Causal Relationship Between Obstructive Sleep Apnea and Temporomandibular Disorders: A Bidirectional Mendelian Randomization Analysis

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Objective: This study was conducted to investigate the bidirectional causal relationship between obstructive sleep apnea (OSA) and temporomandibular disorders (TMD).

Methods: Using an online pooled dataset of genome-wide association studies (GWAS), a two-sample bi-directional Mendelian randomization (MR) method was implemented. Inverse variance weighting was used as the primary analyses approach, and other methods of MR Egger, weighted median method, MR-Egger, Simple mode, and Weighted mode analysis were conducted as supplements to evaluate the causal relationship between OSA and TMD with odds ratios (OR) and 95% confidence interval (CI). Furthermore, the Cochran Q, MR-Egger, and MR-PRESSO approaches were used to perform the heterogeneity test and multiple validity.

Results: The general results of the forward MR analysis indicated that OSA had a significant causal influence on TMD (OR=1.241, 95% CI: 1.009–1.526, P=0.041), but no significant correlation was observed in the reverse MR analysis (IVW: OR=0.975, 95% CI=0.918–1.036, P=0.411).

Conclusion: In summary, our research demonstrated a hereditary causative relationship between OSA and TMD, indicating that appropriate intervention is required for both prevention and treatment of TMD.

Keywords: Mendelian randomization analysis, obstructive sleep apnea, temporomandibular disorders

Introduction

Temporomandibular disorders (TMD) refers to a group of disorders affecting the temporomandibular joints (TMJ) and masticatory muscles and associated structures, which can manifest by persistent TMJ and muscular pain, TMJ sounds, restricted mouth opening, motion deviation and other abnormal mandibular function.1,2 With the rapid development of society and the increasing pressure of life, the number of patients with TMD is rising over time. According to recent studies, the prevalence of TMD is about 31% in adults and 11% in children.3 The etiology of TMD is very complex and has not yet been clarified. Sleep disorders or bruxism, anxiety, depression, genetic predisposition, developmental abnormalities, and many biopsychosocial factors have been identified as potential causative risks.4–9 In addition, women are more susceptible to TMD than men, and the risk of TMD in women is approximately twice that of men.10 TMD affects people throughout their lives, and the prevalence of TMD peaks between 45–64 years of age in the general population.11
Obstructive sleep apnea (OSA) is one of the most common sleep disorders that is characterized by repeated collapse of the upper respiratory tract, leading to partial or complete cessation of airflow, changes in chest pressure, decreased arterial oxygen saturation, usually terminated by sleep arousal, resulting in muscle activation and restoration of airway patency. According to the AASM 2012 diagnostic criteria, approximately 20% of adult males and 10% of postmenopausal women worldwide, totaling over 936 million and 425 million adults, respectively, suffer from mild to severe or moderate to severe OSA. In addition to directly causing recurrent arousal, hypercapnia, intermittent hypoxia, and elevated respiratory rate, OSA also causes secondary sympathetic nervous system activation, oxidative stress, and systemic inflammation. A large number study indicated that OSA is associated with numerous serious complications, including heart disease, stroke, cerebrovascular illnesses, and even death. These complications have a major impact on people’s quality of life and safety.

To date, the connection between OSA and TMD has been the subject of an increasing number of studies, however the underlying mechanism is still unknown. Mendelian randomization (MR) is a new approach to assess the causal effects in observational epidemiology by using genetic variants as instrumental variables (IVs). So, we conducted a bidirectional MR analysis to investigate the causal relationship between OSA and TMD with large-scale genome-wide association studies (GWAS) data. As far as we know, this is the first time the causal relationship between OSA and TMD has been investigated, which has a profound impact on further understanding the pathogenesis of OSA or TMD.

Materials
The collected data that originated from public large-scale GWAS, ethical approval and consent were obtained by the original from the participants, and no ethical approval from an ethics committee was required further. This study was approved with exemption by Taihe Hospital Review Board due to the analysis being defined as minimal risk.

Data Sources
All utilized genetic summary data were extracted from FinnGen database (https://www.finngen.fi/en). For OSA (finngen_R9_G6_SLEEPAPNO), there were 375,657 samples with 38,998 cases and 336,659 controls; for TMD (finngen_R7_TEMPOROMANDIB), there were 181,934 samples with 4273 cases and 177,661 controls. Finnish Biobank is a large-scale biomedical database that contains health information and genetic data from more than 500,000 Finns. All statistical data were gathered from the descendants of Europeans, reducing the potential bias due to racial differences.

Study Design Description
In our study, some single-nucleotide polymorphisms (SNPs) were extracted from GWAS datasets as IVs to investigate the potential causal effects between OSA and TMD. The schematic overview of our study design is displayed in Figure 1. All included IVs should meet the following criteria: (1) a high statistical power of the exposure threshold in OSA ($p < 5 \times 10^{-8}$) and TMD ($p < 5 \times 10^{-6}$), due to the insufficient number of SNPs obtained; (2) IVs are not influenced with any confounding.

Figure 1 Flowchart of the study design. The red represented the forward MR analyses, with obstructive sleep apnea as exposure and temporomandibular disorders as the outcome. The blue represented the reverse MR analyses, with temporomandibular disorders as exposure and obstructive sleep apnea as the outcome.
factors that affect exposure and outcomes; and (3) IVs only affect outcomes through exposure factors and not via alternative pathways. To eliminate the weak IVs bias for all candidate SNPs, a strong linkage disequilibrium (LD) condition (R2<0.001 and a window size=10,000 kb) and a higher power than 10 of the IV’s F-statistics were used. The formula for the F-statistic is as follows: F=R2×(N−2)/(1−R2) and R2=2×(1−EAF)×EAF×β2, R2 was use to employ as a metric to signify the strength of the instruments of exposure factors, N refers to the sample size of the exposure, β signifies the effect size of each SNP on the exposure GWAS data, and EAF refers to the effect allele frequency.

Statistical Analysis
In this study, the statistical method of inverse variance-weighted (IVW) and weighted median method were conducted as the primary approach to evaluate the causal effect. Heterogeneity test was conducted with Cochran’s Q test and the fixed-effect model was employed with P>0.05, otherwise, a random-effects model was used. MR-Egger, weighted median, simple mode, and the weighted mode were also performed for causal assessment as supplementary tests. Moreover, MR-Egger intercept and MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) global tests were used to identify any horizontal pleiotropy. Lastly, the sensitive analysis with “leave-one-out” method and funnel plots were used to examine any possible variations in the results for each SNP locus. All MR analyses were performed with the “TwoSampleMR” and “MRPRESSO” packages in R software version 4.3.2. A causal effect was presumed to exist if a P<0.05 was observed in statistics.

Results
Causal Effects of OSA on TMD
In the first step, 20 independent SNPs of the OSA were identified. Then, a polymorphism locus of rs13333522 was eliminated for being palindromic with intermediate allele frequencies. Finally, 19 SNP loci identified as IVs were included in this study; no further variants were eliminated using F-statistics analysis and other tests (Supplementary Table 1).

The causal impact of OSA on TMD was identified with MR analysis. According to funnel plot (Supplementary Figure 1), no significant heterogeneity was found (IVW: Q=16.269, I²=18, P=0.574; MR-Egger: Q=14.620, I²=17, P=0.623) (Table 1). In line with the scatter plot, the IVW method’s findings suggested that OSA may increase the risk of TMD (OR=1.241, 95% CI: 1.009–1.526, P=0.041) (Table 2, Figure 2, Supplementary Figures 2 and 3). Additionally, no horizontal pleiotropy (Egger intercept=0.030, SE=0.023, P=0.216) (Table 1) was identified and no outliers SNPs (P=0.527) were deleted. In addition, the plot of leave-one-out analysis was conducted, and no significant influence was identified with each SNPs (Supplementary Figure 4).

Causal Effects of TMD on OSA
After systematic screening, 13 independent SNPs of the TMD were identified as the IVs (Supplementary Table 2). An apparent heterogeneity was identified with Cochrane’s Q test (IVW: P_heterogeneity=0.006; MR-Egger: P_heterogeneity=0.005) (Table 1), which was confirmed with funnel plot (Supplementary Figure 5). Then, a random-effects model was adopted and no significant causal effects of TMD on OSA was detected with our MR analysis (IVW: OR=0.975, 95% CI=0.918–1.036, P=0.411; MR Egger: OR=1.011, 95% CI=0.882–1.160, P=0.878) (Table 2, Figure 2), which were also consistent.

Table 1 Heterogeneity Test and Horizontal Pleiotropy Test

<table>
<thead>
<tr>
<th>Exposure/ Outcome</th>
<th>Heterogeneity Test (IVW)</th>
<th>Heterogeneity Test (MR-Egger)</th>
<th>Horizontal Pleiotropy Test (MR-Egger)</th>
<th>MR-PRESSO Global Test</th>
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<tr>
<td></td>
<td>Q</td>
<td>df</td>
<td>P-value</td>
<td>Q</td>
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<tr>
<td>OSA on TMD</td>
<td>16.269</td>
<td>18</td>
<td>0.574</td>
<td>14.620</td>
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<td>TMD on OSA</td>
<td>27.703</td>
<td>12</td>
<td>0.006</td>
<td>26.868</td>
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</table>

Abbreviations: OSA, Obstructive sleep apnea; TMD, Temporomandibular disorders; IVW, Inverse variance-weighted; MR, Mendelian randomization; PRESSO, Pleiotropy RESidual Sum and Outlier.
with the scatter plot further (Supplementary Figures 6 and 7). Additionally, no horizontal pleiotropy (Egger intercept = -0.007, SE=0.011, P=0.571) (Table 1) was found and no outliers SNPs (P=0.275) were deleted. Furthermore, the plot of leave-one-out analysis was conducted, and no significant influence was identified with each SNPs (Supplementary Figure 8).

**Discussion**

TMD is a serious public health issue that contributes to chronic pain and dysfunction around the TMJ area, affecting the patient’s psychosocial functions and quality of life.2,18 OSA is the most common type of sleep breathing disorder, characterized by repetitive shallow and halted breathing during sleep, accompanied by intermittent hypoxia, awakening, and sleep fragmentation usually.19 OSA has traditionally been related with a variety of disorders, including hypertension, heart failure, stroke, metabolic disorder syndrome, sexual dysfunction, nervous system diseases, and so on.20–23 The incidence of the two diseases has been increasing in recent years, posing a significant worldwide health burden. However, it has been challenging to establish a definite causal link between OSA and TMD.

It is worth noting that OSA and TMD may share certain characteristics, such as chronic inflammation, organizational restructuring, muscle tone abnormalities, and emotional abnormalities. Patients with OSA typically have structural abnormalities in both soft and hard tissue; thus, oral and maxillofacial deformities are frequently accompanied with TMJ structural and positional abnormalities. Langaliya et al and other researchers discovered substantial changes in the

<table>
<thead>
<tr>
<th>Exposure/Outcome</th>
<th>SNP</th>
<th>Methods</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
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<tr>
<td>OSA on TMD</td>
<td>19</td>
<td>MR Egger</td>
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<td>0.356–1.646</td>
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<td></td>
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<td>Weighted median</td>
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<td>0.991–1.771</td>
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<td>1.009–1.526</td>
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<td>Simple mode</td>
<td>1.457</td>
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<td>MR Egger</td>
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<td>0.882–1.160</td>
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<td>Simple mode</td>
<td>1.008</td>
<td>0.915–1.110</td>
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<td>Weighted mode</td>
<td>1.021</td>
<td>0.935–1.115</td>
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</table>

**Abbreviations:** OSA, Obstructive sleep apnea; TMD, Temporomandibular disorders; OR, Odd ratios; CI, Confidence interval.

![Figure 2](https://doi.org/10.2147/NSS.S476277)

Figure 2 The funnel plot to detect any protentional heterogeneity of obstructive sleep apnea on temporomandibular disorders.

**Abbreviations:** OSA, obstructive sleep apnea; TMD, temporomandibular disorders; MR, Mendelian randomization; OR, odd ratios; CI, confidence interval.
position of the TMJ disc, condylar structure, and intra-articular pressure in OSA patients and the normal population.\textsuperscript{24,25} Furthermore, long-term inadequate and/or disrupted sleep in OSA patients leads to poor sleep quality, hyperalgesia, and triggers the onset of TMD further.\textsuperscript{26}

With the growing body of studies focusing on the impact of sleep quality on health, the causal link between OSA and TMD is being gradually valued. In 2020, a recent population-based cohort study reported that the TMD incidence rate was significantly higher in patients with OSA than in the controls (HR=2.5, P<0.0001) and Multivariable Cox regression analysis indicated that the OSA was an independent risk for the development of TMD (P<0.0001) based on Taiwan National Health Insurance (NHI) Research Database.\textsuperscript{26} Similarly, a high likelihood of OSA being associated with higher incidence of TMD was observed in both a prospective cohort study (adjusted HR=1.73; 95% CI=1.14–2.62)\textsuperscript{27} and a case-control study (adjusted OR=3.63; 95% CI=2.03–6.52) in a US population.\textsuperscript{27} A cross-sectional study indicated that patients with untreated OSA had a higher prevalence of TMD symptoms than healthy controls.\textsuperscript{28} According to Ning et al’s research, moderate to severe OSA can worsen orofacial pain and tooth wear, change the TMJ’s volume and superficial area, and consequently change the condyle’s position.\textsuperscript{25} Furthermore, a prospective cohort research by Alessandri-Bonetti et al demonstrated that the OSA treatment would assist to dramatically reduce the clinical symptoms of pain-related TMD.\textsuperscript{29}

In addition, aberrant mental states frequently coexist with OSA or TMD. Depression, irritation, anxiety and sensitivity to environmental stressors are the common characteristics of a neurotic personality, and it has been demonstrated that these mental disorders are more susceptible to OSA or TMD.\textsuperscript{30,31} Sleep disruption is a characterized symptom of OSA that results in fragmented and low-quality sleep.\textsuperscript{32} For example, chronic intermittent hypoxia and oxidative stress caused by OSA can have a deleterious impact on the brain, both of which are related with an increased risk of anxiety.\textsuperscript{33} Yap et al showed that anxiety is the common risk factor for the occurrence of TMD,\textsuperscript{34} while Liou et al found that patients with TMD had an approximately 7-fold higher risk of anxiety development than those without TMD.\textsuperscript{35} For depression, a recent meta-analysis based on five longitudinal studies found that patients with OSA were at a higher risk of depression than those without OSA (RR=2.18), and a cross-sectional study also revealed than patients with TMD had significantly worse depression and somatization status than controls.\textsuperscript{36} With the increasing pressure of life, stress has become more prevalent. Wong et al found that the psychological stress index of OSA patients was considerably greater than that of the healthy control groups.\textsuperscript{37} Park et al also discovered that perceived stress was strongly related with TMD in male, and TMD is more prevalent in women who experience both stress and suicidal ideation.\textsuperscript{38} Furthermore, several studies have revealed that obesity,\textsuperscript{39,40} thyroid dysfunction,\textsuperscript{41,42} inflammatory cytokines,\textsuperscript{43,44} and even wealth or educational level can contribute to the development of OSA or TMD.\textsuperscript{45,46}

**Strengths and Limitations**

Based on these features, there were some possible links between OSA and TMD. For the first time, we investigate the causal link between OSA and TMD in European descendants with MR analysis. According to statistical analysis, our findings imply that OSA has a directly harmful effect on TMD, while we did not find the causal link of TMD on OSA in the reverse study. The current result will help us to gain a better grasp of the relationship between OSA and TMD. MR analysis leverages the advantages of randomized controlled studies by utilizing existing large-scale GWAS data and grouping based on genotype instead of exposure, which can reduce the influence of confounding bias and provide stronger operability. Even though MR provides a strong framework for determining causal links, some limitations still cannot be avoided. Firstly, stratified analysis, such as the subgroups based on sex, age, income, order of severity, could not be conducted with aggregated information from the GWAS data; secondly, all used sample data were extracted from the European descendants, and the generalizability of the conclusion to other regions and races is largely limited; thirdly, some heterogeneity was observed in the casual analysis of TMD on OSA, which may have affected the reliability of the findings.

**Conclusions**

In summary, our findings showed that OSA has a causal effect on TMD, but not of TMD on OSA. The aforementioned findings indicate that an effective intervention should be implemented to prevent and relieve TMD symptoms. To examine the complicated interplay between OSA and TMD in the future, more MR studies with larger samples and robust statistical approaches would be required.
Data Sharing Statement
All data are publicly available GWAS summary data. This data can be found at open GWAS (https://gwas.mrcieu.ac.uk/) and from FinnGen database (https://www.finngen.fi/en).

Ethics Declaration
The collected data that originated from publicly genome-wide association studies (GWAS), ethical approval and consent were obtained by the original from the participants, and no ethical approval from an ethics committee was required further. This study was approved with exemption by Taihe Hospital Review Board due to the analysis being defined as minimal risk.

Acknowledgments
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Author Contributions
Yu-Pei Wang contributed to conception, design, acquisition, analysis, interpretation, drafted manuscript. Hui-Xia Wei contributed to acquisition, analysis, interpretation, drafted manuscript. Yuan-Yuan Hu contributed to analysis, interpretation, drafted manuscript. Yu-Ming Niu contributed to conception and design, critically revised manuscript. 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 declare no conflicts of interest in this work.

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Prevalence of signs and symptoms of temporo-mandibular disorder in patients

Alessandri-Bonetti A, Scarano E, Fiorita A, Cordaro M, Gallenzi P. Prevalence of signs and symptoms of temporo-mandibular disorder in patients


