Randomized Control Study

The Causal Relationship Between Opioid Use and Obstructive Sleep Apnea: A Bidirectional Mendelian Randomization Study

Guoliang Shan, MD[1], Yufeng Ma, MD[1], and Yanwu Jin, MD[1,2]

From: [1]Department of Anesthesiology, The Second Hospital, Cheeloo College of Medicine, Shandong Province, People's Republic of China; [2]Department of Anesthesiology, Shandong Public Health Clinical Center, Shandong Province, People's Republic of China

Address Correspondence:
Yanwu Jin, MD
Department of Anesthesiology, The Second Hospital, Cheeloo College of Medicine
247 Beiyuan Avenue, Jinan, Shandong Province, 250033
People's Republic of China
E-mail: jinyanwu_aa@163.com

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Background: Opioid medications are widely used for pain management, but their impact on obstructive sleep apnea (OSA) remains controversial. Given the high prevalence of OSA and the increasing use of opioids, understanding the causal relationship between the condition and this type of medication is critical.

Objectives: This study aims to investigate the causal relationship between opioid use and OSA using a bidirectional 2-sample Mendelian randomization (MR) analysis. Specifically, the study seeks to determine whether exposure to opioid use increases the risk of developing OSA and whether OSA influences the likelihood of opioid use.

Study Design: The study employed a bidirectional 2-sample MR analysis to explore the causal relationship between opioid use and OSA. Genetic variants from large-scale genome-wide association studies (GWAS) were used as instrumental variables to ensure robust causal inference.

Setting: The study utilized data from 2 large-scale GWAS datasets. Opioid use data were obtained from the UK Biobank, while OSA data were sourced from the FinnGen study. Both datasets predominantly included patients of European ancestry with similar demographic characteristics.

Methods: This study employed a 2-sample bidirectional Mendelian randomization (MR) approach to investigate the causal relationship between opioid use and obstructive sleep apnea (OSA). Genetic instruments for opioid use and OSA were selected from large-scale genome-wide association studies (GWAS) conducted in European populations, ensuring consistency in genetic backgrounds. The inverse variance-weighting (IVW) method was used as the primary analysis to estimate causal effects, supplemented by the weighted median, MR-Egger, simple mode, and weighted mode methods to ensure robustness. Sensitivity analyses, including MR-Egger regression, leave-one-out analysis, and MR-PRESSO, were conducted to assess pleiotropy, heterogeneity, and the influence of individual SNPs on the results.

Results: The IVW method demonstrated a significant causal effect of opioid use on the risk of developing OSA, with a causal effect size of 0.28 (OR = 1.32, 95% CI = 0.09 to 0.46, *P*-value = 0.004). This association was supported by the weighted median method, though the MR-Egger, simple mode, and weighted mode methods did not achieve statistical significance but showed a consistent direction of effect. Conversely, no significant causal relationship was observed between OSA and opioid use across all methods, suggesting that OSA did not significantly influence opioid use.

Limitations: The primary limitations of this study include the use of binary phenotypes for opioid use and OSA, which precludes the assessment of dose-response relationships. Additionally, the genetic data were derived predominantly from European populations, limiting the generalizability of the findings to other ethnic groups. Potential pleiotropy and unmeasured confounders, although addressed through various sensitivity analyses, may still introduce bias into the results.

Conclusion: This study provides strong evidence of a unidirectional causal relationship in which opioid use increases the risk of developing OSA. These findings underscore the importance of monitoring patients who use opioids for potential respiratory complications, particularly OSA.

Key words: Mendelian randomization, opioid, Obstructive Sleep Apnea (OSA)

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Opioid medications, widely utilized for their potent analgesic properties, have become a critical component in managing acute and chronic pain (1). In 2021, approximately 296 million people globally (5.8% of the population aged 15-64) used drugs at least once, including about 60 million who used opioids. Of those individuals, 39.5 million were living with drug use disorders, and the proportion of persons using prescription opioids is growing (2).

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by the repeated occurrence of complete (apnea) or partial (hypopnea) blockage in the upper airway during sleep (3). Impacting over one billion individuals between the ages of 30 and 69 globally, OSA is associated with significant risk factors, including obesity, anatomical abnormalities, alcohol and sedative use, smoking, and associated conditions like hypertension and diabetes (4). Additionally, OSA impacts the patient's quality of life significantly by increasing the risk of hypertension, heart disease, stroke, diabetes, and accidents. OSA also causes daytime sleepiness, cognitive impairment, mood issues, and impairments in social and occupational functioning, while imposing considerable economic burdens due to health care costs and productivity losses (5-7).

Opioid drugs induce significant respiratory depression through multiple mechanisms, including the inhibition of central respiratory centers in the brainstem (notably the pre-Bötzinger complex and Kölliker-Fuse nucleus), reduction of respiratory rate and tidal volume due to decreased chemoreceptor inputs, impairment of respiratory muscle function, partial obstruction of the upper airway, and the accumulation of carbon dioxide (hypercapnia) resulting from decreased minute ventilation (8,9). These mechanisms are generally thought to be related to central apnea. While the relationship between opioid use and central sleep apnea has been well-documented, the impact of opioid use on OSA remains controversial, with existing research presenting conflicting findings (10-18).

The high prevalence and serious health impacts of OSA, combined with rising opioid use and unclear causal links between the condition and the type of medication, underscore the urgent need to clarify how OSA interacts with opioid use. Mendelian randomization (MR) offers a robust approach to address the limitations of observational studies, such as confounding and reverse causation, and the challenges of randomized controlled trials, including small samples, implementation difficulties, and ethical concerns; currently, no MR studies have explored the relationship between opioid use and OSA (19). By using genetic variants as instrumental variables (IVs), MR can provide more reliable evidence on the causal relationships between OSA and opioid use (19). This method helps to mitigate the confounding factors and reverse causation common in observational studies (19). Understanding these relationships is crucial for developing targeted interventions and informing clinical guidelines, especially given the rising use of opioids for pain management and the significant health burden associated with OSA.

Objectives

This study aims to investigate the causal relationship between opioid use and OSA using a 2-sample bidirectional MR analysis. Specifically, the objectives are to determine whether exposure to opioid use increases the risk of developing OSA and to evaluate if OSA influences the likelihood of opioid use. The hypotheses are that exposure to opioid use will increase the risk of developing OSA significantly, while exposure to OSA will have a similarly significant effect on the likelihood of opioid use. By addressing these objectives, this study seeks to provide new insights into the interplay between opioid use and OSA, potentially guiding more effective prevention and treatment strategies for these interrelated conditions.

Study Design

This study utilized a 2-sample bidirectional MR analysis to explore the causal relationship between opioid use and OSA. The analysis proceeded through 4 main steps. Initially, single-nucleotide polymorphisms (SNPs) associated with exposures were identified from large-scale GWAS available in public databases. These SNPs served as IVs to enhance the robustness of the MR analyses. Instrument validity tests were performed to verify the strength of the IVs. Secondly, genetic data related to outcomes were selected from various databases to avoid sample overlap and potential biases. In the third step, the bidirectional 2-sample MR analysis was performed using the identified SNPs as IVs to investigate causal relationships in both directions. Lastly, sensitivity analyses were conducted to confirm the robustness of our results, and statistical power (1-β) tests were used to ensure the study had sufficient power to detect causal effects.

To guarantee the reliability of the MR findings, 3 key assumptions were satisfied: (i) the IVs were strongly associated with the specific exposures; (ii) the IVs were

independent of any confounders; and (iii) the IVs influenced the outcomes solely through the exposures (20). Figure 1 illustrates the design framework for this study.

Setting

This study utilized data from 2 large-scale genome-wide association studies (GWAS) datasets. Additionally, to prevent biases from ethnic differences, the genetic data for both exposures and outcomes in our MR study were sourced from populations of European ancestry.

Summary statistics for opioid use were derived from a GWAS meta-analysis of 78,808 patients in the UK Biobank (UKB), including 22,982 opioid users and 55,826 controls (21). The UKB is a large-scale resource collecting genetic, lifestyle, and health data from over 500,000 UK volunteers for research purposes. Approximately 54% of patients profiled in the UKB were female, ranging from 37 to 73 years of age, with an average age of 56.5 years (SD 8.1) at their first assessment. The prescription opioids involved in the GWAS analysis predominantly included morphine, oxycodone, codeine, buprenorphine, tramadol, pethidine, and fentanyl. Only regular medications taken weekly, monthly, or thrice-monthly were recorded, based on self-reports from patients in the original GWAS, with medication information obtained through nurse-led interviews.

Summary statistics for OSA were extracted from a recent GWAS involving 16,761 patients and 201,194 controls in the FinnGen study, a large-scale biobank project in Finland aimed at analyzing the genomic and health data of 500,000 patients (22). In the FinnGen project, the patients were 56.5% women, with an average age of 52.4 years (SD 17.5). OSA diagnoses were based on the International Statistical Classification of Diseases (ICD) codes (ICD-10: G47.3, R06.5; ICD-9: 3472A) and were supplemented by clinical examination, subjective symptoms, and sleep registration with an apnoea-hypopnoea index ≥ 5/h or a respiratory event index ≥ 5/h. Both datasets include a wide range of demographic and clinical characteristics, ensuring robust and representative samples.

Methods

Selection of Instrumental Variables

IVs for opioid use were selected from the summary statistics obtained from the (UKB) GWAS meta-analysis. The selection criteria for SNPs included genome-wide significance (P-value < 5×10^{-6}), independence ensured by linkage disequilibrium (LD) pruning (r^2 threshold of 0.01) (23), and relevance assessed through F-statistics (F > 10 indicating strong instruments) (24). The threshold of $P < 5\times10^{-6}$ was chosen to increase the number of available SNPs for analysis, enhancing statistical power while still maintaining a stringent level of significance to minimize the risk of including false positives. Additionally, SNPs associated with confounding factors and outcomes were manually excluded using information from the GWAS Catalog. For OSA, IVs were selected from the FinnGen GWAS data, with the same criteria applied.

Data harmonization was performed to align effect alleles and exclude palindromic SNPs with intermediate allele frequencies, ensuring compatibility between the

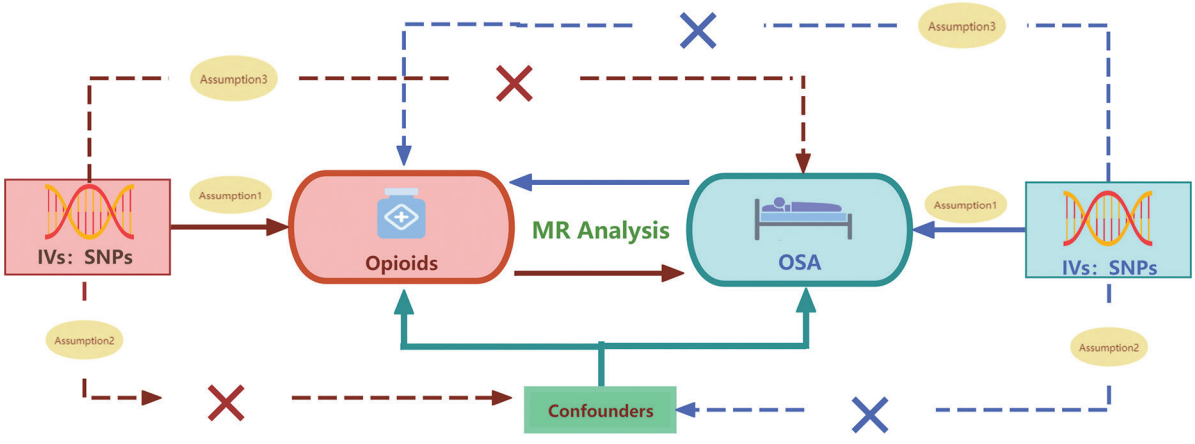

Fig. 1. *Study design for investigating the causal relationship between opioid use and OSA using bidirectional 2-sample MR.* MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms; OSA, obstructive sleep apnea; opioids, opioid use.

exposure and outcome datasets. During instances in which SNPs were missing for either the exposure or the outcome datasets, no proxy SNPs were sought. Instead, we opted to proceed with the available genetic instruments to maintain the integrity of the analysis.

Statistical Analysis

Statistical Methods: Main Analysis

The primary analysis to estimate the causal effect between opioid use and OSA was conducted using the inverse variance-weighting (IVW) method, which combines effect estimates from multiple SNPs to provide an overall causal estimate, assuming balanced pleiotropy (25). This method offers higher statistical power than do other MR analysis methods. In addition to IVW, we utilized the weighted median method, MR-Egger, simple mode, and weighted mode methods to supplement our analysis. The Weighted Median method offers a robust causal estimate even if up to 50% of the instrumental variables are invalid (26), while the MR-Egger method provides robust estimates even if all SNPs violate the IVs' validity assumption (25). Simple mode and weighted mode add further validation by evaluating the most frequent effect size and calculating a weighted average based on SNP strength, respectively (25). These methods together ensure comprehensive analysis by leveraging different statistical models to account for various potential biases and data complexities (27).

Sensitivity Analysis

To ensure the robustness of our results, several sensitivity analyses were performed. MR-Egger regression was used to detect and adjust for directional pleiotropy by examining whether the intercept of the regression line was significantly different from zero, indicating potential pleiotropy (27). Leave-one-out analysis was conducted systematically to remove one SNP at a time for the purpose of identifying any single SNP that might influence the results disproportionately, ensuring that the findings were not driven by any one genetic variant (28). Additionally, MR-PRESSO was used to detect and correct for horizontal pleiotropy by identifying and removing outlier SNPs that contributed to pleiotropic bias (29). To assess heterogeneity among the SNP-specific causal estimates, Cochran's Q test was employed to detect inconsistencies across the SNPs, which might indicate the presence of invalid instruments or pleiotropy (29). Statistical power (1-β) tests were conducted to ensure the study had sufficient power to detect causal effects, considering the sample size, effect size, and number of instrumental variables used.

Software and Preregistration

All statistical analyses were performed using the TwoSampleMR package in R. To ensure comprehensive and accurate analyses, additional statistical tests and visualizations were also conducted using R, as were related packages.

Due to constraints related to the availability of data and the retrospective nature of our analysis, this study was not preregistered.

Ethical Considerations

All data in this study were sourced from publicly accessible GWAS databases, with ethical approvals and consents already secured by the original researchers. Since our study involved only the re-analysis of existing data, no additional ethical reviews were required.

Results

Descriptive Data

This study utilized data from the datasets of 2 large-scale GWAS. The populations in both datasets had similar demographic characteristics, with comparable age distributions, gender ratios, and predominantly European ancestry, which helped ensure consistency and reduces potential biases in the analysis.

Primary Mendelian Randomization Analysis

Selection and Validation of Instrumental Variables

Instrumental variables for opioid use were selected based on genome-wide significance ($P < 5\times10^{-6}$), independence ($r^2 < 0.01$), and relevance (F-statistic > 10), with confounding SNPs excluded manually. SNPs were harmonized, and palindromic SNPs with intermediate allele frequencies were removed. All selected SNPs had strong F-statistics, confirming instrument validity. Leave-one-out analysis checked for SNPs influencing results disproportionately, and MR-PRESSO was used to correct for potential horizontal pleiotropy. This comprehensive process resulted in the identification of 12 SNPs for opioid use (Table 1). For obstructive sleep apnea (OSA), the same criteria were applied, resulting in the selection of 6 SNPs (Table 2).

Effect of Opioid Use on OSA

The analysis that used the (IVW) method revealed a

Table 1. *Basic information of each SNP in the opioid use on OSA.*

SNP	Effect Allele	Other Allele	EAF	Opioid Use			OSA		
				Beta	SE	*P*-value	Beta	SE	*P*-value
rs10114416	C	T	0.608228	0.0488	0.0099	8.26E-07	0.03	0.0125	0.01591
rs12238134	G	A	0.779647	0.0633	0.0109	6.38E-09	0.0256	0.0156	0.1002
rs1493241	G	T	0.545491	-0.0466	0.0102	4.59E-06	-0.0166	0.0126	0.1881
rs3763317	T	C	0.611978	0.0528	0.0099	1.07E-07	0.0076	0.0148	0.6052
rs4258296	C	T	0.493929	0.0495	0.0102	1.13E-06	-0.0138	0.0125	0.2689
rs521956	C	T	0.63185	0.0498	0.01	5.97E-07	0.0286	0.0125	0.0222998
rs7428430	T	C	0.729709	-0.0605	0.0102	2.95E-09	-0.0068	0.0125	0.588
rs769656	C	T	0.285407	-0.0531	0.0106	5.69E-07	-0.0277	0.0132	0.0356
rs9309184	G	A	0.713473	-0.0505	0.0103	9.19E-07	-0.0052	0.0125	0.676

Table 2. *Basic information of each SNP in the OSA on opioid use.*

SNP	Effect Allele	Other Allele	EAF	OSA			Opioid Use		
				Beta	SE	*P*-value	Beta	SE	*P*-value
rs10860169	G	A	0.2906	-0.0653	0.0137	2.01E-06	0.0051	0.0103	0.619901
rs11758441	T	C	0.378	0.0602	0.0129	2.98E-06	0.0069	0.0102	0.5013
rs1896039	A	G	0.5349	0.062	0.0126	9.24E-07	-0.0214	0.0309	0.489
rs193546	A	G	0.7438	0.0739	0.0143	2.27E-07	0.0032	0.0113	0.7784
rs6021831	G	C	0.2973	-0.0632	0.0136	3.47E-06	-0.0266	0.0103	0.00974294
rs6845679	T	C	0.5898	0.0588	0.0127	3.53E-06	-0.0089	0.0103	0.3879

significant causal effect of opioid use on the risk of developing OSA, with an OR of 1.32 (95% CI: 0.09 to 0.46, *P* = 0.004), indicating strong statistical significance. This finding suggests that increased opioid use is associated with a higher risk of OSA. The weighted median method supported this finding, showing a similar causal effect size of 0.25 (OR = 1.28, 95% CI = 0.02 to 0.48, *P*-value = 0.031), reinforcing the association. Although the MR-Egger regression did not achieve statistical significance (effect size = 0.08, OR = 1.09, 95% CI = -2.01 to 2.17, *P*-value = 0.941), the direction of the effect remained consistent with the IVW method, suggesting that opioid use may still influence OSA risk despite the lack of significance in this model. Interestingly, while the simple mode and weighted mode methods did not reach statistical significance, with effect sizes of 0.44 (OR = 1.20, 95% CI = 0.06 to 0.83, *P*-value = 0.055) and 0.21 (OR = 1.24, 95% CI = -0.17 to 0.60, *P*-value = 0.308) respectively, they also pointed in the same direction, indicating a consistent trend across all methods. Overall, the consistent direction of effect across all 5 methods strengthens the evidence that opioid use is likely to increase the risk of developing OSA, even though not all methods achieved statistical significance (Figs. 2,3).

Effect of OSA on Opioid Use

The analysis using the IVW method did not reveal a significant causal effect of OSA on opioid use (OR = 1.07, 95% CI: -0.11 to 0.24, *P* = 0.483), indicating no statistically significant association. The weighted median method also did not show a significant causal relationship, with an effect size of 0.025 (OR = 1.03, 95% CI = -0.17 to 0.22, *P*-value = 0.804), consistent with the IVW method. Similarly, the MR-Egger regression method did not show a significant causal effect (effect size = 0.20, OR = 1.22, 95% CI = -2.33 to 2.72, *P*-value = 0.885), although the direction was consistent with the IVW method. Interestingly, the simple mode and weighted mode methods also did not demonstrate significant causal effects, with effect sizes of -0.029 (OR = 0.97, 95% CI = -0.30 to 0.24, *P*-value = 0.844) and -0.011 (OR = 0.99, 95% CI = -0.26 to 0.23, *P*-value = 0.934) respectively. Despite the lack of statistical significance across all 5 methods, the consistent direction of effect across most methods suggests a potential, albeit weak, influence of OSA on opioid use. However, these results do not provide strong evidence to support a causal relationship between OSA and increased opioid use (Figs. 2,3).

These findings provide evidence for a unidirectional causal effect in which opioid use increases the risk of developing OSA, but OSA does not influence opioid use significantly. The statistical significance and confidence intervals further support the robustness of these results.

Sensitivity Analyses

To ensure the robustness of our primary findings, several sensitivity analyses were performed, including MR-Egger regression, leave-one-out analysis, MR-PRESSO, and Cochran's Q test for heterogeneity (Table 3).

The MR-Egger regression analysis detected no significant pleiotropy, with an intercept of 0.010 (P = 0.860). The causal effect estimates for opioid use on OSA (0.08, 95% CI: -2.01 to 2.17, P = 0.941) and for OSA on opioid use (0.20, 95% CI: -2.32 to 2.72, P = 0.884) were directionally consistent with the IVW method but statistically nonsignificant.

Leave-one-out analysis confirmed that no single SNP exerted a disproportionate influence on the causal estimates, with consistent effect sizes across all iterations. Similarly, MR-PRESSO identified no outlier SNPs for either the effect of opioid use on OSA (P = 0.18) or OSA on opioid use (P = 0.19), indicating no significant horizontal pleiotropy (Fig. 4).

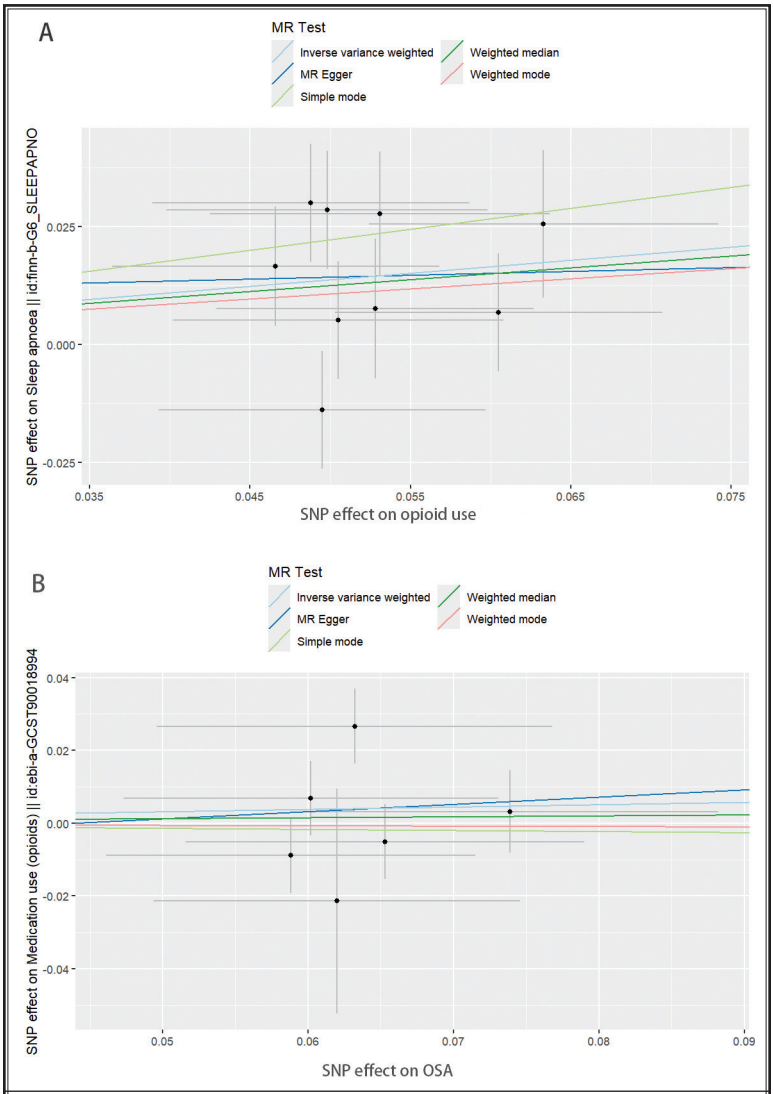

Fig. 2. *Scatter plots for opioid use on OSA (A), OSA on opioid use (B).*
SNP, single-nucleotide polymorphisms; OSA, obstructive sleep apnea

Cochran's Q test showed no significant heterogeneity among SNP-specific causal estimates, with Q values of 10.61 (P = 0.157) using the MR-Egger method and 10.66 (P = 0.22) using the weighted median method for opioid use on OSA, and Q values of 7.87 (P = 0.15) and 7.90 (P = 0.22), respectively, for OSA on opioid use. These results suggest homogeneity in causal estimates and support the validity of the findings.

Overall, the sensitivity analyses confirmed the robustness of the significant association between opioid use and increased OSA risk, while consistently showing no significant association between OSA and opioid use.

Discussion

Our study provides strong evidence for a unidirectional causal relationship between opioid use and the risk of developing OSA. The primary MR analysis using the IVW method demonstrated a significant causal effect (OR = 1.32), supported by the weighted median method. Although MR-Egger, simple mode, and weighted mode did not reach statistical significance, they indicated a consistent direction of effect, suggesting that opioid use may increase OSA risk. Conversely, no significant causal relationship was found between OSA and opioid use. To ensure robust results, we employed a bidirectional 2-sample MR analysis to minimize confounders and reverse causality. The IVW method was chosen for its higher

statistical power, which we complemented with MR-PRESSO and MR-Egger tests to address pleiotropy. Additional methods, including leave-one-out analysis and Cochran's Q test for heterogeneity, were used to validate our findings. We carefully selected genetic instruments with strong F-statistics and used large-scale GWAS datasets to enhance statistical power and minimize errors, reinforcing the reliability of our results.

The significant association between opioid use and the increased risk of OSA has important clinical implications. This finding is consistent with multiple previous observational studies and previous knowledge (30-32). In a meta-analysis of 40 studies, Cozowicz et al (33) found that opioids significantly increased the risk of dose-dependent postoperative respiratory complications, including life-threatening opioid-induced respiratory depression (OIRD), in OSA patients, due to their heightened pain perception and sensitivity to opioids. The relationship between opioids and central sleep apnea is well-established. Opioids depress respiratory drive in multiple ways, including inhibiting central respiratory centers in the brain stem and reducing chemoreceptor sensitivity (9,34). Additionally, opioids stimulate μ-opioid receptors, leading to the inhibition of motor output from the central respiratory motor neuron pool, which activates the tongue muscles. This phenomenon results in the relaxation of the upper airway muscles, increasing the propensity for airway collapse during sleep (35). Furthermore, opioids can affect several nonanatomical traits that influence OSA, including the control of breathing stability, pharyngeal dilator responses, and arousability from sleep (9). These mechanisms may provide a rationale for the increased risk of OSA observed in individuals using opioids. However, our study also contradicts the conclusions of some previous studies. A meta-analysis of 14 studies found that while 57% of patients reported no significant relationship between opioid use and OSA severity, 36% indicated worsening, and 7% suggested a reduction. Meanwhile, opioids overall had no significant effect on the apnea-hypopnea index (AHI), with a pooled mean

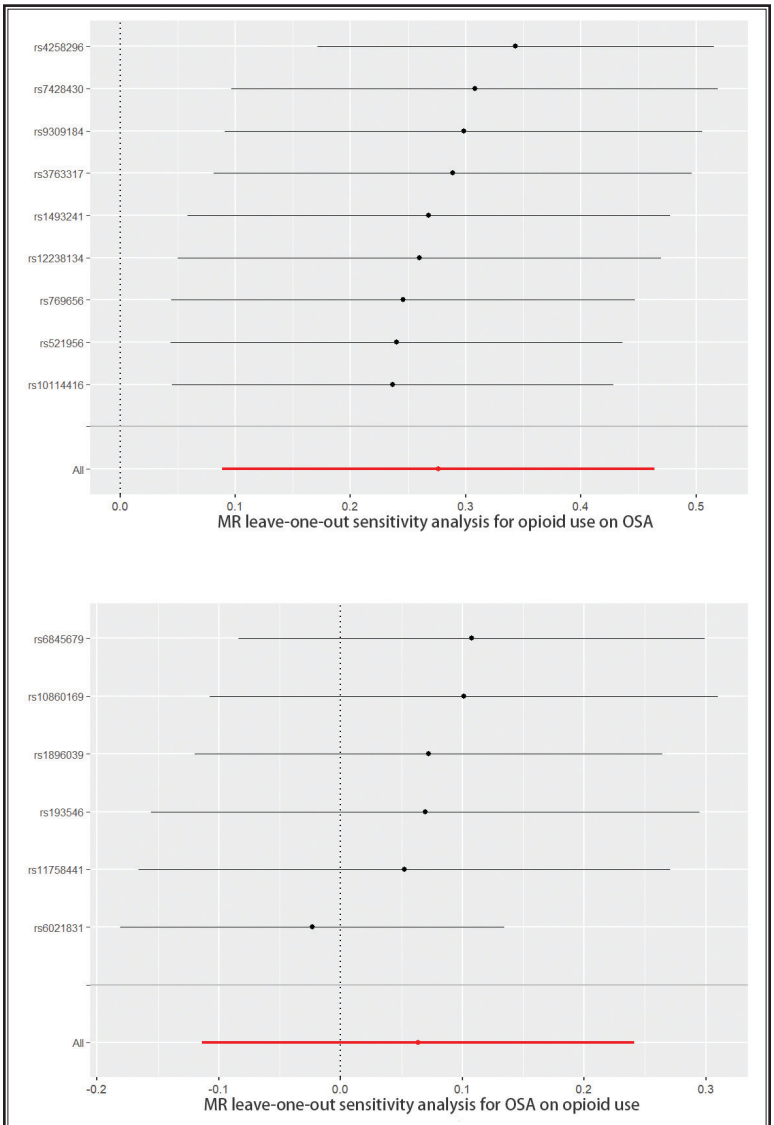

Fig. 3. *Single SNP analysis. The Single SNP analysis showed IVW and MR-Egger for opioid use on OSA (A), OSA on opioid use (B).*

Table 3. *Sensitivity analysis of the causal association.*

Exposure	Outcome	Cochran's Q test		MR-Egger		MR-PRESSO Global Test
		Q-value	*P*-value	Intercept	*P*-value	*P*-value
Opioid use	OSA	10.61	0.157	0.08	0.941	0.18
OSA	Opioid use	7.90	0.22	0.20	0.884	0.19

difference of 1.47 (95% CI: -2.63 to 5.57), despite high study heterogeneity (18). The differences in conclusions can be attributed to biases, such as confounding and reverse causation, common in observational studies, as well as high heterogeneity in study results and varying data quality from studies with different designs. Additionally, these differences may stem from the limitations of our own study.

The clinical relevance of our findings is significant. With the global rise in opioid consumption (36,37), there has been a parallel increase in opioid-related fatalities, which almost always occur during sleep (38,39). Moreover, the prevalence of OSA is notably high among opioid users (31,40). Medical providers should be aware of the adverse effects of opioid use on respiratory function during sleep, including its association with OSA, as emphasized by the American Academy of Sleep Medicine and American Society of Anesthesiologists (41,42). Regular monitoring and management of patients using opioids are crucial to preventing the development or exacerbation of OSA. These findings also underscore the importance of developing pain management strategies that reduce opioid reliance, thereby mitigating the risk of OSA.

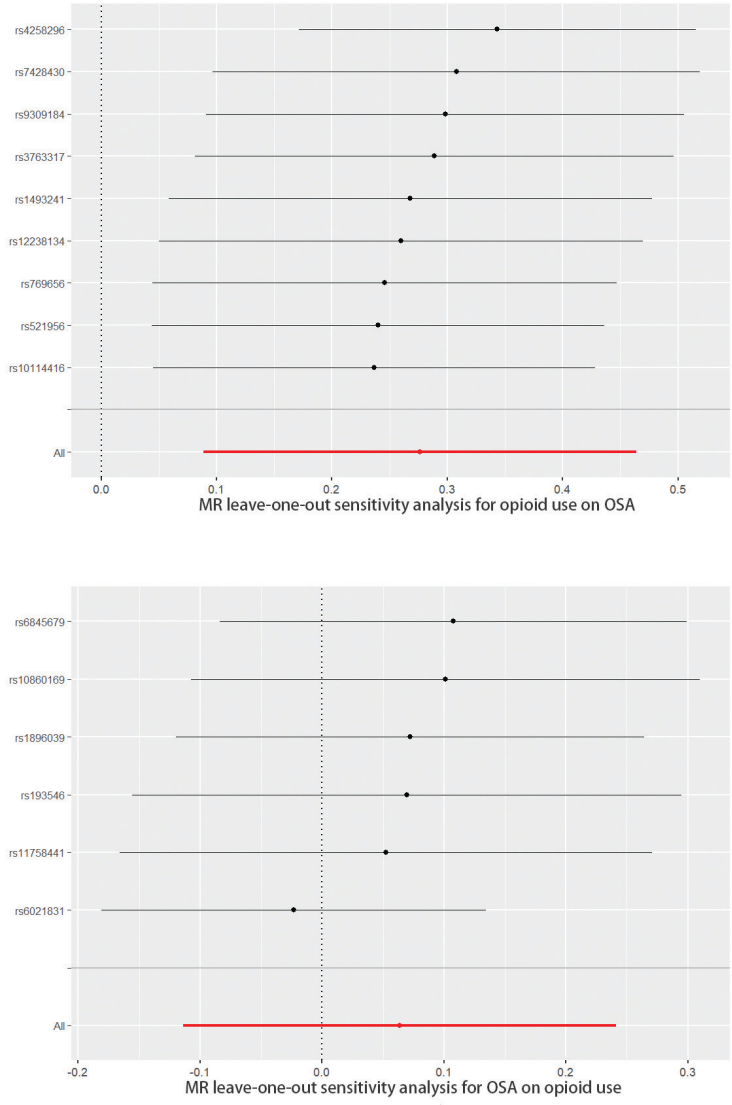

Fig. 4. *Leave-one-out sensitivity analysis. Both "leave-one-out" sensitivity analyses showed that the included SNPs had no significant impact on the results.*

Our findings primarily apply to populations of patients with European ancestry, which may limit the results' generalizability. Validation studies using diverse patient datasets that include various ethnic and racial groups are needed to determine if the identified genetic loci are consistent across different populations. Additionally, future research should explore the dose-response relationship between opioid use and the risk of OSA, since our study's use of binary phenotypes for opioid use and OSA prevented the assessment of dose-dependent effects. Investigating the impact of specific types of opioids on OSA risk and potential moderating factors, such as stress, medication use, and lifestyle factors, could provide a more comprehensive understanding of the causal pathways involved. Incorporating more detailed patient information and potential confounding variables in future analyses could also enhance the accuracy of the causal estimates.

Limitations

Our study has several limitations. First, the validity of the instrumental variables (IVs) is crucial for MR studies. Although we selected IVs based on genome-wide significance (P-value < 5×10^{-6}), independence (r^2 threshold of 0.01), and relevance (F-statistic > 10), potential violations of MR assumptions, such as pleiotropy, could bias the results. Additionally, our study primarily used data from a European population, which may limit the generalizabil-

ity of the findings to other ethnic and racial groups due to potential variability in genetic predispositions and environmental exposures. Another limitation is that the phenotypes for opioid use and OSA in our study are binary variables, which means we cannot assess the dose-dependent relationship between opioid use and the risk of OSA. Although MR has a greater ability to reduce the likelihood of confounding than do traditional observational studies, MR does not eliminate confounding entirely. Unmeasured confounders might affect both the genetic instruments and the outcomes. Furthermore, distinguishing between direct causal relationships and indirect associations mediated by other factors, such as comorbid conditions, medication use, or lifestyle factors, presents a challenge.

Conclusion

In conclusion, this study, through the use of MR, provides strong evidence that while opioid use causally increases the risk of developing OSA, the presence of OSA does not significantly influence opioid use. These findings highlight the need for careful monitoring and management of patients who use opioids to prevent the occurrence and progression of OSA.

Contribution of Each Author

Guoliang Shan: Guoliang Shan contributed to the conceptualization and design of the study, data analysis, and manuscript writing. He is the first author of the manuscript.

Yufeng Ma: Yufeng Ma contributed to the data collection and analysis. She assisted in revising the manuscript critically for important intellectual content.

Yanwu Jin: Yanwu Jin supervised the entire study, provided critical revisions, and approved the final version of the manuscript for submission. He is the corresponding author.

We hereby declare that the listed authors have contributed significantly to the research work and manuscript preparation. All authors have reviewed and approved the final version of the manuscript and agree to its submission.

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