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SYSTEMATIC REVIEW

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# Association between juvenile idiopathic arthritis and periodontal diseases: a systematic review and meta-analysis

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## Abstract

Although periodontal diseases have been widely reported in patients with juvenile idiopathic arthritis (JIA), their association with JIA remains controversial. This systematic review and meta-analysis aimed to evaluate the association between JIA and periodontal diseases to facilitate oral health management and periodontal disease prevention in JIA patients. We conducted a comprehensive search of Web of Science, Cochrane Library, PubMed, Embase, Chinese Scientific and Technological Journal (VIP) database, Wan Fang Data, China National Knowledge Infrastructure (CNKI), and China Biomedical Literature Database (CBM) up to 30 September 2022, without publication dates or language restrictions. Two authors independently evaluated observational studies for inclusion, and the quality of the included studies was assessed using the Newcastle Ottawa Scale (NOS) and the Agency for Healthcare Research and Quality (AHRQ). Continuous variables are presented as mean difference (MD) and 95% confidence interval (CI). Parameters of the simplified oral hygiene index (OHI-S), plaque index (PI), gingival index (GI), clinical attachment loss (CAL), and probing depth (PD) were considered as outcome measures and were compared between JIA patients and healthy controls. The initial search comprised 15 studies with a total of 1537 individuals. The meta-analysis showed the parameters of OHI-S (MD = 0.12, 95% CI: 0.04–0.19, $p = 0.002$), PI (MD = 2.08, 95% CI: 1.67–2.50, $p < 0.00001$), GI (MD = 0.50, 95% CI: 0.17–0.82, $p = 0.003$), CAL (MD = 0.22, 95% CI: 0.01–0.43, $p = 0.04$), and PD (MD = 1.42, 95% CI: 0.08–2.77, $p = 0.04$) in JIA patients were significantly higher than those of healthy controls. All of the included studies were of high quality. This systematic review and meta-analysis showed a possible association between JIA and periodontal diseases. Therefore, it is recommended to continuously pay attention to the periodontal health of JIA patients and fully explore the underlying mechanism.

## Keywords

Juvenile idiopathic arthritis; Periodontal diseases; Periodontitis; Gingivitis; Meta-analysis

## 1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common childhood chronic autoimmune disease affecting children under the age of 16, persisting for more than 6 weeks and featuring idiopathic arthritis, except for other triggers [1]. JIA affects approximately 1 in every 1000 teenagers [2]. Unfortunately, the disease often persists into adulthood, with up to 50% of patients experiencing either persistent active disease or disease flares after reaching puberty [3].

JIA is often characterized by systemic and local developmental disorders, osteoporosis, muscular dysplasia, exudative arthritis, chronic uveitis, and visceral organ involvement, which have a great adverse impact on the physical and mental development of the affected children [4, 5]. Though its etiology and pathogenesis remain unclear, it is believed to result from a combination of genetic factors such as bacterial infection (Chlamydia pneumoniae, Mycoplasma pneumoniae, Campylobacter jejuni) and virus (hepatitis B virus, Epstein-Barr virus), psychological damage, involvement of human leukocyte antigen (HLA) histocompatibility gene and primary immunodeficiency may lead to JIA [6]. The International Federation of Rheumatic Associations (ILAR) currently classifies JIA into six subtypes based on medical history, clinical features, and laboratory results, namely, systemic arthritis, polyarthritis (negative or positive for rheumatoid factor (RF)), oligoarthritis (persistent or widespread), adhesion-associated arthritis, psoriatic arthritis, and undifferentiated arthritis [7].

Arthritis in JIA can destroy cartilage, affect bone growth, and eventually affect mandibular growth [8]. The administra-

tion of systemic corticosteroids for the treatment of JIA has been shown to have detrimental effects on oral health. Specifically, it can cause periodontal degradation, alveolar bone osteoporosis, and premature tooth development [9], which may impede oral wound healing and increase the susceptibility to infection [10]. The inflammatory characteristics and drug treatment of JIA can lead to several oral manifestations [11], such as decreased saliva flow, periodontal tissue inflammation, mucosal lesions, dental caries, and temporomandibular joint involvement [12]. About 40% to 96% of JIA can develop into unilateral or bilateral temporomandibular arthritis [13, 14], resulting in TMJ injury and altered muscle function and affecting mandibular development. These changes can cause maxillofacial pain, morning stiffness, occlusal disorders, limited mouth opening, joint clicking, reduced range of motion of condyle and mandible, and obvious asymmetric growth of the left and right joints, which can further exacerbate the joint injury and form a vicious circle [15, 16]. Additionally, limited mouth opening, occlusal disorders, and upper limb joint involvement can create challenges for JIA patients in maintaining proper oral hygiene and dental care [10].

Periodontal diseases are chronic infectious diseases of progressive destruction of the periodontal complex caused by the interaction between bacterial infection and host defense function, mainly including gingivitis and periodontitis [17]. Severe periodontitis can lead to loosening, displacement or even loss of teeth, masticatory function impairment, facial depression, and affect the digestive system [18]. Existing literature provides compelling evidence that JIA patients are more susceptible to plaque, gingivitis, and periodontitis compared to healthy controls, which in turn, significantly increases the risk of developing periodontal diseases among this population [19–22]. In the absence of effective preventive strategies and timely treatment, the complications associated with periodontal diseases, such as severe malnutrition and facial deformities, can significantly impair the physical and mental health of patients, increase the financial burden on the patients' families, and strain healthcare resources.

In recent years, more and more studies have been conducted to explore the relationship between JIA and periodontal diseases. Some scholars have found that the relationship between JIA and periodontal diseases may be caused by the common disorder of immune-inflammatory response [23–25]. In addition, studies have noted the occurrence of Porphyromonas gingivalis in JIA [26]. At the same time, although there are reports of dental plaque and gingival bleeding in JIA patients [27, 28], some scholars did not find a significant relationship between JIA and periodontal diseases [10, 29–31]. Thus, there is no consensus on the relationship between JIA and periodontal diseases in present literature. This knowledge gap is significant and may hinder effective oral health management and periodontal disease prevention in JIA individuals.

Hence, the present study was conducted to systematically review and analyze existing evidence on periodontal diseases in JIA patients, with the aim to determine their periodontal status, provide baseline data for future research, and offer theoretical support for the development of a periodontal disease prevention policy and clinical management.

## 2. Methods

The present systematic review and meta-analysis was registered in the International Prospective Register of Systematic Review (PROSPERO, ID: CRD 42022381066) and was conducted in accordance with the Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32].

### 2.1 PICO/PECO research question

The present study aimed to address the clinical question using the PICO framework: "Is there an association between JIA and periodontal diseases?". The population of interest consisted of JIA patients and healthy controls. The intervention or exposure was the presence or absence of JIA, and the comparison was made between periodontal parameters in JIA and non-JIA participants. The primary outcome measures included periodontal parameters, such as simplified oral hygiene index (OHI-S), plaque index (PI), gingival index (GI), clinical attachment loss (CAL), and probing depth (PD).

### 2.2 Search strategy

Comprehensive electronic searches were conducted on Web of Science, Cochrane Library, PubMed, Embase, Chinese Scientific and Technological Journal (VIP) database, Wan Fang Data, China National Knowledge Infrastructure (CNKI), and China Biomedical Literature Database (CBM) from inception to 30 September 2022. The following search terms were used: (1) "Arthritis, Juvenile" or "Juvenile Arthritis" or "Juvenile Idiopathic Arthritis" or "Juvenile Chronic Arthritis". (2) "Periodontal Diseases" or "Periodontitis" or "Gingivitis" or "Oral Health". For instance, relevant studies were retrieved from PubMed using: ((((((Arthritis, Juvenile MeSH)) OR (Juvenile Arthritis Title/Abstract)) OR (juvenile idiopathic arthritis Title/Abstract)) OR (juvenile rheumatoid arthritis Title/Abstract)) OR (juvenile chronic arthritis Title/Abstract)) AND ((((Periodontal Diseases MeSH) OR (Periodontitis Title/Abstract)) OR (Gingivitis Title/Abstract)) OR (Oral Health Title/Abstract)).

### 2.3 Eligibility criteria

The inclusion criteria were: epidemiological studies (cross-sectional studies, case-control studies, cohort studies) that assessed the frequency of periodontal diseases in JIA patients and healthy controls. No publication dates or language restrictions were used during the literature search. If needed, the authors of the studies were contacted through e-mail in case extra data were needed.

The exclusion criteria were: systematic reviews, meta-analyses, case reports, conference presentations, contained animal experiments, lack of control groups, and studies with insufficient data.

### 2.4 Periodontal parameters definition

OHI-S: the amount of debris or calculus found on six preselected tooth surfaces [33].

PI: based on quantifying and locating the amount of plaque

adhering to the dental surface [34].

GI: the criteria were entirely confined to qualitative changes in the gingival soft tissue [34].

CAL: distance between the cementoenamel junction to the pocket base [35].

PD: depth of a sulcus or periodontal pocket was determined by measuring the distance from a gingival margin to the base of the sulcus or pocket with a calibrated periodontal probe [36].

### 2.5 Study selection and data collection

The two researchers screened and cross-checked the literature in the above databases, and in the case of disagreements, a third researcher was consulted to resolve any discrepancies. During the screening process, duplicate studies were removed, and titles and abstracts were screened to identify studies that met the inclusion and exclusion criteria. The suitability of the studies for inclusion in this review was also evaluated. Data extraction was independently performed by two reviewers, and the accuracy of the results was verified by a third reviewer. The main information retrieved from the eligible studies were: name of first author, year of publication, country, type of study, age, sex and the number of participants, periodontal parameters, and research outcomes.

### 2.6 Quality assessment

Two researchers used the Newcastle-Ottawa scale (NOS) to evaluate the methodological quality of the case-control and cohort studies [37]. This assessment scale comprises selection, comparability, and outcome, with a maximum of 9 points (low risk of bias = 7–9, medium risk of bias = 4–6, high risk of bias = 0–3). Meanwhile, two researchers used the Agency for Healthcare Research and Quality (AHRQ) criteria to evaluate the methodological quality of the cross-sectional studies [38]. Two (items 5 and 9) of the 11 items in the AHRQ recommended criteria were not suitable for our study. The cross-sectional studies also scored a maximum of 9 points (low risk of bias = 7–9, medium risk of bias = 4–6, high risk of bias = 0–3). If there was any disagreement, a third researcher was involved to solve it.

### 2.7 Statistical analysis

The meta-analysis was performed using the Review Manager 5.4 software (The Cochrane Collaboration) at a test level of $\alpha = 0.05$ according to the guidelines proposed by the Cochrane manual. The heterogeneity of the results among studies was tested using $I^2$ statistics [39], and statistical significance was defined as $p < 0.05$. The fixed-effect model was used when $I^2$ was $\leq 50\%$ or $p$ was $>0.1$; otherwise, the random-effect model was used. The fixed effect model considered that all studies in the meta-analysis shared a common true effect, while the random effect model considers various true effects across the studies [40]. If there was significant heterogeneity in the included study, sensitivity, descriptive, or subgroup analysis were performed as appropriate. This systematic review and meta-analysis was exempted from review by the local ethics committee due to no direct involvement of any patients' data.

## 3. Results

A total of 626 studies were initially screened, including 303 from Web of Science, 67 from Cochrane Library, 202 from PubMed and 54 from Embase. After removing duplicated articles, 234 articles remained. Following a careful assessment of the title, abstract and full text of the remained articles, 15 were found eligible for this meta-analysis [8, 9, 20, 21, 23, 27–30, 41–46]. The screening process is shown in Fig. 1.

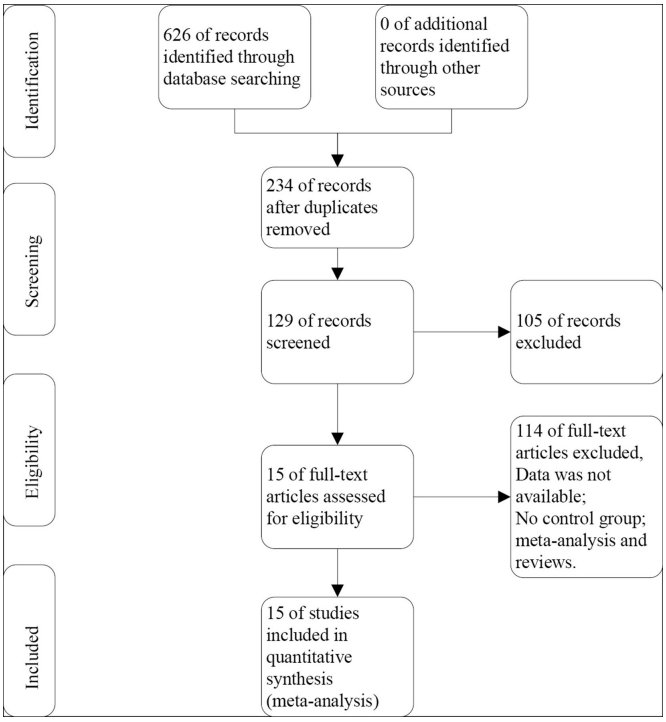



**FIGURE 1. Flow diagram of the study selection process.**

Through a comprehensive analysis of the 15 included articles generated by the above search strategy, relevant data of interest were extracted. Most of the original articles assessed were cross-sectional studies, with one study by Vahabi *et al.* [30] having a case-control study design and a study by Miranda *et al.* [43] having a cohort study design. These articles involved 1537 participants with a mean age ranging from 4.6 to 27 years old. In each article, 27 to 324 JIA patients and healthy control of the same age were selected. All JIA patients assessed in the 15 investigated studies received systemic immune-related therapy. Their basic information is shown in Table 1. The quality of the included articles was assessed according to NOS and AHRQ, as shown in Tables 2 and 3, respectively.

Not all of these 15 investigated studies analyzed OHI-S, PI, GI, CAL and PD. We found that only 4 studies [8, 28, 45, 46] provided available results for OHI-S, and 6 groups of data were extracted. As a result of low heterogeneity ($I^2 = 0\%$), the random effect model was employed for the meta-analysis, revealing that JIA patients had significantly higher OHI-S scores than healthy controls (MD = 0.12, 95% CI: 0.04–0.19, $p = 0.002$) (Fig. 2).

**TABLE 1. Characteristics of the included studies.**

| Study | Country | Study design | JIA Sample size (M/F) | JIA Age (yr) | Controls Sample size (M/F) | Controls Age (yr) | Periodontal health parameters | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Welbury 2003 [27] | Britain | Cross-sectional | 149 (42/107) | Mean 17.9 | 149 (42/107) | Mean 17.9 | ②③ | Assessment of gingival inflammation and oral hygiene, as measured by the gingival index, plaque index, and oral cleanliness index, showed that the study groups had more gingival inflammation ($p < 0.0001$), more dental plaque ($p < 0.0001$) and poorer oral cleanliness ($p < 0.0001$) in each age band. |
| Gil 2022 [28] | Norway | Cross-sectional | 162 (29/133) | 12.0 ± 3.2 | 162 (28/134) | 12.0 ± 3.2 | ① | Plaque and gingival bleeding were more frequent in individuals with JIA than in controls. Adjusted analyses showed an association between JIA status and OHI-S >0 (OR = 2.33, 95% CI: 1.47–3.67, ICC = 0.45). Surface-specific distribution of plaque varied among the two groups. |
| Ahmed 2004 [29] | Britain | Cross-sectional | 55 (21/34) | 8.9 ± 3.2 | 55 | 9.2 ± 3.2 | ②③ | The mean gingivitis score for the permanent teeth only was significantly greater in the JIA children compared with the controls ($p = 0.02$). |
| Vahabi 2015 [30] | Iran | Case-control | 30 | <16.0 | 30 | <16.0 | ②④⑤ | In JIA patients, no significant relationships were found between JIA findings and periodontal parameters. |
| Miranda 2003 [23] | Brazil | Cross-sectional | 32 (10/22) | 15.9 ± 2.7 | 24 (12/12) | 14.7 ± 2.3 | ②④⑤ | The percentage of JIA patients having at least one site with proximal CAL ≥2 mm was 25 versus 4.2 in the control group (one-tailed Fisher's exact test, $p = 0.0370$). The mean percentages of visible plaque and bleeding were similar in both groups. However, the mean percentage of sites with PD ≥4 mm was significantly higher in the JIA group than in the control group and that of sites with proximal CAL ≥2 mm was 0.71 in JIA patients and 0.0001 in controls. |
| Saviloi 2004 [20] | Brazil | Cross-sectional | 36 (10/26) | Mean 10.8 (4.7–20.0) | 13 (4/9) | Mean 4.6 (1.0–13.0) | ② | The indexes of plaque and gingival bleeding were significant in juvenile idiopathic arthritis patients with a higher number of superior limb joints involved ($p = 0.055$). |

**TABLE 1. Continued.**

| Study | Country | Study design | JIA Sample size (M/F) | JIA Age (yr) | Controls Sample size (M/F) | Controls Age (yr) | Periodontal health parameters | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Pugliese 2016 [41] | Brazil | Cross-sectional | 35 (0/35) | 11.9 ± 2.0 | 35 (0/35) | 12.5 ± 3.0 | ②③④ | Complete periodontal assessments revealed that gingival index, dental plaque, gingival bleeding, and clinical dental attachment indices were alike in JIA patients and controls ($p > 0.05$), except for gingival enlargement in the former group ($p < 0.0001$). |
| Reichert 2006 [42] | Germany | Cross-sectional | 78 (33/45) | 12.0–19.0 | 75 (41/34) | 13.0–19.0 | ④ | JIA patients had slightly higher mean percentages of sites with CAL 43.5 mm (0.58% versus 0.22%, $p = 0.041$). There was no significant difference in the prevalence of patients and controls who had sites with CAL 43.5 mm (25.6% versus 17.3%, $p = 0.212$). |
| Miranda 2006 [43] | Brazil | Cohort | 18 (9/9) | 17.3 ± 2.6 | 14 (9/5) | 16.6 ± 1.5 | ②④⑤ | The number of sites with plaque decreased, and the number of pockets ≥4 mm increased, whereas bleeding levels and the extension of AL remained unchanged. |
| Anne 2006 [44] | Denmark | Cross-sectional | 10 (0/10) | 27.0 ± 4.3 | 25 (15/10) | 25.0 ± 3.1 | ②④⑤ | In JIA patients, the percentage of sites with PD ≥4 mm correlated significantly with the percentage of sites with CAL ≥2 mm (r = 0.84; $p = 0.003$). |
| Kobus 2019 [8] | Poland | Cross-sectional | 34 (13/21) | 6.0–18.0 | 34 (13/21) | 6.0–18.0 | ①③ | There were no differences in dental hygiene or dental and periodontal status between the JIA and C groups. A positive correlation of MMP-2 with the OHI-S index and a negative correlation of MMP-2 with SF was found in JIA. |
| Feres de Melo 2014 [45] | Brazil | Cross-sectional | 36 (16/20) | 9.3 ± 1.9 | 36 (17/19) | 9.5 ± 1.8 | ①③ | JIA individuals presented poorer oral hygiene ($p \leq 0.05$) but no difference in dental caries and gingival indices. |

**TABLE 1. Continued.**

| Study | Country | Study design | JIA Sample size (M/F) | JIA Age (yr) | Controls Sample size (M/F) | Controls Age (yr) | Periodontal health parameters | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Leksell 2008 [9] | Sweden | Cross-sectional | 41 (12/29) | 13.6 ± 2.3 | 41 (16/25) | 13.1 ± 1.1 | ②⑤ | The frequencies of sites with plaque (32% *vs.* 19%, $p = 0.013$), calculus (11% *vs.* 5%, $p = 0.034$), bleeding on probing (26% *vs.* 14%, $p < 0.01$), and probing depth ≥2 mm (32% *vs.* 2%, $p < 0.001$) were higher among JIA patients. No sites with attachment loss or a reduced marginal bone level were observed. |
| Santos 2015 [46] | Brazil | Cross-sectional | 17 (4/13) | 9.8 ± 2.9 | 15 (3/12) | 10.7 ± 2.2 | ① | Children and adolescents with JIA had fewer caries in their primary dentition and more gingival bleeding after probing than those without JIA. The frequency of temporomandibular disorders was 50.0% for JIA patients and 46.7% for their healthy counterparts. |
| Grevich 2019 [21] | America | Cross-sectional | 85 (16/69) | 14.0 ± 2.2 | 11 (9/2) | 14.0 ± 2.4 | ②③ | JIA patients overall had significantly more gingival inflammation compared to dental patients, as evidenced by bleeding on probing of the gingiva, the most specific sign of active inflammation ($p = 0.02$). |

*Notes: in the sample size, M is male and F is female; in age, Mean is the average; periodontal health parameters: ① simplified oral hygiene index (OHI-S), ② plaque index (PI), ③ gingival index (GI), ④ clinical attachment loss (CAL); ⑤ probing depth(PD); JIA is Juvenile Idiopathic Arthritis; OR is odds ratio; CI is confidence interval; ICC is intra-class correlation coefficient; AL is attachment loss; MMP-2 is matrix metalloproteinase-2; SF is salivary flow rate.*

**TABLE 2. Results of NOS of included studies.**

| Study | | | | | * | | | | Total | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Vahabi 2015 [30] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 | High |
| Miranda 2006 [43] | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 8 | High |

*Notes: item—represents 8 items of NOS scoring criteria. "*" means the maximum of 2 points for each item; each of the remaining items will have a maximum of 1 point.*

In regard to PI, 5 studies [23, 27, 29, 30, 43] contained related results, and there were 9 groups of data. Due to low heterogeneity ($I^2$ = 0%), the random effect model was adopted. The meta-analysis showed that: JIA patients had a significantly higher PI than healthy controls (MD = 2.08, 95% CI: 1.67–2.50, $p < 0.00001$) (Fig. 3).

For GI, 4 studies [8, 27, 29, 45] contained related results, and comprised 9 groups of data. Due to the high heterogeneity ($I^2$ = 88%), the random effect model was adopted. Our meta-analysis showed that: JIA patients had a significantly higher GI than healthy controls (MD = 0.50, 95% CI: 0.17–0.82, $p$ = 0.003) (Fig. 4).

For CAL, 5 studies [23, 30, 42–44] reported related results, and 5 groups of data were extracted. Due to high heterogeneity ($I^2$ = 72%), the random effect model was adopted. The meta-analysis showed that: JIA patients had a significantly higher CAL ≥2 mm than healthy controls (MD = 0.22, 95% CI: 0.01–0.43, $p$ = 0.04) (Fig. 5).

For PD, 4 studies [23, 30, 43, 44] reported on related results, from which 5 groups of data were extracted. Due to high heterogeneity ($I^2$ = 79%), the random effect model was adopted, and the meta-analysis results showed that JIA patients had a significantly higher PD ≥2 mm than healthy controls (MD = 1.42, 95% CI: 0.08–2.77, $p$ = 0.04) (Fig. 6).

A subgroup analysis of the GI was conducted according to the age of the participants (mixed dentition group, permanent dentition group). The results showed no significant change in heterogeneity (mixed dentition group: MD = 0.20, 95% CI: −0.07–0.48, $p$ = 0.15; permanent dentition group: MD = 1.47, 95% CI: −0.13–3.08, $p$ = 0.07) (Fig. 7), indicating no significant correlation between the age of JIA patients and the risk of periodontal diseases. Heterogeneity might have been due to the sample size of the included studies. Individual studies were eliminated one by one to identify the source of PD and CAL heterogeneity. We found that when excluding the study of Vahabi 2014 [30], the heterogeneity of PD and CAL changed significantly (PD: $I^2$ = 78% to $I^2$ = 0, CAL: $I^2$ = 72% to $I^2$ = 36%), suggesting that this study might be the source of heterogeneity.

The fixed effects model and random effects model were alternately used to analyze the 5 outcome indicators of this meta-analysis, and the results showed no significant change, indicating that the meta-analysis results of corresponding outcome indicators were stable and reliable.

## 4. Discussion

The present systematic review and meta-analysis aimed to evaluate the correlation between JIA and periodontal diseases. JIA is the most common chronic autoimmune disease in childhood and often results in multiple large joint involvements and limited function [1–5]. Periodontal diseases are chronic infectious diseases of periodontal tissue that can lead to gingival bleeding, periodontal pocket formation, alveolar bone resorption, as well as loosening, displacement and even loss of teeth, which may seriously harm to patient's oral health [19]. Compared with their healthy peers, the incidence of periodontal diseases in JIA patients is significantly increased [17, 18]. Exploring the relationship between JIA and periodontal diseases is beneficial to oral health management and periodontal disease prevention of JIA patients. Therefore, we conducted this systematic scientific review and meta-analysis to clarify the relationship between JIA and periodontal diseases.

The 15 investigated studies were published between 2003 and 2022, and all of them were found to be of high quality. The findings revealed that JIA patients had significantly higher levels of OHI-S, PI, GI, CAL ≥2 mm, and PD ≥4 mm than the healthy controls.

Poor oral hygiene and the accumulation of dental plaque in the mouth were common oral problems and the main pathogenic factors of periodontal diseases [47]. Studies have revealed that the poor oral hygiene and the increased risk of OHI-S and PI in JIA patients were related to the functional limitation of the upper limb and temporomandibular joint involvement in JIA patients and inadequate oral cleanliness. On the other hand, this risk was closely related to low oral saliva flow velocity and changes in saliva calcium, phosphorus, potassium and other chemical parameters in JIA patients [22].

With an increase in dental plaque and the imbalance in the saliva biochemical environment, JIA patients exhibit an increase in GI score and gingivitis symptoms such as gingival swelling and bleeding [29]. Porphyromonas gingivalis, a gram-negative anaerobe implicated in the pathogenesis of periodontitis and the only known prokaryote with citrulline foreign antigen ability [48], is also associated with JIA [26]. In JIA patients with positive anti-cyclic citrullinated peptide (CCP) antibodies, a citrullinated peptide produced by Porphyromonas gingivalis may impair the immune system's recognition of endogenous citrulline antigens, leading to a strong immune response to self-and non-autogenous-citrulline antigens, increasing the likelihood of periodontitis development [21, 48, 49]. Moreover, drugs taken by JIA patients, such as methotrexate (MTX), often change the local immune response of periodontal tissues and aggravate gingival inflammation [28]. As a folate antagonist, MTX affects neutrophil superoxide anion formation and adhesion, modulates cytokine responses at multiple levels, and promotes apoptosis of activated lymphocytes [43]. Since MTX mainly targets rapidly renewing cells such as those of the oral mucosa [9], JIA patients often exhibit a significantly higher gingivitis score than healthy controls [29], Resulting in episodes of pain and discomfort that the examiner

**TABLE 3. Results of AHRQ of included studies.**

| Study | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | Total | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Welbury 2003 [27] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 7 | High |
| Gil 2022 [28] | √ | √ | √ | - | × | √ | √ | √ | √ | √ | - | 8 | High |
| Ahmed 2004 [29] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 7 | High |
| Miranda 2003 [23] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 7 | High |
| Saviloi 2004 [18] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 7 | High |
| Pugliese 2016 [41] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 7 | High |
| Reichert 2006 [42] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 7 | High |
| Anne 2006 [44] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 7 | High |
| Kobus 2019 [8] | √ | √ | √ | - | × | √ | √ | √ | √ | √ | - | 8 | High |
| Feres de Melo 2014 [45] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 7 | High |
| Leksell 2008 [9] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 8 | High |
| Santos 2015 [46] | √ | √ | √ | - | × | √ | √ | √ | √ | √ | - | 8 | High |
| Grevich 2019 [21] | √ | √ | √ | - | × | √ | √ | √ | × | √ | - | 7 | High |

*Notes: item 1–11 represents the 11 items of the AHRQ recommended criteria. "√" means "YES", "×" means "NO", and "-" means "not suitable".*

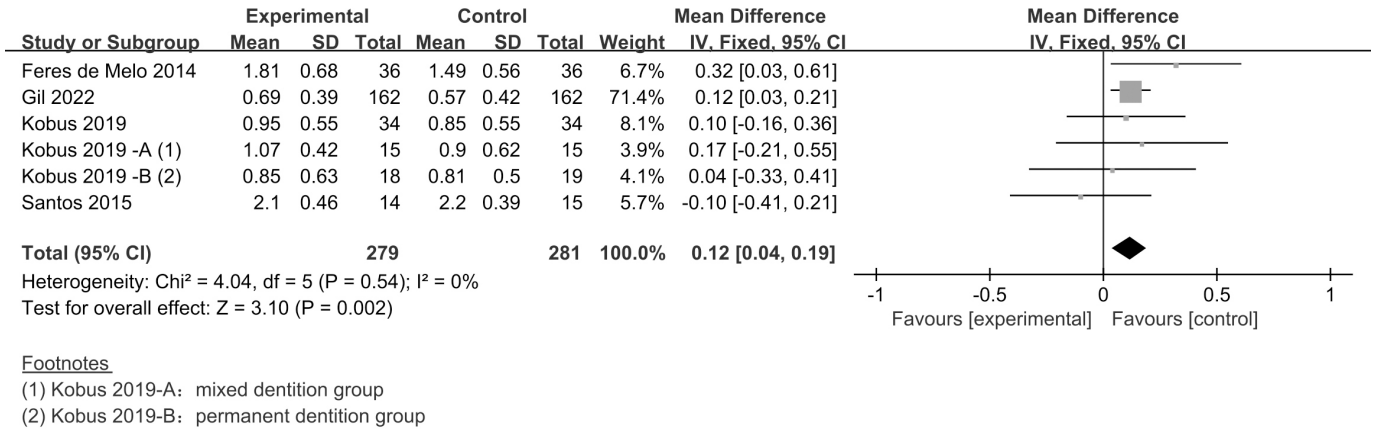
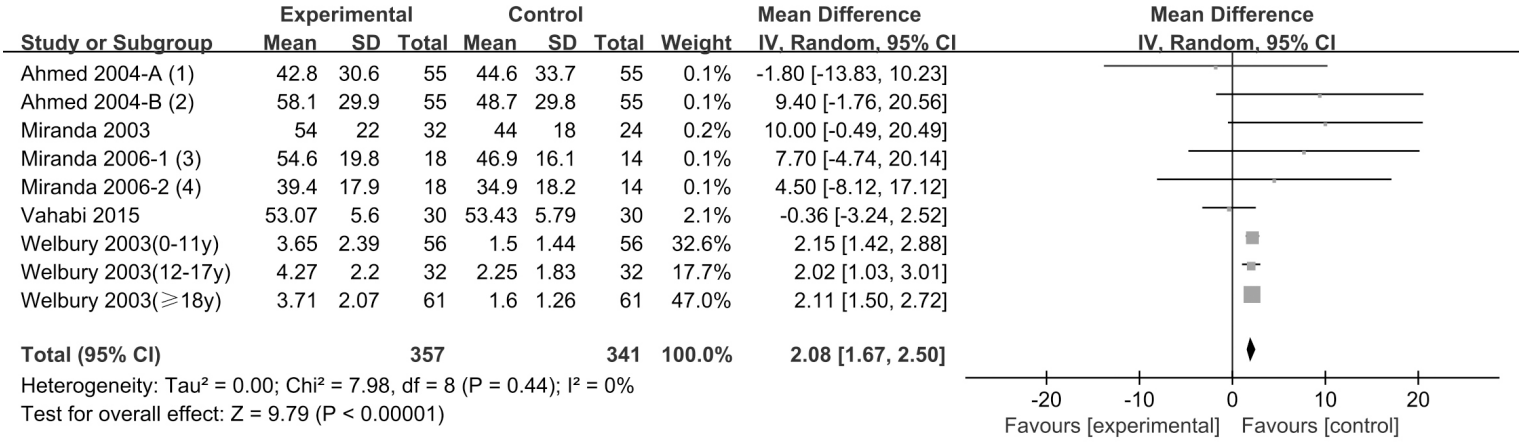
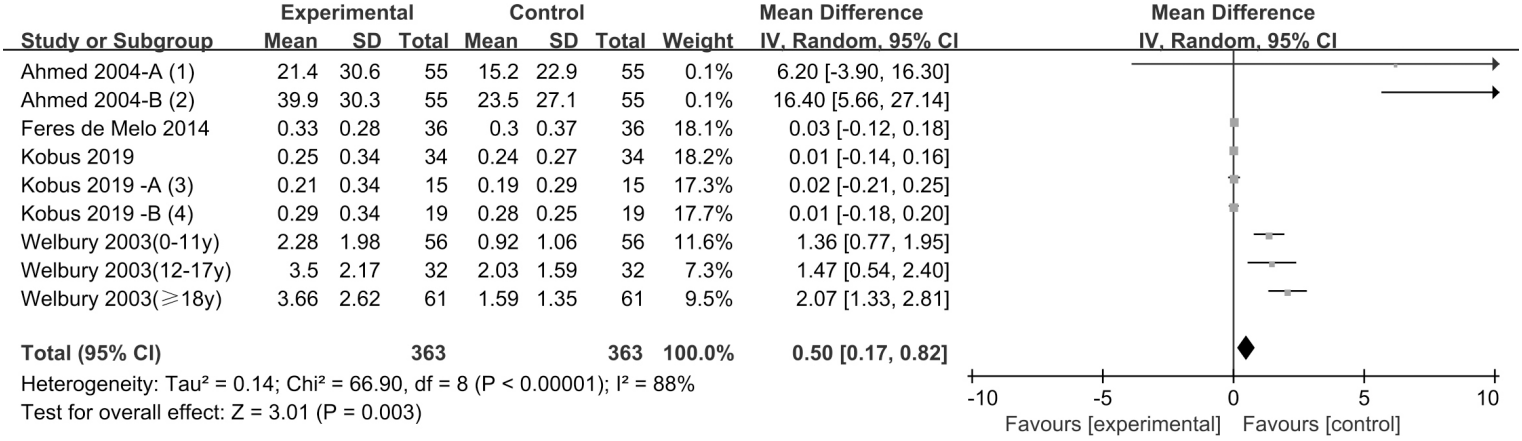



**FIGURE 2. Forest plot of OHI-S.** Notes: SD is standard deviation; CI is confidence interval.



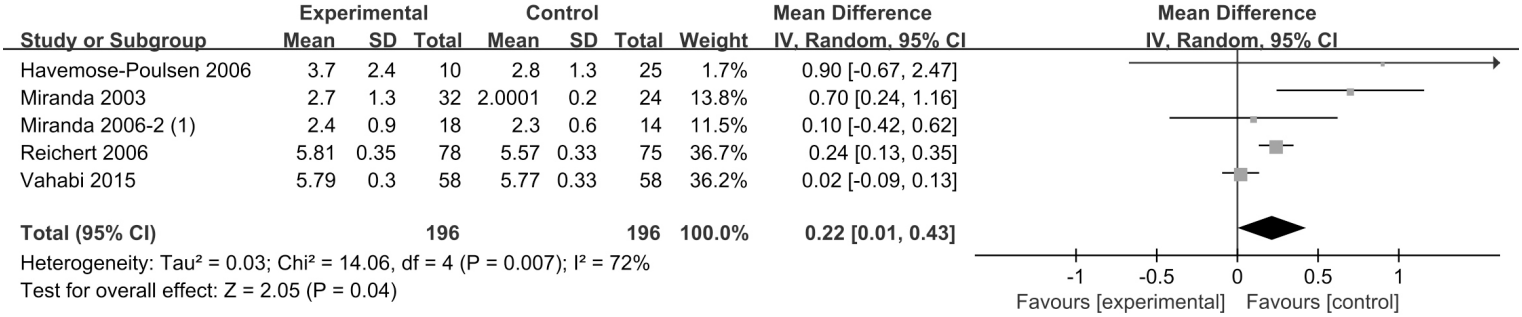

Footnotes
(1) Ahmed 2004-A：mixed dentition group
(2) Ahmed 2004-A：permanent dentition group
(3) Miranda 2006-1：baseline
(4) Miranda 2006-2：after two years

**FIGURE 3. Forest plot of PI.** Notes: SD is standard deviation; CI is confidence interval.




Footnotes
(1) Ahmed 2004-A：mixed dentition group
(2) Ahmed 2004-A：permanent dentition group
(3) Kobus 2019-A：mixed dentition group
(4) Kobus 2019-B：permanent dentition group

**FIGURE 4. Forest plot of GI.** Notes: SD is standard deviation; CI is confidence interval.




Footnotes
(1) Miranda 2006-2：after two years

**FIGURE 5. Forest plot of CAL ⩾2 mm.** Notes: SD is standard deviation; CI is confidence interval.

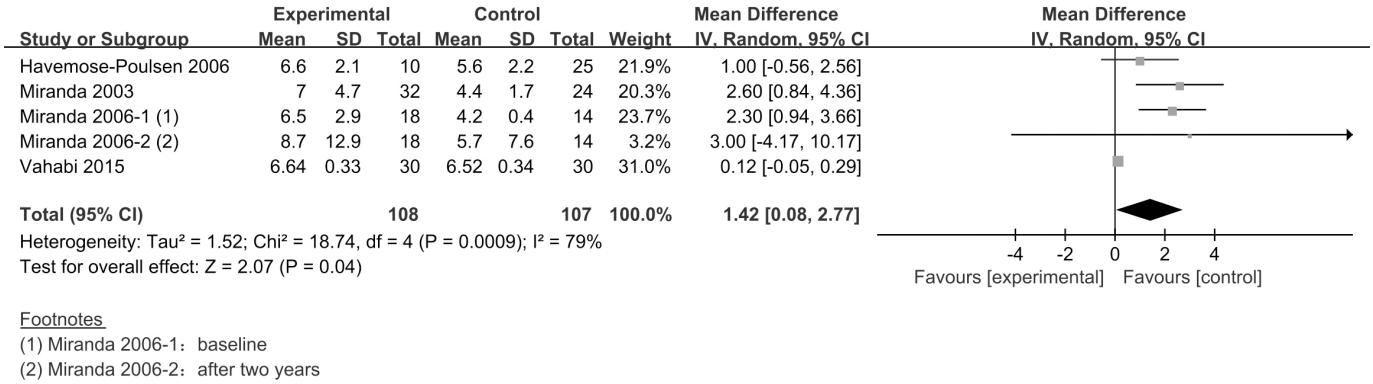



**FIGURE 6. Forest plot of PD ≥4 mm.** Notes: SD is standard deviation; CI is confidence interval.

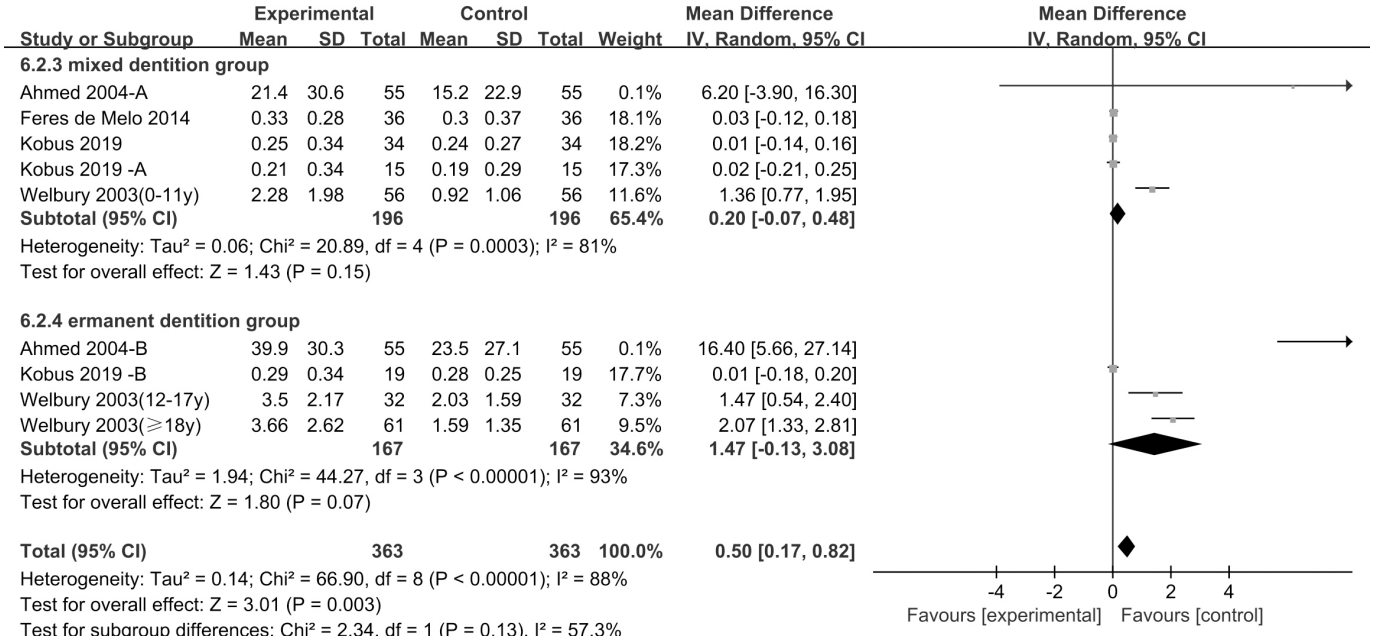



**FIGURE 7. Forest plot of GI subgroup.** Notes: SD is standard deviation; CI is confidence interval.

might record as a generalized reddish color of the mucosa. The reddish color may also result from an increased count of microorganisms, such as Candida albicans [9]. Additionally, when patients develop immunosuppression due to corticosteroids and antirheumatic drugs, such as MTX, oral infections may occur as a result of poor oral hygiene and unhealthy gum conditions, which are significant risk factors for systemic infections [25]. It is worth noting that hormonal changes during puberty can aggravate gingival inflammation (Puberty Associated Gingivitis), which occurs at different ages in girls and boys [50], while adolescents with chronic rheumatism may have delayed puberty [51]. In a study by Gil *et al.* [28], following the strengthening of age and sex control, they still found that JIA patients were more likely to develop plaque and gingival inflammation than healthy adolescents of the same age.

CAL is the gold standard for periodontal disease, representing cumulative destruction and increased mean CAL in JIA patients [42]. Miranda *et al.* [43] found that the serum levels of IL-18 and IL-1b were elevated in JIA patients with CAL, and the production of pro-inflammatory cytokines such as IL-18 and IL-1b was associated with the onset of JIA [43], implicating the involvement of IL-18 and IL-1b in periodontal tissue destruction in JIA patients [43]. Miranda *et al.* [43] also reported that after systemic treatment of JIA patients, their rheumatic symptoms were significantly controlled, the level of IL-1b in periodontal tissues was reduced, and gum inflammation was relieved. These findings suggest that treating JIA could correct periodontal disease, which was consistent with the study of Grevich *et al.* [17, 21, 28, 43].

Studies have also shown that JIA patients have increased concentrations of matrix metalloproteinases (MMPs) in their saliva, which can aggravate the degradation of periodontal tissue, increase PD, deepen periodontal pockets, and eventually lead to the aggravation of CAL and the formation of periodontitis [8]. MMP-8 is the most sensitive biomarker to reflect the degree of alveolar bone destruction, especially in periodontal pocket depth and attachment loss, which are closely related to clinical and radiological symptoms. In addition, JIA patients are at increased risk of osteopenia, bone growth retardation and systemic osteoporosis due to a systemic decrease in bone mineral density, which can accelerate the absorption and destruction of alveolar bone, affect tooth and periodontal function and food intake and nutrition intake, ultimately leading to a

reduction in the quality of life of JIA patients [47, 52].

JIA patients have a high incidence of temporomandibular arthritis, which can lead to mandibular growth disorders, facial deformities and occlusal disorders, and can affect muscle function [14–16, 53–55]. Peripheral and central nervous system sensitization and decreased activity of anti-nociceptive descending pathways in the temporomandibular joint and masseter region can result in abnormal pain, hyperalgesia, pain diffusion, involved pain, and functional musculoskeletal imbalance during mastication and maximum mouth opening [54, 55]. Painful chewing can lead to the substitution of harder foods with softer alternatives, which may be more difficult to remove with a toothbrush, thereby complicating oral hygiene management in JIA patients [27]. When evaluating temporomandibular joint and periodontal health, stomatologists should be cautious and take into consideration the overall condition of the patient, especially young patients with periodontal diseases, as they may have undiagnosed JIA.

To the best of our knowledge, this systematic review and meta-analysis represents the first attempt to synthesize the existing evidence regarding the relationship between JIA and periodontal diseases. Despite these interesting findings reported, there were still some limitations that should be addressed. First, the studies included in this review measured only some indexes of periodontal diseases, which may not fully capture the complexity of the relationship between JIA and periodontal disease. Second, the possibility of selective publication bias cannot be ruled out, as all of the included studies were published. Third, due to the limited number of studies and data available, we were unable to analyze the impact of common risk factors (*i.e.*, oral health system, socioeconomic and behavioral factors) on JIA and periodontal diseases. Thus, future well-designed, high-quality longitudinal studies are needed to clarify the relationship between JIA and periodontal diseases.

## 5. Conclusion

At present, literature on the association between juvenile idiopathic arthritis and periodontal diseases remains limited. However, the results of this meta-analysis and systematic review suggest a moderate association between JIA and periodontal diseases. Thus, it is recommended that the cooperation between stomatologists and rheumatic immunologists be strengthened and regular oral examinations be conducted for JIA patients to monitor their temporomandibular joint condition and periodontal health. Additionally, stomatologists should be cautious and consider the possibility of undiagnosed JIA in young patients presenting with temporomandibular joint arthritis and periodontal diseases. Despite the significance of the current findings, this study also had some limitations, and further research is warranted to comprehensively investigate the potential mechanism linking JIA and periodontal diseases.

### AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

### AUTHOR CONTRIBUTIONS

JT and YDL—designed the research study. JT—performed the research. JT, LSD, JXR and ZBL—analyzed the data. JT and LSD—wrote the manuscript. All authors read and approved the final manuscript.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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