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Original Research

Gastroesophageal reflux disease increases the risk of essential hypertension: results from the Nationwide Readmission Database and Mendelian randomization analysis

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Abstract

Background: The link between gastroesophageal reflux disease (GERD) and essential hypertension (EH) and its causal nature remains controversial. Our study examined the connection between GERD and the risk of hypertension and assessed further whether this correlation has a causal relationship.
Methods: First, we utilized the National Readmission Database including 14 422 183 participants to conduct an observational study. Dividing the population into GERD and non-GERD groups, we investigated the correlation between GERD and EH using multivariate logistic regression. Next, bidirectional two-sample Mendelian randomization was adopted. The summary statistics for GERD were obtained from a published genome-wide association study including 78 707 cases and 288 734 controls. We collected summary statistics for hypertension containing 70 651 cases and 223 663 controls from the FinnGen consortium. We assessed causality primarily by the inverse-variance weighted method with validation by four other Mendelian randomization approaches as well as an array of sensitivity analyses.
Results: In the unadjusted model, GERD patients had a higher risk of EH than the non-GERD group, regardless of gender (odds ratio, 1.43; 95% confidence interval: 1.42–1.43; $P < .001$). Further adjusting for critical confounders did not change this association. For Mendelian randomization, we found that genetically predicted GERD was causally linked to an enhanced risk of EH in inverse-variance weighted technique (odds ratio, 1.52; 95% confidence interval: 1.39–1.67; $P = 3.51 \times 10^{-18}$); conversely, EH did not raise the risk of GERD causally.
Conclusions: GERD is a causal risk factor for EH. Further research is required to probe the mechanism underlying this causal connection.

What is already known on this topic

- GERD can increase the risk of hypertension and increase with worsening disease severity. The association between GERD and EH and whether the link is genetically determined are still controversial.

What this study adds

- Our study revealed that GERD is an upstream causal risk factor for EH.

How this study might affect research, practice, or policy

- Preventing GERD may serve as a prevention policy for EH.

Keywords: gastroesophageal reflux disease; essential hypertension; national readmission database; Mendelian randomization

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Introduction

Gastroesophageal reflux disease (GERD) is one of the most widespread chronic inflammatory gastrointestinal disorders marked by acid reflux and heartburn, which can greatly impact the quality of life and improve health care expenses due to its long-term course [1]. According to a meta-analysis, it affects ~13% of people worldwide [2]. In recent years, the potential play of GERD in the progression of essential hypertension (EH) has attracted the interest of researchers [3–6]. A growing set of observational research has demonstrated that GERD can increase the risk of EH and increase with worsening disease severity [7, 8].

Nevertheless, to date, the findings derived from epidemiological studies are not entirely coherent concerning the contribution of GERD to the development of EH. For instance, one observational study stated that gastroesophageal reflux symptoms may lower the risk of the occurrence of EH [9]. In contrast, another large-scale cohort study of 29 688 GERD patients and 29 597 controls in Taiwan showed no significant discrepancy in the occurrence of hypertension between the GERD patient group and the control group [10]. Otherwise, there are still several reports that failed to detect the link between GERD and EH [11–13]. The inconsistency of these findings may be attributed to inherent limitations in observational studies, including diverse diagnostic approaches to GERD (e.g. gastroscopic presentation, reflux monitoring, or questionnaires), inadequate adjustments for confounders, population heterogeneity, short follow-up periods, etc. Hence a duplication of their results in wider study samples is desired. Besides, estimates from observational studies can readily reverse causality. Consequently, whether GERD is a cause of EH or a downstream effect merits further exploration.

Mendelian randomization (MR), an emerging epidemiological approach, considers genetic variants as instrumental variables (IVs) for exposure to estimate the causal role of the exposure on the outcome [14]. As genetic variables are assigned at random during the meiosis and fertilization process and are established far ahead of disease onset, the MR approach maximizes overcoming unmeasured confounding as well as reverse causality [15]. Currently, the most widespread type of MR study is the two-sample MR (TSMR), which relies on summary statistical data obtained from two nonoverlapping genome-wide association studies (GWAS) with optimal statistical power [16]. Meanwhile, the bidirectional MR analysis is a novel extension of the basic MR analysis to sort out the temporal order of occurrence of two related variables. In this approach, MR analysis is initially conducted in the forward direction (i.e. “exposure” to “outcome”) and subsequently in the reverse direction (i.e. “outcome” to “exposure”) [16]. The bidirectional model can be coupled with the TSMR method to generate an eloquent way to explore causal associations [17].

The present study aimed to incorporate a large-scale observational analysis (including a sex-stratified study) and a bidirectional TSMR analysis to discover the correlation between GERD and EH and to examine the causal properties of potential links. First, we utilized the National Readmission Database (NRD) to explore the association between GERD and the risk of hypertension. Second, publicly available GWAS summary data were employed to explore whether the connection between GERD and hypertension was causal and the direction of the causal relationship.

Materials and methods

Study design

At first, we implemented an observational study of baseline data from the NRD 2018 involving 14 422 183 participants to examine the independent linkage between GERD and EH. Then, a bidirectional TSMR analysis was performed utilizing GWAS summary statistics to examine the biennial causal relationship between them. Forward MR analysis treated GERD as the exposure and EH as the outcome, whereas reverse MR regarded EH as the exposure and GERD as the outcome (Supplementary Fig. 1). This paper was written taking into account the STROBE and STROBE-MR guidelines of the observational and MR study.

Study population in National Readmission Database

We used the 2018 NRD for our observational study (https://www.hcup-us.ahrq.gov/nrdoverview.jsp). The database is the largest publicly available readmission database in the USA from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP). The NRD 2018 includes patient and hospital-level discharge data collected from 28 geographically scattered US states, covering nearly 60% of the total US resident population. In the NRD, there are up to 40 discharge diagnoses and 25 procedures captured for each patient utilizing the International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS). We followed the checklist that has been recommended by HCUP for working with the NRD.

The patients were determined for inclusion using the ICD-10 procedure codes. The ICD-10-CM code for patients with GERD is K21, while the ICD-10-CM code for EH is I10. Covariate diagnosis information regarding ICD-10-CM codes for alcohol consumption, smoking, obesity, and hyperlipidemia are shown in Supplementary Table 1. We ultimately selected 14 422 183 participants for the analysis of the correlation between GERD and EH following the exclusion of 1 241 749 participants under age 18, and 2 022 579 pregnant participants from the 2018 NRD according to the relevant studies. Inclusion and exclusion criteria details as well as the ICD-10 diagnosis codes used are provided in Supplementary Fig. 2 and Supplementary Table 1, respectively.

Statistical analyses of the observational study

For the observational study, participants’ characteristics were presented as median (interquartile range; for nonnormally distributed data) or percentage (for categorical variables), respectively, in the entire study population. We performed multivariate logistic regression to compute odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) to check the correlation between GERD and the risk of EH. Adjustments to variables in the logistic regression were conducted to manage confounders and alleviate their influence in the assessment of the association between GERD and EH. Four models were conducted: Model 1 was unadjusted; Model 2 was adjusted for age, the base variable; Model 3 was further adjusted for smoking and alcohol consumption status; and Model 4 was additionally adjusted for obesity, diabetes, and hyperlipidemia. Based on the previously observed gender gap in GERD prevalence, this study examined subgroup analysis among participants according to their sex [2]. SPSS 26.0

Table 1. Data sources used in MR analysis.

Trait	Phenotype definition	Sample size	PubMed ID or web-link	Studies involved	Adjustments in the GWAS
GERD	Cases inferred by self-reporting GERD symptoms, use of GERD medication, and ICD-10 codes	Total: 367 441 Cases: 78 707 Controls: 288 734	31 527 586	UK Biobank, QSKIN	Recruitment age, genetic sex, the first 10 principal components, and cryptic relatedness
EH	Cases inferred through ICD-10/9/8 codes	Total: 294 314 Cases: 70 651 Controls: 223 663	FinnGen consortium (https://www.finngen.fi/fi)	FinnGen	Age, sex, 10 genetic principal components, and genotyping batch

software was applied in our study to perform the statistical analysis. All hypothesis tests were two-sided at a level of significance of $P < .05$.

Data sources for Mendelian randomization analyses

The largest GWAS summary statistics for GERD were obtained from the UK Biobank and Australian QSKIN cohorts containing 71 522 GERD cases and 261 079 controls derived from European descendants [18]. These two cohorts were both based on European populations and the participants were primarily middle-aged. Additionally, all cases with GERD were defined by self-reported, ICD9 and 10, office of population census and treatment/drug in the UK Biobank study (68 535 cases and 250 910 controls), and medical records of self-reported heartburn and reflux medications in the QSKIN and Health Study (2987 cases and 10 169 controls).

Summary GWAS data for EH were drawn from the FinnGen Consortium, an undergoing queue study initiated in 2017 to collect and analyze genomic and health data from half a million Finnish participants. Further information on participants, gene platforms, and statistical analysis agreements is available on the FinnGen website: https://www.finngen.fi/fi. We utilized the seventh version of this consortium's genome-wide association results (released 01 June 2022) for our current study, in which data for EH included 70 651 cases (defined by ICD-8 codes 401-404, ICD-9 codes 4039A or 4019X, and ICD-10 codes I10) and 223 663 controls (Table 1).

Selection of instrumental variables

IVs in MR studies have to satisfy the three core assumptions to sustain the effectiveness of the study: (i) relevance assumption, i.e. the genetic variants employed to assess causality ought to be strongly correlated with the exposure, (ii) independence assumption, i.e. the applied genetic variables were free from underlying confounding factors, and (iii) exclusion-restriction assumption, i.e. IVs affect the outcome only through the exposure but are not directly connected to the outcome. The filtering process of our IVs was conducted as follows: First, we chose a single nucleotide polymorphisms (SNPs) strongly related to the exposure with P values reaching genome-wide significance ($P < 5 \times 10^{-8}$). Second, as linkage disequilibrium (LD) may lead to biased findings, we set the parameter r^2 threshold of 0.001 and kilobase pair (kb) of 10 000 to exclude the interference of LD by reference to the European 1000 Genome Project. Third, we did not use proxy SNPs because a narrow set of missing IVs had a marginal impact on the results. Fourth, we eliminated SNPs that were robustly linked to both the exposure and the outcome ($P < 5 \times 10^{-8}$) to alleviate potential pleiotropy [19]. Fifth, we removed SNPs containing A/T or G/C alleles, which were labeled as palindromic SNPs and might cause ambiguity [20]. Finally, effects were harmonized to ensure that the identical SNPs corresponded to the same effect alleles in both the exposure and outcome datasets. After these stringent selections, 65 SNPs for GERD and 33 SNPs for hypertension were chosen for subsequent analyses, details of which are shown in Supplementary Tables 2 and 3.

To ascertain the efficacy of our MR results, we utilized the online calculator to compute the statistical capacity in the IVW analysis (https://sb452.shinyapps.io/power/) [21]. The strength of instrumental variants was measured by the application of the F-statistic which was calculated to avoid weak instrumental bias [22, 23]. The following equation was applied to obtain the F-statistic: $F = [R^2/(1\text{-}R^2)] * [(N\text{-}K\text{-}1)/K]$; R^2 represents the variance of the exposure explained by the IVs: $R^2 = (\text{beta.exposure}^2)/(\text{se.exposure}^2 * N + \text{beta.exposure}^2)$, N represents the sample size in the selected GWAS, and K represents the number of SNPs eventually utilized. If the F-statistic is substantially greater than 10, the probability of weak IV bias is slim.

Statistical analyses of the Mendelian randomization study

In this study, we applied the inverse-variance weighted (IVW) technique as the main causal effect estimation approach [24]. This method is a relatively ideal state estimation, a valid analysis assuming the basic premise that all genetic variables are valid, which provides a robust power to detect causality. The Wald ratio used to evaluate the causal effect of each IV was computed as the Beta ratio of the correspondent SNP in the outcome dataset over the Beta of the identical SNP in the exposure dataset. IVW analysis was conducted in a meta-analysis of each Wald rate to give an estimation of the global causal effect of the exposure on the outcome. Given that both the exposure and the outcome in this present study were dualistic, the association evaluations between them were stated as ORs with the corresponding 95% CIs. Then, four alternative univariate MR methods were adopted for sensitivity analyses to test the reliability and robustness of the results, i.e. MR-Egger regression, weighted median (WME) method, simple mode, and weighted mode. MR-Egger can provide

estimates following correction for horizontal pleiotropy; however, this approach may lower the statistical power [25]. When valid IVs are >50%, the WME can be used to deliver robust causal estimates [26].

Although this study had excluded known confounding SNPs to the extent possible, there were still multiple unclear confounding factors that can contribute to gene pleiotropy and create bias in the estimation of effect values. Thus, we performed an array of sensitivity analyses to address pleiotropy in causal estimations. We first applied Cochran's Q test to examine the heterogeneity arising from distinct genetic variants. If significant heterogeneity was observed ($P < .05$), a random-effect IVW model was applied, else a fixed-effect IVW model was used [27–29]. Next, we performed the MR-Egger interception trial to check whether any latent horizontal pleiotropy existed [25]. An indicator of horizontal pleiotropy was the intercept drawn from the MR-Egger regression, which proved the existence of directional pleiotropy if its $P < .05$. In addition to it, we evaluated and rectified the horizontal pleiotropy by using the MR-Pleiotropy Residual Sum and Outlier methods (MR-PRESSO). Finally, to visualize the MR analysis results, four diagnostic plots were drawn: (i) Leave-one-out plots employed to infer if the MR causal estimates were powered by a solitary SNP; (ii) funnel plots showing horizontal pleiotropy; (iii) forest plots to display the effect of a single SNP in MR analysis, and lastly; (iv) scatter plots of the results obtained from various MR analysis approaches [25, 30, 31].

The bidirectional TSMR analyses in this paper were performed via the TwoSampleMR (version 0.5.6) R package in R version 4.1.3 based on RStudio-2022.02.0–443. Results with $P < .05$ and statistical power above 80% were statistically significant.

Ethical approval

In our observational study, the NRD is publicly available and de-identified with no personal information so that no ethical research board review is required; Likewise, the GWAS data used in this MR study are openly accessible and no additional ethical approval or informed consent is critical.

Results

Observational results between gastroesophageal reflux disease and hypertension in National Readmission Database

Clinical characteristics are shown in Table 2. A greater incidence of EH was observed in the GERD group than that in the non-GERD group ($P < .001$). Accounting for potential confounding factors related to the occurrence of EH, such as age and obesity, we further examined the relationship between GERD and EH using four multivariate logistic regression models in the current research (Table 3). GERD was an independent risk factor of EH as revealed in multivariate logistic regression analysis. In the unadjusted model (Model 1), GERD patients had a higher risk of occurring EH as opposed to controls, irrespective of gender (OR 1.43; 95% CI: 1.42–1.43, $P < .001$). Further adjusting for potential confounders such as age, smoking, alcohol use, obesity, diabetes, and hyperlipidemia did not change this association. When further stratified by gender, this link was statistically significant in both males and females. It was shown in our observational analysis that GERD could be a risk factor for EH.

Mendelian randomization analyses in evaluating the causal effects of gastroesophageal reflux disease on essential hypertension (forward direction)

In the forward MR analysis conducted to examine the causal effect of GERD on EH, the 65 SNPs enrolled as IVs accounted for an approximate total of 4.6% of the variance, with F statistics >10 for individual SNPs, indicating no potential weak instrumental bias in our conclusions. Our MR analysis results are shown in Table 4 and Fig. 1. IVW results revealed that genetically predicted GERD was positively associated with the risk of developing EH (OR = 1.52; 95% CI: 1.39–1.67, $P = 3.51 \times 10^{-18}$; Table 4). Likewise, similar causal estimates were found in MR Egger (OR = 1.83; 95% CI: 1.02–3.27, $P = 4.66 \times 10^{-2}$), WME (OR = 1.41; 95% CI: 1.28–1.55, $P = 6.02 \times 10^{-12}$), Simple mode (OR = 1.32; 95% CI: 0.26–0.63, $P = 2.86 \times 10^{-2}$), and Weighted mode (OR = 1.31; 95% CI: 0.26–0.63, $P = 2.32 \times 10^{-2}$), supporting the harmful effect of GERD on the risk of hypertension (Table 4). These results are also shown in Fig. 2 as a scatter plot. Concurrently, the forest plot reflected the causal effect of individual SNPs on EH (Supplementary Fig. 3).

In addition, the intercept from the MR-Egger regression analysis failed to reach statistical significance ($P = 0.536 > 0.05$), i.e. there was no horizontal pleiotropy (Supplementary Table 4). The symmetry of the funnel plot indicated a similar finding (Supplementary Fig. 4). Nonetheless, MR-PRESSO detected rs2613505 as an outlier, pointing to significant horizontal pleiotropy in IVs ($P < .001$). After removing this outlier, we reapplied the MR approach to assess the causal relationship between GERD and hypertension with no substantial changes in the results (IVW, OR′ = 1.52; 95% CI′: 1.38–1.67, $P' = 1.52 \times 10^{-17}$). Besides, Cochran's Q test revealed significant heterogeneity ($P < .05$), so the random effects IVW model was used as a sensitivity analysis, with the result still being significantly associated (Supplementary Table 4). Finally, the leave-one-out approach demonstrated that the causal relationship between genetically determined GERD on hypertension was not triggered by an individual SNP, indicating the stability of our MR analysis (Supplementary Fig. 5). In conclusion, our MR analysis results showed that genetically predicted GERD can increase the risk of EH.

Mendelian randomization analyses in evaluating the causal association of genetically determined essential hypertension with GERD (reverse direction)

In the reverse MR analysis investigating the causal effect of hypertension on GERD, 33 SNPs were enrolled as IVs. The results of all MR analysis methods demonstrated no causal connection between genetically predicted hypertension on the risk of GERD (Table 4). Such findings were also exhibited in the forest plot in Fig. 2. In addition, individual and summarized effect estimates were presented in the forest plot (Supplementary Fig. 6).

Furthermore, the leave-one-out method suggested that this causal relationship was not determined by a lone SNP (Supplementary Fig. 7). Additionally, the intercept of the MR-Egger regression analysis did not reach statistical significance ($P = .293 > .05$), i.e. there was no horizontal pleiotropy (Supplementary Table 4). Simultaneous results were indicated by the symmetry of the funnel plot (Supplementary Fig. 8). Meantime, no notable outliers were detected by MR-PRESSO. Nevertheless, Cochran's Q test displayed significant heterogeneity ($P < .05$), hence the random effects IVW model was applied as a sensitivity

Table 2. Characteristics of participants by GERD categories in the NRD 2018.

	GERD (*N* = 3 148 459)	Non-GERD (*N* = 11 273 724)	*P*
Age(years), Median (IQR)	68 (57–78)	64 (50–76)	<.001
Sex			
Male, *n* (%)	1 334 879 (42.4)	5 682 018 (50.4)	<.001
Female, *n* (%)	1 813 580 (57.6)	5 591 706 (49.6)	<.001
Alcohol consumption, *n* (%)	173 444 (5.5)	825 381 (7.3)	<.001
Smoker, *n* (%)	506 572 (16.1)	2 234 356 (19.8)	<.001
EH, *n* (%)	1 370 496 (43.5)	3 946 014 (35)	<.001
Obesity, *n* (%)	738 261 (23.4)	2 022 417 (17.9)	<.001
Diabetes, *n* (%)	1 053 729 (33.5)	3 394 966 (30.1)	<.001
Hyperlipidemia, *n* (%)	1 451 235 (46.1)	3 513 344 (31.2)	<.001

IQR, interquartile range; NRD, Nationwide Readmissions Database.

Table 3. Logistic regression analysis results for the relationship between GERD and the occurrence of EH in study participants (*n* = 14 422 183).

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
All								
Non-GERD	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
GERD	1.43 (1.43–1.44)	<.001	1.33 (1.33–1.34)	<.001	1.34 (1.34–1.34)	<.001	1.26 (1.26–1.27)	<.001
Male								
Non-GERD	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
GERD	1.43 (1.42–1.43)	<.001	1.35 (1.34–1.35)	<.001	1.35 (1.35–1.36)	<.001	1.27 (1.27–1.28)	<.001
Female								
Non-GERD	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
GERD	1.43 (1.42–1.43)	<.001	1.32 (1.32–1.33)	<.001	1.32 (1.32–1.33)	<.001	1.25 (1.25–1.25)	<.001

Model 1: no adjustment; Model 2: adjustment for age; Model 3: adjustment for age, smoker, drinking; Model 4: adjustment for age, smoker, drinking, obesity, diabetes, hyperlipidemia.

Table 4. Bidirectional MR results for the relationship between genetically instrumented GERD and EH.

Exposure	Outcome	SNPs	Methods	OR (95% CI)	*P*
GERD	EH	65	Inverse variance weighted	1.52 (1.39–1.67)	3.51E-18
			MR Egger	1.83 (1.02–3.27)	4.66E-02
			WME	1.41 (1.28–1.55)	6.02E-12
			Simple mode	1.32 (1.04–1.69)	2.86E-02
			Weighted mode	1.31 (1.04–1.64)	2.32E-02
EH	GERD	33	IVW	1.03 (0.97–1.09)	.33
			MR Egger	0.93 (0.76–1.13)	.46
			WME	0.98 (0.93–1.03)	.44
			Simple mode	0.98 (0.9–1.08)	.74
			Weighted mode	0.98 (0.92–1.05)	.66

SNP, single-nucleotide polymorphism; $P < .05$ was considered significant.

analysis which remained not significantly associated with the results (Supplementary Table 4). In summary, our data indicated the absence of causality regarding hypertension on the risk of GERD.

Discussion

In the present study, we united an observational study with a bidirectional TSMR study to investigate the correlation between GERD and EH. At first, we identified that GERD was positively linked to the risk of hypertension following control for a host of potential confounders in a cross-sectional study of 2018 NRD baseline data. Simultaneously, gender-stratified analyses yielded consistent results. And then, our bidirectional TSMR findings revealed that genetically predicted GERD was causally linked to an elevated risk of EH; in contrast, hypertension was not causally correlated with a higher risk of GERD.

The results obtained from our cross-sectional study are generally consistent with previous statements on the risk of GERD and hypertension [3–5, 32–34]. For instance, Li et al. found in research involving 86 Chinese participants with EH that the rate of high blood pressure episodes and average nocturnal blood pressure were both significantly higher in the GERD group than that in the control group. They also discovered a statistically significant drop in blood pressure in GERD patients after 14 days of antacid treatment compared to pretreatment [8]. The primary disadvantages of their study were the comparatively modest sample size and confined follow-up time, which enabled a limited capacity to observe associations. In addition, a prior study found that plasma nitric oxide-metabolite levels elevated markedly following

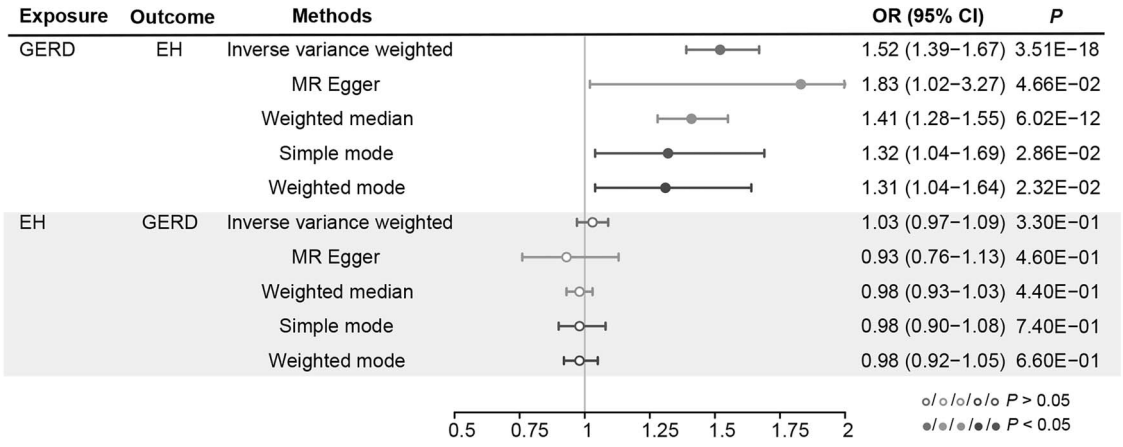

Figure 1 Forest plot showing bidirectional TSMR analysis results to estimate the causal association between GERD and EH; results above gray shading represent forward MR analysis (i.e. treating GERD as exposure and EH as outcome), while gray shading denotes reverse MR analysis (i.e. treating EH as exposure and GERD as outcome); circles and horizontal bars represent the ORs and CIs, respectively.

inhibition of gastric acid production for 8 weeks, which could contribute to the overall blood pressure management enhancement; nevertheless, this needed more accurate evidence [35]. Similarly, a cross-sectional study of 28 949 subjects found that the prevalence of hypertension in GERD participants was greater versus non-GERD participants [36] . Nevertheless, another observational study involving 52 GERD patients and 465 control patients concluded the opposite: GERD was probably a protective factor for hypertension [37]. These inconsistent findings were likely driven by sample size constraints and the inherent confounders and back-causality in conventional observational analyses. Consequently, the role of GERD on the risk of occurrence of hypertension needed to be validated by further MR analyses. Several MR analyses were performed in this study and all generated consistent findings that GERD can elevate the risk of EH.

The potential mechanisms underlying that GERD increases the risk of hypertension are still obscure, so we can only make reasonable speculations based on some of the currently available evidence in the literature. First, GERD is a long-term inflammatory disease in which acid reflux from the inferior esophagus triggers the secretion of multiple proinflammatory cytokines, including IL-8, IL-6, IL-1β, Nuclear Factor-Kappa B (NF-κB), and Tumor Necrosis Factor-Alpha (TNF-α) [38–40]. EH, similar to GERD, is a slow inflammatory process under which a number of the same proinflammatory cytokines are raised in the circulating blood of patients with hypertension [41–44]. Such intermediates can facilitate oxidative impairment and endothelial disorders, which in turn lead to vessel remodeling, tubular narrowness, fibrosis, and stiffness, resulting in increased systemic vascular resistance [41–43]. In addition, since our esophagus borders the heart, propagation of the regional inflammation via the esophageal wall may also result in local atrial myocarditis, which will consequently cause hypertension [44].

Second, sympathetic hyperfunction is a key mechanism that leads to hypertension [45]. GERD is a gastrointestinal dysfunctional disease, behind which lies sympathetic nerve dysfunction [46]. The refluxed gastric fluid and food will cause esophageal spasm, which then stimulates the nerves in the esophagus, and the nerves in the esophagus will reflect the irritation to the sympathetic and coronary nerves, resulting in cardiovascular spasms and generating hypertensive symptoms [40, 47]. In addition, GERD may lead to chest pain, which subsequently provokes reflex sympathetic nerve activity, and then increases peripheral vascular resistance, the abnormal release of renin and catecholamines, and eventually elevates blood pressure [48, 49]. At last, a novel mechanism proposed by Dean et al. may alternatively explain the causal association between GERD and the risk of developing hypertension. It is hypothesized that cardiopulmonary and digestive reflexes are simultaneously activated by identical stimuli under the modulation of caudal solitary complex neurons, of which most prominently are hypercapnic acidosis and orexin [50].

This study possesses the following strengths: First, the study includes a large sample size with strong statistical efficacy, so that our results are generalizable and representative. Second, we integrated an observational study and MR analysis to intensively probe the link between GERD and hypertension, which led to fairly coherent conclusions. Compared with results only determined by MR analysis or a cross-sectional study, our findings are more comprehensive, reliable, and credible. Third, the GWAS data for the exposure and the outcome included in our MR analysis were from individuals of European ancestry, rendering the study results unlikely to be affected by population stratification or ethnic bias. Fourth, a variety of MR statistical methods and sensitivity analyses were applied in this study, all of which generated relatively unanimous conclusions, ensuring the rigorousness and high level of causal inference of this study.

Nevertheless, there are still several limitations in our study. First, MR analysis offers valuable perspectives on causal connections but does not delve into or elucidate the underlying biological mechanisms. Second, we selected GWAS summary statistics for GERD and EH from European descendants to mitigate issues related to heterogeneity. However, genetic associations may exhibit disparities among the populations in both the exposure and outcome GWASs, potentially influenced by population stratification. Third, it is crucial to acknowledge that our MR study focused on individuals of European descent, whereas the observational research was rooted in American populations, potentially diminishing the generalizability of our findings. Fourth, our capacity to perform further stratified analyses based on different stages or subtypes of GERD was constrained due to limitations in the available GWAS summary statistics for the MR study. Fifth, it is important to note that genetic factors explain only a portion of the variability in GERD and EH. Other sources of variation likely stem from pathways unaffected by genetic factors. Sixth, despite the ample size of our GERD dataset, we must acknowledge the potential for missing weak associations, especially when dealing with exposures constructed from a limited number of SNPs with minimal phenotypic variance. Finally, the absence of data on

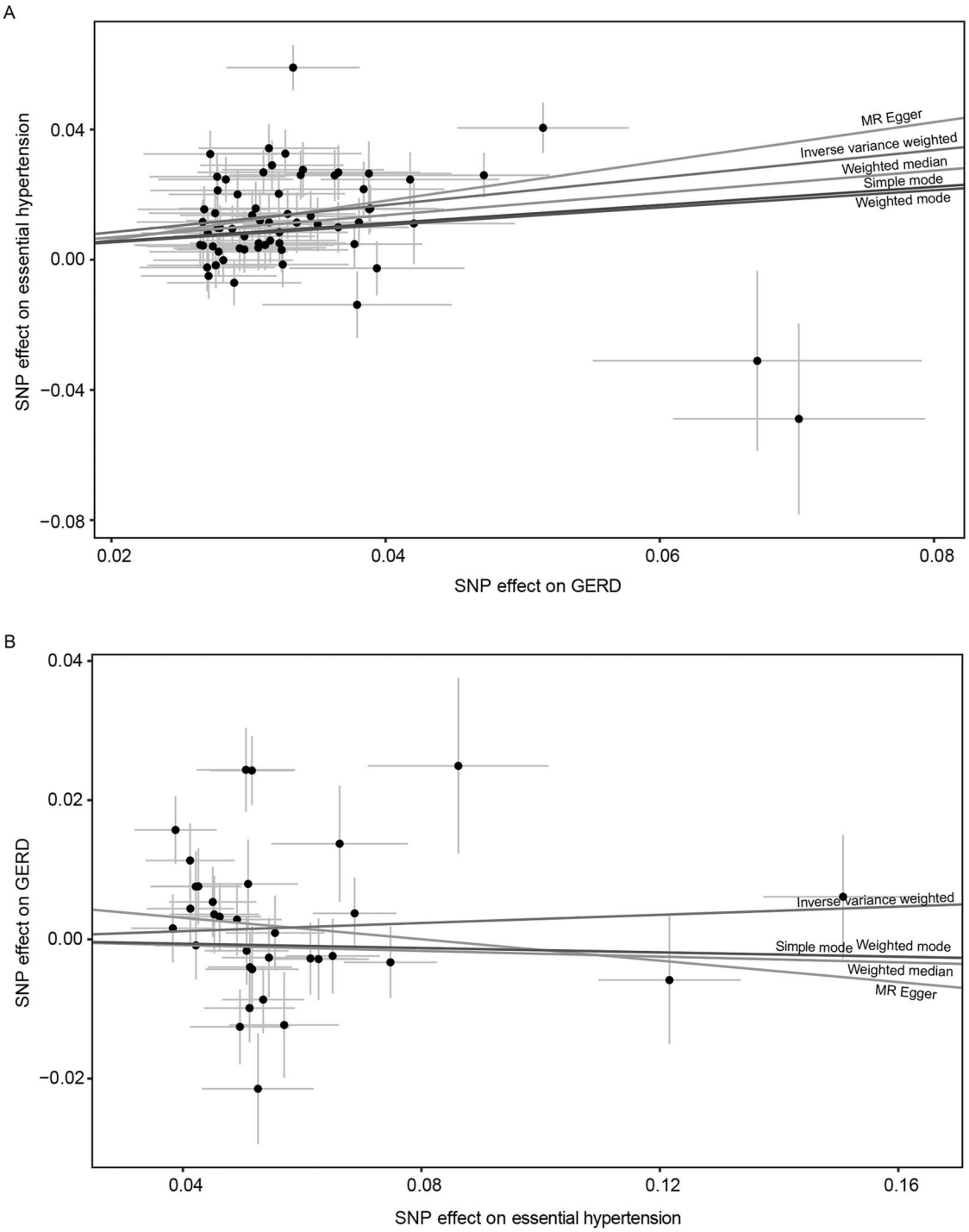

Figure 2 Scatter plots of MR analyses using two models to investigate causal relationships between GERD and EH; (A) scatter plot of the forward model showing the associations of the SNP effects on the GERD (log OR) against the SNP effects on the EH (log hazard ratio); (B) scatter plot of the reverse model showing the associations of the SNP effects on the EH (log OR) against the SNP effects on the GERD (log hazard ratio); the slope of each line indicates the causal relationship of each method; the dots denote the SNPs utilized in the present analysis, and the bars represent the 95% CIs. SNP, single-nucleotide polymorphism;

potential confounding variables, such as the use of nonsteroidal antiinflammatory drug or aspirin use, in the NRD may introduce bias into our work.

Conclusion

Our large-scale observational study found that GERD may be a risk factor for EH. MR analysis further showed that this association is genetically determined. These findings recommended that, in clinical practice, early screening, diagnosis, and primary prevention of EH may be imperative in GERD patients. Physicians ought to seek signs of hypertension in GERD patients as well. In addition, further studies are inevitable to illustrate the molecular pathways involved in the effects of GERD on hypertension to develop new antihypertensive strategies.

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Supplementary data

Supplementary data is available at *POSTMJ Journal* online.

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Authors' contributions

X.F., D.Z., and L.G. have given substantial contributions to the conception of the manuscript, C.Z., Z.Y., Y.Z., X.F., and D.Z. to acquisition, formal analysis and interpretation of the data. Z.Y., C.Z., D.Z., and L.G. wrote the manuscript. All authors read and approved the final version of the manuscript.

References

1. Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal reflux disease: a review. *JAMA* 2020;**324**:2536–47. https://doi.org/10.1001/jama.2020.21360 [published Online First: 2020/12/23].
2. Eusebi LH, Ratnakumaran R, Yuan Y. *et al.* Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. *Gut* 2018;**67**:430–40. https://doi.org/10.1136/gutjnl-2016-313589 [published Online First: 2017/02/25].
3. Eisa M, Sandhu A, Prakash R. *et al.* The risk of acute myocardial infarction in patients with gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2020;**26**:471–6. https://doi.org/10.5056/jnm19192 [published Online First: 2020/09/30].
4. Wang R, Wang J, Hu S. Study on the relationship of depression, anxiety, lifestyle and eating habits with the severity of reflux esophagitis. *BMC Gastroenterol* 2021;**21**:127. https://doi.org/10.1186/s12876-021-01717-5 [published Online First: 2021/03/22].
5. Lei WY, Wang JH, Wen SH. *et al.* Risk of acute myocardial infarction in patients with gastroesophageal reflux disease: a nationwide population-based study. *PLoS One* 2017;**12**:e0173899. https://doi.org/10.1371/journal.pone.0173899 [published Online First: 2017/03/21].
6. Song JH, Kim YS, Choi SY. *et al.* Association between gastroesophageal reflux disease and coronary atherosclerosis. *PLoS One* 2022;**17**:e0267053. https://doi.org/10.1371/journal.pone.0267053 [published Online First: 2022/05/21].
7. Almalki ZS, AlOmari BA, Alshammari T. *et al.* Uncontrolled blood pressure among hypertensive adults with rheumatoid arthritis in Saudi Arabia: a cross-sectional study. *Medicine (Baltimore)* 2022;**101**:e28763. https://doi.org/10.1097/MD.0000000000028763 [published Online First: 2022/01/29].
8. Li ZT, Ji F, Han XW. *et al.* The role of gastroesophageal reflux in provoking high blood pressure episodes in patients with hypertension. *J Clin Gastroenterol* 2018;**52**:685–90. https://doi.org/10.1097/MCG.0000000000000933 [published Online First: 2017/09/30].
9. Murray LJ, McCarron P, McCorry RB. *et al.* Inverse association between gastroesophageal reflux and blood pressure: results of a large community based study. *BMC Gastroenterol* 2008;**8**:10. https://doi.org/10.1186/1471-230X-8-10 [published Online First: 2008/04/17].
10. Huang CC, Chan WL, Luo JC. *et al.* Gastroesophageal reflux disease and atrial fibrillation: a nationwide population-based study. *PLoS One* 2012;**7**:e47575. https://doi.org/10.1371/journal.pone.0047575 [published Online First: 2012/10/19].
11. Lin YH, Tsai CL, Chien LN. *et al.* Newly diagnosed gastroesophageal reflux disease increased the risk of acute exacerbation of chronic obstructive pulmonary disease during the first year following diagnosis–a nationwide population-based cohort study. *Int J Clin Pract* 2015;**69**:350–7. https://doi.org/10.1111/ijcp.12501 [published Online First: 2014/11/02].
12. Min YW, Song BG, Kim HS. *et al.* Associations between reflux esophagitis and the progression of coronary artery calcification: a cohort study. *PLoS One* 2017;**12**:e0184996. https://doi.org/10.1371/journal.pone.0184996 [published Online First: 2017/10/06].
13. Bunch TJ, Packer DL, Jahangir A. *et al.* Long-term risk of atrial fibrillation with symptomatic gastroesophageal reflux disease and esophagitis. *Am J Cardiol* 2008;**102**:1207–11. https://doi.org/10.1016/j.amjcard.2008.06.048 [published Online First: 2008/10/23].
14. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. *JAMA* 2017;**318**:1925–6. https://doi.org/10.1001/jama.2017.17219 [published Online First: 2017/11/23].
15. Lawlor DA, Harbord RM, Sterne JA. *et al.* Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med* 2008;**27**:1133–63. https://doi.org/10.1002/sim.3034 [published Online First: 2007/09/22].
16. Zheng J, Baird D, Borges MC. *et al.* Recent developments in Mendelian randomization studies. *Curr Epidemiol Rep* 2017;**4**:330–45. https://doi.org/10.1007/s40471-017-0128-6 [published Online First: 2017/12/12].
17. Evans DM, Davey SG. Mendelian randomization: new applications in the coming age of hypothesis-free causality. *Annu Rev Genomics Hum Genet* 2015;**16**:327–50. https://doi.org/10.1146/annurev-genom-090314-050016 [published Online First: 2015/05/06].
18. Ong JS, An J, Han X. *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* 2022;**71**:1053–61. https://doi.org/10.1136/gutjnl-2020-323906 [published Online First: 2021/07/01].
19. Kamat MA, Blackshaw JA, Young R. *et al.* PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics* 2019;**35**:4851–3. https://doi.org/10.1093/bioinformatics/btz469 [published Online First: 2019/06/25].

20. Hemani G, Zheng J, Elsworth B. *et al.* The MR-Base platform supports systematic causal inference across the human phenome. *elife* 2018;**7**:e34408. https://doi.org/10.7554/eLife.34408 [published Online First: 2018/05/31].
21. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol* 2013;**42**:1497–501. https://doi.org/10.1093/ije/dyt179 [published Online First: 2013/10/26].
22. Burgess S, Thompson SG, Collaboration CCG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol* 2011;**40**:755–64. https://doi.org/10.1093/ije/dyr036 [published Online First: 2011/03/19].
23. Bowden J, Del Greco MF, Minelli C. *et al.* Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: the role of the I2 statistic. *Int J Epidemiol* 2016;**45**:1961–74. https://doi.org/10.1093/ije/dyw220 [published Online First: 2016/09/13].
24. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol* 2013;**37**:658–65. https://doi.org/10.1002/gepi.21758 [published Online First: 2013/10/12].
25. 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. https://doi.org/10.1093/ije/dyv080 [published Online First: 2015/06/08].
26. Bowden J, Davey Smith G, Haycock PC. *et al.* Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol* 2016;**40**:304–14. https://doi.org/10.1002/gepi.21965 [published Online First: 2016/04/12].
27. Shi Q, Wang Q, Wang Z. *et al.* Systemic inflammatory regulators and proliferative diabetic retinopathy: a bidirectional Mendelian randomization study. *Front Immunol* 2023;**14**:1088778. https://doi.org/10.3389/fimmu.2023.1088778 [published Online First: 2023/02/28].
28. Zhao H, Han X, Zhang X. *et al.* Dissecting causal associations of diet-derived circulating antioxidants with six major mental disorders: a Mendelian randomization study. *Antioxidants (Basel)* 2023;**12**:162. https://doi.org/10.3390/antiox12010162 [published Online First: 2023/01/22].
29. Ma XY, Liu HM, Lv WQ. *et al.* A bi-directional Mendelian randomization study of the sarcopenia-related traits and osteoporosis. *Aging (Albany NY)* 2022;**14**:5681–98. https://doi.org/10.18632/aging.204145 [published Online First: 2022/07/03].
30. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol* 2017;**46**:1985–98. https://doi.org/10.1093/ije/dyx102 [published Online First: 2017/10/19].
31. Gronau QF, Wagenmakers EJ. Limitations of Bayesian leave-one-out cross-validation for model selection. *Comput Brain Behav* 2019;**2**:1–11. https://doi.org/10.1007/s42113-018-0011-7 [published Online First: 2019/03/25].
32. Hsu CK, Lai CC, Wang K. *et al.* Risk of lung cancer in patients with gastro-esophageal reflux disease: a population-based cohort study. *PeerJ* 2016;**4**:e2753. https://doi.org/10.7717/peerj.2753 [published Online First: 2016/12/29].
33. Sheu JJ, Kang JH, Lou HY. *et al.* Reflux esophagitis and the risk of stroke in young adults: a 1-year population-based follow-up study. *Stroke* 2010;**41**:2033–7. https://doi.org/10.1161/STROKEAHA.110.588558 [published Online First: 2010/07/24].
34. Suyu H, Liu Y, Jianyu X. *et al.* Prevalence and predictors of silent gastroesophageal reflux disease in patients with hypertension. *Gastroenterol Res Pract* 2018;**2018**:7242917. https://doi.org/10.1155/2018/7242917 [published Online First: 2018/06/01].
35. Swiatkowski M, Budzynski J, Klopocka M. *et al.* The effect of eight weeks of rabeprazole therapy on nitric oxide plasma level and esophageal pH and motility and motility nitric oxide plasma level in patients with erosive esophagitis. *Med Sci Monit* 2004;**10**:CR46-51 [published Online First: 2004/01/23].
36. Park JH, Park DI, Kim HJ. *et al.* Metabolic syndrome is associated with erosive esophagitis. *World J Gastroenterol* 2008;**14**:5442–7. https://doi.org/10.3748/wjg.14.5442 [published Online First: 2008/09/23].
37. Sarnelli G, Santonicola A, D'Aniello R. *et al.* P.20.15 GERD is a protective risk factor for hypertension. *Digest Liver Dis* 2012;**44**:S219. https://doi.org/10.1016/S1590-8658(12)60623-9.
38. O'Riordan JM, Abdel-latif MM. *et al.* Proinflammatory cytokine and nuclear factor kappa-B expression along the inflammation-metaplasia-dysplasia-adenocarcinoma sequence in the esophagus. *Am J Gastroenterol* 2005;**100**:1257–64. https://doi.org/10.1111/j.1572-0241.2005.41338.x [published Online First: 2005/06/03].
39. Dvorakova K, Payne CM, Ramsey L. *et al.* Increased expression and secretion of interleukin-6 in patients with Barrett's esophagus. *Clin Cancer Res* 2004;**10**:2020–8. https://doi.org/10.1158/1078-0432.ccr-0437-03 [published Online First: 2004/03/26].
40. Mehta AJ, de Caestecker JS, Camm AJ. *et al.* Gastro-oesophageal reflux in patients with coronary artery disease: how common is it and does it matter? *Eur J Gastroenterol Hepatol* 1996;**8**:973–8. https://doi.org/10.1097/00042737-199610000-00007 [published Online First: 1996/10/01].
41. Hengel FE, Benitah JP, Wenzel UO. Mosaic theory revised: inflammation and salt play central roles in arterial hypertension. *Cell Mol Immunol* 2022;**19**:561–76. https://doi.org/10.1038/s41423-022-00851-8 [published Online First: 2022/04/01].
42. Kandulski A, Malfertheiner P. Gastroesophageal reflux disease–from reflux episodes to mucosal inflammation. *Nat Rev Gastroenterol Hepatol* 2011;**9**:15–22. https://doi.org/10.1038/nrgastro.2011.210 [published Online First: 2011/11/23].
43. McMaster WG, Kirabo A, Madhur MS. *et al.* Inflammation, immunity, and hypertensive end-organ damage. *Circ Res* 2015;**116**:1022–33. https://doi.org/10.1161/CIRCRESAHA.116.303697 [published Online First: 2015/03/15].
44. Kanoupakis EM, Manios EG, Mavrakis HE. *et al.* Relation of autonomic modulation to recurrence of atrial fibrillation following cardioversion. *Am J Cardiol* 2000;**86**:954–8. https://doi.org/10.1016/s0002-9149(00)01129-2 [published Online First: 2000/10/29].
45. DiBona GF. Sympathetic nervous system and hypertension. *Hypertension* 2013;**61**:556–60. https://doi.org/10.1161/HYPERTENSIONAHA.111.00633 [published Online First: 2013/01/30].
46. Liu Y, He S, Chen Y. *et al.* Acid reflux in patients with coronary artery disease and refractory chest pain. *Intern Med* 2013;**52**:1165–71. https://doi.org/10.2169/internalmedicine.52.0031 [published Online First: 2013/06/04].
47. Chauhan A, Petch MC, Schofield PM. Effect of oesophageal acid instillation on coronary blood flow. *Lancet* 1993;**341**:

1309–10. 10.1016/0140-6736(93)90817-z [published Online First: 1993/05/22].
48. Singh S, Richter JE, Hewson EG. *et al.* The contribution of gastroesophageal reflux to chest pain in patients with coronary artery disease. *Ann Intern Med* 1992;**117**:824–30. https://doi.org/10.7326/0003-4819-117-10-824 [published Online First: 1992/11/15].
49. Garcia-Pulido J, Patel PH, Hunter WC. *et al.* Esophageal contribution to chest pain in patients with coronary artery disease. *Chest* 1990;**98**:806–10. https://doi.org/10.1378/chest.98.4.806 [published Online First: 1990/10/01].
50. Dean JB. Theory of gastric CO2 ventilation and its control during respiratory acidosis: implications for central chemosensitivity, pH regulation, and diseases causing chronic CO2 retention. *Respir Physiol Neurobiol* 2011;**175**:189–209. https://doi.org/10.1016/j.resp.2010.12.001 [published Online First: 2010/12/15].