Research Article

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Causal Relationship Between Temporomandibular Disorders And Rheumatoid Arthritis: A Bidirectional Mendelian Randomization Analysis.

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ABSTRACT

Objective: In this study, we aimed to explore the reciprocal cause-and-effect relationship between temporomandibular disorders (TMDs) and rheumatoid arthritis (RA).
Materials and Methods: We perfomed a two-sample bidirectional Mendelian randomization (MR) analysis from genome-wide association studies. The primary analysis approach used was inverse variance weighting (IVW), with supplementary analyses using MR-Egger, weighted median method, simple mode, and weighted mode to assess the causal relationship between TMD and RA, with odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity testing and assessment of multiple validity were performed using Cochran's Q, MR-Egger, and MR-pleiotropy residual sum and outlier methods.
Results: The general results of the forward MR analysis indicated that TMD had a significant causal effect on RA (IVW: OR = 1.125, 95% CI = 1.013–1.249, P = .028). However, the reverse MR analysis results suggested that RA had a dramatic causal effect on TMD (IVW: OR = 1.074, 95% CI = 1.025–1.126, P = .003). Finally, the stability and reliability of the causal association between the above combinations were confirmed through sensitivity analyses and other tests.
Conclusion: Our results demonstrated a hereditary causative relationship between TMD and RA. The findings emphasize the need for clinicians to additionally consider patients with RA when consulting for TMD and give more attention to patients with TMD, especially those undergoing pain control.

Keywords : *Temporomandibular Disorders, Rheumatoid Arthritis, Mendelian Randomization Analysis.*

INTRODUCTION

Temporomandibular disorders (TMDs) include several conditions that affect the temporomandibular joints (TMJs) and muscles involved in chewing and other related structures. Symptoms include persistent pain in the TMJs and muscles, clicking or popping sounds in the TMJs, limited mouth opening, jaw movement issues, and other jaw function abnormalities [1-3]. Notably, TMD incidence increases with increasing societal advances and life pressures. Recent research suggests that TMDs affect approximately 31% of adults and 11% of children [3]. However, women have a higher susceptibility to TMDs than men and are approximately twice as likely to develop TMDs [4]. TMDs can affect individuals at any stage of life[5]. Furthermore, the etiology of TMD remains unclear because of its complexity, and anxiety, depression, sleep disorders or bruxism, genetic predisposition, developmental abnormalities, and numerous biopsychosocial factors have been identified as possible contributing factors [4, 6-11]. Therefore, TMD arises from a combination of environmental, emotional, cognitive, and social factors, biological, [12]
Rheumatoid arthritis (RA) is a autoimmune disease that reslut to inflammatory polyarthritis and joint damage, increasing disability or deformity risk. According to a recent study, the global prevalence of RA has remained at approximately 0.46% over the last four decades and is projected to increase over time [13]. The inflammatory response in patients with RA can also negatively affect bone health by affecting bone mineral density. RA independently increases the risk of osteoporosis, leading to a dramatic increase in fracture risk and a decrease in bone mineral density [14, 15]. The causes of the two diseases have not been completely clarified; however, they

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are believed to be influenced by genetic, environmental, and other factors. Notably, the genes involved in the development of these two diseases are considered to overlap; however, this does not completely explain their connection.

Mendelian randomization (MR) is a novel approach used in observational epidemiology to determine causal effects using genetic variants as instrumental variables (IVs). In this study, we conducted a bidirectional MR analysis using data from large-scale genome-wide association studies (GWASs) to explore the potential causal relationship between TMD and RA. This is the first study to investigate the causal relationship between TMD and RA to provide valuable insights into the pathogenesis of the conditions and potentially guide early clinical assessment strategies for RA or TMD in prospective cases.

METHODS

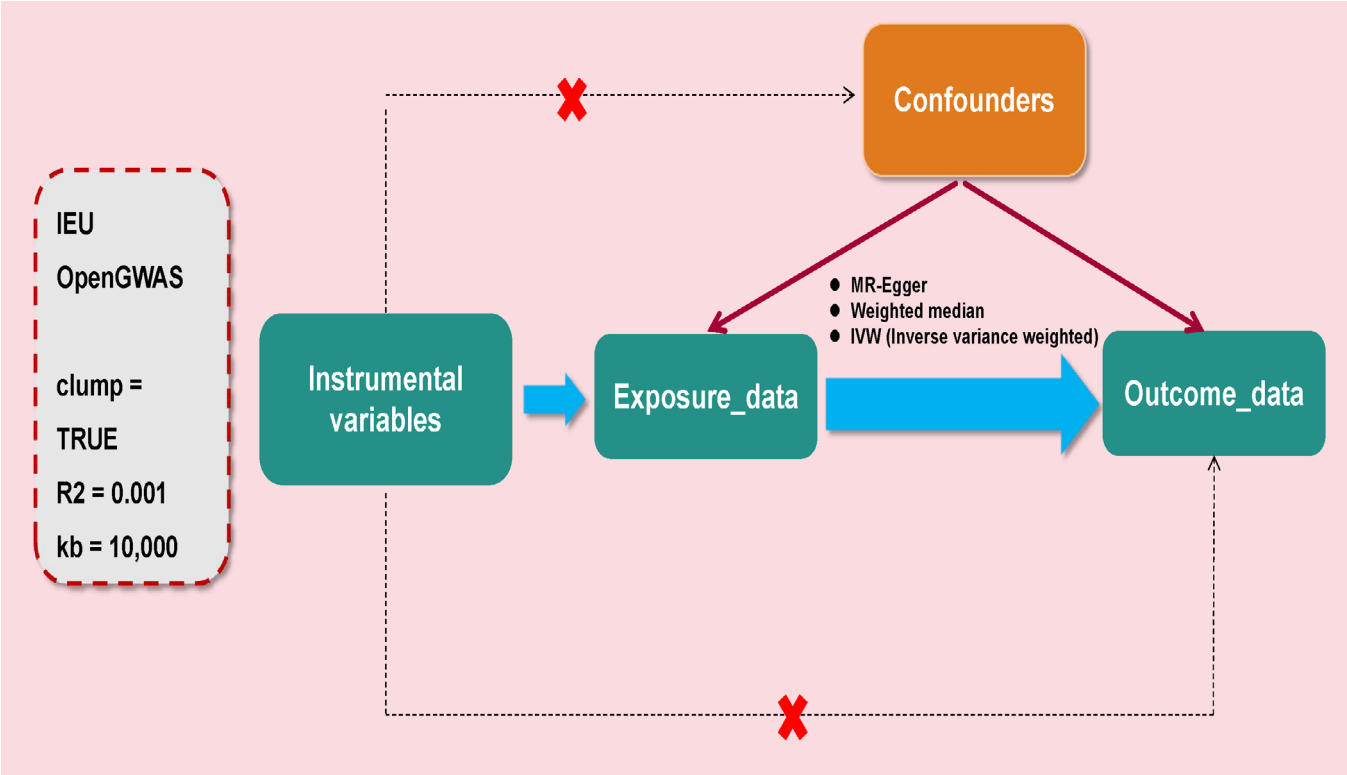
The data used in this study were derived from publicly available large-scale GWASs. The original investigators obtained ethical approval and informed consent from the participants involved. Consequently, no additional ethical review or approval from the institutional review board was required for this analysis.

Data sources

The datasets finn-b-TEMPOROMANDIB and ieu-a-833 were obtained by searching the GWAS database (https://gwas.mrcieu.ac.uk/) using the keywords "temporomandibular joint disorders" and "rheumatoid arthritis." The finn-b-TEMPOROMANDIB dataset included single-nucleotide polymorphism (SNP) data from 134,280 TMD samples (16,379,953 SNPs). The ieu-a-833 dataset for the RA dataset included 80,799 samples and 9,739,304 SNPs. After searching the PhenoScanner V2 website and removing SNPs that were palindromic with intermediate allele frequencies, one SNP (rs9663425) for TMD in RA and 11 SNPs (rs12652317, rs13330176, rs168962, rs25983, rs28986295, rs34536443, rs6479800, rs6879067, rs7532275, rs876938, and rs909685) for RA on TMD were excluded from the study.

This study had two parts. In the first part, TMD was considered the exposure_data, and RA was investigated as the outcome_data. However, in the second part, RA was examined as the exposure_data, and TMD was considered the outcome_data. **Figure 1** presents an overview of the study design.

Figure 1. Overall flow chart of the MR analysis.



GWAS: genome-wide association study; IEU: integrative epidemiology unit; MR: Mendelian randomization. MR: Mendelian Randomization; GWAS: Genome-Wide Association Study.

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Pre-processing of data

MR studies rely on three fundamental principles: firstly, demonstrating a robust and statistically significant correlation between IVs and primary exposure, secondly, verifying the independence of IVs from potential confounders, and thirdly establishing that IVs exclusively affect outcomes through the designated exposure, with no other pathways. Exposure factors were examined, and IVs were identified using the "extract_instruments" feature in the TwoSampleMR package ($P < 5\times10\text{-}6$) [16]. Furthermore, the parameter 'clump' was set to TRUE to eliminate independent variables for the linkage disequilibrium analysis (with a threshold of R2 = 0.001 and kb = 10,000). An R2 value of zero indicated that the two SNPs were in complete linkage equilibrium, suggesting that their assignments were random. Independent variables showing a significant correlation with exposure factors were selected. Outcome variables were then extracted using the "extract_outcome_data" function from the R package. Independent variables associated with exposure factors were combined with screening metrics, with proxy settings enabled. Additionally, weak independent variables were excluded based on the F-statistic for each SNP.

$$F = \frac{R^2}{1-R^2} \times \frac{(N-K-1)}{K}$$

Therefore, R2 denotes the proportion of variance in exposure factors explained by the selected IVs, N refers to the number of participants in the GWAS, and K signifies the number of SNPs screened for exposure. An F-statistic threshold of ≥10 suggested the exclusion of weak instruments, underscoring the strong predictive power of IVs for the outcome.

MR analysis

The TwoSampleMR package's "harmonize_data" function was used to standardize the effect size estimates. The primary MR methods applied were MR-Egger [14] weighted median [15] and inverse variance weighted (IVW) analyses, which incorporate random- and fixed-effects models [17]. The results are graphically represented using scatter, forest, and funnel plots. The scatter plot emphasized the IVW method. The forest plot was used to determine the diagnostic accuracy of individual SNP loci in forecasting exposure elements. Furthermore, funnel plots were used to evaluate the randomness of the data distribution; symmetrical dispersion of IVs around the IVW line confirmed compliance with MR principles.

Sensitivity analysis

Sensitivity analysis was performed to ensure that the MR analysis results were robust. A leave-one-out (LOO) analysis was conducted by sequentially excluding each SNP. The consistency of the effect of the remaining SNPs on the outcome variable confirmed the reliability of the MR analysis.

RESULTS

Causal effects of TMD on RA

After a thorough screening process, seven SNPs were identified as IVs (Table 1). Subsequently, the causal effect of TMD on RA was evaluated using MR analysis with TMD as the exposure_data and RA as the outcome_data. The results of the four methods consistently indicated a positive causal relationship between TMD and RA, highlighting its role as a risk factor (IVW model: OR = 1.124, P = .028; Table 2).

Furthermore, to further elucidate the relationship between TMD and RA, scatter plots were used to analyze the SNPs. The plots indicate a positive linear trend for TMD, demonstrating that increased TMD expression correlated with an increased probability of RA development (Figure 2A). Forest plots were used to evaluate the predictive power of the SNP loci for exposure factors and their associations with outcomes. In these visualizations, dots to the left signify a reduced risk, whereas those to the right indicate an increased risk. The forest plots consistently showed dots on the right, suggesting that higher exposure levels were associated with greater disease risk based on the IVW method (Figure 2B). Concurrently, the randomness of the IVs was assessed and depicted in funnel plots, which display a balanced distribution of IVs around the IVW line, affirming the adherence to MR principles (Figure 2C).

Table 1. Detailed genome-wide association study (GWAS) data for TMD and RA.

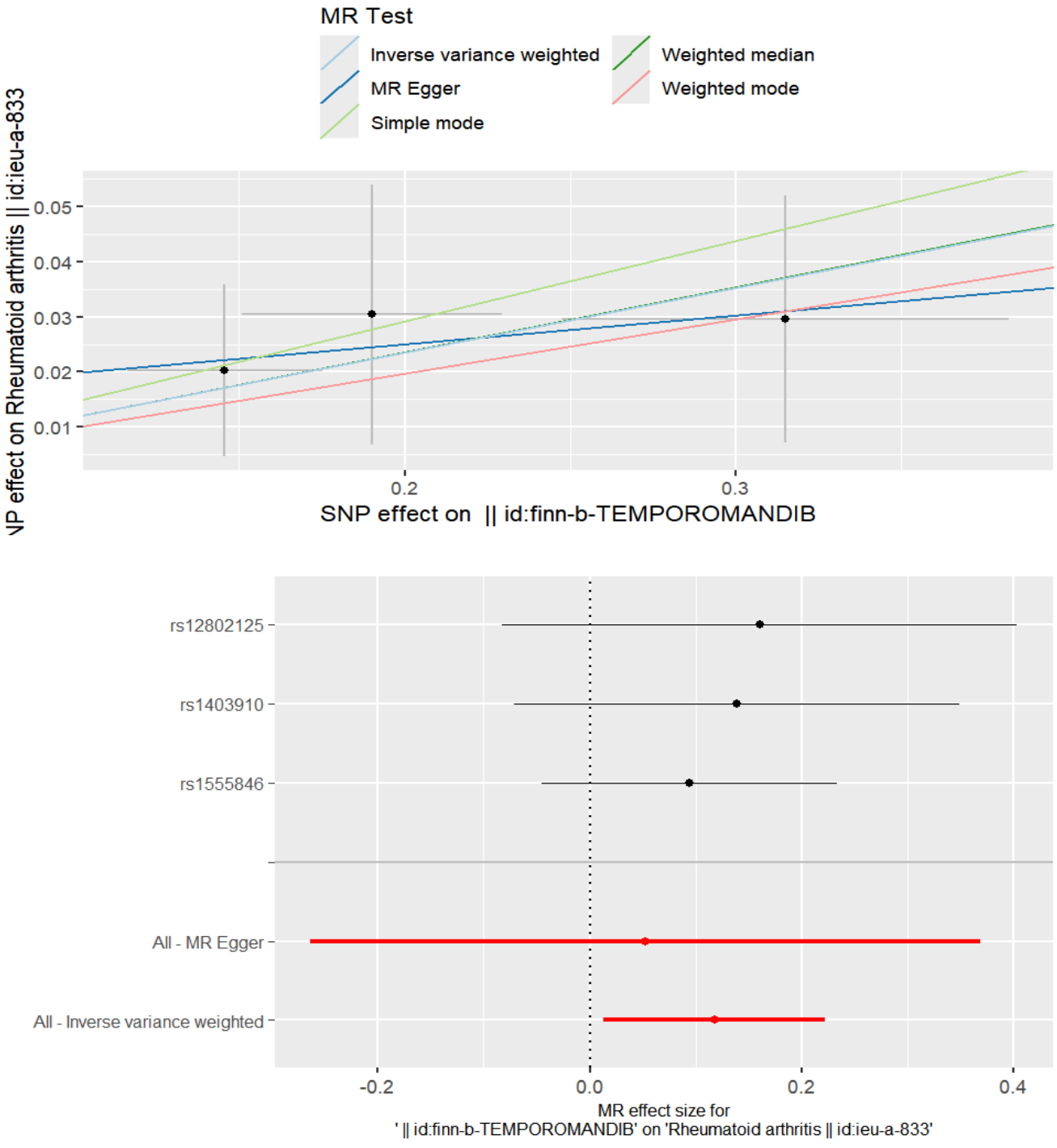
Item	Finn-b-TEMPOROMANDIB (TMD)	Ieu-a-833 (RA)
Year	2021	2014
Category	Binary	Disease
Sub category	NA	Autoimmune/ inflammatory
Population	European	Mixed
Trait	Temporomandibular joint disorders	Rheumatoid arthritis
Number of Case Group	2,730	19,234
Number of Control Group	131,550	61,565
Sample size	134,280	80,799
Number of SNPs	16,379,953	9,739,304
Consortium	NA	NA

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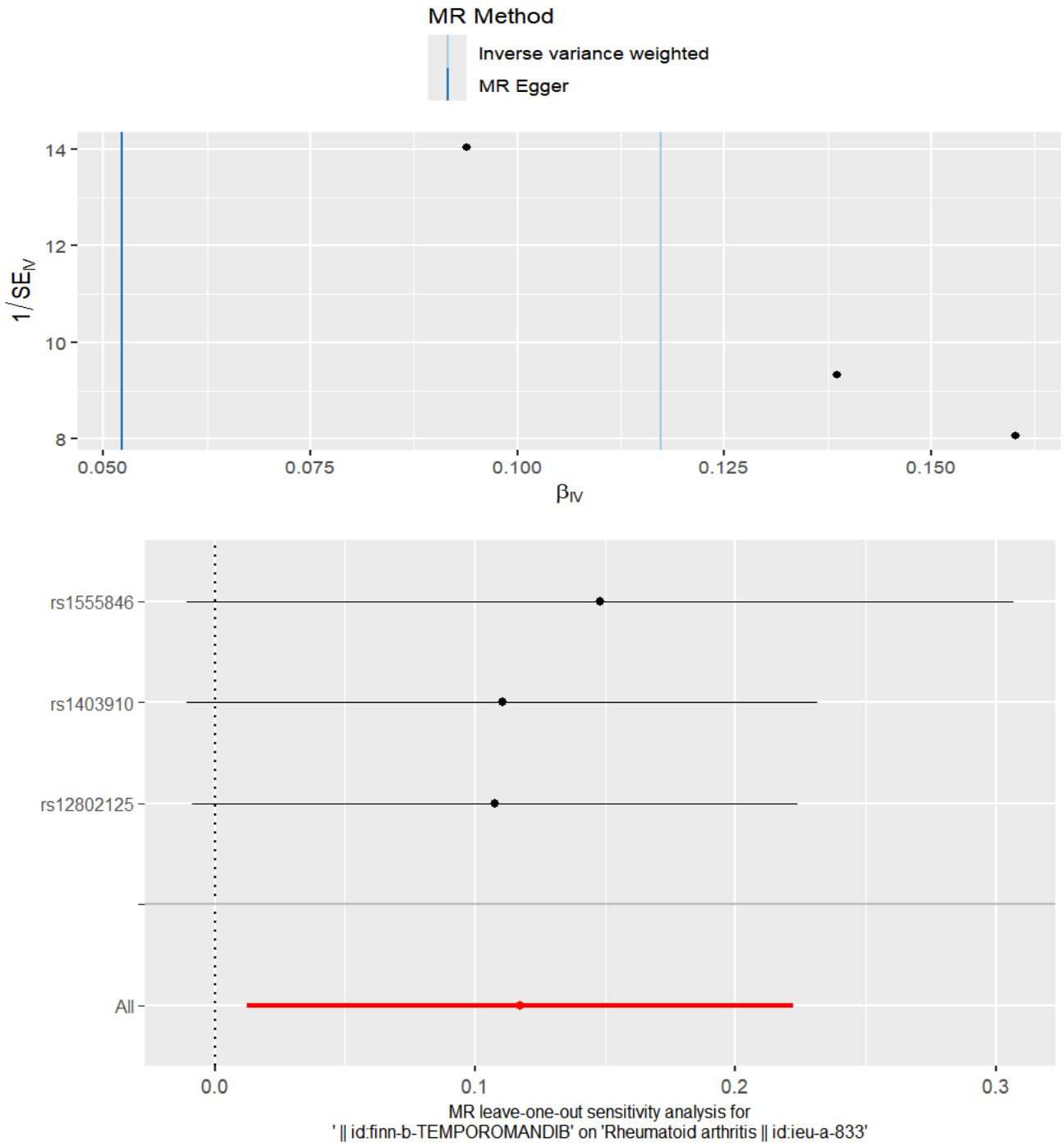
Table 2. Statistical data of mendelian randomization analysis for TMD and RA.

GWAS ID	GWAS ID	Method	nSNP	P-value	OR (95% CI)
Finn-b-TEMPOROMANDIB (exposure_data)	Ieu-a-833 (outcome_data)	MR Egger	3	0.800	1.054 (0.768-1.445)
		Weighted median	3	0.063	1.125 (0.994-1.274)
		IVW	**3**	**0.028**	**1.125 (1.013-1.249)**
Ieu-a-833 (exposure_data)	Finn-b-TEMPOROMANDIB (outcome_data)	MR Egger	89	0.285	1.042 (0.966-1.124)
		Weighted median	89	0.138	1.057 (0.982-1.138)
		IVW	89	0.003	1.074 (1.025-1.126)

Figure 2. MR analysis for TMD as exposure_data and RA as outcome_data.



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(A) Scatter plot. (B) Forest plot. (C) Funnel plot. (D) LOO sensitivity analysis.

MR: Mendelian Randomization; TMD: Temporomandibular disorders; RA: rheumatoid arthritis.

Sensitivity analysis of TMD on RA

A thorough sensitivity analysis was conducted to confirm the reliability of the findings. Initially, all Q_pval values from the heterogeneity tests were > .05, indicating no heterogeneity among the UK samples and highlighting the primary use of the IVW (fixed-effects) method in the MR analysis (Table 3).

Subsequently, MR-Egger and MR-pleiotropy residual sum and outlier (PRESSO) regression analyses were conducted to detect any potential pleiotropic effects of the genetic instruments. These tests consistently showed no evidence of pleiotropy affecting the relationship between TMD and TA (P values > .05; Table 4).

Additionally, a LOO analysis was conducted to evaluate the stability of the findings. This method, which entails successively omitting a single SNP and then applying the remaining SNPs for MR analysis, measures the extent to which a specific SNP may affect outcomes. The LOO analysis primarily aimed to verify whether the curve connecting the dark spots is consistent without

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any noticeable outliers. The results of the LOO analysis indicated no substantial outliers in the graphs, confirming the reliability of the findings (Figure 2D).

Table 3. Measures of heterogeneity using Cochran's Q test.

ID exposure_data	ID outcome_data	Method	Q	Q_df	Q_pvalue
Finn-b-TEMPOROMANDIB	Ieu-a-833	MR Egger	0.084	1	0.772
Finn-b-TEMPOROMANDIB	Ieu-a-833	IVW	0.268	2	0.875
Ieu-a-833	Finn-b-TEMPOROMANDIB	MR Egger	84.187	87	0.565
Ieu-a-833	Finn-b-TEMPOROMANDIB	IVW	85.150	88	0.566

Abbreviations: IVW: Inverse variance weighted; MR: mendelian randomization; Q_df: degree of freedom associated with the Cochran Q test of heterogeneity; Q_pvalue: p-value of Q-test for heterogeneity test.

Table 4. Examination of horizontal pleiotropy effects using MR-Egger regression tests.

ID exposure_data	ID outcome_data	Egger_intercept	Se	P-value
Finn-b-TEMPOROMANDIB	Ieu-a-833	0.015	0.034	0.742
Ieu-a-833	Finn-b-TEMPOROMANDIB	0.006	0.006	0.329

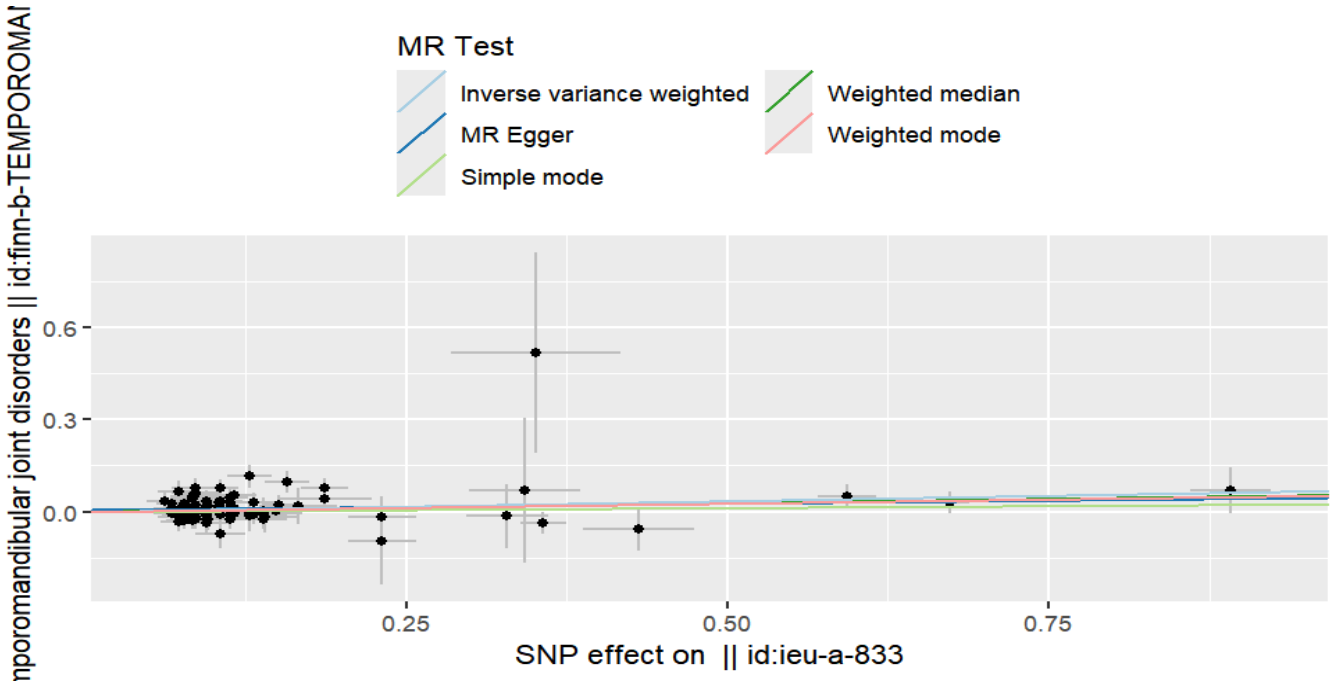
Abbreviations: SE: standard error

Causal effects of RA on TMD

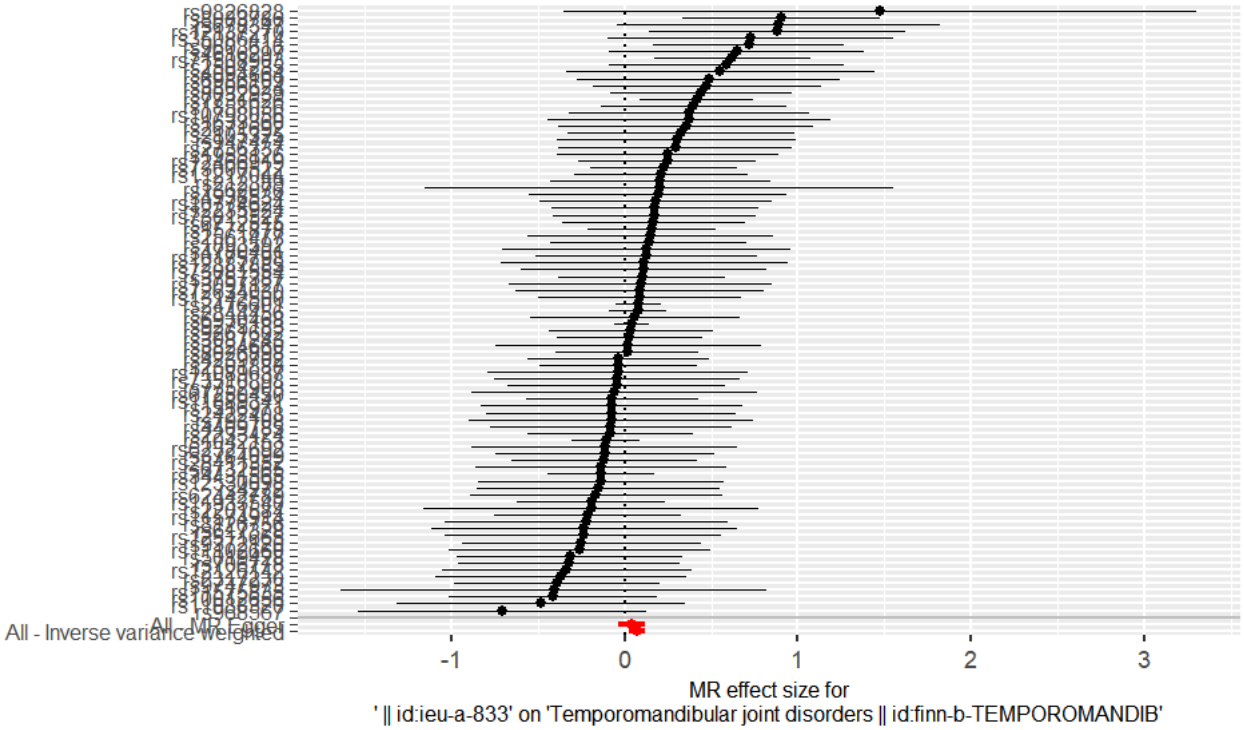
In the second step, after comprehensive screening, 107 SNPs were confirmed as IVs (Table 1). Using MR analysis, the causal effect of RA on TMD was examined with RA as exposure_data and TMD as outcome_data. The results from multiple methods consistently showed a positive causal relationship between RA and TMD, suggesting that RA was a risk factor (IVW model: OR = 1.074, P = .003; Table 2).

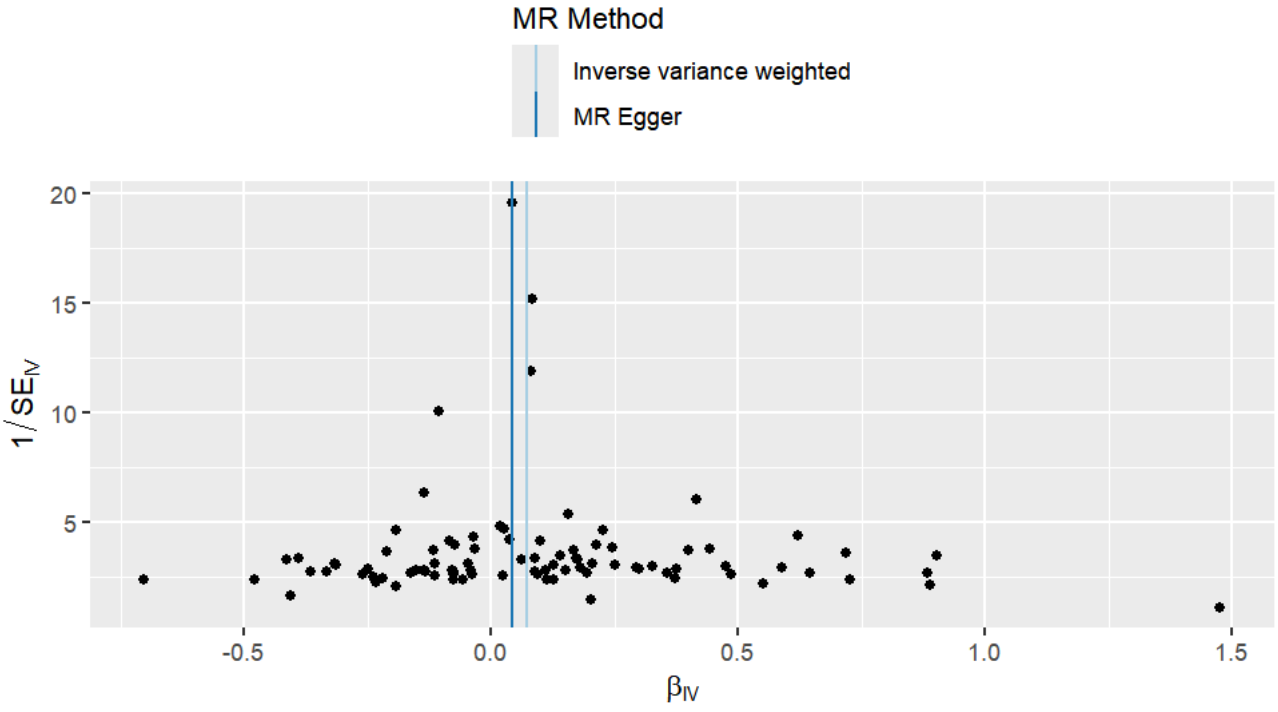
Scatter plots further supported this association, demonstrating a positive linear relationship between RA expression and the likelihood of developing TMD (Figure 3A). Forest and funnel plots were generated. The results from the forest plot consistently displayed substantial dots on the right, indicating that higher exposure levels were associated with an increased likelihood of TMD development based on the IVW method (Figure 3B). Funnel plots revealed a balanced arrangement of IVs around the IVW line, validating that the MR analysis conformed to the MR grouping criteria (Figure 3C).

Figure 3. MR analysis for RA as exposure_data and TMD as outcome_data.

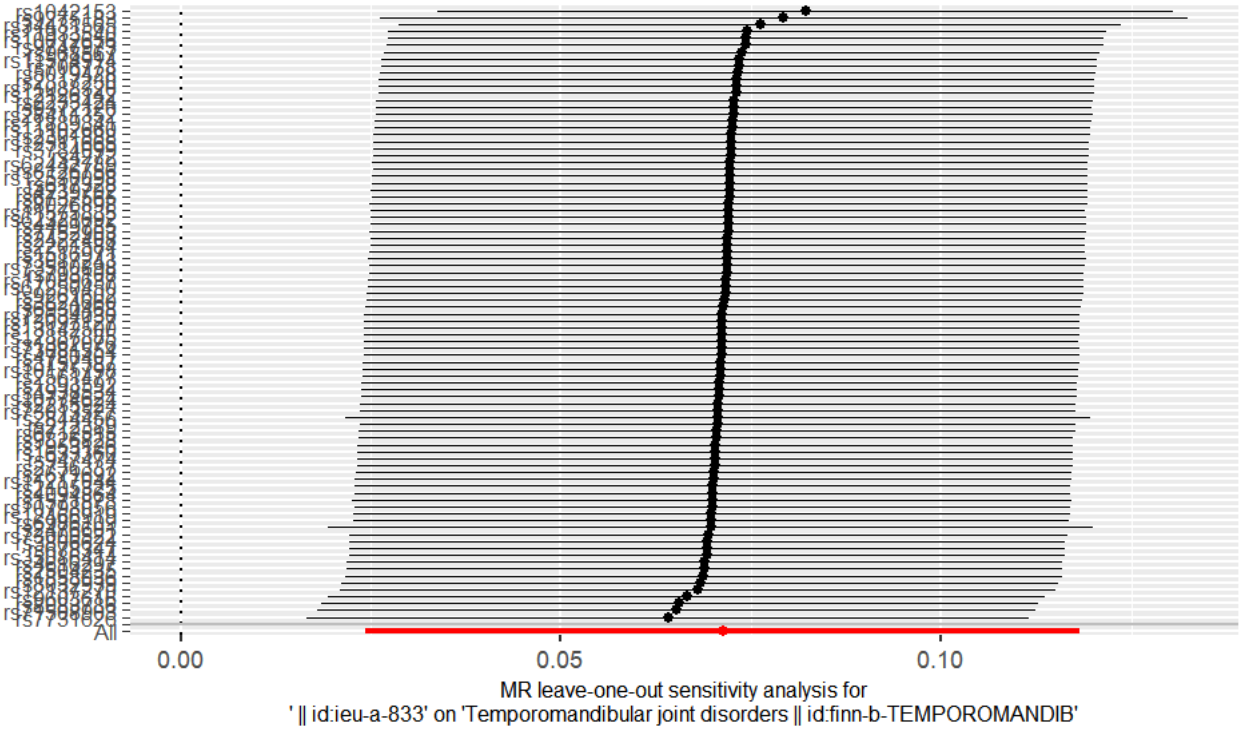


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(A) Scatter plot. (B) Forest plot. (C) Funnel plot. (D) LOO sensitivity analysis.

MR: Mendelian Randomization; RA: rheumatoid arthritis; TMD: Temporomandibular disorders.

Sensitivity analysis of RA on TMD

We conducted a comprehensive sensitivity analysis that included tests for heterogeneity and analyses of horizontal pleiotropy (MR-Egger and MR-PRESSO regression tests). A heterogeneity test, with P values > .05, indicated the absence of heterogeneity (Table 3). The horizontal pleiotropy analysis showed no correlation between the two factors (P > .05; Table 4). Additionally, the results of the LOO analysis revealed no substantial bias (Figure xx), thereby validating the reliability of the analysis results (Figure 3D).

DISCUSSION

There has been an increasing interest among scientists regarding the relationship between immunity and the risk of TMD. Therefore, in this study, we used aggregated GWAS data to explore the causal relationship between TMD and RA. To our knowledge, this is the first study to estimate the bidirectional causal relationship between TMD and RA using the MR method. In this study, we conducted a bidirectional two-sample MR analysis using GWAS data derived from UKB, FinnGen, GLIDE, and consortia. Our findings provide significant evidence supporting a causal relationship between TMD and RA. This indicates that TMD has a direct harmful effect on RA; furthermore, RA could also affect TMD in a reverse study. This study established a correlation between TMD and RA and emphasized the necessity of early diagnosis of TMD or RA in patients with clinical RA or TMD.

TMD is a joint disease that affects the masticatory system through multiple factors[18]. Bruxism is a prevalent issue in the oral chewing systems of adults and children and has been recognized as a contributing factor to abnormal occlusion and TMD occurrence [19, 20]. Additionally, facial macrotrauma, such as whiplash injuries, intubation procedures, and prolonged mouth opening, can cause inflammation and degenerative changes in TMJs, ultimately leading to the onset of TMD [21-23]. Moreover, an abnormal psychological status, including depression, anxiety, and stress, significantly affects the development of TMD [24, 25]. Recently, there has been a noticeable increase in the incidence of TMD and autoimmune arthritis (AA), with a growing overlap between these two common diseases [26-28]. Therefore, it is important to evaluate the potential connections between these conditions to develop preventive and treatment strategies. Recent research has suggested a higher occurrence of TMD in individuals with inflammatory arthritis than in the general population, which is supported by clinical and radiological findings [29]. Additionally, several observational studies have demonstrated that various types of AA increase the risk of developing TMD.

RA is characterized by inflammation, autoimmune response, and joint damage. Patients with RA have higher risks of developing TMD than those without RA, with symptoms often appearing early during disease progression [30, 31]. Notably, most patients with RA-related TMD experienced symptoms before or within 1 year of developing issues in other joints in the body [30, 32]. In a cross-sectional study, the average follow-up period for patients with RA was 4.97 years, with over

half of these patients falling into Group IIIb (osteoarthritis). Therefore, owing to the long-term history of RA in this study, it is likely that TMJ findings were common. Additionally, condylar erosion was the most prevalent pathology in patients with RA, affecting 33.3% of patients on both sides, which is similar to the findings of previous studies [33, 34]. RA can accelerate connective tissue inflammation, degeneration, and degenerative changes in the TMJ, leading to a more rapid progression of symptoms. However, despite pain control with RA medications, patients may overlook their awareness of TMJ concerns [35]. Shoohanizad et al. [36] found that TMD can occur in patients with autoimmune disorders such as RA, lupus erythematosus, and systemic sclerosis. Sadura-Sieklucka et al. recruited 60 patients with RA (n = 30) and healthy controls (n = 30); in the RA group, 17 patients (57%) reported TMD, whereas only three (10%) healthy people reported TMD (P = .0001) [37]. Furthermore, Lin et al. [38] conducted a study on 17,317 patients with RA, comparing them to an equal number of controls. Their findings revealed that individuals in the RA group were 2.5 times more likely to experience TMD (P < .001). Furthermore, a significant correlation was observed between TMD and female sex, mental health issues, or stroke (P < .001). They also discovered that 13 (23%) patients did not achieve an abduction norm of 40 mm for TMD. However, in Sadura-Sieklucka's study, a higher percentage of patients (60%, or 18 of 30 cases) fell into this category [37].

In the present study, we observed a robust relationship between TMD and RA. When TMD was used as exposure_data and RA as outcome_data, a positive causal relationship was observed between TMD and RA, highlighting its role as a risk factor (IVW model: odds ratio [OR] = 1.124, P = .028). Furthermore, when RA was used as exposure_data and TMD as outcome_data, a similar positive causal relationship was found between RA and TMD, suggesting RA as a risk factor (IVW model: OR = 1.074, P = .003). Subsequently, heterogeneity tests and MR-Egger and MR-PRESSO regression analyses were conducted to confirm the reliability of the results (P > .05). The studies cited above demonstrated a strong association between TMD and RA, which is consistent with our findings. However, further research is required to delve deeper into the specific influencing factors and their pathogenesis. Therefore, this study revealed a robust association between TMD and RA regarding genes, genetics, and autoimmunity, emphasizing the notable correlations among genetic variables. However, despite the absence of a connection with environmental factors, ongoing research should explore and analyze the relationship between the pathogenesis of TMD and RA.

CONCLUSIONS

There is a mutual causal relationship between TMD and RA, which could offer guidance for the early assessment of RA or TMD in prospective clinical cases. Our findings suggest that patients with RA should undergo regular screening for TMD, and those with TMD should also be routinely tested for RA. However, with only a few studies currently available on comorbid TMD and RA, future research should focus on exploring the mechanisms linking these two conditions.

Acknowledgments

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Conflict of interest

The authors confirm that the research was conducted without any commercial or financial relationships that could be regarded as potential conflicts of interest.

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Author contributions

ZB: conception, technique, formal analysis, data collection, first draft preparation, and visualization; YP and LX: preparation of the first draft, visualization, and data curation in writing; PY: editing, monitoring, and writing evaluation. The final draft of the manuscript was approved by all authors who contributed to this work.

Data availability statement

This study includes original contributions that can be found in the article/supplementary material. Please contact the corresponding author for additional inquiries.

Ethics statement

Ethical review and approval were not necessary for studies involving human participants, as they complied with local laws and institutional guidelines. Written informed consent from the participants' legal guardians or next of kin was not required, which conformed to national legislation and institutional requirements.

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