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Is drug use associated with the presence of periodontitis and oral lesions? A meta-analysis

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ABSTRACT

Purpose: This systematic review investigated whether drug use is associated with the presence of oral lesions and periodontitis.
Methods: A search was performed for studies that analyzed the presence of periodontitis and/or oral lesions in users of crack, cocaine, and/or marijuana in the PubMed, Scopus, and Web of Science databases. Observational studies in English, Spanish, or Portuguese, without limitation of year, age, and sex, were included. Studies that did not evaluate periodontitis and oral lesions according to the eligibility criteria were excluded. Two authors independently performed study selection and data extraction using a standardized form. The risk of bias of studies included in the meta-analysis was assessed using the Joanna Briggs Institute Critical Appraisal Checklist. The meta-analysis included studies that investigated the association of drug use with the outcome.
Results: The initial search resulted in 9,279 articles, from which 16 studies with 15,434 participants were included in the review and 8 studies were included in the meta-analysis. Most studies that evaluated periodontitis in drug users and non-users found a positive association in users. Most studies that analyzed oral lesions reported a higher prevalence, association, or risk of oral lesions in drug users than in non-users. A critical evaluation identified a need to improve the control and reporting of confounding factors in studies on this topic. An association was found between periodontitis and the use of crack, cocaine, and/or marijuana (odds ratio [OR], 1.84; 95% confidence interval [CI], 1.04–3.27; P=0.04) and between oral lesions and the use of these drugs (OR, 2.13; 95% CI, 1.58–2.86; P<0.001).
Conclusions: Drug users are more likely to develop oral lesions and periodontitis than non-users. However, the results should be interpreted with caution, considering the heterogeneity and quality of the studies included in the analysis.

Keywords: Cocaine; Marijuana use; Oral manifestations; Periodontitis

INTRODUCTION

It is estimated that 271 million individuals worldwide, aged 15 to 64, regularly use at least 1 drug, whether illicit or not [1]. The chemical substances most frequently used and typically administered through smoking include marijuana and crack [2]. The prevalence of consumption of these substances varies between countries, with drug use generally more

prominent in developing nations, particularly during the years 2000–2018, compared to developed countries [3]. The rise in unemployment and decrease in opportunities brought about by the pandemic could disproportionately impact underprivileged strata of society, potentially making them more susceptible to drug use, trafficking, and production for their livelihood [3].

Crack is derived from cocaine and can be heated and smoked, producing intense excitement and euphoria [4]. Research indicates that the primary systemic issues associated with this drug include respiratory and cardiac diseases, hepatitis, human immunodeficiency virus, and even death [5-7]. However, users may also exhibit alterations in the oral mucosa due to cellular changes. These changes are associated with the extreme heat of the smoke, the impact of its chemical content, reduced blood supply due to vasoconstriction, and the effects on the user's immune response [8].

Marijuana is derived directly from the leaves of the female *Cannabis sativa* plant, with its primary psychoactive component being delta-9-tetrahydrocannabinol (THC). This substance is known to induce effects such as euphoria, sedation, and dysphonia [9]. Beyond the recognized cognitive impacts of marijuana, there is speculation that it may contribute to other health conditions in users. The smoke generated by the drug could potentially have carcinogenic properties, given that it contains aromatic hydrocarbons known for this potential [10]. Furthermore, cannabinoids, upon binding to their receptors, can influence immune cells and alter inflammatory processes [11,12].

The increased presence of dental caries and biofilm at the cervical level is often seen as a pathognomonic sign of the misuse of certain substances [13]. Previous studies have suggested that the use of substances such as cocaine, crack, and/or marijuana can lead to oral complications. These complications may include erosion and dental abrasion, oral cancer, xerostomia, *Candida albicans* infection, atypical caries, periodontal disease, and even tooth loss. Furthermore, the prevalence of caries lesions and periodontal disease may rise when individuals combine the use of these and other drugs, thereby heightening the risk of tooth loss [14-16].

Several deleterious effects are caused by these substances; however, evidence regarding the association between these substances and the occurrence of periodontitis and oral lesions remains inconclusive.

The present study aimed to investigate the association between the use of crack, cocaine, and/or marijuana and the presence of oral lesions and periodontitis. The hypothesis was that crack, cocaine, and/or marijuana users are more likely to have periodontitis and oral lesions than individuals who do not consume these substances.

MATERIALS AND METHODS

The reporting of this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [17]. The protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO), under the identification number CRD42020170154 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=170154).

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Research question

The following population, exposure/intervention, comparison, outcome (PECO) question was used: P, drug users/smokers; E, crack, cocaine, and/or marijuana; C, non-drug users/smokers; O, periodontitis and/or oral lesions.

Search strategies

Three online scientific databases were used to search for articles: MEDLINE/PubMed, Web of Science, and Scopus. The detailed search strategy for the terms used, considering the specific characteristics of each database, is shown in **Table 1**. There was no restriction regarding the language and year of publication. A manual search was performed in the references of the selected articles, in the most relevant journals, and in Google Scholar to identify any other relevant studies. The last search was carried out in March 2021.

Eligibility criteria

Inclusion criteria

The studies were reviewed, and those that met the following inclusion criteria were included: observational studies (cross-sectional, cohort, case-control, retrospective, and prospective) in English, Spanish, or Portuguese that analyzed the presence of periodontitis and oral lesions in users and non-users of crack, cocaine, and/or marijuana. There was no limitation regarding the publication period, age, and sex of individuals.

Exclusion criteria

Randomized clinical trials, case series, case reports, literature reviews, and systematic reviews were excluded. In addition, consensuses, official notes, letters to editors, guidelines, and conference abstracts were not considered.

Table 1. Search strategy

Database	Keywords
PubMed	(“Adolescent” [Mesh] OR “Adolescent” OR “Adolescents” OR “Adolescence” OR “Teens” OR “Teen” OR “Teenagers” OR “Teenager” OR “Youth” OR “Youths” OR "Adolescents, Female" OR "Adolescent, Female" OR "Female Adolescent" OR "Female Adolescents" OR "Adolescents, Male" OR "Adolescent, Male" OR "Male Adolescent" OR "Male Adolescents" OR “Adult” [Mesh] OR “Adult” OR “Adults” OR “Aged” [Mesh] OR “Aged” OR “Elderly” AND “Crack cocaine” [Mesh] OR “Crack Cocaine” OR “Cocaine, crack” OR “Cocaine Smoking” [Mesh] OR “Cocaine Smoking” OR “Smoking, Cocaine” OR “Crack “Cocaine Smoking” OR Cocaine Smoking, Crack” OR “Smoking, Crack Cocaine” OR “Crack Smoking” OR “Smoking, Crack” OR “Cannabis” [Mesh] OR “Cannabis” OR “Cannabi” OR “Hemp Plant” OR “Hemp Plants” OR “Plant, Hemp” OR “Plants Hemp” OR “Cannabis indica” OR “Cannabis indicas” OR “Indicas, Cannabis” OR “Marihuanna” OR “Marihuannas” OR “Marijuana” OR “Marijuanas” OR “Ganja” OR “Ganjas” OR “Hashish” OR “Hashishs” OR “Hemp” OR “Hemps” OR “Bhang” OR “Bhangs” OR “Cannabis sativa” OR “Cannabis sativas” OR “sativas, Cannabis” AND “Case-control study” OR “Case-control studies” OR “Cross-sectional study” OR “Cross-sectional studies” OR “Cohort study” OR “Cohort studies” OR “Observational study”)
Web of Science	(Adolescent OR Adolescents OR Adolescence OR Teens OR Teen OR Teenagers OR Teenager OR Youth OR Youths OR “Adolescents, Female" OR "Adolescent, Female" OR "Female Adolescent" OR "Female Adolescents" OR "Adolescents, Male" OR "Adolescent, Male" OR "Male Adolescent" OR "Male Adolescents" OR Adult OR Adults OR Aged OR Elderly AND “Crack Cocaine” OR “Cocaine, crack” OR “Cocaine Smoking” OR “Smoking, Cocaine” OR “Crack Cocaine Smoking” OR “Cocaine Smoking, Crack” OR “Smoking, Crack Cocaine” OR “Crack Smoking” OR “Smoking, Crack” OR Cannabis OR Cannabi OR “Hemp Plant” OR “Hemp Plants” OR “Plant, Hemp” OR “Plants Hemp” OR “Cannabis indica” OR “Cannabis indicas” OR “Indicas, Cannabis” OR Marihuanna OR Marihuannas OR Marijuana OR Marijuanas OR Ganja OR Ganjas OR Hashish OR Hashishs OR Hemp OR Hemps OR Bhang OR Bhangs OR “Cannabis sativa” OR “Cannabis sativas” OR “sativas, Cannabis” AND “Case-control study” OR “Case-control studies” OR “Cross-sectional study” OR “Cross-sectional studies” OR “Cohort study” OR “Cohort studies” OR “Observational study”).
Scopus	(Adolescent OR Adolescents OR Adolescence OR Teens OR Teen OR Teenagers OR Teenager OR Youth OR Youths OR "Adolescents, Female" OR "Adolescent, Female" OR "Female Adolescent" OR "Female Adolescents" OR "Adolescents, Male" OR "Adolescent, Male" OR "Male Adolescent" OR "Male Adolescents" OR Adult OR Adults OR Aged OR Elderly AND "Crack Cocaine" OR "Cocaine, crack" OR "Cocaine Smoking" OR "Smoking, Cocaine" OR "Crack Cocaine Smoking" OR "Cocaine Smoking, Crack" OR "Smoking, Crack Cocaine" OR "Crack Smoking" OR "Smoking, Crack" OR Cannabis OR Cannabi OR "Hemp Plant" OR "Hemp Plants" OR "Plant, Hemp" OR "Plants Hemp" OR "Cannabis indica" OR "Cannabis indicas" OR "Indicas, Cannabis" OR Marihuanna OR Marihuannas OR Marijuana OR Marijuanas OR Ganja OR Ganjas OR Hashish OR Hashishs OR Hemp OR Hemps OR Bhang OR Bhangs OR "Cannabis sativa" OR "Cannabis sativas" OR "sativas, Cannabis" AND “Case-control study” OR “Case-control studies” OR “Cross-sectional study” OR “Cross-sectional studies” OR “Cohort study” OR “Cohort studies” OR “Observational study” AND "Dentistry" OR "Odontology" OR "Oral").

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Criteria considered for periodontitis

Periodontitis is defined as a chronic, multifactorial, and inflammatory disease associated with a dysbiotic biofilm and characterized by the progressive destruction of the teeth insertion apparatus. Studies that used a periodontal probe (demarcated in millimeters) for the diagnosis of periodontitis and considered the measurements of the probing depth and especially the level of clinical attachment (at least 2 sites with depth ≥4 mm and at least 3 sites with a loss of insertion length ≥4 mm) were included in the study [18,19]. The current classification of periodontal diseases and conditions defines periodontitis as at least 2 teeth with interproximal clinical attachment loss or with buccal clinical attachment loss ≥3 mm and probing depth >3 mm [20].

Criteria considered for oral lesions

The included studies evaluated individuals' oral mucosa, observing the labial mucosa and vestibular sulcus (upper and lower), labial portion of the commissures and oral mucosa (right and left), tongue (ventral and dorsal surfaces and edges), mouth floor, hard and soft palate and alveolar/gingival crest (upper and lower), and noted the presence of any of the following lesions: spot (change in normal color), erosion (superficial lesion with partial browning of the epithelium), ulcer (loss of epithelial surface, with exposure of underlying connective tissue), plaque (a slight raised lesion with a flat surface), nodule (an elevated, solid lesion, measuring ≥5 mm in diameter), papule (a raised, solid lesion, measuring <5 mm in diameter), vesicle (superficial lesion, with liquid content, measuring <5 mm in diameter), blister (superficial lesion, with liquid content, measuring ≥5 mm in diameter), fissure (a narrow ulceration, similar to a groove), pseudo-membrane (a covered ulcer by a removable membrane), and hyperplasia (an elevation, similar in color to the surrounding mucosa) [21].

Selection of studies

The references found were managed in EndNote (version X9, Clarivate Analytics, Philadelphia, PA, USA). Duplicates were excluded. Afterward, 2 independent reviewers investigated the titles and abstracts according to the inclusion and exclusion criteria of the study and classified them into "include," "exclude," and "uncertain." The full texts were obtained to determine whether to include articles classified as "include" and "uncertain." A third person from the research group was consulted when there was disagreement until a consensus was reached.

Data extraction and synthesis

A standardized data extraction form was created using the Excel program (Microsoft Excel for Mac, Microsoft Corp., Redmond, WA, USA). The following data were collected: author and year of publication, year of study, country where the study was conducted, study design, total sample, and number of exposed and unexposed, drugs used, diagnostic method for periodontitis, presence of periodontitis in exposed and unexposed individuals, the appearance of lesions in exposed and unexposed individuals, and the results. Two reviewers extracted data and another reviewer checked for consistency. There was no training for data extraction.

Risks of bias of the included studies

The risks of bias of the studies included in the meta-analysis were assessed by applying the critical appraisal checklist of the Joanna Briggs Institute (JBI) to analytical cross-sectional studies (JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies). The instrument has 8 items: (1) Were the inclusion criteria in the sample clearly defined? (2) Were the study subjects and setting described in detail? (3) Was exposure validly and reliably

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measured? (4) Were objective and standardized criteria used to measure the condition? (5) Have confounding factors been identified? (6) Have strategies been stated for dealing with confounders? (7) Were the results validly and reliably measured? (8) Was adequate statistical analysis used? There are 4 possible answers for each item: yes (+), no (−), unclear (/), and not applicable (-) [22]. In this way, the quality was peer-reviewed, and disagreements were resolved by consensus.

Due to the inclusion of a cohort study in our meta-analysis, we also used the JBI Critical Appraisal Checklist for Cohort Studies. This instrument has 11 questions: (1) Were the two groups similar and recruited from the same population? (2) Were the exposures measured similarly to assign people to both exposed and unexposed groups? (3) Was the exposure measured in a valid and reliable way? (4) Were confounding factors identified? (5) Were strategies to deal with confounding factors stated? (6) Were the groups/participants free of the outcome at the start of the study (or now of exposure)? (7) Were the outcomes measured in a valid and reliable way? (8) Was the follow-up time reported sufficient to be long enough for outcomes to occur? (9) Was follow-up complete, and if not, were the reasons for loss to follow-up described and explored? (10) Were strategies to address incomplete follow-up utilized? (11) Was appropriate statistical analysis used? There are 4 possible answers for each item: yes (+), no (−), unclear (/), and not applicable (-). In this way, the quality was peer-reviewed, and disagreements were resolved by consensus.

Analysis of results

Analyses were carried out in the Excel program. A descriptive analysis of the data was performed, considering the outcome of interest (periodontitis or oral lesions) for the 16 included studies. Data were summarized in tables. When sufficient data were present in the studies, associations between crack, cocaine, and/or marijuana use, and outcomes (periodontitis/elementary oral lesions) were estimated through a meta-analysis. The odds ratio (OR) was applied to measure the effect size, with a 95% confidence interval (CI), and a random-effect model was used at a value of $P<0.05$, assuming the variation between the included studies. The RevMan (version 5, Nordic Cochrane Centre, The Cochrane Collaboration, London, UK) review manager was used, and an individual meta-analysis was performed for each outcome. The data entered in the software were as follows: total exposed sample, total non-exposed sample, and the occurrence of periodontitis and oral lesions in both groups.

RESULTS

The initial search resulted in 9,279 articles, from which 1,137 were removed because they were duplicates, leaving 8,142 articles. After reading the titles and abstracts, 8,119 studies were excluded for not being related to the research proposal, focusing on other areas of knowledge, or presenting other unrelated outcomes. In the gray literature, 1 article was identified and included, and the full texts of the remaining 24 works were read. Eight studies were excluded according to the eligibility criteria. The excluded articles and reasons for exclusion are presented in the supplemental material. Ultimately, 16 studies were identified as eligible and were included in the systematic review, totaling 15,434 participants. **Figure 1** presents the PRISMA flowchart based on the study inclusion criteria.

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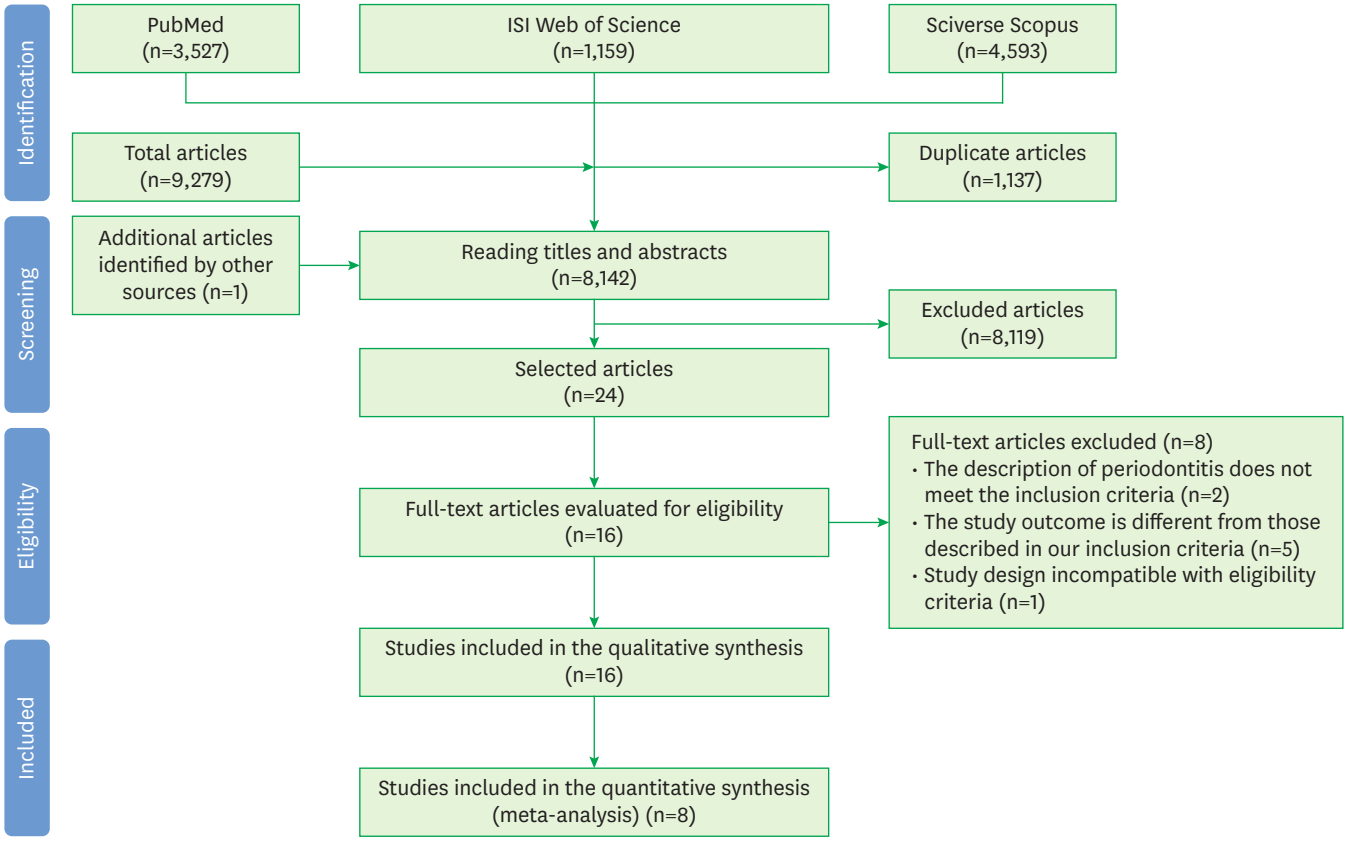

Figure 1. PRISMA flowchart used to capture articles included in the systematic review.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, ISI: Institute for Scientific Information.

Synthesis of the descriptive results and meta-analyses

Periodontitis and the use of crack, cocaine and/or marijuana

Table 2 shows the descriptive characteristics of the studies included in the review with periodontal outcomes. Thirteen studies on periodontal outcomes were included [13,14,23-33]. Most studies were cross-sectional [14,23-32], and only 2 were cohort studies [13,33]. The studies were published from 2008 to 2018. The country that appeared the most was Brazil with 3 studies [14,24,25], followed by the United States [31,32] and New Zealand [30,33] with 2 each. The sample size ranged from 43 to 9,153 individuals. As for the drugs used, most studies evaluated only marijuana users.

Most studies that evaluated periodontitis in drug users and non-users found a positive association in users [14,26-28,30-33]. Those studies that did not find a significant association investigated possible relationships with gingivitis [23], plaque index [25], higher bacterial counts [24], and necrotizing ulcerative gingivitis [29]. Another explained the presence of periodontitis in users in terms of their lifestyle, not drug consumption itself [13]. Three studies comparing drug users and non-users according to the presence of periodontitis were considered for meta-analysis (**Figure 2**) [14,24,25]. The meta-analysis revealed an association between drug use (crack, cocaine, and/or marijuana) and periodontitis, with users having a 2-fold greater likelihood of having the disease (OR, 1.84; 95% CI, 1.04–3.27; I^2=91%).

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Table 2. Characteristics of the studies on periodontitis included in the review

Author/year of publication	Year(s) when the study was conducted	Country of the study	Study design	Sample	Drugs	Results/conclusion
Antoniazzi et al. [14], 2016	2012/2013	Brazil	Cross-sectional	212	Crack and marijuana	Crack users were approximately 3 times more likely to have periodontitis than non-users (OR, 3.44; 95% CI, 1.51–7.86).
Candina et al. [23], 2013	2010/2011	Cuba	Cross-sectional	43	Crack and marijuana	The use of illicit drugs was only associated with gingivitis.
Casarin et al. [24], 2017	2012/2013	Brazil	Cross-sectional	155	Crack	Although some crack users had higher (>75th percentile) bacterial counts, it was suggested that the higher occurrence of periodontal disease in users may be related to non-bacterial factors.
Cury et al. [25], 2017	2013/2014	Brazil	Cross-sectional	160	Crack and cocaine	Periodontitis was not associated with crack and cocaine use (OR, 2.35; 95% CI, 0.82–6.46), but it was associated with plaque index (OR, 6.46; 95% CI, 1.95–21.42).
Gupta et al. [26], 2012[a]	2008	India	Cross-sectional	252	Marijuana and heroin	The use of marijuana and other drugs was associated with a higher Community Periodontal Index score (OR, 2.21; 95% CI, 1.08–4.52).
Jamieson et al. [27], 2010	-	Australia	Cross-sectional	442	Marijuana	Marijuana use was associated with a 1.5-fold increase in the prevalence of periodontal disease.
Kayal et al. [28], 2014	2012	Saudi Arabia	Cross-sectional	57	Cocaine, marijuana, and heroin	Cocaine and heroin use was associated with the most severe forms of periodontitis.
López and Baelum [29], 2009	2001	Chile	Cross-sectional	9.153	Marijuana	Necrotizing ulcerative gingivitis was identified (OR, 0.4; 95% CI, 0.2–0.9), but no association between attachment level loss/periodontitis and marijuana use in the adolescent population of this study.
Mateos-Moreno et al. [13], 2013[a]	-	Spain	Cohort	98	Cocaine, marijuana, and heroin	Users of these drugs had caries and periodontitis, but these conditions were more related to lifestyle than drug consumption.
Meier et al. [30], 2016	-	New Zealand	Cross-sectional	947	Marijuana	Even after adjusting for tobacco, marijuana use between ages 18 and 38 was associated with worse periodontal health.
Ortiz et al. [31], 2018	2014/2016	United States	Cross-sectional	735	Marijuana	Marijuana users were more likely to develop periodontal disease (OR, 2.91; 95% CI, 1.06–7.96).
Shariff et al. [32], 2017	2011/2012	United States	Cross-sectional	1.938	Marijuana	Frequent use of marijuana was associated with greater probing depths and loss of clinical attachment level, suggesting greater odds of periodontitis.
Thomson et al. [33], 2008	2005	New Zealand	Cohort	903	Marijuana	Regardless of tobacco, the drug (marijuana) was considered a risk factor for the development of periodontitis (OR, 1.6; 95% CI, 1.2–2.2).

OR: odds ratio, CI: confidence interval.
[a]Articles that present data on periodontitis and on oral lesions.

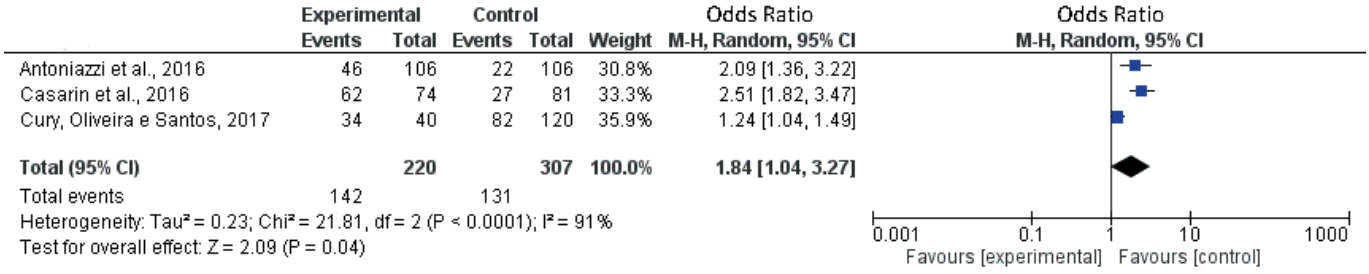

Figure 2. Meta-analysis of drug consumption with the presence of periodontitis.
CI: confidence interval.

Oral lesions and the use of crack, cocaine, and/or marijuana

Table 3 shows the descriptive characteristics of the studies included in the review with the outcome of oral lesions. Five studies evaluated the relationship between certain substances and elementary oral lesions [8,13,26,34,35]. The studies were published between 2012 and 2018. One study was carried out in Spain [13], another in India [26], and 3 in Brazil [8,34,35]. All studies were cross-sectional, except for the study by Mateos-Moreno et al. [13], which had a retrospective cohort design. The total sample ranged from 70 to 252 individuals. As for the

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Table 3. Characteristics of the included studies on oral lesions

Author/year of publication	Year(s) when the study was conducted	Country of the study	Study design	Sample	Drugs	Results/conclusion
Antoniazzi et al. [8], 2018	2012/2013	Brazil	Cross-sectional	108	Crack	Crack use was associated with clinical and cellular changes in the oral mucosa.
Cury et al. [34], 2018	2013/2014	Brazil	Cross-sectional	161	Crack and cocaine	Crack and cocaine users were 2.87 times more likely to develop lesions (traumatic ulcer and actinic cheilitis) (OR, 2.87; 95% CI, 1.08–7.67; *P*=0.03).
Gupta et al. [26], 2012[a]	2008	India	Cross-sectional	252	Marijuana and heroin	Users had a higher prevalence of leukoplakia than non-users; however, in the multivariate analysis, the presence of the lesion was not statistically significant.
Mateos-Moreno et al. [13], 2013[a]	-	Spain	Cohort	98	Cocaine, marijuana, and heroin	Users of different types of substances had a higher prevalence of oral lesions (mucositis, angular cheilitis, herpes, papilloma, ulceration, and leukoplakia).
Sordi et al. [35], 2017	2014	Brazil	Cross-sectional	70	Crack, cocaine, and marijuana	The use of crack, cocaine, and marijuana contributed to the increase in the prevalence of oral lesions (aphthous stomatitis, frictional keratosis, and candidiasis).

OR: odds ratio, CI: confidence interval.
[a]Articles that present data on periodontitis and on oral lesions.

drugs evaluated in the studies, most studies considered the use of more than 1 drug in the included patients.

Four of the 5 studies [8,13,34,35] reported a higher prevalence, association, or risk of oral lesions in drug users than in non-users. Even the study that did not identify a statistically significant association found a higher prevalence of leukoplakia in drug users (marijuana and heroin) than in non-users [26]. A comparison between users and non-users according to the presence of oral lesions, obtained from the meta-analysis, is presented in **Figure 3**. An association was identified between drug use and the presence of oral lesions, where users of these substances were twice as likely to have lesions than non-users (OR, 2.13; 95% CI, 1.58–2.86, I^2=2%).

Publication bias and critical appraisal tools

The publication bias could not be analyzed, as fewer than 10 publications were included. The risk of bias in these studies was assessed using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies and for Cohort Studies. **Table 4** presents the results of each article included in the meta-analysis. Of the 8 studies evaluated, only 3 showed positive results in all 8 items evaluated [8,14,24]. Items 5 and 6 for Analytical Cross-Sectional Studies, which dealt with the identification and how to deal with confounding factors, were classified as unclear for most studies. In the analysis of the cohort study, only 3 items were considered adequate. Items referring to confounding factors were also a problem in this study.

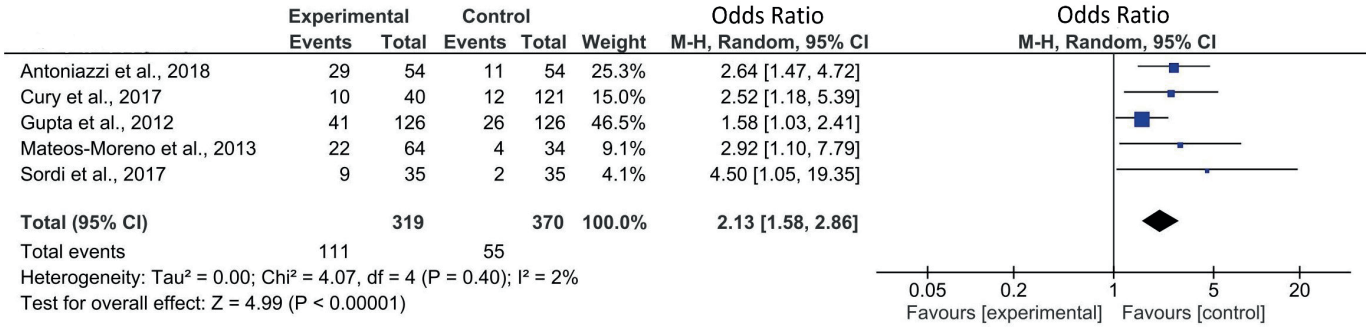

Figure 3. Meta-analysis evaluating drug consumption with the presence of oral lesions.
CI: confidence interval.

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Table 4. Critical appraisal checklist for cross-sectional studies (JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies) and cohort studies (JBI Critical Appraisal Checklist for Cohort Studies)

Studies	1	2	3	4	5	6	7	8	9	10	11
Cross-sectional analytical studies											
Antoniazzi et al. [8], 2018	+	+	+	+	+	+	+	+	N/A	N/A	N/A
Antoniazzi et al. [14], 2016	+	+	+	+	+	+	+	+	N/A	N/A	N/A
Casarin et al. [24], 2017	+	+	+	+	+	+	+	+	N/A	N/A	N/A
Cury et al. [34], 2018	+	+	+	+	/	/	+	+	N/A	N/A	N/A
Cury et al. [25], 2017	+	+	+	+	/	/	+	+	N/A	N/A	N/A
Gupta et al. [26], 2012	+	+	+	+	/	/	+	+	N/A	N/A	N/A
Sordi et al. [35], 2017	+	+	+	+	/	/	+	+	N/A	N/A	N/A
Cohort studies											
Mateos-Moreno et al. [13], 2013	/	+	/	–	–	/	+	N/A	N/A	–	+

JBI: Joanna Briggs Institute, +: yes, –: no, /: unclear, N/A: not applicable.

DISCUSSION

The results of our study suggest that, despite the limited number and quality of studies included in the meta-analysis, exposed individuals were more likely to develop periodontitis and oral lesions than the control group (non-drug users); thus, both hypotheses were confirmed. Marijuana contains active compounds, such as delta-9-THC, which interact with cannabinoid receptors in the body and oral cavity. Chronic marijuana use can affect local immune system function, decreasing the normal inflammatory response to bacterial infections such as periodontitis. Additionally, marijuana smoke contains irritating and carcinogenic chemicals that can damage epithelial cells in the mouth and reduce the effectiveness of defense cells in the oral mucosa [9-12]. Crack is a processed form of cocaine and has a pronounced vasoconstrictive effect. Crack use leads to the constriction of blood vessels, which decreases blood flow to the tissues of the oral cavity. This reduction in blood supply compromises the nutrition and oxygenation of the gingival tissues, making them more vulnerable to injuries and periodontitis [8].

Regarding periodontitis, the study by Antoniazzi et al. [14] showed that periodontitis was also significantly associated with age >24 years, education ≤8 years, tobacco use, moderate/heavy alcohol use and plaque rate ≥41%. Adjustment for these factors reduced the effect of crack on periodontitis from an OR of 3.44 to an OR of 3.12, thus suggesting that a small portion of the drug's effect on periodontitis was mediated by the increased presence of plaque.

The study by Nogueira-Filho et al. [36] reinforces the possibility of mediation by the presence of plaque. That study tested cannabis inhalation in rats with and without teeth with induced periodontitis. They observed that bone loss was greater in teeth with the disease that were exposed to cannabis, while there was no difference in teeth without the disease that were exposed to cannabis. This evidence suggests that cannabis may not initiate bone loss, but increase bone loss, when present.

It is known that the appearance of certain oral lesions can be caused by cellular alterations caused by drug consumption. In the study by Almeida et al. [37], cytological evaluations demonstrated suggestive alterations in epithelial cells of future injuries. In the analyses by Oliveira et al. [38] and Webber et al. [39], genomic damage was found in the cells of users, suggesting that such substances cause cytotoxicity to epithelial cells. Genotoxicity and oxidative stress were induced in mammalian cells in the study by Malacarne et al. [40]; however, the inflammatory response after exposure was not conclusive, furnishing evidence only that there is a possibility that crack is a carcinogen chemical.

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The use of other drugs along with crack, cocaine, and/or marijuana may have an additional effect on the deterioration of the periodontium. However, multiple use of other drugs was not considered in the multivariate analyses of the studies, probably due to the difficulty in estimating the level of exposure to each substance. The study by Cury et al. [34], for example, considered the use of drugs other than crack and cocaine as an exclusion criterion. However, users do not use just 1 type of psychoactive drug; evidence shows that polysubstance drug use is a pattern for drug addicts [33,37,38].

One must also consider the way in which these substances are prepared (crack, cocaine, and marijuana); due to their illegality in several countries, there is no standard of preparation. Crack is a byproduct, originating from the remnants of cocaine, and to increase the scale of production, substances such as solvents, marble powder, and talc are added. This also occurs in the commercialization of marijuana—specifically, the concentrated form is common in Latin America, where psychotropic drug concentrates are used instead of less-processed forms because high-quality cultivars/strains are not grown [41]. This can impact the results of studies from different locations around the world.

Another important point that should not be overlooked in research is the fact that smoking can interfere with the results for the prevalence of both periodontitis and oral lesions [42]. It is already known that this habit is a risk factor for periodontal disease, as it simultaneously suppresses gingival inflammation and promotes the destruction of periodontal tissues [42]. In addition, the occurrence of oral lesions can be influenced by smoking. Subsequent studies must take this point into consideration and should appropriately match individuals who use cigarettes. Electronic cigarettes should also be considered, as evidence shows that some oral lesions (nicotinic stomatitis, hairy tongue, and angular cheilitis) may be significantly more common in people using these products [43].

The study by Antoniazzi et al. [8] considered smoking when matching groups. They also established several exclusion criteria for the study, including individuals with systemic diseases that could potentially affect the immune system, those taking medications known to increase gingival tissue volume, and those currently undergoing orthodontic treatment. Other studies [14,24] also considered tobacco use. Casarin et al. [24] also added pregnancy as an exclusion criterion. In the study by Cury et al. [25], patients who had previously undergone subgingival periodontal treatment and individuals who had used long-term anti-inflammatory drugs and antibiotic therapy in the last 6 months were excluded. All these are relevant points for analysis in this type of study.

One of the limitations of the present study is the lack of cross-sectional studies that sample individuals with specific patterns of drug use, which would eliminate biases and improve the organization and presentation of data. This study found discrepancies in the methods used to evaluate periodontal disease (periodontitis) and elementary oral lesions. After the critical evaluation, a need was identified to improve the control and reporting of confounding factors in studies in this regard. In addition, further longitudinal observational studies are needed to identify oral problems caused by drug use over time.

In conclusion, the results of this systematic review and meta-analyses revealed that crack and marijuana use were associated with the presence of elementary oral lesions and periodontitis, with users of these substances being more likely to develop these conditions than non-users.

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However, the results should be interpreted with caution considering the heterogeneity and quality of the studies included in the analysis.

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