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Abstract

Background: Previous studies have linked sleep quality to temporomandibular joint disorders (TMD), suggesting a role for snoring in this association. However, the directionality of this relationship remains a subject of debate. This investigation aimed to elucidate the connections between snoring and TMD.

Methods: Mendelian randomization methods.Genetically predicted.Genetic associations with temporomandibular joint disorders.

Results: First, a total of 38 SNPs predicting snoring at genome-wide significance (p?<?5?×?10?8) were obtained in the published GWAS, but 35 SNPs were used to assess the association with TMD after merging with the outcome dataset. Then, 7 SNPs that were palindromic with intermediate allele frequencies were removed via the "harmonize_data" tool. Next, we excluded 5 SNPs with a single F-statistic < 10 or linked to phenotypes related to potential confounding factors. The PhenoScanner database was queried to examine phenotypes associated with each genetic variant. Variants linked to phenotypes related to potential confounding factors, such as OSA, pain, smoking, or psychosocial conditions, were excluded based on PhenoScanner[64]. Finally, 23 SNPs (F ranging from 15.730 to 1070.37) were selected for subsequent MR analysis. The information gathered for the SNPs for snoring used in the current study is summarized in Supporting Information Table S1, mainly including effect alleles, other alleles and summary statistics.
Fig. 2 summarizes the results in the flow chart.
The relationships between snoring and TMD were investigated independently using IVW, MR?Egger, Weighted median, weighted mode, and simple mode approaches. Table 1 and Fig. 3 show that statistical significance was observed in the IVW analysis [odds ratio (OR) = 0.156, 95% confidence interval (CI) = 0.028 to 0.843, p = 0.0309]. A forest plot showing the effects of snoring on TMD is shown in Fig. 4. No significant effects were detected in the MR?Egger (OR = 0.210, 95% CI = 0.038 to 1.649, p = 0.7266), WM (OR = 0.091, 95% CI = 0.0074 to 1.129, p = 0.0506), weighted mode (OR = 0.017, 95% CI = 0.065 to 4.696, p = 0.1703) or simple mode (OR = 0.028, 95% CI = 0.0138 to 6.000, p = 0.2063) analyses. What's more, a high statistical power (90%) was identified in our study analyzed in mRnd (https://shiny.cnsgenomics.com/mRnd/)[60].

Conclusion: This MR study provides preliminary but novel genetic evidence supporting a potential causal link between snoring and a decreased risk of developing TMD. On the other hand, it does not substantiate a effect of TMD on the likelihood of snoring.

Objective: The objective of this study was to employ a MR analytical framework to investigate the impact of snoring on TMD. This approach aims to provide complementary information to that obtained from RCTs, contributing to a more comprehensive understanding of the relationship between snoring and TMD.

Conclusions: The study utilized MR to explore the relationship between snoring and TMD, finding that a genetic predisposition to snoring may reduce the risk of TMD. No link was found in the opposite direction. It hypothesized that snoring could have a protective effect on TMD through several possible mechanisms like intermittent hypoxia and vibratory disruption of pain signals, offering a new perspective on their association.

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Abstract

Background: Previous studies have linked sleep quality to temporomandibular joint disorders (TMD), suggesting a role for snoring in this association. However, the directionality of this relationship remains a subject of debate. This investigation aimed to elucidate the connections between snoring and TMD. **Methods:** This research employed a two-sample Mendelian randomization (MR) approach, leveraging publicly available large-scale genome-wide association study (GWAS) data on snoring and TMD. We utilized a suite of analytical methods, including the inverse variance weighted (IVW) method, maximum likelihood estimation, adjusted profile score, weighted median, MR–Egger regression, and a series of sensitivity analyses, to rigorously assess the existence of relationships. **Results:** Our findings indicate that a greater genetic predisposition to snoring is significantly associated with a reduced risk of TMD (IVW method; odds ratio [OR] = 0.156, 95% confidence interval [CI] = 0.028 to 0.843, p = 0.0309). Conversely, the analysis did not support a potential influence of TMD on snoring susceptibility (IVW method; 95% CI = 0.990 to 1.002, p = 0.1926). Additionally, our sensitivity analyses did not reveal any significant pleiotropy that could bias these findings. **Conclusion:** This MR study provides preliminary but novel genetic evidence supporting a potential causal link between snoring and a decreased risk of developing TMD. On the other hand, it does not substantiate a effect of TMD on the likelihood of snoring.

Keywords: snoring, temporomandibular joint disorders, Mendelian randomization analysis, genome-wide association study

1. Introduction

Snoring and sleep apnea syndrome impact millions of individuals, significantly reducing sleep quality for both patients and their partners. In one study, 16 couples were analyzed, with the average age of patients being 45.3 years and that of partners being 44.6 years [1]; Additionally, the syndrome is linked to increased daytime anxiety, as demonstrated in another study involving 45 couples, where the average age of patients was 50.5 years (range 44.0–58.3 years) and that of partners was 47 years (range 38.0–55.0 years)[2]; and is a risk factor for depression, fatigue, and sleepiness[1]. In a previous study, all participants underwent clinical examinations and were deemed healthy except for their snoring issues. Notably, individuals who snored exhibited significantly lower levels of energy, as measured by the Nottingham Health Profile, and diminished vitality, according to the Psychological General Well-Being Index, when compared to samples from the general population[3]. Another research was specifically designed to assess the effects of snoring, separate from obstructive sleep apnea syndrome, on the general population[4]. It revealed a significant correlation between a history of snoring and reports of daytime sleepiness and chronic fatigue in a diverse sample of 4,151 males and 707 females, with an average age of 54 years (range 13-95). Furthermore, habitual snoring, irrespective of sleep apnea, has been associated with excessive daytime sleepiness and fatigue[5]. Snoring was identified as a traditional risk factor for cardiovascular disease[6]. Furthermore, heavy snoring has been significantly linked to an increased risk of carotid atherosclerosis. This association persists even after controlling for other risk factors, including measures of nocturnal hypoxia and the severity of obstructive sleep apnea[7]. Additionally, snorers have twice the risk of carotid stenosis compared to nonsnorers[8]. This link is thought to arise from the vibrations and increased left ventricular wall tension and afterload caused by snoring[9]. However, a multi-ethnic study of atherosclerosis found no association between self-reported snoring and carotid atherosclerosis[10]. The sound of snoring originates from the vibration of the tissues in the pharyngeal walls, soft palate, tonsillar pillars, uvula, and tongue during sleep[11]. As it is associated with relaxation of airway muscles[12] and narrowing of the airways, leading to turbulent airflow[13]. Such snoring has been correlated with daytime sleepiness and fatigue in various demographics, including school-age children[14], young adult men undergoing compulsory conscript service[15], women from the general population[5],and community-dwelling adults[16]. Observational studies, a subtype of epidemiologic research[17], are conducted without direct control over interventions or outcomes. These studies are essential in epidemics for describing the basic properties of a pathogen, its transmission, clinical symptoms, associations between interventions and patient outcomes, and the effectiveness of public health measures in curbing disease spread[18].

The temporomandibular joint disorders (TMD) serves as a comprehensive designation for a constellation of musculoskeletal and neuromuscular conditions that involve the temporomandibular joint (TMJ), masticatory muscles, and all pertinent tissues[19]. It is the predominant etiology of orofacial pain and is characterized by salient symptoms such as facial and preauricular pain, restricted jaw movement, and audible manifestations from the TMJ during jaw activities[20]. The estimated global prevalence of TMD ranges is approximately 34%[21], and the global prevalence of snoring is up to 30% in the adult population[22], indicating that it is a significant health concern. Moreover, TMD is frequently correlated with a spectrum of adverse health outcomes, including but not limited to compromised general health, depression, sleep disturbances, and other psychological disorders, thereby substantially influencing patients' quality of life[23-26]. The financial burden associated with the diagnosis and management of orofacial pain and TMD is considerable, with

conservative estimates suggesting a societal cost nearing $100 billion in the United States alone[27]. Such studies have indicated a positive correlation between snoring and TMD[28]. However, the multitude of factors influencing the outcomes of observational studies, including unknown or unmeasured variables, complicates the analysis[29]. Additionally, sleep disorders and TMDs may form a mutually interacting cycle[30], making it challenging for researchers to establish causality or determine the precise direction of impact[31]. The relationship between pain and sleep appears to be bidirectional and complex: pain may disrupt sleep, and sleep disorders may lower pain thresholds and exacerbate spontaneous pain[32]. There is compelling evidence indicating that sleep disorders may induce hyperalgesia and contribute to the onset or exacerbation of spontaneous pain symptoms[33]. According to current understanding, inadequate sleep quality seems to inhibit several systems and mediators known for their analgesic effects, such as the orexinergic[34], melatonin[35], and dopamine signaling systems[36]. Conversely, it activates systems and mediators with hyperalgesic properties, including nitric oxide [37] and adenosine signaling[38], as well as inflammatory mediators of the immune system[39].

Therefore, the need to find more comprehensive evidence to clarify the causal relationship between sleep disorders, such as snoring, and TMD could help to elucidate the biological mechanisms of this disease and inform the development of treatment strategies for TMD. Large randomized controlled trials (RCTs) are considered the gold standard for studying causal relationships due to their high comparability and minimal bias[40]. However, they are costly and pose potential medical ethical limitations[40, 41]. Complementing traditional epidemiological methods, Mendelian randomization (MR) offers a valuable approach for assessing causality. By using single nucleotide polymorphisms as genetic instrumental variables, MR can address some of the limitations inherent in observational studies[42]. This technique can also inform and improve the design of RCTs[43].

The objective of this study was to employ a MR analytical framework to investigate the impact of snoring on TMD. This approach aims to provide complementary information to that obtained from RCTs, contributing to a more comprehensive understanding of the relationship between snoring and TMD.

2. Materials and Methods

2.1. Genetically predicted snoring

Single nucleotide polymorphisms (SNPs) that were strongly associated with snoring ($p<5\times10^{-8}$) and independently associated with snoring ($r^2<0.001$) were used as instrumental genetic variables. First, we obtained pooled data on genetic variants associated with snoring from published genome-wide association studies. The GWAS for snoring was derived from the UK Biobank data of 408,317 individuals of white British ancestry, with 152,302 (63833 female and 88469 man) snorers [44] and we collected the dataset on 14 February 2020. The GWAS sample comprised individuals of European ancestry registered in the UK Biobank. This biobank recruited participants from 2006 to 2010, aiming to evaluate lifestyle, anthropometric measurements, and health-related variables. Sleep-related traits were reported by participants themselves, with snoring evaluated through a singular item (Field-ID: 1210)[44].The snoring GWAS summary statistics from UKB were obtained from the NHGRI-EBI Catalog[45].

2.2. Genetic associations with temporomandibular joint disorders

To reduce bias from sample duplication and sample population genetic variation induced by population stratification, we selected data from different population samples of the same European ancestry based on previous studies[29, 46-49]. Genetic variants are fixed at conception and therefore not susceptible to conventional confounding factors such as age, sex or environmental risk

exposures[50].

The FinnGen study, initiated in August 2017, represents a comprehensive 10-year project structured into two distinct phases: FinnGen 1, covering the first to third years, and FinnGen 2, spanning the fourth to sixth years[51]. This period is dedicated to the collection and genotyping of biobank samples. The data release from FinnGen in February 2023 was selected for its contribution to achieving ethnic homogeneity within the study population, as well as to minimize the overlap of samples. Specifically, the dataset pertaining to TMD encompasses 13,282 cases, of which 10,769 are female and 2,513 are male, against a control group comprising 363,995 individuals. This dataset was acquired from the FinnGen project on October 25, 2023, which is focused on the European population, ensuring a targeted approach to understanding the genetic underpinnings of TMD within this demographic (https://results.finngen.fi/en). The dataset was based on the revised International Classification of Disease (ICD-10: K07.6) code, which is widely accepted and used in clinical and research settings globally[52].

2.3. Statistical analysis

2.3.1. Study Design and Criteria for Instrumental Variables

This MR study aimed to explore the potential causal relationship between TMD and snoring. The approach adhered to the principles ensuring that the genetic variants used as instrumental variables (IV) emulate the random assignment typical of RCT [53]. The criteria for the selection of IV included:

Relevance: The genetic variants used as instrumental variables should be strongly associated with the exposure of interest. This is often quantified by the p-value of the association, with more stringent thresholds (e.g., $p < 5x10^{-8}$) being used to denote genome-wide significance. A strong association ensures that the IV can explain a significant portion of the variation in the exposure, which is crucial for the MR analysis to have enough power to detect a potential causal effect[54].

Exclusion Restriction Criterion: IV must influence the outcome solely through the exposure, with no alternate pathways. This criterion helps in eliminating potential biases due to pleiotropy, where a gene might affect multiple traits[55].

Statistical Analysis Techniques

Assessing Instrument Strength: Instrument strength was quantified using the F-statistic, with a value above 10 considered sufficient to avoid weak instrument bias.

Pleiotropy Assessment: Techniques like MR-Egger regression, the weighted median estimator, and MR-PRESSO were utilized to identify and adjust for any pleiotropic effects, ensuring the integrity of the exclusion restriction criterion[56].

2.3.2. Analytical Procedures and Tools

Extract single nucleotide polymorphism and clumping process: This is quantified by the p-value with more stringent thresholds ($p < 5x10^{-8}$) being used to denote genome-wide significance. In the reverse MR analysis, a lenient threshold ($p < 5\times10^{-6}$) was adopted to incorporate additional TMD-associated SNPs, following the precedent of other MR studies[57]. SNPs were grouped by linkage disequilibrium with a threshold of $r^2 < 0.001$ within 1000 kb windows by clumping process.

Alignment of SNPs: For palindromic SNPs (A/T or C/G coded), alignment with the effect allele for both exposure and outcome was achieved using the "harmonize_data" tool, which is based on allele frequency and coding

Exclude weak instrumental variable and potential confounders: The R^2 and F-statistics for each SNPs were calculated to evaluate instrument strength[58]. The formulas of R^2 and F statistics are provided in Supplementary Fig. 1 and Fig. 2. R^2 is the fraction of variation explained by IV in

exposure factors, and an F-statistic < 10 indicates that weak IV are excluded. Potential confounders such as pain and smoking were screened using the PhenoScanner V2 platform(http://www.phenoscanner.medschl.cam.ac.uk). The screening aimed to identify and exclude genetic variants linked to potential confounders, ensuring that the instrumental variables used in the MR analysis were robust and reliable.

MR Analysis: SNP-specific Wald estimates were analyzed through meta-analysis using the IVW method with multiplicative random effects.

Sensitivity Analysis: Different assumptions were tested using methods like the weighted median, MR-Egger, and MR-PRESSO to derive MR estimates. MR-PRESSO additionally helped in identifying and correcting for outliers due to horizontal pleiotropy.

Statistical Power Calculation: The potential bias due to environmental confounders was evaluated, especially when exposure and outcome data overlapped, using a specialized web tool. Environmental confounding factors can skew the potential causal effect estimate toward an observational relationship when the exposure and outcome come from overlapping samples. An environmental confounding factor is a variable associated with both the exposure and the outcome of a study. It acts as a common cause for both the exposure and the outcome, creating a spurious association between them. When the exposure and outcome are measured from overlapping samples, this environmental confounder can bias the estimated potential causal effect, leading to an observational correlation that may not accurately reflect the true causal relationship. These factors, such as OSA, pain, smoking, or psychosocial conditions, were considered potential environmental confounding factors in this study. Therefore, the spurious association necessitates evaluating the potential bias due to sample overlap through the analysis of bias and Type 1 Error Rate in MR with Sample Overlap using a web-based tool (https://sb452.shinyapps.io/overlap/)[59]. The sample size was predetermined by the public GWAS databases utilized, and we estimated the statistical power of our analysis through the mRnd tool (https://shiny.cnsgenomics.com/mRnd/)[60].

2.3.3. Software and Data

Software Used: For all the statistical analyses within this MR investigation, we utilized the "TwoSampleMR"[61], "MendelianRandomization"[62], and "MRPRESSO" [63]packages in R software, version 4.3.0. provided by the R Foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/).

Data Source: The study utilized publicly available summary data from GWAS databases[44, 51], thus exempting it from specific ethical approvals.

A detailed flowchart (Fig. 1) outlined the complete methodology, enhancing the clarity and reproducibility of the study design.

3. Results

3.1. Genetic instrumental variables

First, a total of 38 SNPs predicting snoring at genome-wide significance ($p < 5 \times 10^{-8}$) were obtained in the published GWAS, but 35 SNPs were used to assess the association with TMD after merging with the outcome dataset. Then, 7 SNPs that were palindromic with intermediate allele frequencies were removed via the "harmonize_data" tool. Next, we excluded 5 SNPs with a single F-statistic < 10 or linked to phenotypes related to potential confounding factors. The PhenoScanner database was queried to examine phenotypes associated with each genetic variant. Variants linked to phenotypes related to potential confounding factors, such as OSA, pain, smoking, or psychosocial conditions, were excluded based on PhenoScanner[64]. Finally, 23 SNPs (F ranging from 15.730 to 1070.37) were selected for subsequent MR analysis. The information gathered for the SNPs for snoring used in the current study is summarized in Supporting Information Table S1, mainly

including effect alleles, other alleles and summary statistics.

Fig. 2 summarizes the results in the flow chart.

3.2. Mendelian randomization results

The relationships between snoring and TMD were investigated independently using IVW, MR–Egger, Weighted median, weighted mode, and simple mode approaches. Table 1 and Fig. 3 show that statistical significance was observed in the IVW analysis [odds ratio (OR) = 0.156, 95% confidence interval (CI) = 0.028 to 0.843, p = 0.0309]. A forest plot showing the effects of snoring on TMD is shown in Fig. 4. No significant effects were detected in the MR–Egger (OR = 0.210, 95% CI = 0.038 to 1.649, p = 0.7266), WM (OR = 0.091, 95% CI = 0.0074 to 1.129, p = 0.0506), weighted mode (OR = 0.017, 95% CI = 0.065 to 4.696, p = 0.1703) or simple mode (OR = 0.028, 95% CI = 0.0138 to 6.000, p = 0.2063) analyses. What's more, a high statistical power (90%) was identified in our study analyzed in mRnd (https://shiny.cnsgenomics.com/mRnd/)[60].

3.3. Sensitivity analysis

The current two-sample MR analysis produced strong results when using the leave-one-out method (as shown in Fig. 5), demonstrating that no instrumental variables altered the potential causal inference. Our Cochrane Q test revealed no significant heterogeneity among the included SNP estimations (p = 0.694). The funnel plot analysis showed a symmetry result (as shown in Fig. 6) that was not significant for horizontal or directional multipolarity. MR–Egger regression analysis (p = 0.873) and the MR-PRESSO global test (p = 0.45) also failed to detect genetic pleiotropy, proving that the polymorphisms had no impact on our results. Regarding population overlap, we not only selected exposure and outcome datasets from different data sources but also analyzed bias and the Type 1 Error Rate for MR with Sample Overlap. With sample overlap (377277/408317), the bias and Type 1 error rate were < 0.001 and 0.05, respectively, indicating that our results were less likely to be influenced by sample overlap bias. The use of data related to different European populations in a genetic study is remarkable. In genetic studies, especially two-sample MR analyses, the use of GWAS data from different populations reduces the overlap of samples, which in turn can be effective in reducing the impact of environmental confounders on the results[65].

3.4. Reverse mendelian randomization analysis

The reverse relationship between snoring and TMD was investigated independently using the IVW, MR–Egger, weighted median weighted mode, and simple mode approaches. Overall, Table 2 shows that no statistical significance was detected in the IVW analysis [OR = 0.996, 95% CI = 0.990 to 1.002, p = 0.1926]. In addition, the MR–Egger test, weighted median test, weighted mode method and simple mode method showed consistent results. The heterogeneity test indicated that there was no heterogeneity among specific SNPs. Leave-one-way analysis demonstrated that no single SNP was responsible for the potential causal estimation of periodontitis. Diagrams for the scatter plots of SNP effects, leave-one-way analysis, forests, and funnels are displayed in Supplementary Fig. 3-6.

4. Discussion

4.1. Principal findings

We employed the largest GWAS summary-level dataset available to date from various sources in this study to perform a two-sample MR analysis to fully investigate the causative effect of snoring on TMD. This is the first study to use various complementary MR methods to evaluate the bidirectional causal link between snoring and TMD. Snoring was linked to TMD according to a two-sample MR

analysis, and snoring reduced the risk of TMD. Furthermore, no evidence of snoring or TMD supporting genetic prediction was found in the reverse MR analysis. Noticeably, the results of other approaches, including MR–Egger, weighted median, weighted mode and simple mode analysis, did not demonstrate a potential causal relationship between snoring and TMD. In the primary MR analyses, the IVW method was utilized. This method is effective and consistent when all IV are valid, efficiently combining IV-specific ratio estimates through inverse-variance weighting[66-68]. Additionally, the weighted median, weighted mode, MR-Egger regression, and simple mode methods were employed to estimate causal effects. The weighted median method provides credible results when over 50% of the weights derive from invalid IVs, reducing type I errors and offering a more accurate evaluation of causal associations in the presence of horizontal pleiotropy[69]. Conversely, the weighted mode method yields credible overall causal estimates when the majority of individual estimates stem from valid IV[66]. The MR-Egger regression method delivers a relatively stable estimate independent of IV validity and adjusts for horizontal pleiotropy through the regression slope and intercept[70, 71]. However, compared to the IVW method, these alternative methods have lower power, as evidenced by broader CI[72]. Thus, they are considered complementary methods in this study. Given that there was no heterogeneity or pleiotropy in this study, the IVW results were preferred. In addition, IVW is the most widely used method and usually yields dominant results[73-75].

4.2. Comparison with other studies

The relationship between sleep disorders like snoring and OSA and TMD has been a subject of extensive research, though conclusions remain varied. Some studies highlight the potential exacerbation of TMD due to poor sleep quality and sleep deprivation resulting from sleep fragmentation in individuals with snoring or OSA. This connection suggests that frequent arousals during sleep could contribute to the development of TMD, as supported by references in existing literature[24, 76, 77].

Despite this potential link, systematic exploration of sleep quality in TMD patients using tools like polysomnography and standardized diagnostic interviews is limited. These methods are crucial for a comprehensive understanding of the spectrum of sleep disorders in TMD patients and their associations with pain sensitivity. However, data on these associations are still scarce[78-81], indicating a need for more focused research in this area.

Numerous studies suggest a close relationship between deteriorated sleep quality, impaired sleep structure, and the maintenance and exacerbation of TMD symptoms[23, 78, 82, 83]. However, a limited number of studies have found no significant associations between sleep quality and TMD. For example, Dias et al. reported no significant relationship between the two [84]. However, the OPPERA cohort and case-control studies have documented a notable correlation between OSA prevalence and the onset of TMD symptoms, with higher OSA likelihood correlating with an increased frequency of TMD onset[85] and chronic TMD conditions[86]. Further complicating the landscape, some investigations have found no significant differences in the prevalence of OSA between TMD patients and matched controls. For instance, in one study utilizing the Douglass Disorders Questionnaire, similar rates of OSA were observed in both groups [87]. Similarly, a large case-control study using a web-based registry did not find significant differences in OSA prevalence between TMD patients and controls [88].

Nevertheless, some analysts suggest that a high risk of TMD pain might serve as a protective factor against OSA. This was evidenced in studies using multinomial logistic regression models and network analysis[89], indicating that the relationship between sleep disorders and TMD can vary based on the underlying causes and manifestations. Moreover, disorders such as sleep bruxism—often characterized by nocturnal teeth grinding—are less consistently associated with, or even

negatively correlated with, TMD pain[90, 91]. This suggests that the physiological processes behind bruxism, potentially as arousal-related phenomena, might differ significantly from those leading to TMD[92, 93]. These non-positive or inverse relationships are consistent with our MR findings, which indicate that genetically predicted increased risk of snoring is associated with lower odds of TMD.

This highlights the value of MR for clarifying direction of potentially complex condition relationships. These disparate findings underscore the complexity of the relationship between sleep disorders and TMD. It is evident that while some sleep disturbances may predispose individuals to TMD, others might not significantly affect or may even protect against TMD. More comprehensive and methodologically rigorous studies are required to untangle these relationships and to better understand the physiological underpinnings that connect sleep disorders with TMD.

4.3. Possible mechanisms

Snoring, one of the most common manifestations of obstructive sleep apnea[94], has the potential to cause intermittent hypoxia in the body, a process that can be considered similar to repeated ischemia–reperfusion events[95]. Ischemia–reperfusion is an oxidative stress event that can generate endogenous oxygen free radicals. High levels of reactive oxygen species (ROS) promote inflammation and injury; however, numerous studies have demonstrated that low and moderate levels of ROS play important roles in inhibiting disease progression and in the repair and regeneration of organ tissues [96, 97]. A recent study reported that dopamine is significantly elevated in the plasma of TMD patients, suggesting that peripheral dopamine may be involved in the modulation of peripheral pain[98]. Experimental animal studies demonstrated the existence of D1 receptors in the periphery and showed that dopamine injections elicited a nociceptive response[99, 100]. Since dopamine, an antioxidant, can react with ROS[101], the ROS produced by snoring may reduce the amount of dopamine in the peripheral plasma, thus preventing TMD.

In addition, studies have demonstrated that several transient and intermittent ischemia–reperfusion processes can exert protective effects by activating various reactive oxygen and nitrogen species-dependent signaling pathways, such as ischemic preconditioning [102, 103]. Considering the similarities between the pathophysiological processes of intermittent hypoxia and ischemia–reperfusion, researchers have conducted numerous animal studies to demonstrate that intermittent hypoxia has a protective effect on the heart, brain and other organs[104-107]. Therefore, it is possible that snoring may prevent the development of TMD through a protective mechanism caused by intermittent hypoxia.

Interestingly, studies have shown that vibration stimulation can have a therapeutic effect on musculoskeletal pain [108]. Roy EA et al. conducted a clinical trial to demonstrate for the first time that vibratory analgesia can be used for chronic pain in TMD patients and hypothesized that the mechanism involves stimulation of high-frequency-sensitive Pacinian channels or interference with nociceptive signals within the central nervous system[109]. Snoring vibrates in the frequency range of 100 Hz to 2000 Hz[110, 111], which causes the tissues around the TMJ to vibrate, thus possibly relieving TMD through the potential mechanism described above.

4.4. Strengths and limitations

Our study has several significant strengths. First, the substantial sample size inherent in our two-sample MR design, coupled with the use of genetically predicted phenotypes as exposures, markedly diminishes the risks of reverse causation and confounding bias typically associated with observational studies. Additionally, by deliberately focusing on the European population, we effectively mitigate confounding from demographic heterogeneity. Furthermore, we have taken measures to minimize the risk of sample overlap by meticulously selecting GWAS data from distinct

European national databases, further bolstering the integrity and reliability of our findings.

Our study, however, has certain limitations. First, misclassification was unavoidable in the current investigation because snoring was included via self-reports. However, it was shown by the genetic correlation analyses from the GWAS that the genetic architecture of these categories is similar. After all, GWASs of complex features with relatively high sample numbers make it difficult to identify snoring cases using objective measurements. Second, the use of snoring and OSA as poles at either end of the disease course has resulted in unclear clinical definitions and classifications[112]. To diagnose simple snoring, polysomnography or respiratory polygraphy should be conducted according to the American Academy of Sleep Medicine. However, our primary aim was to investigate the sleep phenotype associated with snoring within a large population. As such, we focused on self-reported snoring, as it is a commonly used approach in large-scale epidemiological studies due to its practicality and cost-effectiveness[113-115]. In addition, only 1.47% of people had OSA in the GWAS data, and variants linked to phenotypes related to potential confounding factors, such as OSA, were excluded based on PhenoScanner. Third, it is important to note that the use of questionnaires to capture epidemiological information regarding snoring has limitations and requires improvement. Fourth, the scope of our research is restricted to people in Europe. Therefore, further research is required to ascertain whether our work can be applied to other populations. In addition, each method in our MR analysis has both benefits and drawbacks. However, because we used four separate methodologies, each of which was based on a different set of assumptions, the study's conclusions may have been tainted by inconsistent outcomes. What’s more, population stratification can skew results in MR studies[116, 117]. Using within-family MR[118], which analyzes data from family members like sibling pairs or parent-child trios, helps control these biases by accounting for genetic variations within families[117]. However, this approach is limited by the scarcity of family-based GWAS data[50]. Expanding family-based GWAS could improve MR's accuracy by integrating family structures, thus enhancing causal inferences[119]. Collecting more family-level data is vital to develop this method further and address stratification issues in conventional MR. Meanwhile, this study focused on general TMD. It is important to note that the protective effects of snoring observed may not apply uniformly across all TMD subtypes. Future studies need to incorporate more detailed classified and longitudinal data to provide deeper insights into these relationships as the GWAS database develops. Finally, the bidirectional relationship between sleep and pain, influenced by circadian rhythms and the light/dark cycle, plays a significant role in genetic and epigenetic phenotypes. These factors vary between the two countries of database collection, suggesting that using databases from different European countries for TMD and snoring diagnoses may not be the most appropriate methodology. Therefore, future databases should be selected from datasets within the same region to ensure consistency and accuracy.

5. Conclusion

The study utilized MR to explore the relationship between snoring and TMD, finding that a genetic predisposition to snoring may reduce the risk of TMD. No link was found in the opposite direction. It hypothesized that snoring could have a protective effect on TMD through several possible mechanisms like intermittent hypoxia and vibratory disruption of pain signals, offering a new perspective on their association.

Figure legends

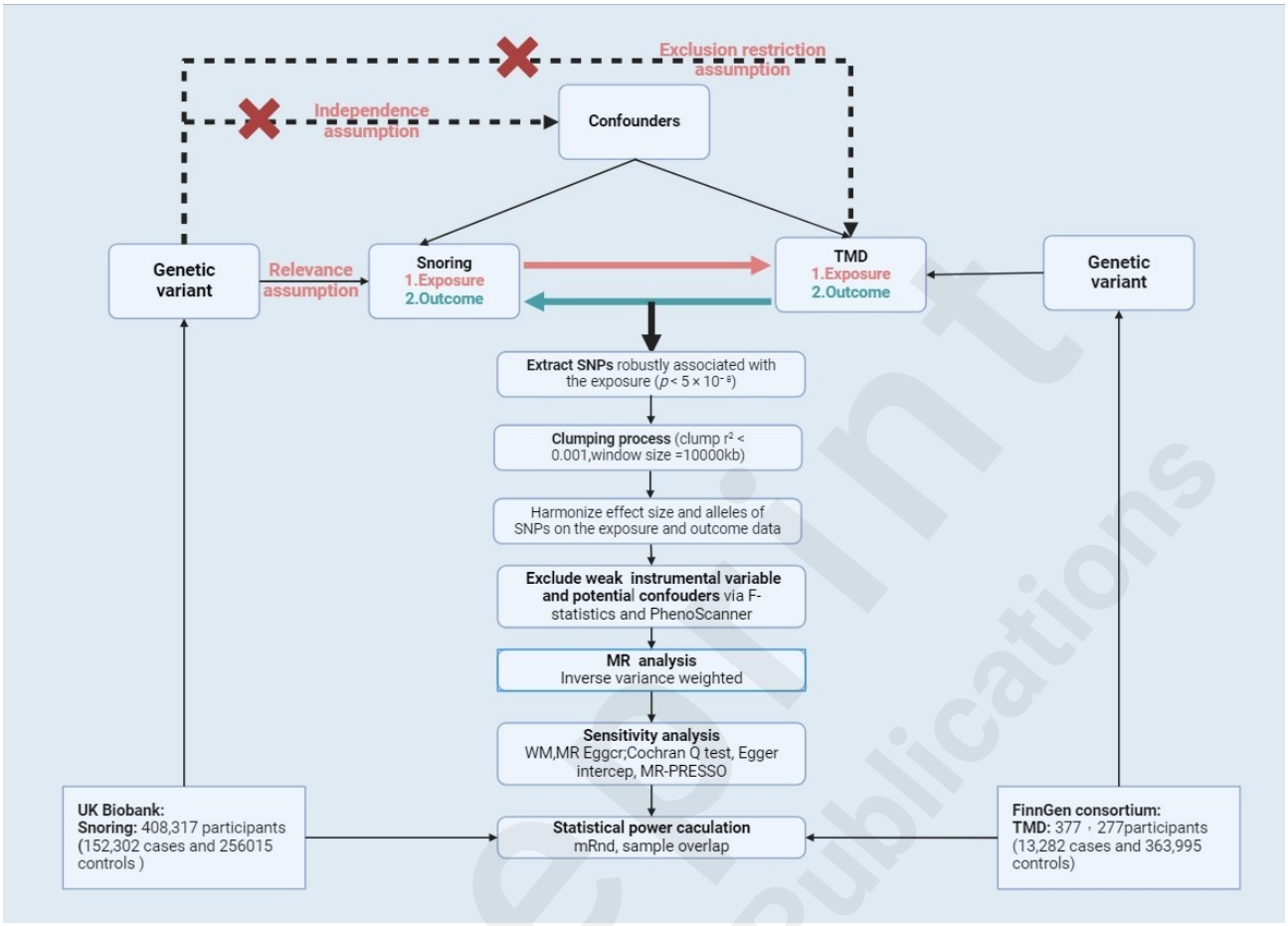

Fig. 1: Flowchart of the MR study design.

Genetic summary statistics were obtained from the UK Biobank and The FinnGen study. After selecting qualified genetic instruments, a two-sample MR was performed to estimate the causal effect between snoring and TMD, mainly including MR inverse-variance weighted. Cochran's Q test and MR-Egger regression were used to assess the outliers, heterogeneity, and pleiotropy. Lastly, statistical power was calculated. TMD: temporomandibular joint disorders; SNPs, single-nucleotide polymorphisms; MR analysis, Mendelian randomization analysis.

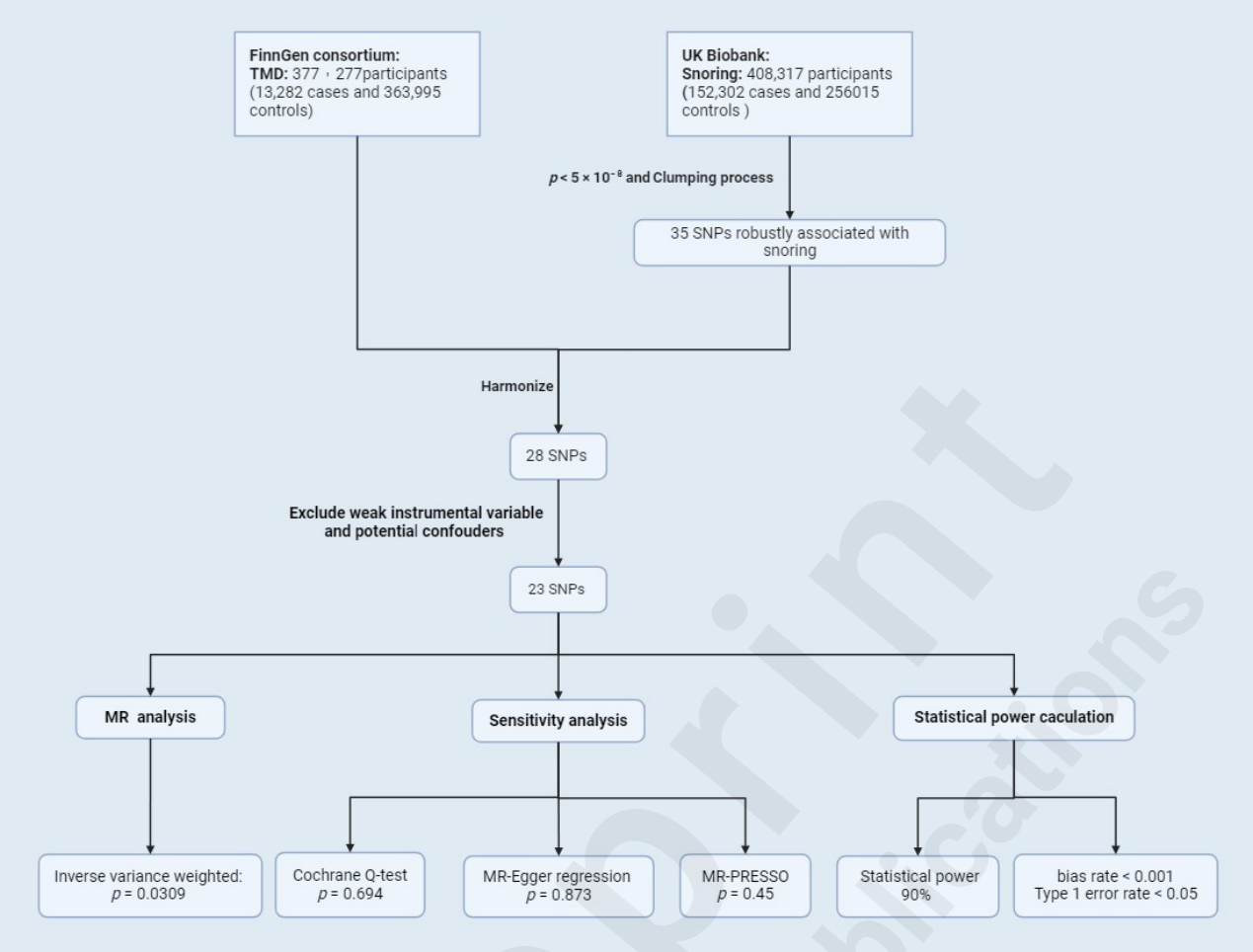

Fig. 2: Flow chart of the MR study results.

This flowchart presents the MR analysis pathway, starting with data from the FinnGen consortium and the UK Biobank. The process and results involve harmonizing data, selecting single nucleotide polymorphisms (SNPs) through a clumping process, and excluding weak instrumental variables. It further details the MR analysis using inverse variance weighting, sensitivity analysis with Cochrane Q-test and MR-Egger regression, and concludes with a statistical power calculation to assess potential biases and error rates.

SNPs, single-nucleotide polymorphisms; MR analysis, Mendelian randomization analysis.

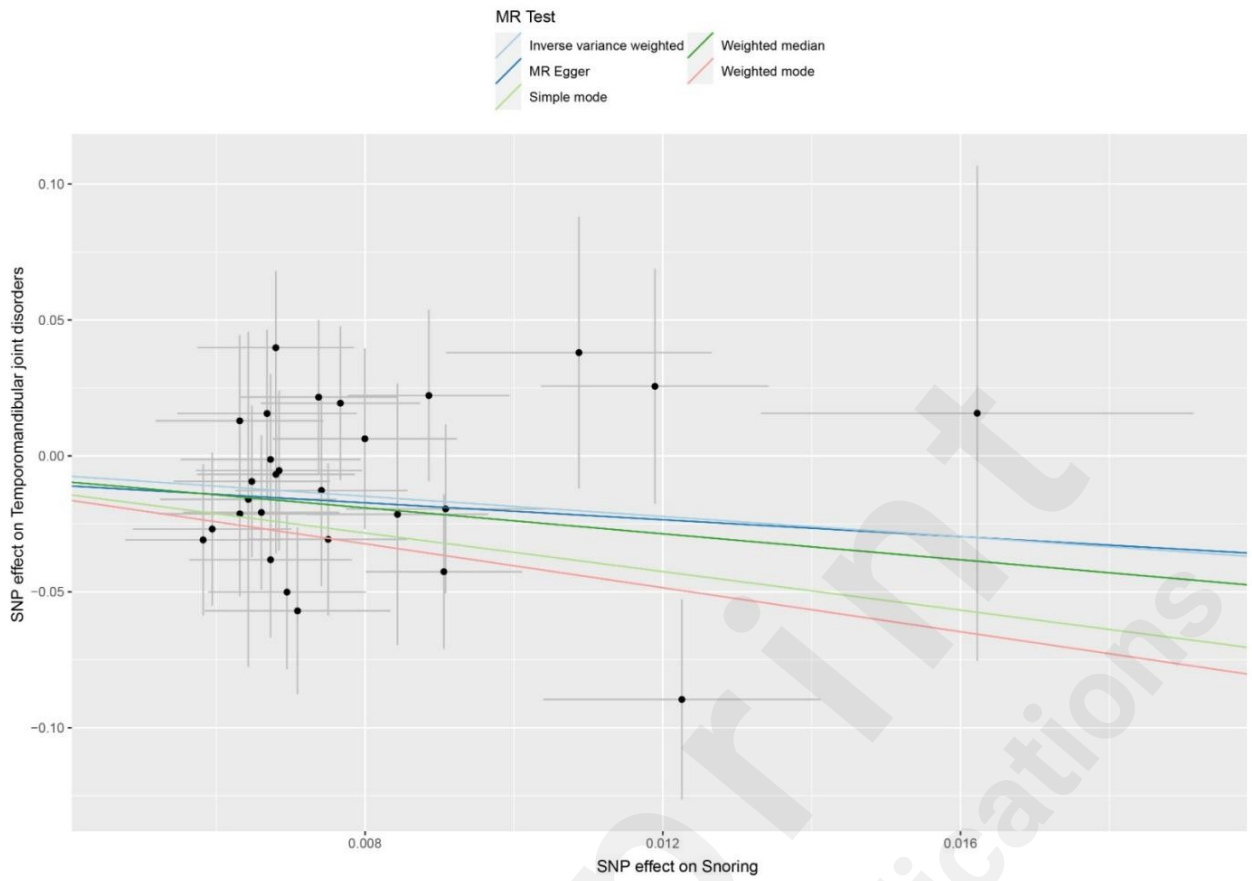

Fig. 3: Scatter plot visualizing the potential causal effect between snoring and TMD.

This scatter plot illustrates the potential causal relationship between snoring and TMD as analyzed through MR. The x-axis represents the effect sizes of individual SNPs on snoring, while the y-axis quantifies their effects on TMD. The plotted data points reflect the influence of each SNP, with the lines of best fit indicating the results from different MR methods, such as inverse variance weighted (IVW), MR-Egger, weighted median, and simple mode. The intersection of these lines with the axes suggests the magnitude of the potential causal effect. SNP, single-nucleotide polymorphism; MR analysis, Mendelian randomization analysis.

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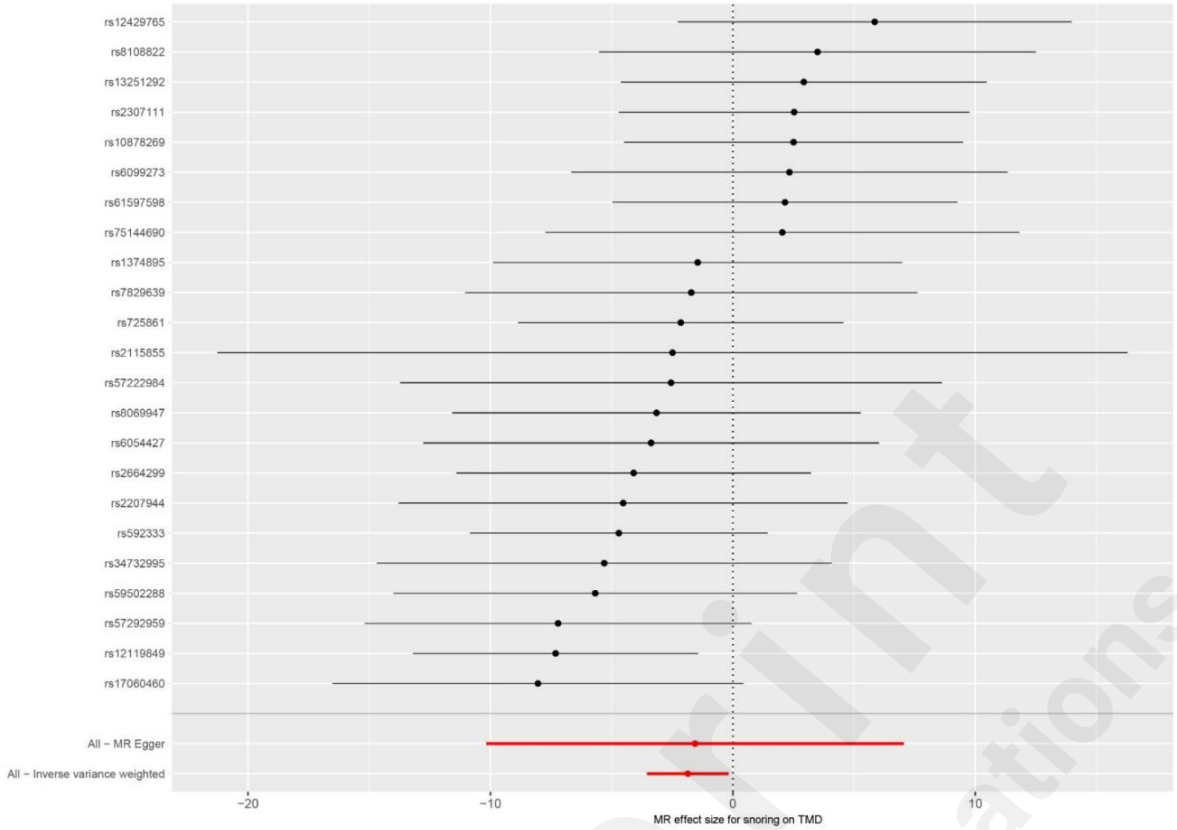

Fig. 4: Forest plots of effects of snoring-associated SNPs on TMD.

The forest plot visualizes the effects of various snoring-associated SNPs (Single Nucleotide Polymorphisms) on Temporomandibular Disorder (TMD). Each line represents a different SNP, with the square marker indicating the mean effect size and the horizontal lines denoting the confidence intervals. The dashed vertical lines serve as reference points for the MR Effect Size. This figure provides a comprehensive overview of the genetic influence on the relationship between snoring and TMD as analyzed through MR. The inverse variance weighted methods showed that there was a significant correlation between the total effect of SNPs of snoring and TMD. The MR-Egger analysis did not show horizontal pleiotropy.

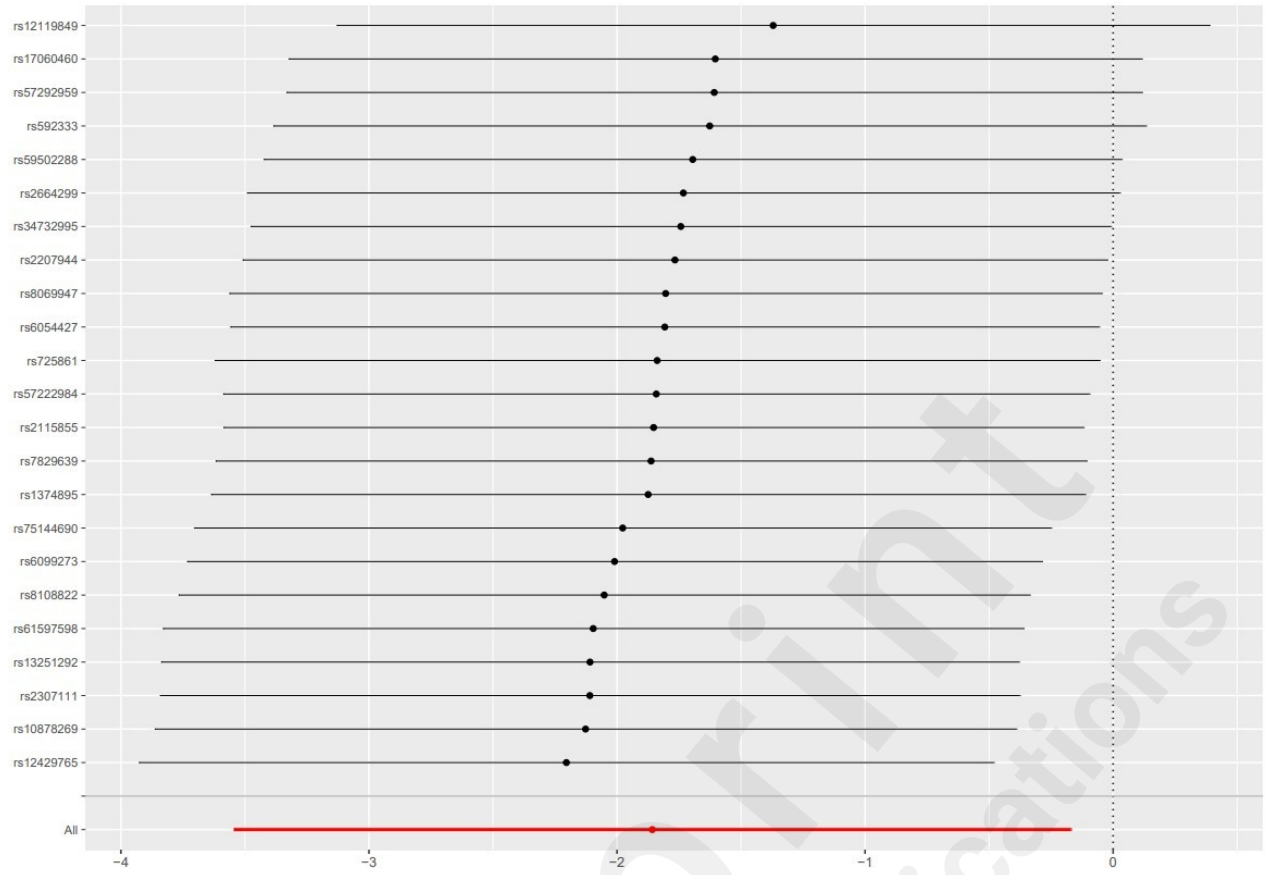

Fig. 5: Forest plot of the "leave-one-out" sensitivity analysis.

This forest plot represents the “leave-one-out” sensitivity analysis in a MR study. Each horizontal line corresponds to an individual data point, with the central round dot denoting the effect estimate and the line’s extent reflecting the confidence interval. The vertical dashed line indicates the null effect, and the red dot and line at the bottom aggregates the overall effect size, excluding one study at a time to assess the robustness of the results. This analysis ensures that no single data point disproportionately influences the study’s conclusions.

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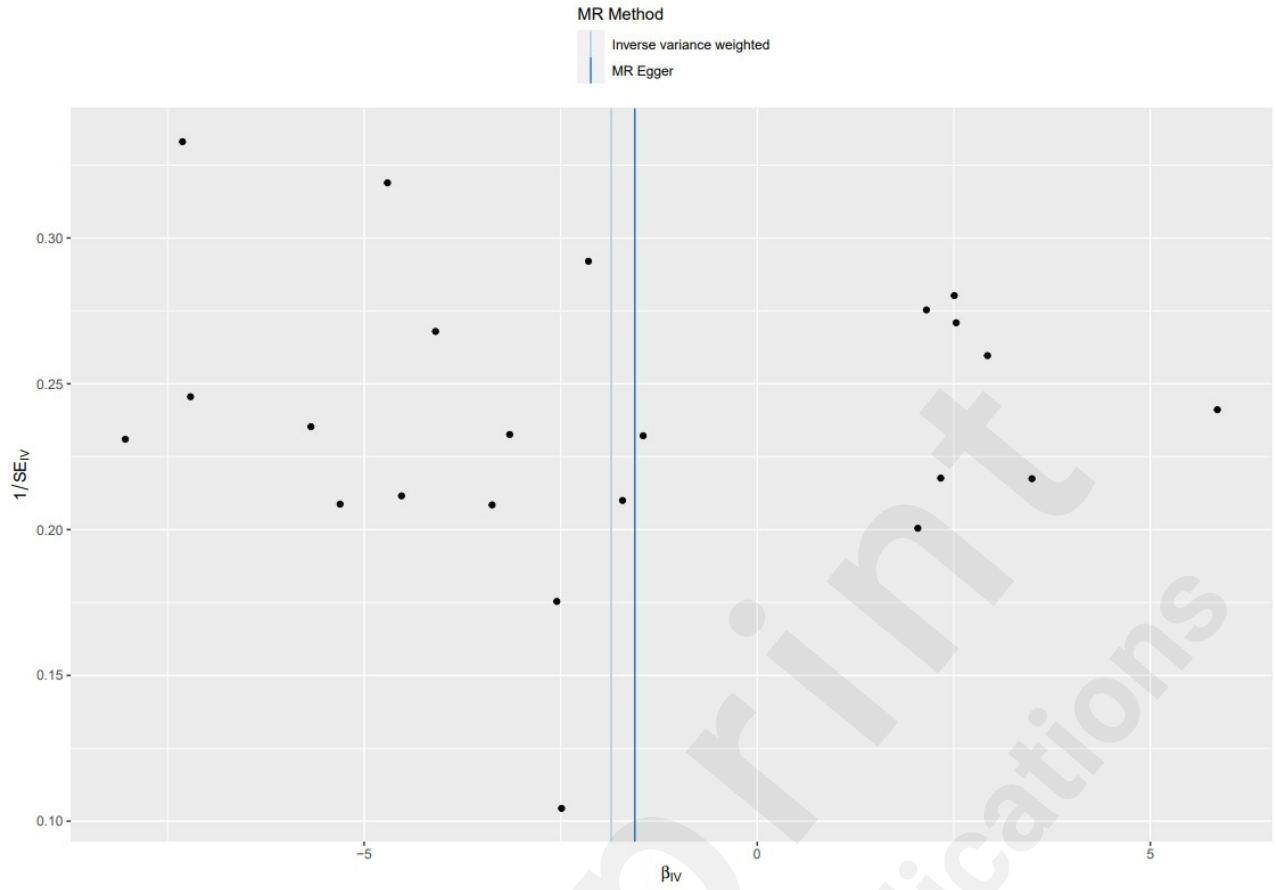


Fig. 6: Funnel plot of MR assessment.

This funnel plot graphically represents the heterogeneity across studies in a MR assessment. The x-axis, labeled “Beta,” indicates the estimated effect size, while the y-axis, labeled “1/SE,” denotes the inverse of the standard error of the estimate. Points on the left side represent “Inverse variance weighted” estimates, and those on the right side correspond to “MR Egger” estimates.

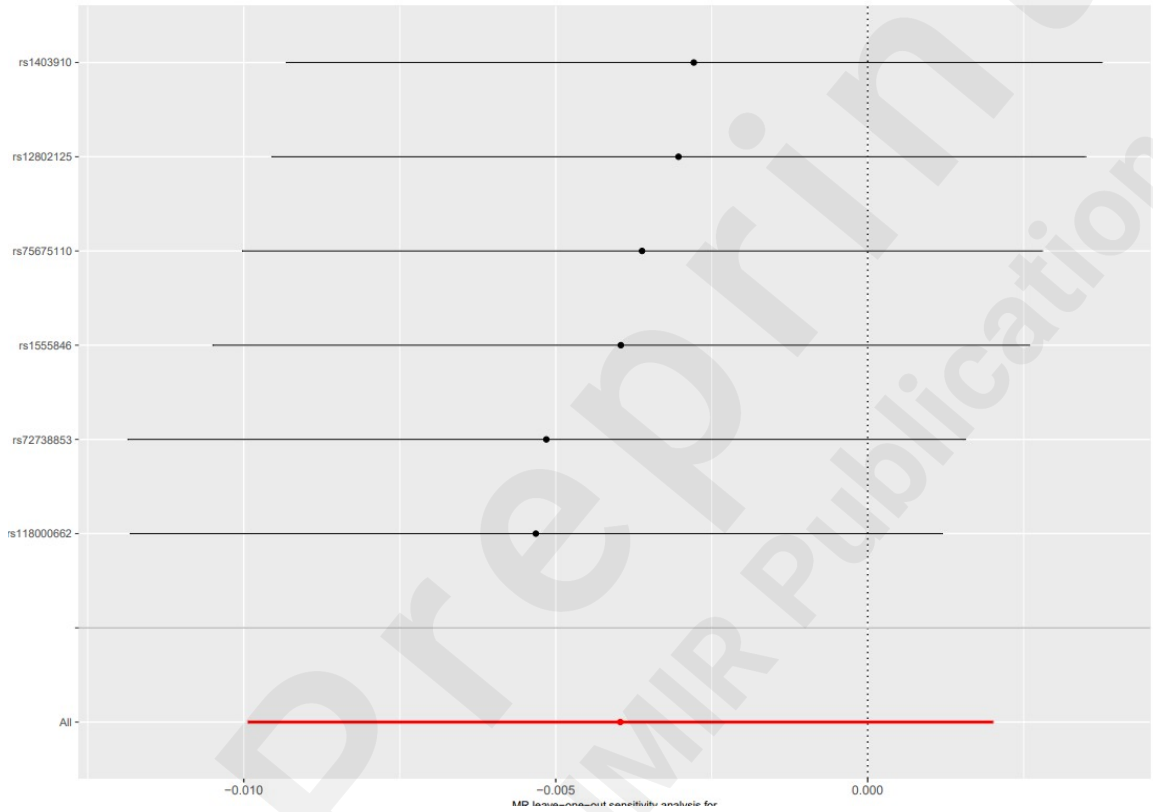
Supplementary Figures

$$R^2 = 2 \times MAF \times \left(1 - MAF \right) \times \beta^2$$

Supplementary Fig. 1 Formulas of R^2.
MAF, Minor Allele frequencies; β, effect size on the exposure.

$$F = \left(\frac{R^2}{1 - R^2} \right) \times \left(\frac{n - k - 1}{k} \right)$$

Supplementary Fig. 2 Formulas of F-statistics.
The R^2 refers to the portion of exposure variance explained by the instrumental variable (IV), N represents the effective sample size, and k represents the number of variants included in the IV model. An F-statistic >10 indicates a strong correlation between the IVs and exposure.



Supplementary Fig. 3 Diagrams of leave-one-way analysis.
This forest plot represents the “leave-one-out” sensitivity analysis in a MR study. Each horizontal line corresponds to an individual data point, with the central round dot denoting the effect estimate and the line’s extent reflecting the confidence interval. The vertical dashed line indicates the null effect, and the red dot and line at the bottom aggregates the overall effect size, excluding one study at a time to assess the robustness of the results. This analysis ensures that no single data point disproportionately influences the study’s conclusions.

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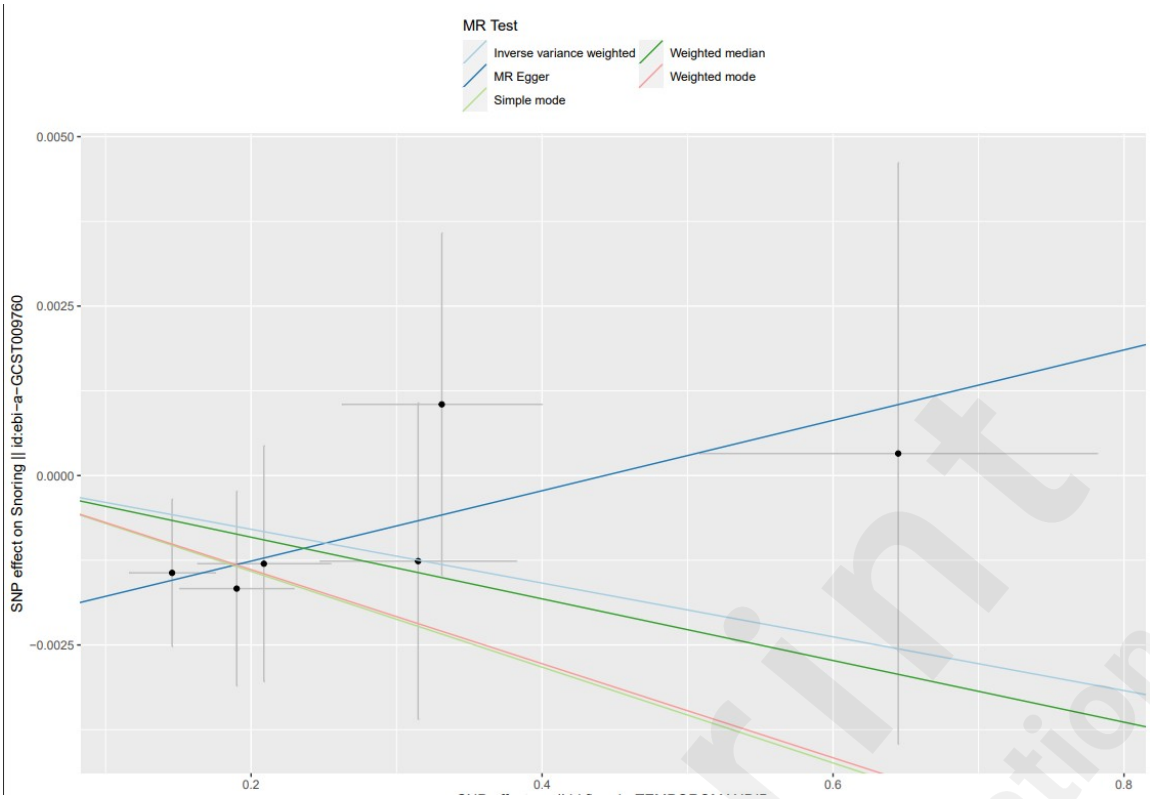

Supplementary Fig. 4 Scatter plot visualizing the potential causal effect between TMD on snoring. This scatter plot illustrates the potential causal relationship between snoring and TMD as analyzed through MR. The x-axis represents the effect sizes of individual SNPs on snoring, while the y-axis quantifies their effects on TMD. The plotted data points reflect the influence of each SNP, with the lines of best fit indicating the results from different MR methods, such as inverse variance weighted (IVW), MR-Egger, weighted median, and simple mode. The intersection of these lines with the axes suggests the magnitude of the potential causal effect. SNP, single-nucleotide polymorphism; MR analysis, Mendelian randomization analysis.

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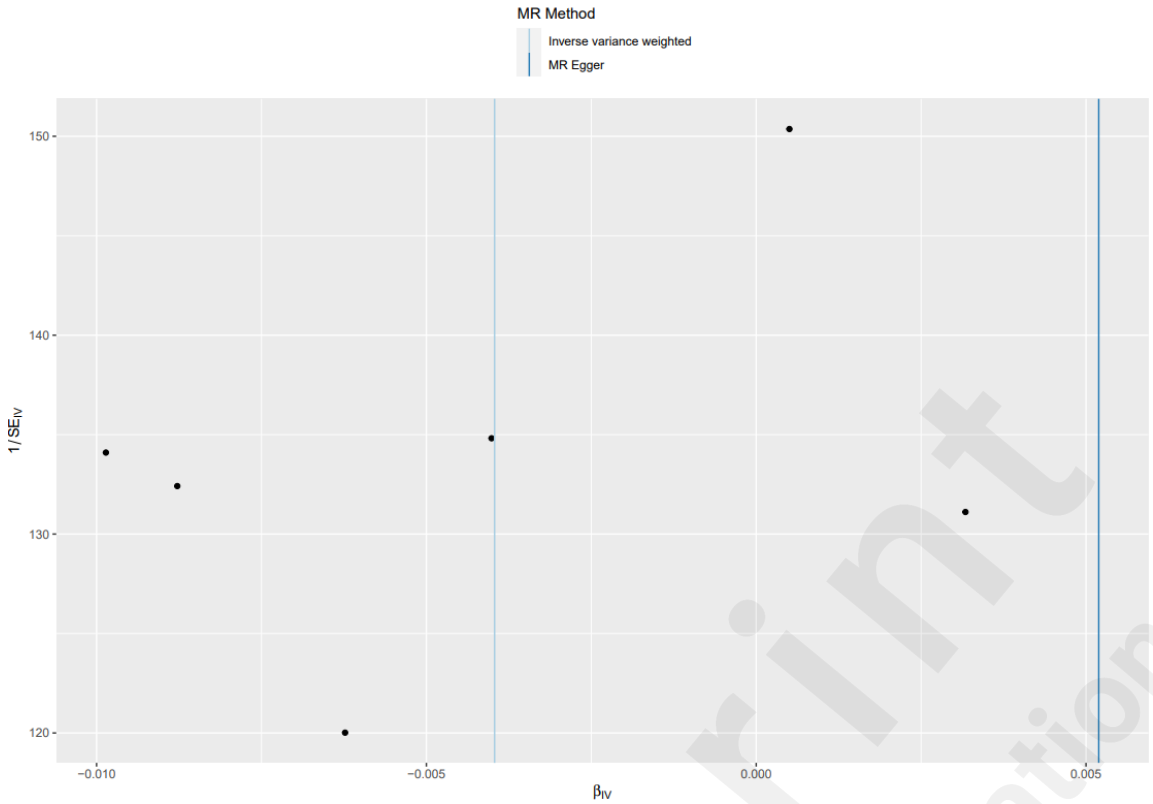

Supplementary Fig. 5 Funnel plot of MR assessment.
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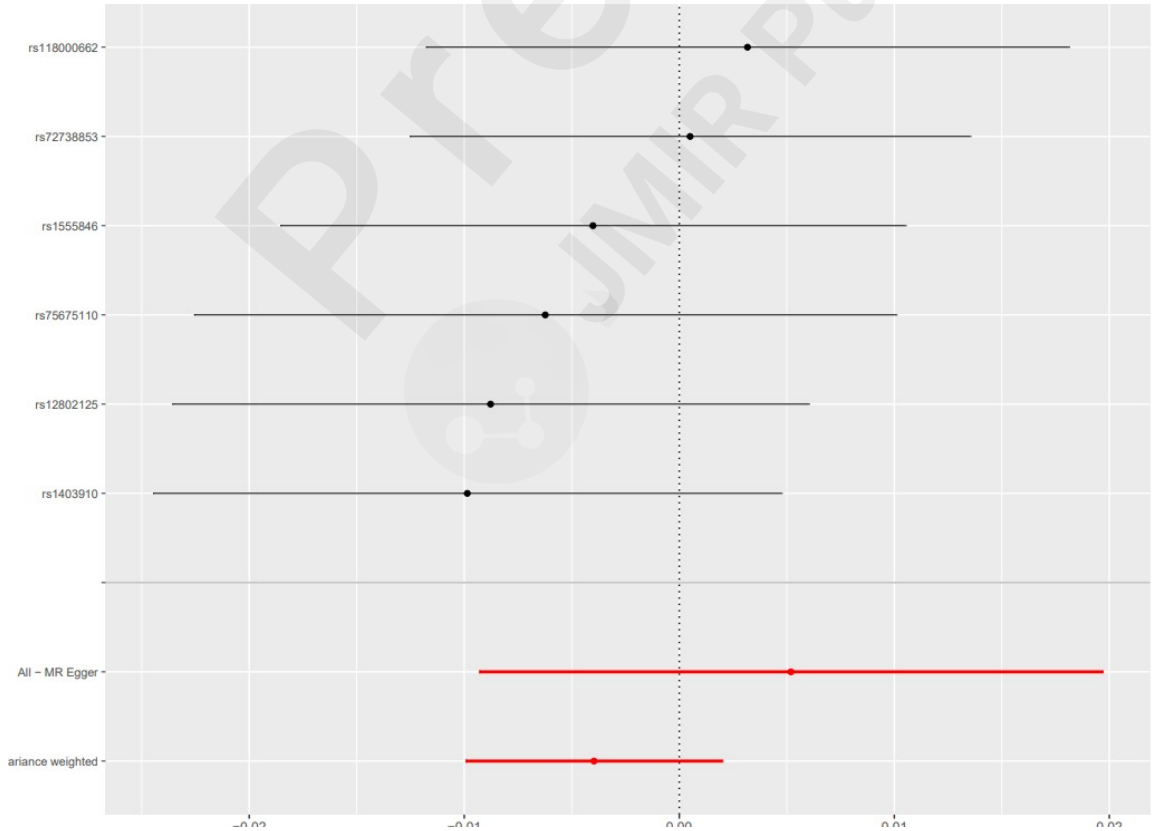

Supplementary Fig. 6 Forest plots of effects of TMD -associated SNPs on snoring.

The forest plot visualizes the effects of various snoring-associated SNPs (Single Nucleotide Polymorphisms) on Temporomandibular Disorder (TMD). Each line represents a different SNP, with the square marker indicating the mean effect size and the horizontal lines denoting the confidence intervals. The dashed vertical lines serve as reference points for the MR Effect Size. This figure provides a comprehensive overview of the genetic influence on the relationship between snoring and TMD as analyzed through MR. The inverse variance weighted methods showed that there was a significant correlation between the total effect of SNPs of snoring and TMD. The MR-Egger analysis did not show horizontal pleiotropy.

Table

Table 1 MR associations of snoring with temporomandibular joint disorders

Method	Number of SNPs	Beta	SE	OR (95%CI)	*P* value
IVW	23	-1.857	0.843	0.156 (0.028-0.843)	0.0309*
MR Egger	23	-1.557	4.278	0.210 (0.038- 1.649)	0.7266
Weighted median	23	-2.388	1.254	0.091 (0.0074-1.129)	0.0506
Simple mode	23	-3.546	2.701	0.028(0.0138-6.000)	0.2063
Weighted mode	23	-4.042	2.639	0.017 (0.065-4.696)	0.1703

This table presents the results of various MR methods used to explore the effect of snoring on TMD. The MR methods applied include IVW、MR-Egger, weighted median, simple mode, and weighted mode analyses. Method: The MR method was utilized for the analysis. Number of SNPs: The count of single nucleotide polymorphisms used as instrumental variables. Beta: The regression coefficient that represents the change in the risk of TMD associated with snoring. SE: Standard Error of the beta coefficient. OR (95%CI): Odds Ratio with a 95% Confidence Interval, indicating the likelihood of TMD associated with snoring. P-value: The statistical significance of the results, with a p-value less than 0.05 typically considered statistically significant, denoted by an asterisk (*).

Table 2 Reverse MR associations of snoring with temporomandibular joint disorders

Method	Number of SNPs	Beta	SE	OR (95%CI)	*P* value
IVW	7	-0.0039	0.003	0.996(0.990-1.002)	0.1926
MR Egger	7	0.0051	0.0074	1.01(0.991-1.020)	0.5212
Weighted median	7	-0.0045	0.0038	0.995(0.987-1.003)	0.2394
Simple mode	7	-0.0071	0.0055	0.992(0.982-1.003)	0.2602
Weighted mode	7	-0.0069	0.0055	0.993(0.982-1.003)	0.2659

This table presents the results of various Mendelian randomization (MR) methods used to explore the effect of TMD and snoring. The MR methods applied include IVW，MR-Egger, weighted median, simple mode, and weighted mode analyses. Method: The MR method was utilized for the analysis. Number of SNPs: The count of single nucleotide polymorphisms used as instrumental variables. Beta: The regression coefficient that represents the change in the risk of TMD associated with snoring. SE: Standard Error of the beta coefficient. OR (95%CI): Odds Ratio with a 95% Confidence Interval, indicating the likelihood of TMD associated with snoring. P-value: The statistical significance of the results, with a p-value less than 0.05 typically considered statistically significant, denoted by an asterisk (*).

List of Abbreviations

Abbreviations	Definition
TMD	temporomandibular joint disorders
TMJ	temporomandibular joint
MR	mendelian randomization
GWAS	large-scale genome-wide association studies
ICD-10	International Classification of Disease
SNP	Single Nucleotide Polymorphism
IVW	multiplicative random effects-inverse variance weighted
IV	instrumental variable
LD	linkage disequilibrium
CI	confidence intervals
OR	odds ratio
SE	standard error
OSA	obstructive sleep apnea
ROS	reactive oxygen species

Table S1 Summary information on the snoring genetic instruments used in the Mendelian randomization analyses.

	SNP	Effect allele	Other allele	Beta	SE	F statistic	EA.Freq	P-value
1	rs10878269	T	C	0.00885643	0.0010863	91.84931879	0.2691	2.30E-16
2	rs12119849	A	G	0.0122562	0.0018604 6	1098.116209	0.1745	4.10E-11
3	rs12429765	G	A	-0.0067995	0.0010508	371.8812583	0.4512	6.20E-11
4	rs13251292	G	A	0.00737472	0.0010671 7	108.5524011	0.4332	4.30E-12
5	rs1374895	T	C	-0.0064773	0.0010513 1	20.92794227	0.4988	4.50E-10
6	rs17060460	G	A	0.00709136	0.0012470 4	644.5251826	0.2978	1.40E-08
7	rs2115855	G	T	0.00642997	0.00118582	19.75007587	0.08943	3.60E-08
8	rs2207944	C	T	0.00594528	0.0010647 1	170.9777139	0.526	2.00E-08
9	rs2307111	C	T	-0.0076674	0.0010698 2	87.20050921	0.426	4.80E-13
10	rs2664299	C	T	-0.0075029	0.0010606 4	222.0873418	0.4628	1.10E-12
11	rs34732995	CTA	C	-0.0058233	0.0010478 6	226.2323383	0.5037	1.70E-08
12	rs57222984	G	A	0.00843452	0.0012201 4	37.85137426	0.09556	5.40E-12
13	rs57292959	T	G	0.00694978	0.0010592 7	583.0980287	0.4287	5.10E-11
1	rs592333	G	A	0.00905794	0.0010512	429.5082637	0.52	1.00E-17

4								
15	rs59502288	GTCATCCA	G	0.00672921	0.00109415	330.1558477	0.3935	9.10E-10
16	rs6054427	A	G	0.00631646	0.00108007	91.98619337	0.6898	4.00E-09
17	rs6099273	T	C	0.00668196	0.00120584	48.00050577	0.2955	2.60E-08
18	rs6159759	A	G	0.0118947	0.0015292	66.37252934	0.1217	5.10E-15
19	rs725861	G	A	0.00908198	0.00133779	72.36350646	0.2783	1.00E-11
20	rs75144690	G	T	-0.0063145	0.00112857	30.90717344	0.7323	1.80E-08
21	rs7829639	G	A	0.00741278	0.00115501	24.32970734	0.8013	1.40E-10
22	rs8069947	T	C	-0.0066059	0.00105133	101.0899417	0.4416	2.80E-10
23	rs8108822	T	C	-0.0108729	0.00178271	106.1916907	0.0848	6.20E-10

This table provides detailed information on the single nucleotide polymorphisms (SNPs) used as genetic instruments in the Mendelian randomization analyses for snoring. Each row represents a specific SNP, with the following columns: SNP: The identifier for the single nucleotide polymorphism. Effect allele: The allele associated with the effect on snoring. Other allele: The alternative allele. Beta: The estimated effect size of the effect allele on snoring.SE: The standard error of the beta estimate. F statistic: A measure of the strength of the instrument, with higher values indicating stronger instruments. EA Freq: The frequency of the effect allele in the population.
P-value: The significance level of the association between the SNP and snoring.These genetic instruments were selected based on their statistical strength and relevance to snoring, ensuring Mendelian randomization analyses.

Ethics approval and consent to participate

The current MR investigation did not require specific ethical approval because it used publicly accessible summary data.

The studies were conducted with the approval of the respective institutional ethical review boards and in accordance with the Declaration of Helsinki.

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Consent for publication

All the participants in our study provided consent for publication.

Disclosure of interest

The authors declare no conflicts of interest.

Data availability statement

The GWAS summary statistics for snoring are publicly available from a GWAS conducted by Campos A I et al. (10.1038/s41467-020-14625-1). The summary statistics of GWASs for TMD are derived from

https://r9.finngen.fi/pheno/TEMPOROMANDIB_INCLAVO.

author contributions statement

Zhiguo Bi、Long Jin、Jianguo Liu have outlined the main framework of Mendelian randomization.Jintian Chen, Zhijun Bi, Xin Song, Yazhou Yang、and Xujia Zhao collected the data and created graphs and tables by using the R language.

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