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Association of chronic periodontitis with chronic migraine: A systematic review and meta-analysis

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ABSTRACT

Background: Chronic periodontitis (CP) is a chronic inflammatory disease, primarily caused by microbial infections and characterized by immune system dysfunction. The latter ultimately leads to the progressive destruction of the alveolar bone supporting the teeth in the jawbones. Chronic migraine (CM) is a complex disorder characterized by repetitive episodes of moderate to severe headaches that unfold over hours to days. The episodes are usually unilateral and generally associated with nausea and light and/or sound stimuli sensitivity. The disease is a common cause of disability and loss of working hours, as it significantly burdens the patient's daily life. CP and CM association is clinically relevant as both involve inflammatory mechanisms and immune dysfunction.

Aim: To systematically review the literature on the epidemiological association between CP and CM in adults.

Methods: The study protocol followed the PRISMA 2020 statement. The design of the study adhered to the Cochrane methodology. A comprehensive literature search was conducted in PubMed, Scopus, and Cochrane databases, as well as a manual search and evaluation of gray literature sources. The Review Manager (RevMan) 5.4 software was used for the meta-analysis. The effect size of the outcome was expressed as odds ratio (OR) with a 95 % confidence interval (CI), providing a measure of the association between CP and CM. The Chi-square test and I^2 statistic were employed to assess heterogeneity among the included studies. The inclusion criteria were English language, observational (case-control) design, and report of the diagnostic criteria for CP and CM. Duplicate entries were excluded. The reliability and quality of the included studies were assessed using the Newcastle-Ottawa Scale (NOS) and GRADE tools. Two independent reviewers performed all evaluations and a third resolved discrepancies.

Results: The meta-analysis included three observational studies with 522 participants. CM patients were 2.82 times more likely to be diagnosed with CP compared with healthy controls. This association was statistically significant (OR 2.82, 95 % CI 1.96–4.05, $p < 0.0001$); however, the external generalizability is limited because of the examination of data originating from populations with specific ethnic backgrounds.

Conclusion: A high prevalence of CP was found among patients with CM compared with healthy controls. Healthcare professionals should be aware of the correlation between these pathological conditions to provide patients with high-quality care through an effective and comprehensive diagnostic and therapeutic approach.

Abbreviations: CP, chronic periodontitis; CM, chronic migraine; PRISMA, preferred reporting items for systematic reviews and meta-analyses; NOS, Newcastle-Ottawa scale; GRADE, grading of recommendations assessment, development and evaluations.

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1. Introduction

Migraine is a genetic disorder characterized by episodes of moderate to severe headache, usually unilateral, generally associated with nausea and sensitivity to light and sound stimuli. Migraine episodes are complex and repetitive brain events that unfold over hours to days. The most common type of migraine, about 75 % of cases, is the one without aura [1]. According to the International Headache Classification Committee, a chronic migraine (CM) is defined as a "headache occurring on 15 or more days per month for more than three months, which, on at least eight days per month, has the features of migraine headache" [1,2]. The disease is a common cause of disability and loss of working hours, as it significantly burdens the patient's daily life [1]. CM ranked among the top five causes of years lived with disability (YLD) among all socioeconomic groups in 1990 and 2016 [3]. In 2019, the age-weighted prevalence was estimated to be 14,107.3 per 100,000, while the annual incidence was 1142.5 per 100,000 [4]. The underlying pathophysiology of CM is poorly understood [5]. The evolution of theories to explain migraine in terms of its underlying mechanism has led to two hypotheses: the first suggests that external triggering stimuli cause migraines, while the second concludes that migraines manifest largely due to changes within the same brain [6]. The immune system plays a key role in the pathogenesis of migraine, as various cytokines, including tumor necrosis factor (TNF), interleukin 1 (IL-1) and adiponectin, are involved in inflammatory processes, modulation of pain threshold, sensitization of the fibers of the trigeminal nerve and finally in the manifestation of migraine [5].

Chronic periodontitis (CP) is a long-lasting, complex infectious and inflammatory disease caused by harmful bacterial biofilms known as dental plaque [7]. It is characterized by the gradual and irreversible deterioration of the hard and soft tissues that support the teeth. The clinical picture includes the loss of periodontal tissue support, such as clinical attachment loss (CAL) and radiographic alveolar bone loss, periodontal pockets, and bleeding gums. The bacteria and their byproducts directly or indirectly affect the periodontal tissues [8]. Initially, the pathogenic bacteria and their byproducts trigger an inflammatory response in the periodontal tissues, resulting in swelling, bleeding gums, and an indirect immune reaction from the body [9]. The destruction of periodontal tissues is mainly caused by activating defensive cells like monocytes, lymphocytes, fibroblasts, and other immune cells [10]. Even bacterial-derived lipopolysaccharides stimulate the production of destructive cytokines and mediators, which further activate metalloproteinases, a group of enzymes that break down collagen [11]. The prevalence of CP is around 45–50 % in adults with mild forms, increasing to over 70 % in individuals aged 65 and above [12,13]. Severe CP affects approximately 11.2 % of the global adult population and significantly contributes to tooth loss, compromised nutrition, speech difficulties, lower self-esteem, and diminished overall quality of life. Unfortunately, these periodontal issues necessitate expensive dental treatments that significantly burden the healthcare system [14]. Since 2018, a new classification system for periodontal diseases has been introduced, which categorizes periodontitis based on severity (stage) and progression rate (grade) [7]. The stage refers to the extent of bone and attachment loss and the complexity of required treatment, while the grade indicates the rate of disease progression and biological characteristics [15]. A substantial body of evidence has established a link between CP and systemic conditions, including diabetes, cardiovascular disease, and pregnancy complications [16].

Given that periodontal lesions serve as a reservoir for periopathogenic bacteria, CP can potentially contribute to systemic inflammation, which could be implicated in developing neurological disorders characterized by an inflammatory basis, such as CM.

2. Materials and methods

2.1. Protocol and registration

PRISMA 2020 statement [17] implemented in the protocol, which registered to the PROSPERO database (Record ID: CRD 42,022,361, 022).

2.2. Information sources

A systematic search was conducted in three databases (MEDLINE/PubMed, Scopus, Cochrane Central Register of Controlled Trials - CENTRAL) from inception until September 5th, 2022. In addition, a manual search was performed on Google and Google Scholar to identify relevant studies. Gray literature was also assessed through opengrey.eu. The search terms "chronic periodontitis" and "chronic migraine" were utilized to retrieve pertinent literature. The search strategy in MEDLINE is presented in Supplemental Table 1.

2.3. Inclusion and exclusion criteria

The inclusion criteria for the studies in the systematic review and meta-analysis were as follows:

(i) Study design: Only observational studies, including cross-sectional, case-control, and cohort studies, were considered for inclusion.
(ii) Language: Studies written in English were included without any time limits imposed.
(iii) Ethical Approval: Included studies were required to have obtained approval from relevant ethics committees or institutional review boards.
(iv) Diagnostic Criteria: Studies had to report specific diagnostic criteria for CP and CM. CP diagnosis could be based on clinical or imaging findings or rely on self-report. CM diagnosis was defined according to the International Classification of Headache Disorders criteria.
(v) Study arms: Included studies were expected to provide data on two study arms: (a) patients with CM and (b) healthy controls.

Excluded studies were:

(i) Case Reports and Case Series: Studies falling into the case reports or case series category, considered to provide a lower level of evidence, were excluded.
(ii) Studies written in any language other than English were excluded.
(iii) Age restriction: Studies including participants under 18 years were not included.
(iv) Special conditions: Studies focusing on patients with special conditions, such as malignancies, pregnancy, recent periodontal treatment (scaling, root planning) within the last six months, or having less than five remaining teeth, were also excluded from the analysis.

2.4. Study records

References obtained from the electronic databases were imported into the Mendeley platform for effective study record management. After removing duplicates, the study files were transferred to the Rayyan platform [18]. Two reviewers (AG, IT) independently evaluated the eligibility of each study based on the title and abstract. For the remaining studies, the full text was independently assessed by the same two reviewers (AG, IT). Any conflicts that emerged during any stage of the process were resolved by a third reviewer (AT). This rigorous review process ensured the accuracy and reliability of the study selection

process.

2.5. Data extraction

Data extraction was performed using Microsoft Excel. A dedicated sheet was created to record the identification data of each study, including the first author's name, publication year, and country. Additionally, the demographic characteristics of the study population, such as sample size, age, gender distribution, and the number of male and female participants, were documented for each study separately.

The matching criteria between patients and controls, such as sex and age, were noted. For CM, the number of cases and controls and the presence or absence of chronic periodontitis among patients diagnosed with neurological disease were recorded. The diagnostic method and criteria used for identifying CM were also documented.

Regarding CP, the number of positive and negative individuals within the total sample of each study was recorded, along with the diagnostic methods employed to identify the disease.

Data extraction was conducted independently by two reviewers (AG, IT), with any discrepancies resolved through discussion or with the assistance of a third reviewer (AT). This systematic approach ensured the accurate and reliable extraction of relevant information from the included studies.

2.6. Outcomes

The outcome of the systematic review and meta-analysis focused on determining the prevalence of CP among patients with CM and neurologically healthy controls.

2.7. Bias assessment and confidence

The Newcastle-Ottawa Scale (NOS) was utilized to evaluate the quality of the included observational studies [19]. Each study was assessed independently by two reviewers (AG, IT) based on the quality stars allocated in the areas of selection, comparability between patients and controls, and exposure (for patient-control studies) or outcome (for cohort and cross-sectional studies). The risk of bias was determined as "low", "high", or "moderate-unclear". Any discrepancies during the assessment process were resolved by a third reviewer (AT), ensuring consensus.

To assess the strength of the included studies in the meta-analysis, the GRADE (Grading of Recommendations Assessment, Development and Evaluations) tool was applied [20]. Two members of the authors (AG, IT) independently evaluated the power of the studies as "high", "moderate", "low" or "very low". In case of conflicts, a third reviewer (AT) intervened to resolve them, maintaining the integrity and accuracy of the assessment.

2.8. Statistical analysis

The meta-analysis of the included studies was performed using Review Manager (RevMan) 5.4 software. The effect of the outcome, which in this case was the presence of chronic periodontitis (a dichotomous variable), was measured using the odds ratio (OR) with a corresponding 95 % confidence interval (CI). A random-effects model based on the inverse variance method was employed for the quantitative synthesis. This model considers both within-study and between-study variability when estimating the overall effect size. To assess the heterogeneity among the included studies, the Chi-square test and I^2 statistic were utilized.

3. Results

The literature search identified 636 studies. After removing duplicate entries, 530 studies were assessed based on title and abstract. Five studies of them [21–25] were examined as full-text articles. 2 studies [24,25] were excluded because no exact number of CM cases and controls was reported. Three studies [21–23] were included in the qualitative and quantitative synthesis (meta-analysis) (PRISMA 2020 flow-chart – Fig. 1). There was no need to contact authors during the study selection process. Data from studies included in the meta-analysis are presented in Table 1.

3.1. Risk of bias assessment

The NOS scale was employed to evaluate the quality of the studies included in the analysis. As per the scale, the risk of bias was deemed low (Fig. 2). Fig. 3 provides a comprehensive graph and assessment of the bias elements investigated using the NOS for each study. All primary studies included in the meta-analysis were determined to have a low risk of bias.

3.2. Association between chronic periodontitis and chronic migraine

The meta-analysis included 522 participants, comprising 296 patients with CM and 226 healthy controls. Among the CM patients, 173 were diagnosed with CP, while there were 75 controls with CP. The odds of CP presence in patients with CM were significantly higher compared with healthy controls (OR 2.82, 95 % CI 1.96–4.05, $p < 0.0001$, Fig. 4). No significant heterogeneity was demonstrated across the studies ($I^2 = 0$ %, $p = 0.88$ for heterogeneity, Fig. 4).

3.3. Evaluation for publication bias

Due to the limited number of included studies ($n = 3$), an evaluation could not be conducted [26].

3.4. Evidence strength

The GRADE tool was utilized to evaluate the strength of the data from the primary studies included in the meta-analysis. Initially, the rating was determined to be low since all the included studies were observational. However, based on the pre-defined GRADE criteria, the overall power of the data was assessed to be high (Table 2). Certain domains, namely "inconsistency", "publication bias", and "dose-response association", were deemed not applicable in this context.

4. Discussion

The mechanisms of association between CP and migraine remain unclear. Various factors could explain the link between the two diseases. A possible mechanism of association involves common inflammatory mediators. Higher concentrations of IL-1 and IL-6 were measured in the saliva of periodontal patients compared to periodontally healthy controls [27]. Also, bacterial endotoxins (lipopolysaccharides, LPS) that are part of the outer cell wall of Gram (-) periopathogenic bacteria, released into the systemic circulation, cause an increase in the expression of endothelial leukocyte adhesion molecules-1 and stimulate the release of high levels of proinflammatory mediators from macrophages or monocytes, such as IL-1β, IL-6, TNF-α, prostaglandin E_2 (PGE_2) and nitric oxide (NO) [28,29].

In parallel, leptin, a hormone/cytokine produced during active CP infection, could enhance the production of other cytokines as a regulator of the inflammatory response. Leptin, as it affects the thymus gland, can disturb the immune balance since it promotes the secretion of acute phase inflammatory factors such as IL-1 and TNF-α. The decrease in its concentration values leads to a weakened immune function. It has been shown in animal model studies that leptin promotes the differentiation of T-helper 1 (Th1) cells and can thus regulate the initiation and progression of autoimmune responses [30]. Indications such as changes in leptin concentration levels, both in periodontal patients (detection in

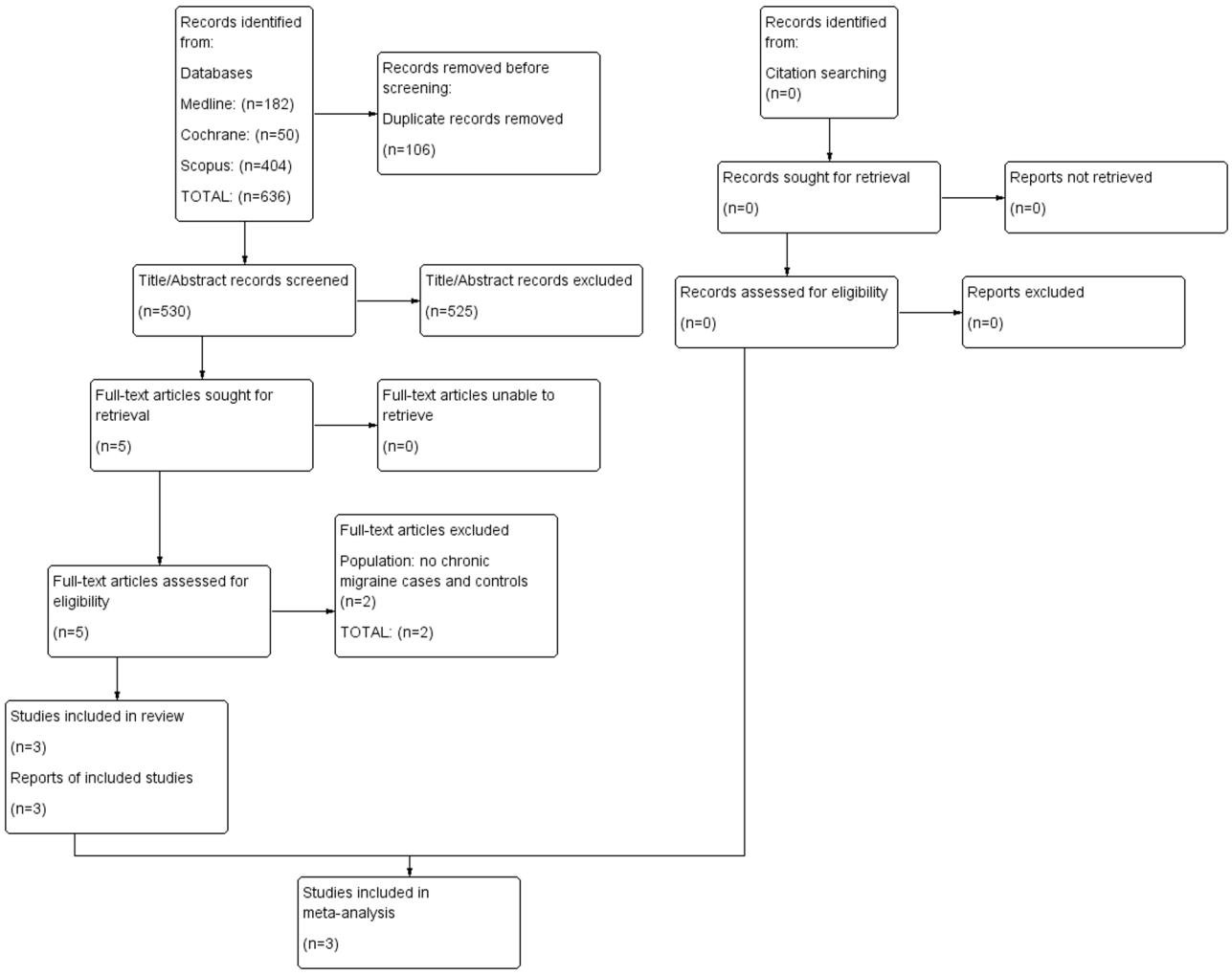

Fig. 1. PRISMA 2020 flow diagram of the systematic review and meta-analysis illustrating the study selection process.

gingival crevicular fluid and serum) [31] and in migraine patients (serum leptin levels are increased in patients diagnosed with chronic migraine) [32] led to direct evidence demonstrating the role of leptin as a key biomarker of CP and CM association [21].

CM is thought to be related to hypersensitivity of the trigeminal sensory system. Despite the attention paid to the role of central sensitization in migraine pathophysiology, Olesen et al. (2009) [33] concluded that migraine is nociceptive pain because of neurogenic infection, as the neuronal hyperexcitability that leads to a migraine episode depends on the activation of peripheral nociceptors. Although the initiation of a migraine episode may occur in deep brain structures, some evidence suggests that the headache phase depends on the stimulation of perivascular sensory nerve terminals [33]. During neurogenic inflammation, neuropeptides and chemical mediators are released from the peripheral terminals of sensory neurons. An important neuropeptide for migraine pathophysiology is Calcitonin-Gene Related Peptide (CGRP) [34,35], whose role in inflammation is debated whether it is pro- or anti-inflammatory [35]. Procalcitonin, a precursor form of the calcium regulatory hormone, the secretion of which is regulated by CGRP [34], is significantly increased during conditions of intense inflammation and has been associated with mortality and severity of conditions such as septicemia [36]. The study by Leira et al. (2018a) [25] found high procalcitonin values in the serum of patients with CP and chronic migraine; in another study, it was shown that patients with migraine have a higher prevalence of CP compared to neurologically healthy controls, while patients with migraine and CP showed increased levels of CGRP in their serum concerning periodontally healthy controls [22]. All the above substantiates the role of CGRP in the possible association of CP and migraine.

Also, vascular inflammation, because of the action of inflammatory mediators, is associated with migraine episodes [37]. Increased levels of inflammatory factors such as C-reactive protein (CRP) or PTX3 (Pentraxin-related protein) were found in the systemic circulation of migraine patients compared to non-migraine controls [38]. The finding of high levels of PTX3 and the cytokine sTWEAK (serum Tumor Necrosis Factor-Like Weak Inducer of Apoptosis) in the serum was associated with periodontal patients [39], while recently, researchers associated the advanced form of periodontitis in migraineurs patients, with systemic vascular inflammation which manifests as a consequence of increased levels of PTX3 and sTWEAK [40]. It appears that CP and migraine could be causally related to inflammatory processes and vascular endothelial changes resulting from the action of common inflammatory mediators.

However, links of association of CP with migraine could also be sought in microbial factors. Helicobacter pylori (H. pylori) is a spiral bacterium that grows in the digestive tract and is detected in more than half of the world's population. The main clinical manifestations related to the bacterium include asymptomatic gastritis to gastrointestinal malignancy [41]. The oral cavity plays an important role as a reservoir of H. pylori, as it is detected in dental plaque, saliva and oral mucosa [42,43], while at the same time, good oral hygiene and the treatment of periodontitis appears to be essential prevention against the recurrence of

Table 1
Characteristics of the included studies.

	Study						Population		Chronic Periodontitis			Chronic Migraine				
id	First author	Year	Country	Type	Matching	N	Sex (M/F)	Age (y)	Definition	Positive	Negative	Definition-criteria	Positive	Negative	PerioPositive	PerioNegative
1	Leira [21]	2017	Spain	case-control	sex, age	150	M: 5, F:145	45.7 ± 11.0	CP when≥2 interproximal sites with CAL ≥3 mm and ≥2 interproximal sites with PPD ≥4 mm (different tooth) or 1 site with PPD ≥5 mm	74	76	International Classification of Headache Disorders 3rd edition criteria (IHS 2013)	92	58	53	39
2	Ameijeira [23]	2019	Spain	case-control	sex, age	193	M: 4, F:189	47.0 ± 9.6	Mild CP when ≥ 2 interproximal sites with CAL ≥ 3 mm and ≥ 2 interproximal sites with PPD ≥ 4 mm (not on the same tooth) or 1 site with PPD ≥ 5 mm. Moderate CP when ≥ 2 interproximal sites with CAL ≥ 4 mm (not on the same tooth) or ≥ 2 interproximal sites with PPD ≥ 5 mm, also not on the same tooth. Severe CP when≥ 2 interproximal sites with CAL ≥ 6 mm (not on the same tooth) and ≥ 1 interproximal site with PPD ≥ 5 mm.	88	105	International Classification of Headache Disorders 3rd edition criteria (IHS 2013)	102	91	60	42
3	Leira [22]	2019	Spain	case-control	sex, age	179	M:4, F:175	47,2	CP when ≥ 2 interproximal sites with CAL ≥ 3 mm and ≥ 2 interproximal sites with PPD ≥ 4 mm (not on the same tooth) or one site with PPD ≥ 5 mm	87	92	International Classification of Headache Disorders 3rd edition criteria (IHS 2013)	102	77	61	41

CAL: clinical attachment loss; CP: chronic periodontitis; F: female; M: male; PPD: probing pocket depth;.

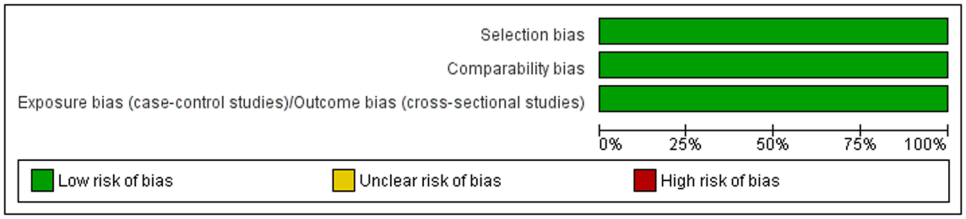

Fig. 2. Newcastle-Ottawa Scale (NOS). Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

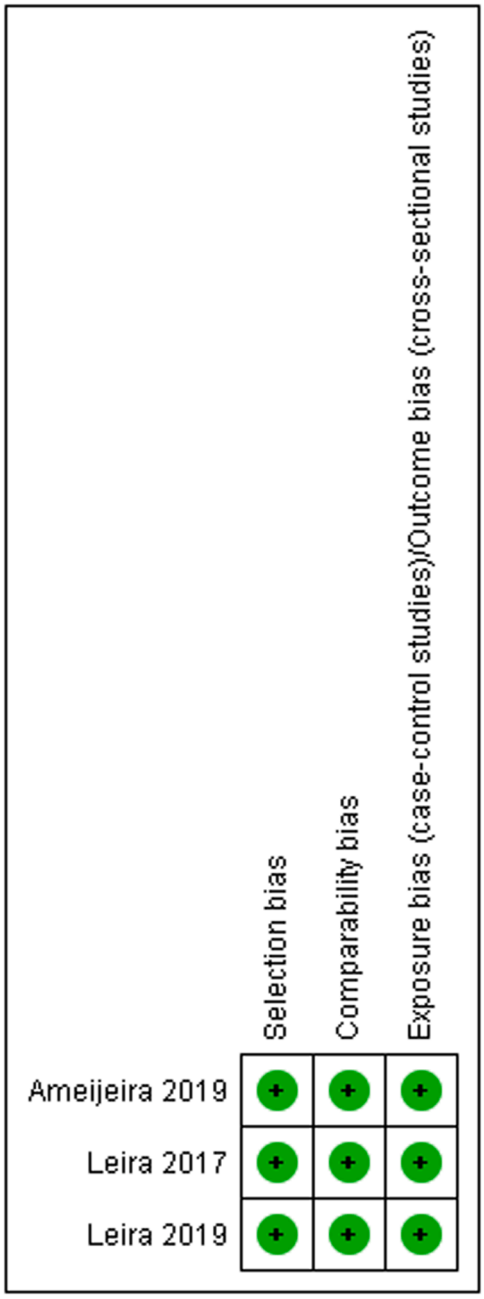

Fig. 3. Newcastle-Ottawa Scale (NOS). Risk of bias summary: review authors - judgments about each risk of bias item for each included study.

gastric helicobacter infection [42,44]. A systematic review and meta-analysis by Wei et al. (2019) [45] concluded that CP is potentially associated with oral H. pylori infection in adults and that H. pylori colonization of the oral cavity may be a potential risk factor for CP, as detection of the bacterium in the mouth increases the risk of CP event by 3.42 times. At the same time, the authors of another meta-analysis that reviewed five studies performed on 903 patients concluded a statistically significant prevalence of H. pylori infection in patients with CM compared with healthy controls [46]. Taking these into account, it seems that H. pylori could play a role as a key pathogenetic link between CP and migraine as the cross-antigenicity of H. pylori and periopathogenic organisms via heat shock proteins induces a strong immunopathological inflammatory response [47,48].

The present study has several strengths worth noting. Firstly, it employs a rigorous methodology, including a comprehensive literature search, assessment of published and unpublished literature, and consideration of publication bias. Additionally, the study follows the latest PRISMA 2020 guidelines, ensuring a standardized and transparent approach to the review process. Furthermore, the absence of heterogeneity among the included studies enhances the reliability of the study results. This lack of heterogeneity is also why a sensitivity analysis was not conducted. Moreover, despite not being an exclusion criterion, none of the primary studies incorporated a self-reported diagnosis of periodontitis. Another strength of this review is its focus on chronic periodontitis rather than encompassing all periodontal diseases, including gingivitis. By narrowing the scope to CP, the study assesses the long-term impact that established periodontal inflammation may have on neurologic disease. This targeted approach provides valuable insights into the chronicity of the effect and its potential implications.

This meta-analysis has a few limitations that should be acknowledged. Firstly, the included studies are observational, lacking randomized controlled trials (RCTs), considered the gold standard for establishing high-quality evidence. As a result, the reliability of the evidence provided by the included studies may be limited, and a causal association between the two diseases cannot be firmly established. Another limitation is the small number of selected studies, which restricts the ability to conduct additional analyses, such as funnel plots that assess publication bias. The limited sample size may also impact the generalizability of the findings, as all the studies pertain to a specific population from Spain. Therefore, the applicability of these findings to populations with different characteristics is uncertain. Additionally, the evaluation of some domains of the GRADE tool was deemed not applicable, further diminishing the reliability and utility of the tool in this context. This highlights the challenges in applying the GRADE criteria to observational studies and underscores the need for well-designed future studies.

Despite these limitations, this meta-analysis represents the current state of the evidence. Conducting meta-analyses with high-quality observational studies in the future could potentially generate sufficient evidence to establish an association between the two diseases, in particular the effect of periodontitis according to its severity, and identify areas for further research.

5. Conclusion

In summary, there is a statistically significant CP prevalence among patients with CM compared with healthy controls. Regular dental check-

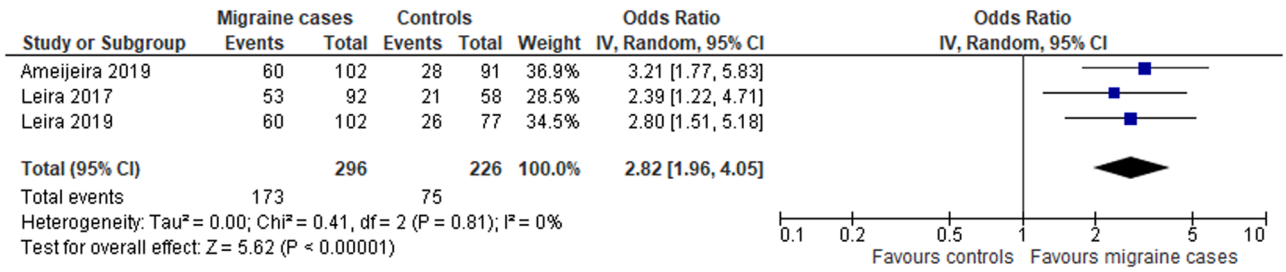

Fig. 4. Forest plot demonstrating the association of chronic periodontitis and chronic migraine (CM).

Table 2
GRADE-strength of the evidence.

	First author	Ameijeira [23]	Leira [21]	Leira [22]
	Year	2019	2017	2019
	Study type	Case-control	Case-control	Case-control
	Initial rating	Low	Low	Low
	Comparison	CM cases vs. healthy controls	CM cases vs. healthy controls	CM cases vs. healthy controls
	Outcome	Prevalence of CP	Prevalence of CP	Prevalence of CP
Rating down	Study limitations (risk of bias)	Low risk (no reason to downgrade)	Low risk (no reason to downgrade)	Low risk (no reason to downgrade)
	Inconsistency	Not applicable (no reason to downgrade)	Not applicable (no reason to downgrade)	Not applicable (no reason to downgrade)
	Indirectness of evidence	Direct evidence (no reason to downgrade)	Direct evidence (no reason to downgrade)	Direct evidence (no reason to downgrade)
	Imprecision	No reason to downgrade	No reason to downgrade	No reason to downgrade
	Publication bias	Not applicable (no reason to upgrade)	Not applicable (no reason to upgrade)	Not applicable (no reason to upgrade)
Rating up	Magnitude of effect	Strong association (+1)	Strong association (+1)	Strong association (+1)
	Dose-response relationship	Not applicable (no reason to upgrade)	Not applicable (no reason to upgrade)	Not applicable (no reason to upgrade)
	All plausible biases-confounders	Plausible confounders-adjustment (+1)	Plausible confounders-adjustment (+1)	Plausible confounders-adjustment (+1)
	Final rating	High	High	High

CM: chronic migraine; CP: chronic periodontitis.

ups and the treatment of CP may benefit the general treatment of migraine attacks; therefore, the respective health professionals should consider the possible association between the two diseases.

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Declaration of competing 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.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dentre.2024.100083.

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