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ORIGINAL RESEARCH

Mendelian Randomization Analysis Identifies Causal Effects of Multi-Site Chronic Pain on Obstructive Sleep Apnea

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Background: Observational studies have suggested an association between obstructive sleep apnea (OSA) and chronic pain disorders, but causal evidence have not been confirmed.

Methods: Here we performed Mendelian randomization (MR) study to explore the potential causal association and mediating roles of modifiable factors between multi-site chronic pain (MCP) and OSA. Independent single nucleotide polymorphisms (SNPs) (N=26) from MCP GWAS (n=387,649) in the UK Biobank were used as instrumental variables to test associations with OSA from the FinnGen consortium, which encompassed 16,761 individuals with OSA cases and 201,194 individuals without OSA.

Results: MR analyses provide genetic evidence to predict MCP on the risk of OSA. Specifically, a per-site increase in multi-site chronic pain was linked to a 184% higher risk of OSA (OR_{IVW} = 1.84, 95% CI = 1.29–2.63, p = 7.24×10^{-4}). However, we also performed reverse association analyses and found no significant casual effect of OSA on MCP. MR estimates were in agreement regardless of the method used, such as MR-egger, weighted median and weighted mode, thereby demonstrating the accuracy of the causal associations. Through mediation analyses, we found that body mass index (BMI), waist circumference, and educational attainment explained a substantial proportion of the association between MCP and OSA (proportion mediated=21.13%; 26.57% and 9.66% respectively).

Conclusion: Our findings suggest that both pain management interventions, prevention of obesity and health education are likely to be effective strategies to reduce OSA risk in individuals with MCP.

Keywords: Mendelian randomization, multi-site chronic pain, obstructive sleep apnea, causal effect, mediation effect

Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder, affecting approximately 2–4% in all middle-aged adults. It is characterized by recurrent episodes of upper airway collapse during sleep, leading to chronic intermittent hypoxia and sleep fragmentation.[1] Similar to OSA, pain disorders have a prevalence of headache (42%), unspecified chronic pain (34%), musculoskeletal pain (25%), and back pain (21%). These conditions impose a significant socioeconomic burden and contribute to excess mortality.[2]

Observational studies have shown OSA is associated with increased pain sensitivity and decreased pain tolerance.[3] On the contrary, a meta-analysis suggested that objective polysomnographic indices indicate that individuals with chronic pain experience poor sleep quality, particularly with respect to sleep initiation and maintenance.[4] People with chronic pain also experience fatigue, depression, and anxiety symptoms, and sleep disturbances irrespective of the pain etiology.[5]

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Multi-site chronic pain (MCP), a chronic pain phenotype defined as the number of sites at which chronic pain is experienced lasting longer than 3 months.[6] It was reported that the number of sites is negatively correlated to physical and psychological health and has a complex trait with moderate heritability.[7] Despite both OSA and MCP traits exhibit a significant genetic component in their development,[8] but evidence directly linking each other is still scant at present.

Epidemiological studies have associated chronic pain with several lifestyle factors and diseases, including obesity, smoking, drinking habits, and hypertension, which may influence subsequent mortality risk.[3] A systematic review found an association between OSA and pain intensity or experimental pain, but there was considerable variability among these studies, and treatment with continuous positive airway pressure (CPAP) could improve pain and decrease opioid use.[9] Another systematic review found that CPAP treatment increases pain tolerance and threshold but only improves chronic headache outcomes in adults with OSA.[10] A possible reason may be that some lifestyle factors are substantially involved in mediating pathways between chronic pain and OSA and contributed to the variation in treatment outcomes among these studies. We hypothesized that the effect of chronic pain on the risk of OSA might be mediated through several lifestyle factors or some diseases. However, investigations using cohorts to explore the mediators between chronic pain and OSA require a long follow-up period, and evidence has been scarce.

Mendelian randomization (MR) design is an alternative technique to appraise causal inference in epidemiological studies by using genetic variants as instrumental variables. In this study, we firstly employed a two-sample MR study to thoroughly disentangle the causal association between MCP and OSA. Given that lifestyle factors or diseases, as modifiable factors, are critical in the prevention and management of OSA and chronic pain, we then performed a two-step MR analysis to investigate the mediating effect from these modifiable factors on the causal association between MCP and OSA.

Methods

Study Design

We conducted a two-sample MR design, genetic instrumental variables (IVs) analyses utilizing summary-level data with SNPs as instruments for the risk factor. The MR design has to meet three conditions: 1) genetic instruments should strongly associated with the exposure of interest; 2) genetic instruments must be independent of any potential confounders; and 3) genetic instruments must affect the outcome only through the risk factors.[11,12] First, following the standard procedure, we selected all SNPs that met the specified criteria. Subsequently, a confounding analysis was conducted using Phenoscanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/)[13] to identify potential mediators and confounders. After removing SNPs overlapping with confounding factors, a two-sample MR analysis was performed to investigate the causal association between MCP and OSA. Lastly, a two-step MR analysis was conducted, utilizing traits sourced from Phenoscanner, to explore the mediating role of traits in the relationship between MCP and OSA. Additionally, a reverse MR analysis was conducted to investigate potential causal effects of OSA on MCP. The study design is depicted in Figure 1.

Exposure

Chronic pain exposure was identified through a genome-wide association study (GWAS) involving 387,649 individuals aged 40–79 residing in the UK between 2006 and 2010, drawn from the UK Biobank. The phenotype, MCP, was assessed via a self-reported questionnaire. Participants were queried about pain across up to 7 non-mutually exclusive body sites (neck/shoulder, headache, back, hip, knee, abdominal, facial). MCP was defined as the total number of body sites where chronic pain lasting more than 3 months was reported. This measurement has been utilized previously, and evidence indicates that chronic pain is better conceptualized as a "continuum of widespreadness" rather than distinct pain conditions localized to specific areas.[4]

Outcome

GWAS data for OSA was acquired from the FinnGen consortium, which encompassed 16,761 individuals with OSA cases and 201,194 individuals without OSA, all of European descent.[14] In the FinnGen consortium, OSA diagnosis is

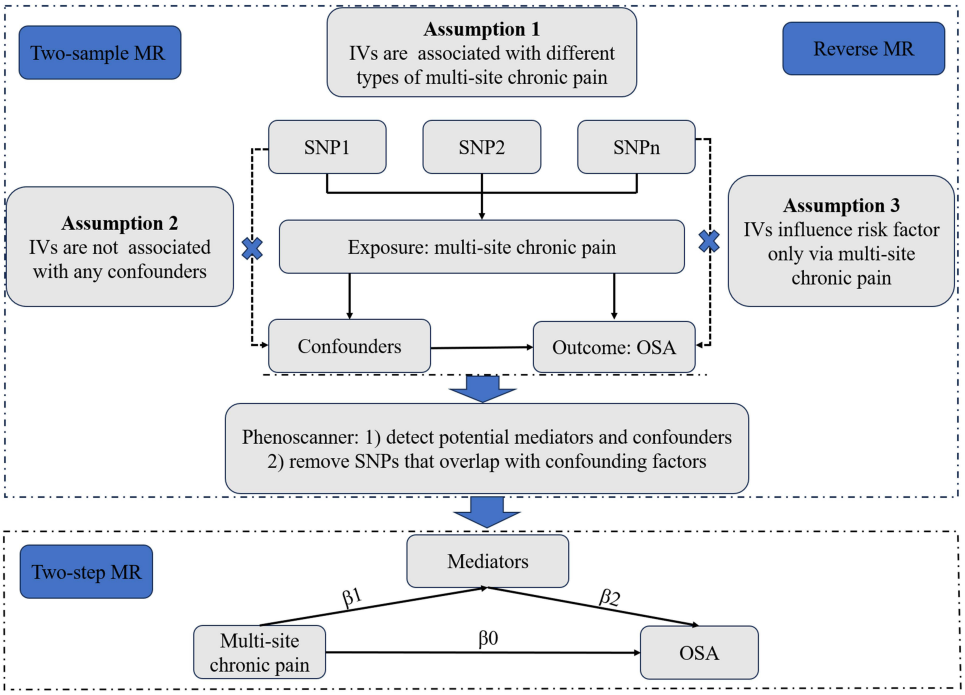

Figure 1 Overview of the MR study design.Two-sample and two-step MR analysis were used to assess the causal relationship between multi-site chronic pain and OSA. MR analysis is based on three assumptions: (i) IVs should be strongly associated with different types of pain, (ii) IVs should be independent of the outcome, and (iii) IVs should be independent of all confounders of the exposure-outcome relationship. The next step was to use Phenoscanner to search for possible confounders and mediators. In order to exclude the impact of confounders, we will remove the overlapping SNPs between pain and confounders, and then conducted a two-sample MR analysis on pain and OSA to verify the causal relationship between them. We performed two-step MR to explore the mediating effects of traits from Phenoscanner between pain and OSA. The causal effect of exposure on mediator, mediators on outcome and exposure on outcome were assumed to be β1, β2 and β0, respectively. To assess the presence and confidence interval of mediation effects, we employed interactive mediation tests Delta method.

based on ICD codes obtained from the Finnish National Hospital Discharge Registry and the Causes of Death Registry. The diagnosis incorporates subjective symptoms, clinical examination, and sleep registration, with a focus on the Apnea-Hypopnea Index (AHI) ≥ 5 events per hour or Respiratory Event Index (REI) ≥ 5 events per hour.

Mediators and Confounders

We employed Phenoscanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/)[13] to incorporate GWAS data sources encompassing potential confounders and mediators, while prioritizing maximum sample sizes and meticulously avoiding any sample overlaps. We compared SNPs meeting the criteria for MR analysis in multi-site chronic pain with SNPs significantly associated ($p < 1 \times 10^{-5}$) with various diseases, lifestyles, and physical conditions, identifying overlapping SNPs and their associated phenotypes. The initial screening results are provided in Supplementary Table S4. As shown in Table 1, the following phenotypes were included in our two-step MR analysis.

Body mass index (BMI),[15] waist circumference, hip circumference,[16] and height,[17] involving 339,224, 232,101, 213,038, and 253,288 participants, respectively, sourced from the Genetic Investigation of Anthropometric Traits (GIANT).

Cigarettes per day, smoking initiation, age of smoking initiation, and alcoholic drinks per week, with 337,334, 632,802, 341,427, and 335,394 participants, respectively, sourced from the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN).[18]

Educational attainment, involving 765,283 participants, sourced from the Social Science Genetic Association Consortium (SSGAC).[19]

Major depressive disorder (MDD), featuring 170,756 cases and 329,443 controls, sourced from the Psychiatric Genomics Consortium (PGC) and UK Biobank.[20]

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Table 1 GWAS Data Sources Included in the Mendelian Randomization Study

Phenotype	Unit	Sample Size (Overall or Case/Control)	Ancestry	Consortium or Cohort Study	PubMed ID
Exposure					
Multi-site chronic pain	Event	387,649	European	UK Biobank	31194737
Outcome					
Obstructive sleep apnea	Event	16,761/201,194	European	FinnGen	33243845
Mediators					
Body mass index	1 s.d.	339,224	European	GIANT	25673413
Waist circumference	1 s.d.	232,101	European	GIANT	25673412
Hip circumference	1 s.d.	213,038	European	GIANT	25673412
Cigarettes per day	1 s.d.	337,334	European	GSCAN	30643251
Smoking initiation	Event	311,629/321,173	European	GSCAN	30643251
Age of smoking initiation	1 s.d.	341,427	European	GSCAN	30643251
Alcoholic drinks per week	1 s.d.	335,394	European	GSCAN	30643251
Educational attainment	1 s.d.	765,283	European	SSGAC	35361970
Major depressive disorder	Event	170,756/329,443	European	PGC, UK Biobank	30718901
Insomnia	Event	109,548/277,440	European	CNCR	35835914

Abbreviations: PGC, Psychiatric Genomics Consortium; CNCR, Center for Neurogenomics and Cognitive Research; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; GIANT, Genetic Investigation of Anthropometric Traits; SSGAC, Social Science Genetic Association Consortium.

Insomnia, including 109,548 cases and 277,440 controls, sourced from the Center for Neurogenomics and Cognitive Research (CNCR).[21]

IVs Selection

All relevant SNPs selected as genetic instruments met the widely accepted threshold of 5×10^{-8}.[22,23] Linkage disequilibrium (LD) clumping was performed on the candidate instrumental SNPs to identify independent ones ($r^2 < 0.001$ within 10000 kb). Subsequently, the exposure and outcome datasets were harmonized to determine the genetic instrument effects on different types of pain and remove palindromic SNPs. The relevance assumption was tested by calculating F-statistics for all selected SNPs. Only SNPs with F-statistics greater than 10 were included, ensuring the instruments are strongly associated with MCP.[24] The exchangeability assumption was evaluated by conducting a confounder analysis using Phenoscanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/),[13] to ensure that the selected SNPs are not associated with confounders. Overlapping SNPs associated with potential confounders, such as insomnia and BMI, were excluded to prevent bias. The remaining SNPs were chosen as IVs for the final analysis.

Statistical Analysis

We executed four distinct approaches to MR analysis, specifically: random-effect inverse-variance weighted (IVW), MR Egger, weighted mode, and weighted median. The IVW method served as the primary outcome, enabling us to quantify causal effects without requiring individual-level data.[25] To ensure the reliability of the findings, it's essential to compare the causal effect assessed using the IVW approach with results obtained from the MR Egger, weighted mode, and weighted median methods. The MR-Egger approach accommodates the possibility of genetic variants exerting pleiotropic effects, provided these effects remain uninfluenced by the variant-exposure association.[26] In the weighted median analysis, potentially less dependable instruments can be utilized, assuming that at least half of the instruments used are reliable. This approach yields an unbiased causal effect estimate by calculating the median of weighted ratio estimates.[27] The weighted mode method identifies causal effects that are less pronounced than those from IVW, yet it offers reduced bias and lower rates of type-I errors.[28] In instances where only one instrument variant was available, the Wald ratio was employed to assess the resulting connection.[29]

Sensitivity analysis is crucial in MR research for uncovering pleiotropy and addressing disparities in MR estimates. To achieve this, we utilized several techniques. Firstly, we applied Cochran's Q tests and MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) global test to identify heterogeneity, considering significance at $p < 0.05$ indicative of heterogeneity. Additionally, the exclusion restriction assumption was assessed through MR-Egger intercept and MR-PRESSO, to test for horizontal pleiotropy.[25,29] The MR-Egger intercept was evaluated to detect any pleiotropic effects that could violate this assumption, while MR-PRESSO was used to detect and correct for outliers contributing to pleiotropy.[29] Furthermore, leave-one-out analyses were conducted to explore the individual impacts of genetic variants on outcomes.[29]

To assess the presence of mediation, we employed two-step MR analysis wherein genetic instruments for pain were utilized to gauge the causal effect of the exposure on potential mediators (denoted as β1) in the first step. In the second step, the genetic instruments for the identified mediators were utilized to measure the causal effect of the potential mediators on OSA risk (denoted as β2). The causal effects of the pain on OSA were assumed as β0. The interactive mediation testing method was utilized to examine mediation effects,[30] and the delta method was employed to calculate the standard error of the mediating effect.[31]

We employed the Bonferroni correction to address multiple comparisons. A causal relationship was considered significant if the *p*-value was below 0.003 (adjusted for 16 exposures). Effect estimates were presented as odds ratios (ORs) and β-values with 95 confidence intervals (CIs) for binary outcomes and continuous variables. The OR indicates the odds of having OSA for individuals with a per-site increase in MCP compared to those without. The percentage increase in risk can be calculated as (OR - 1) × 100. All tests were conducted as two-sided analyses and all calculations were performed using TwoSampleMR (version 0.5.7), MendelianRandomization (version 0.8.0), and MRPRESSO (version 1.0.0) packages in R (version 4.3.0).

Results

Basic Characteristics of the MR Study

An overview of the study design is shown in Figure 1. The information on genome-wide association study (GWAS) datasets for MCP exposures, candidate mediators, and OSA outcomes in this MR study is listed in Table 1.

MR Estimates

As demonstrated in Supplementary Table S1, prior to the removal of confounding SNPs, a total of 32 SNPs meeting the criteria were harmoniously selected. After eliminating potential confounders, 26 SNPs remained, with F values ranging from 33.27 to 54.81, as shown in Supplementary Table S2. As presented in Figure 2, MCP exhibited a significant causal relationship on OSA. Specifically, a per-site increase in MCP was linked to a 84% higher risk of OSA ($OR_{IVW} = 1.84$, 95% CI = 1.29–2.63, $p = 7.24\times10^{-4}$). MR estimates were in agreement regardless of the method used, such as MR-egger, weighted median and weighted mode, thereby demonstrating the accuracy of the causal associations. We also performed reverse association analyses and found no significant casual association between OSA and MCP (Supplementary Table S3).

Exposure	Outcome	No.of SNP	Method	OR(95% CI)	P
Multi−site chronic pain	OSA	26	IVW	1.84 (1.29 to 2.63)	7.24×10^{-4}
			MR Egger	1.47 (0.28 to 7.76)	0.65685
			Weighted median	1.84 (1.13 to 3.00)	0.01421
			Weighted mode	2.19 (0.77 to 6.22)	0.15457

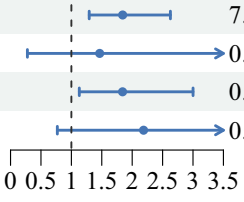

Figure 2 Causal effects for multi-site chronic pain on OSA.
Abbreviation: OSA, Obstructive Sleep Apnea.

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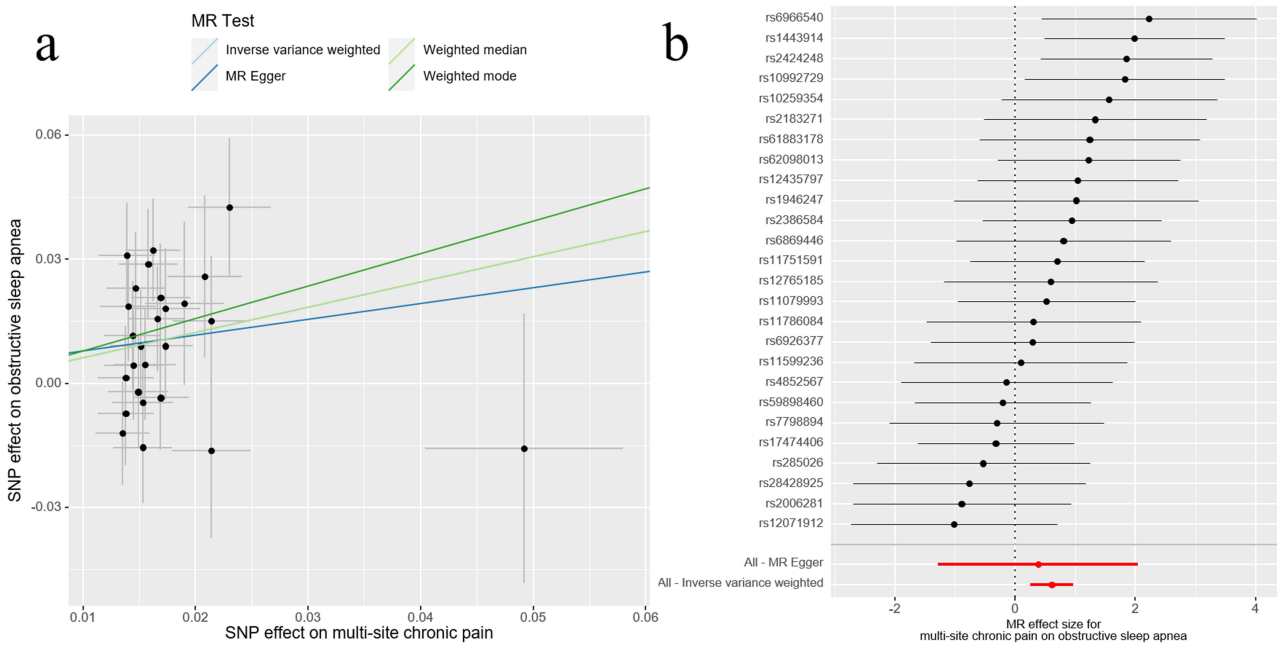

Figure 3 Sensitivity analysis (**a**) Scatter plots of SNP effects of multi-site chronic pain on obstructive sleep apnea, with the slope of each line corresponding to the estimated MR effect per method. (**b**) Forest plots of individual and combined SNP MR-estimated effect sizes.

Sensitivity Analysis

To assess the robustness of the aforementioned findings, a series of sensitivity analyses were conducted, including MR-Egger intercept test, MR-PRESSO global test and Cochran's Q test. Firstly, the *p*-values from the heterogeneity Q test were 0.23, Secondly, both the MR-PRESSO test ($p = 0.24$) and the MR-Egger intercept test ($p = 0.78$) did not reveal any evidence of horizontal pleiotropy. Scatter plots of the multi-site chronic pain on OSA risk association for the instruments were shown in Figure 3a, with coloured lines indicating the slopes of the different regression analyses. Additionally, Figure 3b, forest plots presented the MR estimates for the effects of the SNPs associated with MCP on OSA risk. Thirdly, leave-one-out analyses demonstrated that no single SNP significantly influenced the causal assessments (Supplementary Figure S1a). Lastly, the funnel plot exhibited symmetry, suggesting the absence of pleiotropy (Supplementary Figure S1b).

Mediation Analysis

The 10 included mediator variables were derived from the confounding analysis. As illustrated in Figure 4, BMI (21.13%), waist circumference (26.57%), and educational attainment (9.66%) were found to mediate the causal impact of MCP on OSA. However, the remaining 7 mediators did not exhibit any mediating effects in the causal relationship between MCP and OSA.

Discussion

In this research, we analysed data from large-sample GWAS to explore the causal relationship between MCP and OSA using MR analysis. Through various methods, we discovered that (1) MCP dramatically increases the risk of developing OSA; (2) BMI, waist circumference and education attainment mediate the causal connection between MCP and OSA.

In the current MR study, we have provided compelling evidence to support the causal effects of MCP on OSA, with no evidence of reverse causality. Our results are in line with previous observational studies. For example, one study indicated a high prevalence of OSA in patients with high-impact chronic pain referred for interdisciplinary pain treatment; however, the clinical pain profiles were similar in patients with and without OSA.[5] Another investigation by Chen et al reported a strong association between chronic pain and trouble sleeping, even after adjusting for socio-

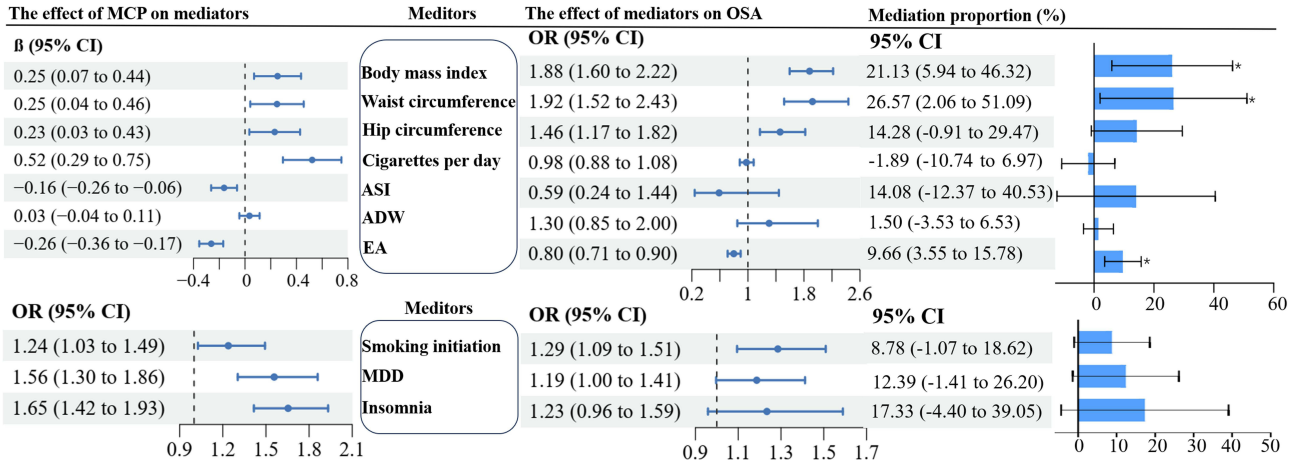

Figure 4 Mediating role of each mediator in the causal associations of multi-site chronic pain on obstructive sleep apnea.Two-step MR was used to evaluate the mediating role of each mediator in the causal associations of multi-site chronic pain on obstructive sleep apnea. Left: two-sample MR estimates for the causal effect of multi-site chronic pain on each mediator. Middle: two-sample MR estimates for the causal effect of each mediator on obstructive sleep apnea. Right: the mediation proportion of each mediator in the causal association between multi-site chronic pain on obstructive sleep apnea. MR estimates were derived from the IVW method in two-sample MR. The data are presented as ORs, β coefficients or proportions, with corresponding 95% CIs. The squares represent ORs or β coefficients, and the bars represent proportions, with the error bars indicating 95% CIs. All statistical tests were two-sided. P < 0.05 was considered significant. * It indicates that the mediating effect of the mediator is significant in the causal associations of multi-site chronic pain on obstructive sleep apnea.
Abbreviations: ASI, Age of smoking initiation; ADW, Alcoholic drinks per week; EA, Educational attainment; MDD, Major depressive disorder.

demographic characteristics, chronic conditions, and health behaviors.[32] Our findings are reasonable because some shared mechanisms underlying the pathophysiology of chronic pain, mediator and OSA may partially explain their interaction. It is important to recognize that sleep-related disruptions to dopaminergic and opioidergic signaling and the influence of disrupted sleep on affect and maladaptive coping responses have been posed as potential mechanisms for the relationship between sleep disturbance and pain.[33] Hypoxemia, for instance, contributes to the sensitization of pain receptors and is associated with an increase in inflammatory markers.[9,34] Additionally, repeated arousals associated with apneas may contribute to sleep fragmentation and inefficiencies in sleep, encouraging aberrant glial activity which alters the nociceptive system, increasing susceptibility to maladaptive plasticity and central sensitization of pain.[35,36] Notably the glymphatic system has been proposed as a potential shared neural pathway linking sleep-wake disorders and pain. The impaired sleep from untreated sleep apnea may contribute to disruption of the glymphatic system and, if left unaddressed, could have a compounding effect on hyperalgesia for those in a critical window of neural repair in the development of some chronic pain conditions.[37] MCP is widely accepted as a neuroinflammatory condition involving various cytokines, while elevated levels of proinflammatory cytokines play causal roles in the development of OSA.[33] Autonomic activation and resistance to insulin are other theorized mechanisms involved in the sleep inflammation pathway.[33] Preclinical and clinical studies suggest that nocturnal hypoxemia and sleep fragmentation enhance pain sensitivity and is mediated by several sleep-regulating cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6.[34,38–40] This may further escalate reliance of respiratory suppressing medications (ie, opioids), possibly contributing to a multitude of risk factors associated with poor opioid therapy outcomes.[33,39] On the contrary, ventilatory depression is a potentially dangerous complication of opioid therapy in pain patients. Opioids, by inhibiting chemical, behavioral, and motor control of respiration, could further raise arousal thresholds, prolong airway obstruction, and precipitate hypoxemia.[41] Opioids also may indirectly impact pain experience by contributing to the presence or exacerbation of sleep apnea symptoms, including increased apneas and worse oxygen desaturation. Previous observational studies have indicated that adults with OSA have higher odds of comorbid moderate/severe pain compared to those without OSA.[42] However, we observed no reverse causality from chronic pain to OSA or causal associations between other pain types and OSA. We were unable to conclude whether the null associations were due to the absence of causal effects or the low phenotypic variance explained by genetic instruments.

We performed a two-step MR for mediation analysis, revealing that the adverse effect of MCP on OSA risk was significantly mediated by obesity, including an increase in BMI or waist circumference (proportion mediated, >20%).

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This aligns with previous observations and indicates some association with demographic, lifestyle, and health-related factors.[43] Numerous studies have demonstrated an association between excess weight and chronic pain, as individuals with severe pain are more likely to adopt poor eating habits, such as overeating.[44] In a cross-sectional study, it was observed that a greater number of painful sites consistently correlated with poorer physical work capacity, increased low-intensity physical activity, and reduced moderate to vigorous physical activity.[45] Emotional overeating, driven by negative emotions as the number of painful sites increased, exacerbates overweight conditions accordingly.[46] The mediating effects of MCP via obesity can be explained by the finding that genetic liability to chronic pain is associated with various lifestyle factors and socio-economic status.[47,48] It had been suggested that obesity increases prevalence of sleep apnea syndrome in patients suffering from chronic pain and receiving chronic opioid therapy.[49] We are aware that obesity plays a central causal role in OSA risk, supported by genetic analysis.[14] We have previously reported that obesity, especially abdominal obesity indicated by waist circumference, is a known risk factor for OSA.[50] Therefore, obesity plays a pronounced mediating role in facilitating the impact of MCP on the development of OSA. Moreover, we found that educational attainment plays a protective mediating role in the effects of MCP on OSA outcomes. Our findings may be plausible because higher education level as a modifiable factor often broadly represent easier access to have better healthcare knowledge or better healthcare facilities for diminished exposure to chronic pain or other mediating roles between the chronic pain and OSA.[51] Understanding these pronounced mediating roles may open alternative avenues for OSA prevention for individuals suffering from chronic pain.

This study elucidates the causal effect of MCP on OSA outcomes and presents a comprehensive profile of mediators, including common lifestyle factors and diseases or disorders in the pathway from MCP to OSA. The main strengths of this study lie in its rigorous MR study design, encompassing normative and specific criteria for mediator screening, and the robust causal associations inferred from the main analysis, supported by various sensitivity analyses. However, the study has several limitations. Firstly, our findings were derived from GWASs primarily conducted in individuals of European ancestry from high-income countries. The generalizability of our results to other ethnic groups or low- and middle-income countries requires further investigation. Secondly, while we utilized the PhenoScanner database to search for pleiotropy SNPs associated with potential confounders, this study may not fully capture all mediation pathways, especially non-heritable factors such as environmental pollution. Additionally, the accuracy of OSA diagnoses in the GWAS dataset, which relied on subjective symptoms, clinical assessments, and sleep monitoring, is a critical consideration.[14] Although we believe the diagnostic criteria used are robust, they do not account for the severity of OSA, which may affect the associations observed. Moreover, potential biases could influence our findings. Selection bias may arise if the individuals included in the GWAS do not represent the broader population with OSA, potentially skewing the results. Collider bias could occur if MCP and OSA share common causes, leading to a distortion in the causal relationship we aimed to analyze.[30] Using a binary outcome variable in MR analysis may oversimplify the complex nature of OSA, masking variations in severity and limiting the interpretability of the findings. Lastly, in our study, MCP was assessed through self-reported data,[4] presenting limitations due to variations in individuals' pain perceptions that can affect the validity of the measurements and their associations with OSA. In contrast, OSA diagnoses were based on clinical assessments and standardized criteria, enhancing reliability.[30] However, the reliance on self-reported MCP data necessitates cautious interpretation of the findings. Future research should explore additional methodologies, such as structured clinical interviews, standardized pain assessment scales, wearable technology for real-time monitoring, and longitudinal studies, to better understand the interrelationship between MCP and OSA and enhance the robustness of the findings. While we found robust genetic evidence for a risk association between chronic pain and OSA risk, and to a certain extent, obesity or educational attainment mediated this effect. The potential implications of our results for OSA prevention policies warrant validation in well-powered randomized clinical trials.

In conclusion, this MR study demonstrates that MCP has a causal impact on OSA and delineates mediators, including obesity and educational attainment, that underlie the causal pathway especially in the European population. Our findings suggest that screening and monitoring for OSA and these mediators should be prioritized in patients with MCP.

Statement of Significance

In the USA, approximately 50 million individuals live with pain disorders. These individuals often have comorbid OSA, but causal evidence have not been confirmed. Given that lifestyle factors or diseases, as modifiable factors, are critical in the prevention and management of OSA and chronic pain. This MR study demonstrates that multi-site chronic pain (MCP) has a causal impact on OSA and delineates mediators, including obesity and educational attainment, that underlie the causal pathway. Our findings suggest that MCP and these mediators should be prioritized in the development of health strategies, policies, or health-risk surveillance for OSA patients.

Data Sharing Statement

All data used in the current study are publicly available GWAS summary data.

Ethics Statement

All analyses were publicly based on data available; ethical approval and consent were obtained in the original studies. The study was exempted by the Internal Review Board of the Institutional Ethics Committee of Sichuan Provincial People's Hospital.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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