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Associations between gastroesophageal reflux disease and otolaryngological diseases

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Abstract

In this study, we conducted a 2-sample Mendelian randomization (MR) analysis to explore the relationship between gastroesophageal reflux disease (GERD) and 16 common otolaryngological diseases. Single-nucleotide polymorphisms that are strongly associated with GERD were used as instrumental variables. The primary estimation of the causal effect utilized the inverse variance weighting method, supplemented by MR Egger, weighted median, simple mode, and weighted mode as alternative methods for estimating the causal effect. Then, sensitivity analyses, including heterogeneity, pleiotropy, and leave-one-out analyses, were performed to verify the robustness of the results. The analysis of MR showed that genetically predicted GERD was associated with an increased risk of acute upper respiratory infection (odds ratios [OR] = 1.1418, 95% confidence intervals [CI] = 1.0664–1.2225, $P = 1.00 \times 10^{-4}$), chronic pharyngitis (OR = 1.483, 95% CI = 1.1495–1.9132, $P = 2.40 \times 10^{-3}$), vocal cord dysfunction (OR = 2.2963, 95% CI = 1.4174–3.7201, $P = 7.00 \times 10^{-4}$), sleep apnea (OR = 1.0022, 95% CI = 1.0009–1.0035, $P = 8.00 \times 10^{-4}$), acute sinusitis (OR = 1.3247, 95% CI = 1.1774–1.4905, $P = 2.94 \times 10^{-6}$), chronic sinusitis (OR = 1.3649, 95% CI = 1.1854–1.5715, $P = 1.52 \times 10^{-6}$), chronic suppurative otitis media (OR = 2.085, 95% CI = 1.3292–3.2704, $P = 1.40 \times 10^{-3}$). Further sensitivity analyses showed no evidence of pleiotropy. The results of this study indicate that GERD may contribute to the development of some otolaryngological diseases. Further research and mechanistic investigations are warranted to elucidate the underlying connections and potential therapeutic implications.

Abbreviations: CI = confidence intervals, GERD = gastroesophageal reflux disease, GWAS = genome-wide associated studies, IVs = instrumental variables, IVW = inverse-variance weighting, MR = Mendelian randomization, OR = odds ratios, SNPs = single nucleotide polymorphisms.

Keywords: causal relationship, gastroesophageal reflux disease, Mendelian randomization, otolaryngological diseases, risk factors

1. Introduction

Gastroesophageal reflux disease (GERD) is a prevalent digestive system disorder, defined as a condition where symptoms or complications result from the reflux of stomach contents.[1] It is estimated that the prevalence of GERD in adults is between 20% to 30% in Western countries.[2]

Prevention and treatment of diseases in otolaryngology practice constitute a complex and comprehensive task. Common otolaryngological diseases, such as sinusitis,[3] otitis media,[4] and hearing loss,[5] not only impact patients' health and quality of life but also contribute to an increased economic burden. Thorough understanding of the pathophysiology of these diseases is still needed. Recognizing potentially modifiable risk factors and causal relationships associated with these diseases is crucial for a deeper comprehension of their etiology. The association between gastroesophageal reflux disease (GERD) and various diseases has been extensively investigated, including the potential to induce various symptoms in the ear, nose, and throat systems.[6] Many observational studies have also indicated correlations between GERD and otolaryngological diseases such as chronic sinusitis,[7] laryngeal cancer,[8] otitis media,[9] and sleep apnea.[10] However, these pieces of evidence are primarily derived from observational studies, and due to inherent limitations in such research, the results concerning the relationship between GERD and related otolaryngology diseases may be influenced by potential confounding factors and reverse causation.

YX and HZ contributed to this article equally.

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The datasets generated during and/or analyzed during the current study are publicly available.

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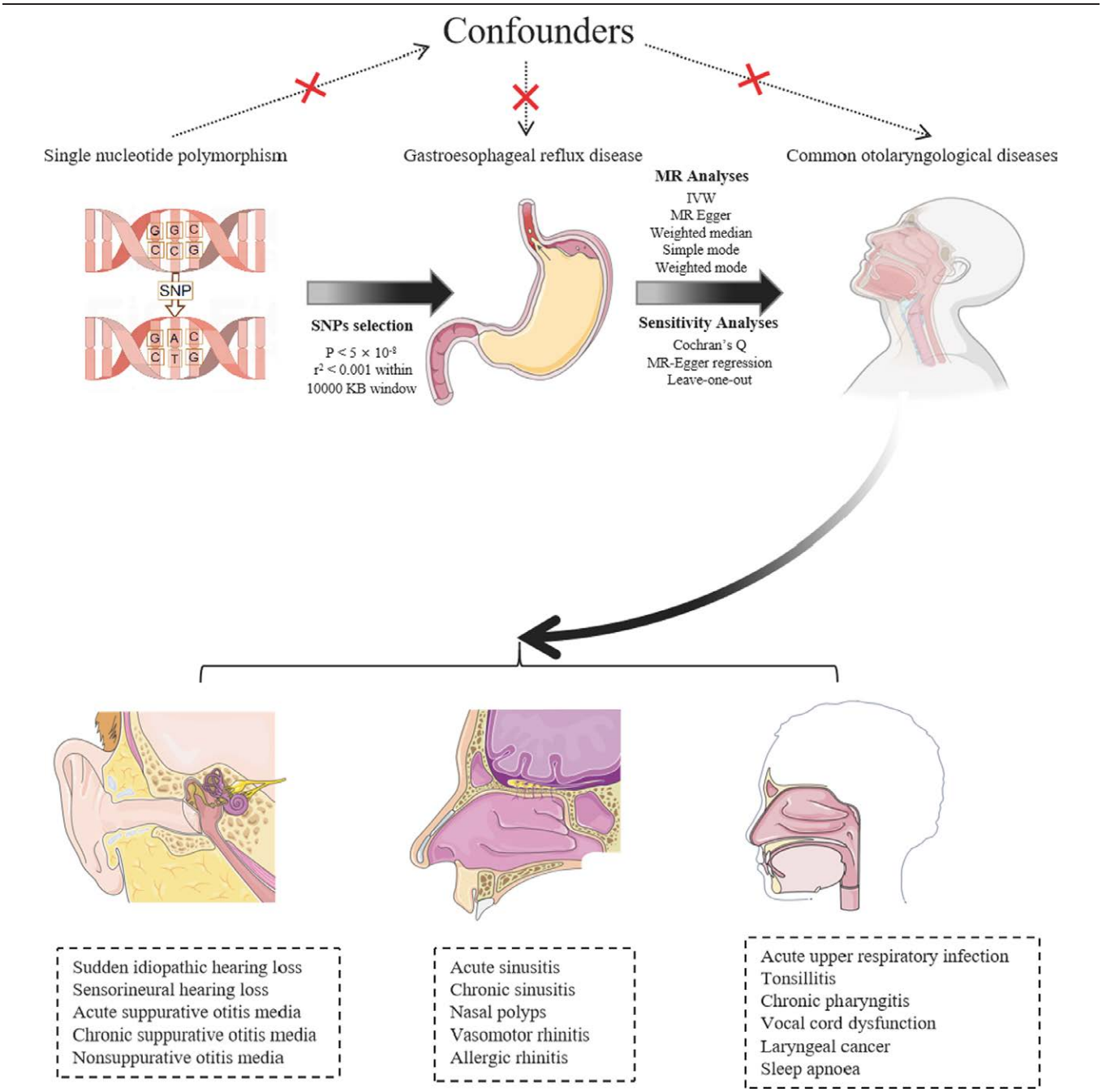

Figure 1. The schematic representations of our study.

Mendelian randomization (MR) is a statistical method based on genetic variation that uses the random allocation of genes to assess the causal relationship between exposure factors and disease outcomes. In epidemiological studies, it is commonly used to evaluate the causal association between certain risk factors (such as lipid levels and blood pressure) and health outcomes (such as cardiovascular disease and diabetes).[11] As the alleles associated with exposure factors are randomly allocated during conception, they are less susceptible to the influence of confounding factors and adhere to a normal causal sequence.[12,13] Therefore, based on the high prevalence in otolaryngological clinical practice, the significant impact on patients' quality of life,[14,15] the gaps in existing literature,[16] and to overcome the limitations of traditional observational studies and elucidate the role of GERD in the development of common otolaryngological diseases, we used a 2-sample MR method and estimated the relationship between single nucleotide polymorphisms (SNPs) associated with GERD and the risk of 16 common otolaryngological diseases.

2. Materials and methods

Publicly available genome-wide associated studies (GWAS) summary statistics from https://gwas.mrcieu.ac.uk/ were utilized, and they did not contain identifiable information. Consequently, a new ethical review was unnecessary, and obtaining informed consent was not required. MR relies on 3 hypotheses.[14] An overview of the study design is presented in Figure 1.

2.1. Data resources

The summary statistics of genetic variants associated with GERD, as previously published, were acquired from GWASs. This research

applied the GWAS approach to scrutinize and assess the correlation between 2,320,781 genetic variants and GERD in a cohort consisting of 129,080 patients and 473,524 control individuals.[15]

For outcomes, we identified 16 common otolaryngological diseases, namely acute upper respiratory tract infection, tonsillitis, chronic pharyngitis, vocal cord dysfunction, laryngeal cancer, sleep apnea, acute sinusitis, chronic sinusitis, nasal polyps, vasomotor rhinitis, allergic rhinitis, sudden idiopathic hearing loss, sensorineural hearing loss, acute suppurative otitis media, chronic suppurative otitis media, nonsuppurative otitis media. The tonsillitis GWAS summary statistics included 458,829 European individuals.[16] The summary-level data for laryngeal cancer and sleep apnea were obtained respectively from the UK Biobank and the MRC-IEU Consortium. The summary-level data for acute upper respiratory tract infection, chronic pharyngitis, vocal cord dysfunction, acute rhinosinusitis, chronic rhinosinusitis, nasal polyps, vasomotor rhinitis, allergic rhinitis, sudden idiopathic hearing loss, sensorineural hearing loss, acute suppurative otitis media, chronic suppurative otitis media, nonsuppurative otitis media were obtained from the FinnGen consortium. Table S1, Supplemental Digital Content, http://links.lww.com/MD/O489 shows an overview of the demographics included in this study.

2.2. Statistical analyses

We used the PhenoScanner tool (http://www.phenoscanner.medschl.cam.ac.uk/) to exclude any selected SNPs associated with other phenotypes that might influence CVD outcomes, ensuring a stronger instrument effect. In the process of identifying robust genetic instruments for GERD, SNPs meeting both statistical significance ($P < 5.00 \times 10^{-8}$) and independence criteria ($r^2 < 0.001$ within a 10,000 KB window) with GERD phenotypes were specifically obtained. For MR analysis, the primary method utilized was the inverse-variance weighting (IVW) analysis. The supplementary MR methods, namely MR Egger, weighted median, simple mode, and weighted mode were also incorporated into our analysis. We further explored the likelihood of weak instrument bias by calculating F statistics to estimate the strength of correlation between genetic instruments and GERD phenotypes.[17]

To enhance the dependability of our results, we executed various sensitivity analyses, encompassing evaluations of heterogeneity, horizontal pleiotropy, and the leave-one-out test. Heterogeneity detection involved the application of both IVW and MR Egger regression methods. Heterogeneities were quantified using the Cochran *Q* statistic, with significance established at *P* values below .05. The intercept term in MR Egger regression assessed the horizontal pleiotropy of instrumental variables (IVs).[18] Absence of horizontal pleiotropy was indicated when the intercept term approached 0 (<0.1) and the *P* value exceeded .05. Moreover, leave-one-out analysis was conducted to scrutinize whether any individual SNP influenced the observed correlation.

With an adjusted *P* value after Bonferroni correction (*P* .05/16 = .0031, adjusting for 1 exposure and 16 outcomes), associations were considered statistically significant. The assessment of association utilized odds ratios (OR) along with their corresponding 95% confidence intervals (CI). All MR analyses were carried out in RStudio (version 4.1.0) with R packages TwoSampleMR (version 0.5.6).

3. Results

A set of IVs strongly associated with GERD were extracted from GWASs. The *F* statistics for each SNP exceeded 10, suggesting a low probability of weak instrument bias.[17] Table S2, Supplemental Digital Content, http://links.lww.com/MD/O489 displays the summarized statistics for all correlated SNPs.

According to the MR analysis results, genetic susceptibility to GERD was found to be significantly associated with 7 common otolaryngological diseases. Specifically, GERD increases the risk of acute upper respiratory infection (OR = 1.1418, 95% CI = 1.0664–1.2225, $P = 1.00 \times 10^{-4}$), chronic pharyngitis (OR = 1.483, 95% CI = 1.1495–1.9132, $P = 2.40 \times 10^{-3}$), vocal cord dysfunction (OR = 2.2963, 95% CI = 1.4174–3.7201, $P = 7.00 \times 10^{-4}$), sleep apnea (OR = 1.0022, 95% CI = 1.0009–1.0035, $P = 8.00 \times 10^{-4}$), acute sinusitis (OR = 1.3247, 95% CI = 1.1774–1.4905, $P = 2.94 \times 10^{-6}$), chronic sinusitis (OR = 1.3649, 95% CI = 1.1854–1.5715, $P = 1.52 \times 10^{-6}$), chronic suppurative otitis media (OR = 2.085, 95% CI = 1.3292–3.2704, $P = 1.40 \times 10^{-3}$; Fig. 2). Although these findings do not support a causal relationship between GERD and other otolaryngological diseases, an inverse trend was observed between GERD and the risk of these diseases (Fig. 2). The MR estimates of GERD's causal effect on outcomes based on each method are provided in Table S3, Supplemental Digital Content, http://links.lww.com/MD/O489.

For sensitivity analyses, most *P* values from both Cochran's *Q* tests for IVW and MR Egger exceeded .05, indicating an absence of heterogeneity in the IVs. Simultaneously, upon conducting MR Egger intercept testing, we observed that all MR Egger regression intercepts were below 0.1, and all corresponding *P* values were above .05, confirming the absence of horizontal pleiotropy between SNPS and outcomes. The funnel plot incorporated into the analysis revealed a symmetrical distribution of individual effect estimates around the point estimates, further supporting the absence of potential pleiotropy. The leave-one-out sensitivity analyses indicated that no single SNP significantly influenced the causal effect of AR on any cancer outcome. The results of the heterogeneity and pleiotropy analyses are provided in Table S4, Supplemental Digital Content, http://links.lww.com/MD/O489. Leave-one-out, forest plots, scatter plots and funnel plots are presented in Supplementary Material 1, Supplemental Digital Content, http://links.lww.com/MD/O488.

4. Discussion

In this study, a significant association was identified between GERD and 7 common otolaryngological diseases out of the 16 investigated. These include acute upper respiratory infections, chronic laryngitis, vocal cord dysfunction, sleep apnea syndrome, acute sinusitis, chronic sinusitis, and chronic suppurative otitis media. No significant correlation was observed with the other 9 otolaryngological diseases.

GERD is characterized by abnormal structure and function of the lower esophagus, resulting in reflux of gastric contents to the esophagus, airway, throat, and mouth. Our findings are in accordance with previous epidemiological evidence, which suggested a higher prevalence of GERD in otolaryngological diseases. In a US outpatient cross-sectional study, a significant positive correlation was identified between GERD and obstructive sleep apnea, even after controlling for potential confounders.[19] GERD has also been associated with ear diseases,[20] with evidence of gastric contents found in the middle ear.[21] In a prospective observational study, most chronic otitis media patients exhibited signs of pharyngolaryngeal reflux, suggesting GERD's possible role in the development of chronic otitis media.[22] Similarly, a multicenter case-control study found that, after adjusting for confounders, gastroesophageal reflux disease increased the risk of non-allergic rhinitis and sinusitis, with a smaller effect on allergic rhinitis risk.[23] This aligns with our findings, indicating that GERD raises the risk of sinusitis, while its impact on allergic rhinitis is less pronounced. Previous studies have also reported a link between GERD and vocal cord dysfunction. Vocal cord dysfunction, characterized by intermittent glottic closure due to adduction of the vocal cords, causes

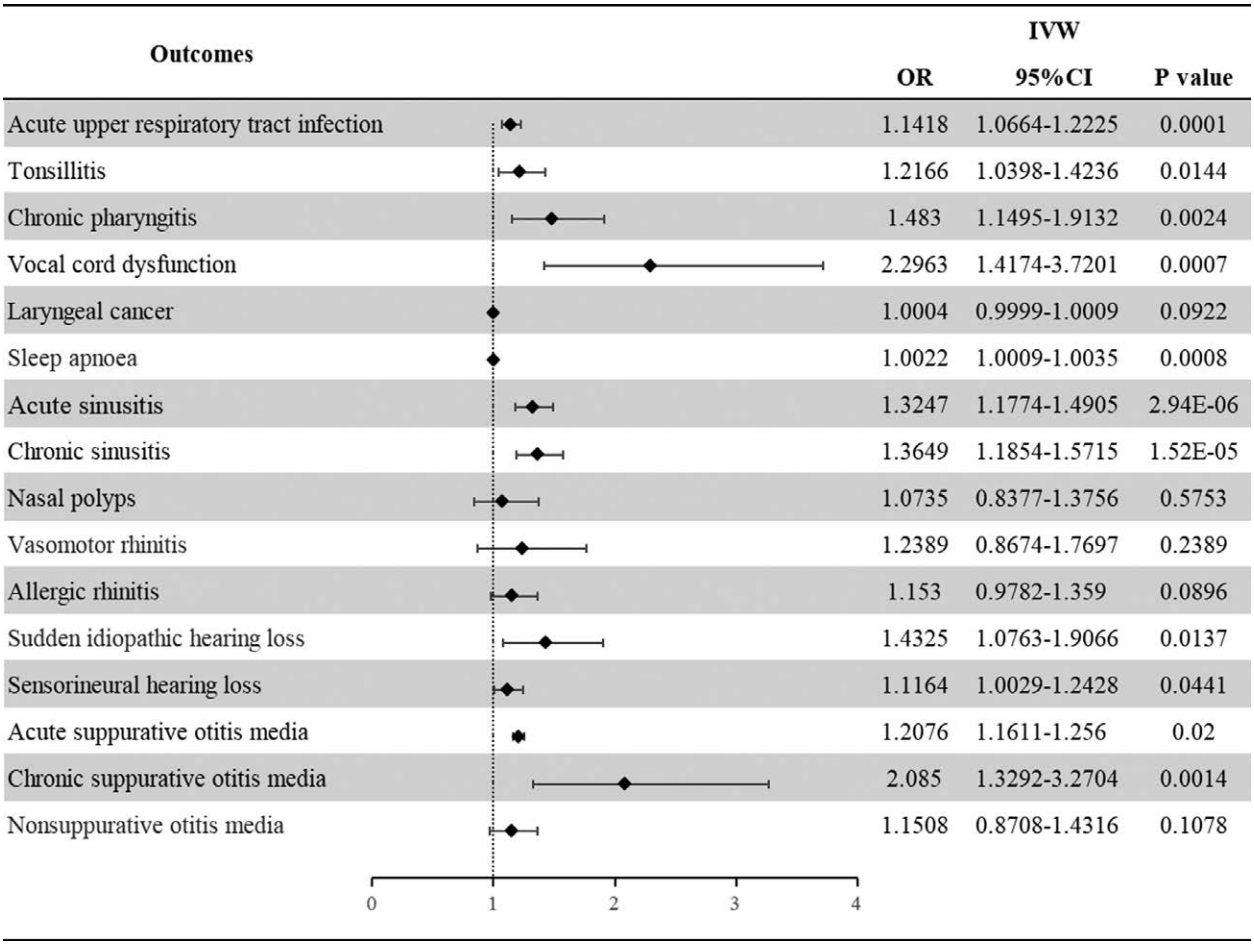

Figure 2. MR estimates of GERD's causal effect on otolaryngological diseases. GERD = gastroesophageal reflux disease, IVW = inverse-variance weighting, MR = Mendelian randomization.

respiratory difficulty and noisy breathing and is considered one of the triggers of GERD.[24–26] Symptomatic relief of vocal cord dysfunction has been observed following acid-suppressive therapy.[26] Additionally, an estimated 60% of patients with chronic laryngitis and persistent throat pain are associated with acid reflux.[27] Treatment with proton pump inhibitors (PPIs) appears effective in reducing throat swelling and alleviating both subjective and objective symptoms related to laryngopharyngeal reflux,[28] supporting the physiological relevance of GERD in otolaryngologic diseases.

Regarding the pathophysiological mechanisms of GERD in the development of otolaryngological diseases, 1 possible mechanism involves components in gastric contents, such as hydrochloric acid, gastric proteases, and bile acids, directly coming into contact with the mucosa of the throat, triggering an inflammatory response. In experiments conducted in vivo, exposure of the throat to gastric contents resulted in observable mucosal inflammation, including increased infiltration of inflammatory cells, submucosal gland hyperplasia,[29] and expansion of intercellular gaps,[30] as well as an acute reduction in transepithelial resistance of throat epithelial cells.[31] Unlike the esophageal epithelium, the laryngeal epithelium is more susceptible to the damaging effects of gastric reflux. Carbonic anhydrase is one of the mucosal protective components[32] and may act as an intrinsic defense mechanism by generating a barrier of bicarbonate ions to counteract refluxed contents.[33] However, under the chronic acidic influence of gastric proteases, the expression of carbonic anhydrase in the laryngeal and hypopharyngeal mucosa decreases,[34] a phenomenon observed in most laryngopharyngeal reflux patients.[33,35,36] Additionally, research has noted a reduction in activity among mouse middle ear epithelial cells under acidic pH conditions, coupled with an increase in Muc5b expression.[37] This observation might contribute to explaining the impact of laryngopharyngeal reflux on the development of otitis media.

Another potential mechanism is the vagal nerve reflex arc triggered by gastroesophageal reflux. Some studies have pointed out that gastric acid stimulation of the esophagus may lead to vagal neuritis changes and then cause airway mucositis and swelling.[38,39] This theory is based on the shared embryonic origin and vagal nerve innervation of the esophagus and respiratory tract, explaining why stimuli in the distal esophagus can cause respiratory symptoms through vagally mediated reflexes.[2] Hamamoto et al[40] found that stimulating the guinea pig esophagus with hydrochloric acid resulted in the release of tachykinin-like substances and caused plasma extravasation in the airways. However, this response was significantly inhibited in guinea pigs with bilateral vagotomy, further supporting the connection of nerve pathways between the esophagus and the airway. Overall, these research findings provide profound insights into the relationship between GERD and otolaryngological diseases. Research has shown that GERD plays a significant role in the development of various otolaryngological diseases, such as chronic pharyngitis, vocal cord dysfunction, sleep apnea, and chronic sinusitis. Clinically, for patients with otolaryngological symptoms that do not respond to conventional treatments, GERD should be considered a potential contributing factor and incorporated into the management plan. Acid-suppressive therapy and lifestyle modifications may help alleviate both GERD symptoms and related otolaryngological issues. This integrated approach may reduce the severity of

conditions like vocal cord dysfunction and sleep apnea, thereby improving overall patient outcomes. Future research should further explore GERD-targeted interventions to mitigate its impact on otolaryngological diseases and provide additional guidance for the clinical management of these co-occurring conditions.

Compared with traditional observational studies, MR is less susceptible to confounding or reverse causality, as an individual's genetically predicted GERD exists before the occurrence of outcomes. However, like all analytical methods, MR relies on assumptions, and the reasonableness of these assumptions must be assessed.[12] First, we assessed the strength of the IVs and calculated *F* statistic values, all of which exceeded 10. Second, sensitivity analyses were conducted on genetic variation, and the *P* value of the statistical test for pleiotropy exceeded .05, suggesting an absence of residual pleiotropy. These assessments enhance the credibility of our results.

Nevertheless, our study has several limitations. Firstly, the absence of information regarding the severity of GERD and outcomes in our dataset prevented us from exploring the correlation between varying GERD severities and specific otolaryngological diseases. Secondly, to reduce the issue of population stratification, we restricted the analysis to individuals of European ancestry to minimize genetic heterogeneity and reduce bias from population stratification as much as possible. However, this also limits the generalizability of our findings to other racial and ethnic groups. Consequently, future investigations should encompass diverse populations, coupled with observational studies and explorations into fundamental mechanisms, to comprehensively examine these associations.

5. Conclusion

In conclusion, this MR study provides new evidence indicating a significant increase in the risk of various otolaryngological diseases with GERD, including chronic sinusitis, chronic rhinitis and pharyngitis, disorders of the vocal cords and larynx, head and neck cancers, thyroid cancer, and sleep apnea. Future research should further explore the potential mechanisms underlying the development of these diseases in relation to GERD and include more diverse populations to enhance the generalizability of the findings. Longitudinal studies and interventional trials evaluating GERD-targeted treatments will provide valuable insights into preventing or mitigating these comorbid conditions and improving patient outcomes.

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Writing – original draft: Yixi Xiao.
Writing – review & editing: Yixi Xiao, Haowei Zhang, Fang Zhang, Jing Luo, Jianhui Zhang.

References

[1] Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900–20; quiz 1943.
[2] Hait EJ, McDonald DR. Impact of gastroesophageal reflux disease on mucosal immunity and atopic disorders. Clin Rev Allergy Immunol. 2019;57:213–25.
[3] Hellings PW, Fokkens WJ, Orlandi R, et al. The EUFOREA pocket guide for chronic rhinosinusitis. Rhinology. 2023;61:85–9.
[4] Principi N, Esposito S. Unsolved problems and new medical approaches to otitis media. Expert Opin Biol Ther. 2020;20:741–9.
[5] Chandrasekhar SS, Tsai Do BS, Schwartz SR, et al. Clinical practice guideline: sudden hearing loss (Update). Otolaryngol Head And Neck Surg. 2019;161(1_suppl):S1–s45.
[6] Megale SR, Scanavini AB, Andrade EC, Fernandes MI, Anselmo-Lima WT. Gastroesophageal reflux disease: its importance in ear, nose, and throat practice. Int J Pediatr Otorhinolaryngol. 2006;70:81–8.
[7] Sella GCP, Tamashiro E, Anselmo-Lima WT, Valera FCP. Relation between chronic rhinosinusitis and gastroesophageal reflux in adults: systematic review. Brazilian J Otorhinolaryngol. 2017;83:356–63.
[8] Tran CL, Han M, Kim B, Park EY, Kim YI, Oh JK. Gastroesophageal reflux disease and risk of cancer: findings from the Korean National Health Screening Cohort. Cancer Med. 2023;12:19163–73.
[9] Miura MS, Mascaro M, Rosenfeld RM. Association between otitis media and gastroesophageal reflux: a systematic review. Otolaryngol Head And Neck Surg. 2012;146:345–52.
[10] El Hage Chehade N, Fu Y, Ghoneim S, Shah S, Song G, Fass R. Association between obstructive sleep apnea and gastroesophageal reflux disease: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2023;38:1244–51.
[11] Burgess S, Foley CN, Zuber V. Inferring causal relationships between risk factors and outcomes from genome-wide association study data. Annu Rev Genomics Hum Genet. 2018;19:303–27.
[12] Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ (Clinical research ed). 2018;362:k601.
[13] Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol. 2016;27:3253–65.
[14] Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization. JAMA. 2017;318:1925–6.
[15] Ong JS, An J, Han X, et al; 23andMe Research team. 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. 2022;71:1053–61.
[16] Sakaue S, Kanai M, Tanigawa Y, et al; FinnGen. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet. 2021;53:1415–24.
[17] Burgess S, Thompson SG; CRP CHD Genetics Collaboration. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol. 2011;40:755–64.
[18] Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44:512–25.
[19] Gilani S, Quan SF, Pynnonen MA, Shin JJ. Obstructive sleep apnea and gastroesophageal reflux: a multivariate population-level analysis. Otolaryngol Head And Neck Surg. 2016;154:390–5.
[20] Poelmans J, Tack J, Feenstra L. Chronic middle ear disease and gastroesophageal reflux disease: a causal relation? Otolaryngol Head And Neck Surg. 2001;22:447–50.
[21] Abdel-aziz MM, El-Fattah AM, Abdalla AF. Clinical evaluation of pepsin for laryngopharyngeal reflux in children with otitis media with effusion. Int J Pediatr Otorhinolaryngol. 2013;77:1765–70.
[22] Han H, Lv Q. Characteristics of laryngopharyngeal reflux in patients with chronic otitis media. Am J Otolaryngol. 2018;39:493–6.
[23] Finocchio E, Locatelli F, Sanna F, et al. Gastritis and gastroesophageal reflux disease are strongly associated with non-allergic nasal disorders. BMC Pulm Med. 2021;21:53.
[24] Morris MJ, Christopher KL. Diagnostic criteria for the classification of vocal cord dysfunction. Chest. 2010;138:1213–23.
[25] Malaty J, Wu V. Vocal cord dysfunction: rapid evidence review. Am Fam Physician. 2021;104:471–5.
[26] Woolnough K, Blakey J, Pargeter N, Mansur A. Acid suppression does not reduce symptoms from vocal cord dysfunction, where gastrolaryngeal reflux is a known trigger. Respirology (Carlton, Vic). 2013;18:553–4.
[27] Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease. Clin Cornerstone. 2003;5:32–8; discussion 39.
[28] Aviv JE, Liu H, Parides M, Kaplan ST, Close LG. Laryngopharyngeal sensory deficits in patients with laryngopharyngeal reflux and dysphagia. Ann Otol Rhinol Laryngol. 2000;109:1000–6.
[29] Hu Y, Xu XB, Chen SY, et al. Laryngoscopy findings and histological results in a rabbit gastroesophageal reflux model. Eur Arch Oto-Rhino-Laryngol. 2012;269:1939–44.

[30] Hu Y, Xu X, Xu L, Lai C, Zhang T. Dilated intercellular space in the larynx and esophagus of a rabbit reflux model. Auris, nasus, larynx. 2013;40:379–82.
[31] Erickson E, Sivasankar M. Simulated reflux decreases vocal fold epithelial barrier resistance. Laryngoscope. 2010;120:1569–75.
[32] Mirić M, Turkalj M, Nogalo B, Erceg D, Perica M, Plavec D. Lung diffusion capacity in children with respiratory symptoms and untreated GERD. Med Sci Monitor. 2014;20:774–81.
[33] Axford SE, Sharp N, Ross PE, et al. Cell biology of laryngeal epithelial defenses in health and disease: preliminary studies. Ann Otol Rhinol Laryngol. 2001;110:1099–108.
[34] Lechien JR, Saussez S, Harmegnies B, Finck C, Burns JA. laryngopharyngeal reflux and voice disorders: a multifactorial model of etiology and pathophysiology. J Voice. 2017;31:733–52.
[35] Johnston N, Bulmer D, Gill GA, et al. Cell biology of laryngeal epithelial defenses in health and disease: further studies. Ann Otol Rhinol Laryngol. 2003;112:481–91.
[36] Kowalik K, Krzeski A. The role of pepsin in the laryngopharyngeal reflux. Otolaryngologia polska = Polish Otolaryngol. 2017;71:7–13.
[37] Block BB, Kuo E, Zalzal HG, Escobar H, Rose M, Preciado D. In vitro effects of acid and pepsin on mouse middle ear epithelial cell viability and MUC5B gene expression. Arch Otolaryngol Head Neck Surg. 2010;136:37–42.
[38] Stein MR. Possible mechanisms of influence of esophageal acid on airway hyperresponsiveness. Am J Med. 2003;115(Suppl 3A):55S–9S.
[39] Schreiber S, Garten D, Sudhoff H. Pathophysiological mechanisms of extraesophageal reflux in otolaryngeal disorders. Eur Arch Oto-Rhino-Laryngol. 2009;266:17–24.
[40] Hamamoto J, Kohrogi H, Kawano O, et al. Esophageal stimulation by hydrochloric acid causes neurogenic inflammation in the airways in guinea pigs. J Appl Physiol (Bethesda, Md. : 1985). 1997;82:738–45.