

# Fatigue in Adults with Chronic Arthralgia/Myalgia in the Temporomandibular Region: Associations with Poor Sleep Quality, Depression, Pain Intensity, and Future Pain Interference

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**Aims:** To examine associations between fatigue and poor sleep quality, depression symptoms, and pain intensity in an adult population with chronic arthralgia/myalgia in the temporomandibular region and to test whether fatigue predicted future pain-related interference above and beyond these other constructs.

**Methods:** The sample included 40 participants with chronic arthralgia and/or myalgia in the temporomandibular region and 21 healthy controls. Participants self-reported fatigue (PROMIS fatigue score), sleep quality (PSQI), depression symptoms (PROMIS depression score), and average pain intensity and completed four weekly surveys of pain-related interference with daily activities. **Results:** The chronic arthralgia/myalgia group reported greater fatigue than healthy controls ( $t = 4.85, P < .001$ ). Fatigue was significantly correlated with poor sleep quality ( $r = .46$ ), higher depression symptoms ( $r = .41$ ), and higher pain intensity ( $r = .46$ ) in the chronic arthralgia/myalgia group, and these three variables together explained 39% of variance in fatigue. Greater fatigue—above and beyond sleep quality, depression symptoms, and average pain intensity—was associated with a higher average level of pain-related interference ( $\beta = 0.56, t \text{ score} = 3.30, P = .002$ ) over the following month. Depression symptoms, poor sleep quality, and pain intensity did not significantly predict pain interference above and beyond fatigue (all  $P > .05$ ). **Conclusion:** The results suggest that fatigue is a clinically relevant symptom distinct from depression, poor sleep quality, or pain intensity and may be related to worse pain outcomes over the following month in adults with chronic temporomandibular arthralgia/myalgia. Clinicians should assess, monitor, and treat fatigue to the best of their abilities when working with this population. *J Oral Facial Pain Headache 2022;36:XX-XX. doi: 10.11607/ofph.2944*

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Fatigue, defined as a pervasive, generalized, and overwhelming feeling of tiredness, is a common and debilitating symptom in those with chronic temporomandibular pain and other pain conditions.<sup>1-4</sup> Over one-third of patients with chronic arthralgia or myalgia in the temporomandibular region, defined as joint or muscle pain in the temporomandibular region persisting longer than 3 months, report that fatigue causes functional impairment with daily activities<sup>1,5</sup> and predicts poor satisfaction with life and increased pain intensity.<sup>2,6,7</sup> Yet, patients with chronic pain conditions often report feeling that fatigue is clinically ignored or undertreated by their providers.<sup>8-10</sup> This may be because fatigue is positively correlated with other symptoms that commonly co-occur in temporomandibular pain, including poor sleep, depression, and high pain intensity, and as such is often overlooked as a standalone symptom in and of itself.

People experiencing chronic arthralgia/myalgia in the temporomandibular region often report impaired sleep,<sup>11-18</sup> which may contribute to higher levels of fatigue in this population. Fatigue and poor sleep are correlated in orofacial pain and other chronic pain conditions, with  $r$  values ranging from 0.26 to 0.47.<sup>1,4,19</sup> In a population-based study of Dutch young adults, associations between sleep and musculoskeletal pain severity 3 years later were mediated by fatigue.<sup>20</sup> These results cumulatively highlight that fatigue and sleep quality are closely related in chronic pain populations; however, they also suggest that there is a

substantial proportion of unshared variance between the constructs. Thus, fatigue may predict unique variance in concurrent and future pain outcomes above and beyond sleep quality, although to the present authors' knowledge this has not been tested in those with chronic arthralgia/myalgia in the temporomandibular region.

Fatigue has also been linked to depression symptoms.<sup>21,22</sup> The diagnostic criteria for depression in the Diagnostic and Statistical Manual of Disorders, fifth edition (DSM-5) and the International Classification of Diseases, version 10 (ICD-10) list fatigue as one of the possible symptoms, creating overlap between both constructs. Fatigue also has an emotional and motivational component, making it difficult to distinguish from depression.<sup>23–26</sup> In a small cross-sectional sample of young, middle-aged, and older adults with chronic orofacial pain, fatigue was significantly associated with pain-related interference, but the result became nonsignificant when controlling for depression.<sup>26</sup> However, in a larger cross-sectional study, the effect of fatigue on pain interference was still significant (albeit attenuated) when controlling for depression.<sup>1</sup> These findings suggest a considerable overlap between fatigue and depression, but the ability of fatigue to predict pain interference in those experiencing chronic arthralgia/myalgia in the temporomandibular region above and beyond depression symptoms remains unclear.

Finally, fatigue is greater when pain is more intense,<sup>1</sup> which in turn is greater in those with multiple pain comorbidities and longer pain duration.<sup>27</sup> The close associations between fatigue and pain intensity are noteworthy because they present the possibility that associations between fatigue and pain outcomes are merely pain intensity effects in disguise. To have a true understanding of the meaning and impact of fatigue in temporomandibular pain, it is thus important to control for average levels of pain intensity.

The present study had three goals. The first was to replicate previous literature demonstrating that people with chronic arthralgia/myalgia in the temporomandibular region had higher levels of fatigue than healthy controls. The second was to examine the amount of overlapping variance between fatigue and poor sleep quality, depression symptoms, and pain intensity in the arthralgia/myalgia group specifically. The third was to examine whether fatigue predicted average pain interference over the following month above and beyond poor sleep quality, depression symptoms, and pain intensity. Pain interference was chosen as the primary outcome because it is a common target for pain interventions/treatment<sup>28</sup> and provides a good representation of how well people are functioning with chronic facial pain. It was hypothesized that participants with chronic temporomandib-

ular arthralgia/myalgia would report greater fatigue than healthy controls. Fatigue was hypothesized to be moderately correlated with poor sleep quality, depression symptoms, and pain intensity. Based on the literature showing that fatigue only shares some variance with poor sleep quality, depression symptoms, and pain intensity, it was also hypothesized that it would predict worse pain interference over the next month above and beyond these other variables.

## Materials and Methods

### Participants

The measures and procedures for this study were part of a parent study using the same sample that was designed to measure immunologic changes following experimental pain in adults with temporomandibular joint disorder and healthy controls. Only the procedures and measures described below were analyzed for this manuscript; a full list of procedures and questionnaires completed by the participants is available by request to the senior author. Power for the current study was based on an a priori power analysis for the parent study that provided 80% power ( $\alpha = .05$ ) to detect inflammatory changes (eg, tumor necrosis factor alpha, interleukin-6; log<sub>10</sub> transformed) between people with temporomandibular joint disorder and healthy controls following repeated experimental pain induction.

Participants with chronic jaw pain (either arthralgia or myalgia) and healthy controls were recruited for the current study from the Cincinnati Children's Hospital Medical Center (CCHMC) and the surrounding areas using study flyers posted on bulletin boards around the hospital, digital flyers posted on the CCHMC digital research pages, and from referrals from other research studies in the lab. Data were collected between September 2016 and October 2018.

Inclusion criteria for the current study included being aged 18 to 50 years and being able to understand English. Participants in the chronic arthralgia/myalgia group had to additionally have an arthralgia and/or myalgia diagnosis as outlined in the DC/TMD<sup>29</sup> and have the diagnoses confirmed during a diagnostic exam; have pain for 5 or more days in the past month; and have a positive history of facial pain for greater than 6 months. To meet the criteria for myalgia, participants had to self-report pain in the right or left temporalis or masseter in the last 30 days, have familiar pain in any of these sites during movement and palpation, and report impact on chewing or other jaw-related activities. To meet the criteria for arthralgia, participants had to self-report pain in the right or left temporomandibular joint in the past 30

**Table 1 Demographic and Descriptive Statistics of the Study Sample**

	Full sample (n = 61)	Healthy control group (n = 21)	Chronic arthral- gia/myalgia group (n = 40)	95% CI of difference	t, P
Age, y	29.51 (6.63)	27.81 (7.24)	30.40 (6.19)	-0.95 to 6.13	1.52, .13
Female sex, n (%)	52 (85.2)	17 (80.1)	35 (87.5)	-	-
Race, n (%)					
Caucasian	49 (80.3)	13 (61.9)	36 (90.0)	-	-
African-American	4 (6.6)	3 (14.3)	1 (2.5)	-	-
Asian/Asian-American	3 (4.9)	2 (9.5)	1 (2.5)	-	-
Biracial/other	5 (8.2)	3 (14.3)	2 (5.0)	-	-
PROMIS Fatigue, raw score	15.95 (4.56)	12.62 (2.84)	17.70 (4.33)	2.98 to 7.18	4.85, < .001
PROMIS Fatigue, T-score	49.99 (7.36)	44.50 (5.47)	52.87 (6.58)	3.23 to 6.93	4.99, < .001
How often did you feel tired? <sup>a</sup>	3.33 (0.93)	2.67 (0.91)	3.68 (0.73)	0.58 to 1.44	4.70, < .001
How often did you experience ex- treme exhaustion? <sup>a</sup>	1.79 (0.82)	1.38 (0.59)	2.00 (0.85)	0.20 to 1.03	2.99, .004
How often did you run out of energy? <sup>a</sup>	2.13 (0.97)	1.43 (0.68)	2.50 (0.91)	0.62 to 1.52	4.76, < .001
How often did fatigue limit you at work (including work at home)? <sup>a,b</sup>	2.02 (1.03)	1.29 (0.46)	2.40 (1.03)	0.73 to 1.50	5.80, < .001
How often were you too tired to think clearly? <sup>a</sup>	1.93 (1.01)	1.48 (0.68)	2.18 (1.08)	0.24 to 1.15	3.08, .003
How often were you too tired to take a bath or shower? <sup>a,b</sup>	1.46 (0.79)	1.14 (0.48)	1.63 (0.87)	0.14 to 0.83	2.80, .007
How often did you have enough energy to exercise strenuously? <sup>a,c</sup>	2.70 (1.19)	2.76 (1.41)	2.68 (1.07)	-0.73 to 0.56	0.27, .79

Data are reported as mean (SD) unless otherwise indicated.

<sup>a</sup>Item scored on a 5-point scale ranging, from 1 (never) to 5 (always).

<sup>b</sup>Levene test revealed unequal variance between groups; thus, 95% CI of the difference, t, and P values are adjusted using Satterthwaite correction.

<sup>c</sup>Item is reverse scored in the raw score total.

days, have familiar pain in any of these sites during movement and palpation, and report impact on chewing or other jaw-related activities. Participants in the control group had to be absent of arthralgia and myalgia symptoms.

Exclusion criteria for both groups included being pregnant, using opioids, having a hospitalization or surgery within the past 6 months, and having a positive lifetime history of the following: cancer, diabetes mellitus, thyroid disorder, hypertension, pulmonary disease, neurologic disorders, irregular menstrual cycles (> 40 days) that caused pain and interfered with daily activities, or psychiatric disorders requiring hospitalization in the past year.

Sixty-seven participants were consented for the study. Of these, 5 from the arthralgia/myalgia group were terminated at the first visit when they self-reported a positive history of pulmonary disease (n = 1), cardiovascular disease (n = 2), or irregular menstrual cycles (n = 2). One participant in the control group did not return for the second visit and was thus missing key study variables and removed from the analyses. The final sample (N = 61) consisted of 40 participants in the chronic arthralgia/myalgia group and 21 healthy controls. Table 1 describes the demographic, pain, and study-related variables for both groups. No other missing data were present.

## Procedures

The study visits were conducted in the Schubert Research Clinic at the CCHMC. Participants came into the hospital for two visits. Before visit one, participants completed a brief phone screening to determine their potential eligibility for the study. At visit one, participants provided informed consent, completed a health history questionnaire to confirm the inclusion criteria and to report average pain intensity over the last 3 months, and underwent a standardized clinical examination to determine the presence of arthralgia and/or myalgia or absence thereof (for healthy controls). After the clinical examination, participants in both groups self-reported their sleep quality using the Pittsburgh Sleep Quality Index (PSQI), as described below.

At the second visit, scheduled approximately 1 week after the first, participants returned to the lab and self-reported their average fatigue and depression symptoms using the questionnaires described below. These measures were completed by participants in both the arthralgia/myalgia group and the healthy control group. For each of 4 consecutive weeks following the second visit, participants in the chronic arthralgia/myalgia group only were emailed weekly surveys to assess average levels of jaw pain and pain-related interference with daily functioning.

Participants completed this survey using REDcap, an online data administration tool. Procedures were approved by the institutional review board at the CCHMC (IRB #2015-4992). Full details on the methods, including additional tasks and measures that were not analyzed in this study, are reported elsewhere.<sup>17</sup>

This study was conducted in accordance with STROBE (Standardized Reporting of Observational Studies in Epidemiology) guidelines. All study sessions, including the clinical examination in visit one, were conducted by the same research coordinator (V.S.). Before starting the study, this research coordinator was trained to conduct the diagnostic clinical exam by a dentist using the procedures and criteria described in the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).<sup>29</sup>

## Nonpain Outcomes

### **Demographics.**

At the start of the first visit, participants reported their age, biologic sex, and pain characteristics (duration, pain severity).

### **Pain Intensity.**

At visit one, participants rated the average pain intensity of all their pain conditions over the last 3 months using a single item that stated “In the last 3 months, how intense was your pain on average?” They rated this item on an 11-point numeric rating scale with anchors of “no pain” (0) and “pain as bad as it could be” (10).

### **Sleep Quality.**

At visit one, participants completed the PSQI.<sup>30</sup> The PSQI assesses seven components of sleep over the past month and is the most widely used self-report questionnaire to assess sleep quality in chronic pain populations. A total score was produced by summing all seven components (possible range: 0–21;  $\alpha = .77$ ), with higher scores indicating poorer self-reported sleep quality.

### **Depression Symptoms.**

Depression was assessed at visit two using the 8-item PROMIS Depression (8a) questionnaire. Participants reported the extent to which they experienced different depression symptoms over the past 7 days using a scale of “never” (1) to “always” (5). A total score was computed by summing all items together (possible range: 8 to 40,  $\alpha = .93$ ), with higher scores indicating greater depression.

### **Fatigue.**

Fatigue was assessed at the second visit using the 7-item PROMIS (7a) short-form questionnaire. Specifically, participants reported how often in the past 7 days they experienced different symptoms of fatigue using a scale of “never” (1) to “always” (5). One item was reverse scored. A total raw score was

computed by summing the 7 items (possible range: 7 to 35,  $\alpha = .80$ ), with higher scores indicating greater fatigue. A T-score was also computed to compare the results from the current sample to those from a normative sample.

## Pain Outcomes

### **Pain-Related Interference.**

On each of 4 consecutive weeks following the second study visit, participants in the arthralgia/myalgia group completed an online survey assessing the average jaw pain-related interference with daily activities. Pain interference was assessed using three questions: (1) impact on daily activities (In the past week, how much has your facial pain interfered with your daily activities?); (2) social activities (In the past week, how much has your facial pain interfered with your ability to take part in recreational, social, and family activities?); and (3) work (In the past week, how much has your facial pain interfered with your ability to work?). Each question was rated on a numeric rating scale ranging from “no interference” (0) to “unable to carry on any activities” (10). Responses to the three questions were averaged at each time point. Responses from each of the 4 weeks of data were then averaged to produce a total score, with higher scores indicating greater levels of interference.

## Statistical Analyses

Before data analyses, all variables were visually examined for missing data and were checked for normality using a criterion of  $\pm 1.5$  on kurtosis score. First, to accomplish Aim 1, an independent sample *t* test was conducted, and descriptive statistics were used to compare the chronic arthralgia/myalgia and HC groups on PROMIS fatigue raw score, T-score, and individual items. Levene test for equality of variance was used to test the assumption of equal variances between both groups, as the groups differed in sample size. In cases where Levene test was significant (ie, there was unequal variance between the groups), Satterthwaite *t* test was used to adjust the degrees of freedom between the groups.<sup>31</sup>

To accomplish Aim 2 of examining the amount of overlapping variance shared between fatigue and poor sleep quality, depression symptoms, and average pain intensity, bivariate Pearson correlation coefficients (*r*) were computed among the variables. These correlations between fatigue and depression/sleep quality were examined with and without controlling for average pain intensity. Further, to test the amount of variance in fatigue that was explained by these three other variables combined, a linear regression was computed with fatigue as the outcome, and the other three variables were entered as simultaneous predictors. The statistic of interest in this

**Table 2** Bivariate Correlations Between Study Variables in Participants with Chronic Temporomandibular Arthralgia/Myalgia (N = 40)

	2		3		4		5	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
<b>Unadjusted</b>								
1. Fatigue (PROMIS)	0.46	.003	0.41	.008	0.46	.004	0.48	.002
2. Sleep quality (PSQI)	1		.10	.54	.26	.13	.21	.19
3. Depression symptoms (PROMIS)			1		-.03	.87	.05	.75
4. Average jaw pain intensity					1		.55	.001
5. Average pain-related interference <sup>a</sup>							1	
<b>Controlling for average pain intensity</b>								
1. Fatigue (PROMIS)	0.39	.02	0.38	.02	0.47	.005		
2. Sleep quality (PSQI)	1		0.09	.62	0.15	.40		
3. Depression symptoms (PROMIS)			1		0.09	.60		
4. Average pain-related interference <sup>a</sup>					1			

Note: <sup>a</sup>Variable was computed by averaging four weekly surveys for the month following the second study visit.

model was the adjusted total  $R^2$ , representing the total amount of variance in fatigue explained by all variables in the model.

To accomplish Aim 3 of determining whether fatigue was associated with pain interference over the following month, linear regression was used. The model included age, sleep quality, depression symptoms, average pain intensity, and fatigue, entered simultaneously as predictor variables, and average jaw pain interference over the following month as the outcome. The statistic of interest was the standardized beta coefficient ( $\beta$ ) for the fatigue variable, which represents the standardized unit change in interference associated with a one-standardized unit change in fatigue above and beyond the associations of sleep quality, depression symptoms, and pain intensity.

Post hoc power analyses were computed using a publicly available online calculator<sup>32</sup> to determine the observed power of the obtained results for each of the linear regression models (Aims 2 and 3).

All analyses were conducted using SPSS version 25 (IBM). To control for Type 1 error from multiple comparisons, Holm-Bonferroni procedure was used; this procedure adjusts the *P* value considered significant according to the number of significant comparisons within a set of analyses.<sup>33</sup>

## Results

### Participants

The mean age of the sample was 29.51 years (SD = 6.63). The sample was primarily female (85.2%) and Caucasian (80.3%). In the chronic arthralgia/myalgia group, 25.8% (*n* = 16) of participants self-reported their jaw pain as mild, 37.1% (*n* = 23) reported it as moderate, and 1.6% (*n* = 1) reported it as severe. Thirty-seven participants in the arthralgia/myalgia

group had both arthralgia/myalgia, and 3 had myalgia only. The average self-reported duration of jaw pain in the arthralgia/myalgia group was 92.55 months (7.71 years), but there was substantial variability (SD = 68.49 months, observed range = 12 to 240 months). Table 1 provides descriptive statistics and compares the two groups on all study variables.

### Aim 1: Group Differences in Fatigue

Table 1 provides means, overall raw score, and T-scores of the PROMIS Fatigue survey, as well as descriptive statistics for the individual items. As expected, the chronic arthralgia/myalgia group reported significantly greater fatigue than the control group. At the individual item level, the differences were greatest between groups on the items "How often did you feel tired?"; "How often did you run out of energy?"; and "How often did fatigue limit you at work (including work at home)?"

### Aim 2: Bivariate Associations Among Fatigue, Sleep Quality, Depression Symptoms, and Pain Outcomes

Table 2 shows bivariate associations between fatigue, poor sleep quality, depression symptoms, and pain intensity and interference over a month in the chronic arthralgia/myalgia participants only. Fatigue was significantly but only modestly positively correlated with poor sleep quality ( $r = .46$ ), depression symptoms ( $r = .41$ ), greater average jaw pain intensity ( $r = .46$ ), and greater pain-related interference over the following month ( $r = .50$ ). Poor sleep quality and depression symptoms were not correlated with each other ( $r = .10$ ), nor were they correlated with pain interference over the following month ( $r = .05$  to  $.21$ ). Even after controlling for average pain intensity, fatigue was still significantly correlated with poor sleep quality ( $r = .39$ ), depression ( $r = .38$ ),

**Table 3** Linear Regression Predicting Average Pain-Related Interference in the Month Following the Second Study Visit in Participants with Chronic Temporomandibular Arthralgia/Myalgia

Predictor	Standardized	Unstandardized	95% CI for B	t	P	Adjusted R <sup>2</sup>	Observed power
	$\beta$	B					
Constant	–	–4.81	–7.57 to –2.04	–3.54	.001	.446	.989
Age	0.26	.06	–0.001 to 0.13	2.02	.052		
Sleep quality total score (PSQI)	–0.09	–0.04	–0.18 to 0.10	–0.63	.54		
Depression symptom total score (PROMIS)	–0.10	–0.03	–0.12 to 0.06	–0.72	.48		
Average pain intensity	0.29	0.28	–0.01 to 0.58	1.96	.06		
Fatigue total score (PROMIS)	0.56	0.21	0.08 to 0.34	3.24	.003		

and future pain-related interference ( $r = .47$ ; Table 2).

Furthermore, results from a linear regression revealed that, when entered simultaneously, sleep quality ( $\beta = 0.27$ ,  $B = 0.39$ , 95% CI of  $B = 0.03$  to  $0.76$ ,  $t = 2.21$ ,  $P = .03$ ), depression symptoms ( $\beta = 0.38$ ,  $B = 0.32$ , 95% CI of  $B = 0.10$  to  $0.54$ ,  $t = 2.91$ ,  $P = .006$ ), and average pain intensity ( $\beta = 0.39$ ,  $B = 1.01$ , 95% CI of  $B = 0.33$  to  $1.81$ ,  $t = 2.93$ ,  $P = .006$ ) together explained just under 40% of the variance of fatigue (adjusted  $R^2 = 0.39$ ), demonstrating that approximately 60% of the variance in fatigue was not explained by these other constructs. A post hoc power analysis revealed that with 3 predictors, an observed  $R^2$  of 0.39, a probability level of  $\alpha = .05$ , and a sample size of  $n = 40$ , the observed power of the linear regression was 0.988.

### **Aim 3: Associations of Fatigue with Average Jaw Pain Intensity and Pain-Related Interference in the Month Following the Second Visit**

As seen in Table 3, higher self-reported fatigue during the second visit was significantly associated with greater self-reported jaw pain interference over the following month. This association was significant after controlling for poor sleep quality, depression symptoms, and average pain intensity. Of note, the full model with age, fatigue, sleep quality, depression symptoms, and average pain intensity together explained 44.6% of the variance in average jaw pain interference during the month, highlighting the clinical importance of assessing these variables. Of all the variables included in the final model, only fatigue was significant above and beyond the other variables (Table 3).

## **Discussion**

Fatigue is a prevalent and disruptive symptom experienced by those with chronic temporomandibular pain and other orofacial pain conditions, but it remains

poorly understood, in part due to the fact that it is linked to poor sleep quality, depressive symptomatology, and pain intensity. The goal of this study was to better understand how much variance in fatigue was shared by these other variables in participants with chronic arthralgia/myalgia in the temporomandibular region and to examine the unique role of fatigue in predicting future pain-related interference above and beyond poor sleep quality, depression symptoms, and pain intensity.

Replicating the previous literature, the chronic arthralgia/myalgia group reported significantly higher levels of fatigue than the healthy control group.<sup>2</sup> The largest differences between the groups were seen on items that assessed general fatigue symptoms (eg, “How often do you feel tired?”). This is corroborated by previous research that has examined associations between specific fatigue subtypes and pain outcomes in patients with chronic temporomandibular joint disorders and has found that general fatigue (as opposed to cognitive fatigue or emotional fatigue) is the subtype most closely associated with negative pain outcomes<sup>1,26</sup> in this population. These findings highlight the need for future work to examine the mechanisms by which pain influences general fatigue in those with chronic arthralgia/myalgia in the temporomandibular region.

The correlation results from the present study support the idea that fatigue is correlated with poor sleep quality, depression symptoms, and pain intensity, but also conceptually distinct from each of these three constructs. In the present data, fatigue shared approximately 21% of the variance with poor sleep quality and average pain intensity, whereas fatigue and depression symptomatology shared approximately 17% of the variance (Table 2). This is consistent with findings from other studies that have used different measures of fatigue, sleep, depression, and pain intensity in different chronic pain populations,<sup>1,4,19</sup> supporting the generalizability of these findings. The present results suggest that there is a substantial part of fatigue that is unique (ie, nonoverlapping) from

these other constructs.<sup>1,34</sup> It may be that the experience of fatigue encompasses distinct cognitive or motivational components that are not well captured by these other constructs. For example, with regard to possible cognitive components, those who frequently report high levels of general fatigue also tend to report difficulty sustaining attention and concentrating, as seen in patients with fibromyalgia and other chronic pain populations.<sup>35</sup> With regard to possible motivational components, it may be that fatigue is experienced as an overwhelming urge to stop, disengage, or not to start, which is different from the anhedonia or the affectively mediated motivational components of depression. These possibilities are speculative, and future theoretical work needs to be conducted to determine what is generalized fatigue if it is not poor sleep, depression, or intense pain. This is an important question given that approximately 60% of the variance in fatigue appears to be unique from the combined variance explained by these other constructs.

Whereas most studies of fatigue in orofacial pain have examined cross-sectional associations between fatigue and pain outcomes, the results from the present study suggest that fatigue may contribute unique variance to pain-related interference with daily activities over the following month. The effect sizes from the model were moderate, with each standardized unit in fatigue being associated with a 0.56 standardized unit increase in pain interference over the following month. Additionally, the full set of predictors in the models explained approximately 45% of variance in average pain interference over the following month. This is theoretically important because it highlights the need for future research to uncover the potential mechanisms by which fatigue may be associated with future pain outcomes. One possibility is that when people feel more fatigued, they engage in less physical and social activities, which in turn leads to greater pain and pain-related interference.<sup>36</sup> Another possibility is that fatigue may contribute to inflammation, which in turn can be related to these outcomes.<sup>37</sup> Although multiple mediators and mechanisms are possible for explaining the relationship between fatigue and poor pain outcomes, no study to date to the present authors' knowledge has explicitly tested these mechanisms in adults with chronic temporomandibular pain. It may also be that fatigue is not causally linked to pain interference and that a third variable explains the perceived relationship between the two.

Clinically, the findings from the present study have significant clinical implications. The case/control differences in levels of self-reported fatigue, along with the associations of fatigue with sleep,

depression, pain intensity, and future pain interference, suggest that fatigue may be a significant and impairing symptom for those with chronic arthralgia/myalgia in the temporomandibular region. As such, clinicians working with this population should routinely assess and monitor fatigue. Patients with chronic pain often report that fatigue is ignored or poorly managed by clinicians, further highlighting the important need for clinicians to inquire about this potentially impactful symptom.<sup>8</sup> The PROMIS measure used in the present study may be a useful tool for tracking fatigue in those with chronic arthralgia/myalgia in the temporomandibular region. When fatigue is identified to be a significant problem area in a particular individual, recommendations like regular light-intensity physical exercise,<sup>38,39</sup> dietary changes,<sup>40</sup> and cognitive behavioral therapy for fatigue<sup>41</sup> may be helpful, although more research in this particular population is needed to establish the value of these interventions. Nevertheless, even in the absence of intervention, the mere act of discussing fatigue and its impact on patients may be important, as this may make the patients feel that the provider is getting a more complete understanding of their pain experience.

The present study has significant limitations. For one, the sample size was small. The power analyses for the study were based on the parent project and not the study described in this manuscript. Future work should replicate these results with a larger sample. Second, the chronic arthralgia/myalgia group consisted largely of participants with both myalgia/arthralgia, and only 3 of the 40 participants had myalgia only. Given the well-established differences in psychologic functioning and fatigue between those with myalgia vs arthralgia,<sup>7</sup> future work should aim to test whether fatigue is differently associated with depression or sleep in these two groups. Relatedly, because the present study did not exclude participants with comorbid pain and medical conditions, how much of the participants' fatigue was due specifically to myalgia or arthralgia (as opposed to other pain conditions) cannot be assessed. Third, because variables were not experimentally manipulated, relationships described in the manuscript are not causal, and the authors have been careful to avoid the word "predictor" and instead use "correlate" to describe those relationships. Unmeasured third variables may potentially explain the relationships described. Fourth, the present study only examined associations between fatigue and pain interference over the following month. Fifth, potential side effects from medications (ie, antidepressants, antihistamines) were not controlled for, and whether participants switched or started medications during the course of the study

was also not assessed. Thus, some of the observed fatigue effects may have been medication-related. Future work should examine these associations over several months or years to gain a better understanding of the long-term impact of fatigue on chronic orofacial pain. Finally, the sample was relatively homogenous with regard to gender (female), race/ethnicity (Caucasian), and pain severity (mild to moderate pain) and may not be generalized to other chronic pain populations.

## Conclusions

Fatigue appears to be a significant symptom in adults with chronic temporomandibular pain. Fatigue was found to be greater in those with chronic arthralgia/myalgia than in healthy controls. Although fatigue was cross-sectionally correlated with poor sleep quality, depression symptoms, and average pain intensity, in those with chronic arthralgia/myalgia in the temporomandibular region, these variables together only accounted for approximately 40% of variance in fatigue, suggesting that fatigue may potentially explain unique variance in pain outcomes above and beyond these variables. To that end, it was found that even after adjusting for poor sleep quality, depression symptoms, and average pain intensity, greater fatigue was associated with greater pain interference over the following month. Clinically, these results highlight the importance of assessing fatigue when working with people with chronic arthralgia/myalgia in the temporomandibular region and elucidate the need for greater theoretical work exploring the causes and consequences of fatigue in chronic orofacial pain.

## Highlights

- Community-dwelling adults with chronic arthralgia/myalgia in the temporomandibular region reported greater levels of fatigue than healthy controls.
- Fatigue in this population was associated with poor sleep, greater depression symptomatology, and higher average pain intensity; however, approximately 60% of the variance in fatigue was not explained by these other variables.
- Greater fatigue was associated with greater pain-related interference with daily activities over the following month, above and beyond poor sleep quality, depression symptoms, and pain intensity.
- Clinicians should assess fatigue when working with those reporting chronic temporomandibular pain.

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