

Subtypes of acute and chronic temporomandibular disorders: Their relation to psychological and sleep impairments

Ye Cao^{1,2,3,4,5} | Adrian Ujin Yap^{1,6,7,8} | Jie Lei^{1,3,4,5} | Min-Juan Zhang^{1,3,4,5} | Kai-Yuan Fu^{1,3,4,5} 

¹Center for TMD & Orofacial Pain, Peking University School & Hospital of Stomatology, Beijing, China

²Department of Prosthodontics, Peking University School & Hospital of Stomatology, Beijing, China

³National Clinical Research Center for Oral Diseases, Beijing, China

⁴National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing, China

⁵Beijing Key Laboratory of Digital Stomatology, Beijing, China

⁶Department of Dentistry, Ng Teng Fong General Hospital, National University Health System, Singapore, Singapore

⁷Faculty of Dentistry, National University of Singapore, Singapore, Singapore

⁸Duke-NUS Medical School, National Dental Research Institute Singapore, National Dental Centre, SingHealth, Singapore, Singapore

Correspondence

Prof. Kai-Yuan Fu, Center for TMD & Orofacial Pain and Department of Oral & Maxillofacial Radiology, Peking University School & Hospital of Stomatology, Beijing, China. Email: kqkyfu@bjmu.edu.cn

Funding information

This work was supported by the Capital Clinical Research Project [Z141107002514157] from the Beijing Municipal Science & Technology Commission and the Capital Health Research and Development of Special Fund Program [2020-4-4106] from Beijing Municipal Health Commission.

Abstract

Objectives: To determine the differences in psychological states and sleep quality in patients with various temporomandibular disorder (TMD) subtypes, and to ascertain the relationships between TMD duration with psychological and sleep impairments.

Methods: A total of 830 TMD patients were recruited categorized into pain-related (PT), intra-articular (IT), and combined (CT) TMD groups. Each group was further divided into acute and chronic subtypes. The Depression, Anxiety, and Stress Scales-21 (DASS-21), and Pittsburgh Sleep Quality Index (PSQI) were used to assess emotional states and sleep problems.

Results: Although chronic TMDs generally had higher levels of anxiety, depression, stress, and sleep impairments than acute TMDs, significant differences were only observed for the PT group. Ranking of the mean depression, anxiety, and stress scores was as follows: acute TMDs: CT > PT > IT; chronic TMDs: PT > CT > IT. For both acute and chronic TMDs, the ranking of mean PSQI global and component scores was PT ≥ CT ≥ IT. Logistic regression analyses indicated that stress (ORs = 4.40) and depression (ORs = 2.82) increased the risks of chronic pain-related TMDs ($p < .05$).

Conclusions: Chronic pain-related TMDs are associated with high levels of psychological distress and poorer sleep, while chronic intra-articular TMDs are not. Stress and depression increased the probability of chronic pain-related TMDs.

KEYWORDS

DASS-21, DC/TMD, PSQI index, sleep disturbance, temporomandibular disorders

1 | INTRODUCTION

Pain has been defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (Loeser & Treede, 2008). Acute pain, which functions as a warning of physiological nociception, is typically caused by a specific disease or injury. Pain is generally regarded as chronic when it lasts or recurs for more than 3 months (Nicholas et al., 2019). However, chronic pain is not merely long-term acute pain. It involves a different pathological process and is currently treated as an independent disease (Nicholas et al., 2019).

Temporomandibular disorders (TMDs) are the most common cause of non-dental orofacial pain and refer to a group of conditions characterized primarily by dysfunction of the masticatory muscles and temporomandibular joints and/or pain. After about ten decades of exploration, the etiopathology of TMDs had shifted from biomechanical theories to the biopsychosocial model of illness, in which several predisposing psychological (emotional, temperamental, and constitutional) factors had been identified (Greene & Laskin, 2000).

Chronic TMDs occur in a subgroup of patients who do not respond to previous treatment. The transformation rate from acute to chronic TMDs is about 30 to 40% (Ohrbach & Dworkin, 1998; Rammelsberg et al., 2003). Its transition mechanism remains unclear. Psychological distress (e.g., somatization, catastrophizing, and depression), poor sleep, and genetic polymorphisms related to generalized alterations in pain processing were more commonly associated with chronic TMDs development and persistence (Maisa Soares & Rizzatti-Barbosa, 2015). Furthermore, acute and chronic TMDs have different impacts on patients, and chronic TMDs linked to higher levels of depression, somatization, impaired quality of life, and sleep disturbance (Celic et al., 2011; Ismail et al., 2016; Maisa Soares & Rizzatti-Barbosa, 2015; Shueb et al., 2015; Slade et al., 2013, 2016). However, very few existing studies had involved large TMD patient samples, and even fewer had differentiated acute and chronic TMDs in terms of TMD subtypes (Jasim et al., 2014; Shueb et al., 2015). Moreover, the emotional states of anxiety and stress, which are separate psychological constructs from depression, are still not widely explored.

The objectives of the study were thus to ascertain the associations between acute and chronic pain-related/intra-articular TMDs and the psychological constructs of depression, anxiety, and stress as well as sleep quality variables for both acute and chronic TMDs. In addition, the influence of TMD illness duration on psychological symptoms and impaired sleep was verified. The null hypothesis was the following: The associations between psychological states/sleep quality and TMDs were not dependent on acute and chronic TMD subtypes or TMD duration.

2 | MATERIALS AND METHODS

2.1 | Study design

Approval for this cross-sectional study was attained from the Biomedical Institutional Review Board of Peking University

(PKUSSIRB-201732009). Between May 2019 and December 2019, some 907 consecutive patients (aged 11 to 86 years old) who attended the Center for TMDs and Orofacial Pain, Peking University School and Hospital of Stomatology, were invited to take part in the study. All subjects underwent a standardized history taking, examination, and diagnosis by a single-trained TMD specialist based on the diagnostic criteria (Schiffman et al., 2014) for TMDs to ensure diagnostic consistency. Patients taking painkillers, anxiolytics or central nervous system drugs, history of local trauma or operations, diseases that may affect TMJ, muscles, metabolisms, and other systematic diseases including psychiatrics, and finally, the patients with missing recalls were excluded. The subjects were directed to complete a questionnaire consisting of socio-demographic information, medical and TMD history, the Depression, Anxiety, and Stress Scales-21 (DASS-21), and the Pittsburgh Sleep Quality Index (PSQI).

2.2 | TMD subtypes

TMDs were classified into (a) pain-related TMDs that include myalgia, arthralgia or headache attributed to TMDs, and (b) intra-articular TMDs that encompass disk displacement with reduction, disk displacement with reduction with/without intermittent locking, disk displacement without reduction with/without limited opening, degenerative joint disease, and subluxation. The subjects were subsequently classified into three groups based on their primary symptoms, namely, pain-related TMDs (PT), intra-articular TMDs (IT), and combined TMDs (CT). Each group was further subdivided into acute (≤ 3 months) and chronic (> 3 months) according to the duration of TMD symptoms.

2.3 | Psychological and sleep disturbances

Psychological states, specifically depression, anxiety, and stress, were assessed with the validated Chinese version of the DASS-21 (Osman et al., 2012; Wang et al., 2016). It consists of 21 items with seven items dedicated to each domain. Each item response is scored on a four-point Likert scale with 0 = did not apply to me at all to 3 = applied to me very much, or most of the time over the past week. Total and domain sum scores are subsequently calculated. The cut-points for the various severity ratings (i.e., no to extremely severe) are presented in the DASS manual (Lovibond & Lovibond, 1995).

Sleep characteristics were established with the Chinese version of PSQI that appraises sleep quality over a month (Tsai et al., 2005). It involves 19 items with seven components, specifically subjective sleep quality, latency, duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The majority of items are scored on a four-point Likert scale. A global PSQI score of ≥ 10 is the cutoff for poor sleep quality (Tsai et al., 2005).



TABLE 1 Descriptive characteristics of the subjects

Demographics	pain-related TMD N = 112		intra-articular joint TMD N = 340		Combined TMD N = 378		Total N = 830		p
	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic	
N (%)	68 (60.71)	44 (39.29)	111 (32.65)	229 (67.35)	199 (52.65)	179 (47.35)	378 (45.54)	452 (54.46)	
Age (years) (Mean ± SD)	40.58 ± 16.60a	40.73 ± 18.53	27.11 ± 12.17b	30.14 ± 14.99	32.57 ± 15.30c	34.25 ± 15.65	31.42 ± 14.95	29.12 ± 13.84	<.01*
Male N (%)	26 (38.24)	7 (15.91)	25 (22.52)	59 (25.76)	32 (16.08)	25 (13.97)	83 (22.96)	91 (20.13)	
Female N (%)	42 (61.76)	37 (84.09)	86 (77.48)	170 (74.24)	167 (83.92)	154 (80.03)	295 (78.04)	361 (79.87)	
Duration (months) (Mean ± SD)	7.30 ± 12.34a	1.22 ± 0.95	24.97 ± 37.74b	1.48 ± 0.91	9.53 ± 18.37a	18.47 ± 23.68	15.55 ± 28.61	27.36 ± 34.60	<.001*

Note: Results of one-way ANOVA and post hoc Tukey's test*. The same letter indicates no significant difference while different letters indicate significant differences between the groups ($p < .05$).

TABLE 2 Mean DASS-21 scores for the PT, IT, and CT groups and the comparisons between acute and chronic TMD subgroups

	Pain-related TMD (PT)		Intra-articular TMD (IT)		Combined TMD (CT)		Post hoc comparisons	
	Acute	Chronic	Acute	Chronic	Acute	Chronic	acute	chronic
D	5.74 ± 8.38	15.32 ± 12.80	4.86 ± 8.02	5.78 ± 7.52	7.42 ± 9.52	8.06 ± 9.90	.520	CT > IT [*] PT > IT ^{**} , PT > CT ^{**} , CT > IT [*]
A	7.62 ± 8.11	13.86 ± 10.86	7.50 ± 7.96	8.46 ± 8.17	8.92 ± 8.26	9.40 ± 8.56	.586	PT > IT ^{**} , PT > CT ^{**}
S	8.88 ± 9.76	17.77 ± 13.41	8.77 ± 10.18	9.89 ± 9.52	11.66 ± 10.71	11.63 ± 10.48	.980	PT > IT ^{**} , PT > CT ^{**}

Note: Differences between acute and chronic groups were compared by independent samples t test. Differences between the three subgroups for acute and chronic states were conducted by one-way ANOVA and post hoc Tukey's test.

* $p < .05$.

** $p < .01$.

TABLE 3 Mean PSQI component and global scores for the three TMD groups and the comparisons between acute and chronic states

	pain-related TMD (PT)		intra-articular TMD (IT)		combined TMD (CT)		Post hoc comparisons	
	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Global score	7.54 ± 4.22	9.43 ± 4.74	.030*	5.93 ± 3.17	5.86	6.63 ± 3.62	.961	PT > IT*, PT > CT**
Subjective sleep quality	1.29 ± 0.87	1.52 ± 0.76	.156	1.09 ± 0.71	.329	1.12 ± 0.75	.525	PT > IT*, PT > CT**
Sleep latency	1.16 ± 0.99	1.48 ± 1.07	.112	1.02 ± 0.96	.973	1.17 ± 1.00	.125	PT > IT*
Sleep duration	1.24 ± 0.83	1.45 ± 1.02	.216	0.89 ± 0.85	.300	1.08 ± 0.88	.597	PT > IT*, PT > CT**
Habitual sleep efficiency	0.84 ± 1.18	0.80 ± 1.11	.848	0.37 ± 0.79	.615	0.52 ± 0.96	.581	PT > IT*, PT > CT**
Sleep disturbances	1.19 ± 0.55	1.36 ± 0.61	.126	0.98 ± 0.45	.057	1.07 ± 0.59	.976	PT > IT*, PT > CT**
Use of sleep medication	0.31 ± 0.82	0.93 ± 1.30	.002*	0.11 ± 0.45	.040*	0.18 ± 0.61	.312	PT > IT*, PT > CT**
Daytime dysfunction	1.51 ± 0.95	1.89 ± 1.08	.059	1.47 ± 1.00	.646	1.49 ± 0.97	.833	PT > IT*, PT > CT**

Note: Differences between acute and chronic groups were compared by independent samples t test. Differences between the three subgroups for acute and chronic states were conducted by one-way ANOVA and post hoc Tukey's test.

**p* < .05.

***p* < .01.

2.4 | Statistical analyses

Statistical analyses were carried out using the Statistical Package for Social Sciences version 28 (IBM Corporation, Armonk, NY, USA) with the significance level set at 0.05. Psychological and sleep data were examined with P-P plots and found to be normally distributed. Numerical variables were examined with independent samples *t* test and one-way ANOVA/post hoc Tukey's test. Pearson's correlation was utilized to ascertain the relationships between duration of TMDs and depression, anxiety, stress, and global PSQI scores for the three TMD groups. Strength of correlations was classified according to Dancey and Reidy as follows: weak (*r_s* = 0.1–0.3), moderate (*r_s* = 0.4–0.6), or strong (*r_s* = 0.7–0.9) (Dancey & Reidy, 2017). Stepwise logistic regression analysis was used to explore the independent associations between acute/chronic TMD subgroups, psychological states, and sleep quality.

3 | RESULTS

3.1 | Descriptive statistics

Of the 907 patients, a total of 830 consented to and qualified for the study, and their distribution was shown in Table 1. Based on the type of TMDs, the CT group presented an almost equal distribution of acute and chronic cases, while the PT and IT groups had more acute (60.71%) and chronic (67.35%) TMDs, respectively. With regard to age, the mean age of the patients was 31.42 ± 14.95 years. The PT group (40.58 ± 16.60 years) was significantly older than the CT group (32.57 ± 15.30 years), which in turn was significantly older than the IT group (27.11 ± 12.17 years). Concerning sex distribution, the proportion of females was generally more than twofolds that of males except for acute painful TMDs. For both chronic PT and CT groups, the proportion of females was about five times more than males. As regards TMD duration, the mean symptom duration for the IT group (24.97 ± 37.74 months) was significantly longer than for both PT and CT groups.

3.2 | Psychological distress

The mean DASS-21 scores for the three TMD subgroups and the results of intergroup statistical comparisons are presented in Table 2. For acute TMDs, mean depression scores were 5.74 ± 8.38, 4.86 ± 8.02, and 7.42 ± 9.52 for the PT, IT, and CT groups, respectively. Mean anxiety scores were 7.62 ± 8.11 for the PT group, 7.50 ± 7.96 for the IT group, and 8.92 ± 8.26 for the CT group. Mean stress scores were 8.88 ± 9.76, 8.77 ± 10.18, and 11.66 ± 10.71 for patients with PT, IT, and CT accordingly. When acute TMDs were compared, the ranking of mean depression, anxiety, and stress scores was CT > PT > IT. No significant differences in scores were noted apart from depression scores between CT and IT groups.

For chronic TMD, mean depression scores were 15.32 ± 12.80 for the PT group, 5.78 ± 7.52 for the IT group, and 8.06 ± 9.90 for the CT group. The mean anxiety scores were 13.86 ± 10.86 , 8.46 ± 8.17 , and 9.40 ± 8.56 , while mean stress scores were 17.77 ± 13.41 , 9.89 ± 9.52 , and 11.63 ± 10.48 for the PT, IT, and CT groups correspondingly. Although mean depression, anxiety, and stress scores were generally greater in subjects with chronic TMDs, differences were only significant for the PT group ($p \leq .001$). For chronic TMDs, the ranking of mean scores for the three psychological states was similar and as follows: PT > CT > IT. Significant differences in depression scores were observed between all three TMD groups. However, anxiety and stress scores were significantly different between the PT and CT/IT groups ($p \leq .001$).

3.3 | Sleep impairment

The mean PSQI scores for the various TMD groups and intergroup statistical comparisons are displayed in Table 3. For acute TMDs, mean global scores for the PT, IT, and CT groups were 7.54 ± 4.22 , 6.14 ± 3.61 , and 6.61 ± 3.61 . Ranking of mean PSQI component scores was similar for all sleep variables and was as follows: PT \geq CT \geq IT. Significant differences in "habitual sleep efficiency" and "sleep disturbances" scores were noted among the three TMD groups ($p < .01$). The PT group had significantly higher "habitual sleep efficiency" scores than the IT and CT groups ($p < .01$). With regard to "sleep disturbances," the PT and CT groups reported significantly higher scores than the IT group.

For chronic TMDs, mean global scores were 9.43 ± 4.74 , 5.93 ± 3.17 , and 6.63 ± 3.62 for the PT, IT, and CT groups, respectively. Ranking of mean PSQI component scores was PT \geq CT \geq IT for all sleep variables. Global scores between acute and chronic TMDs were only significant for the PT group. The only other significant difference observed between acute and chronic TMDs was for "use of sleep medication" for the PT and IT groups ($p < .05$). When comparing chronic TMDs, significant differences in global and all component scores were observed between the three TMD groups. The PT group exhibited significantly higher global PSQI scores than the CT and IT groups ($p < .01$). Aside from "sleep latency" and "habitual sleep efficiency," the PT group generally had significantly higher scores than the IT and CT groups for all sleep components ($p < .05$). However, the component scores between the IT and CT groups were insignificant (Table 3).

3.4 | Correlations and logistic regression

The correlations between TMD duration and depression, anxiety, stress and global PSQI scores were significant and positive for the PT group (Table 4). However, the strength of correlations was weak with r_s ranging from 0.20 to 0.34. A weak significant correlation was also noted between TMD duration and anxiety for the CT group

($r_s = 0.11$). For the IT and CT groups, all other correlations were insignificant. Stepwise logistic regression analysis indicated that gender (ORs = 3.36), depression (ORs = 2.82), and stress (ORs = 4.40) increased the likelihood of chronic pain-related TMDs ($p < .05$) (Table 5). Although chronic intra-articular and combined TMDs were significantly associated with age, the odds ratios were less than 1.0 (i.e., 0.91 and 0.99 respectively).

4 | DISCUSSION

Our findings revealed that the associations between TMDs and psychological states as well as sleep impairments were dependent on TMD subtypes and duration. As such the null hypothesis was rejected.

The present study used the DC/TMD protocol and diagnostic algorithms due to its better validity when compared to the RDC/TMD (Schiffman et al., 2014). The DASS-21 is the short-form version of the original DASS that consists of 42 items. It excludes common somatic and general distress contents from the depression measure but is still capable of differentiating anxiety from depression and stress. The reduced number of items translates to substantial time saving and greater subject acceptance (Henry & Crawford, 2005; Osman et al., 2012). Validation of Chinese version of the DASS-21 has been confirmed (Wang et al., 2016). The PSQI had been used to categorize sleep quality into either good or poor in other TMD studies (Tsai et al., 2005). Despite the high occurrence of TMDs in population studies, only 3.6%–7.0% of TMD patients require treatment with pain as the most common reason for treatment-seeking (Agerberg & Inkapool, 1990; Gesch et al., 2004; Goncalves et al., 2010; Kino et al., 2005; Pedroni et al., 2003). The prevalence of painful TMDs was reported to range from 4.2% to 7.2% and can negatively impact the individual's daily activities, psychosocial functioning, and quality of life (Graue et al., 2016; Nilsson et al., 2005). In our study, about 60% of the TMD patients presented with a diagnosis of painful TMDs. However, three-quarters of them had both pain-related and intra-articular TMDs. This was consistent with other similar researches (Kino et al., 2005; Lei et al., 2015). In the present study, higher ratios of 5.5 females:1 male were noted for chronic painful TMDs (i.e., PT and CT), while lower ratios of 1.6:1 were attained for acute pain-related TMDs. The latter was supported by the results of logistic regression that indicated female gender as a risk factor for chronic pain-related TMDs. The gender difference may be attributed in part to the dissimilarity in pain prognosis with females having more persistent pain than males whose conditions tend to resolve more quickly (Slade et al., 2016). The age distribution of patients suggested that pain-related TMDs tend to affect middle-aged persons whereas intra-articular TMDs were associated with youths. The same inclinations were also reported in past studies (Fillingim et al., 2013; Kino et al., 2005).

This study allowed for the comparison of psychological states and sleep quality between acute and chronic TMD subtypes.

Our findings corroborated other studies indicating the impact of pain-related TMDs on psychological distress and sleep quality among TMD samples (Fillingim et al., 2013; Lei et al., 2015; Poveda-Roda et al., 2012; Rener-Sitar et al., 2016). Pain is thus the key factor for higher levels of psychological distress and poorer sleep in TMD patients, while intra-articular symptoms had nominal effects. This can be explained by central sensitization (the feature of chronic pain) that is triggered by increased nociceptive inputs caused by injury or inflammation and is an outcome of physiological plasticity and long-lasting changes in the central nervous system (Kuner, 2010; Latremoliere & Woolf, 2009). Alternatively, unlike the possibility of pain chronification, most of the intra-articular symptoms are self-limiting and effects on oral functions are alleviated progressively.

On the other hand, psychological distress and sleep disturbances have been shown to impact pain chronification (Blackburn-Munro & Blackburn-Munro, 2001; Linton, 2000). More attention should thus be paid to the psychological well-being of patients with chronic pain-related TMDs. The severity of depression, anxiety, and stress generally increased with TMD duration. The correlation between TMD duration and psychological distress was, however, weak (Table 5). Nonetheless, the probability of chronic pain-related TMDs was found to be increased by depression and stress. Anxiety was also reported to play a significant role in TMDs in other studies (Kindler et al., 2012; Reiter et al., 2015). The incongruence between studies may be explained by the lack of differentiation between acute and chronic TMDs as well as pain-related and intra-articular TMDs. Centralized pain with widespread tenderness, sleep and psychological disturbances are often present in chronic pain conditions like fibromyalgia, chronic fatigue syndrome, and TMDs. Previous studies had indicated that sensory and emotion amplified pain appear to be more influenced by the affective component of pain (Diatchenko et al., 2006; Harper et al., 2016). In addition, other psychosocial factors have also been implicated as potential risk factors for the development of painful TMDs (Fillingim et al., 2013; Galli et al., 2010; Maisa Soares & Rizzatti-Barbosa, 2015). An interesting finding from the present work was the stronger correlation between the duration of TMDs and emotional/sleep disturbance for the PT group when compared to the other groups. It is plausible that during the process of pain chronification, changes in other functions occur. The

interactions between pain chronification and biopsychosocial risk factors need to be further explored in TMD patients.

In our present study, painful TMDs (i.e., PT and CT groups) were more often acute as compared to the IT group where it was largely chronic. This suggests that patients with pain-related TMDs tended to seek treatment earlier (Nilsson & Willman, 2016). Pain duration, pain intensity, and pain frequency played important roles in treatment-seeking behaviors (Macfarlane et al., 2003; Rollman et al., 2012). The significantly higher emotional distress noted in the chronic PT group was not observed with the chronic CT group, although both groups had painful TMDs. This may be explained in part by the possible attenuation effect of intra-articular symptoms in CT group as pain is no longer the only symptom. Another possible explanation could be the cause of pain. In the PT group, most of the pain originated from masticatory muscles (muscle pain 36/112; joint pain 69/112; muscle and joint pain 7/112), while in the CT group, joint pain formed the majority (muscle pain 19/378; joint pain 320/378; muscle and joint pain 39/378). Some researchers had reported on the different pain features and psychosocial features of myofascial and joint pain (Bertoli et al., 2007; McCreary et al., 1991; Reissmann et al., 2008).

The cross-sectional design and the use of self-reported instruments are limitations of this study. With the cross-sectional design, the causal relations between psychological/sleep impairments and chronification of TMDs cannot be established. The DASS-21 and PSQI are self-reported instruments and are subject to various biases. Future work should include repeating this study in the general population and at multiple centers. A longitudinal design should also be considered to identify the causality of psychological/sleep factors and TMDs.

5 | CONCLUSION

The differences in psychological states and sleep quality in patients with various subtypes of acute and chronic TMDs were determined, and the relationships between TMD duration, psychological, and sleep impairments were established in this study. Patients with chronic pain-related TMDs, but not intra-articular TMDs, reported higher levels of psychological distress and poorer sleep quality.

TABLE 4 Correlations between duration of TMDs and DASS-21/global PSQI scores

	PT		IT		CT	
	r_s	<i>p</i> value	r_s	<i>p</i> value	r_s	<i>p</i> value
Duration × Depression	0.341**	<.001	0.015	.784	0.063	.225
Duration × Anxiety	0.315**	.001	0.022	.682	0.113*	.027
Duration × Stress	0.296**	.002	0.004	.936	0.062	.228
Duration × PSQI	0.203*	.032	-0.018	.745	0.091	.076

Note: Results of Pearson's correlation.

*Indicates significant correlation at $p < .05$.

**Indicates significant correlation at $p < .01$.



TABLE 5 Variables and risk indicators for chronic TMDs

	PT		IT		CT	
	ORs (95% CI)	p	ORs (95% CI)	p	ORs (95% CI)	p
Gender	3.36 (1.15–9.90)	.027*	0.83 (0.48–1.45)	.528	1.25 (0.70–2.24)	.455
Age	1.00 (0.97–1.03)	.866	0.91 (0.95–0.99)	.002*	0.99 (0.97–1.00)	.026*
Depression	2.82 (0.96–8.28)	.049*	1.20 (0.50–2.89)	.685	1.36 (0.82–2.25)	.237
Anxiety	1.24 (0.40–3.88)	.713	1.32 (0.80–2.19)	.281	1.29 (0.75–2.23)	.352
Stress	4.40 (1.32–14.63)	.016*	0.76 (0.37–1.58)	.461	0.58 (0.29–1.15)	.115
PSQI	1.45 (0.53–3.98)	.466	0.75 (0.39–1.46)	.403	1.42 (0.81–2.50)	.224

Note: Results of Logistic regression.

Abbreviations: CI, confidence interval; OR, odds ratio.

*Significant correlation at $p < .05$.

Among the various factors analyzed, stress and depression were significantly associated with chronic pain-related TMDs.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTION

Ye Cao: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing-original draft. **Adrian Yap:** Conceptualization; Methodology; Supervision; Validation; Visualization; Writing-original draft. **Jie Lei:** Data curation; Formal analysis; Investigation; Methodology. **Min-Juan Zhang:** Data curation; Formal analysis; Investigation; Methodology. **Kai-Yuan Fu:** Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing-review & editing.

INFORMED CONSENT

The authors declare that an informed consent was obtained from patients and that the study was performed in accordance with the Declaration of Helsinki.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/odi.13692>.

ORCID

Kai-Yuan Fu  <https://orcid.org/0000-0001-7049-9888>

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How to cite this article: Cao Y, Yap AU, Lei J, Zhang M-J, Fu K-Y. Subtypes of acute and chronic temporomandibular disorders: Their relation to psychological and sleep impairments. *Oral Dis*. 2021;27:1498–1506. <https://doi.org/10.1111/odi.13692>