Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Causal associations between obstructive sleep apnea and COVID-19: A bidirectional Mendelian randomization study

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ABSTRACT

Backgrounds: The COVID-19 pandemic has caused significant impact on human health. Whether obstructive sleep apnea (OSA) increases the risk of COVID-19 remains unclear. We sought to clarify this issue using two-sample Mendelian randomization (TSMR) analysis in large cohorts.

Methods: Bidirectional two-sample Mendelian randomization (MR) was used to evaluate the potential causality between OSA and COVID-19 by selecting single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs) from genome-wide association studies (GWAS). The inverse-variance weighted (IVW) method was selected as the main approach for data analysis to estimate the possible causal effects. Alternative methods such as MR-Egger, the MR pleiotropy residual sum and outlier (MR-PRESSO), and leave-one-out analysis methods were implemented as sensitivity analysis approaches to ensure the robustness of the results.

Results: All forward MR analyses consistently indicated the absence of a causal relationship between OSA and any COVID-19 phenotype. In the reverse MR analysis, the IVW mode demonstrated that severe respiratory confirmed COVID-19 was correlated with a 4.9% higher risk of OSA (OR, 1.049; 95%CI, 1.018−1.081; $P = 0.002$), consistent in MR-PRESSO (OR = 1.049, 95%CI 1.018−1.081, $P = 0.004$), weighted median (OR = 1.048, 95%CI 1.003−1.095, $P = 0.035$), and MR-Egger (OR = 1.083, 95%CI 1.012−1.190, $P = 0.041$) methods.

Conclusions: There is no significant evidence supporting a causal association between OSA and any COVID phenotype, while we identified potential evidence for a causal effect of severe COVID-19 on an increased risk of OSA.

1. Introduction

For some individuals, the global COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in serious conditions such as pneumonia and respiratory insufficiency [1]. Globally, as of June 1, 2022, 527 million confirmed cases of COVID-19, including 6 million deaths, have been reported to the World Health Organization (WHO). Given the broad spectrum of individuals susceptible to SARS-CoV-2 infection and the wide range of disease severity, ranging from asymptomatic to fatal, earlier studies have identified higher susceptibility and various comorbidities linked to severe COVID-19 outcomes. These include obesity, hypertension, diabetes, thyroid disease, dyslipidemia, cardiovascular disease, and pulmonary disease [2,3].

Obstructive sleep apnea (OSA) is a prevalent and under-diagnosed

Abbreviations: CI, confidence interval; COVID-19, Corona Virus Disease 19; DPP9, dipeptidyl peptidase 9; FINNGen, Finnish Gene; GWAS, genome-wide association studies; ICD, International Classification of Diseases; IV, instrumental variable; IVW, inverse-variance weighted; MR, Mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlier; NLRP3, nucleotide-binding oligomerization domain-like receptor 3; OSA, obstructive sleep apnea; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNP, single-nucleotide polymorphism; TSMR, two-sample Mendelian randomization; UKBB, UK Biobank; WM, weighted median; WHO, World Health Organization.

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disorder characterized by repeated closure of the upper airway tract during sleep, resulting in sleep fragmentation and intermittent hypoxia [4]. This disorder not only causes daytime drowsiness, but also exacerbates cardiovascular issues, obesity-related metabolic dysfunction, systemic inflammation, and a weakened immunological response to infection [5,6]. Whether OSA is a risk factor for COVID-19, particularly severe COVID-19, has long been a subject of debate. Recently, several observational studies have suggested that OSA is associated with an increased risk of severe COVID-19 [7–11]. According to two meta-analyses of epidemiological research, OSA increased the risk of severe COVID-19 1.7- and 2.0-fold, respectively [7,9]. However, after controlling for common confounding factors such as obesity and cardiovascular disease, Mashaqi et al. reported that there was insufficient evidence to demonstrate OSA was associated with severe COVID-19 [12]. In the reverse direction, although COVID-19 is a multi-systemic disease, the lungs are the primary source of infection and injury [13], subsequently decreased lung volumes and upper airway inflammation might causally associate with OSA. An observational study has demonstrated highly prevalent (73%) of OSA among COVID-19 related moderate to severe survivors [14]. Thus, there are complicated and potentially bidirectional relationships between COVID-19 and OSA, whereby the progression of one disease process causes the progression of the other. However, it is difficult to speculate on their causal relationship given traditional observational studies investigating the association between COVID-19 and OSA are vulnerable to unmeasured confounding and reverse causation. Thus, whether individuals with OSA are at a greater risk of developing COVID-19, and if the severity of COVID-19 is causally associated with OSA remains undiscerned.

Mendelian randomization (MR) is an analytical approach that examines the causal effects of changeable exposure to diseases using human genetic variation. MR has the appealing strength of being frequently less vulnerable to reverse causality and confounders than other study methods since the two alleles of an SNP are randomly segregated under the Mendel's law [15]. We may be able to reduce their impact on disease risk by establishing causative relationships between OSA and COVID-19 susceptibility or severity and avoid incorrect conclusions that lead to inaccurate information or undue anxiety. Data from genome-wide association studies (GWAS), which can provide regression coefficients summarizing the associations between multiple genetic variations and several phenotypes, could be a valuable source of information for MR analysis.

As a result, we performed bidirectional MR analyses to determine the causal relationship between COVID-19 (which includes COVID-19, hospitalized COVID-19 compared with non-hospitalized COVID-19, hospitalized COVID-19 compared with the general population, and severe COVID-19) and OSA using summary statistical results from GWAS data. Understanding the bidirectional relationship between COVID-19 and OSA is critical to provide accurate information to the public health sector regarding disease prevention and complication management.

2. Methods

We used a univariate bidirectional two-sample MR analysis to evaluate the causal relationship between OSA and COVID-19. First, we explored the effects of OSA on COVID-19 and then the causal effects of COVID-19 on OSA. The design of our MR framework is illustrated in Fig. 1.

3. Data sources

3.1. GWAS of OSA

The OSA summary-level data were obtained from recently published genome-wide association studies (GWAS), which included 16,761 OSA patients and 201,194 controls in the FinnGen study (Table 1) [16]. OSA was diagnosed using the International Classification of Diseases, 10th edition (ICD-10) and 9th edition (ICD-9) codes (ICD-10: G47.3, ICD-9: 3472A), which are based on subjective symptoms, clinical examination, and sleep registration using the apnea-hypopnea index of five per hour or respiratory event index of five per hour [17]. Principal covariates, such as age and sex, were adjusted in the association tests for all sources.

3.2. GWAS of COVID-19

The COVID-19 Host Genetics Initiative [18], launched on January 18, 2021, provided genetic connections with COVID-19 phenotypes. This GWAS yielded the following four phenotypes: 1) COVID-19 patients vs. the general population (38,984 cases vs. 1,644,784 controls), 2) hospitalized COVID-19 patients vs. the general population (3159 cases vs. 7206 controls), 3) hospitalized COVID-19 patients vs. non-hospitalized COVID-19 patients (9986 cases vs. 1,877,672 controls), 4) severe respiratory confirmed COVID-19 patients vs. the general population (5101 cases vs. 1,383,241 controls) [19].

4. Statistical analysis

4.1. Selection of instruments

First, we chose single nuclear polymorphisms (SNPs) for OSA that met the genome-wide significance criteria ($P < 5 \times 10^{-8}$). For only a few significant SNPs of COVID-19 were found using the $P < 5 \times 10^{-8}$ threshold, SNPs were chosen as IVs for COVID-19 at $P < 1 \times 10^{-5}$. To ensure that the effect of SNPs on COVID-19 and OSA was related to the same allele, the effect direction was harmonized. Furthermore, we removed SNPs that were in linkage disequilibrium (r^2 threshold <0.001 within a 10 Mb window) from the outcome datasets and retrieved the remaining SNPs.

To ensure the strength of the exposures, we calculated the F statistic, and an F statistic of 10 was regarded as sufficiently robust to counteract weak instrument bias. The R^2 and F statistics of the SNPs were determined using the following formula: $R^2 = 2 \times EAF \times (1\text{-}EAF) \times \beta^2$ and the F statistic $= R^2 \times (N\text{-}2)/(1\text{-}R^2)$ [20]. Using non-centrality parameter-based approach, the statistical power was calculated using an online tool at http://cnsgenomics.com/shiny/mRnd/ [21].

4.1.1. MR analyses

To analyze putative causal effects, the IVW method was used as the main analytical strategy [22]. To address variant heterogeneity and pleiotropic effects, we applied five different two-sample MR approaches (MR-Egger, Weighted median [WM], the MR pleiotropy residual sum and outlier (MR-PRESSO), simple mode, and weighted mode). When less than half of the weights came from invalid variants, the WM technique yielded effect estimates [23]. Even when up to 50% of the genetic variation was invalid, the MR-Egger technique produced consistent results [24]. The MR-PRESSO approach provides a corrective test by recognizing and deleting potentially pleiotropic outliers [25]. The non-zero intercept of the MR-Egger intercept test indicated that the inverse-variance weighted (IVW) results might be invalid because of horizontal pleiotropy [26]. Furthermore, we performed a leave-one-out study to determine how eliminating one genetic variant from the MR analysis affected the results [27]. $P < 0.05$ was considered to indicate a statistically significant difference when Cochran's Q statistic was used to assess the heterogeneity among genetic variations [28]. R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) with the

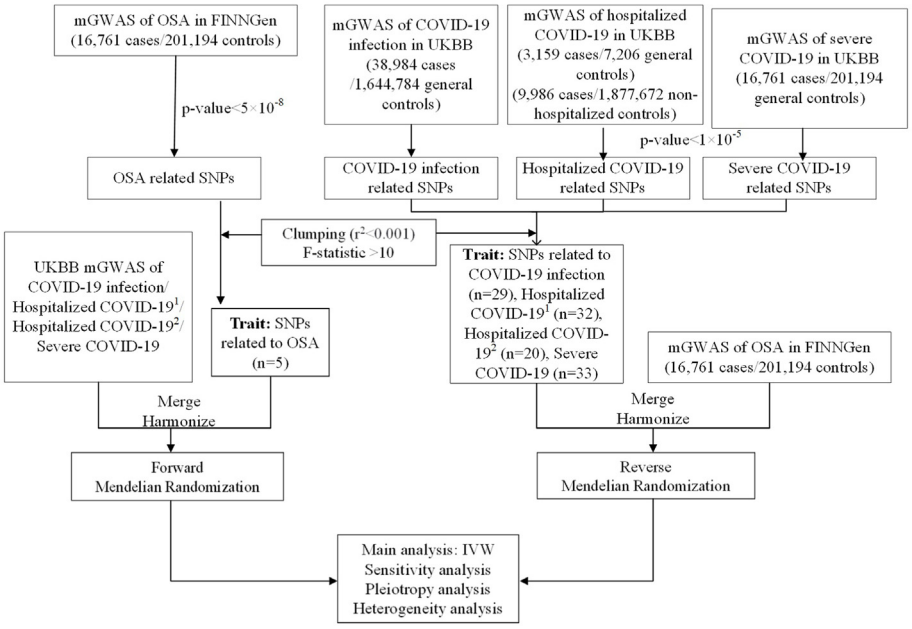

Fig. 1. Flowchart of our bidirectional two-sample Mendelian randomization analysis. OSA, obstructive sleep apnea; UKBB, UKbiobank; SNPs, single nuclear polymorphisms; mGWAS, mata-analysis of genome-wide association studies; hospitalized COVID-19, hospitalized COVID-19 compared with the general population; hospitalized COVID-19[2], hospitalized COVID-19 compared with non-hospitalized COVID-19; IVW analysis, inverse-variance weighted analysis.

Table 1
Characteristics of GWAS consortiums used for each variable.

Traits	Sample size (cases/controls)	Population	Consortium	Journal
Obstructive sleep apnea	16,761/201,194	European	FINNGen	European Respiratory Journal
COVID-19 vs. general population	38,984/1,644,784	European	UKBB	European Journal of Human Genetics
Hospitalized COVID-19 vs. general population	3159/7206	European	UKBB	European Journal of Human Genetics
Hospitalized COVID-19 vs. non-hospitalized COVID-19	9986/1,877,672	European	UKBB	European Journal of Human Genetics
Severe respiratory confirmed COVID-19 vs. general population	5101/1,383,241	European	UKBB	European Journal of Human Genetics

GWAS, genome-wide association studies; COVID-19, Corona Virus Disease 19; UKBB, UK Biobank; FINNGen, Finnish Gene.

two-sample MR and MR-PRESSO packages was used for all statistical analyses.

5. Results

5.1. Causal effects of OSA on COVID-19 risk

All models in forward MR analyses consistently revealed no statistically significant evidence for a causal relationship between OSA and COVID-19 (IVW: OR, 0.984; 95%CI, 0.764–1.268; $P = 0.903$), hospitalized COVID-19 vs. the general population (IVW: OR, 0.945; 95% CI, 0.704–1.269; $P = 0.708$), hospitalized COVID-19 vs. non-hospitalized COVID-19 (IVW: OR, 1.233; 95% CI, 0.756–2.012; $P = 0.401$), or severe respiratory confirmed COVID-19 (IVW: OR, 0.726; 95% CI, 0.471–1.121; $P = 0.149$). The MR-Egger intercept test and Cochran's Q statistic did not identify any directional pleiotropy or heterogeneity. Furthermore, no indication of horizontal pleiotropy was observed in the MR-PRESSO global test (all $P > 0.10$).

5.2. Causal effects of COVID-19 on OSA risk

In the IVW mode, we found that severe respiratory-confirmed COVID-19 had a causal risk effect on OSA (OR, 1.049; 95% CI, 1.018–1.081; $P = 0.002$). The other three sensitivity analyses also consistently revealed causality between them (MR-Egger: OR, 1.083; 95% CI, 1.012–1.190; $P = 0.041$; MR-PRESSO: OR, 1.049; 95% CI, 1.018–1.081; $P = 0.004$; WM: OR, 1.048; 95% CI, 1.003–1.095; $P = 0.035$). The scatter plot in Fig. 2 shows the relationship between severe respiratory-confirmed COVID-19 and OSA risk. In this study, the MR-Egger intercept test revealed no pleiotropic effects ($P = 0.681$). Furthermore, neither Cochran's Q test nor the MR-PRESSO global test revealed any significant heterogeneity for severe respiratory-confirmed COVID-19 and OSA (all $P > 0.10$) (Table 2). We also applied leave-one-out analysis and failed to identify one SNP that substantially influenced the IVW estimate (Fig. 3). The other three features (COVID-19 vs. the general population, hospitalized COVID-19 vs. the general population, and hospitalized COVID-19 vs. non-hospitalized COVID-19) did not appear to have a causal effect on OSA (Table 3). The minimum F-statistic was 32 and is shown in Supplementary Tables S1 and S2. Leave-one-out plots are presented in Supplementary Figs. S1–S7. Required sample size is shown in Supplementary Table S3.

6. Discussion

Understanding the causal link between OSA and COVID-19 is crucial for developing disease prevention and therapy methods, given the significant impact of both on human health. To the best of our knowledge, this is the first study that evaluates the causal relationship between COVID-19 and OSA using a bidirectional two-sample MR analysis. In the current investigation, using publicly

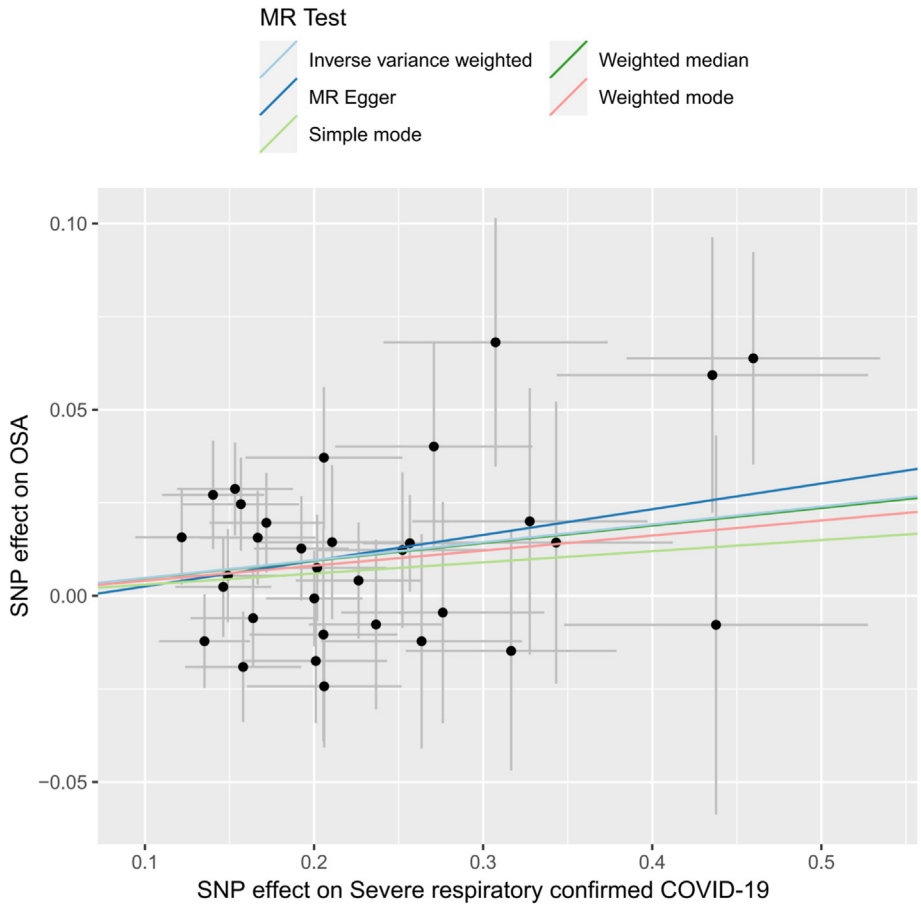

Fig. 2. Scatter plot of the SNP effects on severe respiratory-confirmed COVID-19 and OSA, with the slope of each line corresponding to the estimated MR effect per method. OR, odds ratio; CI, confidence interval; MR, Mendelian randomization; SNP, single-nucleotide polymorphism; OSA, obstructive sleep apnea.

accessible summary statistical data, no substantial evidence was found to suggest that genetic susceptibility to OSA increases the likelihood of any COVID-19 trait (including non-hospitalized COVID-19, hospitalized COVID-19 and severe respiratory-confirmed COVID-19). On the other hand, there was MR evidence that genetic susceptibility to severe respiratory-confirmed COVID-19 was associated with increased risk of OSA, which provides a novel direction for future clinical therapy for patients who experience severe COVID-19 infection.

Our MR study did not find genetic predisposition to OSA traits would alter the susceptibility to SARS-CoV-2 infection, COVID-19 hospitalization, or severe. This finding is consistent with retrospective studies which have failed to uncover substantial evidence for a causal relationship after adjusting obesity and cardiovascular disease [12]. Although a growing number of observational studies have reported that individuals with OSA have a greater risk of severe COVID-19 [8,10,11], there are various possible explanations for this disparity in the results. First, the discrepancy could be ascribed to reverse causality and unmeasured confounders in observational studies, such as socioeconomic status and smoking. In addition, factors other than genetics may play a role in COVID-19 vulnerability. For example, the deterioration of the pulmonary inflammatory process in patients with OSA may be due to a lack of body immunity caused by intermittent hypoxia and sleep fragmentation [29]. Another possible explanation for the disparity is that the condition of individuals with a genetic susceptibility to OSA may deteriorate with age. Further investigation is required to identify relevant discrepancies.

Based on public GWAS data, we performed two-sample MR to evaluate whether genetic predisposition and severity of COVID-19 are causally associated with OSA susceptibility. Novelly and unexpectedly, genetic susceptibility to severe respiratory-confirmed COVID-19 was causally associated with increased risk of OSA in IVW mode, implying that OSA surveillance should be intensified in severe respiratory-verified COVID-19 patients. Multiple sensitivity studies were performed using various methodologies (e.g., MR-Egger and MR-PRESSO) and instrument selection, with consistent results. Therefore, we suspect that severe COVID-19 could lead to OSA.

There was no meaningful difference in OSA susceptibility between hospitalized and non-hospitalized COVID-19 patients, indicating that various host response mechanisms may alter susceptibility to SARS-CoV-2 infection and development of more severe COVID-19. According to the COVID-19 HGI's GWAS meta-analysis, there are four loci for severe COVID-19 that are distinct from those for SARS-CoV-2 infection and hospitalized COVID-19 [30]. A variant of rs2109069, an intronic variant of the gene encoding dipeptidyl peptidase 9 (DPP9), encodes a serine protease with a number of intracellular functions including cleavage of the major antiviral signaling mediator CXCL [31], antigen presentation [32], and inflammasome activation [33]. Idiopathic pulmonary fibrosis is associated with variants in this locus [34]. A recent study by Díaz-García et al. reported that inflammasome activation plays a crucial role in the proinflammatory response in severe OSA [6]. According to their findings, the activity of nucleotide-binding oligomerization domain-like receptor 3 (NLRP3) in monocytes

Table 2
Forward causal relationships between obstructive sleep apnea and COVID-19 risk performed by MR.

Phenotype	nSNPs	OR (95%CI)	*P*	Q pval	Intercept pval	Global *P*
COVID-19 vs. general population						
IVW	5	0.984 (0.764, 1.268)	0.903	0.082		
MR-Egger	5	0.746 (0.354, 1.572)	0.497		0.491	
MR-PRESSO	5	0.984 (0.764, 1.268)	0.909			0.134
WM	5	0.962 (0.740, 1.251)	0.772			
Simple mode	5	0.818 (0.525, 1.275)	0.425			
Weighted mode	5	1.147 (0.816, 1.612)	0.475			
Hospitalized COVID-19 vs. general population						
IVW	5	0.945 (0.704, 1.269)	0.708	0.044		
MR-Egger	5	0.620 (0.266, 1.444)	0.349		0.374	
MR-PRESSO	5	0.945 (0.704, 1.269)	0.727			0.122
WM	5	0.971 (0.733, 1.288)	0.840			
Simple mode	5	0.933 (0.563, 1.548)	0.803			
Weighted mode	5	1.118 (0.814, 1.535)	0.529			
Hospitalized COVID-19 vs. non-hospitalized COVID-19						
IVW	5	1.233 (0.756, 2.012)	0.401	0.393		
MR-Egger	5	1.311 (0.218, 7.902)	0.787		0.948	
MR-PRESSO	5	1.233 (0.756, 2.012)	0.448			0.399
WM	5	1.302 (0.690, 2.456)	0.415			
Simple mode	5	0.853 (0.293, 2.480)	0.784			
Weighted mode	5	1.866 (0.806, 4.321)	0.219			
Severe respiratory confirmed COVID-19 vs. general population						
IVW	5	0.726 (0.471, 1.121)	0.149	0.149		
MR-Egger	5	0.324 (0.131, 0.801)	0.093		0.156	
MR-PRESSO	5	0.726 (0.471, 1.121)	0.222			0.226
WM	5	0.761 (0.489, 1.185)	0.227			
Simple mode	5	0.511 (0.245, 1.068)	0.149			
Weighted mode	5	0.817 (0.492, 1.357)	0.478			

nSNPs, number of single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; Q_pval, P-value of the Cochran Q statistic; IVW, inverse-variance weighted; WM, weighted median; MR-PRESSO, Pleiotropy Residual Sum and Outlier.

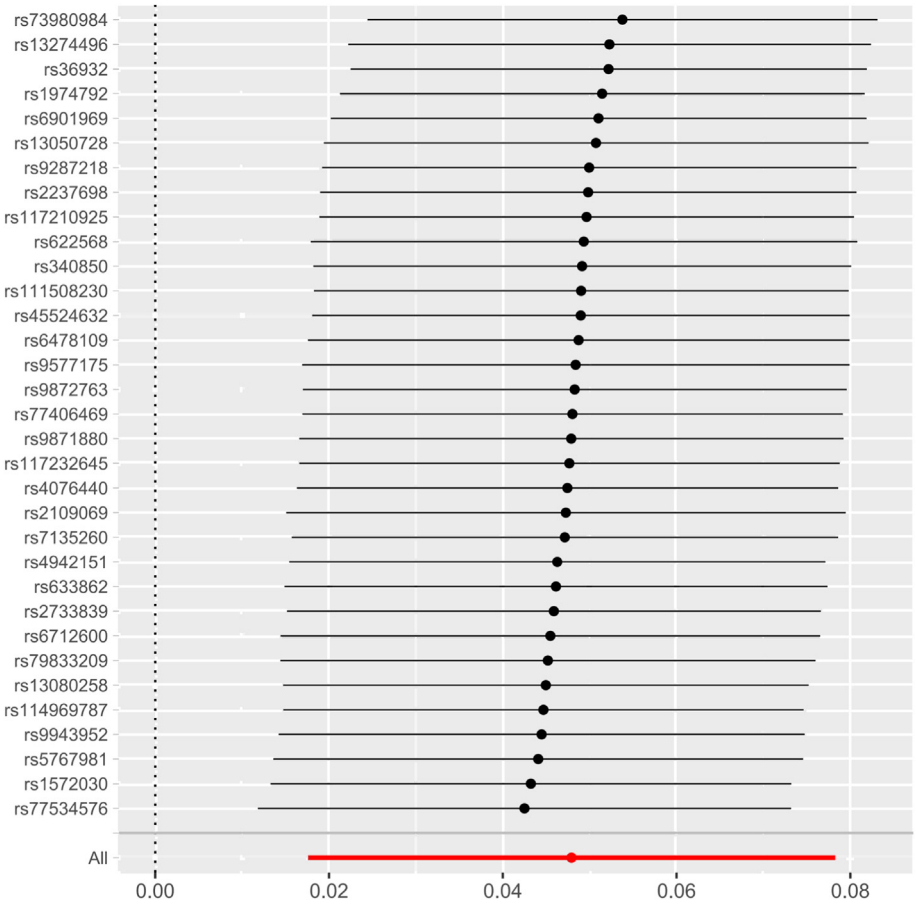

Fig. 3. Leave-one-out plot: MR sensitivity analysis for severe respiratory-confirmed COVID-19 and OSA. MR, Mendelian randomization; OSA, obstructive sleep apnea.

Table 3
Reverse causal relationships between obstructive sleep apnea and COVID-19 risk performed by MR.

Phenotype	nSNPs	OR (95%CI)	*P*	Q pval	Intercept pval	Global *P*
COVID-19 vs. general population						
IVW	27	1.057 (0.943, 1.184)	0.341	0.163		
MR Egger	27	0.885 (0.646, 1.212)	0.452		0.247	
MR-PRESSO	27	1.050 (0.944, 1.169)	0.376			0.154
WM	27	1.061 (0.910, 1.237)	0.453			
Simple mode	27	1.131 (0.778, 1.642)	0.525			
Weighted mode	27	0.824 (0.578, 1.175)	0.295			
Hospitalized COVID-19 vs. general population						
IVW	32	0.989 (0.946, 1.034)	0.633	0.625		
MR Egger	32	1.088 (0.969, 1.222)	0.164		0.092	
MR-PRESSO	32	0.989 (0.948, 1.032)	0.619			0.605
WM	32	1.003 (0.942, 1.068)	0.931			
Simple mode	32	0.966 (0.851, 1.097)	0.597			
Weighted mode	32	1.016 (0.922, 1.119)	0.757			
Hospitalized COVID-19 vs. non-hospitalized COVID-19						
IVW	20	0.997 (0.959, 1.037)	0.892	0.707		
MR Egger	20	0.989 (0.901, 1.085)	0.815		0.845	
MR-PRESSO	20	0.997 (0.963, 1.033)	0.881			0.698
WM	20	0.979 (0.926, 1.036)	0.468			
Simple mode	20	0.982 (0.895, 1.077)	0.699			
Weighted mode	20	0.966 (0.893, 1.045)	0.401			
Severe respiratory confirmed COVID-19 vs. general population						
IVW	33	1.049 (1.018, 1.081)	0.002	0.311		
MR Egger	33	1.083 (1.012, 1.190)	0.041		0.681	
MR-PRESSO	33	1.049 (1.018, 1.081)	0.004			0.332
WM	33	1.048 (1.003, 1.095)	0.035			
Simple mode	33	1.030 (0.943, 1.126)	0.514			
Weighted mode	33	1.041 (0.961, 1.128)	0.329			

nSNPs, number of single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; Q_pval, P-value of the Cochran Q statistic; IVW, inverse-variance weighted; WM, weighted median; MR-PRESSO, Pleiotropy Residual Sum and Outlier.

from patients with severe OSA is directly connected to apnea-hypopnea and hypoxia indices. Furthermore, decreasing lung volumes associated with idiopathic pulmonary fibrosis might impair upper airway stability and resistance, enabling collapse of the upper airway, particularly during REM sleep, when functional residual capacity is further reduced because of decreased intercostal muscle activity [35]. As a result, inflammation and genetic variations may play a role in the higher risk of OSA in individuals with severe COVID-19. However, few clinical or epidemiological studies have investigated this association. Future clinical or functional studies may confirm this, and validated disease-specific questionnaires and/or portable devices may also aid in exploring the role of severe COVID-19 in OSA susceptibility [36,37].

The COVID-19 pandemic has had the greatest impact on people who already have health problems. Not only did it increase the under-diagnosis of OSA, but also probably delayed or affected the treatment of OSA patients who had been diagnosed [38]. Untreated OSA is linked to an increased risk of cardiovascular issues, which increases the risk of severe COVID-19 infection and death in what appears to be a vicious cycle [39]. As a result, telemedicine for OSA management assistance and the use of portable screening equipment combined with artificial intelligence for prescreening suspected OSA might be advantageous [40–42]. According to our results, severe COVID-19 is causally related with OSA, shedding fresh light on the mechanisms underlying the relationship between OSA and COVID-19. Importantly, it may have indications for clinicians to pay more attention to the OSA-monitoring and potential comorbidity therapy such as airway management among severe COVID-19 patients, as they are more likely to fail extubation and require prolonged mechanical ventilation [43].

The main strength of this study is that we used the MR approach to analyze the causal correlations between COVID-19 and OSA. Despite not being able to investigate the causality among whose phenotype for both COVID and OSA considering the available data we used were summary-level statistics rather than individual-level statistics, utilizes nonoverlapping, independent data and sample sets for exposure and outcome groups, two-sample MR analysis provided a more powerful causal relationship between the two diseases, overcoming environmental confounding [44]. Another strength is that the bidirectional analysis guaranteed the inference of causality between OSA and COVID-19 in both directions, avoiding misleading causal effect [45]. In particular, it provides an alternative line of aetiological evidence that severe COVID-19 could cause OSA, which may be frequently influenced by reverse causality in observational studies.

However, various limitations should be considered before interpreting the outcomes of this MR investigation. First, despite the fact that participants in the chosen GWAS were all of European ancestry, residual confounding from other variables potentially bring horizontal pleiotropy and subsequently biased estimation of causal inference. However, no meaningful pleiotropic effect on the results was detected in the multiple sensitivity analyses such as MR-Egger regression. In addition, it is important to note that ethnicity appears to influence craniofacial anatomy traits and obesity liability in individuals with OSA, and which are likely to account for approximately 40% of the OSA risk [46,47]. It remains unclear whether our findings can be applied to other populations. Further work should be carried out in other ethnic groups such as Asian ethnicities. Second, causal estimates from MR should be interpreted with caution. Our results indicate an insufficient sample size through power analysis (Supplementary Table S3), limited by the small proportions of variance explained by the genetic instruments (<1% on any COVID phenotype and OSA) and minor percentage of people with an outcome event. This generated an impetus to perform MR studies on larger sample size populations. Third, we cannot rule out the possibility that our findings were influenced by weak instrument bias, which is dependent on the selection of the genetic instrument through the relatively lenient

threshold of $P = 1 \times 10^{-5}$ for COVID-19 phenotypes although the F statistics did not indicate that our instruments were weak. Fourth, our results represent a lifetime effect between OSA and COVID-19, while the risk of developing OSA may be time-dependent because of age-related attenuation of pharyngeal abductor function. Therefore, the MR method may have underestimated the risk of OSA. The causative estimates from this MR study should be further investigated before being translated into therapeutic action. Fifth, OSA severity is a determinant of the development of severe COVID-19, which could have an impact on the cause-and-effect relationship between the two conditions. However, no subgroup analysis of OSA severity was performed in our study because of the lack of necessary data. Lastly, genetic associations represent odds ratios value, not relative risk value, which may yield biased estimates when testing causality for common outcomes such as OSA. Thus, the estimate from a Mendelian randomization investigation is therefore better interpreted as a test statistic for a causal hypothesis rather than representing the estimated effect of a clearly defined intervention at a particular time [22].

7. Conclusion

There is no evidence to substantiate a causal relationship between OSA and any COVID phenotype; however, we did find potential evidence concerning the causal effect of severe COVID-19 on an increased risk of OSA.

Data availablibity

The raw data of this study were obtained from the GWAS public database (https://gwas.mrcieu.ac.uk), and all data were freely downloaded and used. A variety of data analysis methods are freely available on the R platform.

Ethical statement

Not applicable.

CRediT authorship contribution statement

Demin Han: contributed to the study conception, design and supervision. **Xiang Gao:** mainly drafted and revised the original manuscript. **Tao Wei:** was responsible for data acquisition, statistical analysis and data visualization. **Huijun Wang:** assisted in the completion of original manuscript. **Rongcui Sui:** assisted in the completion of revised manuscript. **Jianhong Liao:** gave substantial suggestions on statistics. **Dance Sun:** assisted with data analysis. All authors have approved for the publication of this study.

Declaration of competing interest

Xiang Gao, Tao Wei, Huijun Wang, Rongcui Sui, Jianhong Liao, Dance Sun and Demin Han have no financial or non-financial conflicts of interest to declare.

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Appendix A. Supplementary data

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