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Association Between Gastroesophageal Reflux Disease, Barrett's Esophagus and Ear Disorders: A Mendelian Randomization Study

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Objective: This study aims to examine the correlation between gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and ear disorders using Mendelian randomization (MR).

Methods: For GERD, BE, and ear disorders, GWAS genetic data from individuals of European ancestry in the IEU GWAS database (https://gwas.mrcieu.ac.uk/) was utilized in this study. Three MR methods were applied for preliminary analysis, with causal estimates determined using the inverse variance weighted method. Sensitivity analysis was conducted to assess heterogeneity and pleiotropy.

Results: Potential effects of genetically predicted GERD on ear disorders were identified in this study. GERD was associated with Ménière's disease (OR = 1.334, 95% CI: 1.073–1.671, $p = 0.009$), sensorineural hearing loss (OR = 1.127, 95% CI: 1.019–1.245, $p = 0.019$), vestibular dysfunction (OR = 1.178, 95% CI: 1.025–1.354, $p = 0.021$), constant tinnitus (OR = 1.019, 95% CI: 1.009–1.029, $p = 0.0003$), tinnitus occurring most of the time (OR = 1.007, 95% CI: 1.001–1.012, $p = 0.019$), and occasional tinnitus (OR = 1.014, 95% CI: 1.005–1.023, $p = 0.002$). Higher GERD levels were linked to an increased risk of these ear disorders. For individuals who never experienced tinnitus (OR = 0.939, 95% CI: 0.923–0.957, $p = 1.2721E-11$), elevated GERD levels were associated with a reduced likelihood of never experiencing tinnitus. No causal association was found between GERD and otitis media (OR = 1.093, 95% CI: 0.884–1.352, $p = 0.412$). BE demonstrated no causal relationship with ear disorder risk.

Conclusion: Under MR assumptions, the findings of this study indicate that GERD may increase the risk of tinnitus, Ménière's disease, vestibular dysfunction, and sensorineural hearing loss.

Keywords: Barrett's esophagus, gastroesophageal reflux disease, Mendelian randomization, ear disorders, Ménière's disease

Introduction

Gastroesophageal reflux disease (GERD) is the second most prevalent upper digestive tract motility disorder in clinical practice, affecting millions worldwide. Global epidemiological studies indicate that, based on the criterion of reflux and/or heartburn occurring at least once per week, the prevalence of GERD is 13.3%. Prevalence rates range from 8.8% to 25.9% in Europe and 18.1% to 27.8% in North America.[1] GERD typically presents as the reflux of gastric contents into the esophagus, leading to symptoms such as heartburn, acid regurgitation, and dysphagia, which significantly impair patients' quality of life. Chronic recurrent episodes can result in severe complications, including ulcers, perforation, and esophageal stricture. Persistent gastroesophageal reflux may lead to BE, causing the transformation of stratified squamous epithelium in the distal esophagus into columnar epithelium, thereby increasing the risk of esophageal cancer. BE is the only established precursor to esophageal adenocarcinoma, a malignant tumor with a significantly rising

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prevalence over the past few decades.[2] A statistical association between GERD and ear disorders was identified in a previous study; however, the causal relationship remains uncertain.[3] Investigating this relationship may contribute to reducing the incidence of ear disorders.

According to statistical data, 4% to 10% of patients seeking care at otorhinolaryngology clinics exhibit symptoms considered extraesophageal manifestations of GERD.[3] Studies indicate that GERD can contribute to the development of chronic rhinosinusitis, chronic otitis media, paroxysmal laryngospasm, postnasal drip, and other conditions, or act as an exacerbating factor for these disorders.[4]

Physiologically, the ear connects to the nasopharynx through the Eustachian tube. Some researchers propose that in patients with GERD, gastric contents may reflux through the Eustachian tube in liquid or gaseous form, reaching the middle ear cavity and potentially triggering otitis media and other inner ear disorders.[5] Furthermore, GERD serves as a risk factor for various medical conditions and contributes to the progression of respiratory diseases, autoimmune diseases, and psychological conditions. Although GERD primarily affects the digestive system, the anatomical connection between the gastroesophageal system and the ear through tubular pathways raises the possibility that it may contribute to ear disorders.

Recent studies increasingly indicated an association between GERD and ear disorders, including tinnitus, Ménière's disease, otitis media, vestibular dysfunction, and sensorineural hearing loss. It was reported in a study on refractory otitis media that patients responded well to anti-reflux therapy (including omeprazole and conservative anti-reflux management), supporting the hypothesis that gastroesophageal reflux may reach the ear via the nasopharynx, leading to chronic ear conditions.[6] Megale et al observed that individuals with GERD frequently experience extraesophageal symptoms, including ear-related issues.[7] It was demonstrated in the study that following GERD treatment, over half of the patients faced resolution of symptoms, with a 100% cure rate in the recurrent acute otitis media group. Additionally, Viliušytė Eet al proposed a link between GERD and peripheral vertigo.[8] Among 120 patients with GERD, 93 (77.6%) exhibited peripheral vertigo, whereas among 126 individuals without GERD, 33 (26%) had peripheral vertigo ($\chi^2 = 9.016$, $p = 0.003$), indicating a statistically significant correlation.

Poelmans et al investigated 217 patients attending otorhinolaryngology outpatient clinics and noted that most individuals with otitis media and ear fullness lacked typical reflux symptoms such as nausea, vomiting, and heartburn.[9] However, following antacid therapy, these patients experienced significant symptom improvement. Despite these findings, existing research has not yet established a causal relationship between GERD and ear disorders or examined its impact on different ear disorder classifications. Traditional observational studies face methodological challenges, including ambiguous temporal relationships, limited sample sizes, short follow-up durations, population variability, and confounding factors. These limitations may obscure the true nature of the association. Employing Mendelian randomization (MR) can address these gaps by providing a strong framework for assessing causal relationships.

Materials and Methods

Study Design

According to Mendelian laws of inheritance—random segregation and independent assortment of genes—MR utilizes genetic variations, typically single nucleotide polymorphisms (SNPs), that are randomly assigned at conception as instrumental variables (IVs) for analysis. This approach estimates the potential causal effects of exposure on risk outcomes while minimizing the influence of confounding factors. Since genetic variations undergo random combination during meiosis, MR effectively simulates a randomized controlled trial (RCT) within the meiotic process. As a result, genetic variations serve as reliable tools to link risk factors with outcomes, allowing for a more precise estimation of causal effects with reduced bias compared to traditional epidemiological methods.[10]

Additionally, MR mitigates the impact of reverse causality, as genetic variations remain unchanged by disease development and progression. Compared to traditional observational studies, MR offers significant advantages in inferring the direction of exposure-outcome associations, excluding confounding factors, and identifying causal determinants of outcomes, thereby facilitating meaningful clinical interpretations.[11] Currently, MR is widely applied in genetic epidemiology research to elucidate risk factors for various diseases. MR analysis has identified multiple risk factors for

GERD and established causal relationships between GERD and other conditions.[12–14] However, no comprehensive assessment appears to have been conducted regarding the causal relationship between GERD and ear disorders.

Given the potential adverse effects of gastroesophageal reflux on ear disorders and the relatively high prevalence of GERD among affected patients, determining whether a causal relationship exists between GERD and ear disorders is crucial. Establishing such a link could provide significant insights for the comprehensive clinical treatment and management of GERD in conjunction with ear disorders.

A two-sample MR study was conducted utilizing publicly available large-scale GWAS data on GERD, BE, and ear disorders (tinnitus, Ménière's disease, otitis media, vestibular dysfunction, and sensorineural hearing loss) from populations of European ancestry. The aim of this study was to investigate potential causal relationships between GERD/BE and five types of ear disorders: tinnitus (including no tinnitus, constant tinnitus, frequent tinnitus, and occasional tinnitus), Ménière's disease, otitis media, vestibular dysfunction, and sensorineural hearing loss. The findings confirmed the effects of GERD on tinnitus, Ménière's disease, otitis media, vestibular dysfunction, and sensorineural hearing loss, as well as the impact of BE on vestibular dysfunction. These results offer valuable insights for the targeted prevention and management of GERD/BE and ear disorders. They also indicate that adopting a comprehensive treatment approach for these co-occurring conditions could lead to improved therapeutic outcomes, enhancing patients' quality of life and health.

Methods

To investigate the causal relationship between GERD/BE and the risk of ear disorders (tinnitus, Ménière's disease, otitis media, vestibular dysfunction, and sensorineural hearing loss), the MR method was employed to examine causal effects. The genetic IVs used in this study must satisfy three key assumptions:[15] (1) The genetic IVs extracted should be strongly associated with GERD and BE ($p < 5\times10^{-8}$), (2) The genetic IVs should not be correlated with any confounding factors that could induce pleiotropy, and (3) The genetic IVs should influence the outcomes solely through the exposure. As the publicly available GWAS summary data was utilized in this study, ethical approval was not necessary. To ensure the reliability of the findings, multiple MR methods and sensitivity analyses were employed.

The aim of this study was to assess whether a causal relationship existed between GERD and several ear disorders, which were prevalent and affected both men and women. To accomplish this objective, five ear-related conditions were included as outcomes in the primary analysis: tinnitus (including never experiencing tinnitus, constant tinnitus, tinnitus most of the time, and occasional tinnitus), Ménière's disease, otitis media, vestibular dysfunction, and sensorineural hearing loss.

Data Sources for GERD and BE

The genetic summary data related to GERD and BE used in this study were derived from a large GWAS published by Ong et al in *Gut* in 2022 (accessed through studies GCST90000514 and GCST90000515).[16] This multi-trait genetic association analysis identified 88 independent GERD loci and 7 previously unreported BE risk loci. The GERD data included European populations (n = 602,604; 129,080 cases and 473,524 controls, covering 2,320,781 SNPs), while the BE data comprised European populations (n = 56,429; 43,017 cases and 13,358 controls, covering 2,320,718 SNPs).

Database Sources for 5 Types of Ear Disorders

GWAS data from individuals of European ancestry was selected from the IEU GWAS database (https://gwas.mrcieu.ac.uk/). The genetic samples for tinnitus included 117,882 cases and 12,817,923 controls for "Tinnitus: Yes, now most or all of the time"; 117,882 cases and 13,352,737 controls for "Tinnitus: Yes, now some of the time"; and 11,127,194 cases and 117,882 controls for "Tinnitus: Yes, now a lot of the time." For Ménière's disease (ebi-a-GCST90018880, n = 482,774; 1,526 cases and 481,248 controls, covering 24,194,682 SNPs), otitis media (ebi-a-GCST90018880, n = 216,903; 7,321 cases and 209,582 controls, covering 24,194,289 SNPs), vestibular dysfunction (finn-b-H8_VERTIGO, n = 216,903; 7,321 cases and 209,582 controls, covering 16,380,466 SNPs), and sensorineural hearing loss (finn-b-H8_CONSENHEARINGLOSS, n = 213,929; 17,337 cases and 196,592 controls, covering 16,380,457 SNPs).

All summary statistics for GERD data and the five types of ear disorder data were downloaded from the Integrative Epidemiology Unit (IEU) Open GWAS Database (https://gwas.mrcieu.ac.uk/). All subjects in the database were of European ancestry.

Selection of IVs

For the selection of IVs, a screening criterion of $p < 5\times10^{-6}$ was used in this study, based on relevant literature, to preliminarily select SNPs for GERD and BE.[17] Then, to eliminate the effects of linkage disequilibrium, the clumping function was applied with a linkage disequilibrium coefficient threshold of $r^2 = 0.001$ and a region width of 10,000 kb. Weak instrument bias test: In MR studies, the F-statistic is used to assess the strength of IVs (usually SNPs). An SNP with a strong correlation to the exposure factor is considered a strong IV. An F-statistic >10 is generally interpreted as indicating a strong correlation between the SNP and the exposure factor.[18] The formula for calculating the F-statistic is as follows:

$$F = R^2 \times (N - 1 - K)/K \times \left(1 - R^2\right)$$

$$R^2 = 2 \times EAF \times (1 - EAF) \times \beta^2 / 2 \times EAF \times (1 - EAF) \times \beta^2 + 2 \times EAF \times (1 - EAF) \times N \times S^{2/X}$$

In this formula, N represents the sample size of the exposure factor, K denotes the number of IVs included, R^2 indicates the proportion of exposure factor variation explained by the IVs, EAF refers to the effect allele frequency, β represents the effect value, and $\bar{S}x$ is the standard error of the β value.[19]

MR Analysis

The "TwoSampleMR" package in R software was employed in this study to perform a two-sample MR analysis, utilizing five MR methods: inverse variance weighted (IVW) method, MR-Egger regression, weighted median, weighted mode, and simple mode. The IVW method, a conventional approach that combines the Wald ratio estimates of multiple SNPs, offers the highest statistical power among all MR methods.[20] Consequently, IVW was used as the primary method, with MR-Egger regression, weighted mode, weighted median, and simple mode serving as supplementary methods to ensure the reliability of the results.[21]

Sensitivity Analysis

R software was utilized to perform sensitivity analysis. Cochran's IVW Q method was implemented to assess the heterogeneity of instrumental variable SNPs. A Q statistic (*P*-Q test < 0.05) was considered to indicate heterogeneity.[22] Horizontal pleiotropy was evaluated through the intercept in MR-Egger regression, where a significant intercept (*p*-intercept < 0.05) indicated the presence of pleiotropy.[23] Additionally, a leave-one-out analysis was conducted to determine the combined effect size by sequentially removing individual SNPs, allowing for the identification of potentially influential SNPs.[24] To account for multiple exposures to outcomes, Bonferroni correction was applied to the MR analysis results in this study. A corrected *p* value of < 0.05 was considered indicative of a potential causal relationship.[25]

Results

Information Related to Instrumental Variable SNPs

After applying the criteria of $p < 5\times10^{-6}$, $r^2 = 0.001$, region width kb = 10,000, and F-statistic > 10, 80 SNPs for GERD and 16 SNPs for BE were selected.

Results of MR Analysis and Sensitivity Analysis

Five MR analysis methods were applied, with IVW serving as the primary method and the other methods used for reference. The MR results underwent sensitivity analysis and Bonferroni correction, with a corrected *p* value < 0.05 indicating a potential causal relationship. Cochran's IVW Q test was employed to assess heterogeneity, with a Q statistic ($p \geq 0.05$) indicating no significant heterogeneity. The MR-Egger regression intercept was used to test for horizontal pleiotropy, with a significant intercept ($p < 0.05$) indicating pleiotropy. Conversely, when the intercept ($p \geq 0.05$), pleiotropy is typically considered absent.

In the forward MR analysis, genetic susceptibility to GERD demonstrated causal relationships with Ménière's disease, sensorineural hearing loss, vestibular dysfunction, and various tinnitus conditions, including never experiencing tinnitus, constant tinnitus, tinnitus most of the time, and occasional tinnitus. Ménière's disease (OR=1.334, 95% CI, 1.073–1.671, $p = 0.009$), sensorineural hearing loss (OR=1.127, 95% CI, 1.019–1.245, $p = 0.019$), vestibular dysfunction (OR=1.178, 95% CI, 1.025–1.354, $p = 0.021$), constant tinnitus (OR=1.019, 95% CI, 1.009–1.029, $p = 0.0003$), tinnitus most of the time (OR=1.007, 95% CI, 1.001–1.012, $p = 0.019$), and occasional tinnitus (OR=1.014, 95% CI, 1.005–1.023, $p = 0.002$) were all positively correlated, with higher levels of GERD linked to an increased risk of these ear disorders. However, for never experiencing tinnitus (OR=0.939, 95% CI, 0.923–0.957, $p = 1.2721E-11$), elevated levels of gastroesophageal reflux were associated with a decreased risk. No causal correlation was found between GERD and otitis media (OR=1.093, 95% CI, 0.884–1.352, $p = 0.412$). Data are presented in Table 1.

Table 1 Results of MR Analysis Between GERD and Five Ear Disorders

Outcome	Exposure	Method	Nsnp*	Pval*	OR	OR_Lci95	OR_Uci95
Chronic suppurative otitis media	Gastroesophageal reflux disease	MR Egger	76	0.1526371	2.591042	0.7123536	9.424388
		Weighted median	76	0.2759319	1.187354	0.8717895	1.617144
		Inverse variance weighted	76	0.4120508	1.093081	0.8836827	1.352099
		Simple mode	76	0.2532405	1.590008	0.7220231	3.501444
		Weighted mode	76	0.4916343	1.296743	0.6205764	2.709645
Tinnitus: No, never	Gastroesophageal reflux disease	MR Egger	77	0.1752047	0.9313254	0.8411076	1.03122
		Weighted median	77	1.64478E-08	0.9399674	0.9199802	0.9603888
		Inverse variance weighted	77	1.27211E-11	0.9396324	0.9228498	0.9567202
		Simple mode	77	0.0154839	0.9211958	0.8632584	0.9830218
		Weighted mode	77	0.01384519	0.9253617	0.8711762	0.9829174
Meniere's disease	Gastroesophageal reflux disease	MR Egger	76	0.459177099	1.653353	0.4397161	6.216687
		Weighted median	76	0.006174931	1.560545	1.1348454	2.145932
		Inverse variance weighted	76	0.009659881	1.339338	1.0734518	1.671083
		Simple mode	76	0.13414602	1.978493	0.8180644	4.784995
		Weighted mode	76	0.115393612	1.907069	0.8617515	4.220372
Conductive and sensorineural hearing loss	Gastroesophageal reflux disease	MR Egger	75	0.0719438	1.726891	0.960693	3.104168
		Weighted median	75	0.04857167	1.14602	1.0008526	1.312242
		Inverse variance weighted	75	0.01985728	1.126548	1.0190599	1.245373
		Simple mode	75	0.56023389	1.114903	0.77448	1.60496
		Weighted mode	75	0.3778728	1.174195	0.8234961	1.674244
Disorders of vestibular function (Vertigo)	Gastroesophageal reflux disease	MR Egger	75	0.91214116	0.9545951	0.4193504	2.173008
		Weighted median	75	0.30021736	1.1100319	0.9110935	1.352409
		Inverse variance weighted	75	0.02080536	1.1781475	1.0252434	1.353856
		Simple mode	75	0.78132498	1.0783189	0.6344085	1.832844
		Weighted mode	75	0.77124625	1.0783189	0.6498245	1.789363
Tinnitus: Yes, now most or all of the time	Gastroesophageal reflux disease	MR Egger	77	0.628284731	1.014241	0.9580342	1.073746
		Weighted median	77	0.051027446	1.012476	0.9999444	1.025165
		Inverse variance weighted	77	0.000298812	1.01878	1.0085582	1.029106
		Simple mode	77	0.823115026	1.003479	0.973485	1.034397
		Weighted mode	77	0.790981298	1.004052	0.9745715	1.034425

(*Continued*)

Table 1 (Continued).

Outcome	Exposure	Method	Nsnp*	Pval*	OR	OR_Lci95	OR_Uci95
Tinnitus: Yes, now some of the time	Gastroesophageal reflux disease	MR Egger	77	0.931190817	0.9978285	0.9499436	1.048127
		Weighted median	77	0.041847402	1.0133987	1.0004909	1.026473
		Inverse variance weighted	77	0.001865504	1.0139923	1.0051538	1.022909
		Simple mode	77	0.491457903	1.0115067	0.9792238	1.044854
		Weighted mode	77	0.728502616	1.0056219	0.974401	1.037843
Tinnitus: Yes, now a lot of the time	Gastroesophageal reflux disease	MR Egger	77	0.85105977	1.003068	0.9716087	1.035546
		Weighted median	77	0.21136344	1.004625	0.9973813	1.011922
		Inverse variance weighted	77	0.01915308	1.00676	1.0011008	1.012452
		Simple mode	77	0.96888284	1.000397	0.9807204	1.020468
		Weighted mode	77	0.96860634	1.000397	0.9808921	1.020289

Notes: 1. nsnp: number of instrumental variable single nucleotides. 2. pval: an indicator used to determine whether statistical results are significant.

No causal relationship was found between BE and otitis media, Ménière's disease, sensorineural hearing loss, vestibular dysfunction, and various types of tinnitus, including never experiencing tinnitus, constant tinnitus, tinnitus most of the time, and occasional tinnitus. The results were as follows: otitis media (OR=1.045, 95% CI, 0.899–1.213, $p = 0.563$), never experiencing tinnitus (OR=0.995, 95% CI, 0.984–1.006, $p = 0.373$), Ménière's disease (OR=1.140, 95% CI, 0.974–1.335, $p = 0.103$), sensorineural hearing loss (OR=0.996, 95% CI, 0.921–1.077, $p = 0.919$), vestibular dysfunction (OR=1.092, 95% CI, 0.989–1.206, $p = 0.081$), constant tinnitus (OR=1.005, 95% CI, 0.998–1.012, $p = 0.137$), tinnitus most of the time (OR=0.999, 95% CI, 0.996–1.002, $p = 0.581$), and occasional tinnitus (OR=1.001, 95% CI, 0.992–1.009, $p = 0.896$). Data are presented in Table 2.

Table 2 Results of MR Analysis Between Barrett's Esophagus and Five Ear Diseases

Outcome	Exposure	Method	Nsnp*	Pval*	OR	OR_Lci95	OR_Uci95
Chronic suppurative otitis media	Barrett's esophagus	MR Egger	16	0.2189035	2.1692197	0.6671358	7.053308
		Weighted median	16	0.4837404	1.0745463	0.8786828	1.314069
		Inverse variance weighted	16	0.5633029	1.0450613	0.8999648	1.213551
		Simple mode	16	0.510797	0.8865787	0.6245883	1.258464
		Weighted mode	16	0.6908926	1.0700341	0.7713916	1.484295
Tinnitus: No, never	Barrett's esophagus	MR Egger	16	0.1370691	0.9490652	0.8893688	1.012769
		Weighted median	16	0.8772703	0.9988709	0.9846506	1.013297
		Inverse variance weighted	16	0.3726683	0.995111	0.9844461	1.005891
		Simple mode	16	0.8117499	0.9966609	0.9700683	1.023983
		Weighted mode	16	0.933624	1.001106	0.9758213	1.027046
Meniere's disease	Barrett's esophagus	MR Egger	16	0.9837023	1.012838	0.304359	3.370497
		Weighted median	16	0.192993	1.150055	0.9317482	1.41951
		Inverse variance weighted	16	0.1027601	1.140105	0.9739555	1.334599
		Simple mode	16	0.5083551	1.137368	0.7837887	1.650453
		Weighted mode	16	0.3419261	1.192122	0.839283	1.693296

(*Continued*)

Table 2 (Continued).

Outcome	Exposure	Method	Nsnp*	Pval*	OR	OR_Lci95	OR_Uci95
Conductive and sensorineural hearing loss	Barrett's esophagus	MR Egger	16	0.2670028	0.7165754	0.40726	1.260817
		Weighted median	16	0.7472034	0.984501	0.8952932	1.082597
		Inverse variance weighted	16	0.9188671	0.9959491	0.921121	1.076856
		Simple mode	16	0.7193595	0.9678735	0.8126571	1.152736
		Weighted mode	16	0.9614516	1.0043665	0.8441655	1.19497
Disorders of vestibular function (Vertigo)	Barrett's esophagus	MR Egger	16	0.98967481	1.005063	0.4741362	2.130508
		Weighted median	16	0.03356365	1.161058	1.0116807	1.332491
		Inverse variance weighted	16	0.08072098	1.092299	0.9892668	1.206061
		Simple mode	16	0.12087109	1.242345	0.9592162	1.609045
		Weighted mode	16	0.0942768	1.257658	0.9779531	1.617361
Tinnitus: Yes, now most or all of the time	Barrett's esophagus	MR Egger	16	0.01069909	1.053641	1.0176027	1.090957
		Weighted median	16	0.24647324	1.004712	0.9967562	1.012731
		Inverse variance weighted	16	0.13684152	1.005048	0.9984027	1.011737
		Simple mode	16	0.55275691	1.004658	0.9897008	1.019842
		Weighted mode	16	0.52948324	1.004338	0.9911879	1.017662
Tinnitus: Yes, now some of the time	Barrett's esophagus	MR Egger	16	0.4925052	0.9804979	0.9282389	1.035699
		Weighted median	16	0.197999	0.9942308	0.9855104	1.003028
		Inverse variance weighted	16	0.8957628	1.0005773	0.9919757	1.009253
		Simple mode	16	0.1660634	0.9901648	0.9770758	1.003429
		Weighted mode	16	0.1475013	0.9907354	0.9789716	1.002641
Tinnitus: Yes, now a lot of the time	Barrett's esophagus	MR Egger	16	0.7182769	0.9959685	0.9747764	1.017621
		Weighted median	16	0.6892216	0.999084	0.9946069	1.003581
		Inverse variance weighted	16	0.5805548	0.9990297	0.9955954	1.002476
		Simple mode	16	0.8308241	0.9991228	0.9912487	1.007059
		Weighted mode	16	0.7334456	0.9987335	0.991609	1.005909

Notes: 1. nsnp: number of instrumental variable single nucleotides. 2. pval: an indicator used to determine whether statistical results are significant.

Sensitivity Analysis

In this study, IVW was utilized as the primary reference method. The SNP bias funnel plot for GERD and five types of ear disorders was generally symmetrical, indicating minimal bias and no significant heterogeneity. Cochran's Q test did not detect heterogeneity effects ($p > 0.05$), and the MR-Egger intercept test did not indicate horizontal pleiotropy ($p > 0.05$) (Table 3). Results from the leave-one-out analysis revealed that none of the SNPs associated with GERD were sensitive to the outcomes, and the causal relationships between GERD and ear disorders were not influenced by any single SNP. This indicates a strong potential causal relationship between GERD and the identified ear disorders. As presented in Figures 1–4, the leave-one-out analysis demonstrated no significant bias in SNPs, and both the scatter plot and funnel plot confirmed the stability of the results.

Discussion

The findings of this study indicate that GERD is positively associated with the risk of Ménière's disease, sensorineural hearing loss, vestibular dysfunction, and tinnitus (including constant tinnitus, tinnitus most of the time, and occasional tinnitus), indicating that higher levels of GERD increase the risk of developing these four types of ear disorders. In contrast, GERD is negatively associated with never experiencing tinnitus, meaning that higher GERD levels are linked to a decreased likelihood of never experiencing tinnitus, thus supporting the significant causal relationship between GERD

Table 3 Results of Testing for Heterogeneity and Horizontal Pleiotropy

ID.exposure	ID.outcome	outcome	exposure	method	Q	Q_pval	egger_intercept	pval
ebi-a-GCST90000514	ebi-a-GCST90018809	Chronic suppurative otitis media	Gastroesophageal reflux disease	Inverse variance weighted	61.98228	0.859077	−0.02834666	0.1881968
ebi-a-GCST90000514	ukb-d-4803_0	Tinnitus	Gastroesophageal reflux disease	Inverse variance weighted	127.3327	0.000206446	0.000295114	0.8626533
ebi-a-GCST90000514	ebi-a-GCST90018880	Meniere's disease	Gastroesophageal reflux disease	Inverse variance weighted	66.35711	0.751675	−0.00693555	0.7527775
ebi-a-GCST90000514	finn-b-H8_CONSENHEARINGLOSS	Conductive and sensorineural hearing loss	Gastroesophageal reflux disease	Inverse variance weighted	87.16135	0.1405808	−0.01411562	0.1516937
ebi-a-GCST90000514	finn-b-H8_VERTIGO	Disorders of vestibular function (Vertigo)	Gastroesophageal reflux disease	Inverse variance weighted	81.06805	0.2683301	0.006954065	0.6124626
ebi-a-GCST90000514	ukb-d-4803_11	Tinnitus: Yes, now most or all of the time || id: ukb-d-4803_11	Gastroesophageal reflux disease || id:ebi-a-GCST90000514	Inverse variance weighted	134.7719	3.83475E-05	0.000148387	0.8764608
ebi-a-GCST90000514	ukb-d-4803_13	Tinnitus: Yes, now some of the time	Gastroesophageal reflux disease	Inverse variance weighted	74.03287	0.5424977	0.000534039	0.517148
ebi-a-GCST90000514	ukb-d-4803_12	Tinnitus: Yes, now a lot of the time	Gastroesophageal reflux disease	Inverse variance weighted	104.3852	0.01708376	0.000122108	0.8189778

https://doi.org/10.2147/JMDH.S530915

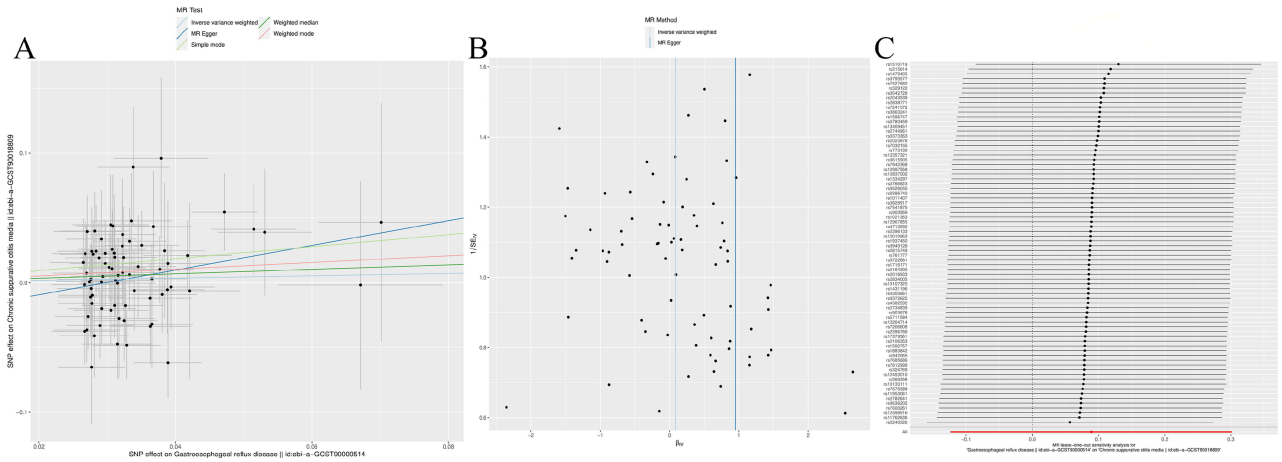

Figure 1 Gastroesophageal reflux disease and chronic suppurative otitis media. (**A**) Scatter diagram; (**B**) Funnel plot; (**C**) Leave-one-out method.

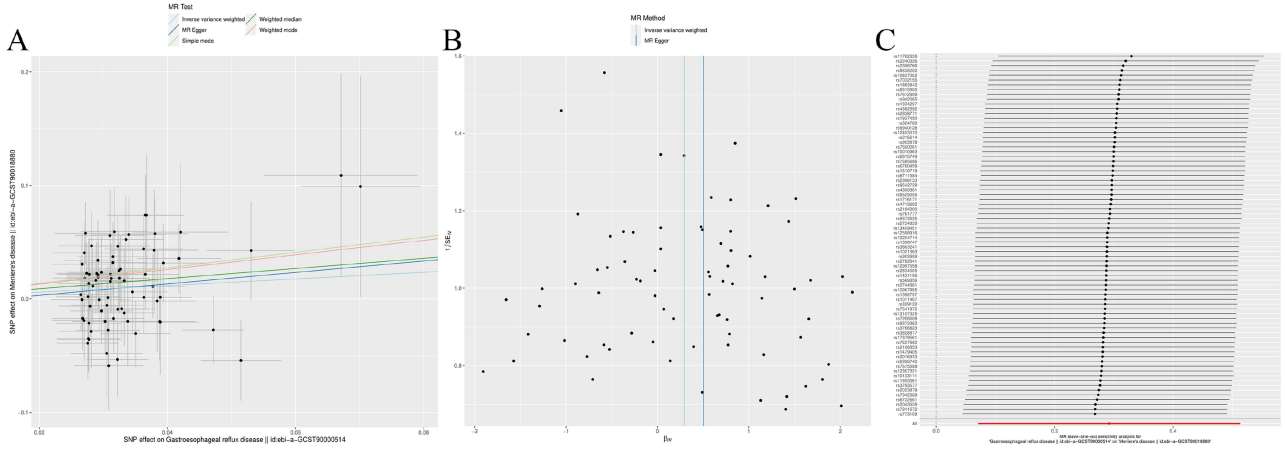

Figure 2 Gastroesophageal reflux disease and Meniere's syndrome. (**A**) Scatter diagram; (**B**) Funnel plot; (**C**) Leave-one-out method.

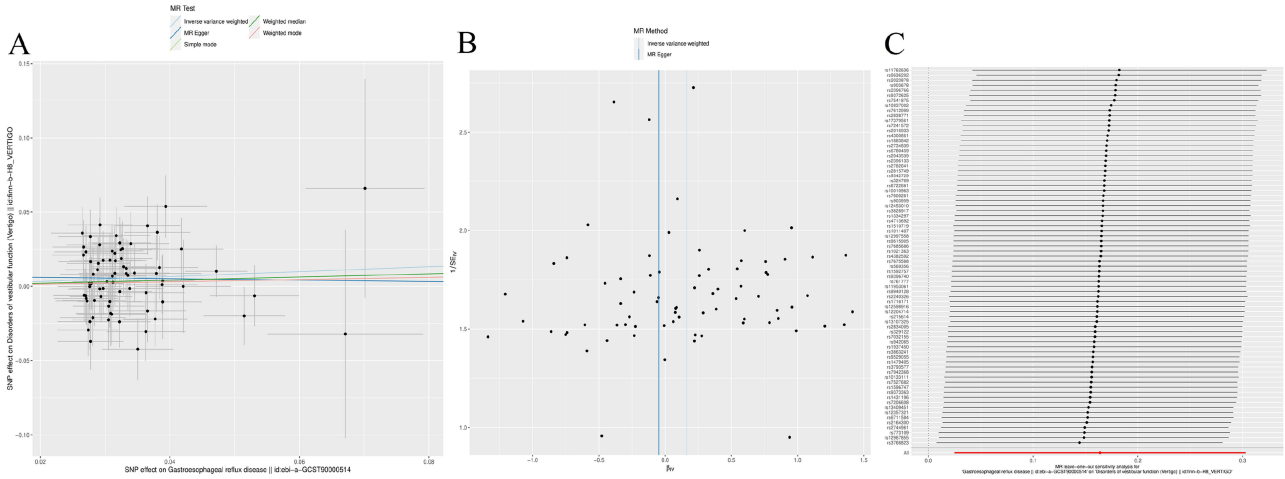

Figure 3 Gastroesophageal reflux disease and vestibular functional vertigo. (**A**) Scatter diagram; (**B**) Funnel plot; (**C**) Leave-one-out method.

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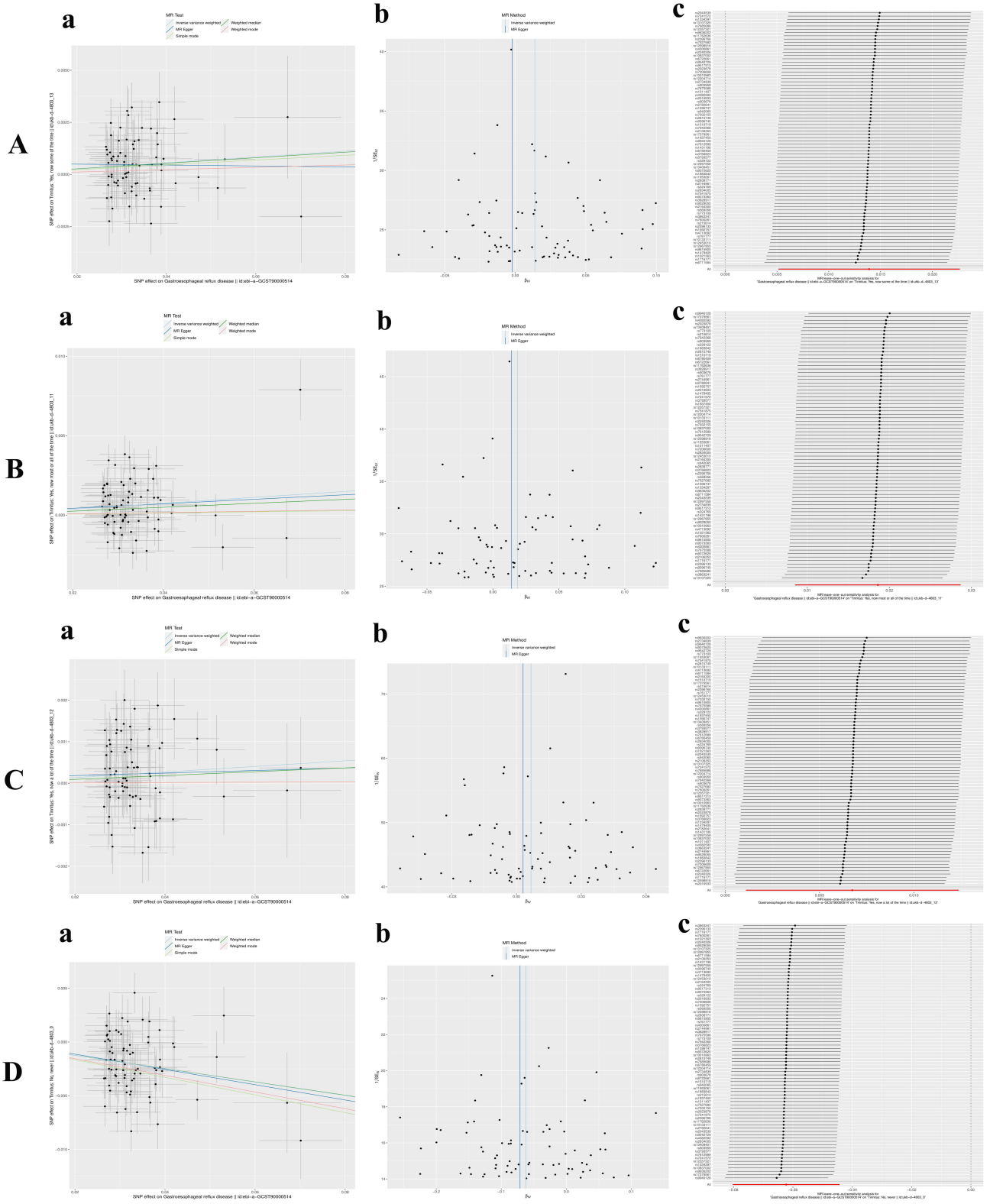

Figure 4 Gastroesophageal reflux disease and tinnitus (**A**) Yes, now some of the time, (a) Scatter diagram; (b) Funnel plot; (c) Leave-one-out method; (**B**) Yes, now most or all the times, (a).Scatter diagram; (b) Funnel plot; (c) Leave-one-out method; (**C**) Yes, now a lot of time, (a).Scatter diagram; (b) Funnel plot; (c) Leave-one-out method; (**D**) No, Never, (a).Scatter diagram; (b) Funnel plot; (c) Leave-one-out method.

and tinnitus. BE was not found to influence the occurrence of ear disorders. Given the potential impact of GERD on the development of ear disorders, the research offers insights into reducing the risk of ear disorder recurrence by emphasizing the monitoring and improvement of esophageal conditions in patients.

The findings indicate that genetically predicted GERD may serve as a potential risk factor for Ménière's disease, sensorineural hearing loss, vestibular dysfunction, constant tinnitus, tinnitus most of the time, and occasional tinnitus, but it does not appear to be a risk factor for otitis media. Poelmans et al proposed that GERD contributes to nasopharyngitis, which subsequently results in chronic otitis media, and it was observed in their study that patients with otitis media responded favorably to anti-GERD treatment.[6] Recent research indicates that gastric acid reflux disrupts the homeostasis of both the middle and inner ear via the Eustachian tube, promoting the development of various ear disorders.[26] Furthermore, elevated levels of pepsinogen and *Helicobacter pylori* in the middle ear fluid of patients with ear disorders, along with multiple studies detecting pepsin in such patients, further substantiate the role of gastroesophageal reflux in the pathogenesis of otological disorders.[27]

Tinnitus is most commonly linked to cochlear dysfunction. Acid reflux within the Eustachian tube associated with GERD may damage the round window membrane, which serves as a critical interface between the middle and inner ear, thus impairing cochlear function. Research reveals that the risk of tinnitus in GERD patients is 6.65 times higher than in non-GERD individuals.[28] A large prospective study of women indicated that a higher frequency and duration of GERD symptoms were independently associated with an elevated risk of sensorineural hearing loss.[29] Gastric exposure to the middle ear may cause Eustachian tube dysfunction, impede mucociliary clearance, and lead to sensorineural hearing loss. Alternatively, the exposure of the round window membrane to gastric contents may increase its permeability, similar to the effects seen in middle ear infections, making the inner ear more vulnerable to damage.[30] A statistically significant association between vestibular dysfunction and GERD was identified in several studies.[8] Gastroesophageal reflux substances, such as gastric acid and pepsin, can ascend through the Eustachian tube, directly affecting bone structures and resulting in ossicular dysfunction and peripheral vertigo. Additionally, *H. pylori* can ascend through the esophagus and upper respiratory tract due to gastroesophageal reflux, potentially contributing to tympanosclerosis and ossicular dysfunction.

BE did not demonstrate any causal relationships with the five ear disorders evaluated in this study. Given that BE presents with lower reflux and heartburn characteristics compared to GERD, patients with BE are not significantly impacted by GERD-related gastric acid reflux on ear disorders. Moreover, the esophageal mucosa and its columnar epithelial metaplasia are adaptive responses to gastric content stimulation, mitigating the irritating effects of gastric acid. Additionally, the GWAS sample size for the BE phenotype is relatively small, necessitating further studies with larger populations to assess the potential impact of BE on the development of ear disorders. In conclusion, the findings indicate that BE does not exert a causal influence on the onset of ear disorders.

Understanding the potential link between GERD and ear disorders through this MR study may assist in reducing the likelihood of ear disorder development and facilitate early prevention and screening by addressing GERD. This discovery holds profound significance for clinical research on GERD: 1. Traditionally, GERD is mainly associated with esophageal and respiratory symptoms. This study strongly suggests that GERD may be a potential trigger or aggravating factor for some ear diseases (especially recurrent or refractory otitis media, sensorineural hearing loss). This requires clinicians to actively inquire about GERD-related symptoms (heartburn, acid reflux, chronic cough, clearing the throat), and even be vigilant in patients without typical digestive tract complaints. Early identification and intervention of potential GERD may interrupt the pathogenic chain, prevent the progression of ear damage, and improve long-term hearing prognosis. 2. For patients with GERD and concurrent ear diseases, the significance of strengthening anti-reflux treatment (such as the regular use of proton pump inhibitors and strict lifestyle management) goes beyond relieving digestive tract discomfort. Effective control of GERD targeting the cause may directly become a key link in the comprehensive treatment of ear diseases, especially for patients with suboptimal responses to conventional otological treatment. This avoids "treating the symptoms rather than the root cause" and promotes the establishment of individualized treatment plans between gastroenterology and otolaryngology departments, ultimately enhancing the overall treatment effect and quality of life of patients. 3. This causal relationship reveals the extensive pathological impact of GERD - reflux substances not only damage the proximal esophagus, throat, and airways, but their effects may indirectly affect the middle ear and inner ear through the eustachian tube or systemic inflammatory responses. This deepens the understanding of the systemic harm of GERD and emphasizes the necessity of

managing it as a systemic disease. At the same time, the research results suggest that actively controlling GERD not only prevents serious complications such as Barrett's esophagus but may also reduce the risk of certain ear diseases, injecting stronger preventive medical connotations into the long-term management of GERD.

Several limitations in the study should be carefully considered. (1) Although a negative correlation between BE and ear disorders was identified in the study, it was not possible to confirm whether BE impacts the function of the lower esophageal sphincter or is linked to congenital genetic abnormalities. (2) The GWAS summary datasets used in this study were restricted to individuals of European ancestry, and the possibility of residual confounding from other variables cannot be entirely excluded. However, multiple cross-ethnic evidence supports that this association may have a broader biological basis and potential universality. The core pathophysiological mechanism of GERD - the reflux of gastric contents causing mucosal damage and neuroinflammatory responses - is a biological process that is common across populations and is not limited by race; the theoretical model that reflux substances reverse through the eustachian tube or trigger a vagus nerve-mediated inflammatory cascade reaction affects the middle ear and inner ear has been confirmed in clinical observations and anatomical studies in different geographical populations. Secondly, although genetic instrumental variables (IVs) have population heterogeneity, localized genetic risk scores constructed using GWAS resources from non-European populations have preliminarily verified the positive association between GERD and ear phenotypes. Although clinical studies from Latin America and Africa are limited by sample size, they reported similar reflux-related ear complication patterns, such as the symptom improvement rate (about 50–60%) of patients with refractory otitis media after intensified anti-reflux treatment, which is similar to that reported in Europe and America, indirectly supporting the commonality of the pathological mechanism. The existing data indicate that the potential harm of GERD to ear health may be a shared pathological process across populations, and its biological rationality and initial cross-ethnic verification provide a scientific basis for exploring strategies to prevent ear complications through anti-reflux treatment globally. (3) Due to the overlap between patients with BE and GERD, there is a lack of sufficiently stratified GWAS data for further subgroup analysis. Additionally, misdiagnosis between non-erosive reflux disease and ear disorders could potentially contribute to these findings.

In conclusion, the MR analysis indicates that GERD may elevate the risk of Ménière's disease, sensorineural hearing loss, vestibular dysfunction, and tinnitus. BE does not appear to have a causal relationship with ear disorders. This association may be anatomically linked to the repeated stimulation of the middle or inner ear by GERD via the Eustachian tube. These findings could offer valuable insights for the prevention of Ménière's disease, sensorineural hearing loss, vestibular dysfunction, and tinnitus. However, since the conclusions are based on MR, which is an innovative genetic approach, further studies with larger multicenter sample sizes are necessary to confirm and strengthen these causal estimates.

Abbreviations

MR, Mendelian randomization; GERD, gastroesophageal reflux disease; BE, Barrett's esophagus; SNP, single nucleotide polymorphism; IVW, inverse variance weighted.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study utilizes data obtained from publicly available online literature. As such, it does not require ethical approval and has been granted an exemption by the Ethics Committee of Hebei Provincial Hospital of Chinese Medicine.

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Disclosure

The authors declare that they have no competing interests.

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