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Research article

Causal relationship between gastroesophageal reflux disease and chronic obstructive respiratory disease: A bidirectional Mendelian randomization study

Shan Lin [a,*,1], Dingfeng Lai [b,1], Wanmei He [b], Qingyuan Zhan [c,**]

[a] Department of Respiratory and Critical Care Medicine, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, China
[b] Department of Medical Intensive Care Unit, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510080, China
[c] Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, National Center for Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China

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ABSTRACT

Background: Numerous observational studies have posited that gastroesophageal reflux disease (GERD) might amplify the risk of chronic airway conditions such as chronic obstructive pulmonary disease (COPD) and asthma. Yet, a definitive causal link remains to be established. To this end, we utilized a two-sample Mendelian randomization approach (MR) to investigate the potential causal dynamics between GERD and these chronic obstructive respiratory diseases.

Methods: Using a two-sample bidirectional MR, we explored the causal influence of GERD on the risks of developing COPD and asthma, drawing on aggregated genome-wide association study data from European cohorts.

Results: Our analysis elucidated a notable causal relationship, with individuals genetically inclined towards GERD exhibiting a significantly elevated propensity to develop COPD (odds ratio [OR] = 1.520, 95 % confidence interval [CI] 1.376−1.680, $P = 2.173 \times 10^{-16}$) and asthma (OR = 1.420, 95 % CI 1.340−1.504, $P = 1.269 \times 10^{-32}$). The absence of heterogeneity and pleiotropy was confirmed through the Cochran Q test, funnel plots, MR-Egger intercept test, and MR-PRESSO. Directional causality was further substantiated by Steiger testing. Conversely, reverse MR analyses did not identify a significant causal pathway between COPD or asthma and GERD onset.

Conclusion: This investigation substantiates a robust positive correlation between GERD and increased risks for COPD and asthma, laying a foundational basis for incorporating GERD management into preventive and therapeutic strategies for these chronic obstructive respiratory diseases.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a multifaceted pulmonary disorder characterized by persistent and chronic

* Corresponding author.
** Corresponding author.drzhanqy@163.com
E-mail address: dr.shanlin@foxmail.com (S. Lin).
[1] Shan Lin and Dingfeng Lai contributed equally to this work.

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inflammation of the airways, which is susceptible to recurrent exacerbations due to ongoing airway obstruction [1]. Such exacerbations inevitably lead to an irreversible decline in lung function, culminating in a diminished quality of life and imposing a considerable social and economic burden on affected individuals [2]. Similarly, asthma is another chronic respiratory condition, distinguished by airway inflammation and constriction [3]. Importantly, COPD and asthma are not standalone conditions; they often co-occur with a range of comorbidities that can accelerate their progression and negatively influence the prognosis for patients. The coexistence of additional health issues such as cardiovascular diseases, diabetes, and depression among individuals with COPD and asthma has been unequivocally demonstrated to significantly impact the management strategies, quality of life, and overall survival rates [4–6].

Gastroesophageal reflux disease (GERD) stands out as a prevalent comorbidity in patients with COPD and asthma, characterized by the regurgitation of gastric contents into the esophagus. This condition presents with hallmark symptoms such as heartburn, acid reflux, and coughing, all of which can significantly aggravate respiratory symptoms [7–9]. Notably, individuals with COPD who also suffer from GERD are predisposed to more frequent and intense exacerbations, culminating in adverse health outcomes compared to those in patients with COPD who do not have GERD [10,11]. In addition, studies in other chronic respiratory conditions, such as idiopathic bronchiectasis (IB), suggest that dysphagia and silent aspiration may contribute to exacerbations and poor health outcomes [12]. Although dysphagia and silent aspiration are often overlooked, research has shown that dysphagia is prevalent in IB patients, with 44.6 % showing signs of swallowing difficulties as measured by the Eating Assessment Tool (EAT-10) questionnaire. In the context of asthma, the substantial occurrence rate of GERD underscores a bidirectional relationship, where GERD not only has the potential to trigger and intensify asthma symptoms but may also be exacerbated by the asthma itself [13–15]. The prevalence rates of GERD in those with COPD and asthma range dramatically from 19 % to 90 %, and based on demographic and diagnostic criteria, the data highlight the profound interconnectedness of these conditions [16]. As seen in IB patients, the link between GERD, aspiration, and airway inflammation may play a significant role in the exacerbation of both asthma and COPD. Given the prevalence of GERD and its potential impact on respiratory function, it is essential to consider undiagnosed swallowing dysfunction and silent aspiration in these patients, as they may further complicate management and worsen clinical outcomes. Despite the abundance of research corroborating the association between GERD and these respiratory diseases, delineating the exact causal mechanisms remains an area of ongoing investigation.

Mendelian randomization (MR) is a sophisticated analytical method that leverages genetic variations to explore the causal relationships between an exposure and a subsequent health outcome [17]. Anchored in the principle that genetic variants are impartially allocated at conception, MR is shielded from the typical confounding factors that may taint observational studies, thus serving as a robust instrument for the exposure under study [18]. The technique is lauded for its myriad of benefits, including its capacity to navigate around issues of confounding and reverse causation and furnish a quasi-experimental framework conducive to evaluating intervention efficacies [19]. The application of MR spans a diverse array of medical research domains, attesting to its versatility and

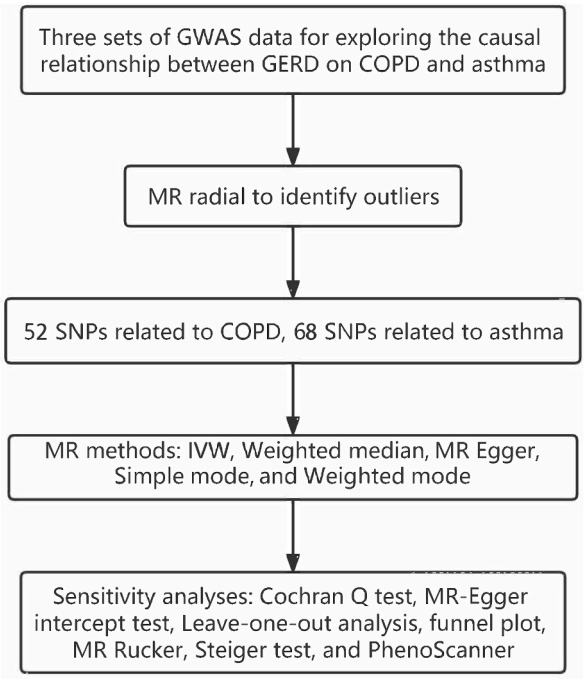

Fig. 1. Workflow of MR study revealing causality from GERD on COPD and asthma.
Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; MR, mendelian randomization; IVW, inverse variance weighting; SNP, single nucleotide polymorphism.

effectiveness in deciphering the causal dynamics between risk factors and diseases. For example, in the context of venous thromboembolism research, MR has elucidated a definitive causal link between body measurements, such as waist and hip circumference, and the risk of developing venous thromboembolism or pulmonary embolism [20]. Concurrently, in neurology, MR analyses have illuminated potential causal associations, suggesting that elevated levels of low-density lipoprotein cholesterol could amplify the risk of Alzheimer's disease, both sporadic and familial [21].

In this research, given the established consequential effects of GERD on COPD and asthma, a meticulous exploration of potential causal associations was conducted employing a two-sample MR framework, informed by genome-wide association study (GWAS) statistics. The outcomes of this investigation not only broaden our comprehension of the underlying mechanisms and progression of COPD and asthma but also offer instrumental insights for the development of targeted screening protocols and preventive measures in a clinical setting, thereby enhancing patient care and health outcomes.

2. Methods

2.1. Study design

In this study, we used a two-sample bidirectional MR study to explore the causal relationship between GERD and chronic obstructive respiratory diseases (COPD and asthma) [Fig. 1]. The robust MR study design was compatible with three principal hypotheses: a) genetic instrumental variables were strongly associated with exposure factors; b) genetic instrumental variables were not associated with confounding factors; c) genetic instrumental variables were not associated with outcomes and only influenced them through exposure factors [22].

2.2. Exposure GWAS data for GERD

The GWAS data for GERD were obtained from the GWAS catalog (ebi.ac.uk) with a total of 602,604 European descents, including 129,080 cases and 473,524 controls [23]. Genetic instruments were selected using the following criteria: single nucleotide polymorphisms (SNPs) strongly associated with exposure were first screened according to P-values less than 5×10^{-8}, and then those with linkage disequilibrium (LD) were further screened according to [LD]$r^2 < 0.001$ and index variants <10000. We also calculated F values to exclude SNPs less than 10. Next, SNPs with palindromic sequences were removed by harmonization, and outlier SNPs with pleiotropy were excluded by MR radial.

2.3. Outcome GWAS data for COPD and asthma

The most recent GWAS data for COPD were meticulously sourced from the FinnGen database (version 10, released on December 18, 2023), accessible at https://www.finngen.fi/en/access_results. This comprehensive database incorporates data from 20,066 COPD case groups juxtaposed with 338,303 controls, providing a robust dataset for our analysis [24]. Concurrently, the GWAS data pertinent to asthma were diligently acquired from the IEU Open Database, which includes 56,167 asthma cases and 352,255 controls [25].

2.4. MR analyses

Five approaches were employed to explore the causality of GERD on COPD and asthma, namely, inverse variance-weighted (IVW), weighted median, MR Egger simple mode, and weighted mode methods. The IVW method functioned in the primary analysis, which was performed by combining the Wald ratios of each SNP on the outcome and finally obtaining the causality on the whole [26]. The other four methods were used as a complement to MR analysis.

2.5. Sensitivity analysis

The Cochran Q test was performed to detect the presence of heterogeneity, and Cochran Q-derived p-values greater than 0.05 were accepted as the absence of heterogeneity [27]. Funnel plots, which are used in meta-analyses, were applied in the assessment of heterogeneity. Pleiotropy was assessed based on MR Egger regression [28]. Leave-one-out (LOO) analysis was performed to detect the effect of SNP removal on IVW results. The goodness-of-fit heterogeneity statistic was used to determine whether the IVW or MR Egger regression model was more suitable for the interpretation of the results, and MR Rucker-derived p-values greater than 0.05 were regarded as more appropriate for designation of the IVW model as the outcome model [29]. Additionally, we verified whether the observed causality was biased by reverse causality using the Steiger test [30]. A Steiger P value greater than 0.05 indicated that the direction of causal inference might be biased; that is, reverse causality might be present. Lastly, we consulted PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/), a platform with comprehensive information on genotypic and phenotypic associations, to identify whether these SNPs were associated with potential risk factors, including body mass index, obesity, smoking, and alcohol consumption, and eliminate SNPs that were associated with these potential confounders [31,32].

2.6. Statistical analysis

All statistical analyses were rigorously conducted utilizing the TwoSampleMR package (version 0.5.8) and the RadialMR package

(version 1.0) within the R programming environment (version 4.2.2). To ascertain the robustness of our findings, statistical power was computed using the mRnd tool available at https://shiny.cnsgenomics.com/mRnd/, with outcomes generally deemed robust at a statistical power threshold of 80 % or higher. Mendelian randomization estimates are presented as odds ratios (ORs) with their respective 95 % confidence intervals (CIs). Statistical significance was set at P values less than the 0.05.

3. Results

3.1. Genetic link of GERD to COPD and asthma

In this comprehensive analysis, a total of 52 SNPs were meticulously selected for delineating the genetic underpinnings of COPD, while a distinct set of 68 SNPs were employed to elucidate the genetic basis of asthma. The robustness of these genetic instruments was underscored by F-statistics ranging impressively from 207.50 to 669.24, suggesting a potent instrumental relevance to the exposure factor [33]. Through the precision of radial MR, outliers were judiciously identified and subsequently removed from further analyses to ensure the integrity of our findings. Subsequent MR analysis robustly established the genetic predilection of GERD towards an increased risk for both COPD ([OR] = 1.520, 95 % [CI] 1.376−1.680, P = 2.173×10^{-16}) and asthma (OR = 1.420, 95 % CI 1.340−1.504, P = 1.269×10^{-32}), as detailed in Table 1 and illustrated in Fig. 2. Utilizing the IVW approach, this primary investigation was further substantiated by corroborative results from additional MR methodologies. For a more granular visualization of these associations, scatter plots depicting the MR outcomes are provided in Supplementary Fig. 1, offering a comprehensive graphical synopsis of the causal inferences drawn. The integrity and reliability of the IVW analysis findings are further bolstered by the fact that the computed powers reached the pinnacle of confidence at 100 %.

3.2. Sensitivity analysis of the causal effect of GERD on COPD and asthma

To ascertain the reliability of the MR estimates, a comprehensive series of heterogeneity assessments were conducted. The Cochrane Q test that was applied to the causal analyses concerning COPD and asthma yielded P values of 0.512 and 0.095, respectively, suggesting an absence of significant heterogeneity within the IVW results [Table 2]. Funnel plot analysis further corroborated these results, in which the SNPs demonstrated symmetrical distribution on both sides of the IVW estimate, reinforcing the consistency and minimizing concerns of heterogeneity [Supplementary Fig. 2A and B].

The IVW method aggregates the effect of Wald ratios for each SNP to elucidate the outcome impact comprehensively. An LOO analysis was performed to scrutinize the influence of individual SNPs on the aggregated results. This analysis confirmed that no single SNP disproportionately affected the robustness of the outcomes related to COPD and asthma, attesting to the stability of our findings [Supplementary Fig. 2C and D]. Further robustness was assessed through MR-Egger regression, and the MR-PRESSO global test substantiated the absence of pleiotropic effects, eliminating another potential source of bias [Tables 2 and 3].

The MR Steiger test was conducted to consolidate the inference of a causal relationship between GERD and the increased risks of COPD and asthma and preclude any assumptions of reverse causality. The results of significant p-values of COPD and asthma (1.95×10^{-92} and 6.44×10^{-95}, respectively) not only confirm the directional correctness of our causal inference but also underscore the substantive link between GERD and the heightened risks for these respiratory conditions [Table 4].

3.3. Genetic link of COPD and asthma to GERD (reverse analysis)

In an endeavor to investigate the potential causal impacts of COPD and asthma on GERD, we conducted a reverse MR analysis. The findings from this reverse-direction analysis did not reveal any significant causal relationships whereby COPD or asthma would contribute to the onset of GERD [Table 5]. These conclusions are further substantiated by a series of comprehensive sensitivity analyses, which consistently demonstrated the absence of significant heterogeneity or pleiotropic effects across the studies, as documented in Tables 6 and 7. This rigorous approach reinforces the specificity of the causal pathway between GERD and respiratory

Table 1
Genetic link of GERD to COPD and asthma.

Exposure	Outcome	Methods	OR	95 % CI	P -value
GERD	COPD	MR Egger	0.899	0.500–1.616	0.722
		Weighted median	1.406	1.209–1.634	9.368×10^{-06}
		IVW	1.520	1.376–1.680	2.173×10^{-16}
		Simple mode	1.133	0.758–1.693	0.546
		Weighted mode	1.117	0.796–1.567	0.525
GERD	Asthma	MR Egger	1.838	1.327–2.546	<0.001
		Weighted median	1.474	1.365–1.593	7.477×10^{-23}
		IVW	1.420	1.340–1.504	1.269×10^{-32}
		Simple mode	1.605	1.243–2.073	<0.001
		Weighted mode	1.614	1.269–2.053	<0.001

Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; IVW, inverse variance weighting; MR, mendelian randomization; OR, odds ratio; CI, confidence interval.

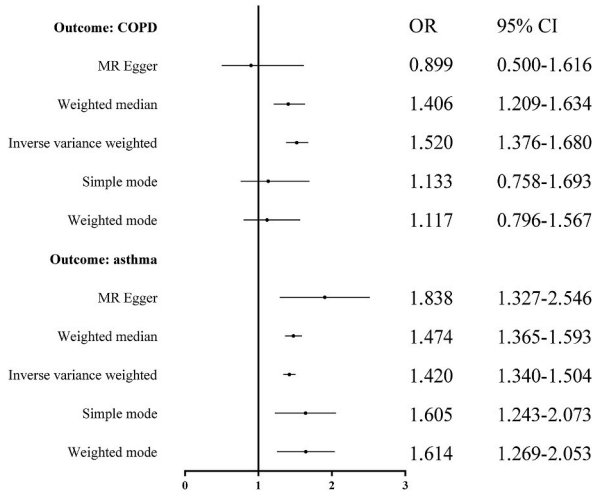

Fig. 2. Forest plot for the causal effect of GERD on the risk of COPD and asthma derived from MR estimates.
Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; MR, mendelian randomization; IVW, inverse variance weighting; OR, odds ratio; CI, confidence interval.

Table 2
Sensitivity analysis of the causal effect of GERD on COPD and asthma.

Exposure	Outcome	Methods	Heterogenity		MR-Egger intercept		
			Q	Q_*P* -value	Egger_intercept	SE	*P* -value
GERD	COPD	IVW	50.028	0.512	0.017	0.010	0.081
		MR Egger	46.848	0.601			
GERD	Asthma	IVW	82.559	0.095	−0.009	0.005	0.120
		MR Egger	79.561	0.122			

Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; IVW, inverse variance weighting.

Table 3
Global test of MRPRESSO analysis.

Exposure	Outcome	RSSobs	*P* -value
GERD	COPD	52.233	0.565
GERD	Asthma	85.10563	0.191

Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease.

Table 4
Steiger direction test from GERD to COPD and asthma.

Exposure	GERD	GERD
Outcome	COPD	Asthma
Direction	True	True
Steiger P	1.95×10^{-92}	6.44×10^{-95}

Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease.

conditions, rather than the converse.

4. Discussion

In our most recent MR analysis, we uncovered a significant causal relationship between GERD and the emergence of COPD and asthma. Specifically, the genetic predisposition to GERD was notably linked with a heightened risk of developing COPD and asthma, manifesting as a 52 % and 42 % increase in risk, respectively. Moreover, when conducting a reverse MR analysis, we found no evidence to suggest a reciprocal causal impact of COPD and asthma on the incidence of GERD. This delineates a clear directional influence of

Table 5
Genetic link of COPD and asthma to GERD (reverse analysis).

Exposure	Outcome	Methods	OR	95 % CI	P -value
COPD	GERD	MR Egger	0.955	0.873–1.046	0.427
		Weighted median	1.000	0.954–1.048	0.999
		IVW	1.016	0.967–1.068	0.534
		Simple mode	1.008	0.912–1.114	0.890
		Weighted mode	1.000	0.953–1.049	0.994
Asthma	GERD	MR Egger	1.046	0.949–1.153	0.376
		Weighted median	1.008	0.952–1.068	0.778
		Inverse variance weighted	0.998	0.960–1.037	0.917
		Simple mode	0.916	0.826–1.015	0.107
		Weighted mode	1.018	0.953–1.088	0.593

Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; IVW, inverse variance weighting; MR, mendelian randomization; OR, odds ratio; CI, confidence interval.

Table 6
Sensitivity analysis of the causal effect of COPD and asthma on GERD (reverse analysis).

Exposure	Outcom	Methods	Heterogenity		MR-Egger intercept		
			Q	Q_*P* -value	Egger_intercept	SE	*P* -value
COPD	GERD	IVW	51.625	0.641	−0.002	0.001	0.127
		MR Egger	49.228	0.694			
Asthma	GERD	IVW	20.331	0.500	−0.003	0.003	0.314
		MR Egger	19.265	0.505			

Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; IVW, inverse variance weighting.

Table 7
Global test of MRPRESSO analysis (reverse analysis).

Exposure	Outcome	RSSobs	*P* -value
COPD	GERD	16.0504	0.448
Asthma	GERD	22.00872	0.536

Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease.

GERD on these respiratory conditions, emphasizing the importance of managing GERD to potentially mitigate the risk of developing COPD and asthma.

Gastroesophageal reflux disease is a common disease in Europe, affecting approximately 10–20 % of the population [34]. In recent years, the prevalence of GERD has increased in Europe, which may be attributed to changes in lifestyle and rising obesity rates [35]. Esophageal motility disorders and GERD can lead to extraesophageal symptoms related to the upper respiratory tract, including chronic cough, hoarseness, and throat clearing [35]. Furthermore, a growing body of literature has explored the link between esophageal disorders and lower respiratory complications, including specific lung diseases. Observational studies have revealed a correlation between GERD and a range of respiratory conditions, such as asthma, COPD, and interstitial lung disease [16,36,37].

The relationship between GERD, COPD, and asthma is intricate and multifaceted. Although epidemiological and observational studies point to the magnitude of this relationship, the underlying pathophysiological mechanisms continue to be a topic of discussion. Numerous theories exist to understand this crucial causal correlation. Anatomically, the esophagus is interconnected with the trachea and lungs through the pharynx, leading to the activation of inflammatory cascades in susceptible cells of the airway epithelium and lung tissue due to GERD-induced reflux contents [38]. Cough, altered respiratory motion, and changes in pulmonary compliance can accentuate the transdiaphragmatic pressure gradient during respiration, which can trigger esophagogastric junction dysfunction and subsequently lead to microaspiration [39]. A decrease in pulmonary compliance could contribute to deformation of the mediastinal structures and esophageal traction, bringing about a diminished lower esophageal sphincter [40]. Mechanistically, microaspiration of gastric contents represents a significant pathway through which GERD may exacerbate or initiate the onset of COPD and asthma. Aspirated material directly irritates and inflames the airways, disrupting the epithelial barrier and increasing vulnerability to external irritants and pathogens [41]. Concurrently, GERD can activate vagus nerve-mediated reflexes, leading to bronchoconstriction that aggravates COPD and increases asthma risks [42]. Furthermore, GERD triggers an esophageal inflammatory response with potential systemic effects, possibly intensifying airway inflammation [43]. Continuous exposure of lung tissue to refluxed content may also alter the immune response, heightening infection risks and exacerbating respiratory conditions [44]. Additionally, GERD might enhance bronchial reactivity, sensitizing the airways to allergens and irritants and thereby increasing susceptibility to asthma [45]. Collectively, the inflammatory response resulting in structural damage and airway resistance due to acid reflux are likely to explain the causal relationship between GERD and COPD as well as asthma. Consequently, it is notable that GERD is responsible for an elevated risk of COPD and asthma, and it is exceedingly crucial to elucidate the mechanisms between them. In future studies, these findings

should be validated, and the underlying mechanisms should be explored, which will facilitate the formulation of relevant clinical recommendations.

Both association and causality analyses can often be time consuming and may not always reflect clinical realities in traditional observational studies. However, using SNPs as instrumental variables to link "exposure factors" and "outcomes," MR offers a more reliable assessment of causality and reduces the risk of confounding. As COPD and asthma frequently lead to recurrent acute exacerbations and poor quality of life, this study employed a two-sample MR analysis and discovered a novel causal relationship between GERD and both COPD and asthma. Our study highlights the importance of early initiation of treatment for GERD to achieve optimal clinical outcomes and prevent complications such as COPD and asthma. Additionally, we recommend early lung function screening for individuals with GERD to facilitate earlier detection and treatment of COPD and asthma. Our systematic MR analysis, which examined the association between GERD and COPD as well as asthma in a large European population, provides valuable insights for preventive care policies and potential interventions for GERD-related COPD and asthma.

The efficacy and implications of the use of proton pump inhibitors (PPIs) in patients with COPD, particularly those with concurrent GERD, have been extensively studied, yielding a spectrum of results. On one hand, certain studies advocate the benefits of PPIs, illustrating their association with decreased risks of acute exacerbations and mortality in patients with COPD presenting with GERD symptoms. In particular, high doses of PPIs have been linked to favorable outcomes, suggesting a potentially valuable role for PPIs in this patient subset [46]. On the other hand, the landscape of research reveals complexity; while PPIs may reduce moderate exacerbation risks, they appear to exert variable effects on severe exacerbations and pneumonia risks, which may escalate in certain patient groups during PPI therapy [7]. The broader context includes a systematic review affirming the correlation between GERD and elevated risk of COPD exacerbations. This review underscores the utility of addressing GERD to alleviate the frequency of exacerbations in those who suffer from COPD, proposing a nuanced advantage in GERD management [47]. Contrastingly, insights from the COPDGene cohort suggest potential drawbacks of PPIs, including an accelerated decline in lung function, despite some positive indicators such as enhanced quality-of-life metrics, hinting at a confounding-by-indication phenomenon [48]. Echoing the need for clarity, a Cochrane review accentuates the current evidence deficit in conclusively endorsing PPIs for COPD management, advocating for further detailed and rigorous investigations to elucidate the true impact of PPIs on COPD-related exacerbations, adverse events, and life quality [49]. In essence, while there is substantiation for PPIs potentially ameliorating exacerbation rates and mortality in patients with COPD who have GERD, the overarching narrative is intricate, with studies reflecting a range of outcomes. It is imperative for healthcare professionals to judiciously evaluate the pros and cons of PPI therapy, tailoring recommendations to the unique profiles and needs of each patient with COPD and GERD. The debate extends into the asthma domain, where the efficacy of PPIs in improving lung function among in patients with asthma having GERD remains inconclusive. Recent meta-analyses and cohort studies suggest that lung function improvement with PPI therapy in such patients is limited, which calls into question the universal recommendation of PPIs for all patients with asthma having GERD [50,51]. Notably, long-term use of PPIs has been associated with an increased risk of asthma, although this association appears to be non-significant in certain GERD subpopulations [52].

The study in question adeptly leverages bidirectional MR to mitigate concerns of reverse causality and residual confounding, underscoring its methodological rigor. The application of multiple MR methods to validate hypotheses enhances the credibility of the findings, with the convergence of results across various MR models reinforcing the dependability of estimates. Moreover, the absence of pleiotropy, as indicated by supplementary statistical analyses, bolsters the study's reliability. However, the study is not without its limitations. The predominantly European descent of the participant pool, while beneficial for reducing population stratification, raises questions about the universality of the findings. The need for replication in diverse populations is crucial to ascertain the broader applicability of the results. Additionally, the intricate biological interplay between GERD and COPD and asthma remains partially understood, which could complicate the interpretation of instrumental variables and potentially challenge the foundational hypothesis of this MR study. The absence of a formal mediation analysis to delineate the pathways linking GERD with COPD and asthma signifies a gap in the exploration of underlying mechanisms. Moreover, while the study delineates a genetic predisposition to COPD and asthma influenced by GERD, it stops short of offering insights into the prognostic implications of GERD treatment for these respiratory conditions. The genetic association does not directly inform treatment efficacy or clinical strategies. Therefore, despite the genetic linkages identified, randomized controlled trials are warranted to confirm these associations and elucidate the potential benefits of GERD management in the context of COPD and asthma prognosis.

5. Conclusion

In this study, an expansive dataset of genetic information was harnessed to reinforce emerging insights into the causal nexus between GERD and the elevated risks of COPD and asthma. The findings underscore the imperative to identify and address GERD as a pivotal risk factor in the landscape of these prevalent respiratory disorders. Given the substantial burden that COPD and asthma place on individual health outcomes and healthcare systems worldwide, integrating GERD management into the broader therapeutic strategy could be instrumental in improving patient prognoses and mitigating their extensive socio-economic impacts.

Ethics approval and consent to participate

Only publicly available GWAS data were used in this study, and the Ethics approval and consent to participate could be available in the original GWAS study.

CRediT authorship contribution statement

Shan Lin: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Dingfeng Lai:** Writing – original draft, Data curation. **Wanmei He:** Software, Data curation. **Qingyuan Zhan:** Writing – review & editing, Formal analysis.

Consent for publication

Not applicable.

Availability of data and material

All data used in the current study are publicly available GWAS summary data.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e42100.

Abbreviation

GERD	gastroesophageal reflux disease
COPD	chronic obstructive pulmonary disease
IVW	inverse variance weighting
MR	mendelian randomization
OR	odds ratio
CI	confidence interval
LOO	leave-one-out
SNP	single nucleotide polymorphism
OR	odds ratio
CI	confidence interval

References

[1] D.R. Tamondong-Lachica, N. Skolnik, J.R. Hurst, et al., GOLD 2023 update: implications for clinical practice, Int. J. Chronic Obstr. Pulm. Dis. 18 (2023) 745–754.
[2] J.L. López-Campos, W. Tan, J.B. Soriano, Global burden of COPD, Respirology 21 (1) (2016) 14–23.
[3] J. Stern, J. Pier, A.A. Litonjua, Asthma epidemiology and risk factors, Semin. Immunopathol. 42 (1) (2020) 5–15.
[4] L.E. Vanfleteren, M.A. Spruit, M. Groenen, et al., Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 187 (7) (2013) 728–735.
[5] M.J. Divo, B.R. Celli, B. Poblador-Plou, et al., Chronic obstructive pulmonary disease (COPD) as a disease of early aging: evidence from the EpiChron cohort, PLoS One 13 (2) (2018) e0193143.
[6] K.M. Scott, M. Von Korff, J. Alonso, et al., Mental-physical co-morbidity and its relationship with disability: results from the world mental health surveys, Psychol. Med. 39 (1) (2009) 33–43.
[7] J. Kang, R. Lee, S.W. Lee, Effects of gastroesophageal reflux disease treatment with proton pump inhibitors on the risk of acute exacerbation and pneumonia in patients with COPD, Respir. Res. 24 (1) (2023) 75.
[8] M. Zou, W. Zhang, Y. Xu, Y. Zhu, Relationship between COPD and GERD: a bibliometrics analysis, Int. J. Chronic Obstr. Pulm. Dis. 17 (2022) 3045–3059.
[9] P.J. Kahrilas, Clinical practice. Gastroesophageal reflux disease, N. Engl. J. Med. 359 (16) (2008) 1700–1707.
[10] T.S. Ingebrigtsen, J.L. Marott, J. Vestbo, B.G. Nordestgaard, J. Hallas, P. Lange, Gastro-esophageal reflux disease and exacerbations in chronic obstructive pulmonary disease, Respirology 20 (1) (2015) 101–107.

[11] T.S. Ingebrigtsen, J.L. Marott, J. Vestbo, B.G. Nordestgaard, J. Hallas, P. Lange, Gastro-esophageal reflux disease and exacerbations in chronic obstructive pulmonary disease, Respirology 20 (1) (2015) 101–107.
[12] T. Perluk, E. Abu Bandora, O. Freund, et al., Asymptomatic dysphagia and aspiration in patients with idiopathic bronchiectasis, Lung 202 (2) (2024) 189–195.
[13] B.D. Havemann, C.A. Henderson, H.B. El-Serag, The association between gastro-oesophageal reflux disease and asthma: a systematic review, Gut 56 (12) (2007) 1654–1664.
[14] B. Liang, Q. Yi, Y. Feng, Association of gastroesophageal reflux disease with asthma control, Dis. Esophagus 26 (8) (2013) 794–798.
[15] A. Ruigómez, L.A. Rodríguez, M.A. Wallander, S. Johansson, M. Thomas, D. Price, Gastroesophageal reflux disease and asthma: a longitudinal study in UK general practice, Chest 128 (1) (2005) 85–93.
[16] C. Broers, J. Tack, A. Pauwels, Review article: gastro-oesophageal reflux disease in asthma and chronic obstructive pulmonary disease, Aliment. Pharmacol. Ther. 47 (2) (2018) 176–191.
[17] G.D. Smith, S. Ebrahim, 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int. J. Epidemiol. 32 (1) (2003) 1–22.
[18] S. Burgess, A. Butterworth, S.G. Thompson, Mendelian randomization analysis with multiple genetic variants using summarized data, Genet. Epidemiol. 37 (7) (2013) 658–665.
[19] C.A. Emdin, A.V. Khera, S. Kathiresan, Mendelian randomization, JAMA 318 (19) (2017) 1925–1926.
[20] J. Wang, J. Tan, L. Hua, Q. Sheng, X. Huang, P. Liu, Genetic predisposition of both waist circumference and hip circumference increased the risk of venous thromboembolism, Thromb. Haemostasis 123 (3) (2023) 347–361.
[21] J.S. Tan, M.J. Hu, Y.M. Yang, Y.J. Yang, Genetic predisposition to low-density lipoprotein cholesterol may increase risks of both individual and familial Alzheimer's disease, Front. Med. 8 (2022) 798334.
[22] A.G. Boef, O.M. Dekkers, S. le Cessie, Mendelian randomization studies: a review of the approaches used and the quality of reporting, Int. J. Epidemiol. 44 (2) (2015) 496–511.
[23] J.S. Ong, J. An, X. Han, et al., Multitrait genetic association analysis identifies 50 new risk loci for gastro-oesophageal reflux, seven new loci for Barrett's oesophagus and provides insights into clinical heterogeneity in reflux diagnosis, Gut 71 (6) (2022) 1053–1061.
[24] M.I. Kurki, J. Karjalainen, P. Palta, et al., FinnGen provides genetic insights from a well-phenotyped isolated population, Nature 613 (7944) (2023) 508–518.
[25] K. Valette, Z. Li, V. Bon-Baret, et al., Prioritization of candidate causal genes for asthma in susceptibility loci derived from UK Biobank, Commun. Biol. 4 (1) (2021) 700.
[26] B.L. Pierce, S. Burgess, Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators, Am. J. Epidemiol. 178 (7) (2013) 1177–1184.
[27] J. Bowden, M.F. Del Greco, C. Minelli, et al., Improving the accuracy of two-sample summary-data Mendelian randomization: moving beyond the NOME assumption, Int. J. Epidemiol. 48 (3) (2019) 728–742.
[28] J. Bowden, G. Davey Smith, S. Burgess, Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression, Int. J. Epidemiol. 44 (2) (2015) 512–525.
[29] J. Bowden, M.F. Del Greco, C. Minelli, G. Davey Smith, N. Sheehan, J. Thompson, A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization, Stat. Med. 36 (11) (2017) 1783–1802.
[30] G. Hemani, K. Tilling, G. Davey Smith, Orienting the causal relationship between imprecisely measured traits using GWAS summary data, PLoS Genet. 13 (2017) e1007081.
[31] J.R. Staley, J. Blackshaw, M.A. Kamat, et al., PhenoScanner: a database of human genotype-phenotype associations, Bioinformatics 32 (20) (2016) 3207–3209.
[32] M.A. Kamat, J.A. Blackshaw, R. Young, et al., PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations, Bioinformatics 35 (22) (2019) 4851–4853.
[33] B.L. Pierce, H. Ahsan, T.J. Vanderweele, Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants, Int. J. Epidemiol. 40 (3) (2011) 740–752.
[34] H.B. El-Serag, S. Sweet, C.C. Winchester, J. Dent, Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review, Gut 63 (6) (2014) 871–880.
[35] D.A. Katzka, J.E. Pandolfino, P.J. Kahrilas, Phenotypes of gastroesophageal reflux disease: where Rome, lyon, and Montreal meet, Clin. Gastroenterol. Hepatol. 18 (4) (2020) 767–776.
[36] J.C. Zhou, S. Gavini, W.W. Chan, W.K. Lo, Relationship between esophageal disease and pulmonary fibrosis, Dig. Dis. Sci. 68 (4) (2023) 1096–1105.
[37] B. Ruaro, R. Pozzan, P. Confalonieri, et al., Gastroesophageal reflux disease in idiopathic pulmonary fibrosis: viewer or actor? To treat or not to treat? Pharmaceuticals 15 (8) (2022) 1033.
[38] S. Gupta, R. Lodha, S.K. Kabra, Asthma, GERD and obesity: triangle of inflammation, Indian J. Pediatr. 85 (10) (2018) 887–892.
[39] L.A. Houghton, A.S. Lee, H. Badri, K.R. DeVault, J.A. Smith, Respiratory disease and the oesophagus: reflux, reflexes and microaspiration, Nat. Rev. Gastroenterol. Hepatol. 13 (8) (2016) 445–460.
[40] K.A. Johannson, I. Strâmbu, C. Ravaglia, et al., Antacid therapy in idiopathic pulmonary fibrosis: more questions than answers? Lancet Respir. Med. 5 (7) (2017) 591–598.
[41] P. Özdemir, M. Erdinç, R. Vardar, et al., The role of microaspiration in the pathogenesis of gastroesophageal reflux-related chronic cough, J Neurogastroenterol Motil 23 (1) (2017) 41–48.
[42] J. Wu, Y. Ma, Y. Chen, GERD-related chronic cough: possible mechanism, diagnosis and treatment, Front. Physiol. 13 (2022) 1005404.
[43] A.L. Lee, R.S. Goldstein, Gastroesophageal reflux disease in COPD: links and risks, Int. J. Chronic Obstr. Pulm. Dis. 10 (2015) 1935–1949.
[44] R. Fass, G.E. Boeckxstaens, H. El-Serag, R. Rosen, D. Sifrim, M.F. Vaezi, Gastro-oesophageal reflux disease, Nat. Rev. Dis. Prim. 7 (1) (2021) 55.
[45] T.L. Griffiths, M. Nassar, A.O. Soubani, Pulmonary manifestations of gastroesophageal reflux disease, Expet Rev. Respir. Med. 14 (8) (2020) 767–775.
[46] V.Y. Su, H.F. Liao, D.W. Perng, et al., Proton pump inhibitors use is associated with a lower risk of acute exacerbation and mortality in patients with coexistent COPD and GERD, Int. J. Chronic Obstr. Pulm. Dis. 13 (2018) 2907–2915.
[47] C. Huang, Y. Liu, G. Shi, A systematic review with meta-analysis of gastroesophageal reflux disease and exacerbations of chronic obstructive pulmonary disease, BMC Pulm. Med. 20 (1) (2020) 2.
[48] A.K. Baldomero, C.H. Wendt, A. Petersen, et al., Impact of gastroesophageal reflux on longitudinal lung function and quantitative computed tomography in the COPDGene cohort, Respir. Res. 21 (1) (2020) 203.
[49] S. Kikuchi, H. Imai, Y. Tani, T. Tajiri, N. Watanabe, Proton pump inhibitors for chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. 8 (8) (2020) CD013113.
[50] Z. Zheng, Y. Luo, J. Li, J. Gao, Randomised trials of proton pump inhibitors for gastro-oesophageal reflux disease in patients with asthma: an updated systematic review and meta-analysis, BMJ Open 11 (8) (2021) e043860.
[51] Y.T. Wang, M.C. Tsai, Y.H. Wang, J.C. Wei, Association between proton pump inhibitors and asthma: a population-based cohort study, Front. Pharmacol. 11 (2020) 607.