-up years, health care utilization, exacerbations, respiratory medications, comedication with other drugs, deaths	Hospitalization/ED or outpatient visit/OCS use

(Continues)

TABLE 1 (Continued)

Author, Year	Country	Participant characteristics		Study size	Number of patients with exacerbation	Risk ratio (95% CI)	Adjustment, restriction, or matching variables	Outcome definition
		Age (years)	Sex (%)					
Temprano et al., 2012	United States	Not reported	Not reported	145,950	Not reported	1.15 (1.13–1.17)	Not reported	Hospitalization/ED or outpatient visit/OCS use
Quinto et al., 2011	United States	5–17	F: 43.2 M: 56.8	32,321	3546 ED visits 801 hospitalizations	1.31 (1.21–1.42)	Age, sex, race/ethnicity, parental education level, asthma controller use, comorbidities	Hospitalization/ED or outpatient visit/OCS use
DiMango, 2009	United States	Mean (SD): 42.1 (13.5)	F: 68.4% M: 31.6%	304	Not reported	1.51 (1.09–2.08)	Age, smoking status, asthma control, acute asthma episodes, asthma treatment, FEV1, antireflux/peptic ulcer surgery, heartburn	OCS use/ED or outpatient visits
Case-control studies								
Ansari et al., 2020	Pakistan	Mean (SD): 35 (15)	F: 54.9% M: 45.1%	Cases: 52 Controls: 50	52	4.23 (1.29–13.95)	Unadjusted	ED visit
Cross-sectional studies								
Yang et al., 2021	United Kingdom	Mean (SD): 49.4 (14.4)	F: 63.1 M: 36.9	1592	1137	1.02 (0.67–1.56)	Age, sex, ethnicity, BMI, smoking status, comorbidities, asthma severity, ACQ-6, FEV1, FeNO, blood eosinophils, maintenance oral corticosteroid use, blood eosinophils, hospitalization, assessment year	OCS use
Szefler et al., 2020	USA	*Recent exacerbators*: Mean (SD): 60.5 (12.9) *Non recent exacerbators*: Mean (SD): 57.0 (17.2)	F: 65.6 M: 34.4	337	79	1.73 (1.04–2.87)	Not reported	OCS use

(Continues)

TABLE 1 (Continued)

Author, Year	Country	Participant characteristics		Study size	Number of patients with exacerbation	Risk ratio (95% CI)	Adjustment, restriction, or matching variables	Outcome definition
		Age (years)	Sex (%)					
Yang et al., 2018	United Kingdom	Mean (SD): 48.5 (17.4)	F: 58.3 M: 41.7	2639	185	0.88 (0.5–1.56)	Age, sex, age of onset, duration of asthma, smoking status, comorbidities, BTS step, ICS dose, asthma review, exacerbations, SABA overuse	OCS use
Maio et al., 2018	Italy	Mean (SD): 58.3 (13.4)	F: 60.6 M: 39.4	493	275	1.42 (0.96–2.09)	Age, sex, age at asthma diagnosis, allergic asthma, positive family history of asthma, asthma severity, comorbidities, aspirin hypersensitivity	Hospitalization/ED or outpatient visit/OCS use
Tay et al., 2016	Australia	Mean (SD): 52 (14)	F: 63.4 M: 36.6	90	39	2.07 (0.77–5.58)	Age, sex, BMI, smoking status, duration of asthma, asthma severity, FEV1, blood eosinophils, comorbidities	OCS use
Bansal et al., 2016	USA	Mean (SD): 32 (16)	F: 54.3 M: 45.7	440,381	Not reported	1.21 (1.16–1.26)	Age, sex, ED attendance	Hospitalization
Westerhof et al., 2016	Netherlands	Mean (SD): 51.6 (11.5)	F: 67.9 M: 32.1	153	66	0.71 (0.36–1.40)	Age, sex, age of asthma onset, smoking, asthma severity, asthma duration, comorbidities, chronic OCS use, blood neutrophils, ICS dose, FEV1, blood eosinophils, sputum eosinophils	OCS use
Steppuhn et al., 2013	Germany	Mean (SD): 52.1 (18.2)	F: 61.1 M: 38.9	1136	102	1.12 (0.64–1.98)	Age, sex, educational attainment, smoking status, BMI status, asthma duration, comorbidities	Hospitalization/ED or outpatient visit
Ten Brinke et al., 2005	Netherlands	Mean (SD): 45.4 (14.3)	F: 69.9 M: 30.1	63	39	4.9 (1.4–17.8)	Age, asthma duration	OCS use

Abbreviations: ACQ, asthma control questionnaire; BMI, body mass index; BTS, British Thoracic Society; ED, emergency department; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; NSAID, non-steroidal anti-inflammatory drug; OCS, oral corticosteroid; PEF, peak expiratory flow; PPI, proton pump inhibitor; SABA, short-acting beta agonist; SD, standard deviation. The reference list of included studies is available in Appendix S1.

[a]Number of patients who suffered ≥2 exacerbations.

[b]Number of exacerbations, rather than number of patients who exacerbated.

TABLE 2 Pooled odds ratio (OR) and 95% confidence interval (CI) of GORD and asthma exacerbation

	Number of studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	R_i	Q test *p*-value
All studies	32	1.26 (1.25–1.27)	1.27 (1.18–1.35)	0.96	<.0001
Study design					
Cohort	22	1.26 (1.25–1.28)	1.27 (1.18–1.38)	0.97	<.0001
Cross-sectional	9	1.21 (1.16–1.26)	1.23 (1.02–1.47)	0.86	.136
Case-control	1	4.24 (1.29–13.25)	—	—	—
Cohort study type					
Prospective	5	0.87 (0.83–0.92)	1.19 (0.83–1.70)	0.96	<.0001
Retrospective	17	1.28 (1.27–1.29)	1.30 (1.21–1.40)	0.97	<.0001
Age category					
Adults	16	1.35 (1.33–1.36)	1.26 (1.07–1.48)	0.99	<.0001
Pediatrics	8	1.31 (1.25–1.37)	1.32 (1.21–1.44)	0.58	.043
Geographical location					
Europe	16	1.37 (1.35–1.39)	1.26 (1.15–1.38)	0.95	<.0001
North America	9	1.15 (1.13–1.16)	1.30 (1.15–1.46)	0.98	<.0001
Other (Western Pacific Region and Eastern Mediterranean)	7	1.20 (1.15–1.25)	1.22 (1.10–1.36)	0.63	.047
Definition of asthma exacerbation					
Any indicator (hospitalization, ED, outpatient or OCS)	18	1.27 (1.25–1.28)	1.26 (1.15–1.38)	0.98	<.0001
Hospitalization only	4	1.22 (1.18–1.26)	1.18 (0.89–1.57)	0.98	<.0001
OCS use only (or increased dose)	11	1.13 (1.11–1.15)	1.24 (1.09–1.41)	0.95	.011
Exacerbation frequency					
≥1 or ≥2 exacerbations	11	1.17 (1.13–1.21)	1.18 (1.12–1.24)	0.32	.178
≥3 or ≥4 exacerbations	6	1.79 (1.56–2.06)	1.59 (1.13–2.24)	0.78	.004
Quality score					
Low quality	14	1.17 (1.15–1.18)	1.37 (1.24–1.52)	0.92	<.0001
High quality	18	1.32 (1.31–1.34)	1.21 (1.09–1.34)	0.98	<.0001
GORD ascertainment					
Medical records or examination	25	1.26 (1.25–1.27)	1.22 (1.13–1.31)	0.97	<.0001
Self-reporting/not specified	7	1.75 (1.52–2.01)	1.63 (1.30–2.04)	0.53	.077
Exacerbation ascertainment					
Medical records or examination	25	1.26 (1.25–1.27)	1.22 (1.13–1.31)	0.97	<.0001
Self-reporting/not specified	7	1.75 (1.52–2.02)	1.65 (1.31–2.08)	0.51	.095
Comparability					
Incomplete adjustment	20	1.14 (1.13–1.16)	1.22 (1.13–1.32)	0.93	<.0001
Complete adjustment	12	1.38 (1.36–1.40)	1.34 (1.24–1.45)	0.92	<.0001

Abbreviations: ED, emergency department; GORD, gastroesophageal reflux disease; OCS, oral corticosteroid.

meta-analysis were published in the last five years. Findings from those studies are inconsistent, raising therefore the need for a meta-analysis to quantify the association between GORD and asthma exacerbation.

This meta-analysis shows that asthma patients with GORD have slightly increased odds of suffering asthma exacerbations than patients without GORD. The association was observed in the analyses stratified by study design, population age category, and geographic location. Our findings are unlikely to be affected by publication bias.

The association between GORD and asthma was shown to be bidirectional, each of the two diseases exacerbating the other.[27,28] On the one hand, GORD patients are at higher risk of developing asthma and the literature examining the association between the two diseases distinguishes between two possible causal mechanisms: reflux and reflex.[11] According to the reflux theory, microaspiration of gastric contents could lead to pulmonary inflammation and increased air resistance, whereas the reflex theory refers to indirect vagal nerve stimulation by distal esophageal reflux, which leads to

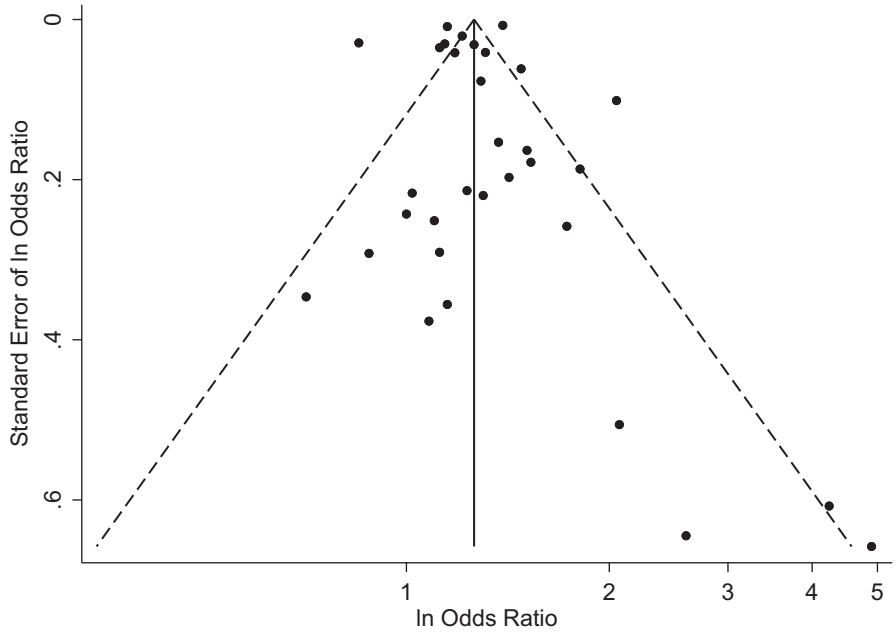

FIGURE 3 Funnel plot of studies on GORD and asthma exacerbation

bronchoconstriction.[11] On the other hand, asthma patients are at higher risk of developing GORD.[27] Some authors have proposed that asthma induces systematic and airway inflammation and therefore causes GORD. Asthmatic cough or asthma medication also exacerbates GORD by increasing the pressure gradient across the lower esophageal sphincter.[29]

This meta-analysis revealed the presence of an association between GORD and asthma exacerbation in cohort studies, suggesting that GORD provokes asthma exacerbations. However, in the stratified analysis by type of cohort study (prospective vs. retrospective), the association between GORD and asthma exacerbation lost its statistical significance in the retrospective study subgroup, probably due to the limited number of studies in this subgroup. Furthermore, we reported a stronger association between GORD and higher frequency of exacerbations which may be related to the hypothetical interrelationship of the two conditions.

Pediatric and elderly patients are among the most vulnerable populations for asthma exacerbation.[30] Indeed, our results show that among people with GORD and asthma, children and adolescents are at higher odds of asthma exacerbation than adults. However, none of the studies included in the meta-analysis examined the association of GORD with asthma exacerbation in older people.

This meta-analysis included studies originating from 14 countries with very different public healthcare systems, which translates into varying access to inpatient and outpatient care for asthma patients.[5] Although asthma is more prevalent in high-income regions, fatal asthma exacerbations are more common in less well-off countries,[31] where barriers to healthcare access tend to be higher. Previous reports have suggested that better access to outpatient care reduces the use of inpatient care[32] and that emergency department visits offer effective treatment, reducing the need for hospitalization.[33] We found higher odds of outpatient OCS use than hospital admissions due to asthma exacerbation. We therefore hypothesize that the resolution of asthma exacerbation episodes in outpatient care results in fewer inpatient admissions.

Establishing a relationship between GORD and asthma exacerbations is complicated by the fact that GORD is often "silent," and as a result, questionnaires and clinical history taking are unreliable diagnostic methods.[34-36] The most reliable method used in the studies included in the meta-analysis was 24-hour pH probe monitoring, and the four studies that employed this technique in at least some patients reported an association between GORD and asthma exacerbation which almost double the magnitude of that estimated for all studies (50% vs. 27%).[12,15,36,37] We therefore hypothesize that GORD was underreported in some studies included in the meta-analysis and that our findings may have been affected by non-differential exposure misclassification. This type of bias increases similarity between the compared groups, leading to underestimation of the effect measure (odds ratio). In our case, therefore, the association between GORD and asthma exacerbation would likely have been stronger had all included studies used more reliable methods for determining GORD status.

Almost one-quarter of the studies included in this meta-analysis relied on self-reporting to ascertain the occurrence of asthma exacerbation. However, this was unlikely to affect our results as restricting the analysis to the studies that determined asthma exacerbation events using medical records or examination yielded a summary estimate similar to that generated for all studies.

Full control of variables known to be associated with both GORD and asthma exacerbation (age, sex, obesity, asthma treatment, smoking), and that could introduce confounding bias in the effect measure, was applied in 40% of the studies eligible for this meta-analysis. The lack of full adjustment in the remaining studies is unlikely to have affected our findings, because excluding them from the calculation produced a pooled OR comparable to the original global OR.

Over half of the studies entered in the meta-analysis were of high quality and the estimate from those studies was similar to that yielded from all studies. This result shows that our findings are robust to methodological imperfections. Moreover, the association between GORD and asthma exacerbation was maintained in all the undertaken sensitivity analyses.

Our meta-analysis has some limitations. Firstly, a substantial amount of heterogeneity existed across studies. Experts have indicated, however, that high heterogeneity is expected in any meta-analysis and represents "expectation" rather than "exception,"[38] especially when the included studies vary in terms of methods and populations.[38] Indeed, some consider that any amount of heterogeneity is acceptable, provided the inclusion criteria are well established and the analysis is properly carried out.[38,39] In our meta-analysis, we relied on random-effect models to account for heterogeneity.[39]

A second limitation concerns the cross-sectional design, known to be prone to inverse causation bias, of one third of the studies of this meta-analysis. However, it is remarkable that the association of GORD with asthma exacerbation could also be observed in studies with a cohort design exclusively and under extreme assumptions in the sensitivity analysis.

Previous reports found that 51% of asthmatic patients suffer from GORD.[10] On the basis of this prevalence of exposure and our results, assuming that the associations we observed were of causal nature, we estimate that one in every eight asthma exacerbations may be attributable to GORD.[40]

5 | CONCLUSIONS

The results of our meta-analysis show that the occurrence of asthma exacerbation is associated with the co-presence of GORD disease in people with asthma.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Narmeen Mallah: Conceptualization (equal); Data curation (equal); Formal analysis (lead); Investigation (lead); Methodology (lead); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (lead); Writing-review & editing (lead). **Julia May Turner:** Data curation (equal); Formal analysis (equal); Investigation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Francisco-Javier González-Barcala:** Investigation (equal); Resources (equal); Writing-review & editing (equal). **Bahi Takkouche:** Investigation (lead); Methodology (lead); Resources (lead); Supervision (lead); Validation (lead); Writing-review & editing (lead).

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13655.

DATA AVAILABILITY STATEMENT

The data generated and analyzed in the meta-analysis are included in the article or made available as supplementary information. The data are available by accessing the cited studies in Appendix S1.

ORCID

Francisco-Javier González-Barcala https://orcid.org/0000-0001-5847-4784

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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