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Investigating the causal links between obstructive sleep apnea and gastrointestinal diseases mediated by metabolic syndrome through mendelian randomization

Zhe Zhang[1,2,3,6], Chunyu Jiang[4,6], Baosheng Yin[2,6], Huan Wang[2,6], Junwei Zong[2], Tianke Yang[2,3], Linxuan Zou[2], Zhuofan Dong[2], Ying Chen[5]✉, Shouyu Wang[2]✉ & Xueling Qu[1]✉

Previous studies have pointed to a potential link between Obstructive Sleep Apnea (OSA) and gastrointestinal diseases, suggesting that this relationship might be influenced by the presence of Metabolic Syndrome. However, the exact role of these factors in determining gastrointestinal diseases has not been thoroughly explored. In our study, we utilized data from the Genome-wide Association Studies (GWAS) database, focusing on OSA, metabolic syndrome characteristics such as Body Mass Index (BMI), waist circumference, triglycerides, cholesterol, hypertension, type 2 diabetes, and common gastrointestinal diseases including chronic gastritis, gastric ulcers, irritable bowel syndrome, colorectal cancer, inflammatory bowel disease, cholecystitis, nonalcoholic fatty liver, and dyspepsia. By applying Single-variable and Multi-variable Mendelian randomization methods, we aimed to assess the correlation between OSA and gastrointestinal diseases and investigate whether this correlation is influenced by metabolic syndrome. Our findings revealed a strong association between OSA and an increased risk of chronic gastritis, gastric ulcers, inflammatory bowel disease, and nonalcoholic fatty liver disease. No significant connections were found with irritable bowel syndrome, colorectal cancer, cholecystitis, or dyspepsia. Additionally, OSA was linked to metabolic syndrome traits like BMI, waist circumference, triglycerides, hypertension, and type 2 diabetes. Further analysis showed that BMI, triglycerides, and hypertension were causally related to inflammatory bowel disease; BMI, waist circumference, hypertension, and type 2 diabetes to nonalcoholic fatty liver disease; and triglycerides, hypertension, and type 2 diabetes to chronic gastritis. The multivariable analysis indicated that hypertension mediates the relationship between OSA and chronic gastritis; BMI, triglycerides, and hypertension mediate the link between OSA and inflammatory bowel disease; and waist circumference mediates the connection between OSA and nonalcoholic fatty liver disease. To wrap up, this finding helps us understand how these issues might be related and stresses the role of metabolic syndrome in preventing them, which could lessen their effect on health.

Keywords Obstructive sleep apnea, Gastrointestinal diseases, Metabolic syndrome, Mendelian randomization

Abbreviations

OSA	Obstructive Sleep Apnea
MetS	Metabolic syndrome

[1]Pelvic floor repair center, Dalian women and Children Medical Center (Group), Dalian, China. [2]Department of Orthopaedic Surgery, The First Affiliated Hospital of Dalian Medical University, Dalian, China. [3]College of Integrative Medicine, Dalian Medical University, Dalian, China. [4]Department of Trauma Surgery, The Second Affiliated Hospital of Harbin Medical University, Dalian, China. [5]Department of Respiratory Medicine, The Second Affiliated Hospital of Dalian Medical University, Dalian, China. [6]Zhe Zhang, Chunyu Jiang, Baosheng Yin and Huan Wang contributed equally to this work. ✉email: yoursjane1934@126.com; wangshouyu666@126.com; quxuelingmm@sina.com

PD	Parkinson's disease
T2DM	Type 2 diabetes
MR	Mendelian randomization
UVMR	Univariable Mendelian randomization
BMI	Body mass index
MVMR	Multivariable Mendelian randomization
IVs	Instrumental variables
SNPs	Single nucleotide polymorphisms
IVW	Inverse variance weighting
TNF	Tumor necrosis factor
IL-1	Interleukin-1
IL-6	Interleukin-6
GERD	gastroesophageal reflux disease
IBDs	Inflammatory bowel diseases
IBD	Inflammatory bowel disease
CRP	C-reactive protein
UC	Ulcerative colitis
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
CIH	Chronic intermittent hypoxia
COPD	Chronic Obstructive Pulmonary Disease
GDs	Gastrointestinal diseases

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by the narrowing of the airway due to relaxation of the throat muscles and collapse of soft tissues, leading to disrupted sleep. Symptoms include insomnia, daytime sleepiness, and loud snoring[1]. The overall prevalence of OSA in the general adult population ranges from 9 to 38%, with rates reaching 78% in certain elderly populations and as high as 90% in men[2]. OSA is associated with various cardiovascular diseases, including hypertension, arrhythmias, stroke, coronary artery disease, atherosclerosis, and increased overall cardiovascular mortality risk. Additionally, OSA is linked to metabolic dysfunction and is commonly associated with conditions such as Parkinson's disease (PD), obesity, and hypertension[3]. In recent years, studies have indicated a correlation between OSA and gastrointestinal disorders such as gastroesophageal reflux disease, Barrett's esophagus, and gastrointestinal cancers, drawing increasing attention to the impact of OSA on gastrointestinal health[4–6].

Sleep disorders often stem from inappropriate lifestyle and dietary habits. Research has shown a correlation between poor sleep quality and functional gastrointestinal disorders and altered gut sensitivity, potentially leading to gastrointestinal symptoms and digestive system diseases in the general population[7,8]. Sleep patterns are primarily influenced by the circadian rhythm and its associated biological clock, which are regulated by multiple mechanisms directly related to gastrointestinal function. Circadian rhythm disruption is a common factor contributing to sleep issues, and sleep problems play a key role in various gastrointestinal diseases[9]. For instance, OSA patients have a higher risk of gastrointestinal disorders such as gastric ulcers and gastritis, which may be attributed to factors like chronic inflammation and immune system abnormalities triggered by OSA[10]. However, due to a lack of high-quality research data and the complexity of assessing the causal bidirectional relationship in traditional epidemiological studies, there is currently no comprehensive study confirming the causal connection between OSA and gastrointestinal diseases.

Metabolic syndrome (MetS) is a collection of metabolic abnormalities associated with increased risks of cardiovascular diseases and diabetes, including hypertension, hyperglycemia, high cholesterol, and obesity. OSA patients often exhibit a higher prevalence of metabolic syndrome[11]. Accumulating evidence suggests that OSA promotes weight gain, obesity, type 2 diabetes (T2DM), hypertension, and hypercholesterolemia through various mechanisms, forming a vicious cycle between metabolic syndrome and OSA[12]. Furthermore, studies have shown a close association between metabolic syndrome and gastrointestinal diseases[13]. Factors such as obesity, high cholesterol, hypertension, and elevated inflammatory markers in metabolic syndrome patients may increase the risk of gastroesophageal reflux, gastrointestinal dysmotility, and gastrointestinal inflammation, thereby contributing to the occurrence of gastrointestinal diseases. As a common risk factor for both OSA and gastrointestinal disorders, metabolic syndrome may play a significant role in their relationship, but further investigation is still needed.

The fundamental principle of Mendelian randomization (MR) is to utilize genetic variations associated with a specific exposure factor (such as lifestyle or physiological indicators) as instrumental variables to assess the causal relationship between the exposure factor and disease or other health outcomes[13]. Mendelian randomization minimizes confounding effects, and as genetic variations are determined at birth and not influenced by subsequent disease states, it helps avoid problems related to reverse causality. Compared to traditional randomized control trials, Mendelian randomization studies are more cost-effective and faster, utilizing existing large-scale genome-wide association study data for analysis. They simulate the effects of randomized control trials since the distribution of genetic variations is random, which aids in evaluating causal relationships between exposure factors and outcomes[14,15]. This article aims to explore the causal relationship between obstructive sleep apnea and gastrointestinal diseases using the Mendelian randomization method, as well as to investigate the influence of other factors on this relationship. This research is crucial for providing beneficial diagnosis, treatment, and prevention strategies for related diseases, ensuring comprehensive and accurate medical services for patients.

Materials and methods

Study design

The framework of this Mendelian randomization study is depicted in Fig. 1. The research is divided into two parts. In the first section, we employed univariable Mendelian randomization(UVMR) to investigate potential causal relationships between sleep apnea syndrome and common gastrointestinal diseases: Chronic gastritis, Gastric ulcers, Irritable bowel syndrome, Colorectal cancer, Inflammatory bowel disease, Cholecystitis, Nonalcoholic fatty liver disease, Dyspepsia, as well as candidate mediators associated with metabolic syndrome: Obesity-Body mass index (BMI), Waist circumference, Triglyceride levels, Cholesterol levels, Hypertension, Type 2 diabetes. We further explored whether there were causal relationships between these candidate mediators and positive outcomes. In the second part, we utilized multivariable Mendelian randomization (MVMR) methods to identify mediators that underlie the causal relationship between sleep apnea syndrome and gastrointestinal diseases. In this study, we used genetic variants as instrumental variables (IVs) for MR analysis. The validity of our MR study's hypothesis is founded on three core assumptions: (1) Relevance assumption: The selected genetic variant

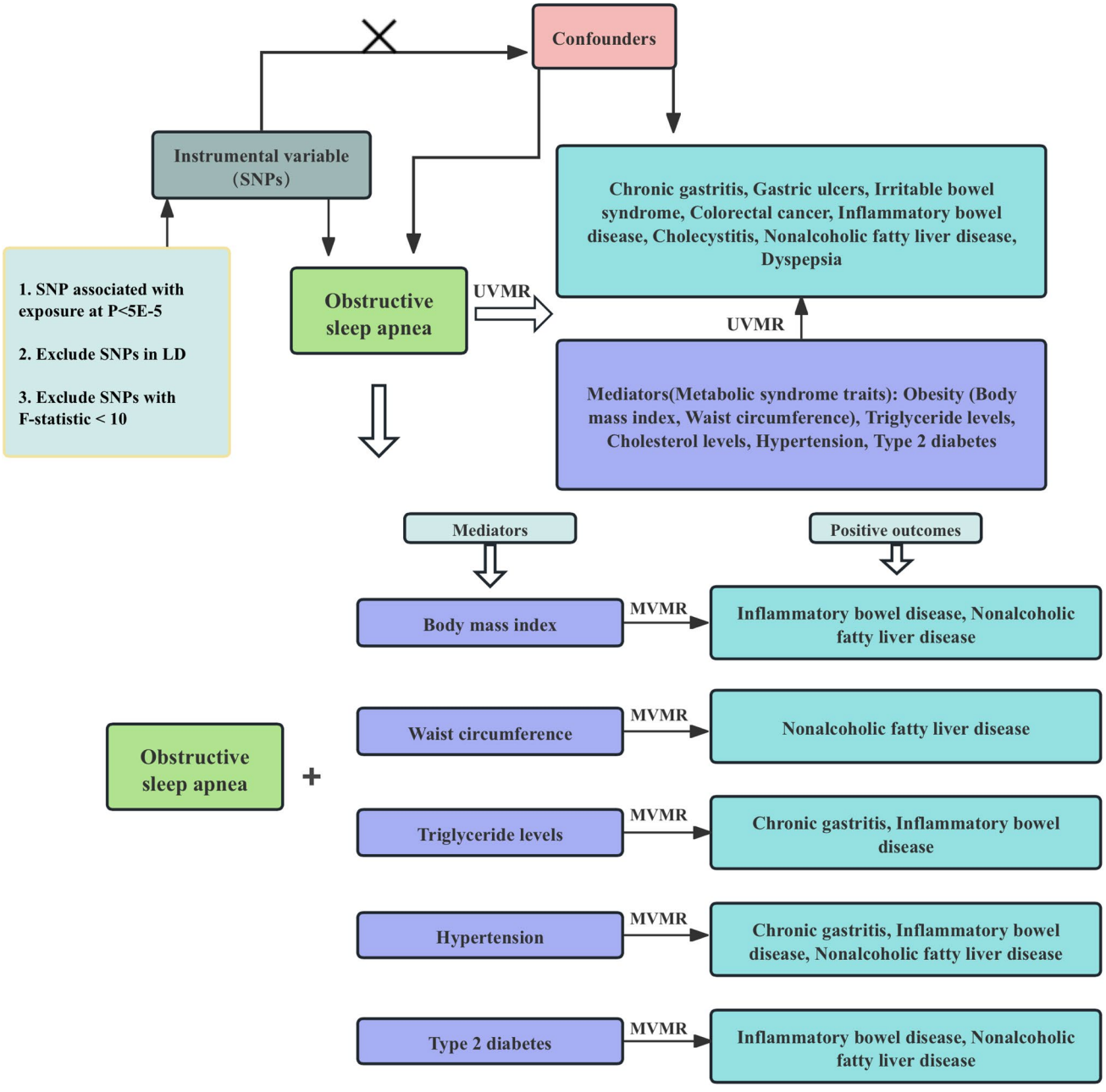

Figure 1. Flowchart of Mendelian randomization analysis conducted in this study. SVMR analysis investigates the effect of Obstructive Sleep Apnea on gastrointestinal diseases and Metabolic Syndrome traits, MVMR analysis evaluates the roles of Metabolic Syndrome traits mediating the association between Obstructive Sleep Apnea and Gastrointestinal diseases.

(usually single nucleotide polymorphisms, SNPs) must be strongly correlated with the exposure factor being studied. This ensures that the genetic variant can serve as an instrumental variable representing changes in the exposure factor. (2) Independence assumption: The chosen genetic variant should be independent of any other confounding factors that may affect the study outcome. This means that the genetic variant influences the outcome solely through the exposure factor and not through other unconsidered pathways. (3) Exclusion restriction assumption: The effect of the genetic variant on the outcome must be exerted exclusively through the exposure factor and not through any other routes[14]. These rules out the possibility of the genetic variant directly affecting the outcome, ensuring the validity of the analysis. These assumptions are fundamental for conducting MR studies and help researchers use genetic variants as instrumental variables to explore the causal relationships between specific exposure factors and disease or health outcomes. To mitigate the impact of heterogeneity, this study employed the random-effects model inverse variance weighting (IVW) as the primary method for analysis.

Data sources

All genetic instrumental variables are derived from the largest publicly available GWAS summary statistics[16] (https://gwas.mrcieu.ac.uk). To avoid population heterogeneity bias, we primarily used summary data from European populations. The datasets for Sleep apnoea, Hypertension, and Type 2 diabetes originate from the FinnGen biobank analysis round 5 (https://www.finngen.fi/fi); Chronic gastritis, Gastric ulcers, Colorectal cancer, Inflammatory bowel disease, Cholecystitis, and Nonalcoholic fatty liver disease data are sourced from the EBI database (https://www.ebi.ac.uk/gwas/downloads/summary-statistics); Body mass index, Waist circumference, Triglyceride, and Cholesterol datasets are from the IEU database (https://gwas.mrcieu.ac.uk/datasets/); Ulcerative colitis and Dyspepsia data are from the UKB database (https://data.bris.ac.uk/data/dataset/pnoat8cxo0u52p6ynfaekeigi). Sample sizes are as indicated in Table 1. All included studies have received ethical approval from their respective institutional review boards, including written informed consent from participants and stringent quality control measures. Since all analyses were conducted using publicly accessible summary data, no additional ethical approval from an institutional review board was required for this study. All details can be found in Table 1.

Selection of genetic instrumental variables

To identify qualified genetic IVs that conform to the MR assumptions, a series of tests must be conducted. Firstly, to obtain a sufficient number of instrumental variables and increase statistical power, we set the p-value threshold for IVs at 5E-05 in this study and established independence to eliminate linkage disequilibrium ($r^2 < 0.001$, window size = 10,000 kb) to select SNPs strongly associated with exposure. Secondly, we calculated the statistical strength of the exposure (F-statistic), where an F-value greater than 10 indicates the absence of weak instrument bias[17], with F statistic values for each instrument-exposure association ranging from 19.571 to 81.281 (Table 2). Thirdly, we harmonized exposure and outcome datasets to ensure that the effect alleles belong to the same alleles. The SNPs selected through these rigorous procedures can be used as IVs for subsequent analysis.

Statistical analysis and data visualization

The analysis in this study utilized R software packages such as TwoSampleMR, MRPRESSO, MVMR, LASSO, and MendelianRandomization. In univariable Mendelian randomization, IVW was used as the default method to evaluate causal estimates, and was validated using MR-Egger and weighted median methods. The main idea behind the IVW method is to use instrumental variables (IVs) to investigate causality and handle confounding factors. This method is advantageous if the SNPs fully comply with the three principles of MR studies: relevance, consistency, and independence, allowing for correct causal estimates[18]. Egger's method is a technique for testing the exogeneity of instrumental variables. It assesses the exogeneity of the IVs by calculating the slope and

Phenotype	Consortium/Author	Ethnicity	Sample size	PubMed ID
Obstructive Sleep Apnea	NA	European	16,761cases, 201,194 controls	34,017,140
Body mass index	GIANT	European	322,154 individuals	25,673,413
Waist circumference	GIANT	European	232,101 individuals	25,673,412
Triglyceride	UK Biobank	European	16,761cases, 201,197 controls	32,203,549
Cholesterol	GLGC	Mixed	187,365 individuals	24,097,068
Hypertension	NA	European	42,857 cases, 175,935 controls	NA
Type 2 diabetes	NA	European	32,469 cases, 183,185 controls	NA
Chronic gastritis	Sakaue S	European	3,645 cases, 441,451 controls	34,594,039
Gastric ulcers	NA	European	3,531 cases, 481,067 controls	33,959,723
Irritable bowel syndrome	MRC-IEU	European	10,939 cases, 451,994 controls	NA
Colorectal cancer	Sakaue S	European	6,581 cases, 463,421 controls	34,594,039
Inflammatory bowel disease	Mbatchou J	European	404,781 individuals	34,017,140
Cholecystitis	Sakaue S	European	9,820 cases, 461,431 controls	34,594,039
Nonalcoholic fatty liver disease	Ghodsian N	European	8,434 cases, 770,180 controls	34,841,290
Dyspepsia	MRC-IEU	European	7,662 cases, 455,348 controls	NA

Table 1. Details of the phenotypes included in the mendelian randomization analyses.

Phenotype	nSNPS	F-statistics
Obstructive Sleep Apnea	169	19.571
Body mass index	232	35.032
Waist circumference	165	30.642
Triglyceride	632	81.281
Hypertension	266	22.926
Type 2 diabetes	343	28.261

Table 2. The number of SNPs and statistical strength of the exposure (F-statistic).

exposure	outcome	method	nsnp	pval	OR(95%CI)	Heterogeneity.pval	Pleiotropy.pval	egger_intercept
Obstructive Sleep Apnea	Chronic gastritis	MR Egger	168	0.003	1.245(1.079 to 1.436)		0.296	−6.29E−03
		Weighted median	168	0.009	1.125(1.030 to 1.227)			
		IVW	168	3.05E−06	1.162(1.091 to 1.238)	0.249		
Obstructive Sleep Apnea	Gastric ulcers	MR Egger	159	0.042	1.001(1.000 to 1.002)		0.385	−3.47E−05
		Weighted median	159	0.090	1.001(1.000 to 1.001)			
		IVW	159	0.011	1.001(1.000 to 1.001)	0.380		
Obstructive Sleep Apnea	Irritable bowel syndrome	MR Egger	121	0.332	0.998(0.995 to 1.002)		0.197	1.58E−04
		Weighted median	121	0.764	1.000(0.999 to 1.002)			
		IVW	121	0.486	1.000(0.999 to 1.001)	0.010		
Obstructive Sleep Apnea	Colorectal cancer	MR Egger	167	0.607	0.979(0.904 to 1.060)		0.251	3.90E−03
		Weighted median	167	0.338	1.027(0.973 to 1.083)			
		IVW	167	0.253	1.021(0.985 to 1.058)	0.521		
Obstructive Sleep Apnea	Inflammatory bowel disease	MR Egger	143	0.038	1.071(1.005 to 1.142)		0.336	−0.003
		Weighted median	143	0.053	1.046(0.999 to 1.095)			
		IVW	143	0.010	1.042(1.010 to 1.075)	0.430		
Obstructive Sleep Apnea	Cholecystitis	MR Egger	168	0.129	1.057(0.984 to 1.134)		0.391	−2.72E−03
		Weighted median	168	0.398	1.024(0.969 to 1.081)			
		IVW	168	0.119	1.029(0.993 to 1.066)	0.854		
Obstructive Sleep Apnea	Nonalcoholic fatty liver disease	MR Egger	148	0.792	0.986(0.890 to 1.093)		0.055	8.43E−03
		Weighted median	148	0.324	1.034(0.968 to 1.105)			
		IVW	148	0.001	1.080(1.030 to 1.132)	0.161		
Obstructive Sleep Apnea	Dyspepsia	MR Egger	107	0.726	1.001(0.997 to 1.004)		0.823	−2.51E−05
		Weighted median	107	0.443	1.001(0.999 to 1.002)			
		IVW	107	0.634	1.000(0.999 to 1.001)	0.436		

P<0.05 was considered statistically significant

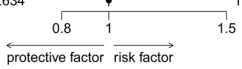

Figure 2. Mendelian randomization results of the effect of obstructive sleep apnea on gastrointestinal diseases (chronic gastritis, gastric ulcers, irritable bowel syndrome, colorectal cancer, inflammatory bowel disease, cholecystitis, nonalcoholic fatty liver, dyspepsia).

intercept of the regression coefficients. If the slope is significantly non-zero, there is bias, meaning the IVs are correlated with the error term, necessitating correction with other methods[19]. The weighted median method is a weight-based approach that multiplies the effect size of each SNP by its corresponding weight and then determines the weighted median of all SNPs as the final causal estimate. This method is beneficial for handling a large number of SNPs and is less affected by outliers[20]. A p-value less than 0.05 is considered statistically significant across all methods. To ensure the reliability of the results, sensitivity analyses (heterogeneity and pleiotropy tests), MR-Egger intercept tests, and leave-one-out tests were conducted for comparison. Finally, the MR-PRESSO method was employed to detect and remove any outlier SNPs. For multivariable Mendelian randomization, we used IVW and LASSO methods to evaluate causal estimates [citation needed], and applied the MR-Egger method to test whether the outcomes have undetected pleiotropy.

Results

Univariable mendelian randomization

Obstructive sleep apnea and gastrointestinal diseases

In the analysis employing the IVW method, we discovered a correlation based on genetic predictions between OSA and an increased risk of Chronic Gastritis (P=3.05E-06, OR=1.162, 95% CI=1.091–1.238), Gastric Ulcers (P=0.011, OR=1.001, 95% CI=1.000-1.001), Inflammatory Bowel Disease (P=0.010, OR=1.042, 95% CI=1.010–1.075), and Non-Alcoholic Fatty Liver Disease (P=0.001, OR=1.080, 95% CI=1.030–1.132). Specifically, the causal link between OSA and Chronic Gastritis was significantly validated in both the MR Egger method and the Weighted Median method. The relationship with Gastric Ulcers and Inflammatory Bowel Disease showed significance in the MR Egger method but did not reach significant levels in the Weighted Median method. However, the causal relationship with Non-Alcoholic Fatty Liver Disease did not exhibit significance in either the MR Egger or the Weighted Median method (Fig. 2). Sensitivity analyses indicated no issues with heterogeneity or pleiotropy. The leave-one-out method indicated that there are no individual SNPs solely driving the causal relationships between the exposure and outcomes (Additional file 1), and with no noticeable deviation of the Egger intercept from 0. Results from MR-PRESSO also showed no abnormal SNPs

(Additional file 2). Furthermore, our analysis indicated no apparent causal relationships between genetically predicted OSA and Irritable Bowel Syndrome ($P=0.486$, OR = 1.000, 95% CI = 0.999–1.001), Colorectal Cancer ($P=0.253$, OR = 1.021, 95% CI = 0.985–1.058), Cholecystitis ($P=0.119$, OR = 1.029, 95% CI = 0.993–1.066), and Dyspepsia ($P=0.634$, OR = 1.000, 95% CI = 0.999–1.001), a finding consistently concluded across three different statistical methods (Fig. 2).

Obstructive sleep apnea and potential mediators

The IVW results indicated that there are causal relationships between genetically predicted OSA and BMI ($P=2.09E-05$, OR = 1.092, 95% CI = 1.049–1.138), Waist Circumference ($P=2.10E-05$, OR = 1.090, 95% CI = 1.048–1.134), Triglycerides ($P=0.028$, OR = 1.009, 95% CI = 1.001–1.017), Hypertension ($P=1.76E-28$, OR = 1.192, 95% CI = 1.155–1.229), and T2DM ($P=1.33E-15$, OR = 1.201, 95% CI = 1.149–1.257). Moreover, the causal links with BMI, Waist Circumference, Hypertension, and T2DM remained significant in both the MR Egger method and the Weighted Median method, whereas the association with Triglycerides was not significant in these two methods (Fig. 3). Sensitivity analyses revealed the presence of heterogeneity but no pleiotropy. The leave-one-out method indicated that there are no individual SNPs solely driving the causal relationships between the exposure and outcomes (Additional file 1). The Egger intercept did not show a significant deviation from 0. Furthermore, the MR-PRESSO method identified the presence of outlier SNPs (Additional file 2), but the causal relationships remained significant after their removal (Fig. 5). Moreover, our findings revealed no discernible causal connections between genetically forecasted OSA and Cholesterol ($P=0.054$, OR = 0.980, 95% CI = 0.961-1.000).

Potential mediators and positive exposure

Body mass index and positive exposure

The IVW results indicate that genetically predicted BMI is associated with an increased risk of Inflammatory Bowel Disease ($P=0.003$, OR = 1.147, 95% CI = 1.048–1.255) and Nonalcoholic Fatty Liver Disease ($P=2.49E-051$, OR = 1.344, 95% CI = 1.171–1.542). The causal relationship with Inflammatory Bowel Disease was not significant in either the MR Egger method or the Weighted Median method, whereas the association with Nonalcoholic Fatty Liver Disease was significant in the Weighted Median method but not in the MR Egger method (Fig. 4). Sensitivity analyses revealed the presence of heterogeneity but no pleiotropy. Leave-one-out results showed no individual SNPs solely driving the causal relationships (Additional file 1), and the Egger intercept did not significantly deviate from 0. MR-PRESSO results showed no outlier SNPs (Additional file 2).

Waist circumference and positive exposure

Genetically predicted waist circumference is significantly associated with an increased risk of Nonalcoholic Fatty Liver Disease ($P=3.74E-07$, OR = 1.470, 95% CI = 1.267–1.705), a causal relationship confirmed by the IVW method, and found to be significant in both the MR Egger method and the Weighted Median method (Fig. 4). Sensitivity analyses indicated the presence of heterogeneity but no signs of pleiotropy. No single SNPs were found to dominate the causal link through leave-one-out testing, and the Egger intercept did not show a trend deviating from 0 (Additional file 1). Additionally, MR-PRESSO results did not detect any abnormal SNPs (Additional file 2).

Triglycerides and positive exposure

In the IVW method, Triglycerides were associated with an increased risk of Chronic Gastritis ($P=0.022$, OR = 1.126, 95% CI = 1.017–1.247) and Inflammatory Bowel Disease ($P=4.73E-05$, OR = 1.126, 95% CI = 1.063–1.192), which were not significant in the other two methods. The causal relationships with Gastric

exposure	outcome	method	nsnp	pval	OR(95%CI)	Heterogeneity.pval	Pleiotropy.pval	egger_intercept
Obstructive Sleep Apnea	Body mass index	MR Egger	85	0.013	1.205(1.043 to 1.392)		0.168	−7.26E−03
		Weighted median	85	0.006	1.031(1.009 to 1.054)			
		IVW	85	2.09E−05	1.092(1.049 to 1.138)	<0.01		
Obstructive Sleep Apnea	Waist circumference	MR Egger	84	0.011	1.208(1.049 to 1.392)		0.142	−7.59E−03
		Weighted median	84	0.001	1.043(1.017 to 1.069)			
		IVW	84	2.10E−05	1.090(1.048 to 1.134)	<0.01		
Obstructive Sleep Apnea	Triglyceride	MR Egger	163	0.451	1.006(0.991 to 1.021)		0.643	3.19E−04
		Weighted median	163	0.121	1.006(0.998 to 1.015)			
		IVW	163	0.028	1.009(1.001 to 1.017)	<0.01		
Obstructive Sleep Apnea	Cholesterol	MR Egger	84	0.221	0.954(0.886 to 1.028)		0.462	1.95E−03
		Weighted median	84	0.373	0.987(0.958 to 1.016)			
		IVW	84	0.054	0.980(0.961 to 1.000)	0.078		
Obstructive Sleep Apnea	Hypertension	MR Egger	168	3.35E−04	1.141(1.063 to 1.224)		0.177	0.004
		Weighted median	168	5.84E−17	1.185(1.139 to 1.234)			
		IVW	168	1.76E−28	1.192(1.155 to 1.229)	<0.01		
Obstructive Sleep Apnea	Type 2 diabetes	MR Egger	168	0.004	1.167(1.053 to 1.293)		0.533	0.003
		Weighted median	168	8.32E−10	1.157(1.105 to 1.213)			
		IVW	168	1.33E−15	1.201(1.149 to 1.257)	<0.01		

P<0.05 was considered statistically significant

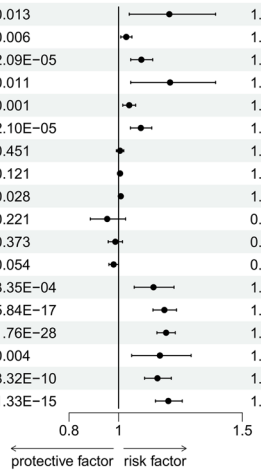

Figure 3. Mendelian randomization results of the effect of obstructive sleep apnea on metabolic syndrome traits (body mass index, waist circumference, triglycerides, cholesterol, hypertension, type 2 diabetes).

exposure	outcome	method	nsnp	pval	OR(95%CI)	Heterogeneity.pval	Pleiotropy.pval	egger_intercept
Body mass index	Chronic gastritis	MR Egger	227	8.62e-01	0.957(0.581 to 1.576)		0.428	4.19E-03
		Weighted median	227	2.30e-01	1.163(0.909 to 1.488)			
		IVW	227	8.00e-02	1.158(0.983 to 1.365)	0.176		
	Gastric ulcers	MR Egger	228	5.15e-01	1.001(0.998 to 1.005)		0.531	-2.47E-05
		Weighted median	228	8.10e-01	1.000(0.998 to 1.002)			
		IVW	228	8.57e-01	1.000(0.999 to 1.001)	0.556		
	Inflammatory bowel disease	MR Egger	217	4.26e-01	1.116(0.852 to 1.462)		0.835	5.96E-04
		Weighted median	217	1.68e-01	1.101(0.960 to 1.262)			
		IVW	217	3.00e-03	1.147(1.048 to 1.255)	0.042		
	Nonalcoholic fatty liver disease	MR Egger	224	7.80e-02	1.458(0.960 to 2.214)		0.686	-1.79E-03
		Weighted median	224	8.00e-03	1.288(1.068 to 1.552)			
		IVW	224	2.49e-05	1.344(1.171 to 1.542)	7.73E-05		
Waist circumference	Chronic gastritis	MR Egger	159	9.53e-01	0.982(0.542 to 1.781)		0.779	1.816E-03
		Weighted median	159	9.55e-01	0.992(0.757 to 1.300)			
		IVW	159	4.88e-01	1.066(0.891 to 1.275)	0.498		
	Gastric ulcers	MR Egger	160	3.01e-01	1.003(0.998 to 1.007)		0.293	-5.487E-05
		Weighted median	160	8.95e-01	1.000(0.998 to 1.002)			
		IVW	160	9.18e-01	1.000(0.999 to 1.001)	0.961		
	Inflammatory bowel disease	MR Egger	150	9.21e-01	1.020(0.691 to 1.506)		0.657	1.85E-03
		Weighted median	150	6.05e-01	1.040(0.897 to 1.205)			
		IVW	150	6.00e-02	1.110(0.996 to 1.238)	0.009		
	Nonalcoholic fatty liver disease	MR Egger	158	2.90e-02	1.775(1.066 to 2.954)		0.449	-4.17E-03
		Weighted median	158	1.20e-02	1.297(1.059 to 1.589)			
		IVW	158	3.74e-07	1.470(1.267 to 1.705)	0.010		
Triglyceride	Chronic gastritis	MR Egger	608	1.40e-01	1.119(0.964 to 1.298)		0.904	2.12E-04
		Weighted median	608	1.05e-01	1.155(0.970 to 1.374)			
		IVW	608	2.20e-02	1.126(1.017 to 1.247)	0.061		
	Gastric ulcers	MR Egger	613	7.85e-01	1.000(0.999 to 1.001)		0.028	2.98E-05
		Weighted median	613	1.61e-01	1.001(1.000 to 1.002)			
		IVW	613	4.00e-03	1.001(1.000 to 1.002)	0.149		
	Inflammatory bowel disease	MR Egger	541	8.30e-02	1.078(0.991 to 1.172)		0.165	1.36E-03
		Weighted median	541	1.33e-01	1.079(0.977 to 1.192)			
		IVW	541	4.73e-05	1.126(1.063 to 1.192)	0.002		
	Nonalcoholic fatty liver disease	MR Egger	574	4.00e-03	1.211(1.065 to 1.377)		0.018	3.46E-03
		Weighted median	574	4.00e-03	1.252(1.076 to 1.458)			
		IVW	574	3.21e-12	1.360(1.247 to 1.482)	1.12E-08		
Hypertension	Chronic gastritis	MR Egger	262	6.40e-02	1.143(0.993 to 1.316)		0.555	-2.81E-03
		Weighted median	262	3.40e-02	1.098(1.007 to 1.197)			
		IVW	262	2.00e-03	1.100(1.036 to 1.167)	0.788		
	Gastric ulcers	MR Egger	248	2.64e-01	1.000(1.000 to 1.001)		0.397	-2.67E-05
		Weighted median	248	7.53e-01	1.000(0.999 to 1.001)			
		IVW	248	4.43e-01	1.000(1.000 to 1.001)	0.965		
	Inflammatory bowel disease	MR Egger	224	4.40e-01	1.023(0.965 to 1.085)		0.682	9.01E-04
		Weighted median	224	1.93e-01	1.032(0.984 to 1.083)			
		IVW	224	4.30e-02	1.034(1.001 to 1.068)	0.021		
	Nonalcoholic fatty liver disease	MR Egger	219	5.08e-01	0.960(0.851 to 1.083)		0.066	7.37E-03
		Weighted median	219	3.44e-01	1.034(0.965 to 1.109)			
		IVW	219	1.20e-02	1.065(1.014 to 1.119)	0.102		
Type 2 diabetes	Chronic gastritis	MR Egger	337	3.39e-01	1.048(0.952 to 1.154)		0.591	2.03E-03
		Weighted median	337	2.43e-01	1.042(0.973 to 1.116)			
		IVW	337	2.00e-03	1.073(1.026 to 1.121)	0.252		
	Gastric ulcers	MR Egger	324	9.70e-02	1.001(1.000 to 1.001)		0.383	-2.58E-05
		Weighted median	324	2.08e-01	1.000(1.000 to 1.001)			
		IVW	324	6.60e-02	1.000(1.000 to 1.001)	0.025		
	Inflammatory bowel disease	MR Egger	291	4.88e-01	1.018(0.968 to 1.071)		0.901	2.52E-04
		Weighted median	291	7.90e-01	1.006(0.960 to 1.055)			
		IVW	291	1.07e-01	1.021(0.996 to 1.047)	0.034		
	Nonalcoholic fatty liver disease	MR Egger	138	8.02e-01	1.008(0.947 to 1.073)		0.074	4.14E-03
		Weighted median	138	1.40e-02	1.031(1.006 to 1.057)			
		IVW	138	1.37e-05	1.062(1.034 to 1.091)	1.12E-52		

P<0.05 was considered statistically significant

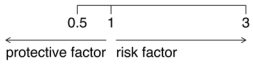

Figure 4. Mendelian randomization results of the effect of metabolic syndrome traits (body mass index, waist circumference, triglycerides, cholesterol, hypertension, type 2 diabetes) on positive outcomes (chronic gastritis, gastric ulcers, inflammatory bowel disease, cholecystitis, nonalcoholic fatty liver).

Ulcers and Nonalcoholic Fatty Liver Disease may be influenced by pleiotropy and thus were not pursued in subsequent multivariable studies (Fig. 4). Sensitivity analyses showed heterogeneity in the causal relationships with Chronic Gastritis and Inflammatory Bowel Disease but no pleiotropy. Leave-one-out results indicated no individual SNPs driving the causality (Additional file 1), the Egger intercept did not significantly deviate from 0, and MR-PRESSO indicated the presence of outlier SNPs (Additional file 2), however, after their removal, the causal relationships remained significant (Fig. 5).

exposure	outcome	method	nsnp	pval	OR(95%CI)	Heterogeneity.pval	Pleiotropy.pval	egger_intercept
Obstructive Sleep Apnea	Body mass index	MR Egger	80	1.48e-01	1.043(0.986 to 1.104)		0.932	-1.75E-04
		Weighted median	80	1.20e-02	1.029(1.006 to 1.053)			
		IVW	80	7.76e-07	1.041(1.024 to 1.058)	0.120		
Obstructive Sleep Apnea	Waist circumference	MR Egger	81	1.82e-01	1.048(0.979 to 1.122)		0.771	-7.13E-04
		Weighted median	81	2.00e-03	1.040(1.014 to 1.066)			
		IVW	81	1.15e-04	1.038(1.018 to 1.057)	0.032		
Obstructive Sleep Apnea	Triglyceride	MR Egger	157	2.52e-01	1.008(0.995 to 1.021)		0.926	-5.64E-05
		Weighted median	157	1.40e-01	1.006(0.998 to 1.015)			
		IVW	157	4.20e-02	1.007(1.000 to 1.014)	<0.01		
Obstructive Sleep Apnea	Hypertension	MR Egger	167	1.00e-03	1.130(1.055 to 1.211)		0.142	0.004
		Weighted median	167	3.58e-14	1.171(1.124 to 1.220)			
		IVW	167	4.01e-27	1.184(1.148 to 1.221)	<0.01		
Obstructive Sleep Apnea	Type 2 diabetes	MR Egger	165	3.00e-03	1.143(1.048 to 1.247)		0.623	1.79E-03
		Weighted median	165	1.61e-09	1.150(1.099 to 1.203)			
		IVW	165	5.92e-15	1.166(1.122 to 1.212)	<0.01		
Triglyceride	Chronic gastritis	MR Egger	606	1.20e-01	1.123(0.971 to 1.300)		0.933	1.46E-04
		Weighted median	606	1.06e-01	1.155(0.970 to 1.374)			
		IVW	606	1.80e-02	1.128(1.021 to 1.247)	1.83E-01		
Type 2 diabetes	Nonalcoholic fatty liver disease	MR Egger	285	1.11e-01	1.065(0.986 to 1.151)		0.268	3.35E-03
		Weighted median	285	7.00e-03	1.075(1.020 to 1.134)			
		IVW	285	2.42e-08	1.107(1.068 to 1.148)	0.039		

P<0.05 was considered statistically significant

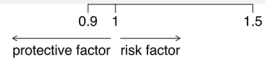

Figure 5. Mendelian randomization results of MR-PRESSO (after removing outlier SNPs).

Hypertension and positive exposure

IVW results suggest that Hypertension is associated with an increased risk of Chronic Gastritis ($P=0.002$, OR = 1.100, 95% CI = 1.036–1.167), Inflammatory Bowel Disease ($P=0.043$, OR = 1.034, 95% CI = 1.001–1.068), and Nonalcoholic Fatty Liver Disease ($P=0.012$, OR = 1.065, 95% CI = 1.014–1.119). Chronic Gastritis was significant in the Weighted Median method but not in the MR Egger method, while Inflammatory Bowel Disease and Nonalcoholic Fatty Liver Disease were not significant in either method (Fig. 4). Sensitivity analyses revealed no heterogeneity for Chronic Gastritis and Nonalcoholic Fatty Liver Disease, with Inflammatory Bowel Disease showing heterogeneity; all three conditions showed no pleiotropy. Leave-one-out results showed no individual SNPs driving the causality (Additional file 1), and the Egger intercept did not significantly deviate from 0. MR-PRESSO results indicated no outlier SNPs (Additional file 2).

Type 2 diabetes and positive exposure

T2DM has a causal relationship with both Chronic Gastritis ($P=0.002$, OR = 1.073, 95% CI = 1.026–1.121) and Nonalcoholic Fatty Liver Disease ($P=1.37E-05$, OR = 1.062, 95% CI = 1.034–1.091). Nonalcoholic Fatty Liver Disease was significant in the Weighted Median method but not in the MR Egger method, whereas Chronic Gastritis was not significant in either method (Fig. 4). Sensitivity analyses showed no heterogeneity for Chronic Gastritis, with Inflammatory Bowel Disease and Nonalcoholic Fatty Liver Disease presenting heterogeneity; all three conditions showed no pleiotropy. Leave-one-out results indicated no individual SNPs driving the causality, and the Egger intercept did not significantly deviate from 0 (Additional file 1). In the MR-PRESSO method, there were no outlier SNPs detected for T2DM in relation to Chronic gastritis, while outlier SNPs were identified in the association with Nonalcoholic fatty liver disease (Additional file 2). Even after the removal of these outlier SNPs, the relationship between T2DM and Nonalcoholic fatty liver disease remained statistically significant (Fig. 5).

Multivariable mendelian randomization

The mediating role of BMI between OSA and gastrointestinal disease

After adjusting for BMI using the IVW method, we observed that the significant association between sleep apnea and inflammatory bowel disease vanished ($P=0.203$, OR = 0.902, 95% CI = 0.770–1.057), whereas the connection with non-alcoholic fatty liver disease persisted ($P=0.044$, OR = 1.282, 95% CI = 1.007–1.632). Conversely, the causal relationship between BMI and inflammatory bowel disease remained significant ($P=0.010$, OR = 1.243, 95% CI = 1.055–1.466), but its association with non-alcoholic fatty liver disease was nullified ($P=0.126$, OR = 1.221, 95% CI = 0.946–1.575). This pattern was consistently reflected in both LASSO regression analysis and the MR Egger method (Fig. 6). Additionally, MR Egger intercept analysis did not indicate the presence of horizontal pleiotropy, suggesting that there was no systematic error due to horizontal pleiotropy in the model (Fig. 7).

The mediating role of Waist circumference between OSA and gastrointestinal disease

Upon correcting for waist circumference, the causal relationship between OSA and non-alcoholic fatty liver disease was no longer significant ($P=0.054$, OR = 1.254, 95% CI = 0.996–1.578), whereas the association between waist circumference and non-alcoholic fatty liver disease remained pronounced ($P=0.030$, OR = 1.394, 95% CI = 1.032–1.885). This result was consistently validated across the IVW, LASSO, and MR-Egger methods (Fig. 6). Additionally, MR-Egger intercept analysis did not reveal signs of horizontal pleiotropy, indicating the absence of systematic bias caused by horizontal pleiotropy (Fig. 7).

exposure/adjustment	outcome	method	nsnp	pval	OR(95%CI)	ivw.Heterogeneity.pval
Obstructive Sleep Apnea	Inflammatory bowel disease	IVW	2	0.203	0.902(0.770 to 1.057)	0.226
Body mass index			63	0.010	1.243(1.055 to 1.466)	
Obstructive Sleep Apnea		LASSO	2	0.203	0.902(0.770 to 1.057)	
Body mass index			63	0.010	1.243(1.055 to 1.466)	
Obstructive Sleep Apnea	Nonalcoholic fatty liver disease	IVW	2	0.044	1.282(1.007 to 1.632)	0.009
Body mass index			66	0.126	1.221(0.946 to 1.575)	
Obstructive Sleep Apnea		LASSO	2	0.044	1.282(1.007 to 1.632)	
Body mass index			66	0.126	1.221(0.946 to 1.575)	
Obstructive Sleep Apnea	Nonalcoholic fatty liver disease	IVW	3	0.054	1.254(0.996 to 1.578)	0.057
Waist circumference			39	0.030	1.394(1.032 to 1.885)	
Obstructive Sleep Apnea		LASSO	3	0.054	1.254(0.996 to 1.578)	
Waist circumference			39	0.030	1.394(1.032 to 1.885)	
Obstructive Sleep Apnea	Chronic gastritis	IVW	3	0.164	1.145(0.946 to 1.384)	1.10E-03
Triglyceride			267	0.092	1.110(0.983 to 1.253)	
Obstructive Sleep Apnea		LASSO	3	0.164	1.145(0.946 to 1.384)	
Triglyceride			267	0.092	1.110(0.983 to 1.253)	
Obstructive Sleep Apnea	Inflammatory bowel disease	IVW	3	0.472	0.964(0.872 to 1.065)	0.036
Triglyceride			238	0.009	1.087(1.021 to 1.158)	
Obstructive Sleep Apnea		LASSO	3	0.453	0.962(0.871 to 1.063)	
Triglyceride			238	0.008	1.088(1.022 to 1.159)	
Obstructive Sleep Apnea	Chronic gastritis	IVW	5	0.265	0.886(0.715 to 1.097)	0.750
Hypertension			25	0.001	1.246(1.094 to 1.419)	
Obstructive Sleep Apnea		LASSO	5	0.265	0.886(0.715 to 1.097)	
Hypertension			25	0.001	1.246(1.094 to 1.419)	
Obstructive Sleep Apnea	Inflammatory bowel disease	IVW	5	0.558	0.955(0.817 to 1.115)	0.336
Hypertension			20	0.005	1.145(1.043 to 1.257)	
Hypertension		LASSO	20	0.004	1.125(1.038 to 1.219)	
Obstructive Sleep Apnea	Nonalcoholic fatty liver disease	IVW	4	2.73E-04	1.495(1.204 to 1.857)	0.281
Hypertension			21	0.892	1.009(0.890 to 1.144)	
Obstructive Sleep Apnea		LASSO	4	2.73E-04	1.495(1.204 to 1.857)	
Hypertension			21	0.892	1.009(0.890 to 1.144)	
Obstructive Sleep Apnea	Chronic gastritis	IVW	59	0.100	1.051(0.990 to 1.116)	0.947
Type 2 diabetes			5	0.242	1.109(0.932 to 1.320)	
Obstructive Sleep Apnea		LASSO	59	0.100	1.051(0.990 to 1.116)	
Type 2 diabetes			5	0.242	1.109(0.932 to 1.320)	
Obstructive Sleep Apnea	Nonalcoholic fatty liver disease	IVW	4	0.001	1.469(1.173 to 1.839)	1.00E-04
Type 2 diabetes			54	0.002	1.123(1.043 to 1.209)	
Obstructive Sleep Apnea		LASSO	4	0.001	1.469(1.173 to 1.839)	
Type 2 diabetes			54	0.002	1.123(1.043 to 1.209)	

P<0.05 was considered statistically significant

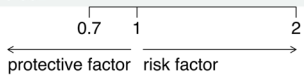

Figure 6. Multivariable MR result of causal relationships of obstructive sleep apnea and metabolic syndrome traits on positive outcomes.

The mediating role of triglyceride between OSA and gastrointestinal disease

After adjusting for triglyceride levels and applying the IVW method, we found that the causal relationships between OSA and chronic gastritis ($P=0.164$, OR = 1.145, 95% CI = 0.946–1.384), as well as inflammatory bowel disease, were eliminated ($P=0.472$, OR = 0.964, 95% CI = 0.872–1.065). Concurrently, the association between triglycerides and chronic gastritis disappeared ($P=0.092$, OR = 1.110, 95% CI = 0.983–1.253), while their relationship with inflammatory bowel disease remained significant ($P=0.009$, OR = 1.087, 95% CI = 1.021–1.158). These findings were consistently confirmed by LASSO regression analysis and the MR Egger method (Fig. 6). Furthermore, MR Egger intercept analysis did not suggest issues with horizontal pleiotropy, ruling out potential influences of such systematic bias on the study's results (Fig. 7).

The mediating role of hypertension between OSA and gastrointestinal disease

In the IVW method, after adjustments for hypertension, the causal relationships between OSA and chronic gastritis ($P=0.265$, OR = 0.886, 95% CI = 0.715–1.097), as well as inflammatory bowel disease ($P=0.558$, OR = 0.955, 95% CI = 0.817–1.115), vanished, while the causal relationships between hypertension and chronic gastritis ($P=0.001$, OR = 1.246, 95% CI = 1.094–1.419), inflammatory bowel disease remained significant ($P=0.005$, OR = 1.145, 95% CI = 1.043–1.257). However, the association between OSA and non-alcoholic fatty liver remained significant ($P=2.73E-04$, OR = 1.495, 95% CI = 1.204–1.857), while the causal relationship between hypertension and non-alcoholic fatty liver disappeared ($P=0.892$, OR = 1.009, 95% CI = 0.890–1.144). These results were mirrored in subsequent LASSO and MR-Egger methods (Fig. 6), with no significant evidence

exposure/adjustment	outcome	method	pval	95% ci	egger.Pleiotropy.pval	intercept
Obstructive Sleep Apnea	Inflammatory bowel disease	MR Egger	0.139	-0.373, 0.052	0.218	0.002
Body mass index			0.017	0.037, 0.373		
Obstructive Sleep Apnea	Nonalcoholic fatty liver disease	MR Egger	0.558	-0.226, 0.419	0.012	0.006
Body mass index			0.221	-0.097, 0.421		
Obstructive Sleep Apnea	Nonalcoholic fatty liver disease	MR Egger	0.758	-0.275, 0.377	0.077	0.008
Waist circumference			0.023	0.048, 0.643		
Obstructive Sleep Apnea	Chronic gastritis	MR Egger	0.765	-0.002, 0.002	0.195	2.59E-06
Triglyceride			0.061	0.000, 0.002		
Obstructive Sleep Apnea	Inflammatory bowel disease	MR Egger	0.126	-0.254, 0.031	0.040	0.002
Triglyceride			0.009	0.021, 0.146		
Obstructive Sleep Apnea	Chronic gastritis	MR Egger	0.898	-0.312, 0.273	0.773	-0.008
Hypertension			0.001	0.095, 0.397		
Obstructive Sleep Apnea	Inflammatory bowel disease	MR Egger	0.87	-0.206, 0.174	0.302	-0.002
Hypertension			0.004	0.045, 0.242		
Obstructive Sleep Apnea	Nonalcoholic fatty liver disease	MR Egger	3.34E-05	0.284, 0.791	0.399	-0.01
Hypertension			0.438	-0.078, 0.179		
Obstructive Sleep Apnea	Chronic gastritis	MR Egger	0.281	-0.064, 0.221	0.938	-0.003
Type 2 diabetes			0.275	-0.098, 0.343		
Obstructive Sleep Apnea	Nonalcoholic fatty liver disease	MR Egger	0.371	-0.083, 0.223	1.00E-04	0.005
Type 2 diabetes			0.005	0.108, 0.597		

Figure 7. MVMR-Egger results of causal relationships of obstructive sleep apnea and metabolic syndrome traits on positive outcomes.

of non-zero intercepts in multivariable MR Egger regression, supporting the reliability of the multivariable MR analysis outcomes (Fig. 7).

The mediating role of type 2 diabetes between OSA and gastrointestinal disease

Within the application of the IVW method and following adjustments for type 2 diabetes, the causal links between OSA and chronic gastritis ($P=0.100$, OR = 1.051, 95% CI = 0.990–1.116), as well as type 2 diabetes and chronic gastritis ($P=0.242$, OR = 1.109, 95% CI = 0.932–1.320), were no longer significant. However, their relationships with non-alcoholic fatty liver disease persisted (OSA: $P=0.001$, OR = 1.469, 95% CI = 1.173–1.839, T2DM: $P=0.002$, OR = 1.123, 95% CI = 1.043–1.209). This trend was also corroborated by LASSO regression and MR Egger methods (Fig. 6). These results suggest that type 2 diabetes is not a mediating factor in the causal relationships between OSA and chronic gastritis, as well as non-alcoholic fatty liver disease. Moreover, MR Egger regression analysis did not uncover significant evidence of non-zero intercepts, further endorsing the credibility of the multivariable MR analysis results (Fig. 7).

Discussion

In this article, we conducted a study on the relationship between OSA and gastrointestinal diseases, and further explored the potential mediating mechanisms. Univariate positive MR results indicated a causal relationship between OSA and chronic gastritis, gastric ulcers, enteritis, and fatty liver. The multivariate MR analysis revealed that these effects were indirect, suggesting the presence of mediating factors. The causal relationship between OSA and gastrointestinal diseases was influenced by features of metabolic syndrome, which aligns with previous observational studies and hypotheses.

In contemporary society, sleep deprivation and decreased sleep quality have been closely linked to various health issues. Numerous clinical cases have shown that the general population faces sleep disorders, which not only significantly increase the risk of chronic diseases such as hypertension, obesity, stroke, and cardiovascular diseases but also potentially contribute to overall mortality rates[21]. In recent years, researchers have started investigating the potential mechanisms linking sleep disorders and gastrointestinal disorders. Inflammatory mediators, including tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6), play crucial roles in regulating sleep and wakefulness cycles. Extensive research has confirmed their involvement in sleep disruption, and these cytokines have also shown abnormal levels in the pathogenesis of gastrointestinal diseases such as gastroesophageal reflux disease (GERD), inflammatory bowel disease, liver disorders, and colorectal cancer. This further emphasizes the potential shared pathophysiological basis between sleep disorders and gastrointestinal diseases[22]. MetS is a clinical syndrome characterized by multiple metabolic abnormalities, including central obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low high-density lipoprotein cholesterol levels, with obesity being a major precursor of MetS[23]. Studies have shown that hypoxemia and hypercapnia in OSA patients can lead to increased insulin resistance and inflammatory responses, thereby promoting the development of MetS. Furthermore, OSA can result in excessive activation of the sympathetic nervous system, further exacerbating MetS symptoms. On the other hand, the presence of MetS also increases

the risk of OSA. Abdominal obesity and insulin resistance in MetS patients may lead to relaxation of the upper airway muscles, increasing the occurrence of OSA. Additionally, the high blood glucose and cholesterol levels in MetS patients may have negative effects on the respiratory system, further worsening OSA symptoms[11]. In recent years, research on the association between metabolic syndrome (MetS) and gastrointestinal diseases has also increased. In MetS patients, central obesity and insulin resistance may trigger excessive gastric acid secretion, providing conditions for GERD. Moreover, the sustained presence of high blood glucose and high cholesterol levels poses a threat to the gastric and intestinal mucosa, increasing the likelihood of gastric and duodenal ulcers[24]. Studies have found that the gut microbiome composition may vary in MetS patients, leading to intensified intestinal inflammation and an increased risk of inflammatory bowel disease[25]. Considering the various metabolic abnormalities involved in MetS, such as abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia, and high cholesterol levels, they may collectively contribute to the development of both OSA and gastrointestinal diseases. Therefore, in-depth research on the role of MetS in these two disease categories is crucial for the development of effective prevention and treatment strategies.

Chronic gastritis is a disease characterized by long-term inflammation of the gastric mucosa. Its main features are inflammation and tissue damage to the gastric mucosa, which may be accompanied by abnormal gastric acid secretion, gastric mucosal atrophy, and Helicobacter pylori infection[26], In developing countries, 50.8% of the population and 34.7% in developed countries suffer from health problems due to gastritis[27]. Research has shown that poor sleep quality can lead to an increase in gastrointestinal diseases, with gastritis being 6.935 times more likely in individuals with low sleep quality compared to those with high sleep quality[22]. This may be because the excessive secretion of pro-inflammatory cytokines in sleep disorders makes the gastric mucosa more susceptible to damage[22,28], leading to the development of gastritis, which is consistent with our research findings. In multivariable MR analysis, we revealed that hypertension plays an important mediating role in the link between OSA and chronic gastritis. OSA has been recognized as an important risk factor for hypertension[29], and extensive medical research has revealed that hypertension may lead to reduced gastric mucosal blood flow, resulting in mucosal damage and an increased risk of developing chronic gastritis and gastric ulcers. Additionally, Helicobacter pylori infection is a well-known major cause of chronic gastritis. It is worth noting that recent scientific literature has indicated a significant and independent correlation between the seropositivity of Helicobacter pylori and primary hypertension, suggesting that hypertensive patients are more likely to exhibit a seropositive reaction to Helicobacter pylori infection[30–32]. This association further supports our findings that hypertension may be a key intermediate link connecting OSA and gastrointestinal diseases. In conclusion, hypertension is not only a complication of OSA but may also serve as a biological bridge between OSA and gastrointestinal diseases such as chronic gastritis. This discovery is of great significance for understanding the complex relationship between OSA and gastrointestinal diseases and provides a new perspective for future prevention and treatment strategies. Gastric ulcer is a type of digestive ulcer that occurs in the inner lining of the stomach. When the gastric mucosa is damaged for specific reasons, ulcers can form in that area, leading to the development of gastric ulcers. The occurrence of gastric ulcers is related to various factors, including Helicobacter pylori infection, the use of non-steroidal anti-inflammatory drugs, and excessive gastric acid secretion[33]. It is worth noting that a study has indicated that patients with sleep apnea syndrome have a 2.4 times higher risk of developing peptic ulcer bleeding compared to normal individuals[34]. This may be related to the repeated respiratory pauses that occur during sleep apnea. These continuous respiratory interruptions lead to intermittent hypoxia, systemic inflammatory response, and sympathetic nervous system activation, which collectively increase the risk of developing peptic ulcers. Therefore, for patients with sleep apnea syndrome, monitoring and preventive measures for gastric diseases should be strengthened to reduce the risk of peptic ulcers and their complications.

Inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis, are a group of chronic inflammatory intestinal diseases that typically result in long-term inflammation and ulcer formation in the intestines, causing symptoms such as diarrhea, abdominal pain, and weight loss. The pathogenesis of IBDs is believed to be the result of interactions between genetic susceptibility and environmental influences on the gut microbiome, leading to impaired intestinal barrier function and inappropriate activation of intestinal immune responses[35]. Sleep disorders have been shown to affect immune function and the development of inflammation. Sleep deprivation leads to upregulation of immune function, activating pro-inflammatory cytokines (such as IL-1, IL-6, and TNF) and increasing levels of C-reactive protein (CRP), which are markers of IBD activity[36]. The chronic inflammation of IBDs and the resulting sleep disturbances form a vicious cycle with negative feedback. Sleep deprivation leads to the production of inflammatory cytokines, which, in turn, worsen colitis, creating a recurring cycle[37,38]. In multivariable Mendelian randomization analysis, we found that BMI, triglyceride levels, and hypertension mediate the impact of OSA on inflammatory bowel disease (IBD). BMI is an internationally used measure of body weight and health status[39], and obese individuals often have higher triglyceride levels[40]. Research has shown a close association between sleep disorders and metabolic syndrome[11,13], and metabolic syndrome is also associated with IBDs. They share common pathophysiological features, such as immune imbalance, chronic inflammation, dysregulation of adipokine secretion, and increased risk of cardiovascular diseases[41]. A large-scale study has indicated that the presence of hypertriglyceridemia is associated with an increased hospitalization rate for inflammatory bowel disease[42]. It is estimated that up to 40% of individuals with Crohn's disease and ulcerative colitis (UC) are either obese or overweight[43]. Obesity can lead to chronic low-grade inflammation, which may impair the intestinal mucosal barrier, leading to dysbiosis and immune system dysregulation. Moreover, obesity can affect the composition and function of the gut microbiome, increasing certain harmful bacterial populations, thereby triggering inflammatory responses in the gut. Additionally, excessive visceral fat accumulation due to obesity is closely related to the characteristics of metabolic syndrome, prothrombotic, and pro-inflammatory states[25],all of which can contribute to the onset of IBD. In recent years, epidemiological studies have suggested a connection between blood pressure and IBD, as hypertension can

alter tight junction proteins and intestinal permeability, thereby increasing the risk of IBD[44]. Previous studies have shown that the gut microbial composition in patients with hypertension can change, where a reduction in butyrate-producing bacteria may decrease the concentration of butyrate and weaken its ability to alleviate chronic inflammatory responses, leading to intestinal epithelial diseases[45,46]. Moreover, hypertension can also activate the proliferation, mobilization, and differentiation of hematopoietic stem cells, thereby increasing peripheral and neuroinflammatory responses, which could potentially induce the development of IBD[47]. Therefore, we can conclude that BMI, triglyceride levels, and hypertension are key biomarkers for OSA exacerbating the risk of inflammatory bowel disease. Monitoring and managing these indicators may help assess the potential risk of OSA patients developing IBD, thereby enabling more targeted preventive and therapeutic measures.

Nonalcoholic fatty liver disease (NAFLD) is a common liver condition characterized by excessive fat accumulation in the liver in the absence of alcohol consumption. This condition is divided into two types: simple steatosis involving only fat buildup without inflammation or fibrosis, and the more severe nonalcoholic steatohepatitis (NASH), which includes varying degrees of hepatocyte inflammation and fibrosis[48]. Statistics show that NAFLD has a prevalence rate of up to 75% among the global obese population, with about one-quarter of the world's population affected[49]. Research has revealed a close association between OSA and the progression of NAFLD[50]. Chronic intermittent hypoxia (CIH) caused by OSA has been identified as one of the key factors promoting the progression of NAFLD[51,52]. Additionally, OSA and CIH can reduce insulin sensitivity and disrupt lipid levels, changes that may contribute to the onset of NAFLD. Under CIH, the level of HIF1α protein in the body increases, activating genes related to lipogenesis and advancing β-oxidation processes in the liver, thereby exacerbating oxidative stress within the liver. Furthermore, OSA disrupts the healthy interaction between the gut and the liver (i.e., the gut-liver axis), increasing gut permeability, which may allow the gut microbiota to play a role in the interaction between OSA and NAFLD, although the specific mechanisms require further investigation[53]. In MVMR, we found that waist circumference act as mediators for OSA-induced NAFLD. Waist circumference is a common indicator of individual obesity, numerous observational studies consistently suggest that obesity plays a significant role in the relationship between OSA and NAFLD. Research by Jia-Chao Qi et al. indicates that if obesity is excluded, the causal link between OSA and NAFLD may no longer exist[54]. OSA can lead to increased levels of serum sulfatase 2 (LaSO2), BMI, and triglycerides (TG). Elevated LaSO2, as a marker of inflammation, reflects a state of systemic inflammation and oxidative stress closely linked to the pathophysiology of NAFLD. An increase in BMI is usually associated with obesity, exacerbating intrahepatic fat accumulation by affecting fatty acid metabolism and insulin sensitivity. Elevated TG levels reflect lipid metabolism disorders, potentially leading to more fatty acids being transported to the liver and converted into harmful fatty acid esters, thereby promoting the development of intrahepatic inflammation and fibrosis[55]. Therefore, for OSA patients, actively managing lipid metabolism, maintaining a healthy weight, and treating hypoxemia caused by OSA are important strategies for reducing or preventing the occurrence of NAFLD. Implementing these measures can significantly reduce the risk of NAFLD and improve overall health and quality of life for patients.

In exploring the broad health implications of OSA, we observe the high prevalence of comorbidities among patients with severe Chronic Obstructive Pulmonary Disease (COPD), which not only significantly hinder the clinical management of COPD but also profoundly impact the health-related quality of life as reflected by COPD Assessment Test scores[56]. Notably, OSA, as another crucial respiratory disorder, has had its genetic predisposition robustly validated through MR analysis, uncovering an independent and notable causal relationship between genetically predicted OSA and elevated risks of inflammatory gastrointestinal diseases (GDs)[57]. This finding underscores OSA's role in facilitating the development of inflammatory conditions, which serve as a common pathological basis for various chronic diseases, including COPD and GDs. In contrast to the aforementioned discovery, however, current research has not observed a direct causal link between OSA and cancer[57]. This result suggests that while OSA is intimately associated with multiple inflammatory diseases, its specific impact on cancer risk may be more intricate and necessitates further investigation in the future. In summary, OSA is not merely an isolated health concern; its underlying pathophysiological mechanisms may intertwine with those of COPD, GDs, and other disorders through inflammatory pathways, collectively influencing patients' overall health status.

The strength of this study lies in selecting data from large-scale research, fully incorporating indicators of obstructive sleep apnea syndrome and related gastrointestinal diseases, systematically exploring the relationship between OSA and gastrointestinal diseases through Mendelian randomization for the first time, and using multivariate MR analysis to explore mediation pathways to identify some possible mechanisms, filling the gap left by randomized controlled trials. This study also has certain limitations. First, the Mendelian randomization method used considers the cumulative lifelong impact of genetic variations and should not be inferred to estimate the effects of clinical interventions; second, to obtain a sufficient number of instrumental variables, the p-value threshold for IV selection was set at 5E-05, which may introduce slight instrument bias into the overall estimates. Furthermore, to avoid population heterogeneity bias, we based our analysis solely on GWAS summary statistics from populations of European descent, and the applicability of these results to other ethnic groups requires further exploration.

Conclusion

In summary, after comprehensively analyzing multiple clinical data and biological mechanisms, this study established a causal link between OSA and chronic gastritis, gastric ulcers, inflammatory bowel disease, and fatty liver, revealing the potential mediating role of MetS in the interaction of these diseases, thus providing strong causal evidence for the shared pathophysiological basis of OSA and gastrointestinal diseases. By delving into the association between OSA and gastrointestinal diseases, this study not only strengthens our understanding of the pathogenesis of these clusters of diseases but also identifies MetS as a potential intervention point, which is of significant public health importance for formulating prevention strategies and intervention measures to reduce

the burden of gastrointestinal diseases and their related conditions. Further research should be dedicated to elucidating the specific biological pathways of interaction between OSA and gastrointestinal diseases, as well as how MetS regulates these pathways, to provide more precise risk management and treatment targets for clinical practice.

Data availability

The datasets generated and/or analysed during the current study are available in the [GWAS] repository, [https://gwas.mrcieu.ac.uk]

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Author contributions
Z.Z proposed the research concept and design, conducted Data analysis and wrote the preliminary draft; CY.J was responsible for Data Curation and Investigation; BS.Y and H.W was responsible for Methodology and the use of software; JW.Z and LX.Z supervised the research process and guided the other authors; while TK, Y, H.W and ZF.D were responsible for the Project Administration; Y.C and XL.Q reviewed and edited the manuscript, while SY.W acquired the funding. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
The data used in this study were all from public databases that can be downloaded directly for research purposes and do not involve the reporting or using of any animal, human, or tissue data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Y.C., S.W. or X.Q.