Research letter

Neurology

Effects of a home exercise program on symptoms and inflammatory markers in temporomandibular disorders

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Temporomandibular disorders (TMD) encompass a range of conditions affecting the temporomandibular joint (TMJ) and masticatory muscles, presenting as pain in the jaw joint, periauricular region, and facial muscles [1]. Etiology is multifactorial, involving arthritis, jaw injury, and bruxism (teeth grinding), which is itself frequently precipitated or exacerbated by psychological stress [2]. First-line management includes self-care measures – avoiding extreme jaw movements, cold/warm compresses, and soft diets – while persistent symptoms may require pharmacological treatment (analgesics, anti-inflammatories, muscle relaxants), oral splints, physical therapy, counseling, or, in refractory cases, surgery.

Inflammation is thought to play a pivotal role in TMD pathogenesis, but the mechanisms linking it to jaw joint pain remain poorly defined [3]. Observational studies have repeatedly reported elevated traditional inflammatory markers (IL-1β, IL-6, IL-8, TNF-α, PGE2, MMP-9) in TMD patients, yet these associations cannot establish causality, and the peripheral immune and metabolomic profiles of TMD patients remain incompletely characterized.

Mendelian randomization (MR), which uses genetic variants as instrumental variables to approximate the random allocation of risk factors, offers a means of inferring causality while reducing susceptibility to confounding and reverse causation [4–6]. It is now widely applied in drug target discovery and repurposing. However, no MR study has yet integrated genome-wide association study (GWAS) data on immune cell traits and circulating metabolites to jointly evaluate their causal roles in TMD – representing a key gap this study addresses.

Here, we leverage large-scale GWAS data within an MR framework to systematically identify metabolites and inflammatory factors potentially associated with TMD, and we separately test, in a randomized clinical trial, whether a structured home exercise program improves TMD-associated symptoms and inflammatory markers in patients with DDWR. The two study components are presented and interpreted separately; any relationship between the genetic findings and the clinical intervention is discussed as hypothesis-generating rather than directly demonstrated.

Methods. Brief methods are summarized here; full details are provided in the Supplementary File.

Mendelian randomization analysis. We performed a two-sample MR analysis using European-ancestry GWAS summary statistics for 1,400 circulating metabolites and 91 inflammatory factors as exposures (331,976 participants) and FinnGen release R11 as the TMD outcome (453,733

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participants; 17,820 cases, 435,913 controls; endpoint finngen_R11_TEMPOROMANDIB_INCLAVO). Instrument selection and harmonization criteria, the five MR methods applied, and pleiotropy/heterogeneity testing are detailed in the Supplementary Methods. We applied Benjamini-Hochberg FDR correction across all tests and report both FDR-adjusted and nominal associations (Supplementary Table SI). To evaluate whether the association between α-hydroxyisocaproic acid and TMD risk was mediated by IL-22RA1, we performed a two-step MR mediation analysis, described in full in the Supplementary Methods.

Clinical home exercise intervention. We conducted a prospective randomized trial in patients with TMJ disc displacement with reduction (DDWR), diagnosed using the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), recruited from the Hospital of Stomatology, Jilin University, between January 2024 and December 2024. The trial was not prospectively registered in a clinical trials registry. Sixty-two patients were assessed for eligibility; 2 were excluded for not meeting DC/TMD criteria for DDWR, leaving 60 patients who were randomized (n = 30 per group) using a computer-generated block randomization sequence (block size of 4, no stratification), with allocation concealed using sequentially numbered, sealed opaque envelopes opened only after baseline assessment. All 60 randomized patients received their allocated intervention, completed the 4-week protocol, and were included in an intention-to-treat analysis; there were no withdrawals and no adverse events were reported. Outcome assessors were blinded to group allocation, and adherence to the home exercise program was monitored via weekly phone calls, with all patients in the exercise group reporting completion of at least 90% of prescribed sessions. Baseline demographic and clinical characteristics are summarized in Table I. Sample size was estimated a priori using G*Power 3.1, based on the prespecified primary outcome of pain intensity during activity, assuming Cohen's d = 0.8, α = 0.05, and 80% power for a two-tailed independent-samples t-test; 26 participants per group were required, and 30 per group were enrolled to allow for approximately 15% attrition. During revision, baseline-adjusted ANCOVA was adopted as the principal between-group analysis because of the substantial baseline imbalances in pain during activity and MFIQ. For each outcome, the post-treatment value was the dependent variable, randomized group was the main predictor, and the baseline value of the same outcome was a covariate. The treatment coefficient was reported with its standard error, 95% confidence interval, exact two-sided p-value, and partial η^2. The originally planned between-group comparison of individual change scores was retained and is reported as a sensitivity analysis with a standardized mean difference. Pain during activity remained the prespecified primary endpoint; pain at rest, MFIQ, and serum IL-22RA1 were secondary endpoints and were interpreted as exploratory without multiplicity adjustment.

Results. ***Mendelian randomization results.*** We first investigated the association between circulating inflammatory factors and TMD risk. IL-22RA1 and CD5 were positively associated with TMD, whereas SCF and CCL25 were negatively associated; all four associations remained significant after Benjamini–Hochberg FDR correction (FDR-adjusted p = 0.048, 0.049, 0.027, and 0.048, respectively; Supplementary Table SIV). IL-17A-treated TMJ synovial fibroblasts showed a trend toward increased IL-22RA1 expression compared with the untreated group (data not shown, GSE74688).

We then investigated the association between circulating metabolites and TMD risk. Thirty metabolites were nominally positively associated with TMD and 24 were nominally negatively associated (Supplementary Figure S1). After Benjamini-Hochberg FDR correction, three metabolites remained significantly associated with TMD: AMP-to-cysteine ratio (negatively; OR = 0.896, FDR-adjusted p = 0.017), citrulline (negatively; OR = 0.895, FDR-adjusted p = 0.032), and α-hydroxyisocaproic acid (positively; OR = 1.112, FDR-adjusted p =

Table I. Baseline demographic and clinical characteristics of the home exercise and education-only groups. No formal statistical matching procedure was performed; both groups were formed by randomization. NPS = Numerical Pain Scale (0 = no pain to 10 = worst pain imaginable); MFIQ = Mandibular Function Impairment Questionnaire

Characteristic	Home exercise group (n = 30)	Education-only group (n = 30)
Age [years] (mean ± SD)	46.2 ±10.6	40.3 ±11.8
Sex, male/female, n	18/12	16/14
Symptom duration [years] (mean ± SD)	3.2 ±2.2	2.8 ±1.6
Baseline pain at rest, NPS 0–10 (mean ± SD)	3.88 ±3.00	3.64 ±2.01
Baseline pain during activity, NPS 0–10 (mean ± SD)	7.91 ±1.84	4.63 ±2.32
Baseline MFIQ total score, 0–68 (mean ± SD)	30.70 ±8.12	21.50 ±8.34
Baseline serum IL-22RA1 [pg/ml] (mean ± SD)	3.16 ±1.12	3.21 ±1.34

0.035) (Supplementary Table SIV). To evaluate the candidate mediator pathway, we then tested the association between each of these three FDR-significant metabolites and serum IL-22RA1; α-hydroxyisocaproic acid showed the strongest evidence for a positive causal association with IL-22RA1 (β = 0.109, OR = 1.11, 95% CI [1.03–1.21], p = 0.009; FDR-adjusted p = 0.031) (Supplementary Figure S2).

Two-step Mendelian randomization mediation analysis. To investigate whether the association between α-hydroxyisocaproic acid levels and TMD risk was mediated by IL-22RA1, we conducted a two-step MR mediation analysis. The total effect of α-hydroxyisocaproic acid on TMD was β = 0.106 (95% CI: 0.041 to 0.171; p = 0.001). Genetically predicted α-hydroxyisocaproic acid was positively associated with IL-22RA1 (path a: β = 0.109, 95% CI: 0.027 to 0.190; p = 0.009), and IL-22RA1 was positively associated with TMD risk (path b: β = 0.129, 95% CI: 0.015 to 0.242; p = 0.027). The estimated indirect effect was 0.014 (95% CI: –0.0023 to 0.0302; p = 0.092), corresponding to approximately 13.1% of the total effect, and the estimated direct effect was 0.092 (95% CI: 0.0262 to 0.1584). Because the confidence interval for the indirect effect included zero, the mediation result is exploratory and does not establish mediation (Supplementary Figure S4).

Clinical home exercise intervention results. We compared pain intensity, MFIQ, and serum IL-22RA1 before and after the 4-week intervention (n = 30 per group; Table I, Supplementary Tables SI–SIII). At baseline, pain at rest was comparable between groups (exercise: 3.88 ±3.00; education-only: 3.64 ±2.01) and serum IL-22RA1 was comparable between groups (3.16 ±1.12 vs. 3.21 ±1.34); however, pain during activity (7.91 ±1.84 vs. 4.63 ±2.32) and MFIQ total score (30.70 ±8.12 vs. 21.50 ±8.34) were higher in the exercise group. Therefore, treatment effects were estimated using baseline-adjusted ANCOVA rather than a simple comparison of post-treatment means. The prespecified individual-level change-score analysis was retained as a sensitivity analysis.

After the 4-week intervention, the exercise group showed significant within-group improvement in pain at rest (3.88 ±3.00 to 1.88 ±1.23, p = 0.006, Cohen's d = 0.53), pain during activity (7.91 ±1.84 to 3.56 ±0.92, p < 0.001, d = 1.36), MFIQ total score (30.70 ±8.12 to 20.07 ±8.65, p = 0.002, d = 1.21), and serum IL-22RA1 (3.16 ±1.12 to 1.57±0.56, p = 0.001, d = 1.19). The education-alone group showed significant within-group improvement in pain at rest (3.64 ±2.01 to 3.12 ±1.99, p = 0.004, d = 0.18) and pain during activity (4.63 ±2.32 to 3.86 ±2.35, p = 0.022, d = 0.23), but no significant within-group change in MFIQ total score (21.50 ±8.34 to 19.99 ±8.69, p = 0.365, d = 0.03) or serum IL-22RA1 (3.21 ±1.34 to 3.15 ±0.69, p = 0.865, d = 0.09).

In the baseline-adjusted ANCOVA, the exercise group had lower post-treatment pain during activity than the education-only group (adjusted mean difference –2.15, SE = 0.45, 95% CI: –3.04 to –1.26, $p = 1.04 \times 10^{-5}$, partial η^2 = 0.291). The corresponding adjusted effects were –1.28 for pain at rest (SE = 0.42, 95% CI: –2.12 to –0.44, p = 0.00348, partial η^2 = 0.140), 2.43 for MFIQ total score (SE = 2.52, 95% CI: –2.62 to 7.47, p = 0.340, partial η^2 = 0.016), and –1.59 pg/ml for serum IL-22RA1 (SE = 0.16, 95% CI: –1.91 to –1.26, $p = 5.41 \times 10^{-14}$, partial η^2 = 0.632). Negative ANCOVA estimates indicate lower post-treatment scores in the exercise group. In the change-score sensitivity analysis, where positive values indicate greater reduction with exercise, the exercise-minus-education mean differences were 3.58 for pain during activity (95% CI: 2.74 to 4.42, $p = 8.25 \times 10^{-12}$, Hedges g = 2.18), 1.48 for pain at rest (95% CI: 0.07 to 2.89, p = 0.0408, g = 0.54), 9.12 for MFIQ (95% CI: 2.19 to 16.05, p = 0.0110, g = 0.68), and 1.53 pg/ml for IL-22RA1 (95% CI: 0.75 to 2.31, p = 0.000292, g = 1.01) (Figures 1 A–D).

Both groups showed within-group changes over 4 weeks, as summarized above. In the baseline-adjusted analysis, the primary outcome of pain during activity favored the exercise group, and the change-score sensitivity analysis gave a concordant result. Pain at rest and IL-22RA1 also favored exercise, whereas the adjusted MFIQ total-score estimate was imprecise and compatible with no group difference. For MFIQ, the change-score sensitivity analysis suggested a between-group difference (mean difference: 9.12, 95% CI: 2.19 to 16.05; p = 0.011), whereas the baseline-adjusted ANCOVA did not (adjusted mean difference: 2.43, 95% CI: –2.62 to 7.47; p = 0.340). Given the substantial baseline imbalance in MFIQ, the ANCOVA estimate is considered the primary interpretation. CBCT images from one randomly selected participant in the exercise group are presented for qualitative illustration only.

Radiographic evaluation of condylar positioning. Representative sagittal CBCT images of the bilateral TMJ are shown to illustrate condylar positioning before and after treatment; these images are presented as a qualitative, illustrative observation in a single representative patient and are not intended as quantitative evidence of a structural therapeutic effect. Before treatment (top panels), both condyles appeared positioned superior-posteriorly within the glenoid fossa, consistent with possible constriction of the superior joint space. After treatment (bottom panels), the images appeared to show a more inferior-anterior condylar

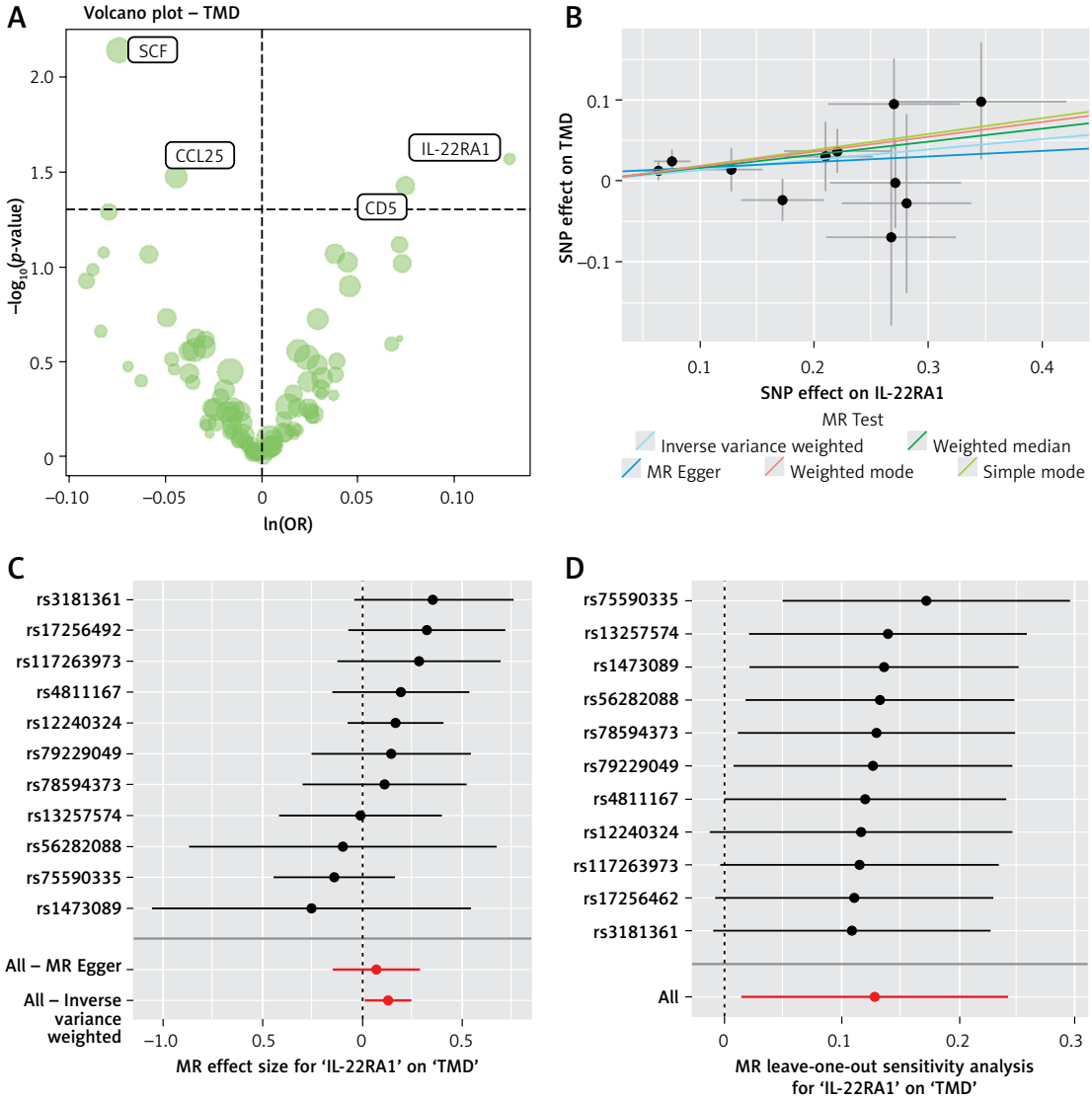

Figure 1. MR analysis for circulating inflammatory factors and TMD. **A** – The bubble plot shows the relationship between inflammatory factors and TMD. **B** – Scatter plot of SNP effects on IL-22RA1 level versus TMD. **C** – Forest plot of individual and combined SNP MR-estimated effect sizes. **D** – MR leave-one-out sensitivity analysis for IL-22RA1 on TMD

position with larger superior and posterior joint spaces (Supplementary Figure S3).

Discussion. ***Interpretation of results.*** Our MR analysis identified a positive association between α-hydroxyisocaproic acid and TMD risk that is consistent with, though not proof of, a contribution to disease pathogenesis. α-Hydroxyisocaproic acid is involved in muscle protein synthesis and recovery pathways and has been linked to elevated alkaline phosphatase, an enzyme associated with active bone and joint remodeling; our findings suggest a plausible, hypothesis-generating route by which this metabolite could relate to the metabolic and inflammatory balance within the TMJ. Elevated ALP has also been observed in TMD patients in our own cohort data, which is consistent with, though does not itself confirm, this candidate pathway.

IL-22RA1 is part of the receptor complex through which IL-22 signaling acts, primarily in epithelial and barrier tissues [7, 8]. The two-step MR point estimate was compatible with a possible indirect pathway from α-hydroxyisocaproic acid to TMD through IL-22RA1, but the indirect effect was not statistically significant and remains exploratory. The baseline-adjusted clinical model showed a lower post-treatment IL-22RA1 concentration in the exercise group, providing evidence of a between-group difference in this biomarker. IL-22RA1 should therefore be regarded as a hypothesis-generating biomarker, not a validated mediator or therapeutic marker in TMD [9, 10]. An IL-22RA1 inhibitor is being evaluated separately in atopic dermatitis [11], which motivates mechanistic study but does not establish relevance to TMD treatment.

These results identify a specific circulating metabolite and a specific inflammatory receptor as candidates for further investigation in TMD within a causal-inference framework rather than a purely observational one. Using genetic instruments reduces, but does not eliminate, the influence of confounding and reverse causation that typically limits interpretation of cross-sectional biomarker studies. Although the findings suggest a candidate relationship involving α-hydroxyisocaproic acid and IL-22RA1, the MR mediation analysis did not establish that IL-22RA1 mediates the association with TMD risk. IL-22RA1 is therefore a candidate biomarker of interest, but its value for monitoring responses to conservative treatments such as home exercise and patient education remains to be established.

Several limitations should be considered. The GWAS data underlying the MR analysis are cross-sectional, and the causal interpretation depends on standard MR assumptions. The TMD phenotype in FinnGen is register-based, whereas DDWR in the clinical cohort was diagnosed using DC/TMD criteria [12]; these phenotypes are not equivalent. Despite randomization, substantial baseline imbalances were observed for pain during activity and MFIQ. Baseline-adjusted ANCOVA was therefore used for between-group estimation, but the small sample limits precision and does not eliminate the possibility of chance imbalance or model sensitivity. The trial was not prospectively registered, so the designation of primary and secondary outcomes relies on the study protocol rather than an independent registry record. Secondary clinical outcomes were not adjusted for multiplicity and should be interpreted as exploratory. Multiple testing across the MR exposures was addressed using FDR correction, but residual false-positive risk remains for nominal findings. Finally, the non-significant mediation estimate and the clinical biomarker findings do not establish the molecular mechanism linking α-hydroxyisocaproic acid, IL-22RA1, and TMD.

In conclusion, the MR analysis identifies candidate associations involving α-hydroxyisocaproic acid, IL-22RA1, and TMD risk. The randomized clinical trial supports beneficial effects of the home exercise program on pain outcomes and serum IL-22RA1, whereas the adjusted MFIQ difference was not statistically significant. The mediation and biomarker findings remain hypothesis-generating.

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Ethical approval

The clinical trial was approved by the ethical committee of the Hospital of Stomatology, Jilin University (2023-K05); written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki. The trial was not prospectively registered in a clinical trials registry. Use of publicly available GWAS summary data for the Mendelian randomization component was separately approved by the ethical committee of Shanghai Pudong New Area People's Hospital (2024-KN03).

Conflict of interest

The authors declare no conflict of interest.

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