

# The Association Between Orofacial Pain and Depression: A Systematic Review

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**Background:** The occurrence of orofacial pain is often accompanied by comorbid conditions such as depression. Even though previous studies suggested a bidirectional correlation between orofacial pain and psychological factors, some studies still provided contradictory results.

**Objective:** This systematic review aimed at providing scientific evidence regarding the association between orofacial pain and depression in published literature.

**Methods:** The current study is a systematic literature review (PROSPERO registration no. CRD42023438596) that was conducted by reviewing cross-sectional studies that investigated the association between orofacial pain and depression. Article selection was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance. Articles searching was performed by using three databases, namely PubMed, ScienceDirect, and Scopus using the Boolean operator method. Article screening was carried out by applying the inclusion and exclusion criteria, as well as duplication checking, suitability checking, and compatibility checking. Reviewed articles went through the risk of bias evaluation form from the Joanna Briggs Institute (JBI). Extracted data were analyzed in a qualitative method.

**Results:** Twelve studies that were conducted on 5557 participants were included in the final review. After all articles were analyzed, the correlation between orofacial pain and depression was revealed. Most articles revealed a positive correlation between orofacial pain and depression, and the rest showed how orofacial pain patients showed significantly higher depression scores compared to those individuals without orofacial pain.

**Conclusion:** The results of this systematic review suggested a correlation between orofacial pain and depression with varying degrees. Incorporating potential depressive symptoms' treatment, when treating orofacial pain patients, should be part of the treatment plan.

**Keywords:** pain, orofacial pain, depression, correlation

## Introduction

Orofacial pain can be defined as “pain that originates primarily from the regions of the face and mouth”.<sup>1,2</sup> According to the International Association for the Study of Pain (IASP), orofacial pain can be defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”.<sup>3</sup> The newest classification of orofacial pain was launched by the International Classification of Orofacial Pain (ICOP) committee that classified orofacial pain into several categories, namely “pain in dentoalveolar and anatomically related tissues, muscle pain, temporomandibular joint (TMJ) pain, neuropathic pain affecting cranial nerves, pain resembling primary headaches, and idiopathic pain”.<sup>4</sup> Based on its duration, it can be differentiated into acute orofacial pain, which is orofacial pain that lasts for a period of three months or less, and chronic orofacial pain, which is a type of orofacial pain that lasts more than three months.<sup>5</sup> Research conducted by de Melo Junior et al regarding the prevalence of orofacial pain among 1342 adolescents aged 10–17 years in Brazil showed that the prevalence of temporomandibular disorders (TMD) was high in teenagers, where 33.2% of the samples experienced chronic pain and headaches in the last six

months. Additionally, it was also found that orofacial pain occurred more frequently in women than in men.<sup>6,7</sup> Orofacial pain has a multifactorial etiology that can be either odontogenic or non-odontogenic. It can be caused by functional disorders, structural abnormalities, as well as psychological factors.<sup>8,9</sup> The National Institute of Dental and Craniofacial Research stated that orofacial pain has an impact on reduced quality of life and psychosocial functioning.<sup>2,10</sup> Orofacial pain conditions have a negative impact on a person's life as they can lead to psychological disorders (depression, anxiety, and stress), sleep disturbances, and disability.<sup>7</sup> A study conducted by the UK Biobank on facial pain revealed that there is a strong bidirectional relationship between chronic facial pain and psychological factors.<sup>11</sup>

Depression can be defined as a global emotional disorder<sup>12</sup> that is characterized by a worsening mood.<sup>13</sup> Symptoms of depression include feelings of distress, poor mood, sadness, panic attacks, as well as a decrease in various psychological and cognitive functions, a tendency towards isolation, demotivation, apathy, abulia, difficulty in experiencing enjoyment, hopelessness, motor inhibition, hypotonia, negative thoughts, and the possibility of delusions in cases of severe severity.<sup>14</sup> Depression is a multifactorial disorder that involves a range of specific behavioral or motor symptoms that make it difficult for individuals experiencing it to function in their daily lives.<sup>13</sup> The estimate from the World Health Organization suggests that over 264 million individuals across all age groups experience depression, positioning it as the primary contributor to global disability.<sup>12</sup> In addition to its high prevalence, depression is known to have a significant impact on the quality of life of individuals, leading to high morbidity rates among those affected by depression.<sup>14</sup>

The relationship between orofacial pain and depression has been studied and evaluated in preliminary research; however, there are still varying results from one study to another regarding the cause-effect relationship, whether it is orofacial pain that causes depression, or is it depression that causes orofacial pain. Research conducted by Back et al in Sweden involving 1059 women aged 38 to 50 years in a cross-sectional study revealed that 77% of chronic orofacial pain patients experience depression and a decline in quality of life.<sup>15</sup> Furthermore, in a study conducted by Greenberg et al involving 303 patients with various orofacial pain diagnoses, a significant association was found between depression and the occurrence of multiple orofacial pain complaints in orofacial pain patients.<sup>16</sup> Another study conducted by Jeremic-Knezevic et al on 200 women aged 18–65 years revealed that 40.4% of individuals with orofacial pain did not show signs of depression, 30.8% had mild to moderate depressive disorders, and 28.8% exhibited severe depressive disorders.<sup>17</sup> These research findings contradict previous studies<sup>15,18,19</sup> where individuals with orofacial pain were assumed to always experience depression with a high prevalence. Considering the contradictory nature of previous research findings, this systematic review aimed to provide scientific evidence from previously conducted research about the association between orofacial pain and depression. The findings of this systematic review can be used as a scientific background in determining appropriate management procedures and prevention strategies, as well as contribute to the overall understanding and knowledge of orofacial pain and its connection to psychological conditions, depression in particular.

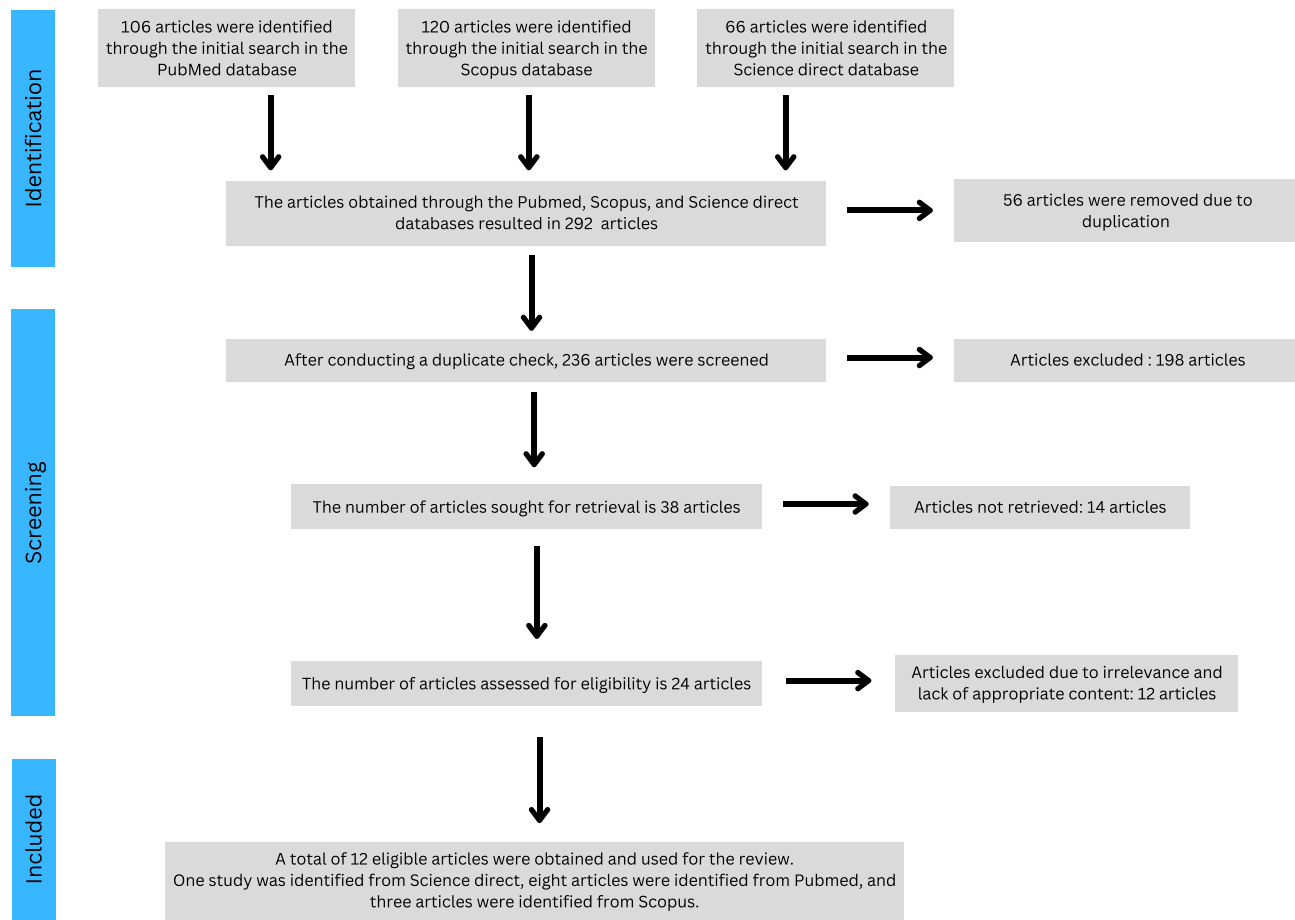
## Methods

### Protocol and Registration

The article search strategy in this study employed a systematic literature review method following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>20</sup> as displayed in [Figure 1](#). The protocol for this review was previously published on PROSPERO (registration no. CRD42023438596) where the study protocol can be reviewed. Three authors [HA, TM, FP] formulated the study protocol, set the inclusion and exclusion criteria, and performed data extraction. Two authors [HA and TM] independently performed the critical appraisal process and data syntheses. The search results were initially screened based on their titles and abstracts, and then the full-text content was reviewed according to the selection criteria. This screening process was conducted from April to July 2023.

### Selection of Studies and Eligibility Criteria

Studies were eligible for inclusion if they satisfied the following inclusion criteria: 1) articles were published in English; 2) conducted on humans; 3) published between 2012 and 2022; and 4) articles were cross-sectional studies that reported the correlation between orofacial pain and depression. Systematic reviews or meta-analysis articles were excluded.



**Figure 1** The PRISMA guidelines for the article selection procedure.

## Information Sources and Search Strategy

The current systematic review was conducted by using three search engines, which were PubMed, Scopus, and Science Direct by using the following keywords: “depression” AND “facial pain” OR “orofacial pain” OR “dental pain” AND “correlation” OR “association” OR “relationship”.

## Risk of Bias Assessment

Bias and quality assessment was conducted to evaluate potential bias in the study. The quality assessment of articles included in this systematic review was conducted by using The JBI Critical Appraisal Checklist.<sup>21</sup> The JBI Critical Appraisal is an instrument used to assess the methodological quality of a study and determine the extent to which a study has addressed potential biases in its design, intervention, and analysis. In this systematic literature review, critical appraisal tools for studies with cross-sectional design issued by The Joanna Briggs Institute (JBI) were used.<sup>22</sup> The quality assessment was categorized into three groups: (1) low risk of bias (fulfilled more than 75% of the assessment criteria), (2) moderate risk of bias (fulfilled 50–74% of the assessment criteria), and (3) high risk of bias (fulfilled less than 49% of the assessment criteria).<sup>23</sup> Based on the assessment all the articles reviewed in this systematic review have low risk of bias and therefore, are considered as high-quality research.

## Data Extraction

The data extracted from each article included article information (author’s name, title, year of publication), sample characteristics (sample size, number of individuals with depression, number of individuals with orofacial pain, and age range), depression assessment scale, orofacial pain measurement scale, statistical analysis, and research interpretation. As

the study was aimed at investigating the association between orofacial pain and depression, statistical analysis results mentioning the association between orofacial pain and depression should be present and extracted.

## Results

One hundred and six articles were identified through the PubMed search, 120 articles through the Scopus search, and 66 articles through the ScienceDirect search, resulting in a total of 292 identified articles. After removing duplicate articles, screening titles and abstracts, and reading the full-text content, 12 relevant articles were selected for review in this study. The search process and study selection are summarized in [Figure 1](#).

## Critical Appraisal

The critical evaluation of included cross-sectional articles is presented in [Table 1](#). Twelve cross-sectional articles included in this study met the low risk of bias category. Therefore, the included cross-sectional articles were of high quality.

Studies that obtained JBI scores higher than 70% are considered to have high quality. Studies with JBI scores between 50% to 70% are categorized as moderate-quality studies, while studies with JBI scores less than 50% are considered to have low quality. Based on the critical appraisal results, there are twelve eligible articles, and all of them received JBI scores greater than 70%, thus classified as high-quality studies.

## Main Findings

Based on our review ([Table 2](#)), data obtained from the reviewed cross-sectional articles included article information (author's name, title, year of publication), sample characteristics (sample size, number of individuals with depression, number of individuals with orofacial pain, and age range), depression assessment scale, orofacial pain measurement scale, statistical analysis, and research interpretation. The final number of articles selected and reviewed was twelve articles.

Twelve cross-sectional studies were included in this review. Two of the reviewed articles reported general orofacial pain, seven studies focused on temporomandibular disorders (TMD), and three studies examined other types of orofacial pain. Three studies involving patients with orofacial pain reported three different types of orofacial pain, namely burning mouth syndrome (BMS), persistent idiopathic facial pain (PIFP), and chronic rhinosinusitis (CRS).<sup>24,25,32</sup> The other studies on orofacial pain included patients with TMD, myalgia pain, arthralgia pain, myofascial pain, osteoarthritis, and osteoarthrosis.<sup>17,30</sup>

In this study, various durations of orofacial pain were found. Most of the studies involved patients with different ranges of pain durations. Eleven articles specifically focused on chronic orofacial pain.<sup>17,24–34</sup> One other article examined both acute/subacute and chronic orofacial pain types.<sup>33</sup> Different measurement scales for orofacial pain and depression were used in the reviewed articles. The most frequently used scale for orofacial pain was the Graded Chronic Pain Scale (GCPS), which was used in five articles. This might be because the scale facilitates the measurement of pain severity and pain-related disability.<sup>17,29,31,33–35</sup> Other scales used included the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) in three articles, and Pain Catastrophizing Scale (PCS) in two articles.<sup>25–27,29,31</sup> Other articles used pain scales such as the Brief Illness Perception Questionnaire (B-IPQ), Brief Pain Inventory Short Form (BPI-SF), Short-Form McGill Pain Questionnaire (SF-MPQ), Sinonasal Outcome Test-22 (SNOT-22), Visual Analog Scale (VAS), Characteristic Pain Intensity (CPI), Oral Behavior Checklist (OBC), Rhinosinusitis Disability Index (RSDI), and brief pain inventory (BPI) to assess pain levels.<sup>24,25,28,30–33</sup>

The measurement of depression in the reviewed articles used various and different scales. Three articles used the Hospital Anxiety and Depression Scale (HADS) in their assessment.<sup>25,28,33</sup> Which is a scale that has been proven to be successful in evaluating the severity and presence of anxiety and depression disorders in somatic, psychiatric, primary care patients, and the general population.<sup>36</sup> Two articles used the Beck's Depression Inventory (BDI), Symptoms Checklist-90-Revised (SCL-90R), Patient Health Questionnaire-2 (PHQ-2), Patient Health Questionnaire-4 (PHQ-4), and Patient Health Questionnaire-9 (PHQ-9).<sup>17,24,26–29,32,34</sup> The rest of the studies used other scales such as Hamilton Depression Rating Scale (HDRS), Symptoms Checklist Depression (SCL-DEP), Symptoms Checklist Somatization

**Table 1** Quality Assessments Results (JBI Critical Appraisal Tools)

Criteria	(Sato (Boku) et al, 2021) <sup>24</sup>	(Jeremic-Knezevic et al, 2021) <sup>17</sup>	(Kazi et al, 2021) <sup>25</sup>	(Omezli, Torul, and Varer Akpınar 2023) <sup>26</sup>	(Chuinsiri 2020) <sup>27</sup>	(Saki, Shadmanpour, and Najafi 2021) <sup>28</sup>	(De la Torre Canales et al, 2020) <sup>29</sup>	(Lee and Auh 2022) <sup>30</sup>	(Bhalang et al, 2020) <sup>31</sup>	(Cox et al, 2017) <sup>32</sup>	(Asquini et al, 2021) <sup>33</sup>	(Wieckiewicz et al, 2022) <sup>34</sup>
Were the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the study subjects and the setting described in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were objective, standard criteria used for measurement of the condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were confounding factors identified?	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Were strategies to deal with confounding factors stated?	No	No	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes
Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
<b>Total score</b>	<b>87,5%</b>	<b>75%</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>75%</b>	<b>87,5%</b>	<b>100%</b>	<b>75%</b>	<b>100%</b>	<b>100%</b>

**Notes:** Adapted from Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P. Chapter 7: Systematic reviews of etiology and risk. Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. JBI; 2020. Available from: <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-08>.

Table 2 Data Extraction Results

Article Information (Author / Title / Year)	Sample Characteristics		Duration of Orofacial Pain	Orofacial Pain Measurement Scale	Depression Assessment Scale	Statistical Analysis	Result Interpretation
	Sample Size and Number of Samples	Age					
Sato (Boku) et al, / Evaluation of patients suffered from burning mouth syndrome and persistent idiopathic facial pain using Japanese version PainDETECT questionnaire and depression scales / 2021 <sup>24</sup>	46 patients with BMS and PIFP	BMS = (61–65) PIFP = (43.5–61)	Chronic	PainDETECT Japanese version	BDI HDRS	Spearman rank-correlation to test correlation. Correlation between BDI and patient with BMS ( $r=0.18$ ), BDI and patient with PIFP ( $r=-0.08$ ), HDRS and patient with BMS ( $r=0.09$ ), HDRS and patient with PIFP ( $r=0.12$ )	Positive correlation
Jeremic-Knezevic et al, / Correlation of somatization, depression, and chronic pain with clinical findings of the temporomandibular disorders in asymptomatic women / 2021 <sup>17</sup>	144	18–65 years old Mean 48.75 $\pm 12.2$ years old	Chronic TMD	GCPS	Depression sub scale score in Axis II RDC/ TMD (SCL-90)	Spearman correlation to test correlation. $r=0.198$ , $p=0.17$	Non-significant positive correlation
Bhalang et al, / The Pain-to-Well-Being Relationship in Patients Experiencing Chronic Orofacial Pain / 2020 <sup>31</sup>	799	10 - >70 years old	Chronic	B-IPQ GCPS PCS	PHQ-4 PHQ-9	Spearman correlation to test correlation and Analysis of Variance (ANOVA) with Bonferroni test or Tamhane correction for post doc testing to test for statistical significance. Correlation between PHQ4 and number of pain locations in the head and neck region ( $r=0.8$ , $p=0.02$ ), PHQ4 and pain duration ( $r=-0.2$ ; $p=0.00$ ), PHQ9 and number of pain locations in the head and neck region ( $r=0.8$ , $p=0.08$ ), PHQ9 and pain duration ( $r=-0.2$ ; $p=0.04$ )	Significant correlations between several pain measurements and depression

Cox et al, / Dyad of Pain and Depression in Chronic Rhinosinusitis Daniel / 2017 <sup>32</sup>	70	Mean 58.59 ±16.06 years old	Chronic CRS	BPI-SF SF-MPQ PPI VAS	PHQ-2	(Two-sided) Spearman's rank correlation to test correlation. Correlation between PHQ2 and pain severity in BPI-SF (r=0.494), PHQ2 and pain interference in BPI-SF (r=0.644), PHQ2 and total SF-MPQ (r=0.564), PHQ2 and PPI score (r=0.556), PHQ2 and VAS score (r=0.486). p-value for all correlations ≅ 0.001	Significant positive correlations
Asquini et al. / The impact of Covid-19-related distress on general health, oral behaviour, psychosocial features, disability and pain intensity in a cohort of Italian patients with temporomandibular disorders / 2021 <sup>33</sup>	45	≥18 years old	Acute/sub-acute Chronic	GCPS CPI CSS	HADS	Spearman correlation to test correlation. Correlation between HADS and CSS score in acute/ subacute TMD (r=0.10, p=0.63), HADS and CSS score in chronic TMD (r=0.72, p=0.002).	(Significant) positive correlations. Patient with chronic TMD had their depression symptom worsened triggered by COVID-related stress.
Kazi et al, / Pain Catastrophizing and Quality of Life in Adults with Chronic Rhinosinusitis / 2021 <sup>25</sup>	75	Mean 47.6 ±14.3 years old	Chronic sinusitis	PCS	HADS (Depression sub-scale)	Pearson's correlation to test correlation. Correlation between HADS (Depression sub-scale) and total PCS score (r=0.644, p<0.001)	Significant positive correlation
Omezli et al, / Temporomandibular disorder severity and its correlation with psychosocial and sociodemographic factors in Turkish adults / 2023 <sup>26</sup>	2580	18–80 tahun Mean 35.29 ± 12.70 years old	Chronic	DC/TMD Axis II	PHQ-4	Chi-square analysis to test correlation. The risk of TMD symptoms to increase in patient with depression symptoms is 1.90 95% CI 1.48–2.42) fold (p=0.001)	Significant correlation

(Continued)

**Table 2** (Continued).

Article Information (Author / Title / Year)	Sample Characteristics		Duration of Orofacial Pain	Orofacial Pain Measurement Scale	Depression Assessment Scale	Statistical Analysis	Result Interpretation
	Sample Size and Number of Samples	Age					
Chuinsiri / Prevalence of self-reported pain-related temporomandibular disorders and correlation with psychological distress in a dental clinic setting / 2020 <sup>27</sup>	221	≥18 years old	Chronic TMD	DC/TMD TMD pain screener	PHQ-4 PHQ-2 (depression screener)	Spearman correlation to test correlation. Correlation between PHQ-4 and TMD pain (r= 0.367, p<0.001), PHQ-2 (depression screener) and TMD pain (r=0.295, p<0.001)	Significant positive correlations
Saki et al / Are individuals with orofacial pain more prone to psychological distress during the COVID-19 pandemic? / 2021 <sup>28</sup>	509	19–39 years old	Chronic	K10 (pain intensity)	Kessler Psychological Distress Scale (K-Depression)	One-way ANCOVA to test for significant differences. Patient with OFP showed higher depression score compared to participants without OFP (F=18.29, p=0.0001)	Significant difference in occurrence rate.
De la Torre Canales et al, / Correlation Between Physical and Psychosocial Findings in a Population of Temporomandibular Disorder Patients / 2020 <sup>29</sup>	737	Mean 39.3 years old	Chronic	RDC/TMD (pain intensity) GCPS	SCL-DEP	Chi-square test to test for significant difference. Patient with painful TMD showed significantly (p<0.001) higher depression scores compared to non-painful TMD patients.	Significant difference in occurrence rate.
Wieckiewicz et al, / Determination of pain intensity, pain-related disability, anxiety, depression, and perceived stress in Polish adults with temporomandibular disorders / 2022 <sup>34</sup>	219	≥18 years old 18–80 years old Mean 40.06 ± 16.37 years old	Chronic TMD	GCPS	PHQ-9	Ordered (three ordinal) logistic regression to test correlation. Correlation between PHQ-9 and GCPS score (OR= 1.040; 95 CI 1.017–1.064, p= 0.0015)	Significant strong correlation
Lee and Auh / Clinical factors affecting depression in patients with painful temporomandibular disorders during the COVID-19 pandemic / 2022 <sup>30</sup>	112	≥18 years old Mean 35.90 ±17.60 years old	Chronic TMD	VAS	BDI-II	Spearman correlation to test correlation. Correlation between BDI-II score and VAS score in mixed-TMD patients with pain (r=0.689, p< 0.001)	Strong positive correlation

**Abbreviations:** TMD, temporomandibular disorder; BMS, burning mouth syndrome; PIFP, persistent idiopathic facial pain; VAS, visual analog scale; HDRS, Hamilton depression rating scale; B-IPQ, brief illness perception questionnaire; PCS, pain catastrophizing scale; PHQ-4, patient health questionnaire-4; PHQ-9, patient health questionnaire-9; PHQ-2, patient health questionnaire-2; BPI-SF, brief pain inventory short form; SF-MPQ, short-form McGill pain questionnaire; GCPS, graded chronic pain scale; CPI, characteristic pain intensity; CSS= Covid Stress Scale; DC/TMD, diagnostic criteria for temporomandibular; SCL-90R, symptoms checklist-90-revised; SCL-DEP, symptoms checklist depression; HADS, hospital anxiety and depression scale; BDI, beck's depression inventory; BPI, brief pain inventory OR, odds ratio; PPI, present pain inventory; K10, Kessler Psychological Distress Scale; ANCOVA, Analysis of Covariance; OFP, Orofacial pain.



(SCL-SOM), Dymorphic Concern Questionnaire (DCQ), Generalized Anxiety Disorder Scale-7 (GAD-7), Beck's Depression Inventory (BDI-II), COVID Stress Scale (CSS), and Coping Strategies Questionnaire-27 (CSQ).<sup>24,29,31,33</sup>

Seven studies reported the results of Spearman correlation coefficients that described the association between orofacial pain and depression,<sup>17,24,27,30–33</sup> one study used Pearson's correlation to report the association,<sup>25</sup> two studies used chi-square test correlation and significant difference where patients with orofacial pain (OFP) showed higher depression score,<sup>26,29</sup> and the last two articles showed the association between orofacial pain and depression through logistic regression analysis<sup>34</sup> and one-way analysis of covariance (ANCOVA), where patients with OFP showed higher depression score compared to patients without OFP.<sup>28</sup> From the results of all the reviewed studies, most articles show a positive correlation between orofacial pain, especially TMD, and depression.

## Discussion

The origin of orofacial pain might vary from the periodontal tissues, muscles, blood vessels, temporomandibular joint, salivary glands, bones, or teeth. Understanding the processes and features of orofacial pain in its manifestations is crucial for both diagnosing and treating patients with orofacial pain. Many patients with orofacial complaints often have other conditions that impact their pain, making the examination, diagnosis, and treatment of orofacial pain complex and multifaceted processes. The process of diagnosis and therapy is strengthened by identifying the clinical forms of chronic pain and the many reasons contributing to it. Medical professionals will be able to establish an accurate diagnosis with the aid of a thorough medical history record.<sup>37</sup> To enhance diagnosis and therapy, it is therefore essential to research factors that are potentially associated with chronic orofacial pain.

While treating acute orofacial pain is typically straightforward, diagnosing and treating persistent pain in the orofacial region can be more challenging. Pain in the orofacial region that persists for more than three months is referred to as chronic orofacial pain.<sup>37,38</sup> Chronic orofacial pain can cause sensory and emotional discomfort and exacerbate the pain. This triggers adaptive responses that stimulate the continuous release of cortisol over a long period, leading to psychological disturbances such as depression.<sup>11,37,39,40</sup> The association between chronic orofacial pain and a psychological condition namely depression, was also investigated by Karamat et al. In their study, it was revealed that orofacial might impact the severity of depression where individuals with multiple orofacial pain conditions significantly have higher levels of depression compared to those with a single condition of orofacial pain.<sup>19</sup> Research on neuropathic OFP revealed a similar pattern of findings. By employing the HADS to measure anxiety and depression in combination, Lopez-Jornet et al, found a positive correlation between BMS, poor sleep quality, and comorbid conditions. Regression analysis showed that the likelihood of worsening sleep quality rose by 1.26 times for every 1-point increase in the HADS depression score.<sup>41</sup> The results of these previous studies supported the findings of this systematic review where patients with OFP showed higher depression scores compared to individuals without OFP.

Temporomandibular pain is one of the most prevalent chronic orofacial pain.<sup>37</sup> This is in line with the findings of the current systematic review where most of the patients investigated were those with TMD symptoms. Research conducted on 737 TMD patients, dividing them into pain and non-pain groups, showed a relationship between TMD and psychosocial factors, which are part of the more complex pain-psychopathology relationship, including symptoms of depression and somatization.<sup>15,29</sup> A study by Omezli et al, also showed a significant relationship between the occurrence and severity of TMD symptoms and depressive symptoms. This indicates that patients with TMD symptoms have a 1.90 times higher risk of experiencing depression.<sup>26</sup>

A study that looked at the correlation between pain and depression in patients with myalgia and arthralgia also discovered a slight to significant correlation between orofacial pain and depression. According to the study, those with myalgia and arthralgia TMD had elevated levels of depressed symptoms.<sup>42</sup> This may be the case because patients may experience more severe symptoms of depression in proportion to the number of physical symptoms they encounter. Consequently, individuals with multiple TMD diagnoses experience increased rates of somatization and depression,<sup>17,29,42</sup> making depression a comorbidity factor for TMD and increasing the prevalence and severity of TMD.<sup>26,30</sup> Additionally, some studies also reported that depression was found more often in patients with chronic TMD compared to those with acute/subacute TMD or individuals without TMD.<sup>33</sup> The presence of depression as a comorbidity of orofacial pain was also mentioned in several articles reviewed in this systematic review.<sup>25,27,33</sup> This is consistent with

previous research theories stating that depression is a comorbidity of chronic pain, increasing the likelihood of individuals experiencing pain that leads to disability and decreased quality of life.<sup>7,25,34</sup>

According to research included in this comprehensive review, those who experience orofacial pain may become more depressed as a result of the pain itself, including those who suffer from burning mouth syndrome (BMS) and persistent idiopathic facial pain (PIFP).<sup>24</sup> Previous research also supported this finding, stating that the severity of pain is associated with the level of depression experienced by individuals.<sup>43</sup> This could be a result of elevated cortisol levels following orofacial tissue damage, which can then result in psychological problems like depression.<sup>39</sup> Previous studies also mentioned that orofacial pain can activate the Hypothalamic-Pituitary-Adrenal (HPA) axis, an axis that is responsible for the release of cortisol hormones in individuals with depression.<sup>39,40,44</sup> To note, depression can occur due to reduced availability of monoamine neurotransmitters such as 5-hydroxytryptamine and norepinephrine in the central nervous system.<sup>30</sup> Damage to structures related to the orofacial region can lead to the emergence of pain in that area.<sup>39,45</sup> The relationship between depression and orofacial pain is also influenced by the increased regulation of cytokines such as IL-1 $\beta$ , TNF $\alpha$ , or IL-6, causing an inflammatory response in the central nervous system.<sup>32</sup> Several studies suggest that depression is likely to exacerbate the degree of pain.<sup>17,29</sup> It is also affected by the (longer) length of symptoms, and in patients with orofacial pain, it becomes a major predictor of the severity of depression.<sup>30</sup>

Regardless of the available evidence regarding the association between orofacial pain and depression, the studies reviewed in this systematic review used different depression and pain scales, which may act as a potential limitation as the homogeneity of evidence provides clearer generalizability.

## Conclusion

Patients with orofacial pain are often accompanied by comorbidities, including depression. In line with most previous studies, the association between orofacial pain and depression was also revealed in this systematic review. The findings of this systematic review suggested a positive correlation between orofacial pain and depression. Additionally, it was also found that chronic orofacial pain might act as a trigger factor for worsened depression. Based on the results of this systematic review, it is recommended that the management of orofacial pain should consider the possible involvement of psychological comorbidity(ies) such as depression.

## Disclosure

The authors report no conflict of interest in this work.

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