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Review article

Is there an association between asthma and periodontal disease among adults? Systematic review and meta-analysis

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ABSTRACT

This systematic review and meta-analysis aimed to investigate a possible association between asthma and periodontal disease in adults. This study was conducted by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the searches were performed on the following databases: PubMed, Scopus, Web of Science, Cochrane, LILACS, OpenGrey e Google Scholar. In this systematic review, observational studies with adult humans, which evaluated patients with and without asthma, were selected to verify the association between both diseases. To qualitative analysis, Fowkes and Fulton guidelines was used and for the quantitative analysis, it was used the mean and standard deviation from each group (with and without asthma), using confidence interval (CI) 95% and heterogeneity were tested using I^2 index. Furthermore, a summary of the overall strength of evidence was presented using Grading of recommendations, assessment, development, and evaluation (GRADE). 3395 studies were identified, 11 were included on this systematic review to qualitative analysis and 6 of them to quantitative synthesis. Six meta-analyses were performed to the following clinical parameters: plaque index (PI), gingival index (GI), bleeding on probing (BOP), papillary bleeding index (PBI), calculus index (CI), clinical attachment loss (CAL). The meta-analysis results for CI was ($p < 0.00001$, I2 = 0%) PBI ($p < 0.00001$, I2 = 0%), CAL ($p = 0,03$, $I^2 = 98\%$) showed higher means for the asthmatic group. For BOP ($p = 0.20$ I2 = 83%), GI ($p = 0.14$ I2 = 97%) and PI ($p = 0.53$ I2 = 95%) non-statistical difference was found. The level of evidence analysis (GRADE) presented a low level of evidence among the clinical parameters. This systematic review and meta-analysis observed that asthmatic individuals present more periodontal disease, especially gingivitis, when compared to healthy individuals, but further studies with similar methods are necessary to evaluate interactions between both diseases.

1. Introduction

Bronchial asthma is characterized by chronic inflammation of the airways causing respiratory changes (wheezing and dyspnoea) and coughing. According to the World Health Organization (WHO), there are 235 million people who have asthma, regardless of socioeconomic factors [1].

Current evidence suggests that asthma-related environmental and hormonal irritants may increase the chances of developing some pathologies, such as cardiovascular diseases [2]. This disease has also been associated with other comorbidities such as diabetes, obesity and fatty-esophageal reflux [3].

Periodontal diseases represent complex interactions of host-responsiveness defenses and bacterial pathogens aggression resulting in inflammatory processes of dental supporting tissues [4]. This condition reflects an epidemiologic issue due to its higher prevalence in different populations as well as being a significant cause of adult tooth loss [5–8]. The signs and symptoms may vary from gingivitis; an inflammation restricted to gingival tissues; and periodontitis, an inflammation of deeper tissues involving loss of attachment, alveolar bone loss, and teeth loss [9]. It was also reported that disorders to pro and anti-inflammatory cytokines can play a worsening on periodontal conditions [10].

Systemic conditions are capable of interfering with the balance of

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periodontal health [11]. Literature depicts that asthmatic individuals are more susceptible to oral health problems as plaque accumulation and salivary flow reduction when compared with healthy individuals [12].

In addition, it is currently suggested that individuals with asthma already have a systemic repercussion disease, since this inflammatory pathology is mediated by different cells, including cytokines (IL-4, IL-5, IL-13, TNF-α), inflammatory cells (eosinophils, T lymphocytes, macrophages, neutrophils), prostaglandins as well as promote changes in biological chemical mediators such as nitric oxide, which physiologically, participate in bronchial remodeling, but its high production may be related to loss of lung function, specifically the isoform iNOS that is toxic to the pulmonary epithelium [13–16]. Asthma can be classified as allergic or non-allergic, and this definition is based on the presence of immunoglobulins, specifically IgE. However, in both types of asthma T-helper infiltration (Th2) occurs and consequently these cytokines stimulate the mast cells causing eosinophilia, leukocytosis, elevated IgE levels [17]. All these pathophysiological changes in asthma may modulate the immunology of other diseases, such as periodontal disease. Recently, a systematic review suggested a strong association between asthma and periodontal disease, but without age restriction in the selection of studies. Recently, a systematic review suggested a strong association between asthma and periodontal disease, but with no age restriction on selection of studies [18].

Asthma can affect individuals at any age, being a heterogeneous disease with several phenotypes that may differ in childhood, adulthood and elderly [19–21]. Severe asthma in the elderly is predominantly atopic and eosinophilic [22] and associated with the fact that the immune system declines with age, these patients are more susceptible to develop infection than younger subjects [23], contributing to high rates of mortality, hospitalization, medical costs or health-related quality of life when compared to younger groups [20,22,23].

Faced with this possible comorbidity, the objective of this systematic review and meta-analysis was to investigate clinical evidence that supports an association between asthma and periodontal disease in adults.

2. Material and methods

2.1. Protocol

This systematic review was registered in the PROSPERO database (CRD 42016048639). This database was created by the University of York which is responsible for the screening and dissemination of systematic reviews. This review followed the PRISMA (Preference Reporting Requirements for Systematic Review and Meta-Analysis) guidelines [24] (Fig. 1).

2.2. Eligibility criteria

To perform this review, a question was elaborated: “Is there an association between the presence of asthma and periodontal disease?”. The PECO strategy was used: Observational studies on adult humans (P) with asthma (E) and without asthma (C) that was evaluated to identify the presence or absence of an association between asthma and periodontal disease (O). As inclusion criteria, we adopted clinical and observational studies which focused in explain an association between asthma and periodontal disease.

Case reports, descriptive studies, review articles, opinion articles, technical articles, guidelines, animal studies, pilot study, in vitro were discarded.

2.3. Search strategy

The following databases were used for the searches: PubMed, Scopus, Web of Science, Lilacs, Cochrane, and also the grey literature through the Open Grey and Google Scholar. No restrictions were applied regarding year or language used in the primary studies. The MeSH terms, keywords and relevant free terms were adapted according to each database (Table S1). The searches were performed until June 2018.

After the searches were obtained, a weekly search alert was created, in each database, to notify new studies according to the outlined search strategy. All relevant citations were imported into a bibliographic reference manager (EndNote®, version X7, Thomson Reuters, Philadelphia, USA).

2.4. Study selection

After importation to the reference manager, the duplicated results were removed using a bibliographic reference manager (EndNote®, version X7, Thomson Reuters), from automatic deletion and manual review.

The selection of the studies was performed from title and summary (phase I) and, later, from the full-text analysis (phase II), according to the previously established eligibility criteria. Furthermore, reference lists of included studies were also hand searched for study search and selection.

All evaluations, including searches, study selection, risk of bias assessment, and data extraction were independently performed by two reviewers (MKMF, ROF and checked by a third-party disagreement assessor RRL).

2.5. Data extraction, quality assessment and risk of bias

In each included article, the country, year of publication, study design, characteristics of participants (source and sample size), mean age, diagnostic criteria for asthma assessment, periodontitis evaluation, results and statistical analysis were extracted and tabulated.

Methodological quality and risk of bias were evaluated using Fowkes and Fulton (1991) checklist [25]. This checklist has domains that relate to the study and sample design, characteristics of the control group, quality of measures and results, and integrity and distorting influences.

For each criterion evaluated using the checklist, a signal (++) was assigned to cases of significant problems in the study or (+) in case of minor problems, in order to evaluate if the methods were able to produce consistent and valid information, as well as if the results offered the expected effects. In the items where the question was not applicable to the type of study, the acronym NA (not applicable) was assigned. When no problem was found, the signal (0) was used. In case of absence of information that makes data extraction or risk of bias evaluation impracticable, we attempted to contact the authors by e-mail. The contact consisted of sending a weekly email, for up to five consecutive weeks.

After a detailed evaluation of the methods and results, the studies were analyzed to verify the possibility of “biased results”, “confusions” and “chance occurrence”. In order to determine the value of the study, three summary questions were then answered: “Were the results biased?”; “Are there confusion or distortion factors present?” and “Is it possible that the results were due to chance?”. “YES” and “NO” answers were assigned. If the answer was NO for all three questions, the article was considered reliable, with a low risk of bias. The criteria established for each question in this review were described in Table 1.

2.6. Meta-analysis

The studies data were analyzed using Review Manager software (Review Manager v. 5.2, The Cochrane Collaboration; Copenhagen, Denmark) to evaluate the association between periodontal disease and asthma. Six meta-analyses were performed with main periodontal

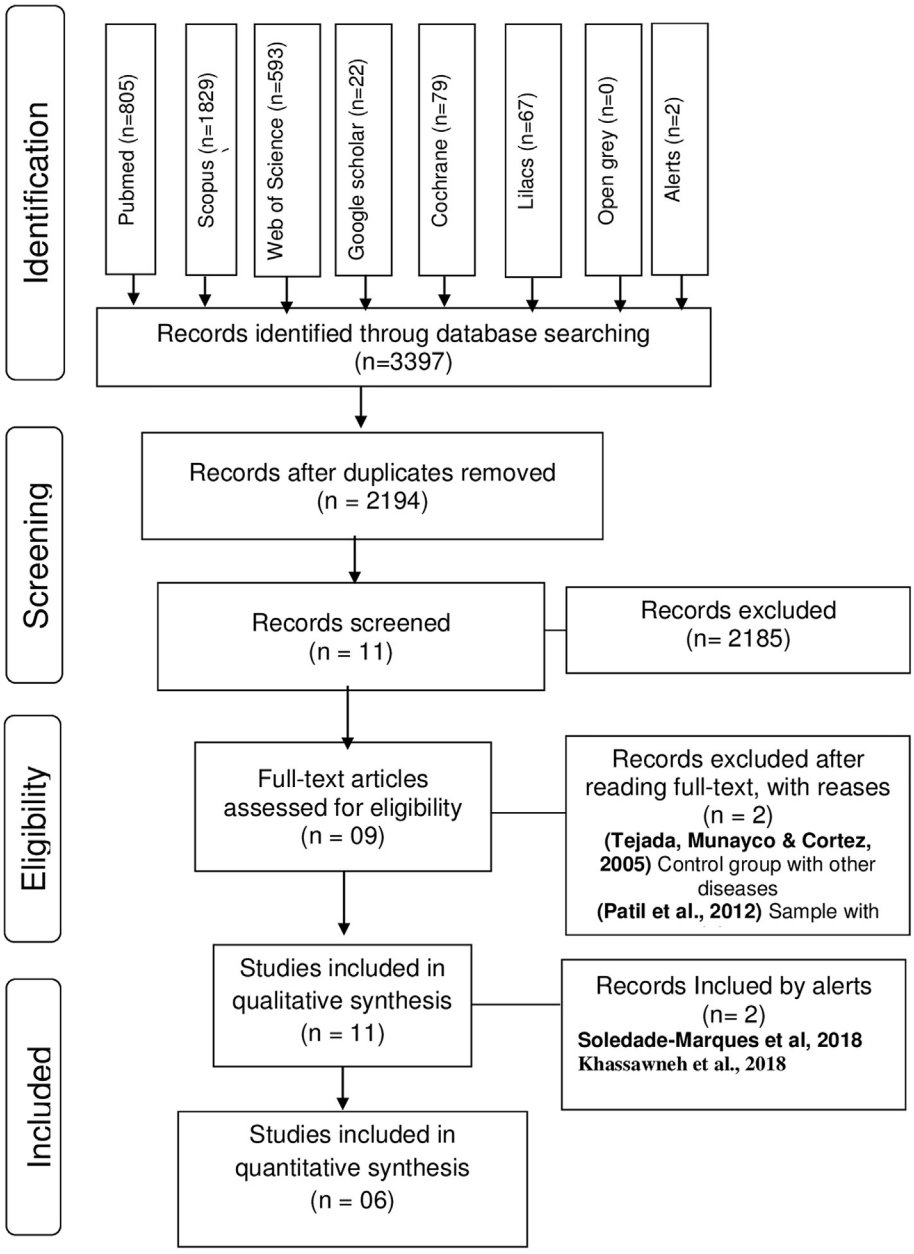

Fig. 1. Flow diagram of search in databases according to PRISMA Statement.

parameters analyzed by the studies: (1st) plaque index, (2nd) gingival index, (3rd) bleed on probing, (4th) papillary bleeding index, (5th) calculus index and (6th) clinical attachment level (CAL). The average and standard deviation of each parameter, and the total number of individuals of each group (case – with asthma- and control – without asthma) were used.

For parameter reported using similar methods, the mean difference (MD) were applied, and for parameters measurement it in a variety of ways, standard mean difference (SMD) was applied [26], with 95% confidence interval (CI). Only studies free of bias were included in meta-analysis. If some of the information needed for the meta-analysis was absent from any of the selected studies, the authors were contacted to provide the missing data.

Heterogeneity was tested using the I^2 index and, if possible, sensitivity analyses were conducted to estimate and verify the influence of studies, one by one, on the subgrouped and pooled results, when the heterogeneity was substantial or considerable (50 to 100%) [26]. Random effect model was employed due to the studies were not functionally equivalent in which the objective was to generalize the results from the meta-analysis [27].

2.7. Level of evidence

The assessment of quality of the evidence was determined for the outcomes meta-analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [28]. Observational studies start as low evidence, and the quality of, or certainty in, the body of evidence decreases to low or very low quality, if serious or very serious issues, related to risk of bias, inconsistency, indirectness, imprecision and publication bias are present and increase if dose-effect, confounding factors and if the magnitude of effect is large or very large were detected. In this way, the quality of the evidence can vary from very low to high.

Table 1
Domains and Risk of Bias considered in Risk evaluation according to Fowkes and Fulton 1991.

Guidelines	Checklist	Description
Study design appropriate to objectives?	Objective common design Prevalence cross-sectional Prognosis cohort Treatment controlled trial Cause cohort, case-control, cross-sectional	The type of study was marked in the appropriate type of study. If the type of study was appropriate according to the study design, it was labeled as "0", and as "++" if it was not appropriate.
Study sample representative?	Source of sample	The domain was considered [0] in cases of detailed origin, [+] to a specified origin of only one group and [++] in cases of absence of specification of the source of the groups.
	Sampling method	The item was assigned [0] for a full description of sampling method, [+] for reduced or no explanation of sample method, with no problem in matching between groups, and [++] for poor or no description of sample method, interfering in the matching of the groups.
	Sample size	A minor problem [+] was considered when the sample was not representative or did not report a sample calculation. To a major problem, [++] was considered when no sample calculation was provided, and the number of participants was < 50 participants, [0] was considered in the absence of the above factors.
	Entry criteria/exclusion	A minor problem [+] was attributed when the control and case group reported current use of antibiotics or anti-inflammatories, diabetes, smoking or pregnancy. In the case of the presence of more than two previously mentioned items, it was considered as a major problem [++].
	Non-respondents	The [0] was attributed when there was no refusal to participate in the study, [+] was assigned when there was the refusal, but did not compromise the sample, and [++] when there were refusal and impairment of the sample size.
Control group acceptable?	Definition of controls	It was attributed [0] when all characteristics of the control group were described, [+] when any information was pendent as the origin of the control group, the selection criterions and a different origin between case and control groups and [++] when two or more items described in previously items.
	Source of controls	It was considered [0] when the control group was referred, [+] when the origin of groups was different, but with reasons and [++] when the groups presented different origins without reasons.
	Matching/randomization	In this item, [0] was assigned to cases of randomized/matched groups, [+] to cases of no description of randomization, but with a matching of groups and [++] to no explanation of randomization or matching.
	Comparable characteristics	It was attributed [0] to matched groups or not matched by the impossibility of being subsequently adjusted and [++] the presence of unpaired variables that were not paired or adjusted.
Quality of measurements and outcomes?	Validity	It was considered [0] when the evaluation method applied is appropriate; [+] when using a single method, but with appropriate sensitivity with good specificity; [++] when using a single method, without an adequate specificity or good sensitivity.
	Reproducibility	It was considered [0] whether the evaluation methods were well described; [+] when a lack description of any step of the method was presented, for example, the identification of the patients of the groups studied in laboratory samples, evaluations at different times or application of various methods between groups of individual pathology; [++] when two or more of the previous items are present.
	Blindness	The condition of the study participants was considered to be "Blind," in this case being assigned the signal [0], in cases of "not blind" the signal [++] was attributed.
	Quality control	It was considered a problem when the examiner was not qualified; a partial periodontal exam was performed [not in all teeth or not in all the six periodontal sites/teeth], the measurement of periodontitis was only radiographic or the absence of the number of evaluated teeth sites. A Minor problem [+] was considered when 2 of these characteristics were present, and a major problem [++] if > 2 of these characteristics were present.
Completeness	Compliance	It was assigned [0] for a sample size that remains the same from the beginning to the end or decreases without compromising the power of the test; [+] for differences in sample size at the end of the study, compromising the power of the test, but with reasons and adjusts; [++] for difference in sample size at the end of the study, compromising the power of the test, without reasons.
	Dropouts	The [0] was scored when there is no loss during the study, [+] when there is a withdrawal that involves the inclusion criteria, such as age, sex, [++] when there is withdrawal and it compromises more than one criterion.
	Deaths	This item was scored as Not Applicable [NA], due to the type of PECO strategy.
	Missing data	In this item, [0] was assigned to cases of randomized/matched groups, [+] to cases of no description of randomization, but with a matching of groups and [++] to no description of randomization or matching.

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Table 1 (*continued*)

Guidelines	Checklist	Description
Distorting influences?	Extraneous treatments	In this item, [0] was considered when there were no external influences; [+] when there are external influences, but that does not interfere in the results; [++] when there are external influences and interferes with the results.
	Contamination	This item was scored as Not Applicable [NA], due to the type of PECO strategy.
	Changes over time	In this item, [0] was attributed to data collected in the same period; [+] to data obtained from the control group and the study group at different times that may cause distortions; [++] when the previous item was associated with data from studies already published.
	Confounding factors	A problem was assigned when the data analysis involved enrollment of persons < 5 years. Menopausal woman, smokers, diabetics and obese. A minor problem [+] was assigned when 1 or 2 of these characteristics were present and a major problem [++] if there were 3 or more.
	Distortion reduced by analysis	It was considered [0] when it cites the adjustments of the covariates that present distortions; [+] when the article report adjustment, but does not say the criteria; [++] when distortion was identified, without adjustment.
Summary questions	Bias: are the results erroneously biased in a certain direction? Confounding: are there any serious confusing or other distorting influences? Chance: is it likely that the results occurred by chance?	YES or "NO" answers were assigned to each question. If the answer is NO to the three questions, the article is considered reliable, with low risk of bias.

3. Results

3.1. Selection and characteristics of included studies

3397 citations were retrieved and 1203 were excluded from the database because they were duplicated results. All 2194 articles were analyzed by title and abstracts based on the inclusion criteria, with the exclusion of 2186.

Regarding the study type, one was cohort [29], eight were case-control studies [30–37] and two studies cross-sectional [38,39]. Articles excluded and the reasons for exclusion are presented on (Table S2). The other studies ($n = 11$) were analyzed in full text and two of them were excluded: due to the inclusion of patients with other diseases in the control group [40] and presence of adolescents in the sample [41]. Two studies were included [31,33] for the alerts created in the databases used in the searches. In total of 11 studies were included in this systematic review [29–39] (Fig. 1).

3.2. Results from individual studies

Ten studies reported an association between asthma and periodontal disease [29–33,35–39]. The studies by Lee et al. [2017] and Shen et al. [2017] approached in their research periodontal disease evaluation [29,39]. Otherwise, two studies evaluated only gingivitis [34,38] and seven studies evaluated gingivitis and periodontitis [30–33,35–37] (Table 2).

The methods for the evaluation of periodontal parameters were plaque index (PI) [31–37], gingival index (GI) [31,32,34–37], clinical attachment loss (CAL) [30–33,36,37], probing depth (PD) [30–33], bleeding on probing (BOP) [30,31,33], community periodontal index (CPI) [38,39], Gingival recession [31], Calculus index (CI) [35–37], Papillary bleeding index (PBI) [35–37] and one study evaluation Periodontal Disease Index (PDI) [35]. Other methods were employed in the studies, such as the radiographic analysis [29,34]. In one of these studies, the authors used the ICD-9 format, not describing the periodontitis clinical evaluation methods used [29].

The selected researches included the countries of, Denmark [38], Turkey [32], Sweden [34], Brazil [30,33], Taiwan [29], Indian [36,37], Iran [35], North Jordan [31], Taiwan [39]. The ages evaluated between the studies ranged from 20 to 68 years and among the samples, the number of participants varied from 40 [30] to 96,000 participants [29]. One of the included studies [39], used a sub-sample of 261 participants to estimate periodontal disease within a sample of 13,409 participants. However, the authors have not reported data regarding periodontal evaluation on manuscript.

A study performed in Jordan [31], with a sample of 260 patients (130 controls and 130 asthma patients) reported that CAL = 2.35 ± 0.6 for the asthmatic group and 2.14 ± 0.27 for the control group. They also reported a Gingival Recession for the asthmatic group 0.31 ± 0.51 and the control group 0.24 ± 0.007, and a Bleeding on probing in the asthmatic group 21.2 ± 15.00% and the control group 19.9 ± 13.60%, used chi-square test for categorical data and *t*-test for continuous variables and later applied the ANOVA test and logistic regression, considering $p < 0.05$.

In the Indian study conducted by Bhardwaj et al. 2017 [37] the periodontal markers used to ascertain the relationship between asthma and periodontal diseases were: PI, CI, GI, PBI, and CAL. In the investigation for gingival inflammation the study showed that the mean for the plaque index (PI) was 1168 ± 0.461 for the asthmatic group and 0.649 ± 0.316.003 for the non-asthmatic group ($p = 0.004$), in the gingival index (GI) the mean in the asthmatic group was 1.491 ± 0.541 and in the non-asthmatic groups 0.592 ± 0.218 0.036 ($p = 0.036$), the average number of patients with asthma was 1.89 ± 0.722 and 1.124 ± 0.618 for the non-asthmatic group ($p = 0.0346$). When assessing the index of calculation (CI), the means found were 1172 ± 0.216 and 0.613 ± 0.516 for the asthmatic and non-asthmatic groups, respectively, with p value of 0.042. The mean value of clinical insertion loss (CAL) between the asthmatic and non-asthmatic groups was 4964 ± 0.87 in the asthmatic group and 3817 ± 0,722 in the non-asthmatic group ($p = 0.004$).

Lee et al. 2017 [39] analyzed in South Korea, through the Sixth Korea National Health and Nutrition Examination Survey (KNHANES VI-1), 5976 patients and their asthmatic and periodontal conditions. Age of participants consisted of 51.42 ± 18.29 and the periodontal evaluation was measured with Community Periodontal Index (CPI). A multivariable logistic regression analysis with weighted observations shows that patients with current asthma condition were 5 times more likely to be associated with periodontitis ORadjusted = 5,36 (95% CI [1.27–22.68]). However, CPI was used only for the diagnostic purpose and not presented in multivariable analysis.

Soledade-Marques et al. 2017 realized, in Brazil, 260 participants divided in a matched control group and asthma group. The mean age between groups was 48.2 ± 14 years and periodontal parameters (PD, CAL and BOP) were tabulated to associate both conditions, severe asthma and periodontal disease. Association between exposure to periodontitis and severe asthma was found: ORadjusted = 3.01–3.25 (95% CI [1.80–5.63]). The frequency of periodontitis in participants with severe asthma was higher than that of those without asthma (46.6% vs

Table 2
Summary of characteristics of the included studies.

Author, year, country	Type of Study	Participants		Age	Evaluation of asthma	Periodontal evaluation	Statistical analysis	Results
		Local of study	Sample size					
Yaghobee et al. 2008; Iran [35]	Case - control	Asthma clinic of Tehran Hospital, Tehran, Iran	(100) Case group (50) Control group (50)	Mean ± SD 39.62	Subjects referred to asthma clinic of Tehran Hospital, Tehran, Iran	PI, GI, PBI, CI, PDI	t-Test	The PI, GI, PBI and PDI howed statistically significant difference ($P < 0.01$) between the test and the control groups, meaning that gingival inflammation was more seen in the asthmatics
Özcan et al. 2011; Turkey [32]	Case-control	Estigarribia e Dental Centro de Saúde Oral Hospital Militar Mediterrâneo, Erzurum	(68) Case group (51) Control group (17)	Mean ± SD 25.35 ± 4.5	Frequency of use of ICS	PD, CAL, PI, GI.	One-way ANOVA Tukey HSD test	The mean values measured in all three subgroups of the saliva, PD, CAL, PI, GI groups were significantly higher than the values measured in the control group ($p < 0.05$)
Stensson et al. 2011; Sweden [34]	Case-control	Jönköping, Sweden	(40) Case group (20) Control group (20)	Mean ± SD Case group 21.6 ± 2.3 Control group 21.7 ± 2.0	Medical treatment for at least 4 years. Use of β2 agonist with ICS for at least 2 years	Radiography (≥ 2 mm), GI, PI, Crevicular fluid (Periopaper strip)	One-way ANOVA Tukey HSD Post Hoc Tests	No statistically significant differences were found between the two groups regarding the number of periodontal pockets or alveolar bone loss
Gomes-Filho et al.,2014; Brazil [30]	Case-control	Asthma Control Program in Bahia (ProAR), Salvador, Bahia, Brazil	(220) Case group (113 both sexes) Control group (107 both sexes)	Mean Case group 43.6–14.4 Control group 46.8 to 11.2 years	GINA criteria for asthma diagnosis	PD, CAL and BOP.	x^2 test, logistic regression analysis	Periodontitis was higher in the group with severe asthma (61.9%) compared to the control group (27.1%). Patients with periodontitis presented 5 times greater chances of having severe asthma than those without periodontal disease, reaffirming the association between the pathologies. (OR adjusted = 4.82, 95% CI = 2.66 to 8.76)
Uppal et al. 2015; India [36]	Case-control	Genesis Institute of Dental Sciences and Research, Ferozepur, Punjab, India	(100) Case group (50) Case control (50)	Mean 40 years	Individuals previously diagnosed with asthma	PI, CI, GI, CAL, PBI	t-Test	All parameters used show statistical significance ($p < 0.05$). It can be concluded that periodontitis and asthma are associated to each other
Goméz Real et al. 2016; Norway, [38]	Cross-sectional	Respiratory Health in Northern Europe (RHINE) III - population-based cohort from seven Northern European centers	(13.409 persons)	Mean 52 years	Questionnaire about the signs and symptoms of asthma	Community Periodontal Index (CPI), in a sub-sample of 261 persons from Bergen 1 year after the RHINE III questionnaire survey	Multiple logistic regression	This analysis of a large population-based study found that gum bleeding was significantly associated with asthma symptoms, asthma, and self-reported COPD. The association was significantly stronger among current smokers and among those with lower socioeconomic status and weaker among people taking asthma medication. ($p < 0.001$)
Bhardwaj, et al. 2017; India [37]	Case-control	Clinic of Department of Chest and tuberculosis, Indira Gandhi Medical College and Hospital, Shimla, Himachal Pradesh	(100) Case group (50) Case control (50)	Mean 40 years	Participants represented the cases of asthma reported	PI, CI, GI, PBI, CAL	*t*-Test	All indices measured were statistically significant in the asthmatic group compared to the control group p value < 0,05.
Soledade-Marques et al. 2017; Brazil [33]	Case-control	Program for Control of Asthma in Bahia (ProAR), Salvador, Bahia, Brazil.	(260) Case Group (130) Case	48.2 ± 14	GINA criteria for asthma diagnosis	PD, CAL, BOP, PI.	Logistic regression model	The PI and BOP showed the worst conditions in the group of individuals with severe asthma (PI: 44.35% vs 29.57% and BOP: 21.47% vs 12.68%).

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Table 2 (*continued*)

Author, year, country	Type of Study	Participants		Age	Evaluation of asthma	Periodontal evaluation	Statistical analysis	Results
		Local of study	Sample size					
			Control (130)					ORadjusted = 3.18 (95% CI: 1.80–5.63). p < 0,01.
Shen, T. C. et al. 2017; Taiwan, [29]	Cause-cohort	Taiwan, universal longitudinal study of National Health Insurance (NHI), Taichung, Taiwan	(96.030) Case group 19,206 Control group 76,824	Mean Case group 41.5 ± 25.9 Control group 41.3 ± 25.7	ICD-9-CM code 493	Clinical and radiographic exams ICD-9CM (code 523.0–523.9)	Chi-squared t-Student Kaplan-Meier Log-rank, Cox regression, variables and multivariable	The study showed that the incidence of the periodontal disease case was 3.2% higher than in the control group (p < 0.001). The overall incidence of periodontal disease was 1.18 times higher in the asthma cohort than in the comparison cohort. The increase in hospital admissions is directly proportional to the risk of developing periodontal diseases
Khassawneh et al., 2018; Northern Jordan [31]	Case-control	University hospital in northern Jordan.	(260) Case group (130) Control group (139)	Mean Case group: 46.43 ± 12.24 Control group: 44.18 ± 11.85	Pulmonary consultant and had been on anti-asthma medications for at least 12 months	PD, CAL and BOP, PI, GI, GR.	Binary logistic regression	Adult Jordanians with bronchial asthma are at higher risk of periodontitis
Lee et al., 2017; Korea [39]	Cross-sectional	Korea National Health and Nutrition Examination Survey (KNHANES) in 2014	(5976 persons)	Mean 51.42 (SD 18.29)	Asthma status was defined from a self-report, based on a question “Are you currently suffering from asthma?” in a sub-sample of 89 persons	Community Periodontal Index (CPI) in a sub-sample of persons from	Multivariable logistic regression	Patients with current asthma conditions were about 5 times more likely to be associated with periodontitis while adjusted by sociodemographic and lifestyle covariates (adjusted OR = 5.36, 95% CI 1.27–22.69)

Table 3
Quality assessment of studies, according to Fowkes and Fulton, 1991.

Guideline	Verification list	Kassawneh et al. 2018 [31]	Soledade-Marques et al. 2018 [33]	Shen et al. 2017 [29]	Goméz Real et al. 2016 [38]	Gomes-Filho et al. 2017 [30]	Stensson et al. 2011 [34]	Özcan et al. 2011 [32]	Lee et al. 2017 [39]	Uppal et al. 2015 [36]	Yaghobee Et al. 2008 [35]	Bhardwaj Et al. 2017 [37]
Study design appropriate to objectives?	Objective common design		−	−	−	−	−	−	−	−	−	−
	Prevalence cross-sectional		−	−	−	−	−	−	−	−	−	−
	Prognosis cohort		−	0	−	−	−	−	−	−	−	−
	Treatment controlled trial		−	−	−	−	−	−	−	−	−	−
	Cause cohort, case-control, cross-sectional	0	0	−	0	0	0	0	0	0	0	0
Study sample representative?	Source of sample	0	0	0	+	0	0	0	0	0	0	0
	Sampling method	++	0	0	0	+	++	++	0	+	+	0
	Sample size	0	0	0	0	0	++	++	0	+	+	0
	Entry criteria/exclusion	0	++	+	0	0	0	+	++	0	0	0
	Non-respondents	0	0	0	0	0	0	0	0	0	0	0
Control group acceptable?	Definition of controls	0	0	0	+	0	+	0	++	0	0	0
	Source of controls	0	0	0	0	0	0	0	0	0	0	0
	Matching/randomization	0	0	0	0	+	0	+	+	0	+	+
	Comparable characteristics	0	0	0	+	0	++	0	++	++	++	++
Quality of measurements and omes?	Validity	0	0	0	+	0	0	0	+	0	0	0
	Reproducibility	+	0	0	0	0	0	0	0	0	0	0
	Blinding	0	0	0	0	0	0	0	++	+	0	0
	Quality control	0	0	0	+	0	0	0	0	0	0	0
Completeness	Compliance	0	0	0	0	0	0	0	0	0	0	0
	Drop outs	0	0	0	0	NA	0	0	0	0	0	0
	Deaths	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Missing data	0	0	0	NA	0	0	0	0	0	+	+
Distortion influences?	Extraneous treatments	+	+	0	0	0	0	0	+	0	0	0
	Contamination	Na	NA	NA	NA	NA	NA	NA	Na	NA	NA	NA
	Changes over time	0	0	0	0	0	0	0	0	0	0	0
	Confounding factors	+	+	+	+	+	0	+	+	0	+	0
	Distortion reduces by analysis	0	0	0	0	0	NA	+	0	++	++	++
Summary questions	Bias: are the results erroneously biased in certain direction?	NO	NO	NO	NO	NO	NO	YES	YES	NO	NO	NO
	Confusion: are there any serious confusing or other distorting influences?	NO	NO	NO	NO	NO	NO	YES	YES	NO	NO	NO
	Chances: is it likely that the results occurred by chance?	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

22.3%, $p \leq 0.05$) [33].

A study performed on Taiwan [29], evaluated 96,030 participants and after analysis of cohort data, the incidence in the periodontal disease case was 3.2% higher than in the control group ($p < 0.001$). The overall incidence of periodontal disease was 1.18 times higher in the asthma cohort than in the comparison cohort.

Gomez-Real et al. 2016, with a sample of 13,409 participants from different centers in Northern Europe. The results showed that Gum bleeding frequency (always/often) was significantly associated with ≥3 asthma symptoms, OR = 2.58 (95% CI [2.10–3.18]), and asthma OR = 1.62 (95% CI [1.23–2.14]). Furthermore, a dose-response relationship between respiratory outcomes and gum bleeding frequency (≥3 symptoms: gum sometimes bleeding OR = 1.42 (95% CI [1.25–1.60]), often/always OR = 2.58 (95% CI [2.10–3.18])) was found from the analysis of self-reported questionnaire cross-sectional [38].

In the study realized in India [36] evaluation periodontal parameters (GI, PI, CI, PBI and CAL) in 100 subjects, 50 controls and 50 cases (27 subjects with mild asthma and 23 individuals with moderate / severe asthma). In their results were no statistical differences for using markers to evaluate periodontal gingival inflammation. In the plate index (PI), the mean value 0.735 ± 0.423 was recorded for the control group in the comparison to 1.152 ± 0.545 of the asthmatic group, in the papillary bleeding index (PBI) the mean value found for the control group was 1.300 ± 0.762 and in the gingival index (GI) group, mean values and deviations were 0.602 ± 0.390 and 1.528 ± 0.585 for the control group and case, respectively. For the evaluation of periodontitis, the averages of the clinical parameters evaluated were: index of calculation (IC) 0.602 ± 0.390 for the control group and 1198 ± 0.691 in the case group and in the index of loss of clinical insertion (CAL) found for the control group was of 3040 ± 0.913 and in the case group it was 5136 ± 1399. There was a statistically significant difference in all periodontal clinical parameters evaluated p value < 0.001.

In the study by Gomes-Filho 2014 performed in Brazil, a sample of 220 patients (107 controls and 113 cases of asthma) was used in which the BOP had a mean of 14.69% and a median of 7.7% (Min 0%/Max 100%) in the patients from the control group and 28.43% and median 24.4% (Min 0%/100%) in the case group, being statistically significant by the chi-squared test, with later adjustment in logistic regression. In the same study, the plaque index had a mean of 31.64% and a median of 22.2% (Min 0%/Max 100%) in the control group 54.14% and a median of 56.2% (Min 0%/Max 100%) in the case group [30].

In the study by Stensson et al. 2011, performed in Sweden, the plaque index was measured in 53 patients (20 controls and 33 cases), without difference between control and asthma groups. For the gingival index, the authors obtained GI 1.3 ± 0.8 for the controls and 1.8 ± 0.4 for the cases ($p = 0.03$). Then, the asthma group had more gingivitis and then the controls [34].

Ozcan et al. 2011, performing their work in Turkey, used gingival index and plaque index in 68 patients (17 controls and 51 cases divided into mild, moderate and severe asthma with 17 participants each). The mean and deviations of plaque index were PI = 0.65 ± 0.367 for the control group, 1.20 ± 0.429 for the mild asthma group, 1.06 ± 0.49 for the moderate asthma group and 1.27 ± 0.392 for the severe asthma group ($p = 0.01$ - ANOVA). In the GI, the authors found mean values of 0.28 ± 0.266 for the control group, 0.67 ± 0.360 for the mild asthma group, 0.89 ± 0.389 for the moderate asthma group and 1.03 ± 0.342 for the severe asthma group. Regarding CAL, 1.21 ± 0.188 for the control group, 1.46 ± 0.299 for the mild asthma group, 1.59 ± 0.230 for the moderate asthma group, 1.68 ± 0.222 for the severe asthma group and $p < 0.01$ [32].

In the study by Yaghobee et al. 2008, conducted in India, periodontal markers for gingival inflammation and periodontitis were evaluated in a group of teeth [16,21,24,36,41,44] and the results were obtained from the indices of each dental element in the group control and asthmatic. The index of plaque (PI) showed a statistically significant difference ($P < 0.01$) between the asthmatic and control groups; in the evaluation of the gingival index (GI) and the index of papillary bleeding (PBI) there was statistical difference between the two groups, control and asthmatics. However, there was no statistically significant difference in the index of calculation (CI) ($P = 0.084$) between the groups. In the index of periodontal disease (PDI) there was a significant difference (P < 0.01) between asthmatics and non-asthmatics [35].

3.3. Risk of bias

Two studies detected the presence of a high risk of bias [32,39]. Both studies presented data with confounding variables which possibly converged the results to an association between diseases.

The other studies showed a low risk of bias [29–31,33–38]. However, minor pitfalls were identified regarding methodological quality. The most frequent problems among selected studies were related to sample methods, including criteria/exclusion; definition of the control group and presence of confounding factors (Table 3).

3.4. Meta-analysis

Authors judged Ozcan et al. 2011 [32] and Lee et al. 2017 [39] with a higher risk of bias, and, for this reason, this study was excluded from the meta-analysis. In addition, Gomes-Filho et al. 2014 [30], Shen et al. 2017 [29] and Gomez Real et al. 2016 [38] did not have sufficient data for quantitative analysis, even after contact attempts, and therefore was not included in the analysis.

3.4.1. Meta-analysis for plaque index (PI)

Six studies [31,33–37] evaluated the mean of plaque index, however, two [31,34] presented your results in mean of plaque index per tooth sites, and the other [33] presented your results in mean of plaque index per individuals sites. In attempt to standard meta-analysis results, both studies that presented your results in mean of plaque index per tooth sites, were included. Heterogeneity was considerable ($I^2 = 96\%$) and, during sensitivity analysis range from 86% to 95%. As no significant reduction was detected, any study was excluded from this analysis. Individuals with ($n = 443$) and without ($n = 430$) asthma presented similar mean of plaque index MD 0.21 [−0.44, 0.87] $p = 0.53$ (Fig. 2) with very low quality of evidence due to serious

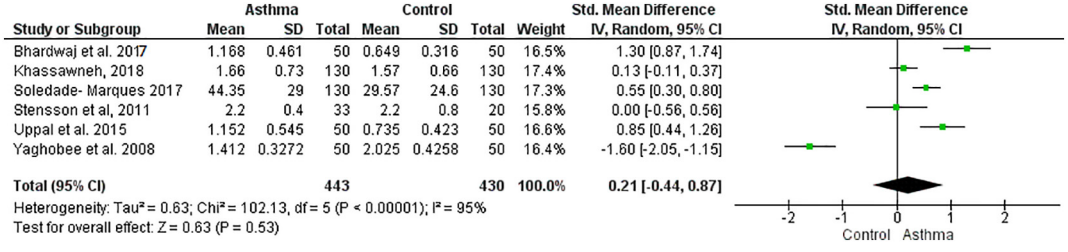

Fig. 2. Forest plot of plaque index in individuals with and without asthma.

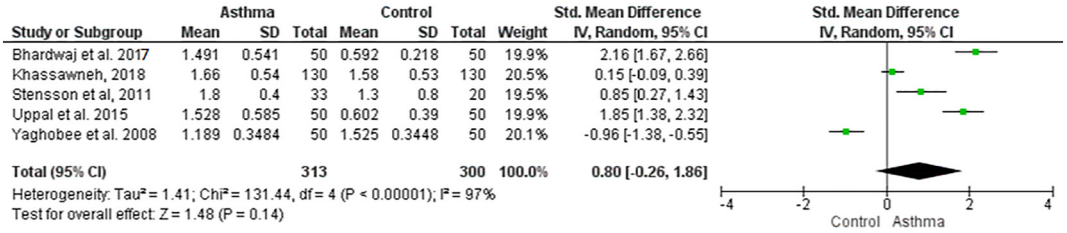

Fig. 3. Forest plot gingival index in individuals with and without asthma.

problems in imprecision and very serious problems in inconsistency.

3.4.2. Meta-analysis for the gingival index (GI)

Five studies [31,34–37] evaluated the mean of gingival index per sites. Pooled results showed considerable heterogeneity (I^2 = 97%), but during sensitivity analysis there was no significant heterogeneity reduction (range from 96 to 98%). Individuals with (n = 313) and without (n = 300) asthma presented similar mean of gingival index MD 0.80 [−0.26, 1.86] p = 0.14 (Fig. 3) with very low quality of evidence due to very serious problems in inconsistency and imprecision.

3.4.3. Meta-analysis of bleed on probing (BOP)

Two studies [31,33] evaluating the mean of BOP, per individuals. Both studies used a similar method of evaluation and Mean Difference (MD) was adopted. Pooled results presented a substantial heterogeneity (I^2 = 83%). However, due the low number of studies included, no sensitivity analysis was conducted. Individuals with (n = 260) and without (n = 260) asthma presented similar mean of BOP MD 4.83 [−2.49, 12.16] p = 0.20 (Fig. 4) with very low quality of evidence due to very serious problems in imprecision and serious problems in inconsistency.

3.4.4. Meta-analysis papillary bleeding index (PBI)

Two studies [36,37] evaluating the mean of sites with papillary bleed. The pooled heterogeneity was null 0%. Individuals with asthma (n = 100) presented greater mean of sites with papillary bleed than individuals without asthma (n = 100) MD 0.72 [0.52, 0.93] p < 0.00001 (Fig. 5) with very low quality of evidence due to serious problems in imprecision.

3.4.5. Meta-analysis for calculus index (CI)

Two studies [36,37] evaluating the mean of individuals with tooth surface with calculus. The pooled heterogeneity was null 0%. Individuals with asthma (n = 100) presented greater mean of calculus index than individuals without asthma (n = 100) MD 0.57 [0.44, 0.70] p < 0.00001 (Fig. 6) with very low quality of evidence due to serious problems in imprecision.

3.4.6. Meta-analysis for CAL

Three studies [31,36,37] evaluating the mean of CAL of individuals. The pooled heterogeneity was considerable 98% and during sensitivity analysis there was no significant heterogeneity reduction (I^2 range from 91% to 98%). This way, no study was excluded from this analysis. Individuals with asthma (n = 230) presented greater mean of calculus index than individuals without asthma (n = 230) MD 1.13 [0.09, 2,18] p = 0.03 (Fig. 7) with very low quality of evidence due to serious problems in imprecision and very serious problems in inconsistency.

3.5. Level of evidence

Overall GRADE analysis showed one clinical parameter with a very low level of evidence Among in PI, GI, BOP, CI, PBI and CAL indexes was observed a very low level of evidence due to serious and very serious problems related to inconsistency and imprecision GRADE domains (Table 4).

4. Discussion

Eleven primary studies were included in this systematic review, and ten demonstrated an association between periodontal disease and asthma [29–33,35–39]. Considering the meta-analysis, asthmatic patients presented more periodontal damage to dental supporting tissues, such as CAL and papillary bleeding, compared to patients without asthma.

Systematic reviews propose a synthesis of clinical situations to perform a critical analysis of the results within published studies. Some reviews use a consolidated method for methodological assessment; and depending of the search strategy outlined; experimental, observational, and randomized clinical studies can be included [26,42]. To perform a link between statistical data from selected studies, meta-analysis can afford an effect size evaluation of issues and provide implications about research question [42]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool is a standardized assessment of evidence quality among studies. Thus, after analysis of evidence, recommendations with levels of strength may lead to clinical decisions and issues management [28].

A previous systematic review and meta-analysis performed by Moraschini et al. [18] proceeded evaluations of periodontal disease in children and adults with and without asthma. However, an important factor must be considered: the difference between the asthma pathophysiology in both age groups. Considering that, our systematic review and meta-analysis analyzed only adult patients, once the adult onset asthma has a complex interaction of several factors as aging, epigenetic factors, environment and microbiological triggers and immune response alterations, featuring different aspects when compared with children patients [22]. In addition, comparing both studies, we highlight different points among them [18]: our study has four more articles included in the analyses [31–33,37]; three different meta-analysis were performed, evaluating clinical attachment loss, salivary calculi and gingival papillary bleeding and the level of evidence evaluation using

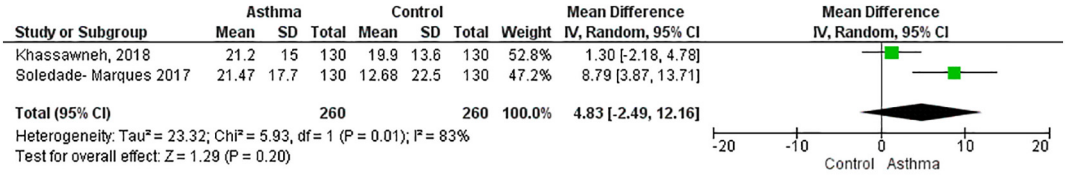

Fig. 4. Forest plot of bleed on probing in individuals with and without asthma.

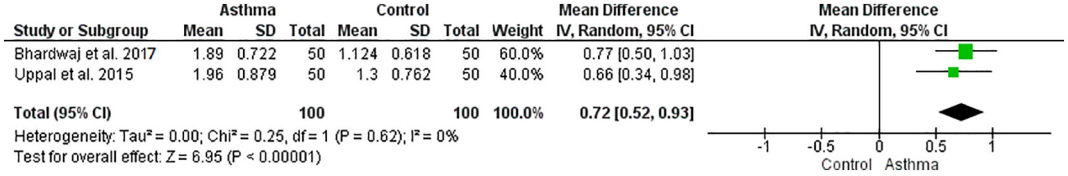

Fig. 5. Forest plot of mean of sites with papillary bleed in individuals with and without asthma.

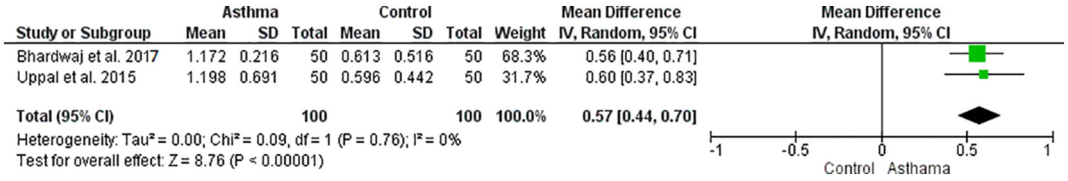

Fig. 6. Forest plot of mean of calculus index in individuals with and without asthma.

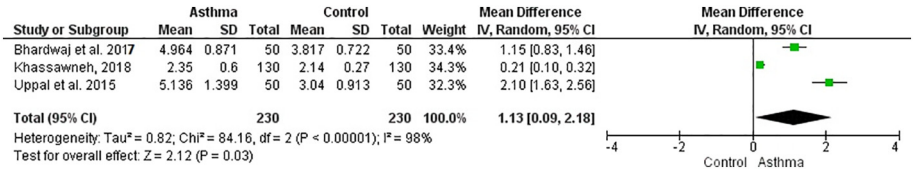

Fig. 7. Forest plot of a mean of CAL in individuals with and without asthma.

GRADE assessment tool.

Asthma was associated with periodontal disease in most of the studies identified in the review [29–33,35–39]. Asthma is characterized by chronic inflammation of the airways, caused by environmental and genetic factors marked by the involvement of several cell types, such as mast cells, macrophages, eosinophils and lymphocytes [44]. The main consequence of the disease is the onset of obstructive respiratory problems such as dyspnea, wheezing and coughing [45]. Although the literature shows three distinctive understandings about the association between asthma and periodontal disease, our search strategy and elected articles obtained a better elucidation about the association between the most prevalent manifestation of periodontal disease, the Periodontitis, and asthma.

Clinical signs and symptoms characteristic of periodontal disease may affect gingiva (Gum bleeding, halitosis, gum edema) or dental supporting tissues (gingiva, periodontal ligament, and alveolar bone) resulting in loss of attachment, dental mobility, and tooth loss [9]. The etiology of periodontal disease is multifactorial, but there is a strong relation to the bacterial component present in dental biofilm. According to Socransky et al. 1998 [46], the multiple bacterial complexes perform defined functions to maintain symbiosis and generate host responses related to inflammatory immunomodulation (pro and anti-inflammatory cytokines, vasoactive products) [46]. Among the types of bacteria present within the biofilm, gram-negative anaerobic bacteria are the major periodontal pathogens, with Porphyromonas *gingivalis* receiving prominence in some studies for its association with other inflammatory diseases, such as rheumatoid arthritis and asthma [47,48].

The possible association between asthma and periodontal diseases has been linked with the interaction between a reduction of Il-10 and the polymorphisms associated with its gene. IL-10 is characterized as an anti-inflammatory cytokine and a B cell proliferation factor that executes production of protective antibodies and the down-regulation of pro-inflammatory cytokines [49]. These two factors have been identified as triggering the progression and worsening of periodontal disease in patients with asthma, who had the lowest levels of IL-10 [50–53]. However, even with a correlation and association, there is a need for disclosure about the mechanisms that cause worsening of periodontal disease [54].

Periodontal evaluation is a combination of clinical parameters to assess the stage, progression, and treatment management. Several indexes for periodontal evaluation have been used for clinical and research application. Regarding the methods of evaluation, PI, GI, PD, and CAL have been recommended by the American Academy of Periodontology and the European Federation of Periodontology [9]. Also, the components of some of these indexes are present in the Community Periodontal Index, widely used to evaluate gingivitis and periodontitis in the periodontology research with larger samples [55].

In addition to clinical parameters, age is an important variable that should be considered for asthma and periodontal evaluation. Adult-onset asthma is different from childhood-onset disease and commonly more severe to lung function [56]. Early-onset adult asthma is more attributed to atopy and potentially genetic factors, while late-onset adult asthma appears to be more related to environmental risk factors [57]. The aging process may be associated with periodontal health with a moderate to severe periodontal attachment loss through biochemical, physiological, anatomical and immunological changes in periodontal tissues [58]. The aging process also presents a decrease in the chemotaxis levels and proliferation of periodontal ligament cells [59] promoting a worsening of periodontal status.

To qualify the methods among studies, an adapted version of Fowkes and Fulton checklist was applied [60]. The risk of bias among the selected studies was classified as high risk in two selected studies [2,32,39]. Overall, the most significant number of problems are related to sampling methods; including criteria/exclusion; definition of the control group and presence of confounding factors. It is understood that the randomization and selection of sample sizes is a valuable tool that allows the evaluation of study groups [61]. When a randomization process is done, the probability of an event occurs is distributed randomly within the study population providing representative analysis of outcome effects [62]. Thus, failures that contemplate this stage result in possible false-positives and false negatives, compromising the information studied and significant findings on the relationship between asthma and periodontal disease.

These problems may result in inapplicable conclusions to different populations due to the possibility of unfair comparison of groups within selected articles. On the other hand, the selected studies presented proper evaluation methods of asthma and periodontitis. Global Initiative for Asthma criteria (Gina Global Initiative for Asthma), American Association of Periodontology classification parameters [63],

Table 4
Evidence profile: association between periodontal parameters and asthma.

Certainty assessment							Summary of findings				
№ of participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Effect (95% CI)	Anticipated absolute effects	
							With control	With asthma		With control	With asthma
Plaque index 443 cases 430 controls (6 observational studies)	Not serious	Very serious[a]	Not serious	Serious[b]	None	⨁◯◯◯ VERY LOW	443 cases 430 controls		**SMD 0.21** (−0.44 to 0.87)	**Low** 0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Gingival index 313 cases 300 controls (5 observational studies)	Not serious	Very serious[a]	Not serious	Very serious[c]	None	⨁◯◯◯ VERY LOW	313 cases 300 controls		**SMD 0.80** (−0.26 to 1.86)	**Low** 0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Bleed on probing 260 cases 260 controls (2 observational studies)	Not serious	Serious[d]	Not serious	Very serious[c]	Strong association	⨁◯◯◯ VERY LOW	260 cases 260 controls		**MD 4.83** (−2.49 to 12.16)	**Low** 0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Calculus index 100 cases 100 controls (2 observational studies)	Not serious	Not serious	Not serious	Serious[e]	None	⨁◯◯◯ VERY LOW	100 cases 100 controls		**MD 0.57** (0.44 to 0.70)	**Low** 0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Papillary bleeding index 100 cases 100 controls (2 observational studies)	Not serious	Not serious	Not serious	Serious[e]	None	⨁◯◯◯ VERY LOW	100 cases 100 controls		**MD 0.72** (0.52 to 0.93)	**Low** 0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
CAL (média CAL do grupo) 230 cases 230 controls (3 observational studies)	Not serious	Very serious[a]	Not serious	Serious[c]	None	⨁◯◯◯ VERY LOW	230 cases 230 controls		**MD 1.13** (0.09 to 2.18)	**Low** 0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

CI: Confidence interval; MD: Mean difference; SMD: Standard Mean difference.
[a] Considerable or substancial heterogeneity ($I^2 > 50\%$) was detected, with wide variation in the effect estimates across studies and little or no overlap of confidence intervals associated with the effect estimates.
[b] Upper or lower confidence limit crosses the effect size of 0.5 in either direction.
[c] Total number of participants is less than 400 and upper or lower confidence limit crosses the effect size of 0.5 in either direction.
[d] Considerable heterogeneity (83%) was detected.
[e] Total number of participants is less than 400.

a Standard questionnaire of Respiratory Health in Northern Europe cohort (RHINE III) were the main parameters to define group characteristics and propose matching of individuals. Thus, some problems related to the definition of groups were bypassed. The statistical adjustment performed by authors [29–31,33,38,39] was considered to reduce the risk of bias occasioned by sample size and matching problems.

In our meta-analyses, parameters involving the staging of periodontal disease were chosen. Plaque index, gingival index, bleeding on probing, calculus index, papillary of bleeding index and level of clinical insertion resulted in six meta-analyses with some involving subgrouping. For the PI analysis, both studies [31,33–37] used the Silness and Löe index applying scores (0–3) for the amount of plaque. In the results, the presence of plaque was similar in both groups. The index of Silness and Löe presents a general biofilm synthesis with a mean score, differing from other indexes such as O'Leary index, which evaluates the percentage of plaque, involving 4 sites in each tooth present.

For the GI and BOP index, similar values between the studies were observed. The evaluation of these indexes commonly varies among observational studies due to the methodological difficulty of evaluating a large number of people. In the process of information synthesis involved in a systematic review and meta-analysis, several evaluation methodologies can be grouped. Consequently, a possible heterogeneity of the studies and inconsistency of the evidence may occur in the quantitative analysis of the results. In the meta-analysis the results obtained for the plaque index were not significant between the groups with 95% heterogeneity and for gingival bleeding 83%, p value > 0.05 for the either indices.

In addition to problems in the sample, failures were detected in the definition of the control group in two studies [34,38] and in the pairing of groups in two studies Stensson et al. 2011 [34], suggesting the existence of confounding factors resulting from unpaired sample characteristics such as caries conditions, salivary pH and mouth breathing [34]. The results of the present study are consistent with the results obtained in the present study [38], concerning the quality of the measures and results, specifically in the validity of the methods used and quality control. In addition, identification of the disease evaluated may compromise data collection and evaluation of results [64].

In CAL analysis, three studies [31,36,37] were included in the meta-analysis. Results showed that individuals with asthma presented greater clinical attachment loss compared to non-asthmatics, however, due to methodologic differences among studies the heterogeneity analysis was $I^2 = 98\%$ and did not change, even after the sensitivity analysis. The study of Soledade-Marques et al. 2018 [33] was excluded of meta-analysis due to a different analysis of CAL, classified in groups according to alveolar bone loss, making it impossible to compare precluding with other studies. Thus, for severe stages of periodontitis, asthma may be classified as a risk rather than a direct aggravating of the disease since obtained level of evidence was very low (problems of inconsistency and imprecision).

In the evaluation of calculus index and papillary bleeding index, the studies included in the meta-analysis were [36,37]. The results showed that the asthmatic group presented more salivary calculi when compared to the non-asthmatic group, and papillary bleeding was also present in the asthmatic group. The heterogeneity and p value for both meta-analysis results were 0% $p < 0.00001$. The study [35] was excluded from the meta-analysis, and the sensitivity analysis I2 changed from 31% to 0%.

Despite the methodological flaws observed, the selected studies suggest that patients with asthma are very likely to develop periodontal disease. Thus, the dentist should be aware of the medical history of each patient and which situations are indicative of asthma, such as, reported episodes of dyspnea with/without force being exercised in the absence of reports of other diagnosed respiratory diseases [64].

We suggest that randomized clinical studies involving periodontal therapies and assessment of remission of disease among healthy and asthmatic patients may highlight the level of impairment of periodontal disease resulting from asthma.

Respiratory disorders (asthma, chronic obstructive pulmonary disease) and periodontal disease may be associated due to the aspiration of oral pathogens, polysaccharides, and release enzymes that result in inflammation and infection of the lower airway. In this sense, we consider that clinical activities aimed at reducing periodontal disease should include measures that modulate the inflammatory process of the respiratory tract [39]. Periodontal clinical follow-up should be included in the periodic pneumological follow-up and frequency of episodes of asthma exacerbation per year. Thus, specialized medical care combining health promotion and prevention measures (oral hygiene guidance, clinical periodontal procedures, dietary) can be determinants for balancing the effects of asthma on periodontal disease worsening [65].

5. Conclusion

The included studies showed evidence that asthma may represent a risk indicator for periodontal disease. Our meta-analysis showed that asthmatic individuals presented more papillary bleeding, salivary calculi and loss of attachment of periodontal tissues. There was considerable heterogeneity between the studies, which resulted in limitations for the proposed assertions among periodontal evaluation parameters. Due to a low level of evidence in our evaluation, we also highlight the lack of similar methods and the necessity of further case-control or randomized clinical trials to establish how asthma impairs periodontal health.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2019.03.005.

Conflict of interest

There are no conflicts of interest between authors.

Authors' contributions

MKMF and ROF performed the searches, data extraction, quality assessment, analysis of results, and manuscript elaboration. MMLC, APCPSCA, NCFF, performed analysis of results and manuscript elaboration. MBM and LCM performed quantitative analysis and manuscript elaboration. RRL performed analysis of results and manuscript elaboration.

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Compliance with ethical standards

This study is a systematic review. This article does not contain any studies with human participants practiced by any of the authors.

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