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Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes – systematic review

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Ide M, Papapanou PN. Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes – systematic review.

Abstract
Background and objectives: There is still debate regarding potential relationships between maternal periodontitis during pregnancy and adverse pregnancy outcomes. The aim of this systematic review was to synthesize the available epidemiological evidence on this association.
Data sources: Combined electronic and hand search of MEDLINE, EMBASE, WEB OF SCIENCE and Cochrane Central Register databases.
Study eligibility criteria: Original publications reporting data from cross-sectional, case-control or prospective cohort epidemiological studies on the association between periodontal status and preterm birth, low birthweight (LBW) or pre-eclampsia. The search was not limited to publications in English. All selected studies provided data based on professional assessments of periodontal status, and outcome variables, including preterm birth (<37 weeks gestation), LBW (<2500 g), gestational age, small for gestational age, birthweight, pregnancy loss or miscarriage, or pre-eclampsia.
Participants: Pregnant women with or without periodontal disease, and with or without adverse pregnancy outcomes, assessed either during pregnancy or postpartum. No intervention studies were included. Study appraisal and synthesis methods – Publications were assessed based on predefined screening criteria including type of periodontal assessment, consistency in the timing of the periodontal assessment with respect to gestational age, examiner masking and consideration of additional exposures and confounders.
Results: Maternal periodontitis is modestly but significantly associated with LBW and preterm birth, but the use of a categorical or a continuous exposure definition of periodontitis appears to impact the findings: Although significant associations emerge from case-control and cross-sectional studies using periodontitis "case definitions," these were substantially attenuated in studies assessing periodontitis as a continuous variable. Data from prospective studies followed a similar pattern, but associations were generally weaker. Maternal periodontitis was significantly associated with pre-eclampsia.
Limitations: There is a high degree of variability in study populations, recruitment and assessment, as well as differences in how data are recorded and handled. As a result, studies included in meta-analyses show a high degree of heterogeneity.
Conclusions and implications of key findings: Maternal periodontitis is modestly but independently associated with adverse pregnancy outcomes, but the findings are impacted by periodontitis case definitions. It is suggested that future studies employ both continuous and categorical assessments of periodontal status. Further use of the composite outcome preterm LBW is not encouraged.

Key words: epidemiology; human; low birthweight; periodontitis; pre-eclampsia; preterm birth; systematic review

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Conflict of interest and source of funding statement

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Rationale

Since early publications in the literature almost 20 years ago, researchers and clinicians have been interested in the potential causal association between the presence or progression of maternal periodontal disease and several adverse pregnancy outcomes. This hypothesis is consistent with other medical literature suggesting that inflammatory processes in the foetal /placental unit and/or elevated systemic inflammation may impact pregnancy outcomes. Unfortunately, despite the efforts of many and the publication of at least nine systematic reviews (Scannapieco et al. 2003, Khader & Ta'ani 2005, Vettore et al. 2006, Xiong et al. 2006, Vergnes & Sixou 2007, Kunnen et al. 2010, Chambrone et al. 2011a,b, Corbella et al. 2011), no consensus has emerged on the existence or relevance of such an association. This has been mainly attributed to variations in the populations assessed, the presence of a range of potential confounding factors and to variations in the definition of periodontitis across studies.

Objectives

The aim of this study is to conduct a systematic review of the epidemiological associations between maternal periodontal status during pregnancy and a number of adverse pregnancy outcomes including birthweight, preterm delivery and pre-eclampsia.

Methods

This project was prepared and completed in accordance with PRISMA guidelines (Moher et al. 2009) for reporting systematic reviews. MEDLINE, EMBASE, WEB OF SCIENCE and Cochrane Central Registers were searched up to and including May 2012, supplemented by a broad hand search of relevant journals and online early peer-reviewed papers. A typical search strategy was employed to identify papers using MesH, key words and other free terms:

((Periodontitis) OR (periodontal disease) OR (gingivitis)) AND ((adverse pregnancy outcome) OR (birthweight) OR (preterm) OR (Preterm) OR (pre-eclampsia) OR (preeclampsia) OR (stillbirth) OR (miscarriage))

Further publications were searched for using bibliographies and reference lists, and by reviewing lists of later papers which had cited the publication of interest where papers were available online.

All selected publications were then reviewed by the authors of this paper and categorized as suitable or not for inclusion in this review. These lists were compared and in the case of disagreements, decisions were reviewed and confirmed following discussion based on the criteria outlined below.

Eligibility criteria

Studies considered for inclusion were original research publications in peer-reviewed journals, reporting on the associations listed above. The search was not limited to publications in the English language. Interventional studies, case series, case reports, editorials, reviews, opinion pieces and animal studies, as well as studies designed to assess pregnancy outcomes in patients with known systemic diseases were not included. We only included studies in which both the exposure and the outcome variable (i.e. periodontal status and adverse pregnancy outcomes) were assessed by health care professionals. Studies relying solely on self-reported data were excluded.

Issues and features of analyses

Adverse pregnancy outcomes

"Adverse pregnancy outcome" is a broad term which encompasses several disparate outcomes, including low birthweight (LBW) (<2500 g) or very LBW (<1500 g), preterm birth (<37 weeks or very preterm <32 weeks), pre-eclampsia (commonly defined as maternal hypertension and proteinuria after the 20th gestational week), and miscarriage and/or still birth. Another commonly used term is "small for gestation age" that reflects restricted growth at any given time during gestation. Although several of these outcomes co-vary, (e.g. a baby born early is likely to be smaller), it remains unclear whether they share common pathological processes. In addition, some researchers have used a composite definition, by combining different adverse pregnancy outcomes in a single group for comparisons with an uncomplicated pregnancy "control" group. In our analyses, we have elected to focus on individual adverse pregnancy outcomes and report "combination" outcomes separately.

Study design

Studies employed to investigate these associations have had a cross-sectional, case-control or longitudinal cohort design and have used the presence or progression of periodontal disease (ranging from gingivitis through to aggressive periodontitis) as exposures in the analysis of pregnancy outcomes. Due to the generally low prevalence of adverse outcomes in the population, a case-control study design has been frequently used, although a longitudinal observational blinded cohort study is the preferred gold standard design, since it allows for assessment of the impact of and interactions between a range of exposures including periodontal disease. However, prospective cohort studies involve the recruitment of considerable larger numbers of participants and are more demanding logistically.

As a result, for each pregnancy outcome, subsets of studies grouped by design were analysed separately. In addition, meta-analyses were carried out whenever feasible assessing risk ratios, for prospective studies, and odds ratios for case-control or cross-sectional studies. In studies where the periodontal status of the participants was described by means of continuous variables, weighted mean differences were calculated for markers of periodontitis between participants with and without certain pregnancy outcomes.

Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (details at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Timing of recruitment and length of follow-up

Longitudinal studies have typically carried out recruitment and periodontal examination in the first or early second trimester. However, given that deterioration of periodontal status during gestation may be relevant in processes involved in adverse pregnancy outcomes, a number of studies have employed repeated periodontal examinations. In contrast, case-control studies have relied on recruitment and examination after delivery. In such studies, reporting that the oral examiner was masked with respect to pregnancy outcome was considered mandatory for inclusion.

Search outcomes and evaluation

The search strategy identified 694 potentially relevant publications. The titles and abstracts of these were reviewed and inappropriate papers (as described above) were excluded, resulting in 189 publications. These papers were then grouped by pregnancy outcomes of interest. Since several papers included data for more than one adverse outcomes, they were considered independently in each group. For each adverse pregnancy outcome, studies were further subdivided into prospective, cross-sectional and case-control studies, and analysed accordingly. Results were subsequently reported for these groups.

Predefined data collection spreadsheets were employed for assessment of each publication. Evaluations were carried out independently by one author (MI) then confirmed by the other (PNP).

Data analysis

Meta-analyses were carried out using Stata 9.2 (StatCorp, College Station, TX, USA), using either Mantel–Haenszel (for categorical analysis) or Cohen's inverse variance methods (for continuous data) to calculate Odds Ratios, Risk Ratios and mean differences, as appropriate.

Results

Studies investigating periodontitis and low birthweight

Following screening, 18 publications were considered suitable for qualitative assessment. These comprised 5 case-control, 3 cross-sectional and 10 prospective studies. After review of available data, two case-control and six prospective studies were deemed suitable for meta-analysis. This is illustrated in Fig. S1.

Case-control studies of maternal periodontitis and low birthweight

Overall, five papers were found to be suitable for qualitative analysis and are summarized in Table S1. Using continuous variables describing periodontitis, Moore et al. (2005) reported data for 154 UK women and found no differences between cases and controls for mean probing depth, sites bleeding after probing, oral hygiene or attachment loss. Gomes-Filho et al. (2006) reported data from women in Brazil and reported no differences between cases and controls for oral hygiene, attachment levels or bleeding. Subsequently, Bassani et al. (2007) reported data for 715 women delivering in Brazil. There was no difference in the incidence or severity of periodontitis between cases and controls defined by absence or presence of periodontal disease, and regression analysis allowing for other established risk factors failed to show any significant association between LBW and periodontal status. In contrast, Vettore et al. (2008a,b) compared 35 Brazilian women who had experienced a LBW delivery with 66 controls, and found slightly deeper probing depths in the control group, but no differences in attachment levels or bleeding, for cases when compared to controls. Cruz et al. (2009) examined 548 women in Brazil (a subsequent analysis of the same population as Bassani et al. (2007)) and, using the definition of López et al. (2002) for a periodontitis case (presence of four or more teeth with one or more sites with probing depths 4 mm or greater accompanied by 3 mm or more attachment loss), reported a significant odds ratio of 1.74 (1.19–2.54) for LBW in the presence of periodontitis. This was a relatively poor population and educational level was found to be an important co-factor with some element of effect modification.

Cross-sectional studies of maternal periodontitis and low birthweight

Three studies were considered suitable for qualitative analysis (Table S2). Lunardelli & Peres (2005) examined 449 Brazilian women up to 48 h postpartum. Periodontal disease was defined as either the presence of at least one site with a pocket of 4 mm or more, and at a second level of severity, the presence of four or more such sites. Unfortunately, data were not reported for birthweight in isolation, but only in combination with prematurity. These data could not be used reliably for pooling for meta-analysis of LBW studies. Another Brazilian group, Siqueira et al. (2007) reported data for 1305 women, of whom 235 had experienced LBW and 1042 had uncomplicated deliveries. Although analyses were carried out using probing depth and attachment level scores, a periodontitis case was also defined using the criteria of López et al. (2002), as in other studies. Around 10% or participants were smokers with no difference between groups, but there was a significant difference in incidence of periodontal disease and extent of gingival bleeding between groups, and overall 41% of women had defined periodontitis, even though around 74% of women were less than 30 years old. Multivariate logistic regression showed significant associations between maternal periodontitis and LBW (OR 1.67, 1.11–2.51), but there were significant interactions between periodontitis and previous preterm birth and also with the number of prenatal visits attended. Toygar et al. (2007) completed a large study in Turkey, but this work relied on the use of the highest community periodontal index of treatment need (CPITN) score from a limited number of assessed teeth to act as the indicator of overall periodontal status. Hence, whilst the study is listed here to acknowledge the recruitment of 3576 participants, it is compromised by the periodontal recording system employed and was excluded from data pooling. The data showed an odds ratio of 3.56 (1.74–7.25) for LBW between those with a CPITN score of 4 and those with scores of no more than 1 in a multivariate regression model in which education, smoking and parity were significant also. Similar results were seen for subgroup analysis of those who did and did not receive prenatal care.

Prospective studies of maternal periodontitis and low birthweight

The prospective studies are summarized in Table S3. Marin et al. (2005) described their findings from a population of 152 pregnant Brazilian women. Only 10% were smokers, but the cohort had a low mean average level of education. Initial periodontal examinations were completed at a range of time throughout pregnancy, which may have affected findings. A unique compound definition for periodontitis cases was employed, making direct comparison with other studies difficult. They found no significant association between oral health status and birthweight, except for mothers aged over 25, where diagnosis of periodontitis was associated with a lower birthweight. Boggess et al. (2006) focused on small for gestational age (SGA) deliveries, in an effort to avoid the potential impact of premature delivery on LBW outcomes. Overall, 1017 American women were examined at or before 26 weeks. Periodontal disease was defined as the presence of 1 or more sites with greater than 4-mm pocket depth or 1 or more tooth pockets greater than 3 mm that bled on probing. It was deemed moderate or severe if there were 15 or more sites with probing greater than 4 mm. Around 15% of the women were smokers. There was a higher tendency for SGA mothers to be smokers, younger and to have a higher prevalence of periodontal disease and of severe disease. Logistic regression showed that SGA was related to maternal age, pre-eclampsia and the presence of moderate or severe periodontitis (risk ratio 2.3, 95% confidence intervals (CI) 1.1–4.5). Offenbacher et al. (2001) also reported data from this study, at an earlier time point with lower numbers recruited.

One study has been completed recruiting Malay women in the second trimester in community clinics by Saddki et al. (2008). Periodontitis was a significant risk factor for LBW (adjusted OR 3.84, 1.34–11.05) following multivariate logistic regression analysis, along with education level and gestation.

Rakoto-Alson et al. (2010) followed up 204 pregnant women from initial examination at 20–34 weeks gestation in Madagascar. Of these, 22 were LBW. Using both mean score data for probing and attachment, and categorization of periodontal disease and severity, it was apparent that the case participants had worse periodontal health than the controls. However, potential covariates were not accounted for in the performed analysis. Vogt et al. (2010) reported data for another cohort of 327 women from Brazil, recruited at 32 weeks gestation or less. Periodontal disease was defined as the presence of four or more teeth showing at least one site with 4 mm probing depth and clinical attachment loss (CAL) at the same site, with bleeding on probing. Univariate regression analysis failed to show a significant risk ratio for LBW or SGA in the presence of periodontal disease, but multivariate analysis allowing for other factors indicated a risk ratio of 2.93 (1.36–6.34) associated with periodontitis. Finally, Al Habashneh et al. (2012) examined (at 20 weeks' gestation) and followed outcomes for 277 Jordanian women. Univariate analysis showed that women with LBW had higher levels of attachment loss, but no differences in terms of probing depths, and this was also confirmed in models accounting for a range of demographic, medical and pregnancy history variables. The risk ratio for LBW per 1 mm increase in CAL was 7.99 (3.99–15.97).

However, not all studies have shown a positive association. Farrell et al. (2006) prospectively followed up 1793 never smoking UK pregnant women who were examined at 12 weeks gestation. There were no differences for any periodontal variables between those who had LBW deliveries and those that did not. Agueda et al. (2008) examined 1296 Spanish women at 20 weeks gestation and followed up pregnancy outcome. Periodontal disease was defined according to López et al. 2002,. Women with LBW were more likely to be smokers, have periodontitis and have a history of previous pregnancy complications, based on univariate analyses. Cases showed a tendency to have a higher percentage of teeth with more advanced CAL, but this was not statistically significant. There was no difference between cases and controls in terms of gingival bleeding. Multivariate logistic regression showed no effect of periodontal status on LBW outcome, although ethnicity, heavy smoking, previous pregnancy complications and means of delivery were associated with LBW. Finally, Srinivas et al. (2009) recruited 152 women from three centres in the USA at between 6 and 20 weeks gestation. At follow-up, there was more bleeding on probing in women who had LBW deliveries and there was a tendency for periodontitis to be associated with higher frequency of LBW, but this was only statistically significant for women aged over 25. Unfortunately, there was no report of multivariate analysis involving other important variables which were described.

Meta-analysis for studies of periodontitis and low birthweight

Cross-sectional studies reporting periodontitis as a categorical variable. Data pooling was not feasible for two of the three studies described above. As a result meta-analysis was not possible.

Case-control studies reporting periodontitis as a continuous variable. Since there was only one study in this group, meta-analysis was not carried out.

Case-control studies reporting periodontitis as a categorical variable. There were two potential studies for analysis in this group, reporting data for 696 cases and 767 controls, a total of 1463 women. Meta-analysis suggested a pooled odds ratio of 1.35 (CI 1.08, 1.68), with an acceptable score for heterogeneity (Table S4, illustrated in Fig. S2).

Prospective studies reporting periodontitis as a categorical variable. Six prospective studies were suitable for meta-analysis, reporting data for 1225 cases and 2291 controls, a total of 3516 women. The overall risk ratio was 1.75 (CI 1.41–2.16). Notably, the smaller studies tended to show more positive associations (Table S5, illustrated in Fig. S3).

Prospective studies reporting periodontitis as a continuous variable. Three studies presenting data on probing depth involving a total of 3361 participants were found to be suitable for meta-analysis and showed that there was no difference in mean probing depth between women with and without LBW deliveries (Table S6, illustrated in Fig. S4). These studies had acceptable homogeneity.

In contrast, meta-analysis of data from two studies with available attachment level data including a total of 431 participants indicated a standardized mean difference of 1.12 mm in mean attachment levels between cases and controls (Table S7, illustrated in Fig. S5). The two studies showed good homogeneity.

Summary for studies of periodontitis and low birthweight

Prospective studies are considered the gold standard for the assessment of the effects of a particular disease as an exposure for an adverse health outcome. Meta-analysis findings from prospective studies were influenced by the means of disease assessment employed: A moderate and significant association emerged in studies, where participants were categorized as periodontally diseased or healthy based on specific case definitions. However, meta-analysis of prospective studies in which periodontitis was assessed by means of continuous variables generated conflicting results: whilst no association emerged between maternal periodontitis and LBW based on probing depth data, a significant association was found when using attachment level data. A positive association between poor periodontal status and LBW was also evident after meta-analysis of the case-control studies that used dichotomous exposure definitions, and was also consistent with the results of the available cross-sectional studies.

Hence, whilst it appears that maternal periodontitis is modestly (conventionally defined as signifying odds ratios that are greater than 1 but usually not exceeding 2–2.5), but significantly associated with LBW, the use of categorical or continuous variables to define exposure to periodontitis appears to impact the strength of the association.

Studies investigating periodontitis and preterm birth

Following screening, 25 publications were considered suitable for qualitative assessment. These comprised 18 case-control and 7 prospective studies, described below. After review of available data, these were further reduced to 13 case-control and 4 prospective studies suitable for meta-analysis. This is illustrated in Fig. S6.

Case-control studies of maternal periodontitis and preterm birth

A relatively large number of case-control studies have been carried out, with a range of locations and various sized study populations (Table S8). A US study of 203 predominantly Hispanic women examined postpartum (Jarjoura et al. 2005) suggested that cases had significantly more CAL and were likely to have periodontitis (defined as five or more sites with 3 mm or more attachment loss) than term delivering women. However, it should be noted that the levels of attachment loss seen in this population are relatively low (1.7 mm and 1.5 mm for cases and controls respectively). There was no difference in gingival bleeding between cases and controls. Multivariate analysis generated an odds ratio of 2.75 (1.02–7.54) for preterm birth (PTB) for each mm increase in CAL, and the gestational age at birth had a tendency to be negatively associated with CAL, although this was not significant ($p = 0.06$). Other important associated risk factors were smoking, previous preterm delivery, BMI and chorioamnionitis. Bosnjak et al. (2006) recruited 81 primiparous Croatian women postpartum, of which 45% were smokers. Levels of attachment loss were high and women who had less that 60% of sites with more than 4 mm CAL were deemed as periodontally "healthy." This may have impacted on the findings of the study. Univariate analysis showed that PTB cases had higher levels of bleeding and deeper mean probing depth, and in a multivariate logistic model, extent of ≥ 4 mm AL at $\geq 60\%$ of the sites was the strongest predictor of PTB (OR 8.128, 2.73–45.9). The odds ratios reported in this study are high compared to many others. Radnai et al. (2006) studied 161 healthy Hungarian women aged 16–41 who were examined within 3 days of delivery. Periodontitis was defined as 50% of sites with bleeding and at least one site with probing depth ≥ 4 mm, yielding an odds ratio of 3.32 (CI 1.64–6.69) in a regression model including smoking. There was a tendency to higher levels of gingival bleeding in cases, although this was only approaching statistical significance.

Another study generating a large odds ratio (4.47, CI 2.43–8.20) for PTB in the presence of periodontitis, (defined as the presence of four or more teeth with at least one site with probing depth ≥ 4 mm and CAL of ≥ 3 mm with bleeding on probing) even after adjustments for a range of associated risk factors, was carried out in Thailand (Le et al. 2007) and included 390 women of predominantly lower socio-economic status and with relatively high levels of attachment loss for age. A Brazilian study of 124 women (Santos-Pereira et al. 2007) found that cases had lower levels of schooling and more CAL and bleeding, and a tendency to higher mean probing depths. Periodontitis was associated with an odds ratio of 4.9 (1.9–12.8) for preterm birth in a multivariate model allowing for several risk factors. A larger Brazilian population was studied by Siqueira et al. (2007), including 238 preterm cases and 1042 controls. Periodontitis was defined as the presence of four or more teeth with one or more sites with probing depths ≥ 4 mm accompanied by ≥ 3 mm or attachment loss, affecting over 55% of participants. Preterm birth was related to educational level, prenatal care utilization, hypertension, previous pregnancy history and presence of periodontitis. Multivariate logistic regression showed significant associations between maternal periodontitis and preterm birth (OR 1.77, 1.12–2.59), but there were significant interactions between periodontitis and previous preterm birth. In a large study form Turkey, Toygar et al. (2007) relied on the use of CPITN scores from a limited number of assessed teeth and reported an odds ratio of 2.96 (1.72–5.09) for preterm birth between those with a CPITN score of 4 and those with scores of ≤ 1 in a multivariate regression model in which education, smoking and parity were significant also. However, as stated above, this study was excluded from data pooling due to the use of the CPITN. Guimaraes et al. (2010) reported data from 1207 Brazilian women, of which 9.5% were smokers. Two different case definitions for periodontitis were assessed, and univariate analysis showed higher periodontal scores in preterm and very preterm cases. Regardless of definition employed, the prevalence of periodontitis significantly increased between term, preterm and very preterm deliveries. Multivariate logistic regression generated an odds ratio of 1.83 (CI 1.28–2.62) to 2.37 (1.62–3.46) depending on the definition of periodontitis used. Giannella et al. (2011) showed a positive association after studying 820 non-smoking women with and without periodontal disease (defined as the presence of four or more teeth with one or more sites with probing depths 4 mm or greater accompanied by 3 mm or more attachment loss, López et al. (2002)). Cases had higher mean probing depths and attachment loss and more sites with probing depth ≥ 4 mm. Logistic regression, adjusted for BMI, resulted in an odds ratio of 2.83 (1.86–4.23) for preterm labour. Piscoya et al. (2012) have also reported large odds ratios for an association between PTB and maternal periodontitis, defined in the same way as López et al. (2002). This study involved 718 Brazilian women, of whom 39% were aged under 20% and 26% lived without a water supply. Income, living conditions, smoking urinary tract infection and pre-eclampsia were all identified as risk factors after multivariate analysis, but the presence of periodontitis was also found to be relevant, with an odds ratio of 6.05 (CI 3.01–12.16).

As expected, studies that do not report a positive association have been published as well. Lunardelli & Peres (2005) examined 449 Brazilian women and found significant differences between preterm birth and the incidence of either one 4 mm pocket or four teeth with such pockets. However, once multivariate regression was carried out, the significance of the differences in oral health between cases and controls are lost. Vettore et al. (2008a,b) compared 40 Italian women with preterm birth with 66 control women and found no association between the unique composite periodontal score used in this study and preterm birth. Nabet et al. (2010) reported a study of 1108 French women primarily designed to investigate links between periodontitis (defined as localized periodontitis if there were probing depths of ≥ 4 mm and attachment loss of ≥ 3 mm same site on two or three teeth, generalized periodontitis as probing depths of 4 mm or more and attachment loss of 3 mm or more on the same site on four or more teeth) and pre-eclampsia, but which also reported preterm birth as an outcome of interest. These investigators subcategorized preterm births by cause, and established that after adjustments for covariates, there was only a significant association between periodontitis and PTB due to pre-eclampsia (OR 2.06, CI 1.21–3.50 for localized disease and 3.19, CI 1.88–5.43 for generalized disease respectively). There were no significant associations for other causes of PTB. Iwanaga et al. (2011) similarly found no differences between periodontal scores between cases and controls.

Other studies have investigated this relationship in case-control studies by comparisons of periodontal scores without categorizing the participants' periodontal status in a dichotomous manner. Moore et al. (2005) reported no differences between groups for oral hygiene, bleeding or other assessments of periodontal status for 154 women in the United Kingdom, with the sole exception of there being a greater proportion of sites probing 5 mm or deeper in controls compared to cases ($p = 0.016$). The study of Wood et al. (2006) reported a study of 151 Canadian women. In this study, cases were more likely to be smokers and have lower levels of education, but there were no significant differences between cases and controls in terms of oral hygiene, bleeding, pocket depths and attachment levels. Furthermore, data reported by Vettore et al. (2008a,b) above failed to show consistent significant differences between cases and controls. Finally, Heimonen et al. (2009) compared 328 Finnish women postpartum, and were unable to find differences between groups for oral hygiene, bleeding or the number of pockets deeper than 4 mm. However, data reported by Bosnjak et al. (2006) and by Giannella et al. (2011), both described above, did report significantly greater mean probing depths and attachment loss for cases compared to controls.

Prospective studies of maternal periodontitis and preterm birth

Seven studies fulfilled the inclusion criteria and are summarized in Table S9. Moore et al. (2004) carried out a prospective study recording and analysing periodontal data as continuous variables for 3738 women delivering in London, UK. There were no significant differences in any measures of oral hygiene, bleeding, probing depths or attachment levels between preterm and term deliveries. Offenbacher et al. (2006) reported findings for a population of 1020 pregnant American women who were largely examined between 11 and 19 weeks gestational age and for whom presence and severity of periodontitis was based on the number of sites with 4 mm probing depths. These data suggested that the presence of moderate to severe periodontitis (15 sites or more with pocketing) was significantly associated with preterm birth (RR 1.6, CI 1.1–2.3) and with spontaneous preterm birth (RR 2.0, CI 1.2–3.2), after adjustment for other established risk factors. Agueda et al. (2008) examined 1296 Spanish women at 20 weeks gestation and followed up pregnancy outcome. Periodontal disease was defined as described by López et al. (2002). Women with preterm birth were more likely to be smokers, have periodontitis and have history of pregnancy complications, based on univariate analyses. Multivariate logistic regression showed a significant effect of periodontal status on preterm birth outcome (RR 1.77, CI 1.08–2.088), together with location of residence and identified caries. In contrast, Srinivas et al. (2009) followed up 786 American women after screening at 6 and 20 weeks gestation. There was no significant association between periodontal disease status (defined as periodontal attachment loss greater than or equal to 3 mm on three or more teeth) and preterm birth. Rakoto-Alson et al. (2010) followed up a cohort of 204 pregnant women from initial examination at 20–34 weeks gestation to delivery in Madagascar, which included 42 preterm births. Using both mean score data for probing and attachment, and categorization of periodontal disease and severity, women with preterm deliveries had worse periodontal status women than those delivered at term.

Vogt et al. (2010) reported data for a cohort of 327 Brazilian women, recruited at 32 weeks gestation or less. Periodontal disease was defined as the presence of four or more teeth showing at least one site with 4 mm probing depth and CAL at the same site, with bleeding on probing. Univariate regression analysis failed to show a significant risk ratio for preterm birth in the presence of periodontal disease, but multivariate analysis adjusting for other factors indicated a risk ratio of 3.47 (1.62–7.43) associated with periodontitis.

Al Habashneh et al. (2012) examined at 20 weeks' gestation 277 Jordanian women and followed their pregnancy outcomes. Univariate analysis showed that women with preterm birth had higher levels of attachment loss, but no differences in terms of probing depths, and this was confirmed in models allowing for a range of demographic, medical and pregnancy history variables. The risk ratio for preterm birth per 1 mm increase in mean CAL was 12.28 (4.98, 30.29). Data on gingival bleeding were not reported.

Meta-analysis for studies of periodontitis and preterm birth

Case-control studies reporting periodontitis as a categorical variable. There were 11 potential studies for analysis in this group. This involved data for 7575 participants, divided into 2721 cases and 4854 controls. Meta-analysis suggested a pooled odds ratio of 2.47 (CI 2.19, 2.77) for preterm birth in the presence of periodontitis (Table S10, illustrated in Fig. S6). It remains clear that there is a degree of heterogeneity between the data sets involved in this analysis, and as reported above, the smaller studies do have a tendency for more positive associations.

Case-control studies reporting periodontitis as a continuous variable. There were seven studies with available probing depth data amenable to analysis in this group totalling 1917 participants with 756 cases and 853 controls. Meta-analysis suggested a mean difference in mean probing depth between cases and controls of 0.035 mm (CI 0.009 mm, 0.063 mm). Again, there was a high degree of heterogeneity between studies (Table S11, illustrated in Fig. S7).

There were seven studies with adequate data for pooling to investigate relationships with clinical attachment. These involved a total of 936 participants with 365 cases and 571 controls. Meta-analysis suggested a very small difference in mean attachment level between cases and controls (Table S12, illustrated in Fig. S8). Again, there was a high degree of heterogeneity between studies.

Finally, there were seven studies with adequate data for pooling to investigate relationships with bleeding on probing. These involved a total of 1776 participants with 594 cases and 1182 controls. Meta-analysis suggested a small but significant mean difference in mean percentage sites bleeding between cases and controls of 4.74% (CI 2.76%, 6.72%). Heterogeneity between studies was high (Table S13, illustrated in Fig. S9).

Prospective studies reporting periodontitis as a categorical variable. There were three potential studies for analysis in this group involving 2469 participants. Meta-analysis suggested a pooled risk ratio of 1.15 (CI 0.89–1.49) for preterm birth in the presence of periodontitis (Table S14, illustrated in Fig. S10).

Prospective studies reporting periodontitis as a continuous variable. There were four studies with available probing depth data amenable to meta-analysis in this group involving 5515 participants. The resulting mean difference in mean probing depth between cases and controls was 0.35 mm (CI 0.26–0.45 mm). Again there was a high degree of heterogeneity between studies (Table S15, illustrated in Fig. S11).

It was possible to use the same four studies to investigate relationships with clinical attachment (Table S16, illustrated in Fig. S12). Meta-analysis suggested a difference in mean attachment level between cases and controls of −0.17 mm (CI −0.03 mm, −0.005 mm). Again, there was a high degree of heterogeneity between studies.

Finally, two of four studies above (4834 participants) were further analysed with respect to gingival bleeding data, and meta-analysis suggested no difference in percentage sites bleeding on probing between cases and controls (Table S17, illustrated in Fig. S13). However, there was limited heterogeneity between the studies involved.

Summary for studies of periodontitis and preterm birth

Meta-analysis of case-control studies using categorical definitions of periodontal status show a strong association between maternal periodontitis and preterm birth. Pooled data from case-control studies using continuous measures of probing depth and gingival bleeding corroborate these findings, but showed no association between attachment loss and preterm birth. Meta-analysis of data from prospective studies resulted in conflicting findings: studies using dichotomous exposure definitions showed no significant association between periodontitis and preterm birth, but use of pooled data of mean probing depth and attachment level pointed to a statistically significant association. Of note, there was a high degree of heterogeneity between studies. No consistent pattern in terms of geographical location or maternal race/ethnicity and outcome was observed.

Studies investigating periodontitis and preterm low birthweight

Following screening, 11 publications were considered suitable for qualitative assessment. These comprised nine case-control (Table S18) and two prospective studies (Table S19). After review of available data, these were further reduced to eight case-control and two prospective studies suitable for meta-analysis. This is illustrated in Fig. S14.

Case-control studies

Case-control studies reporting periodontitis as a categorical variable. Four publications were identified following screening. In a study involving 93 cases and 31 controls, Offenbacher et al. (1996) used a unique periodontal classification cut-off point to achieve a statistically significant odds ratio of 7.5 (1.95–18.8) in an adjusted multivariate model investigating possible associations with PTLBW. Bleeding data were not reported. This population did have relatively high levels of attachment loss considering the age of the group. High odds ratios were also reported by Toygar et al. (2007), in a large study from Turkey which relied on the use of the highest CPITN score at index teeth as an indicator of overall periodontal status. As stated above, this study was excluded from data pooling due to its examination methodology. Gomes-Filho et al. (2007) used the case definition of López et al. (2002) and reported that around 36% of 302 women in Brazil were found to have periodontitis. In this study, there was a significant association (OR 2.10 (1.28–3.44)) between pregnancy outcome and periodontal status after controlling for age and education. In contrast, Mumghamba & Manji (2007) study examining 373 women delivering babies in a hospital in Tanzania failed to show significant associations between the number of periodontal pockets beyond various threshold measures and LBW. This finding was confirmed by multivariate logistic regression, which identified age and marital status as being major risk factors for this population which had low levels of periodontitis but significant gingival bleeding, and low levels of smoking.

Case-control studies reporting periodontitis as a continuous variable. The study by Offenbacher et al. (1996) described above also presented data in terms of mean probing depths and attachment loss, so this study was also considered for data pooling. Davenport et al. (2002) examined 743 women attending a maternity unit in east Inner London, recording maximum probing depth per tooth and bleeding. Although this population did have evidence of periodontal disease with 75% being non-smokers, no association was found between probing depth or bleeding score and pregnancy outcome. This was confirmed by logistic regression after adjustment for identified potential confounders. This is in concordance with the report of Noack et al. (2005), carried out on 101 largely non-smoking and relatively affluent inpatients at a German hospital obstetrics unit. This group found no differences between cases and controls for mean probing depth, sites bleeding on probing or mean attachment levels, confirmed by multivariate regression analysis. Buduneli et al. (2005) carried out examinations of 181 women attending a maternity unit in Turkey within 72 h of delivery, but found no difference in any oral health markers, including periodontal measures, between cases and controls. These women had caries and a high mean probing depth with approximately 68% of sites bleeding on probing. Vettore et al. (2008a,b) reported data from a study of 542 women, which was described as a case-control study although it did in fact have three "case" groups and one control. When considering exclusively mothers with PTLBW and controls, a total of 456 women were involved. Several analyses were carried out but used numbers or percentages of sites beyond certain threshold levels as indicators of disease. These could not be compared to other work. However, mean probing depth, bleeding and attachment level data were reported, and these data were used in the pooled estimates. There were significantly shallower mean probing depths and less attachment loss in the cases compared to control participants. In contrast, Khader et al. (2009) found significant differences between cases and controls in 586 Jordanian women, with poorer oral hygiene, deeper pockets and more loss of attachment in cases, such that an increase in mean probing depth of 1 mm entailed an odds ratio of 2.04 (1.58–2.61) for PTLBW. Similar findings were reported for attachment level.

Prospective studies

Two potential prospective studies were identified. Agueda et al. (2008) followed 1296 women attending for prenatal care at a hospital in Spain over a 22 month period. Periodontal disease was defined as defined by López et al. (2002). Women with PTLBW were more likely to have a history of pregnancy complications and gestational diabetes, based on univariate analyses. There was also a tendency for them to have periodontitis and have a higher percentage of sites with deep pockets, but these were not statistically significant. Multivariate logistic regression showed no effect of periodontal status on PTLBW outcome, although age, previous pregnancy complications, onset of prenatal care and means of delivery were associated with PTLBW. Ercan et al. (2012) reported work with a population of 50 women attending for amniocentesis. Unfortunately, it was not made clear why these participants were scheduled for this non-routine investigation, the reasons for which may have influenced the findings. The mean age of the included women was 35 years and PTLBW only occurred in those categorized as suffering from generalized periodontitis, although this group also contained all the smokers in the study population. Unfortunately, no other data were available and multivariate analyses were not reported. The relatively low number and uniqueness of this study population led us to not consider it for data pooling. Consequently, it was not possible to carry out a meta-analysis for prospective studies looking at combined PTLBW.

Meta-analysis for studies of periodontitis and preterm low birthweight

Case-control studies reporting periodontitis as a categorical variable. Meta-analysis was possible for results from Gomes-Filho et al. (2007) and Mumghamba & Manji (2007) and suggested a significant association between periodontitis and PTLBW (OR 2.06, 1.34–3.16) for a population of 423 women, compromised of 154 cases and 269 controls (Table S20, illustrated in Fig. S15).

Case-control studies reporting periodontitis as a continuous variable. In contrast, meta-analysis of available papers that used continuous variables to describe periodontitis as an exposure in a total of 2148 women (939 cases, 1209 controls) suggest shallower probing depths in cases with PTLBW when compared to controls, no difference in attachment loss in cases (1267 participants), and no difference in gingival bleeding (330 participants) between cases and controls. However, there was a high level of heterogeneity in these studies (Tables S21–23, illustrated in Figs S16–18).

Prospective studies reporting periodontitis as a continuous variable. There were two studies with available probing depth data amenable for metaanalysis in this group involving 1500 participants. The data showed a mean difference in mean probing depth between cases and controls of 0.25 mm, but this was not statistically significant (CI −0.076 mm, 0.568 mm). Again, there was a high degree of heterogeneity between studies (Table S24, illustrated in Fig. S19).

Using attachment level data of the same 1500 participants, meta-analysis suggested no significant difference in mean attachment level between cases and controls of 0.92 mm (CI 0.61 mm, 1.09 mm). Again, there was a high degree of heterogeneity between studies (Table S25, illustrated in Fig. S20). Finally, meta-analysis was not possible for assessment of gingival bleeding, since this was recorded in incompatible ways in each of these studies.

Summary for studies of periodontitis and preterm low birthweight

The literature based on case-control studies reported above appears to give an uncertain picture of this relationship. Pooled data from prospective studies using continuous measures of probing depth, attachment level and gingival bleeding showed a significant, positive association between poor periodontal status and the composite adverse outcome. However, meta-analysis of data from case-control studies generated conflicting results: Although studies using categorical exposure definitions of periodontitis suggested a strong association, studies using continuous variables showed significantly shallower probing depths but more loss of attachment in cases than controls, and no difference in gingival bleeding levels. Importantly, PTLBW is a composite variable seldom used in the obstetrics literature that may encompass disparate underlying aetiologies, therefore, its use in future studies of maternal periodontitis and adverse pregnancy outcomes should not be encouraged.

Studies investigating periodontitis and pre-eclampsia

Following screening, eight publications were considered suitable for qualitative assessment. These comprised seven case-control studies (Table S26) and one prospective study, with the latter study (OCAP) reported in several publications. The case-control studies were suitable for meta-analysis. This is illustrated in Fig. S21.

Case-control studies

Six studies of adequate quality were amenable to meta-analysis examining the association between presence or absence of periodontal disease (according to different definitions used across studies) and pre-eclampsia. In addition, there were three studies in which differences in periodontal scores could be determined for women with or without pre-eclampsia.

Case-control reporting periodontitis as a categorical variable. The studies by Kunnen et al. (2007), Politano et al. (2011) and Ha et al. (2011) were excluded since it was not clear if examiners were masked to pregnancy outcome. Canakci et al. (2004) reported findings from a small sample of Turkish women matched for age, gravidity, parity, smoking and prenatal care. Full-mouth examinations were carried out just before delivery by masked examiners, and periodontal disease was defined as the presence of ≥4 teeth with probing depth ≥4 mm that bled on probing, and with a CAL ≥3 mm at the same site. Around 20% of the participants were current smokers. Cases were found to have higher mean probing depth and attachment loss, and a greater proportion of sites bleeding on probing. Multiple logistic regression suggested an odds ratio of 3.47 (CI 1.07–11.95) for pre-eclampsia in participants with periodontitis, with high serum triglyceride levels being the only additional significant exposure. Contreras et al. (2006) examined a larger, younger, urban population of low socio-economic status comprising 130 cases and 243 controls. Full-mouth recordings were carried out but no covariates were considered part of the data analysis. Periodontal data were analysed either as continuous variables or categorized into gingivitis, or chronic periodontitis, which was further subdivided into mild and moderate / severe. Statistically significant differences were found between cases and controls for all periodontal groupings and for mean probing depth and attachment level.

Cota et al. (2006) examined women within 48 h of delivery in a public hospital in Brazil, involving 109 cases and 479 controls, 14% of whom were smokers. Around 64% of the women were found to have periodontitis, using the same criteria as Canakci et al. (2004). Despite the controls including significantly more smokers, there was a higher incidence of periodontitis in the case population, in terms of defined cases and expressed as numbers of deep sites and of sites with advanced attachment loss. Maternal periodontitis (OR 1.88, CI 1.15–3.06) was found in a multivariate regression model to be associated with pre-eclampsia, along with hypertension, primiparity and maternal age. In another Brazilian study, Unfortunately, a lack of raw mean data prevented data pooling for this study. Siqueira et al. (2008) reported data for 500 women examined in the same hospital for a slightly longer time span, with significant recruitment overlap of the samples included in the two reports. Periodontal data were reported both as a categorical or a series of continuous variables, although the latter were expressed as combinations of different measures, making these data unsuitable for pooling. Assessment of the categorical data showed that maternal periodontitis (OR 1.52, CI 1.01–2.29) was found in a multivariate regression model to be associated with pre-eclampsia. It was decided to exclude the data from Cota et al. (2006) from data pooling in favour of that from Siqueira et al. (2008), since the latter study population was an enlarged version of the former cohort.

The study reported by Nabet et al. (2010) involved 1180 women with preterm deliveries and 1094 women with deliveries at term ($\geq$37 weeks), employed a partial mouth examination, and recruited healthy women delivering at six maternity units in France. Participants were older than those in the studies described above and 25% were current or former smokers. The presence of probing depths $\geq$4 mm accompanied with bleeding or $\geq$3 mm attachment loss were significantly associated with pre-eclampsia, with adjusted odds rations of 1.94–2.21. Taghzouti et al. (2011) reported data from a study of 337 women delivering at four hospitals in Quebec. The demographics of these women resembled those reported by Nabet et al. (2010), and periodontitis was defined in the same manner as Canakci et al. (2004). There were no consistent significant associations between periodontitis case status, or with levels of periodontitis expressed as quartiles of mean probing depth or mean attachment loss, and pre-eclampsia.

Case-control studies reporting periodontitis as a continuous variable. Khader et al. (2006) examined 345 women delivering in hospital in Jordan of whom approximately 20% were aged over 34 years and none were smokers. Although cases had significantly more sites with loss of 3 mm or more periodontal attachment, regression models with adjustments for age, body mass index, gestational age and medical and previous pregnancy history showed no significant association between average periodontal scores or the extent of deep and involved sites and pre-eclampsia. However, the number of decayed surfaces present was associated with pre-eclampsia, possible being a surrogate marker for lifestyle or socioeconomic status.

Prospective study

The three publications reporting on the prospective association between periodontitis and pre-eclampsia (Boggess et al. 2003, Horton et al. 2010 and Riche et al. 2002) all report various aspects of the same study and data set, therefore no meta-analysis was carried out.

Boggess et al. (2003) recruited 850 women at their first or second prenatal visit and related their baseline or their post-partum periodontal status (available for 763 women) to subsequent pre-eclampsia. Full-mouth recordings were obtained, and periodontitis was defined as one or more tooth sites with $\geq$4 mm pocket depth or one or more pockets that bled on probing. In addition, severe disease was defined as >15 tooth sites with pocket depths $\geq$4 mm. Regression analysis generated a model in which severe periodontal disease at delivery and smoking were related to pre-eclampsia. After adjustment for other factors, the odds ratio for severe periodontal disease at delivery was 2.4 (CI 1.1–5.3). However, there were no univariate or multivariate associations found between periodontal disease at enrolment and subsequent pre-eclampsia. Further analysis showed an association between progression of periodontitis during pregnancy and pre-eclampsia.

Meta-analysis for studies of periodontitis and pre-eclampsia

Studies reporting periodontitis as a categorical variable. Meta-analysis based on the five studies of 4224 women (1535 cases, 2689 controls) listed below resulted in a pooled odds ratio of 1.61, with a 95% CI of 1.36–1.92 (see Table S27 and Fig. S22). However, there was a high degree of heterogeneity between these studies.

Studies reporting periodontitis as a continuous variable. Meta-analysis of data from three studies on a total of 800 women (286 cases, 514 controls) resulted in a statistically significant pooled mean difference in mean probing depth of 0.89 mm between cases and controls, with a 95% CI of 0.87–0.91 mm (see Table S28 and Fig. S23).

Further analyses were completed on fewer suitable papers to investigate possible relationships with attachment levels (Table S29, Fig. S24) and with bleeding on probing (Table S30, Fig. S25).

Meta-analysis of data from the same three studies revealed a statistically significant pooled difference in mean attachment level of 0.96 mm between cases and controls, with more attachment loss in controls.

Meta-analysis of data from two studies on a total of 582 women (166 cases, 416 controls) resulted in a statistically significant pooled mean difference in the proportion of sites bleeding on probing of 7.82% between cases and controls.

Summary of studies of periodontitis and pre-eclampsia

Pooled data from case-control studies that used categorical definitions of periodontitis suggest a positive association between poor maternal periodontal status and pre-eclampsia. These findings are consistent with the prospective data by Boggess et al. (2003) who found an odds ratio of 2.4, but only for periodontal data post partum. Meta-analysis of continuous data from case-control studies showed significantly deeper probing depths, higher levels gingival bleeding but less attachment loss in pregnant women with pre-eclampsia than in controls

General Conclusions and Summary

A large number of studies have investigated potential associations between maternal periodontitis and adverse pregnancy outcomes but there is a high degree of variability in study populations, as well as in recruitment and assessment methods. In addition, potentially detrimental exposures that may be shared between periodontitis and adverse pregnancy outcomes may not have been adequately accounted for in all studies. Therefore, presence or absence of multivariate analyses was factored in the quality scores assigned to the studies included in the Tables.

The range of variability in the quality of selected papers was limited, probably as a result of adherence to pre-determined inclusion criteria. Consequently, there was no evidence of an association between perceived quality scores and study outcomes. Although most studies have used full-mouth or partial-mouth probing assessments to record periodontal status, the definition of the "periodontitis case" has varied substantially across studies. Such variation in case definitions has been shown to have an impact on observed relationships between maternal periodontitis and pregnancy outcomes, as described by Manau et al. (2008). These investigators demonstrated that the commonly used periodontitis definitions by López et al. (2002) resulted in significant positive associations between maternal periodontitis and adverse pregnancy outcomes in the populations studied. In contrast, analyses of data from the same populations using mean probing depths and other continuous (as opposed to categorical) variables frequently resulted in non-significant associations. Corroborating findings from the present analyses underscores the need to use both categorical definitions and continuous measures of several relevant variables to define periodontal pathology in the study of these associations. This is particularly important as it is presently unclear whether variables reflecting overall susceptibility to periodontitis and cumulative historical exposure to causative agents (such as CAL), or variables reflecting current inflammatory burden (i.e. gingivitis, bleeding on probing and pocket depths), are more appropriate measures of periodontal disease-associated exposure in the context of risk for adverse pregnancy outcomes. However, use of mean values of probing depth and attachment loss are not ideal in describing periodontal status, given the low number of deep pockets and/or tooth sites with severe attachment that young individuals with periodontitis typically display. Use of frequency distributions of sites at different thresholds of pocketing or attachment loss may be much more meaningful and informative, but requires access to original raw data that were not available in the present review. In addition, differences in methodology and data reporting have precluded the use of data from all studies that fulfilled the qualitative criteria in quantitative meta-analyses.

Notwithstanding the above limitations, this systematic review revealed a positive, independent association between maternal periodontitis and preterm birth and LBW emerging from cross-sectional and case-control studies, and in particular, from those studies that have used dichotomous exposure definitions of periodontal status. These associations were generally attenuated in the more robust prospective studies, as well as in studies where periodontitis was assessed as a continuous variable. A significant association emerged between maternal periodontitis and pre-eclampsia. It is suggested that future studies of the role of maternal periodontitis on adverse pregnancy outcomes employ both continuous and categorical assessments of periodontal status. The use of the composite outcome preterm, LBW is not encouraged.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix S1. Journals hand / electronic searched.
Appendix S2. Papers screened for suitability.
Table S1. Selected case-control studies of maternal periodontitis and low birthweight.
Table S2. Selected cross-sectional studies of maternal periodontitis and low birthweight.
Table S3. Prospective studies of maternal periodontitis and low birthweight.
Table S4. Meta-analysis of case-control studies of low birthweight reporting periodontitis as a categorical variable.
Table S5. Meta-analysis of prospective studies of low birthweight reporting periodontitis as a categorical variable.
Table S6. Meta-analysis of prospective studies of low birthweight reporting periodontitis as a continuous variable: probing depth data.
Table S7. Meta-analysis of prospective studies of low birthweight reporting periodontitis as a continuous variable: clinical attachment level data.
Table S8. Case-control studies of maternal periodontitis and preterm birth.
Table S9. Prospective studies of maternal periodontitis and preterm birth.
Table S10. Meta-analysis of case-control studies of preterm birth reporting periodontitis as a categorical variable.
Table S11. Meta-analysis of case-control studies of preterm birth reporting periodontitis as a continuous variable: probing depth data.
Table S12. Meta-analysis of case-control studies of preterm birth reporting periodontitis as a continuous variable: clinical attachment level data.
Table S13. Meta-analysis of case-control studies of preterm birth reporting periodontitis as a continuous variable: bleeding on probing data.
Table S14. Meta-analysis of prospective studies of preterm birth reporting periodontitis as a categorical variable.
Table S15. Meta-analysis of prospective studies of preterm birth reporting periodontitis as a continuous variable: probing depth data.
Table S16. Meta-analysis of prospective studies of preterm birth reporting periodontitis as a continuous variable: clinical attachment level data.
Table S17. Meta-analysis of prospective studies of preterm birth reporting periodontitis as a continuous variable: bleeding on probing data.
Table S18. Case-control studies reporting periodontitis as a categorical or continuous variable.
Table S19. Prospective studies investigating periodontitis and preterm low birthweight.
Table S20. Meta-analysis of case-control studies of preterm low birthweight reporting periodontitis as a categorical variable.
Table S21. Meta-analysis of case-control studies of preterm low birthweight reporting periodontitis as a continuous variable: probing depth data.
Table S22. Meta-analysis of case-control studies of preterm low birthweight reporting periodontitis as a continuous variable: clinical attachment level data.
Table S23. Meta-analysis of case-control studies of preterm low birthweight reporting periodontitis as a continuous variable: bleeding on probing data.
Table S24. Meta-analysis of prospective studies of preterm low birthweight reporting periodontitis as a continuous variable: probing depth data.
Table S25. Meta-analysis of prospective studies of preterm low birthweight reporting periodontitis as a continuous variable: clinical attachment level data.
Table S26. Case-control studies investigating periodontitis and pre-eclampsia.
Table S27. Meta-analysis of case-control studies for pre-eclampsia reporting periodontitis as a categorical variable.
Table S28. Meta-analysis of pre-eclampsia reporting periodontitis as a continuous variable: probing depth data.
Table S29. Meta-analysis of pre-eclampsia reporting periodontitis as a continuous variable: clinical attachment level data.
Table S30. Meta-analysis of pre-eclampsia reporting periodontitis as a continuous variable: bleeding on probing data.
Figure S1. PRISMA flow chart for studies investigating associations between periodontitis and low birthweight.
Figure S2. Meta-analysis plot of case-control studies of low birthweight reporting periodontitis as a categorical variable.
Figure S3. Meta-analysis plot of prospective studies of low birthweight reporting periodontitis as a categorical variable.
Figure S4. Meta-analysis plot of prospective studies of low birthweight reporting periodontitis as a continuous variable: probing depth data.
Figure S5. Meta-analysis plot of prospective studies of low birthweight reporting periodontitis as a continuous variable: clinical attachment level data.
Figure S6. PRISMA flow chart for studies investigating associations between periodontitis and preterm birth.
Figure S7. Meta-analysis plot of case-control studies of preterm birth reporting periodontitis as a continuous variable: probing depth data.
Figure S8. Meta-analysis plot of case-control studies of preterm birth reporting periodontitis as a continuous variable: clinical attachment level data.
Figure S9. Meta-analysis plot of case-control studies of preterm birth reporting periodontitis as a continuous variable: bleeding on probing data.
Figure S10. Meta-analysis plot of prospective studies of preterm birth reporting periodontitis as a categorical variable.
Figure S11. Meta-analysis plot of prospective studies of preterm birth reporting periodontitis as a continuous variable: probing depth data.
Figure S12. Meta-analysis plot of prospective studies of preterm birth reporting periodontitis as a continuous variable: clinical attachment level data.
Figure S13. Meta-analysis plot of prospective studies of preterm birth reporting periodontitis as a continuous variable: bleeding on probing data.
Figure S14. PRISMA flow chart for studies investigating associations

between periodontitis and preterm low birthweight.
Figure S15. Meta-analysis plot of case-control studies of preterm low birthweight reporting periodontitis as a categorical variable.
Figure S16. Meta-analysis plot of case-control studies of preterm low birthweight reporting periodontitis as a continuous variable: probing depth data.
Figure S17. Meta-analysis plot of case-control studies of preterm low birthweight reporting periodontitis as a continuous variable: clinical attachment level data.
Figure S18. Meta-analysis plot of case-control studies of preterm low birthweight reporting periodontitis as a continuous variable: bleeding on probing data.
Figure S19. Meta-analysis plot of prospective studies of preterm low birthweight reporting periodontitis as a continuous variable: probing depth data.
Figure S20. Meta-analysis plot of prospective studies of preterm low birthweight reporting periodontitis as a continuous variable: clinical attachment level data.
Figure S21. PRISMA flow chart for studies investigating associations between periodontitis and pre-eclampsia.
Figure S22. Meta-analysis plot of studies of pre-eclampsia reporting periodontitis as a categorical variable.
Figure S23. Meta-analysis plot of studies of pre-eclampsia reporting periodontitis as a continuous variable: probing depth data.
Figure S24. Meta-analysis plot of studies of pre-eclampsia reporting periodontitis as a continuous variable: clinical attachment level data.
Figure S25. Meta-analysis plot of studies of pre-eclampsia reporting periodontitis as a continuous variable: bleeding on probing data.

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Clinical Relevance

Scientific rationale for study: The potential association between maternal periodontitis and adverse pregnancy outcomes is important from a public health viewpoint, given that (i) periodontitis is preventable and treatable, (ii) a substantial proportion of adverse pregnancy outcomes occurs in the absence of established risk factors and (iii) adverse pregnancy outcomes result in significant societal and health care burden. *Principal findings and practical applications:* A systematic review of the available epidemiological evidence from non-interventional studies (case-control, cross-sectional and longitudinal prospective) indicates that maternal periodontitis is associated with adverse pregnancy outcomes independent of known confounders. However, the strength of the association is modest and appears to be influenced by study design and methodology. Additional research is encouraged that will further explore this association.