

Associations among gastroesophageal reflux disease, mental disorders, sleep and chronic temporomandibular disorder: a case–control study

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ABSTRACT

BACKGROUND: Temporomandibular disorders (TMDs) are a family of pain-related disorders associated with impaired function in the jaw, temporomandibular joint and muscles of mastication. Our objectives were to evaluate the association between chronic TMD and gastroesophageal reflux disease (GERD) and to determine whether mental disorders or undermined sleep mediates this association.

METHODS: We conducted a case–control study involving 1522 consecutive adult patients with chronic TMD and 1522 matched controls from 2 hospitals in China. All participants were aged between 18 and 70 years and were

recruited from July 2017 to April 2018. Chronic TMD was diagnosed by trained dentists using the criteria in the Orofacial Pain Prospective Evaluation and Risk Assessment Study. Trained gastroenterologists made blinded diagnoses of GERD according to the Montreal definition and classification (at least 2 d of mild symptoms, or 1 d of moderate or severe symptoms per week). We used validated questionnaires to evaluate psychological status and sleep quality.

RESULTS: Of the study participants, we identified 132 patients and 61 controls with GERD. Using conditional logistic regression analysis, we identified GERD

as a risk factor for TMD (odds ratio 2.74, 95% confidence interval 1.88 to 3.98). Mediation analyses identified that somatization, anxiety and undermined sleep moderately mediated the relation between TMD and GERD.

INTERPRETATION: Our study suggests that symptomatic GERD is associated with chronic, painful TMD, and somatization, anxiety and undermined sleep mediate this association to a certain extent. Due consideration should be given to the evaluation and management of gastrointestinal symptoms and mental disorders in the combined therapy for painful TMD.

Temporomandibular disorders (TMDs) are a set of craniofacial pain-related disorders associated with impaired function in the jaw, temporomandibular joint and muscles of mastication.¹ A 2015 clinical review found that pain was most frequently reported in both the muscles of mastication and the temporomandibular joint (myalgia with arthralgia in 73% of cases), followed by myalgia alone (23% of cases).² Pain associated with TMD is found in 13% of the Canadian population.³ Like other musculoskeletal disorders including chronic low back pain, fibromyalgia and headache, chronic painful TMD cannot be explained by physical conditions. The cause of TMD has changed substantially from a mechanistic origin to one that is multifactorial and biopsychosocial in nature.^{1,4}

Chronic TMD has been associated with somatization, anxiety, depression, parafunctional behaviours, jaw injury and other chronic

pain syndromes.^{1,2} Some authors have previously suggested a potential association between TMD and gastroesophageal reflux disease (GERD).⁵ Gastroesophageal reflux disease is diagnosed when reflux of stomach contents precipitates troublesome symptoms.⁶

Sufficient evidence supports the relation between GERD and mental disorders including somatization, anxiety and depression.^{7–9} Psychological factors and somatic symptoms are closely associated with onset of TMD and persistence.¹⁰ Mental disorders are either potential mediators connecting GERD and TMD or comorbidities caused by shared pathophysiological processes.⁵ Undermined sleep mediates the effect of stress on painful TMD.¹¹ Considering the association between GERD and undermined sleep,⁹ it is possible that undermined sleep is a mediator linking GERD with TMD. Current evidence of an association between TMD and GERD from a case–control study provides only descriptive

findings without estimation of the strength of association and consideration of confounding factors, apart from the limited number of participants in the study.⁵

The aims of this study were to evaluate the relation between chronic TMD and GERD in a larger group of patients, to evaluate the strength of association after adjusting for potential confounding factors and to assess whether mental disorders or undermined sleep mediates this association. The null hypotheses examined were that there is no relation between chronic TMD and GERD; and that somatization, anxiety, depression and undermined sleep do not mediate the association between TMD and GERD.

Methods

Reporting of this study defers to the checklist of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.¹²

Study design and participants

We conducted a case-control study involving patients aged 18–70 years who were diagnosed consecutively with chronic TMD and controls without chronic TMD. We recruited patients and controls from the Stomatological Hospital of the Fourth Military Medical University, Xi'an, Shaanxi, China (academic hospital in an urban setting) and the 188th Hospital of the Chinese People's Liberation Army, Chaozhou, Guangdong, China (nonacademic hospital in an urban setting) (details in Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181535/-/DC1). We enrolled participants from July 2017 to April 2018. Each participant signed an informed consent form.

Patients, including those who were referred for care for orofacial pain, were examined by 2 dentists (1 from each study site). The dentists were trained and calibrated at the Stomatological Hospital of the Fourth Military Medical University ahead of participant enrollment (Appendix 1). Chronic TMD was diagnosed using criteria from the Orofacial Pain Prospective Evaluation and Risk Assessment Study (OPPERA).⁴ Briefly, the inclusion criteria were frequently reported pain in the face, muscles of mastication, temples or temporomandibular joints in the last 6 months (more than 14 days in the last month and more than 4 days/month in the previous 5 months); pain in the facial regions defined by the dentists for more than 4 days during the past month; or pain in at least 3 muscles of mastication or at least 1 temporomandibular joint during maneuvering of the mandible or palpation of the muscles.⁴ The facial regions were defined by the dentists via palpating the temporalis, the preauricular region, the masseter muscle, the posterior mandibular region and the submandibular region bilaterally.⁴

We recruited control participants from patients seeking consultation for other dental diseases in the same hospital. One control participant was matched to each TMD case by age (within 2 yr) and sex. We randomly selected potential control participants using SPSS 22.0 software from a list that included age, sex, identification number and mobile phone number of patients who registered on the same day as the participants diagnosed with TMD. Potential participants were invited and were examined by the study dentists to determine if they were qualified for the

study. Inclusion criteria for the control participants were no orofacial pain during the last month and occurring fewer than 5 days/month in the previous 5 months; headaches occurring fewer than 5 days/month in the previous 3 months; pain in the dentist-defined orofacial regions occurring fewer than 5 days in the last month; diagnosed with no myalgia or arthralgia; no previous diagnosis of TMD; and no use of occlusal splint.⁴ Patients seeking general dental treatment for tooth erosion were excluded from the control cohort. Details of participant selection are described in Appendix 1.

Data collection

The 2 study dentists collected data on personal characteristics and potential confounding factors during the face-to-face interviews with the study participants. We collected data for age, sex, place of residence, education, marital status, height, weight, medical history, and consumption of cigarettes, alcohol, tea and coffee. We evaluated smoking status using questions proposed by the World Health Organization.¹³ Amount of alcohol consumption in the past year was asked and recorded. Participants were identified as non-drinkers, moderate drinkers or heavy drinkers based on the Chinese Dietary Guidelines.¹⁴ The frequency of consuming 1 cup of coffee or tea was asked and recorded according to the following categories (never or hardly ever, < 1 time/wk, 1–2 times/wk, 3–6 times/wk, 1 time/d, 2–3 times/d, 4–5 times/d and ≥ 6 times/d).¹⁵ We previously published the procedure for data collection.¹⁵

We also obtained information on oral behaviours involving the jaw over the previous month during the interview by asking 8 questions on the following items: gum chewing, biting hard objects, leaning with the hand on the jaw, cheek biting, chewing food on 1 side, clenching/grinding teeth during waking hours, clenching/grinding teeth when asleep and sleeping on the side.¹⁶ A dichotomous answer (yes/no) was required for each question, with “yes” indicating monthly or more frequently and “no” indicating less than monthly. The frequency of each oral behaviour was also noted. Those who were uncertain of the information were designated as “no.”

We employed validated questionnaires to identify patients with somatization, depression, anxiety and undermined sleep. All questionnaires were scored immediately after they were completed by the patient. A score of 10 or more on the 15-item Patient Health Questionnaire (PHQ-15),¹⁷ the Generalized Anxiety Disorder 7-item (GAD-7) scale¹⁸ and the 9-item Patient Health Questionnaire (PHQ-9)¹⁹ were used to identify patients with somatization, anxiety and depression, respectively. We used a score of 6 or more on the Pittsburgh Sleep Quality Index (PSQI) to identify patients with undermined sleep.²⁰ For the PHQ-15, we allowed as many as 5 missing items for the score to be considered valid; for example, if 5 items were missing, then the remaining 10 items were summed up, divided by 10, and multiplied by 15 to generate a score as though all 15 items had valid scores.²¹ For the GAD-7, the PHQ-9 and the PSQI, we allowed as many as 2 missing items for the score to be considered valid. The Cronbach α values for PHQ-15, GAD-7, PHQ-9 and PSQI were 0.94, 0.90, 0.86 and 0.92, respectively.

We used the GerdQ questionnaire to screen patients with GERD.²² Participants who reported regurgitation, heartburn,

nausea, epigastric pain, additional medication because of reflux symptoms or disturbed sleep resulting from reflux symptoms during the previous week were further examined by 2 trained gastroenterologists (1 from each study site). The gastroenterologists made a blinded diagnosis of GERD according to the Montreal definition and classification: at least 2 days of mild symptoms or 1 day of moderate or severe symptoms per week.⁶ The duration and frequency of symptoms were noted. We recorded how long and how often the participants had reflux symptoms.

Research team members (dentists, gastroenterologists and other investigators) were selected based on their discipline and were trained to diagnose or administer questionnaires as per the study protocol (Appendix 1).

Estimation of sample population size

We conducted a pilot study involving 72 participants-with and 72 participants without chronic TMD that estimated an odds ratio (OR) of 2.5 for TMD related to GERD. If 3.8% of the population in China had GERD²³ and 1 control was matched to 1 case, a sample size of 437 cases would provide 90% power (α 0.05).²⁴ Accordingly, we recruited 1522 cases for the present study to enable adjustment of confounding variables.

Statistical analysis

We performed Mann-Whitney *U* tests to analyze continuous variables and χ^2 tests to analyze categorical variables. We performed conditional logistic regression to evaluate the relation between TMD and GERD, conditioning on matched sets. We used multiple imputation to replace missing data (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181535/-/DC1). Multivariate analyses were adjusted for demographic characteristics (Appendix 2). Teeth clenching or grinding during sleep and during waking hours were also included as potential confounders in regression analyses because these 2 factors were associated with TMD in the univariate analyses and associated with GERD in previous research.¹⁵ We conducted sensitivity analyses using complete cases. We used goodness-of-fit tests to evaluate the calibration of every regression model.

Because GERD increases the likelihood of subsequent mental disorders and sleep disorders,⁹ and the latter contribute to the development of TMD,^{4,10} we assumed that mental disorders and undermined sleep were mediators for the association between GERD and TMD. Accordingly, we used mediation analysis to test the hypothesis that an antecedent variable *X* exerts its effects on a resultant variable *Y* via mediator variables. Mediation analysis may be conducted even if causality cannot be established because of the limitations of study design and data collection.²⁵ The method of mediation analysis in a case-control study has been published elsewhere.²⁶ The mediation proportions of somatization, anxiety, depression and undermined sleep on the association between GERD and TMD were identified by mediation analysis using the PROCESS Procedure, with 5000 bias-corrected bootstrap samples for confidence intervals.²⁷ To examine the mediation proportions of somatization, anxiety, depression and undermined sleep, we analyzed the scores of the questionnaires as continuous parameters. Details of mediation analyses are described in Appendix 2.

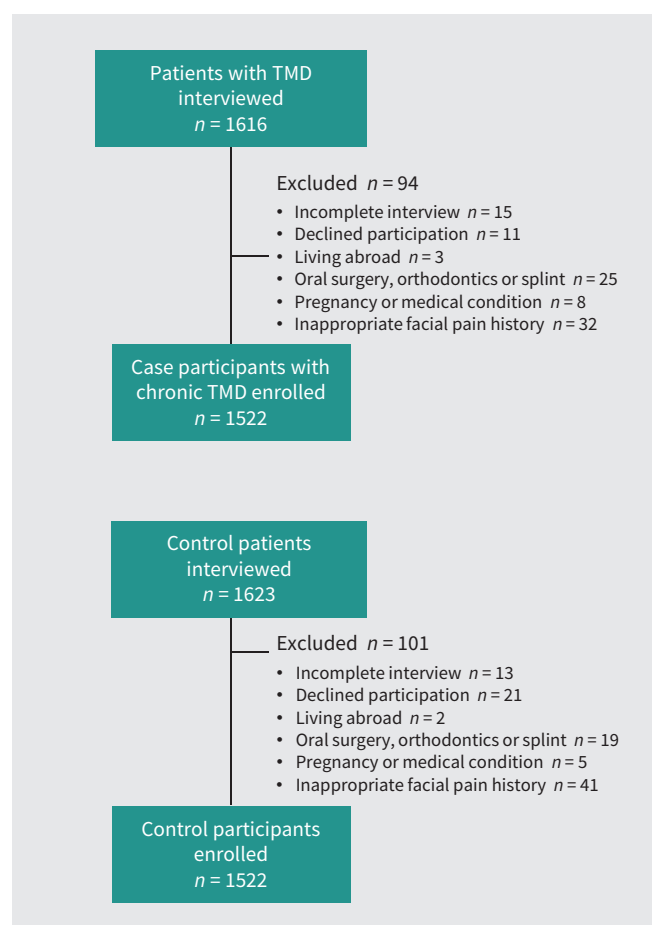


Figure 1: Flow charts for study enrollment of case participants and control participants. Note: TMD = temporomandibular disorder.

We used SPSS 22.0, PROCESS v2.16 and R 2.15 software for all analyses (2-sided α value 0.05).

Ethics approval

This study was approved by the Ethics committees of the Stomatological Hospital of the Fourth Military Medical University and the 188th Hospital of the Chinese People's Liberation Army.

Results

We initially considered 1616 consecutive patients with TMD and ultimately enrolled 1522 case participants (94.2%) with chronic TMD. Figure 1 shows the participant enrollment process for the study. We initially invited 1623 control participants and subsequently enrolled 1522 (93.8%).

Table 1 provides the main characteristics of the 3044 participants. Of all participants, women accounted for 68.9% (1048/1522). Among all participants with TMD, 487 (32.0%) had myalgia (pain in the muscles of mastication) alone, 181 (11.9%) had arthralgia (pain in the temporomandibular joint) alone, and the remaining (854, 56.1%) had both arthralgia and myalgia. Among the 201 participants with GERD, 31 case participants and 12 control participants were taking antacid medications before the start of the study. Twelve participants (5 case and 7 control

participants) did not know the duration of their reflux symptoms and we considered these patients to have a 5-year or shorter duration of symptoms. Information from the interviews was complete except for data about consumption of cigarettes by current smokers and body mass index (BMI; Supplementary

Table S1, Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181535/-/DC1). Because the completeness of all the questionnaires was examined by the dentists immediately following patient completion, there were no missing data on the questionnaires.

Table 1: Characteristics of study participants

Characteristic	No. (%) of participants with TMD (cases) <i>n</i> = 1522*	No. (%) of participants without TMD (controls) <i>n</i> = 1522*	<i>p</i> value
Age, median (IQR); yr	27 (22–38)	28 (23–39)	0.06
Sex			> 0.99
Male	474 (31.1)	474 (31.1)	
Female	1048 (68.9)	1048 (68.9)	
Residence			0.45
Urban	1192 (78.3)	1209 (79.4)	
Rural	330 (21.7)	313 (20.6)	
BMI, median (IQR); kg/m ²	20.8 (18.8–22.9)	21.4 (19.2–23.7)	< 0.001
BMI; kg/m ²			< 0.001
Underweight or normal weight (< 25)	1358 (89.9)	1283 (85.1)	
Overweight (25 to < 30)	138 (9.1)	207 (13.7)	
Obese (≥ 30)	15 (1.0)	18 (1.2)	
Marital status			0.1
Never married	785 (51.6)	745 (48.9)	
Married	709 (46.6)	757 (49.7)	
Divorced or widowed	28 (1.8)	20 (1.3)	
Education level (yr)			0.4
≤ 9	140 (9.2)	158 (10.4)	
> 9–12	257 (16.9)	271 (17.8)	
> 12	1125 (73.9)	1093 (71.8)	
Smoking status			0.7
Never	1291 (84.8)	1303 (85.6)	
Former	61 (4.0)	64 (4.2)	
Current	170 (11.2)	155 (10.2)	
Cigarettes smoked, median (IQR); no. cigarettes/d†	10 (5–20)	10 (6–20)	0.9
Alcohol consumption			0.7
None or moderate	1320 (86.7)	1327 (87.2)	
Heavy	202 (13.3)	195 (12.8)	
Tea consumption			< 0.001
None or less than weekly	983 (64.6)	849 (55.8)	
Weekly	367 (24.1)	472 (31.0)	
Daily	172 (11.3)	201 (13.2)	
Coffee consumption			0.003
None or less than weekly	1311 (86.1)	1243 (81.7)	
Weekly	179 (11.8)	241 (15.8)	
Daily	32 (2.1)	38 (2.5)	

Note: BMI = body mass index, IQR = interquartile range, TMD = temporomandibular disorder.
 *Unless stated otherwise.
 †Consumption by current smokers.

With adjustment of potential confounders, we identified symptomatic GERD as a risk factor for TMD (Table 2). We found that participants with a longer history of GERD symptoms had a slightly higher OR for TMD than those with a shorter duration (Table 2). Sensitivity analyses showed similar results (Supplementary Table S2, Appendix 3). Observed and expected data matched well in the goodness-of-fit tests.

Mediation analyses supported that somatization, anxiety and undermined sleep were mediators in the association between TMD and GERD (Table 3). Somatization, anxiety and undermined sleep mediated 14%, 11% and 10% of the association between TMD and GERD, respectively (Figure 2). Depression was not a mediator of the association.

Interpretation

We found that chronic TMD is associated with symptomatic GERD. Hence, we rejected our first null hypothesis. Somatization, anxiety and undermined sleep but not depression are significant mediators in the association between TMD and GERD. Hence, our second null hypothesis can only be partially rejected.

Although there was evidence from a previous case-control study linking TMD and GERD, these findings were descriptive only.⁵ By evaluating the strength of association and showing

potential mediators in the pathway, our findings add key knowledge to the literature and should prompt further research on the mechanisms.

We note that the positive mediation associations reported in our study are consistent with but could not prove causation. The interactions between chronic musculoskeletal diseases, gastrointestinal diseases, mental disorders and sleep problems are complicated. There is evidence to support the bidirectional nature of the associations among these comorbidities,²⁸ and patients may be stuck in a cycle in which undermined sleep, somatization and anxiety exacerbate the pain, with the pain also leading to sleep problems and mental disorders.²⁸ We found no association between depression and TMD, which is contrary to the studies involving populations in Western countries,^{10,29} but is in line with studies involving populations in Asia.^{5,30} This finding may be explained partially by the more reserved nature of Asian populations when responding to questions about depression compared with Western populations.⁵ The associations among mental disorders, GERD and TMD may also be underestimated for the same reason.

The finding that the mediation association does not make up 100% of the whole association suggests the existence of other mechanisms linking GERD with TMD. The association between

Table 2: Association between gastroesophageal reflux disease and chronic temporomandibular disorder using conditional logistic regression, with missing data imputed by multiple imputation

Variable	No. (%) of participants with TMD (cases) <i>n</i> = 1522*	No. (%) of participants without TMD (controls) <i>n</i> = 1522*	Univariable analysis	Multivariable analysis†
			OR (95% CI)	OR (95% CI)
GERD	132 (8.7)	61 (3.5)	2.61 (1.88 to 3.63)	2.74 (1.88 to 3.98)
GERD, duration ≤ 5 yr	61 (4.0)	25 (1.6)	2.60 (1.62 to 4.19)	2.53 (1.47 to 4.35)
GERD, duration > 5 yr	71 (4.7)	28 (1.8)	2.62 (1.69 to 4.07)	2.90 (1.80 to 4.69)

Note: CI = confidence interval, GERD = gastroesophageal reflux disease, OR = odds ratio, TMD = temporomandibular disorder.
*Adjusted for age, sex, residence, body mass index, education, marital status, smoking status, alcohol consumption, tea consumption, coffee consumption, teeth clenching or grinding during sleep and teeth clenching or grinding during waking hours.

Table 3: Mediation analysis* of the association between gastroesophageal reflux disease and temporomandibular disorder

Mediator	No. (%) of participants with TMD (cases) <i>n</i> = 1522	No. (%) of participants without TMD (controls) <i>n</i> = 1522	Indirect effect (95% CI)	Direct effect (95% CI)	Coefficient (95% CI)
Somatization	549 (36.1)	301 (19.8)	0.13 (0.07 to 0.20)	0.79 (0.44 to 1.13)	0.059 (0.045 to 0.072)
Anxiety	135 (8.9)	80 (5.3)	0.10 (0.06 to 0.17)	0.81 (0.46 to 1.15)	0.052 (0.031 to 0.073)
Depression	217 (14.3)	188 (12.4)	0.03 (−0.01 to 0.08)	0.86 (0.52 to 1.21)	0.014 (−0.003 to 0.031)
Undermined sleep	663 (43.6)	535 (35.2)	0.09 (0.05 to 0.15)	0.81 (0.47 to 1.16)	0.047 (0.025 to 0.070)

Note: CI = confidence interval, TMD = temporomandibular disorder.
*Adjusted for age, sex, residence, body mass index, education, marital status, smoking status, alcohol consumption, tea consumption, coffee consumption, teeth clenching or grinding during sleep and teeth clenching or grinding during waking hours.

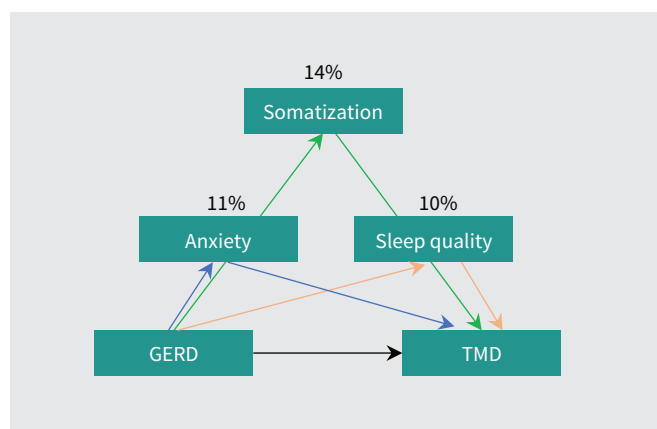


Figure 2: Mediation models for the association between temporomandibular disorder (TMD) and gastroesophageal reflux disease (GERD). Somatization, anxiety and undermined sleep mediated 14%, 11% and 10% of the association between TMD and GERD, respectively. Arrows represent the possible direct and indirect effects of mediation.

GERD and teeth grinding or clenching has been reported previously.^{15,31–34} Esophageal acidification not only increases rhythmic masticatory muscle activity, along with teeth clenching or grinding during sleep,³⁵ but also increases masseter muscle activities during waking hours.³⁶ Muscular pain in patients with TMD could be associated with muscle fatigue caused by these GERD-related oral behaviours.⁵

We did not design our study to evaluate the temporal associations among these conditions; however, this issue is still intriguing. Further longitudinal studies may advance knowledge of the underlying mechanisms. For example, esophageal acidification may sensitize the central nervous system to sensory and pain pathways, resulting in declined pain thresholds in the other organs. Temporomandibular disorders have been associated with gastrointestinal disorders, especially irritable bowel syndrome (IBS).^{2,37} Comorbidity of GERD and IBS is common in the general population.³⁸ Although we did not evaluate these comorbidities systematically, the finding of an association between GERD and TMD is consistent with the literature. Future studies evaluating such comorbidities should be informative.

Chronic pain is a considerable stress on the Canadian economy, with an estimated annual economic cost of about 43 billion dollars in health care and lost productivity.³⁹ The Canadian Pain Task Force was established in 2019 to advance solutions for the management of chronic pain.⁴⁰ Recent evidence supports the effectiveness and cost-effectiveness of multidisciplinary pain management with psychotherapies.⁴¹ Recent clinical guidelines highlight the importance of brain–gut psychotherapies and multidisciplinary rehabilitation in the management of chronic pain⁴² and chronic gastrointestinal diseases, including GERD and IBS.⁴³

Limitations

We completed 1:1 matching between case and control participants, with matching on age and sex. Several principles have been developed in the selection of control participants for case–control studies.^{44,45} Adherence to these principles can reduce bias. However, it is difficult to achieve full compliance with these

principles just as perfect experimental conditions are unlikely to be achieved in a laboratory. Therefore, tolerance of a small deviation from the principles is usually the norm for investigating exposure–disease associations.⁴⁴ Although the matching protocol may not be perfect, useful information can still be generated from our analyses.

Because participants were recruited from hospitals, selection bias is a concern, and the results may not represent the general population conclusively. To enhance the generalizability of the findings, we recruited participants from 2 hospitals at disparate levels (academic tertiary hospital v. nonacademic secondary hospital) from diverse areas of China. If exposure extents were different between hospital controls and the population that generated the cases, selection bias would occur.⁴⁶ Therefore, we excluded patients seeking treatment for tooth erosion related to GERD from the control cohort.⁴⁵ The large patient cohort also contributed to the reduction of selection bias.

A cross-sectional study published in 2016 found that the prevalence of GERD in the adult population in China was 3.8%.²³ When we applied an indirect standardization of rates, the standardized proportion of patients with GERD (4.0%) among the 3044 participants was close to the reported prevalence in the Chinese population. Some participants failed to provide data on BMI because they could not recall their weight or height. Accordingly, we conducted multiple imputation under the assumption of “missing at random” (Appendix 2). The likelihood of bias is minimal because there was no distinct difference between the primary and sensitivity analyses.

Another limitation of our study is that a temporal relation cannot be established because of the study design. In addition, there may be shared risk factors and unmeasured confounders that we did not evaluate in the present study.

Conclusion

We found that symptomatic GERD is associated with painful chronic TMD, and somatization, anxiety and undermined sleep mediate this association moderately. Physicians and patients may overlook the association between chronic musculoskeletal diseases and gastrointestinal symptoms. Patients with both chronic TMD and reflux symptoms may be underdiagnosed, resulting in deferred effective treatment and a prolonged disease course.

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