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Exploring the silent connection: unveiling the intricate relationship between gastroesophageal reflux disease and sleep apnea syndrome

Junming Wang[3,4,5], Pengfei Wang[3,4,5], Jiang Lv[1], Ran Chen[1], Wei Yan[1] and Daikun He[1,2,3,4,5*]

Abstract

Background Gastroesophageal reflux disease (GERD) and Sleep Apnea Syndrome (SAS) are two prevalent medical conditions that significantly affect health and quality of life. GERD involves stomach content reflux into the esophagus, while SAS causes recurrent upper airway obstruction during sleep. Despite recent studies hinting at a link, the precise relationship and causality between GERD and SAS remain unclear. Our research uses bidirectional Mendelian randomization to explore this intricate relationship. Additionally, given SAS's high prevalence in cardiovascular patients (40–80%, as highlighted by the American Heart Association), we also investigated its potential association with various cardiovascular diseases to gain new insights into prevention and treatment.

Methods This study employed genetic data from large-scale genome-wide association studies (GWAS) on GERD (129,080 cases, 473,524 controls) and SAS (25,008 cases, 391,473 controls) for two-sample Mendelian randomization (MR) analysis to estimate the causal effects of GERD on the risk of SAS. All SNPs were selected using a strict clump window ($r^2 = 0.001$ and kb = 10,000). We initially applied the inverse variance weighted (IVW) method and measured horizontal pleiotropy using MR-Egger, weighted median, and weighted mode methods. I^2 index and Cochran Q statistics were used for sensitivity analysis. Funnel plot symmetry of IVW MR estimates versus 1/standard error (1/SEIV) was examined to exclude SNPs potentially causing heterogeneity. Additionally, to exclude reverse causality, bidirectional MR was employed to investigate whether genetic susceptibility to SAS causally influenced the risk of GERD.

Results GERD was associated with an elevated risk of SAS, demonstrating an odds ratio (OR) of 1.750 (95% CI 1.590–1.930; $P < 0.001$). Conversely, there was no compelling evidence to indicate a causal link between SAS and the risk of developing GERD, with an OR of 1.000 (95% CI 0.989–1.011; $P = 0.964$). In addition to the primary findings, our study also revealed significant risks associated with SAS for several cardiovascular conditions, including coronary heart disease, atrial fibrillation, coronary artery disease, heart failure, intracerebral hemorrhage, and ischemic stroke.

Conclusion We discovered compelling evidence indicating an elevated risk of SAS in individuals with GERD, but no significant evidence supporting an increased risk of GERD in those with SAS. Future investigations into SAS risk should take into account the potential therapeutic targeting of GERD. PPI and histamine antagonists can effectively reduce reflux and airway secretions, preventing airway damage and collapse. Furthermore, it is necessary to investigate the underlying mechanisms by which GERD affects SAS. For example, the inflammatory stimulation caused

*Correspondence:
Daikun He
daikun_he@126.com
Full list of author information is available at the end of the article

by gastric acid and pepsin in refluxed fluid, as well as the increased tension of bronchial smooth muscle caused by vagus nerve reflex. Thus, early preventive measures can be implemented for potential complications related to SAS.

Keywords Gastroesophageal reflux disease, Sleep apnea syndrome, Causal effects, Mendelian randomization, Meta-analysis

Introduction

GERD, affecting 13% of the global population, involves stomach acid flowing back into the esophagus, causing heartburn, regurgitation, and chest discomfort [1]. SAS, a common sleep disorder, features recurrent airway obstruction during sleep, leading to fragmented sleep, loud snoring, and daytime fatigue [2, 3]. Both conditions impact quality of life and health [4–7].

Recent meta-analyses have indicated a potential link between GERD and SAS, with odds ratios suggesting an increased association (OR 1.53 and 1.75) [8, 9]. Effective treatment for GERD, such as proton pump inhibitors (PPIs), can effectively improve subjective sleep parameters and reduce the frequency of respiratory pauses [10]. While the exact causal mechanisms remain unclear [11], emerging research explores several pathways, including airway inflammation and vagal nerve effects. Acid reflux can cause throat inflammation like saliva pooling, redness/swelling, hypertrophy, granulomas, and worsen SAS symptoms [12]. Additionally, GERD-associated autonomic dysfunction, particularly vagovascular tone, may cause upper airway sensitivity and eventual obstruction [13, 14]. Understanding these interactions could lead to better treatment strategies for both conditions. Therefore, we hypothesize that GERD causally elevates SAS risk.

This study aimed to investigate the causal effects between GERD and SAS using a method called Mendelian randomization (MR) [15]. MR utilizes genetic variations as instrumental variables to provide unbiased estimates of causal relationships in observational studies [16]. By employing a bidirectional two-sample MR design, we sought to estimate the causal effects of GERD on SAS risk and SAS on GERD risk.

A comprehensive grasp of the causal relationship between GERD and SAS facilitates the development of targeted interventions, such as personalized weight loss and exercise programs tailored [17] to control BMI indices in SAS patients with/without GERD (34.0 ± 7.0 vs. 33.1 ± 6.8, $P = 0.049$) [18], thereby alleviating mechanical pressure and improving ventilation function [17]. Emerging research indicates that 65% of GERD patients exhibit Pittsburgh Sleep Quality Index (PSQI) greater than 5 [19], highlighting the necessity of quantitative sleep monitoring methods such as polysomnography or portable sleep monitoring [20]. As mentioned previously, early diagnosis of GERD and aggressive PPI treatment can prevent the progression of SAS [10]. By promoting deeper cohort studies and refining our clinical strategies, we can enhance patients' quality of life, reduce healthcare costs, and provide comprehensive care for individuals with GERD and co-existing SAS.

Methods

Genetic data

For both our analyses of the effect of GERD on SAS risk and of the effect of SAS on GERD risk we used two-sample MR where summary statistics (effect estimates and standard errors) for the exposure and outcome associations were obtained from separate studies.

For the MR of the effect of GERD on SAS risk, instruments were selected from the largest available genome-wide association study (GWAS) meta-analysis on GERD by Ong et al. [21]. For each instrument (SNP), summary statistics of the exposure association (expressed as log odds ratio for GERD) were obtained from the replication stage of Ong et al. [21]. Summary statistics of the outcome association (log odds ratio for SAS) were obtained from the authors of the GWAS meta-analysis on SAS [22].

Similarly, for the MR of the effect of SAS on GERD risk, instruments were selected from the largest available GWAS meta-analysis on SAS by Wang et al. [23]. For each SNP, summary statistics of the exposure association (log odds ratio for SAS) were obtained from this GWAS, while summary statistics of the outcome association (log odds ratio for GERD) were obtained from the authors of the GWAS meta-analysis on GERD [24].

SNP selection in exposure and outcome

Based on the above assumptions, a search was conducted within the GWAS database for the selection of SNPs. To avoid linkage disequilibrium, all SNPs were clumped using a strict clump window ($r^2 = 0.001$ and kb = 10,000) [25, 26]. These SNPs were then examined in the phenome-wide association studies (pheWAS) catalog databases to ascertain any potential associations with confounding factors of the outcomes, with a significance threshold set at $P < 5 \times 10^{-6}$ [27, 28].

MR and assumptions

This study utilized a bidirectional two-sample MR design using genetic instruments (SNPs) to predict GERD and SAS based on the latest GWAS data (Fig. 1). The bidirectional approach enables us to examine both the association between GERD and SAS, as well as the causal relationship between SAS and GERD [29]. MR analysis relies on three fundamental assumptions: (1) a robust association between genetic predictors (SNPs) and their corresponding exposures (GERD and SAS) [30], (2) independence of genetic predictors from confounding factors in the relationship between exposure and outcome [31], and (3) genetic predictors exclusively influencing the outcome through their impact on the exposure (exclusion-restriction assumption) [32].

The MR analyses were initially conducted using a two-sample inverse variance weighted (IVW) method. In this method, SNP-specific Wald ratios between the effect of the outcome and exposure were meta-analyzed [33]. The analysis employed a random-effects inverse variance approach, with each ratio weighted by its corresponding standard error while also considering potential heterogeneity in the measurements [34].

Directional pleiotropy occurs when there is a non-zero overall effect of horizontal pleiotropy across all SNPs, which can introduce bias into the estimates obtained through the inverse variance weighted (IVW) method [35]. To address this issue, alternative MR methods such as MR-Egger, weighted median, and weighted mode were used to calculate estimates for comparison with the IVW estimates, as these methods are more robust to directional pleiotropy [36–38].

MR-Egger

The MR-Egger method is a variant of Egger regression that incorporates an intercept in the weighted regression model to accommodate directional pleiotropy [39]. It considers the possibility that specific SNPs may affect the outcome through mechanisms unrelated to exposure modification [40], thereby providing more robust estimates of causal effects [41]. A non-zero intercept indicates horizontal pleiotropy [42, 43].

Weighted median mode

The weighted median mode orders the MR estimates derived from individual SNPs, each weighted by the inverse of their variance [44]. By selecting the median result, a single MR estimate is obtained, with its confidence intervals estimated through a parametric bootstrap method [45]. This approach can yield a robust result even when over 50% of the weights originate from invalid SNPs [46]. Moreover, in the presence of horizontal pleiotropy, the weighted median mode helps reduce type I errors, thereby enabling a more precise evaluation of causal associations [47].

Weighted mode

In the weighted mode, the weighted effect estimates for each SNP are sorted, and the effect estimate that appears most frequently (or has the largest weight) is selected as the final causal effect estimate [48]. When the majority of similar individual estimates come from valid SNPs, the weighted mode can obtain a robust overall causal estimate [45].

Sensitivity analysis

For IVW analysis, both the I^2 index and Cochran's Q statistic were used to assess heterogeneity. Additionally, a leave-one-out analysis was employed to identify SNPs with potential impacts and validate the reliability of the results [49]. Furthermore, funnel plot symmetry of IVW MR estimates against 1/standard error (1/SEIV) was examined to exclude SNPs that might be introducing heterogeneity [50].

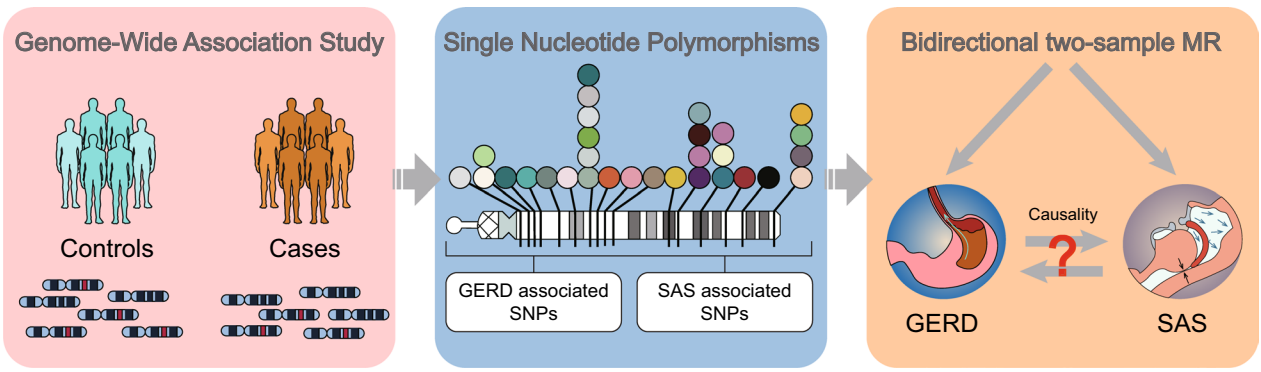

Fig. 1 The Process of Mendelian randomization analysis

Statistical analysis

All statistical analyses were conducted using Stata version 13.1 (StataCorp LP, College Station, TX) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), and the 'TwoSampleMR' and 'MendelianRandomization' packages.

Results

Demographic data for the cohorts

All baseline information of the included cohorts in this study is presented in Table 1. Specifically, for the GERD-SAS risk association analysis, summary statistics of the exposure association were sourced from Ong et al.'s GWAS, while summary statistics of the outcome association were obtained from Sakaue et al.'s GWAS. As for the SAS-GERD risk association analysis, summary statistics of the exposure / outcome association were obtained from the GWAS of Wang et al. / Dönertaş et al.

The impact of GERD on the risk of SAS

In the UK Biobank, a total of 2466 SNPs are found to be associated with GERD ($P < 5 \times 10^{-8}$), 1465 of which were available in the SAS GWAS. After removing SNPs in linkage disequilibrium ($r^2 < 0.001$), a remaining set of 80 SNPs were used in the MR analyses. The detailed information regarding these SNPs and their correlation with SAS is presented in Table 2.

MR analysis revealed a causal relationship between GERD and SAS risk, with an OR of 1.750 (95% CI 1.530–2.010; $P < 0.001$) (Fig. 2A). The pleiotropy P value was 0.546. After exclusion of 3 SNPs which caused significant heterogeneity, as explained later, the 95% CI of OR became narrower (OR 1.750, 95% CI 1.590–1.930; $P < 0.001$) (Fig. 2B). Additionally, the I^2 value changed from 44 to 0%, indicating the absence of heterogeneity. The scatter plots illustrated that there were strong associations between SNP-SAS and SNP-GERD (Fig. 2C). The individual impact of each SNP is as depicted in Fig. 2D. The funnel plot (Fig. 2E) demonstrates the inverse variance weighted MR estimate for each GERD SNP with SAS versus 1/standard error (1/SEIV), with the 3 SNPs (rs12967855, rs7527682, and rs9940128) accountable for substantial heterogeneity highlighted in red.

The impact of SAS on the risk of GERD

Wang et al. performed a meta-analyses on SAS GWAS by combining 5 cohorts from various countries. 35 SNPs were reported to be associated with SAS, all of which can be found in the GERD GWAS database (Table 3).

Table 1 The baseline information of the included cohorts in this study

Study	Participants	Sources / Population	Build	Reference
GERD				
Ong et al.				
Cases	129,080	UK Biobank / European	HG19/GRCh37	[21]
Controls	473,524			
Dönertaş et al.				
Cases	20,381	UK Biobank	HG19/GRCh37	[24]
Controls	464,217			
SAS				
Sakaue et al.				
Cases	13,818	UK Biobank / European	HG19/GRCh37	[22]
Controls	463,035			
Wang et al.				
Cases	7902	UK Biobank	Not known	[23]
	9096	Finngen / Finns		
	3102	Partners Biobank		
	3391	CLSA / Canadian		
	1517	AGDS / Australian		
Controls	248,112	UK Biobank	Not known	
	110,963	Finngen / Finns		
	16,945	Partners Biobank		
	9615	CLSA / Canadian		
	5838	AGDS / Australian		

GERD, Gastroesophageal reflux disease; SAS, Sleep apnea syndrome; CLSA, Canadian longitudinal study of aging; AGDS, Australian genetics of depression study

Table 2 The 80 SNPs associated with GERD from a GWAS involving UK Biobank participants that were available in the SAS GWAS and included in the GERD-SAS MR analyses

SNP	Chr	Position	Effect allele	Other allele	EAF	β[a]	*P*
rs10010963	4	159,839,313	T	C	0.62	−0.03	4.9E−08
rs1011407	2	60,665,768	G	A	0.12	−0.04	1.1E−08
rs10133111	14	103,377,321	A	G	0.16	0.04	1.4E−10
rs1021363	10	106,610,839	G	A	0.64	−0.03	5.1E−10
rs10837002	11	38,565,727	G	C	0.35	0.03	4.0E−08
rs11762636	7	2,061,111	A	C	0.18	−0.05	1.9E−16
rs11953061	5	120,144,025	T	C	0.34	0.03	3.1E−08
rs12204714	6	152,235,339	T	C	0.63	−0.03	7.9E−09
rs12357321	10	21,790,476	A	G	0.31	0.03	1.3E−09
rs12453010	17	50,316,131	T	C	0.40	0.03	1.7E−09
rs12598916	16	60,658,751	G	C	0.28	−0.03	6.9E−10
rs12967855	18	35,138,245	G	A	0.67	−0.04	1.1E−12
rs12997558	2	41,704,580	A	G	0.36	0.03	3.0E−08
rs13107325	4	103,188,709	T	C	0.07	0.07	2.2E−14
rs1334297	13	58,335,375	A	G	0.73	−0.04	1.1E−12
rs13409451	2	144,257,639	G	A	0.39	−0.03	1.9E−08
rs1431196	18	50,832,102	G	A	0.43	0.03	2.7E−11
rs1479405	12	15,387,519	T	C	0.32	0.03	9.9E−10
rs1510719	4	140,938,116	C	T	0.38	−0.04	3.8E−15
rs1592757	5	103,889,998	C	G	0.36	0.03	6.0E−10
rs1596747	2	193,802,478	G	A	0.49	0.03	1.0E−10
rs1716171	12	123,716,376	T	C	0.79	0.04	7.8E−11
rs17379561	1	98,340,139	T	A	0.14	0.05	1.1E−14
rs1883842	20	41,223,062	G	T	0.28	0.03	9.3E−09
rs1937450	1	66,478,840	G	T	0.54	0.03	7.1E−11
rs2016933	3	65,653,157	G	C	0.73	−0.03	1.0E−08
rs2023878	19	18,834,124	T	C	0.19	−0.04	3.0E−09
rs2043539	7	12,253,880	A	G	0.42	0.03	2.2E−08
rs2106353	7	126,506,598	T	G	0.23	0.04	1.4E−10
rs2145318	6	26,496,603	A	T	0.49	0.04	2.0E−13
rs215614	7	32,347,335	A	G	0.63	−0.03	4.1E−11
rs2164300	4	67,813,017	T	C	0.52	−0.03	4.1E−08
rs2240326	3	50,128,386	A	G	0.47	−0.05	1.1E−22
rs2358016	2	162,007,430	G	C	0.50	0.03	4.2E−09
rs2396133	7	109,197,067	G	A	0.48	0.03	1.1E−09
rs2396766	7	114,318,071	A	G	0.47	0.03	2.3E−11
rs2734839	11	113,286,490	T	C	0.61	−0.03	8.8E−09
rs2744961	6	34,655,000	T	C	0.36	0.03	5.8E−09
rs2782641	1	44,013,355	A	G	0.61	0.03	4.3E−08
rs2815749	1	72,814,783	G	A	0.80	0.04	1.1E−10
rs2834005	21	34,291,708	C	T	0.32	0.03	9.4E−09
rs2838771	21	46,501,576	C	G	0.65	−0.03	2.9E−08
rs324769	12	83,969,240	T	C	0.45	−0.03	3.0E−08
rs329122	5	133,864,599	A	G	0.42	−0.03	3.1E−09
rs3766823	1	32,197,257	A	G	0.17	0.04	7.1E−10
rs3793577	9	23,737,627	G	A	0.54	0.03	2.5E−08
rs3828917	6	31,465,917	T	G	0.04	0.07	2.3E−08
rs3863241	8	73,890,335	T	C	0.53	0.03	1.5E−11

Table 2 (continued)

SNP	Chr	Position	Effect allele	Other allele	EAF	β[a]	*P*
rs4300861	2	22,549,441	T	C	0.38	0.03	5.4E−10
rs4382592	9	134,870,755	G	T	0.70	−0.03	8.2E−09
rs4713692	6	33,807,638	T	C	0.37	−0.03	3.1E−08
rs569356	1	29,136,686	G	A	0.14	−0.04	4.1E−08
rs6711584	2	104,421,692	A	G	0.45	0.03	2.7E−11
rs6722661	2	100,806,588	A	G	0.37	−0.03	1.1E−10
rs6780459	3	104,624,105	T	A	0.75	0.03	3.1E−08
rs7032155	9	122,672,771	A	C	0.59	0.03	1.6E−08
rs7206608	16	82,872,628	G	C	0.32	0.03	1.5E−08
rs7241572	18	77,580,712	A	G	0.21	0.04	9.5E−10
rs7527682	1	189,172,684	G	A	0.54	−0.03	3.1E−08
rs7541875	1	190,957,589	G	A	0.43	0.03	1.6E−08
rs7600261	2	212,622,818	T	C	0.31	0.03	9.5E−11
rs7612999	3	35,678,337	A	G	0.25	0.03	4.9E−08
rs761777	10	134,938,075	G	A	0.25	0.04	4.7E−10
rs7675588	4	80,734,978	A	C	0.80	−0.03	1.8E−08
rs7685686	4	3,207,142	G	A	0.42	−0.03	1.1E−08
rs773109	12	56,374,695	A	G	0.34	−0.04	8.7E−14
rs7942368	11	76,465,362	T	C	0.22	−0.03	9.5E−09
rs903678	1	201,809,918	A	G	0.34	0.03	4.9E−08
rs903959	8	142,630,782	A	T	0.40	0.03	3.0E−09
rs9372625	6	98,344,031	A	G	0.38	−0.04	2.6E−14
rs9373363	6	143,150,043	G	A	0.25	−0.03	4.1E−09
rs9396740	6	17,023,108	A	G	0.25	−0.03	1.5E−08
rs942065	14	94,032,065	A	G	0.63	0.03	8.4E−10
rs9517313	13	99,105,892	C	G	0.38	0.03	2.0E−11
rs9529055	13	66,957,533	A	G	0.48	0.03	3.1E−08
rs9542729	13	31,833,578	G	C	0.20	−0.04	1.4E−09
rs957345	14	75,276,079	G	C	0.54	0.03	1.7E−09
rs9615905	22	48,875,699	T	C	0.46	0.03	1.2E−08
rs9636202	19	18,449,238	A	G	0.27	−0.04	1.5E−10
rs9940128	16	53,800,754	A	G	0.42	0.03	8.1E−12

SNP, Single-nucleotidepolymorphism; Chr, Chromosome; EAF, Effect allele frequency

[a] Change in the GERD GWAS population

MR analysis revealed no evidence of a causal relationship between SAS and GERD risk, with an OR of 1.000 (95% CI 0.990–1.010; $P=0.986$) (Fig. 3A). Evidence of pleiotropy was observed, with an I^2 value of 41% and a heterogeneity P value of 0.008. Four potential pleiotropic SNPs were identified, as indicated by the highlighted regions in the funnel plot (Fig. 3C). After removing these SNPs, there was no residual evidence of pleiotropy ($I^2=20\%$; $P=0.167$), and the results remained null (OR 1.000, 95% CI 0.989–1.011; $P=0.964$). Similar null findings were obtained when robust methods adjusting for pleiotropy were used (Fig. 3B).

An increased risk of cardiovascular diseases associated with SAS

Based on the MR analyses conducted on GWAS data from the UK Biobank [22, 24, 51–54], aiming to uncover high-risk cardiovascular diseases associated with SAS, it was found that SAS may increase the risk of coronary heart disease (OR 1.219), atrial fibrillation (OR 1.127), coronary artery disease (OR 1.182), heart failure (OR 1.114), intracerebral hemorrhage (OR 1.273), and ischemic stroke (OR 1.096) (Fig. 4). The MR analysis was conducted following standard procedures and efforts were made to minimize the inclusion of SNPs that may introduce pleiotropy and heterogeneity.

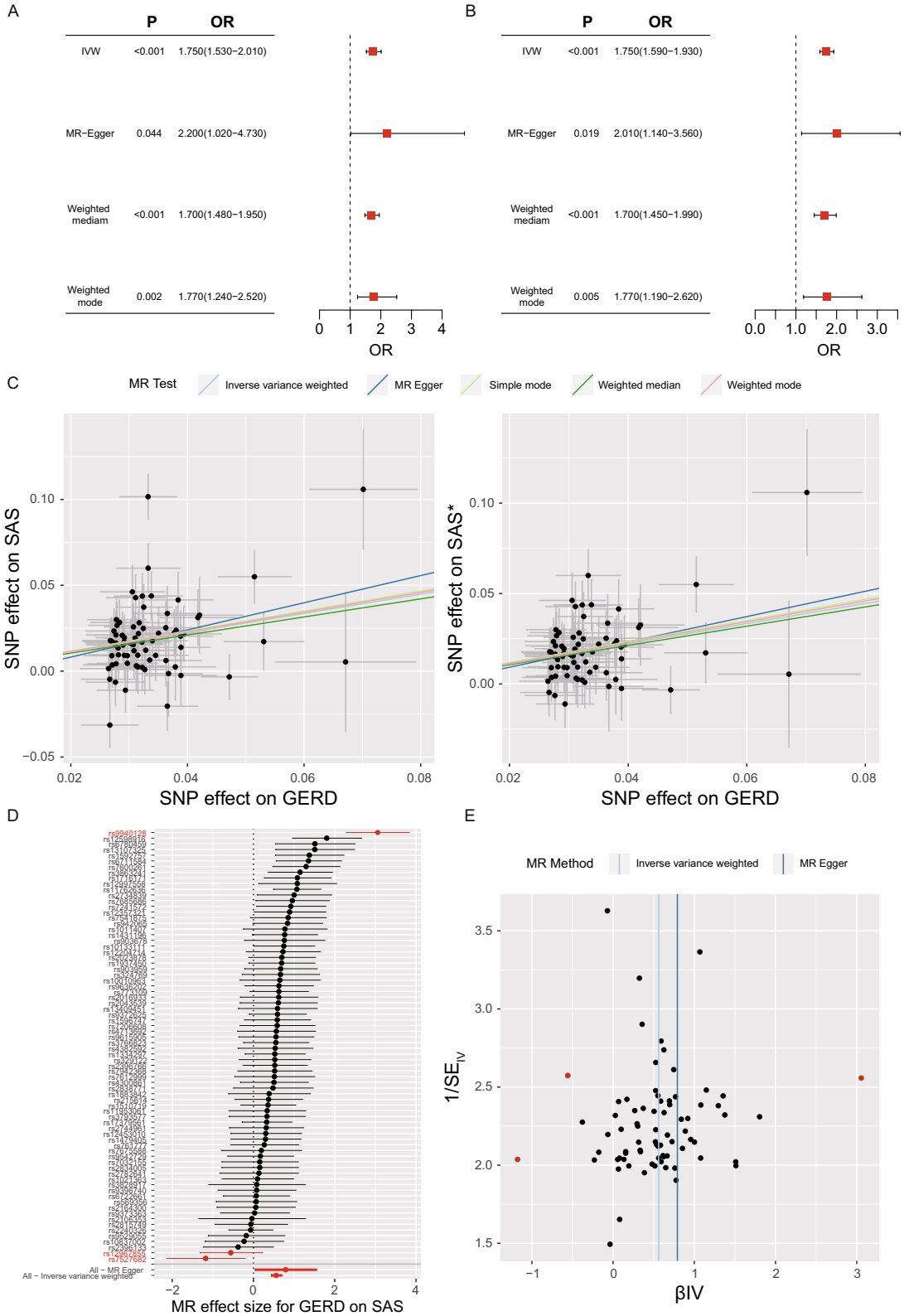

Fig. 2 The forest plot illustrated the MR analysis results based on 80 GERD-related SNPs (**A**) and after excluding 3 SNPs causing heterogeneity (**B**). The correlation of SNPs in both diseases was shown (**C**). The forest plot displayed the individual effects of each SNP (**D**). The funnel plot demonstrated the inverse variance weighted MR estimate for each GERD SNP with SAS versus 1/standard error (1/SEIV) (**E**)

Table 3 The 35 SNPs associated with SAS from a meta-analyses involving 5 cohorts that were available in the SAS and GERD GWAS and included in the MR analyses

SNP	Chr	Position	Effect Allele	Other Allele	EAF	β[b]	P
rs11075985	16	53,805,207	A	C	0.43	0.04	4.46E−24
rs10878269	12	65,791,463	T	C	0.33	0.03	3.86E−16
rs592333	13	51,340,315	G	A	0.53	−0.03	1.69E−14
rs6265	11	27,679,916	T	C	0.18	−0.04	1.79E−14
rs72902175	2	157,013,035	T	C	0.13	0.04	3.67E−14
rs2307111	5	75,003,678	C	T	0.59	0.03	1.53E−13
rs35445111	19	32,172,047	G	A	0.91	0.04	1.62E−11
rs11041997	11	8,602,016	A	G	0.54	0.02	3.42E−11
rs6113592	20	22,229,505	G	A	0.63	0.02	7.82E−11
rs12603115	17	46,248,994	T	C	0.58	−0.02	8.14E−10
rs1444789	10	9,064,361	C	T	0.78	−0.03	1.10E−09
rs1537818	1	39,647,038	A	G	0.7	−0.02	1.31E−09
rs57222984	17	43,758,898	G	A	0.82	−0.03	1.62E−09
rs11634019	15	76,634,680	C	T	0.71	0.02	1.84E−09
rs8176749	9	136,131,188	T	C	0.09	−0.04	3.78E−09
rs227731	17	54,773,238	G	T	0.54	−0.02	3.96E−09
rs4076077	5	170,863,509	T	C	0.49	−0.02	4.26E−09
rs698408	7	127,345,936	A	G	0.32	0.02	4.61E−09
rs4987719	18	60,960,310	T	C	0.03	0.06	4.72E−09
rs1428381	5	122,693,901	G	A	0.29	0.02	4.83E−09
rs4923536	11	28,422,496	G	A	0.54	−0.02	5.39E−09
rs34811474	4	25,408,838	A	G	0.23	−0.02	6.50E−09
rs1403848	3	77,609,655	A	C	0.54	−0.02	9.30E−09
rs7005777	8	78,233,600	T	G	0.75	0.02	1.12E−08
rs1007311	7	150,696,008	G	A	0.58	−0.02	1.22E−08
rs8045335	16	60,607,116	G	A	0.42	−0.02	1.24E−08
rs6842303	4	17,854,055	G	T	0.28	−0.02	1.39E−08
rs2715039	7	84,094,964	C	A	0.6	−0.02	2.04E−08
rs1815739	11	66,328,095	C	T	0.4	0.02	2.10E−08
rs6038517	20	6,458,205	G	A	0.74	−0.02	2.19E−08
rs9933881	16	1,740,691	C	T	0.93	−0.04	2.54E−08
rs10747478	1	96,901,455	G	T	0.41	−0.02	2.90E−08
rs2601764	10	33,815,235	C	A	0.59	−0.02	3.47E−08
rs6988053	8	71,546,963	T	C	0.44	0.02	4.47E−08
rs9551973	13	20,256,342	C	T	0.88	−0.03	4.52E−08

SNP, Single-nucleotide polymorphism; Chr, Chromosome; EAF, Effect allele frequency

[b] Change in the SAS GWAS population

Discussion

The findings of our study on the causal effects between gastroesophageal reflux disease (GERD) and obstructive sleep apnea syndrome (SAS) align with recent research in this field. GERD may trigger SAS through multiple mechanisms, with airway inflammation and vagal reflexes serving as two pivotal pathways. The aspiration of gastric acid and other refluxate into the airways can irritate and damage the mucosa, primarily inducing a neutrophilic inflammatory response [55], which is also evidenced by elevated IL-6 concentrations in sputum [56], further leading to airway hyperreactivity (AHR) [57]. Additionally, higher levels of monocyte chemoattractant protein-1 (MCP-1) and thymic stromal lymphopoietin (TSLP) have been found in the sputum of patients with GERD [58]. On the other hand, gastric acid and pepsin in the refluxate [59] can stimulate vagal receptors located at the glottic inlet and laryngeal regions [60], which possess potent reflex bronchoconstrictive activity. Studies by Nadal et al. have shown that mechanical stimulation of the laryngeal

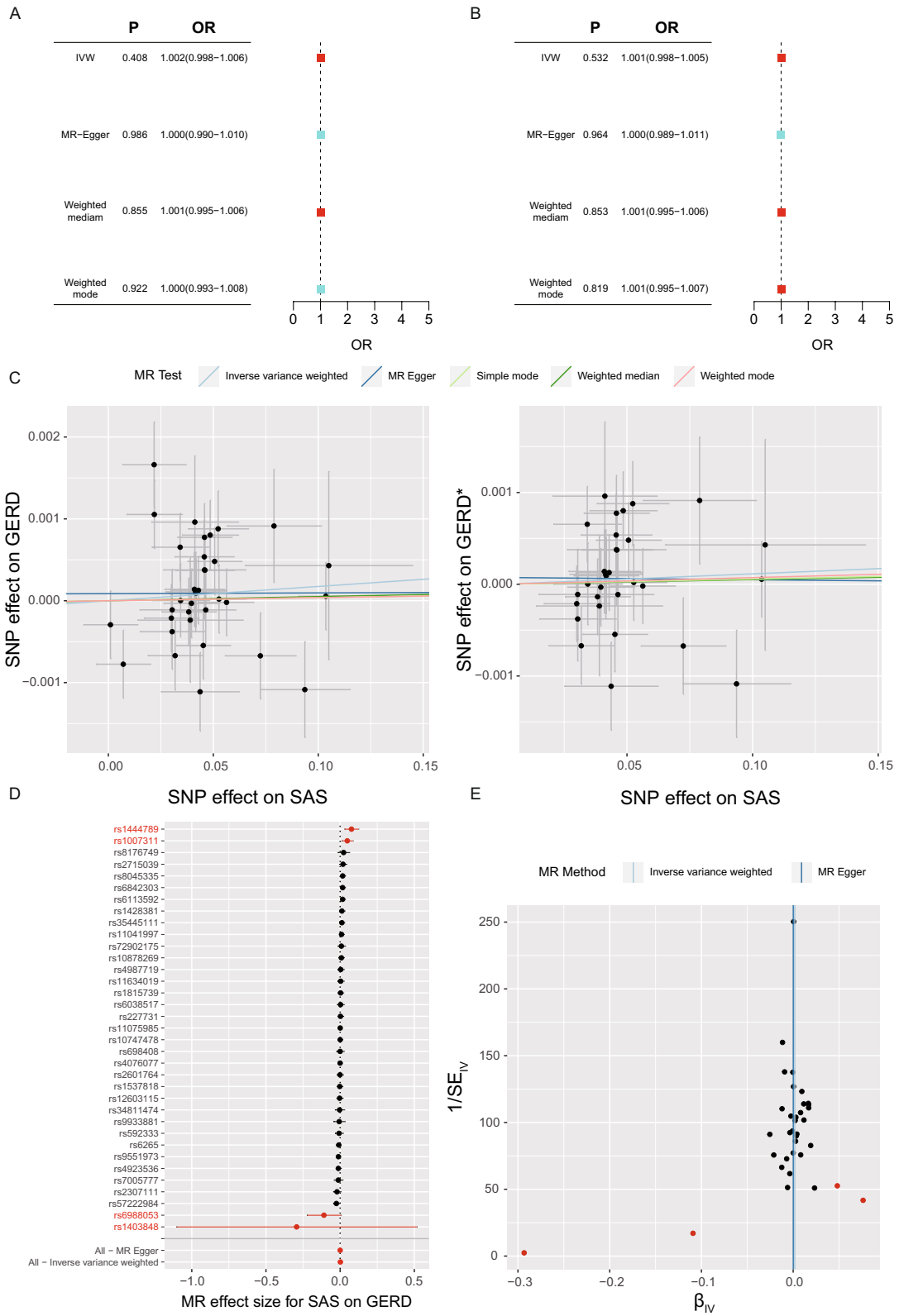

Fig. 3 The forest plot illustrated the MR analysis results based on 35 SAS-related SNPs (**A**) and after excluding 4 SNPs causing heterogeneity (**B**). The correlation of SNPs in both diseases was shown (**C**). The forest plot displayed the individual effects of each SNP (**D**). The funnel plot demonstrated the inverse variance weighted MR estimate for each SAS SNP with GERD versus 1/standard error (1/SEIV) (**E**)

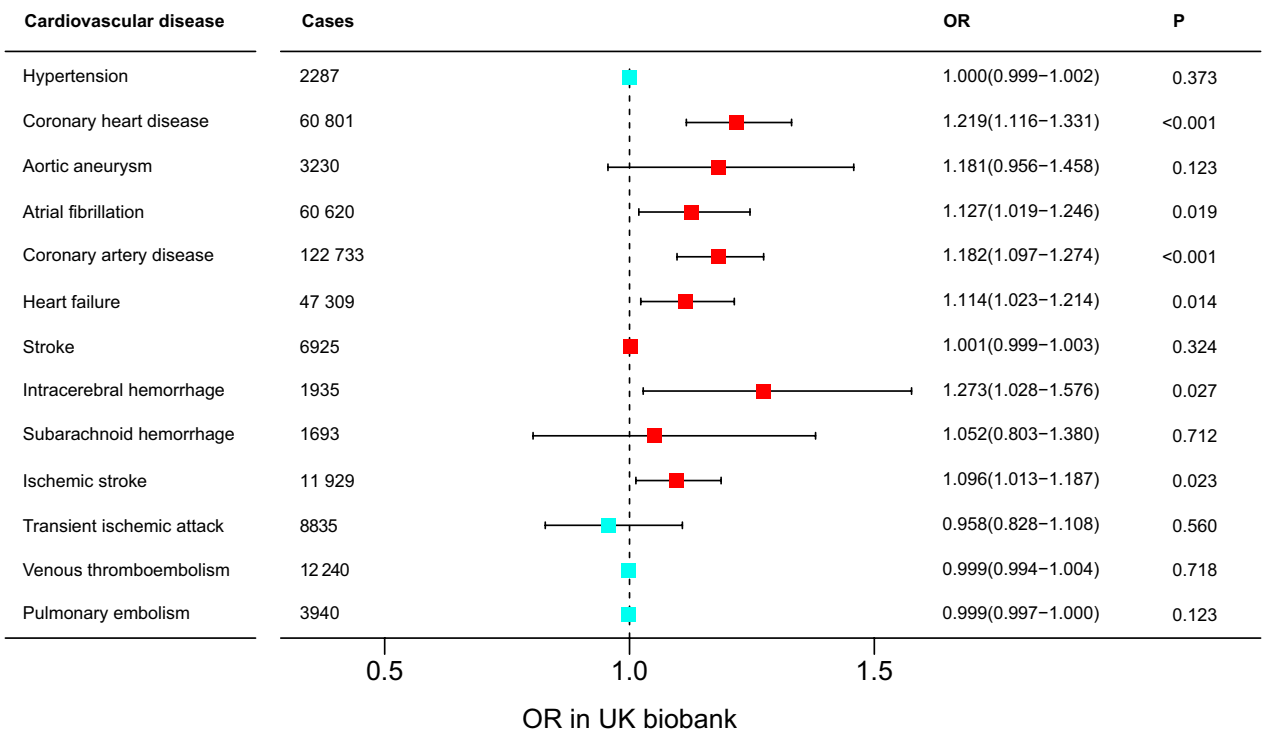

Fig. 4 The forest plot presents the MR analysis results based on the UK Biobank database for various cardiovascular diseases that have potential associations with SAS

mucosa increases total lung resistance in the distal airway of anesthetized and decerebrate cats, further supporting this notion [61]. In canine models, vagotomy abolished the airway resistance induced by esophageal acid infusion [62, 63]. Furthermore, GERD and SAS may share common risk factors such as obesity and smoking [64, 65], which can concurrently impact the health of both the gastrointestinal and respiratory systems.

Our study also highlighted a potential association between SAS and cardiovascular diseases. (1) Coronary heart disease: SAS can lead to intermittent hypoxia [66], blood pressure fluctuations [67], and arrhythmias [68], all of which increase the risk of coronary heart disease. Patients with SAS who undergo continuous positive airway pressure (CPAP) therapy for 4 h per day exhibit a significant reduction in the risk of coronary-related mortality (HR: 0.29, $P=0.026$) [69]; (2) Atrial fibrillation: Repeated episodes of SAS can lead to a hypoxic state, which may trigger arrhythmias, including atrial fibrillation [70]. The chronic recurrence of SAS is associated with structural remodeling of the atrium and alterations in electrical conduction [71]. An expert consensus document identifies SAS as a significant risk factor for the recurrence of arrhythmias following catheter ablation [72]; (3) Heart failure: Periodic apnea and hypopnea in SAS lead to excessive fluctuations in intrathoracic negative pressure [73], increasing Left Ventricular (LV) transmural pressure (the difference between intracardiac and intrathoracic pressure) and afterload [74]. Simultaneously, venous return increases, elevating right ventricular preload, causing right ventricular dilation and leftward septal shift during diastole, which impedes LV filling [75, 76]. This combination of reduced LV preload and increased afterload decreases stroke volume and cardiac output, ultimately leading to heart failure [77]. (4) Cerebrovascular events: SAS has been established as an independent risk factor for both intracerebral hemorrhage and ischemic stroke. During apnea/hypopnea episodes, intracranial blood volume increases [78], leading to elevated intracranial pressure and decreased cerebral perfusion pressure [79]. On the other hand, SAS patients often exhibit endothelial dysfunction [80], potentially due to impaired vascular response to hypercapnia, which increases the risk of hemorrhage [81].

Interestingly, our study did not find evidence of an increased risk of GERD among individuals with SAS. This is in line with a recent cohort study conducted by On et al. [82], which indicated a lack of strong evidence supporting a causal relationship between SAS and GERD ($P=0.61$). Pillai et al. also pointed out that SAS does not contribute to the occurrence of esophageal reflux [83]. This may be attributed to the fact that most genetic

variations associated with SAS involve the upper respiratory tract structure [84], and currently, the position of the hyoid bone has been proven to correlate with the severity of SAS [85]. Additionally, studies have reported that the primary disease-associated gene for SAS is FTO, which is well-defined and associated with BMI [86]. These variations may independently influence the risk of SAS without a direct link to GERD. Alterations in esophageal sphincter function, such as dysregulation of genes regulating the NF-κB pathway, play a crucial role in the pathogenesis of GERD [87].

In the context of potential therapeutic interventions, our study highlights the significance of considering GERD as a potential target for managing SAS. Recent studies exploring novel treatment approaches have shown promising results [88]. For instance, a randomized controlled trial by Wasilewska et al. demonstrated that targeted treatment of GERD using proton pump inhibitors (PPIs) led to a reduction in apnea–hypopnea index (AHI) (from 13.08 ± 3.11/h to 8.22 ± 2.52/h) and improved sleep quality in patients with coexisting GERD and SAS [89]. These findings support the notion that targeting GERD may provide benefit in terms of SAS management.

Despite the valuable insights gained from our study, several limitations merit acknowledgment. The Mendelian randomization approach assumes the validity of instrumental variables and employs specific genetic variants as proxies for exposure and outcome [90]. Although sensitivity analyses were performed to address potential issues, the possibility of unmeasured confounding factors or biases cannot be entirely excluded [91]. Moreover, our study primarily relies on GWAS data from European populations (Table 1), limiting the interpretation due to overlooked genetic differences and environmental factors across diverse populations. Future work will integrate diverse datasets and ethnic groups for comprehensive analysis, and we anticipate larger, more comprehensive GWAS studies. Additionally, leveraging the community resources of Jinshan Hospital's General Medicine Department, we will conduct randomized controlled clinical trials on PPI treatment for SAS patients with GERD, translating our research from bench to bedside.

In conclusion, our study contributes to the existing body of literature by confirming the increased risk of SAS among individuals with GERD. These findings, in line with recent research, support the importance of considering GERD as a potential therapeutic target for managing SAS. Future studies should utilize robust methodologies and explore novel treatment approaches to optimize the management of both GERD and SAS, while also investigating the complex relationships between GERD, SAS, and other related conditions such as cardiovascular diseases.

Acknowledgements
We want to acknowledge the participants and investigators of the UK Biobank, Partner's Biobank, CLSA, AGDS and FinnGen study.

Author contributions
Junming Wang contributed to the design of the study, performed the Mendelian randomization analysis, and conducted the statistical analysis to investigate the causal relationship between gastroesophageal reflux disease (GERD) and sleep apnea syndrome (SAS). Junming Wang also contributed to the interpretation of the results and played a significant role in drafting and revising the manuscript. Pengfei Wang assisted in the statistical analysis and interpretation of the data. Jiang Lv and Ran Chen contributed to the data collection and experimental work related to the GERD and SAS relationship. Wei Yan provided assistance in the writing and editing of the manuscript. Daikun He supervised the project, provided critical revisions, and ensured the overall integrity of the research. All authors reviewed and approved the final version of the manuscript.

Funding
This work was supported by grants from the Shanghai Municipal Health Commission (Grant No. 202040174); Science and Technology Commission of Shanghai Municipality (Grant No. 22Y11900800); Core Discipline Improvement Project, 3-year (2020–2022) Action Plan of Shanghai Public Health System Development (GWV-10.1-XK26); Class A, Core Medicine Discipline Improvement Project of Jinshan District (JSZK2019A01); and Discipline Platform Improvement Project, 3-year Talents Echelon Action Plan of Jinshan Hospital, Fudan University (XPT-2020-3).

Availability of data and materials
Data are available from the authors upon reasonable request and with permission of UK Biobank, Partner's Biobank, CLSA, AGDS and FinnGen study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of General Practice, Jinshan Hospital, Fudan University, No. 1508 Longhang Road, Jinshan District, Shanghai 201508, People's Republic of China. [2]Department of General Practice, Zhongshan Hospital, Fudan University, Shanghai 200032, People's Republic of China. [3]Center of Emergency and Critical Care Medicine, Jinshan Hospital, Fudan University, Shanghai 201508, People's Republic of China. [4]Research Center for Chemical Injury, Emergency and Critical Medicine of Fudan University, Shanghai 201508, People's Republic of China. [5]Key Laboratory of Chemical Injury, Emergency and Critical Medicine of Shanghai Municipal Health Commission, Shanghai 201508, China.

Received: 6 October 2023 Accepted: 12 February 2025
Published online: 06 March 2025

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