



Linking Periodontitis to Adverse Pregnancy Outcomes: a Comprehensive Review and Meta-analysis

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Abstract

Purpose of Review Numerous investigations have explored the potential link between periodontitis and low birth weight (LBW) as well as preterm birth (PTB). However, the evidence remains inconclusive. Bacteria, their by-products, and proinflammatory cytokines originating from periodontal tissues can reach the placenta, inducing inflammatory changes that may contribute to pregnancy complications.

Recent Findings A total of 35 studies involving 2,510,556 women were analyzed. The quality of the studies varied, but the meta-analysis consistently showed a moderate association between periodontitis and low birth weight. The observed association between periodontitis and low birth weight was moderate (OR 2.48; 95% CI 1.72–3.59), and it became even stronger when analyzing case–control studies independently (OR 3.94; 95% CI 1.95–7.96). On the other hand, the association between periodontitis and preterm birth was weak (OR 1.87; 95% CI 1.57–2.22) with highly significant heterogeneity. However, the presence of high heterogeneity and publication bias in the studies casts some limitations on the confidence in the results.

Summary The available evidence, albeit of low quality, supports a moderate association between periodontitis and low birth weight, as well as a weak association with preterm delivery. Nonetheless, these findings must be interpreted cautiously, given the limited confidence in the effect estimates due to potential biases and heterogeneity in the studies.

Keywords Periodontitis · Low birth weight · Preterm birth · Systematic review

Introduction

Periodontitis is an inflammatory process that degrades periodontal supporting tissues which eventually lead to the loss of the tooth. Bacteria in the dental biofilm cause an inflammatory reaction in the marginal gingiva that becomes chronic over time and when it advances to the supporting tissues (alveolar bone, periodontal ligament) produces its irreversible destruction. The formation of the periodontal pocket creates a dysbiotic environment for the thriving of microorganisms (e.g. *Porphyromonas gingivalis*, *Tannerella forsythia*, *Campylobacter* spp.) with pathogenic potential that could eventually have an impact on the systemic health [1, 2].

Low birth weight (LBW) and preterm birth (PTB) are two important complications during pregnancy that can impact the health and survival of newborns. A birth weight of less than 2,500 g, regardless of gestational age, is defined as LBW. PTB is characterized by a birth before 37 weeks of gestation. Both LBW and PTB are associated with increased risk of neonatal morbidity and mortality, as well as long-term developmental problems [3, 4•, 5•].

Several investigations have revealed a link between periodontitis and LBW and PTB, however, the evidence is still uncertain. Two likely explanations have been put forward for this relationship. The direct pathway involves the transfer of bacteria from the dental biofilm or its bacterial products into the bloodstream, traveling to and invading the placenta and, as a result, causing inflammation. The indirect pathway involves the systemic production of proinflammatory cytokines from inflamed periodontal tissues, which can interfere with the feto-placental unit and cause intrauterine growth restriction and preterm birth [4•, 5•, 6].

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Given the great importance of oral health and pregnancy complications and to inform clinical practice and public health policy, this systematic review is necessary to update the current knowledge on the subject. Additionally, it can also help in the identification of potential risk factors, prevention methods, and treatment options for pregnant women suffering from periodontitis. Consequently, the objective of this systematic review was to determine the association between periodontitis and LBW/PTB.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) and registered in the Open Science Framework (OSF; <https://doi.org/10.17605/OSF.IO/GCYPN>).

PECO Question

Population: pregnant women without restrictions of age, ethnicity, race with and without low birth weight/preterm delivery.

Exposure: periodontitis

Comparator: without periodontitis

Outcome: frequency of women with periodontitis in each group

What is the association between periodontitis and low birth weight/preterm delivery in pregnant women?

Population, Exposure and Comparator

The population of interest included pregnant women regardless of age, ethnicity, or race with and without pregnancy complications such as low birth weight or preterm delivery. The exposure of interest was the presence of periodontitis, determined by clearly established periodontal clinical parameters or by means of periodontal indices. The comparator group exhibited no clinical signs of periodontitis, determined by clearly established periodontal clinical parameters or by means of periodontal indices.

Outcomes

The primary outcome of interest was the prevalence of periodontitis associated with the presence of low birth weight or preterm delivery. As a measure of effect size, the odds ratio (Odds Ratio; 95% confidence interval) was calculated. As secondary outcomes, the means of probing depth (PD) and periodontal attachment level (AL) were evaluated.

Search Strategy

A comprehensive search was performed from inception to May 2023 in the following electronic databases: PubMed/MEDLINE and Scopus. The search strategy included appropriate combinations of free keywords and relevant controlled vocabulary (e.g. Medical Subject Headings-MeSH) terms related to 'low birth weight', 'preterm birth' and 'periodontitis'. Keywords were searched in English, Spanish and Portuguese. In addition to the electronic database search and to identify any potentially eligible studies, snowballing and screening of relevant reference lists of included studies, as well as gray literature search, was performed through Google Scholar and SciELO.

Study Selection Process

Only human, case-control, cohort, and cross-sectional studies that focused on evaluating the presence of periodontitis in women with pregnancy complications were included. Intervention studies, animal studies, previous systematic reviews, conference proceedings, and case reports were excluded.

The inclusion language was limited to English, Spanish and Portuguese.

Initial screening of titles and abstracts was performed by two independent reviewers based on pre-determined eligibility criteria. Full text articles were retrieved for potentially eligible studies. Two independent reviewers then assessed the full-text articles for final eligibility based on the inclusion and exclusion criteria. Any discrepancies were resolved by discussion or consultation with a third reviewer.

Data Extraction

A standardized data extraction form was developed to collect relevant data from the included studies. The following data elements were extracted: study characteristics (author, year, study design), participant characteristics, sample size, exposure details, comparison details, outcome measures, and statistical results. Two independent reviewers performed data extraction. Extracted data were checked for accuracy and any discrepancies were resolved by discussion or consultation with a third reviewer.

Risk of Bias (RoB)

The methodological quality and risk of bias of the included studies were assessed using appropriate tools, such as the Newcastle-Ottawa scale for cohort and case-control

studies. The quality result was rated as (7–9) Low risk, (4–6) Moderate risk and (0–3) High risk.

For cross-sectional studies, the National Heart, Lung, and Blood Institute (NHLBI-NIH) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies was used. The guide is not intended to be a checklist, but rather a tool to identify potential issues that could introduce bias. The quality of each study was rated as low, medium or high (good) as follows:

Low quality: High risk of bias for all questions, or any potential bias could seriously affect confidence in the results.

Medium quality: risk of bias is unclear for one or more questions, or any plausible bias raises some concerns about the study results.

High quality: Low risk of bias for all questions, or any plausible bias is unlikely to seriously affect the study results.

Meta-analysis

Heterogeneity between included studies was assessed using statistical tests, such as Cochran's Q test and the I^2 statistic. As substantial heterogeneity ($I^2 > 50\%$) was detected, a random effects model was used for meta-analysis. Sensitivity and subgroup analysis were performed to explore potential sources of heterogeneity, including study design, participant characteristics, and methodological quality. All analyses were performed in Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Publication Bias

We visually analyzed funnel plots and statistical tests such as Egger's regression test to assess for publication bias to detect any potential reporting bias.

Fig. 1 Flow chart of study selection

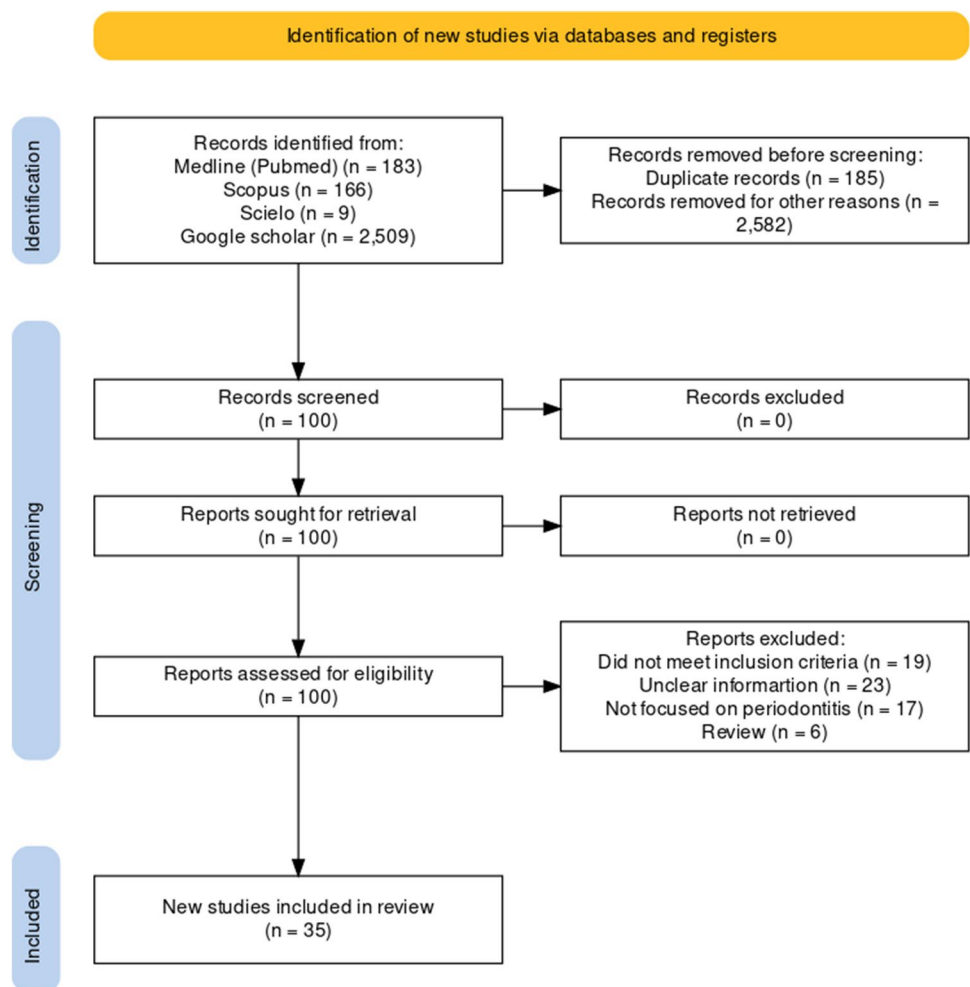


Table 1 General characteristics of the included studies

Authors	Design	Observations	Age	Age case group	Age control group	Participants (n)
Davenport et al. 2002 England	Case-control	Periodontitis was not associated with LBW	26.7	26.7	26.9	743
Moore et al. 2004 United Kingdom	Cohort	There was no association between PTB or LBW and periodontal disease in this population	29.9	29.8	30	546
Cruz et al. 2005 Brazil	Case-control	Periodontal disease is a possible risk factor for LBW	13-48	13-48	13-48	302
Lunardelli et al. 2005 Brazil	Cross-sectional	No association was found between periodontal disease and LBW. An association was found between PTB and periodontal pockets, but it was confounded by maternal health variables	15-40	15-40	15-40	449
Jarjoura et al. 2005 USA	Cross-sectional	The data support the notion that periodontitis is independently associated with PTB and LBW	28.6	28.6	28.6	203
Offenbacher et al. 2006 USA	Cohort	Maternal periodontal disease increases the relative risk of preterm or spontaneous PTB	28.2	28.2	28.2	1,206
Bassani et al. 2007 Brazil	Case-control	Weak association, as a strong association of perinatal outcomes and periodontal disease could not be detected in the present study	20-24	20-24	20-24	915
Siqueira et al. 2007 Brazil	Case-control	Maternal periodontitis is associated with increased risk of PTB and LBW	18-35	18-35	18-35	1,277
Agüeda et al. 2008 Spain	Cohort	This study found a modest association between periodontitis and PTB	29.6	28	29.6	1,296
Saddki et al. 2008 Malaysia	Cohort	Pregnant women with periodontitis are at significantly increased risk of delivering LBW babies	29.1	14-46	14-46	472
Nabet et al. 2010 France	Case-control	Maternal periodontitis is associated with an increased risk of induced preterm labor due to preeclampsia	25-34	25-34	25-34	2,202
Santacruz et al. 2012 Spain	Cohort	The presence and counts of <i>E. corrodens</i> and <i>Capnocytophaga</i> spp. showed a significant association with PTB and LBW	39.5	39.5	39.3	170
Arteaga-Guerra et al. 2010 Colombia	Cross-sectional	Periodontal disease was associated with LBW and PTB	2.,2			46
Wolff et al. 2010 Argentina	Cohort	Moderate to severe maternal periodontitis is a true risk factor for PTB	18-40			44

Table 1 (continued)

Authors	Design	Observations	Age	Age case group	Age control group	Participants (n)
Baskaradoss et al. 2011 India	Case-control	Periodontal disease is an independent risk factor for PTB, resulting in an almost three-fold increased risk for PTB	25.5	25.1	25.7	300
Schenkein et al. 2012 USA	Cross-sectional	No evidence that periodontitis predisposes to LBW	24.6	24.6	24.6	606
Ali et al. 2012 Malaysia	Cohort	Periodontitis was not shown to be a risk factor for PTB orLBW	22–48	22–48	22–48	73
Martinez de Tejada et al. 2012 Switzerland	Case-control	PTB is associated with periodontitis when using the US consensus definitions	18–40	18–40	18–40	429
Jacob et al. 2014 India	Case-control	Periodontitis represents a strong, independent and clinically significant risk factor for low birth weight	23	23.4	24.0	340
Noack et al. 2015 Germany	Case-control	Periodontitis was not a detectable risk factor for low PTB weight in pregnant women	27.8–30.3	28.6	30.2	58
Souza et al. 2015 Brazil	Case-control	No association between maternal periodontal disease and LBW was observed, even after appropriate adjustments for confounding factors	18–35	18–35	18–35	951
Alves et al. 2016 Brazil	Cross-sectional	Periodontitis was an associated factor for prematurity and LBW	18–36	18–36	18–36	59
Meqa et al. 2017 Republic of Kosovo	Cross-sectional	Periodontitis can be considered a risk factor for pregnancy complications	26			187
Wazir et al. 2019 India	Case-control	The findings showed an association of maternal periodontal disease with LBW	23.9			200
Lafaurie et al. 2020 Colombia	Case-control	Periodontal condition assessed by pocket depth was associated with adverse perinatal outcomes	<35	<35	<35	735
Micu et al. 2020 Rumania	Cross-sectional	Maternal periodontal disease and its severity could, in part, be considered as contributing to PTB	29.1	29.3	29.1	194
Pozo et al. 2020 Spain	Cross-sectional	Adverse pregnancy outcomes were associated with periodontitis	29.4			130
Choi et al. 2021 USA	Cross-sectional	Maternal periodontal disease may be associated with an increased risk of complications and neonatal morbidity	27.8			748,792
Ferrillo et al. 2021 Italy	Cross-sectional	High prevalence of PTB and LBW is present in affected pregnant women with periodontal disease and vitamin D deficiency	18–35			72

Table 1 (continued)

Authors	Design	Observations	Age	Age case group	Age control group	Participants (n)
Jyotirmay et al. 2021 India	Cross-sectional	No association between maternal periodontal health and preterm and LBW	21–30			300
Gallagher-Cobos et al. 2022 Spain	Cohort	Periodontal disease in the mother was not related in a statistically significant way with PTB or LBW	18–42			98
Lee et al. 2022 Taiwan	Cross-sectional	Increasing the severity of probing depth was associated with an increased risk of PTB	> 20			1,745,078
Peña-Sisto et al. 2022 Cuba	Case–control	There is a high frequency of periodontal diseases in significant association with the appearance of PTB and LBW	20–35			703
Hussain et al. 2023 Pakistan	Case–control	Periodontitis is a predictor of LBW	25.8	25.8	25.8	180
Bhavsar et al. 2023 India	Case–control	The presence of periodontal pockets and plaque increases the risk of complications during pregnancy	25.0	24.5	25.3	1,200

Case group: women with preterm birth (PTB) or low birth weight (LBW) outcomes

Quality of Evidence and Strength of Recommendation

The quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The GRADE framework

assesses the quality of evidence based on factors such as study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Based on the overall quality of the evidence, the strength of the association between periodontitis and pregnancy complications was determined and graded as high, moderate, low, or very low.

Table 2 Periodontal parameters in women with pregnancy complications (LBW or PTB)

Study	Case group		Control group	
	PD (mm)	AL (mm)	PD (mm)	AL (mm)
Davenport et al. 2002 England	3,72		3,85	
Moore et al. 2004 United Kingdom	2,04	0,22	2,03	0,23
Jarjoura et al. 2005 USA	2,5	1,5	2,4	1,7
Siqueira et al. 2007 Brazil	4	4	4	4
Agueda et al. 2008 Spain	2,2	2,1	2,1	1,9
Baskaradoss et al. 2011 India	3,26	2,17	2,95	1,84
Ali et al. 2012 Malaysia	2,54	2,31	1,65	0,23
Souza et al. 2015 Brazil	1,6	1,59	1,6	1,6
Noack et al. 2015 Germany	2,38	2,4	2,47	2,5
Meqa et al. 2017 Republic of Kosovo	2,45	2,49	2,24	2,47
Hussain et al. 2023 Pakistan		1,26		0,50
Bhavsar et al. 2023 India	4,6		2,9	

Case group: women with preterm birth (PTB) or low birth weight (LBW) outcomes. *PD* Probing depth; *AL* Periodontal attachment level

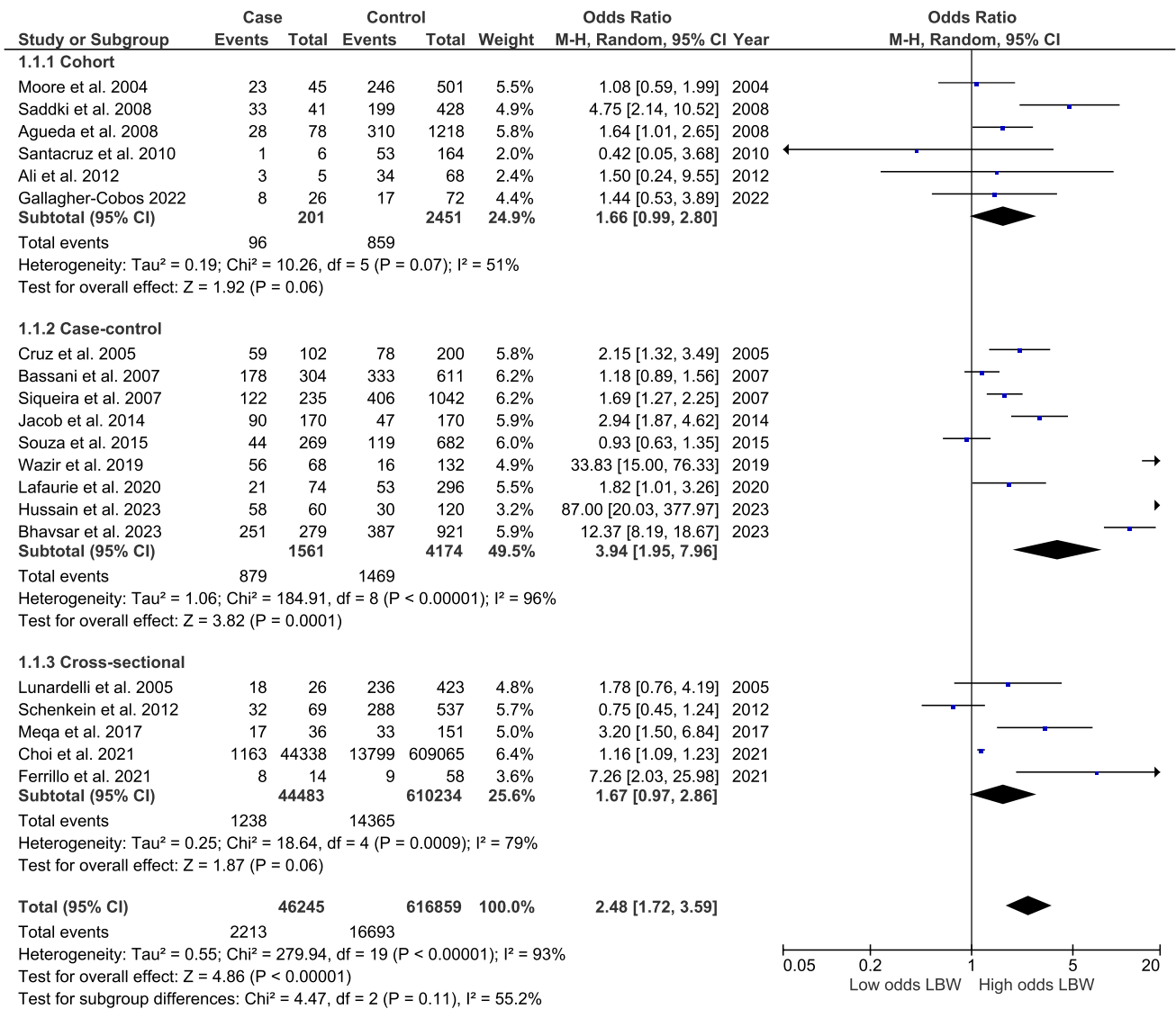


Fig. 2 Forest-plot of the association between periodontitis and low birth weight (LBW). Cases: mothers with LBW. Controls: mothers without pregnancy complications. Events: the number of mothers with periodontitis

Results

A total of 2,867 potential records were identified in the databases. Of these, 2,582 records were excluded during title and abstract review, while 185 records were duplicated and also deleted. Therefore, 100 records were selected for further review. After this review, 65 records were removed as they did not meet the inclusion criteria (see supplement 1). Finally, 35 full-text studies, including a total of 2,510,556 women, were analyzed in their entirety and included in the qualitative and quantitative analysis (Fig. 1; Table 1). Most studies were from Brazil (6) followed by USA (4), India (5), Spain (4), Colombia (2), England (1), United Kingdom (1), Taiwan (1), Cuba (1), Pakistan (1), Italy (1), Argentina (1), Republic of Kosovo

(1), Germany (1), Switzerland (1), Romania (1), Malaysia (2) and France (1). The age of the participating women was between 18 and 48 years of age. Eight studies were cohort, 15 case-control, and 12 cross-sectional.

The quality of the studies (Supplement 2) was rated as low in 4 studies [7–10], medium in 9 studies [11–19] and high in 22 studies [20–37, 38••, 39–41].

No significant differences were observed in probing depth and periodontal attachment level between women with pregnancy complications and the control group except for the study by Bhavsar et al. [41] who reported a considerably greater probing depth (4.6 mm vs. 2.9 mm) in the case group compared to the control group (Table 2).

The studies by Noack et al. [19] and Davenport et al. [20] were excluded from the meta-analysis because they

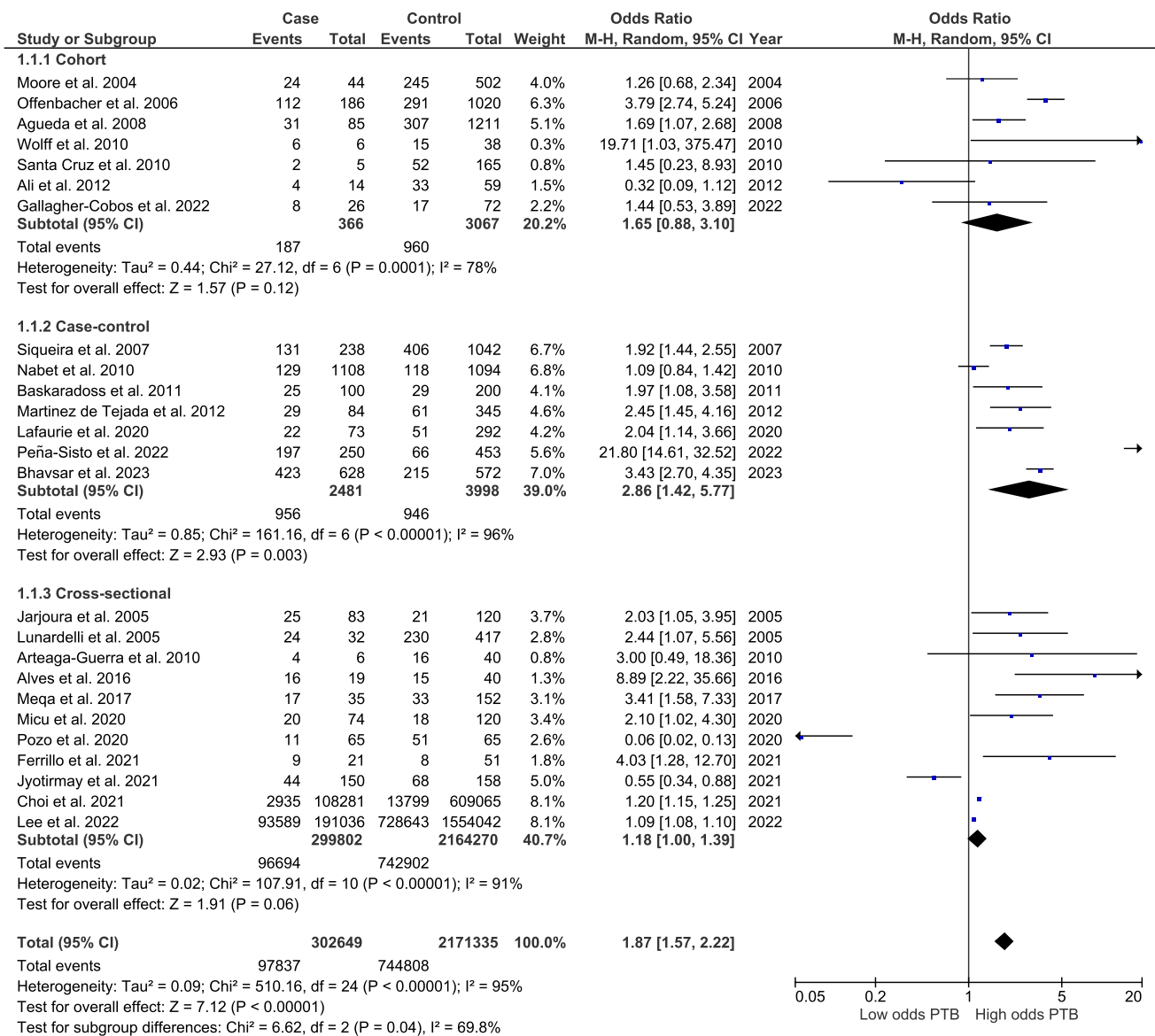


Fig. 3 Forest-plot of the association between periodontitis and preterm birth (PTB). Cases: mothers with PTB. Controls: mothers without pregnancy complications. Events: the number of mothers with periodontitis

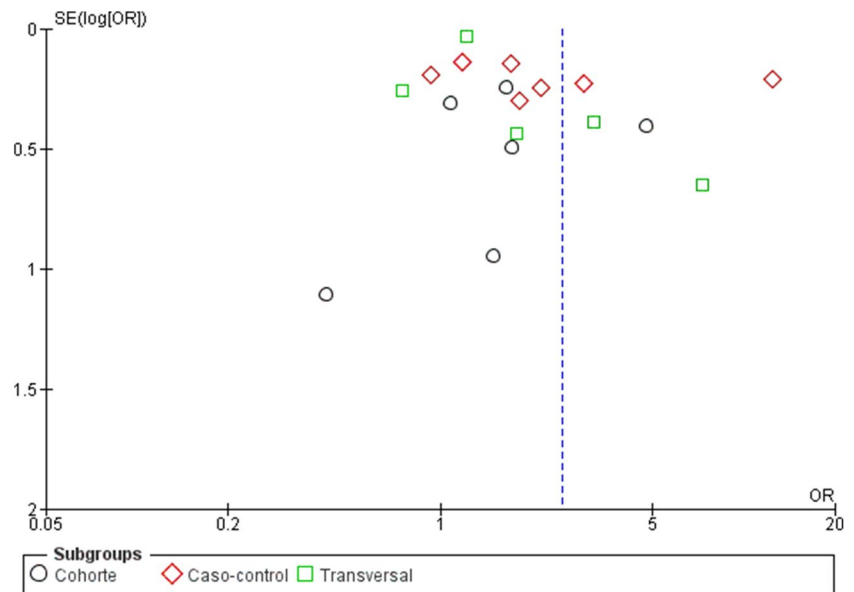
did not report the number of women with periodontitis in each group and therefore only 33 studies were included for analysis. According to the meta-analysis, a moderate association (OR 2.48; 95% CI 1.72–3.59) was observed between periodontitis and low birth weight, and the association was much stronger when case-control studies were analyzed independently (OR 3.94; 95% CI 1.95–7.96) (Fig. 2). The heterogeneity of the studies was significantly high. In contrast, cross-sectional studies did not show an association between periodontitis and low birth weight. However, by excluding the 4 studies [17, 36, 40, 41] with the largest effect size and wide confidence interval, the association between periodontitis and low birth weight was weak (OR

1.54; 95% CI 1.26–1.89) and with less heterogeneity (I² 71%). For its part, the association between periodontitis and preterm birth was weak (OR 1.87; 95%CI 1.57–2.22) with highly significant heterogeneity (Fig. 3). When low-quality studies [7–10] were omitted from the meta-analysis, there was no discernible change in the effect.

The visual analysis of the funnel plot revealed the presence of publication bias, most likely due to the effect of studies with a small sample (Figs. 4 and 5).

The quality level of the evidence was rated as low (Table 3). This means that we have limited confidence in the estimate of the effect, and the actual effect may be far from the estimate.

Fig. 4 Funnel-plot of low birth weight (LBW) studies



Discussion

Main Findings

The results from our analysis showed an association between periodontitis and adverse pregnancy outcomes but some aspects merit the discussion and interpretation of these findings.

In our study, differences in probing depth and periodontal attachment level between women with pregnancy complications and the control group were evaluated but due to limited data, no meta-analysis of periodontal variables was undertaken. The results did not show significant differences

between studies in these variables. Davenport et al. [20] reported in a case-control study that there was no evidence supporting the association between probing depth and the risk of preterm low birth weight after controlling for maternal age, ethnicity, maternal education, smoking, alcohol consumption, infections, and hypertension during pregnancy. Similar findings were reported by Noack et al. [19]. This suggests that the presence of pregnancy complications is not directly related to periodontal disease by itself. In contrast, a recent study [41] found a difference in probing depth of almost 2 mm between groups. Furthermore, research differed in how periodontal condition was evaluated, which could explain the lack of a clear and significant difference

Fig. 5 Funnel-plot of preterm birth (PTB) studies

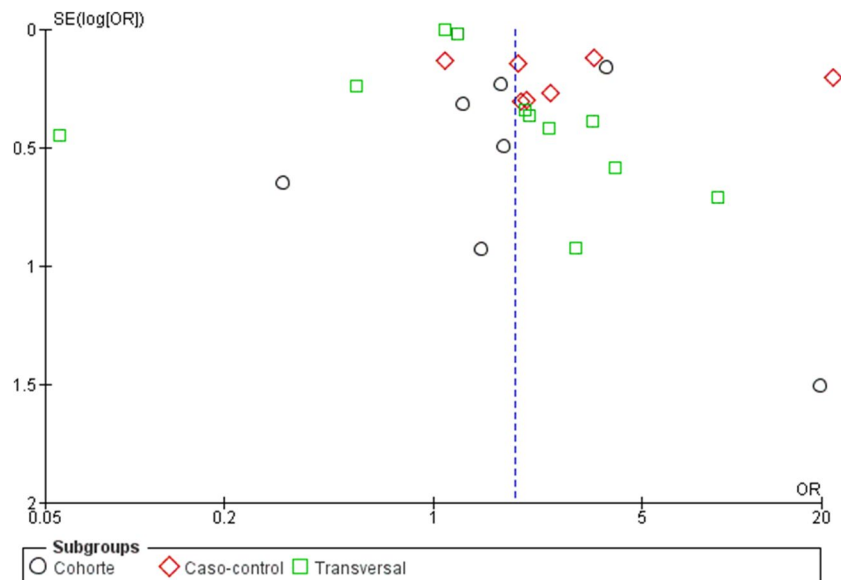


Table 3 Quality of the evidence and strength of the recommendation

Assessment of the certainty of the evidence									
Number of studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	Certainty	Importance
Low birth weight (primary outcome)									
20	Analytical observational	Serious: 4/20 studies carried great weight to the effect. 4/20 studies considered as moderate/high bias	Substantial: I^2 93% and Chi^2 279.94	Not serious	Serious: confidence intervals in some studies are wide	Publication bias detected in asymmetric funnel plot. Small studies with positive results	Some of the studies demonstrated a higher prevalence of periodontitis in the case group compared to the control group	Low	Important
Preterm birth (primary outcome)									
25	Analytical observational	Serious: 4/25 studies carried great weight to the effect. 11/25 studies considered to have moderate/high bias	Substantial: I^2 95% and Chi^2 510.16	Not serious	Serious: confidence intervals in some studies are wide	Publication bias detected in asymmetric funnel plot. Small studies with positive results	Some of the studies demonstrated a higher prevalence of periodontitis in the case group compared to the control group	Low	Important

High certainty: we are very confident that the true effect lies to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different. Low certainty: our confidence on the effect is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect

Quality level: Low. Limited confidence in the estimate of effect. The actual effect may be far from the estimate

between groups. Nevertheless, in the meta-analysis of the prevalence of periodontitis, a moderate association between periodontitis and low birth weight was found and this is in agreement with a previous systematic review [42]. This association was stronger when case–control studies were analyzed independently with high heterogeneity. In contrast, cross-sectional studies did not show a significant association between periodontitis and low birth weight. Furthermore, when studies that carried large effects and confidence intervals were excluded in the sensitivity analysis, the association decreased and was weak. This suggests that the association between periodontitis and low birth weight may vary depending on the study design utilized and the consequent extent of the effect, which should be taken into account when interpreting these findings.

A weak but significant association between periodontitis and preterm birth was detected, which also corresponds with a prior systematic review [42]. However, significant heterogeneity was also observed between

the studies. It is important to mention that the sensitivity analysis according to the quality of the studies did not show significant changes in the results, which supports the robustness of the findings. Furthermore, when examining the funnel plots, publication bias was observed probably due to the influence of studies with small samples. Small study effects and publication bias are closely related. Because of publication bias, smaller studies with statistically significant results may be overrepresented in the literature, while larger studies with non-significant results may go unpublished. Hence, publication bias can have major consequences for evidence-based decision-making, leading to overestimation of association or treatment effects.

Methodological and Quality Issues of the Studies

It was observed that most frequently, cross-sectional studies were medium/low quality which indicates that the risk

of bias was high as compared to cohort and case–control studies. In terms of bias, cross-sectional studies are more prone to biases such as recall bias and selection bias due to their snapshot nature and lack of temporal sequence. In this systematic review, cross-sectional studies generally failed to offer precise information such as a defined purpose, sample size, group characteristics, and measures to prevent bias and confounding. In contrast, cohort studies are generally considered to have lower risk of bias as they allow for the investigation of temporal relationships, and the exposure is measured before the outcome develops. Case–control studies need careful design and analysis to minimize bias, usually related to the selection of cases and controls and the reliance on participant recall of past exposures. Our examination of cohort and case–control studies found that they were of high quality, implying that researchers utilizing these study designs take additional steps to reduce bias. In general, while cross-sectional studies may have higher risk of bias compared to cohort and case–control studies, each study design serves different purposes and can be valuable in specific research contexts. Researchers should be aware of these considerations when interpreting and generalizing the findings of different study designs and specially in challenging topics such as adverse pregnancy outcomes and periodontitis.

Limitations of this Systematic Review

There are some limitations of this systematic review. Some studies may have had significant bias or problems that impacted reliability. Significant outcomes may be presented, while null/negative findings may be withheld, skewing the review. Small sample sizes restrict statistical power and result in weaker evidence. The heterogeneity of included research (study designs, demographics, exposures, and outcome measures) makes meta-analysis difficult and reduces precision.

Perspective

Although there appears to be an association between periodontitis and adverse pregnancy outcomes, causal inference using the Bradford-Hill criteria does not support such an association [43•]. Given the complexities of this topic and the necessity of making informed healthcare decisions, further high-quality research is required to show a definite causal association between periodontitis and pregnancy outcomes. Until then, healthcare providers should emphasize the importance of oral health during pregnancy and incorporate periodontal examinations and relevant therapies into prenatal care. By doing so, we can help to improve maternal and fetal health outcomes while also pursuing

evidence-based approaches in periodontal health management throughout pregnancy.

Conclusion

Low-quality evidence indicates that periodontitis is moderately associated with low birth weight and weakly associated with preterm delivery. This means that we have limited confidence in the estimate of the effect, and the actual effect may be far from the estimate.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40496-024-00371-6>.

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Data Availability Data sharing not applicable – no new data generated.

Compliance with Ethical Standards

Ethics Statement This systematic review did not need review by the institutional ethics committee.

Competing Interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent Not applicable to a review article. No human photographs were included.

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- Of major importance

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