Impact of the Treatment of Periodontitis on Systemic Health and Quality of Life. A Systematic Review.

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Abstract

Aim: To investigate the effect of treatment of periodontitis on systemic health outcomes, pregnancy complications and associated quality of life.

Methods: Systematic electronic searches were conducted to identify randomised controlled trials with minimum 6 months follow-up and reporting on the outcomes of interest. Qualitative and quantitative analyses were performed as deemed suitable.

Results: Meta-analyses confirmed reductions of high sensitivity C-Reactive Protein (hs-CRP) [0.56 mg/L 95% Confidence Interval (CI) (-0.88, -0.25) p<0.001], Interleukin (IL)-6 [0.48 pg/ml 95% CI (-0.88, -0.08) p=0.020], plasma glucose [1.33 mmol/L 95% CI (-2.41, -0.24) p=0.016], and increase of flow-mediated dilation (FMD) [0.31 % 95% CI (0.07, 0.55) p=0.012] and in diastolic blood pressure [0.29 mmHg 95% CI (0.10, 0.49) p=0.003] 6 months after the treatment of periodontitis. A significant effect on preterm deliveries (<37 weeks) was observed [0.77 Risk Ratio 95% CI (0.60, 0.98) p=0.036]. Limited evidence was reported on quality-of-life outcomes in the included studies.

Conclusions: Periodontal treatment improves cardiometabolic risk, reduces systemic inflammation and the occurrence of preterm deliveries. Treatment of periodontitis results in systemic health improvements, but further research is warranted to confirm whether these changes are sustained over time. Further, appropriate quality of life outcomes should be included in the study designs of future clinical trials.

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CLINICAL RELEVANCE

Scientific rationale for the study: Periodontitis has been linked to multiple systemic conditions. Thorough assessment of the impact of the treatment of periodontitis on systemic health is paramount due to its implication in healthcare strategies.

Principal findings: A reduction of high sensitivity C-Reactive Protein (hsCRP), fasting plasma glucose, and an increased in flow-mediated dilation (FMD) and diastolic blood pressure were reported 6 months following the treatment of periodontitis. Additionally, treating periodontitis had a favourable effect on reduction of preterm deliveries at <37 weeks. Quality of life (QoL) was not reported in the vast majority of the trials included in the analysis.

Practical implications: Management of periodontitis has a beneficial effect on systemic health outcomes. Further multi-centre randomized clinical trials are recommended to test the effect of periodontal therapy on hard clinical endpoints and QoL outcomes.

Introduction

Non-communicable diseases (NCDs) are a common cause of death, morbidity and disability worldwide. A recent estimate states that NCDs are responsible for the death of 41 million people each year (71% of the overall deaths). Cardiovascular diseases (17.9 million annual deaths), cancer (9.0 million), chronic respiratory diseases (3.9 million) and diabetes (1.6 million) are the four most prominent NCDs accounting for 80% of "premature" deaths between the ages of 30 and 69 years (WHO, 2021). A cluster of common risk factors (tobacco usage, alcohol intake, diet, stress, physical inactivity, social inequalities) is shared amongst NCDs. This has mandated an unprecedented need for public health systems to campaign globally and all healthcare disciplines to play a part in promoting prevention, screening and treatment of NCDs to improve the health of the public (WHO, 2016).

Periodontitis contributes significantly to overall oral disease burden with its severe form representing the sixth-most prevalent condition estimated to affect 7-11% of the global adult population (Kassebaum et al., 2014; Kassebaum et al., 2017). Periodontitis is a chronic multifactorial inflammatory disease associated with a dysbiotic dental biofilm resulting in progressive periodontal attachment and bone loss (Van Dyke, Bartold, & Reynolds, 2020). If left untreated, the disease will eventually lead to progressive tooth loss and its multiple sequelae including altered masticatory function, speech, aesthetics, psychological repercussions and quality of life (Buset et al., 2016). The World Dental Federation, the World Health Organization, and the International Association for Dental Research in 2003 set the goal to "minimise the impact of diseases of oral and craniofacial origin on health and psycho-social development, emphasising the promotion oral health and reducing oral disease amongst populations with the greatest burden of such conditions and diseases" (Hobdell, Petersen, Clarkson, & Johnson, 2003). The Political declaration of the High-level Meeting of the General Assembly on the Prevention and Control of NCDs states that "oral diseases pose a major health burden for many countries and that these diseases share common risk factors and can benefit from common responses to non-communicable diseases" (United Nations, 2011).

Substantial evidence exists from observational and experimental studies confirming the association of periodontitis with systemic health outcomes. A number of mechanistic pathways have been hypothesised linked to the role of dental biofilm and its ability to trigger not only an altered immune-inflammatory response, and vice versa, but also a variety of direct negative effects on targeted organs/tissues in different parts of the body. Treatment of periodontitis could represent a novel non-pharmacological intervention to improve not only oral but also general health and quality of life (QoL) via acute and chronic changes in several indicators of systemic health.

The aim of the present systematic review was to provide a robust critical appraisal of the evidence of the effect of treatment on systemic health and associated quality of life in patients with severe periodontitis (stages III or IV or equivalent). Three PICOS questions were formulated (Table 1).

PICOS Question 1

In patients with severe periodontitis (stages III or IV or equivalent) who are otherwise healthy, what is the effect of the treatment of periodontitis in comparison with no treatment or control treatment, upon systemic health and quality of life outcomes, as reported in 6 month (minimum follow-up) randomised controlled trials?

PICOS Question 2

In patients with severe periodontitis (stages III or IV or equivalent) and a non-communicable disease, what is the effect of the treatment of periodontitis in comparison with no treatment or control treatment, upon of systemic health and quality of life outcomes, as reported in 6 months minimum follow-up randomised controlled trials?

PICOS Question 3

In patients with severe periodontitis (stages III or IV or equivalent) and pregnancy, what is the effect of the treatment of periodontitis in comparison with no treatment or control treatment, upon perinatal, maternal and quality of life outcomes, as reported in randomised controlled trials?

Material & Methods

This systematic review protocol was registered in PROSPERO on 24th April 2020 with ID no. CRD42020179557. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed in reporting this review (Moher, Liberati, Tetzlaff, & Altman, 2009). A PRISMA statement is attached to follow the reporting of this systematic review (Supplemental Material).

Eligibility Criteria

Studies were eligible for inclusion in the review if they reported on individuals of 18 years of age and above suffering from periodontitis with or without a series of NCDs or during pregnancy (systemic condition). This review was conducted following the recent introduction of new case definitions of periodontitis using a staging and grading system and every attempt was made to facilitate interpretation of evidence on periodontitis published prior to the new classification system. Although

severe periodontitis was the focus of the review, mild/moderate forms were included as it was anticipated that publications of severe periodontitis population samples only would be limited. Any other periodontal diseases and conditions were excluded (e.g. gingivitis or specific syndromes). Studies with unclear or lacking a report of the periodontal case definition were excluded.

Studies reporting a clear case definition of the study population with or without a NCD were eligible for inclusion. The most prevalent NCDs identified by the latest Global Disease initiative were included as follows: Cardiovascular Diseases, Arrhythmias (Atrial fibrillation), Hypertension, Rheumatic Diseases, Neurological Diseases, Respiratory Diseases, Metabolic Diseases, Kidney Diseases, Liver Diseases, Inflammatory Gastrointestinal Diseases, Malignancy (Cancer), Mental Health, and Osteoporosis(GBD 2019 Diseases and Injuries Collaborators, 2020). Pregnancy complications were also included as non-NCD systemic conditions. Study populations without a NCD reporting a clear definition of a systemically healthy study population were also included.

Only studies providing a clear description of the treatment of periodontitis delivered were included. Periodontal treatment and control interventions included were; a) non-surgical supra and sub-gingival and/or surgical therapy compared to i: no treatment, ii: supra-gingival instrumentation/prophylaxis, iii: patient performed oral hygiene alone or iv: a combination thereof or b) non-surgical supra and sub-gingival instrumentation and/or surgical therapy with adjunctive therapies compared to i: no treatment, ii: supra-gingival instrumentation/prophylaxis, iii: patient performed oral hygiene alone or iv: a combination thereof. Studies reporting a subgingival intervention with or without adjunctive chemical therapies were not included as the control group would not fit with the PICOS comparison group definition (Table 1, Comparison) .

Studies reporting validated surrogate outcomes associated with NCDs or systemic health were included as well as studies reporting biomarkers of systemic inflammation. In studies reporting on NCD cohorts, outcome variables varied according to each disease or condition. All systemic outcomes reported at 6 months or later following periodontal therapy and pertaining to each NCD (as listed under study populations) or during pregnancy were included. Quality of life (QoL) outcomes were also of interest in these populations and recorded during data extraction (if available within the selected studies), however, QoL outcomes were not applied as an inclusion/exclusion criteria.

Only randomised controlled trials with systemic outcomes reported following at least 6 months were eligible for inclusion. Articles published in languages other than English were excluded due to limited resources for the translation from different languages.

Search Methods

Preliminary electronic searches designed to locate possible review articles, narrative and systematic reviews were conducted to facilitate development of the electronic search strategy. The strategy was formulated using a combination of controlled vocabulary (MeSH and free text terms), then piloted to confirm high sensitivity over high precision in search results in order to maintain a broad search. The search strategy used consistent terms customised according to each database a priori and included English language restriction (description of all searches is reported in Supplemental Material). Electronic databases searched from 1946 up to 23rd April 2020 included Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (OVID), EMBASE, SCOPUS, and LILACS. Hand searching of bibliographies of previously published reviews were also performed. Search results from all databases were combined and duplicates removed.

Study Selection

Titles and abstracts of all identified reports were independently screened by two reviewers (MO, EMA) based upon the inclusion/exclusion criteria. Full text reports were obtained and assessed independently and in duplicate for studies appearing to meet the inclusion criteria or with insufficient information in the title or abstract to confirm eligibility for inclusion, then confirmed by a third reviewer (JS). Disagreements following full text screening were resolved by discussion and if necessary an additional reviewer was consulted (FD). Excel spreadsheets were created to record information pertaining to the decision to include or exclude each article. The reviewers were trained and calibrated against a series of publications prior to proceeding with the review and a Kappa statistic was used to assess the reviewer agreement based upon the full text screening.

Data Management

Three reviewers (MO, EMA, JS) extracted data into specifically created excel spreadsheets. Data pertaining to study characteristics such as population, interventions, comparisons, type of outcomes reported, and study conclusions were recorded in evidence tables to provide an overview of the included studies and available data. All data in the excel spreadsheets were reviewed to consider

appropriateness for meta-analysis. Data was then entered into Stata (Stata Statistical Software: Release v16 , StataCorp LLC, College Station, TX, USA) in preparation for quantitative analysis.

Outcome measures

Outcomes at 6 months or beyond following periodontal intervention were extracted noting whether they were primary or secondary. For pregnancy outcomes, the assessment was post-partum. Quality of life outcomes reported within the included studies were also extracted.

Risk of Bias Assessment

Assessment for risk of bias of all included studies was undertaken independently by three reviewers (MO, EMA, JS) at the time of data extraction using the ROBINS-2 Tool (RoB 2.0) (Sterne et al., 2019). Each study was graded according to five items (randomisation, deviation, missing data, outcome measurement and selective reporting) and an overall risk of bias score was assigned. Assessments were then discussed amongst the reviewers to confirm agreement (MO, EMA, JS, FD)

Data Synthesis

For continuous data (e.g. HbA1c, hsCRP) sample sizes, mean values and standard deviations from the treatment and control groups of each study were used to provide an estimated standardised mean difference (SMD) relevant to the size of the intervention effect (i.e. the difference in means) and relative to the variability observed in that study. This has the advantage of combining estimates from different studies which use different scales of measurement. For dichotomous data (i.e. pregnancy outcomes), the sample sizes and the number of outcomes with a given attribute in the treatment and control groups were used to provide a study specific estimate of the risk ratio (RR).

Quantitative analysis included a meta-analysis for pooled estimates of interest from all the relevant studies including their weighted mean, where the weight for each study was the inverse of the variance. A random effects model (DerSimonian & Laird, 1986), in which the two components of the variance are the within and between study variability, was used for each meta-analysis, and a forest plot was drawn to illustrate the estimated effect and its 95% confidence interval (CI) from each study, together with the pooled effect and its 95% CI. Statistical heterogeneity in each meta-analysis was explored by performing Cochrane's Q test of homogeneity and by determining the I^2 index (Higgins, Thompson, Deeks, & Altman, 2003) representing the percentage of variation across studies due to heterogeneity. A Z test was used to test the null hypothesis that the true SMD = 0 or the true RR = 1, as relevant. Meta-analyses were performed separately for each NCD chosen or pregnancy outcomes,

when a given outcome in the treatment and control groups was reported for a minimum of two studies. An exploratory analysis combining PICOS 1 & 2 was performed to assess the effect of the treatment of periodontitis in the wider population with regards to systemic health outcomes (regardless of comorbidity/medical status). Publication bias was assessed in a meta-analysis of 4 or more studies by drawing a funnel plot with the standard error on the vertical axis and the effect of interest (Hedges' g) on the horizontal axis: publication bias was indicated if the plot was asymmetrical with a gap towards the bottom left-hand corner. Egger's test for small-study effects (Egger, Davey Smith, Schneider, & Minder, 1997) was also used to assess publication bias.

Pre-specified sensitivity analyses were performed to investigate the potential impact of i) reported study inclusion criteria of periodontitis severity (quantitative analysis performed in severe vs non-severe [mild/moderate (stage I-II using the current classification)] according to the reported case definitions or description in the manuscript), ii) a more objective measure of disease activity (studies which included patients' groups with a mean PPD≥2.8 mm, calculated using average PPD values reported in the manuscript or requested from authors), iii) risk of bias (meta-analysis performed in studies with high vs some concern or low) and iv) type of control treatment (analyses were restricted to studies which included delayed treatment vs delivering a control periodontal therapy). The PPD threshold of ≥2.8 mm used in the above sensitivity analysis was obtained from existing data on a population survey (in this case from the whole mouth assessment from the NHANES 2009-2010 wave) (Johnson et al., 2013) comparing cases with severe periodontitis definition according to the American Academy of Periodontology (AAP)- Centers for Disease Control and Prevention (CDC) criteria versus the remaining study sample.

All analyses were performed with Stata (Stata Statistical Software: Release 16, StataCorp LLC, College Station, TX, USA) using the functions *metan* and *metaprop* for the meta-analysis of continuous variables and binary variables, respectively, and *metafunnel* for the funnel plots. A significance level of 0.05 was used for all hypothesis tests. To illustrate expected treatment effect prediction intervals (PI) were calculated (Borenstein M, 2009).

RESULTS

Search and screening

The combined total of references identified by the electronic search strategy customised for each database was 24,555 citations with handsearching adding 3 more citations. Removal of duplicates

resulted in 13,401 citations to be screened. Independent screening of titles and abstracts resulted in 97 full text articles to be retrieved. Further screening of full text articles resulted in 48 articles eligible for inclusion in qualitative synthesis (47 of which were used for quantitative analysis) (Figure 1). Kappa score calculated for screening agreement was 0.917.

The search retrieved a large number of relevant articles together with a substantial number of irrelevant hits confirming the high sensitivity and relatively low precision of the search in accordance with the search strategy designed to be broad. Numerous citations excluded investigated the effect of the treatment of periodontitis on systemic health, however, were not Randomized Clinical Trials (RCTs) or were studies of less than 6 months follow-up. During full text screening, 49 articles were excluded primarily due to non-RCT design, only conference abstracts available, or control groups not meeting inclusion criteria (detailed exclusion reasons are summarised in Supplemental Material).

Descriptive results

Studies included were conducted in 5 geographic regions, ranged in year of publication from 2002 to 2020 and comprised a range of systemic conditions (Supplemental Material). All 48 studies included were summarised according to the specific PICOS question (Supplemental Material) in chronological order of year of publication (most recent to oldest) and thereafter alphabetically within each year.

Risk of bias

Fourteen of the 48 included studies were judged to be of high risk of bias while 17 studies presented with some concern and the remaining 17 were considered to be of low risk of bias (Supplemental Material).

Results by PICOS question

The following sections present the results according to the different PICOS questions. The results regarding QoL outcomes were reported in the evidence tables (Supplemental Material) with insufficient data retrieved for quantitative assessment.

PICOS question 1

Three randomised controlled trials addressed PICOS question 1, i.e. the effect of the treatment of periodontitis in comparison with no treatment on systemic health and quality of life outcomes in patients who are systemically healthy (Fu, Li, Xu, Gong, & Yang, 2016; Tonetti et al., 2007; Q. B. Zhou

et al., 2017). Systemic outcomes reported in these trials included hsCRP, fasting plasma glucose, tumor necrosis factor (TNF)-alpha, IL-6, total cholesterol (TC), High density Lipoprotein (HDL) cholesterol, Low Density Lipoprotein (LDL) cholesterol, triglycerides (TG) , FMD, systolic blood pressure (SBP), diastolic blood pressure (DBP) and Body Mass Index (BMI) at 6 months follow-up. Meta-analyses were performed by systemic outcome for hsCRP, IL-6, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, systolic blood pressure, and diastolic blood pressure at 6 months (none of these studies reported 12 month follow-up data). No statistically significant overall effect of periodontal therapy was observed for any of the systemic outcomes at 6 months (Table 2) (Forest and Funnel Plots in Supplemental Material)

PICOS question 2

Twenty nine randomised controlled trials addressed PICOS question 2, i.e. the effect of the treatment of periodontitis in comparison with no treatment on systemic health in patients with a noncommunicable disease (Beck et al., 2008; Caula, Lira, Tinoco, & Fischer, 2014; D'Aiuto et al., 2018; Deepti, Tewari, Narula, Singhal, & Sharma, 2017; Engebretson et al., 2013; Fang et al., 2015; Geisinger et al., 2016; Grubbs et al., 2020; Hada, Garg, Ramteke, & Ratre, 2015; Higashi et al., 2009; Kapellas et al., 2014; Katagiri et al., 2009; Kaur, Narula, Rajput, K Sharma, & Tewari, 2015; Koromantzos et al., 2011; Koromantzos et al., 2012; Lobo et al., 2020; Lopez et al., 2012; Masi et al., 2018; Mauri-Obradors et al., 2018; Mizuno et al., 2017; Offenbacher, Beck, Moss, et al., 2009; Pinho, Oliveira, Novaes, & Voltarelli, 2009; Wang et al., 2020; Wang et al., 2017; Wehmeyer et al., 2013; Wu, Chen, Wei, Luo, & Yan, 2015; Zhang, Li, Shang, & Luo, 2013; X. Zhou et al., 2014). NCDs included in the study populations were type 2 diabetes, cardiovascular diseases, polycystic ovary syndrome (POS), end-stage renal disease (ESRD), multiple co-morbidities (MC), rheumatoid arthritis (RA), and chronic kidney disease n (CKD). Systemic outcomes reported in these trials included hsCRP, TNF-alpha, IL-6, ESR, HbA1c, fasting plasma glucose, TC, HDL cholesterol, LDL cholesterol, TG, VLDL, FMD, BMI, SBP, DBP, pulse, sCR and albumi at 6 months follow-up. Meta-analyses were conducted by systemic outcome for hsCRP, fasting plasma glucose, TNF-alpha, IL-6, TC, HDL cholesterol, LDL cholesterol, TG, FMD, SBP, DBP and BMI at 6 months follow-up (Table 3) and for hsCRP, IL-6, HbA1c, TC, HDL cholesterol, Estimated Glomerular Filtration Rate (eGFR) and Asymmetric dimethylarginine (ADMA) at 12 months follow-up.

Periodontal therapy demonstrated a statistically significant effect on hsCRP, fasting plasma glucose, FMD and DBP at 6 months follow-up in patients with non-communicable diseases (Forest and Funnel Plots in the Supplemental Material). No statistically significant effect was identified at 12 months follow-up for hsCRP, IL-6, HbA1c, total cholesterol, HDL cholesterol, eGFR and ADMA. When the threshold for severity defined by the authors was adopted (mean PPD>2.8 mm), the treatment of periodontitis demonstrated a significant effect on hsCRP, and DBP. However, this was also reflected in a lower number of trials available for the meta-analysis.

PICOS question 1 and 2 combined

Studies from PICOS 1 and 2 that reported on similar outcomes providing data for meta-analysis of systemic outcomes including hsCRP, TNF-alpha, IL-6, HbA1c, fasting plasma glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, FMD, BMI, systolic blood pressure, and diastolic blood pressure at 6 months follow-up were combined. Meta-analyses were conducted by systemic outcome for all listed outcomes with the exception of HbA1c which consisted of the same studies as PICOS 2 alone (Table 4).

Treatment of periodontitis demonstrated a statistically significant effect on hsCRP, IL-6, fasting plasma glucose, and FMD at 6 months follow-up in the combined population of systemically healthy patients and those with non-communicable diseases (Forest and Funnel Plots in the Supplemental Material), whereas no statistically significant effect was identified for any of the other outcomes reported. These findings were confirmed when sensitivity analyses were performed (Supplemental Material). When the threshold for severity defined by the reviewers was adopted (mean PPD>2.8 mm), the treatment of periodontitis determined a significant effect on hsCRP, IL-6 and DBP. However, this was also reflected in a lower number of trials available for the meta-analysis

PICOS question 3.

Sixteen randomised controlled trials (Caneiro-Queija et al., 2019; M. Jeffcoat et al., 2011; M. K. Jeffcoat et al., 2003; Khairnar, Pawar, Marawar, & Khairnar, 2015; López, Smith, & Gutierrez, 2002; Macones et al., 2010; Michalowicz et al., 2006; Newnham et al., 2009; Offenbacher, Beck, Jared, et al., 2009; Offenbacher et al., 2006; Oliveira et al., 2011; Pirie, Linden, & Irwin, 2013; Radnai et al., 2009; Reddy, Tanneeru, & Chava, 2014; Sadatmansouri, Sedighpoor, & Aghaloo, 2006; Tarannum & Faizuddin, 2007) addressed PICOS question 3, i.e. the effect of the treatment of periodontitis in comparison with no treatment on pregnancy outcomes (Table 5). The pregnancy outcomes reported in the intention to treat analysis of these trials and included in various meta-analyses comprised preterm birth <37, <35,

and <32 weeks, low birth weight <2500 gr and less than <1500 gr, preterm low birth weight, pre-eclampsia, gestational age at delivery, CRP, stillbirth, birthweight and perinatal loss.

Treatment of periodontitis demonstrated a statistically significant effect on preterm birth <37 weeks (Forest and Funnel Plot in the Supplemental Material), whereas no statistically significant effect was identified at any of the other pregnancy outcomes reported (Supplemental Material). Publication bias could not be ruled out. The sensitivity analysis performed did not changed considerably the size or direction of the effect, but the result was no longer statistically significant (Supplemental Material).

DISCUSSION

This systematic review and meta-analyses found that treatment of severe periodontitis after 6 months to 1 year lowers systemic inflammation (reduction in hs-CRP and IL-6), improved metabolic control (reduction in glucose level) and endothelial function (increase in brachial artery flow mediated dilatation). Furthermore, providing periodontal therapy during pregnancy was associated with a reduced occurrence of preterm deliveries at <37 weeks. Patient reported outcomes were scarcely reported in these studies.

Addressing PICOS 1 and 2, this is one of the first attempts to comprehensively review a large number of non-dental outcomes in patients who received periodontitis treatment. The evidence reported confirms a causal association between periodontitis and systemic inflammation which in turn could affect cardio-metabolic and vascular risk especially in patients already living with another co-morbidity (i.e. diabetes or cardiovascular disease).

Over three decades of research have indicated an independent association between periodontitis and multiple noncommunicable diseases. In fact, the European Federation of Periodontology (EFP)/ American Association of Periodontology (AAP) joint workshop held in 2012 produced consensus reports on the link with cardiovascular diseases (CVDs), diabetes and adverse pregnancy outcomes (Chapple & Genco, 2013; Sanz & Kornman, 2013; Tonetti & Van Dyke, 2013). Furthermore, an increasing body of evidence suggests an independent association with other conditions, such as rheumatic, metabolic (obesity and metabolic syndrome) and respiratory diseases, cancer and neurodegenerative disorders (Genco & Sanz, 2020). Overall, periodontitis has currently been hypothesised to be linked to 57 systemic conditions (Monsarrat et al., 2016).

Systemic inflammation is a common denominator of the majority of NCDs with increased serum concentration of IL-6 and CRP as the most common biomarkers measured. IL-6, an inflammatory

cytokine produced mainly by T cells, macrophages and adipocytes, and CRP, an acute phase reactant whose hepatic synthesis is stimulated by IL-6, are undoubtedly some of the most commonly assayed inflammatory biomarkers. Robust evidence links these molecules with mortality outcomes in cancer, cardiovascular disease, and metabolic syndrome (Li et al., 2017; Schnabel et al., 2013; Singh-Manoux et al., 2017). However, Mendelian randomisation studies have excluded a causal role of CRP in inflammatory related conditions such as atherosclerosis (Wensley et al., 2011).

Pathogen-associated molecular patterns (PAMPs), e.g. bacterial lipopolysaccharides (LPS) disseminated in the circulation could be the trigger by which periodontitis activates inflammasomes presenting cells such as macrophages, neutrophils, and endothelial cells. This process would then unfold the IL-1β pathway leading to the release of additional pro-inflammatory markers such as TNF-α (the presented meta-analysis reported a non-significant reduction trend in TNF-α), increased blood glucose levels and impaired insulin signalling (Chen, Chen, Wang, & Liang, 2015). Subsequently, insulin resistance would maintain high blood glucose levels to secure the immune cells energetic costs.

Chronic inflammation can be a consequence of multiple factors such as persistent low-level infections, autoimmune conditions, dietary components and obesity (Furman et al., 2019). Insulin resistance, dyslipidemia, hypertension, and a higher rate of metabolic syndrome, diabetes and cardiovascular events (stroke and MI) have been associated with autoimmune diseases such as rheumatoid arthritis (RA) in which systemic inflammation is well recognised and increasing evidence from RCTs targeting pro-inflammatory markers, such as interleukin (IL)-1β and TNF-α supports the role of the inflammatory cascade in the onset and progression of NCDs. Anti-TNF-α inhibitor therapy in patients with RA resulted in a reduced insulin resistance and lower risk for Alzheimer's disease onset (Burska, Sakthiswary, & Sattar, 2015; Chou, Kane, Ghimire, Gautam, & Gui, 2016). Interestingly, the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), a trial testing the effect of a therapeutic monoclonal antibody targeting interleukin-1β on atherothrombosis, reported a 35% to 40% reduction in IL-6 and hs-CRP together with a 15% lower cardiovascular risk in the group undergoing the anti-inflammatory therapy (Ridker et al., 2017). These effects were observed in a population with a high inflammatory profile (hs-CRP of 2 mg/L or more). Similarly, the lack of a significant reduction of IL-6 and hs-CRP in a healthy population (PICOS 1) is explainable with a non-substantial systemic inflammation background in such a sample. A reduction in hs-CRP has been previously documented in intervention studies and meta-analyses with short term follow-up (Freitas et al., 2012; Ioannidou, Malekzadeh, & Dongari-Bagtzoglou, 2006; Paraskevas, Huizinga, & Loos, 2008). For the first time, this review reports on the effect size at 6 months gathering data from a consistent

number of RCTs. Additionally, a significantly lower IL-6 plasma concentration following the treatment of periodontitis was observed, confirming the trend suggested in a previous meta-analysis (D'Aiuto, Orlandi, & Gunsolley, 2013).

The evidence appraised in this systematic review strongly support the notion that periodontitis contributes to systemic inflammation and overall risk of progression/complications in NCDs. Furthermore, the results indicate that periodontitis treatment could have a clinically relevant impact on reducing the overall systemic inflammatory burden, particularly for those patients with comorbidities. The long-term sustainability of these outcomes could result in an overall health improvement for individuals living with NCDs. Recent evidence suggests that the management of periodontitis in patients with a common NCD such as type 2 diabetes did not only attain substantial public health benefits but would also provide a cost-effective treatment, reducing the costs associated with disease systemic complications (Choi, Sima, & Pandya, 2020; Smits, Listl, Plachokova, Van der Galien, & Kalmus, 2020). As periodontitis is one of the most prevalent NCDs, implementing oral health strategies as a vehicle of decreasing the systemic inflammation burden should not be underestimated and considered in public health strategies worldwide.

Improvement in endothelium dependent vascular function (assessed by FMD of the brachial artery) further supports a potential systemic health benefit when treating periodontitis, as endothelial dysfunction is an early sign of vasculature pathology and a predictor of future cardiovascular risk. Endothelial activation and redox signalling are part of normal host defence but in combination with pro-inflammatory stimuli could contribute to atherogenesis and clinical events. The rise in inflammatory mediators associated with periodontitis may therefore induce chronic dysregulation of nitric oxide (NO) and reactive oxygen species (ROS) production inducing a prolonged endothelial activation with a consequent vascular damage and further inflammation (Deanfield, Halcox, & Rabelink, 2007). A meta-analysis on 15 studies reported a 0.90 (0.88 –0.92) pooled relative risk (RR) of cardiovascular events and all-cause mortality per 1% increase in brachial FMD (Xu et al., 2014).
Inflammation is also closely linked with glucose level (Mendall, Patel, Ballam, Strachan, & Northfield, 1996) and has been independently related to insulin sensitivity in healthy participants (free from diabetes) (Festa et al., 2000). Cytokine hypersecretion could lead to insulin resistance and potentially diabetes in genetically predisposed individuals. This review demonstrated a decrease in the FPG in parallel with that of hs-CRP. This finding suggests that the treatment of periodontitis, lowering the level of chronic inflammation could also have an impact on metabolic control potentially reducing the risk of developing diabetes and its complications. In line with the current evidence, the effect size of

the treatment of periodontitis and HbA1c from RCTs did not favour the intervention group. The presented meta-analysis only included trials with 6 months follow-up with the results clearly driven by the weight of 2 studies reporting conflicting results (D'Aiuto et al., 2018; Engebretson et al., 2013). Additionally, the only trial reporting 12 months follow up data in a population with type 2 diabetes shows a statistically significant and clinically relevant reduction of HbA1c at 1 year follow-up only. This could indicate the need of a sustained treatment regime and longer follow up to appreciate a long-term reduction in HbA1c in patients with type2 diabetes.

Pregnancy outcomes are the leading cause of death in children under five, accounting for approximately 16% of all deaths, and 35% of deaths among newborns (Blencowe et al., 2012). Consistent associations between periodontitis and preterm birth, low birthweight, and pre-eclampsia have been reported (Vivares-Builes, Rangel-Rincón, Botero, & Agudelo-Suárez, 2018). Furthermore, the treatment of periodontitis during pregnancy has been demonstrated to be safe, with important benefits for the oral and systemic health of the mother (Sanz & Kornman, 2013). Addressing PICOS question 3, this review demonstrated a reduced occurrence of preterm deliveries at <37 weeks but an unclear effect for any of the other pregnancy outcomes investigated.

The plausible mechanism may be a reduction of oral pathogens and associated systemic inflammation could translate into reducing/preventing perinatal and maternal outcomes (Offenbacher et al., 2006). However, inconsistent results have been previously reported. A recent Cochrane review found no evidence that the treatment of periodontitis reduced preterm birth but stated that it could reduce birth weight <2500g (RR=0.67) (Iheozor-Ejiofor, Middleton, Esposito, & Glenny, 2017). In contrast, Bi and co-workers concluded that the treatment of periodontitis during pregnancy was associated with significantly decreased risk of perinatal mortality (RR=0.53) and preterm birth (RR=0.78) and increased birth weight (mean difference of 200.79 gr) (Bi, Emami, Luo, Santamaria, & Wei, 2019).

In comparison with the above reviews, the current systematic review was based upon a more conservative methodology insofar only studies with a clear diagnosis of periodontitis were included and an intention to treat analysis was performed to calculate the risk ratios (including all the randomised participants enrolled in the studies). This may have had a dilution effect on the various outcome estimates, since all the participants lost to follow up were accounted for. Hence, periodontitis treatment during pregnancy could represent a valid intervention resulting in reduction in preterm birth alongside other reported intervention approaches such as cerclage, progesterone, low dose aspirin, lifestyle and behavioural changes (Matei, Saccone, Vogel, & Armson, 2019).

Nevertheless, although promising, these results should be interpreted with caution. The meta-analysis showed high heterogeneity, possibly explained by differences in populations, settings, broad spectrum of periodontitis diagnosis and pregnancy outcomes definitions, gestational age at the time of treatment provided plus different operators and modalities of treatment. Additionally, when sensitivity analysis was performed for those studies grouped at low/some concerns risk of bias the estimate of the effect lost statistical significance (but not the effect size). Hence, future interventional studies with clear definitions of periodontitis and pregnancy outcomes are warranted to further assess perinatal morbidity and mortality. Notwithstanding, given the high prevalence of periodontal diseases in pregnant women and the enormous benefits and safety of oral health promotion in pregnancy, this review supports the treatment of periodontitis to be considered in clinical guidelines as a routine intervention, not only for the management of periodontal diseases but also with a putative effect in reduction of preterm deliveries.

Results of this review should be considered within the context of a number of methodological challenges. First, to avoid missing relevant evidence relating to the three specific PICOS questions, the search strategy was designed to be broad and inclusive, which resulted in a very large number publications and outcomes identified. Nevertheless, data on patients' centred outcomes (quality of life, QoL) was retrieved only from the included studies (and rarely reported in these). It is acknowledged that some evidence/studies might have been missed. Further research in this area is warranted including publications with QoL as a primary outcome. Moreover, we advocate future RCTs on the treatment of periodontitis and systemic health to report on QoL outcomes.

In order to avoid possible errors in extracting, analysing or reporting the information obtained and assessment of risk of bias, the handling of the data was done in duplicate/triplicate and the PRISMA statement was followed for reporting (Liberati et al., 2009). It is acknowledged that bias may have been introduced when combining studies for quantitative synthesis or due to limiting the search to English language(Jüni, Holenstein, Sterne, Bartlett, & Egger, 2002). Nevertheless, a strength of this review was the attempt to implement the knowledge from the new classification of periodontal diseases. Meta-analyses were done by PICOS and outcome, regardless of the outcome being primary or secondary in the study of origin. An exploratory analysis combining the same outcomes from PICOS 1 (ie. otherwise systemically healthy) and PICOS 2 (with specific NCDs) was performed in order to assess generalisability of the data, but the reader should consider the limitation in performing such analysis which does not account for the biological differences according to each co-morbidity or of their treatment when assessing the impact of periodontitis and systemic health outcomes . Reporting

bias may have been introduced due to missing information in the included publications relevant to the review. Multiple attempts were made to retrieve missing data, however this was not possible in all cases. Included studies often presented different case definitions and the outcomes pertaining to solely Stage III or IV periodontitis (the intended focus of this review) were not commonly reported separately or in sub-analysis from other disease stages. Included studies were conducted prior to the classification of periodontitis as Stage III or IV, therefore case definitions differed from the pre-defined focus of this review. Hence, attempts to overcome this limitation were made by performing sensitivity analyses to explore the potential effect variability of results based upon disease severity, however these results should also be interpreted with caution.

In conclusion and notwithstanding the limitations of the present review based on the available clinical evidence based on randomised controlled trials with a minimum of 6-month follow-up, demonstrated that the treatment of periodontitis improves cardiometabolic risk, reduces systemic inflammation and the occurrence of preterm deliveries. Promotion of periodontal health could result in better systemic outcomes and could be valued as a novel non-pharmacological intervention for the management of NCDs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in regard to the present work. There were no external sources of funding to support conduct of this review.

AUTHOR CONTRIBUTIONS

Marco Orlandi, Eva Munoz-Aguilera, Jeanie Suvan and Francesco D'Aiuto contributed to the conception, design and the data collection; Deborah Maletta contributed to the development of the search strategies; Aviva Petrie and Marco Orlandi contributed to the statistical analysis; Marco Orlandi, Eva Muñoz-Aguilera, Jeanie Suvan and Francesco D'Aiuto contributed to interpretation of the

data and drafted and finalized the manuscript. All authors critically reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

Beck, J. D., Couper, D. J., Falkner, K. L., Graham, S. P., Grossi, S. G., Gunsolley, J. C., . . . et al. (2008). The Periodontitis and Vascular Events (PAVE) pilot study: adverse events. *Journal of periodontology, 79*(1), 90-96. doi:10.1902/jop.2008.070223

Bi, W. G., Emami, E., Luo, Z.-C., Santamaria, C., & Wei, S. Q. (2019). Effect of periodontal treatment in pregnancy on perinatal outcomes: a systematic review and meta-analysis. *The Journal of Maternal-Fetal & Neonatal Medicine*, 1-10. doi:10.1080/14767058.2019.1678142

Blencowe, H., Cousens, S., Oestergaard, M. Z., Chou, D., Moller, A.-B., Narwal, R., . . . Lawn, J. E. (2012). National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *The Lancet, 379*(9832), 2162-2172. doi:https://doi.org/10.1016/S0140-6736(12)60820-4

Borenstein M, H. V., Higgins J, Rothstein H,. (2009). *Introduction to Meta-Analysis* (Wiley Ed.).

Burska, A. N., Sakthiswary, R., & Sattar, N. (2015). Effects of Tumour Necrosis Factor Antagonists on Insulin Sensitivity/Resistance in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *PloS one, 10*(6), e0128889. doi:10.1371/journal.pone.0128889

Buset, S. L., Walter, C., Friedmann, A., Weiger, R., Borgnakke, W. S., & Zitzmann, N. U. (2016). Are periodontal diseases really silent? A systematic review of their effect on quality of life. *J Clin Periodontol., 43*(4), 333-344. doi: 310.1111/jcpe.12517. Epub 12016 Mar 12529.

Caneiro-Queija, L., Lopez-Carral, J., Martin-Lancharro, P., Limeres-Posse, J., Diz-Dios, P., & Blanco-Carrion, J. (2019). Non-Surgical Treatment of Periodontal Disease in a Pregnant Caucasian Women Population: Adverse Pregnancy Outcomes of a Randomized Clinical Trial. *International journal of environmental research and public health, 16*(19). doi:https://dx.doi.org/10.3390/ijerph16193638

Caula, A. L., Lira, R., Tinoco, E. M. B., & Fischer, R. G. (2014). The effect of periodontal therapy on cardiovascular risk markers: a 6-month randomized clinical trial. *Journal of Clinical Periodontology, 41*(9), 875-882. doi:10.1111/jcpe.12290

Chapple, I. L., & Genco, R. (2013). Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol, 84*(4 Suppl), S106-112. doi:10.1902/jop.2013.1340011

Chen, L., Chen, R., Wang, H., & Liang, F. (2015). Mechanisms Linking Inflammation to Insulin Resistance. *Int J Endocrinol, 2015*, 508409. doi:10.1155/2015/508409

Choi, S. E., Sima, C., & Pandya, A. (2020). Impact of Treating Oral Disease on Preventing Vascular Diseases: A Model-Based Cost-effectiveness Analysis of Periodontal Treatment Among Patients With Type 2 Diabetes. *Diabetes Care, 43*(3), 563-571. doi:10.2337/dc19-1201

Chou, R. C., Kane, M., Ghimire, S., Gautam, S., & Gui, J. (2016). Treatment for Rheumatoid Arthritis and Risk of Alzheimer's Disease: A Nested Case-Control Analysis. *CNS Drugs, 30*(11), 1111-1120. doi:10.1007/s40263-016-0374-z

D'Aiuto, F., Gkranias, N., Bhowruth, D., Khan, T., Orlandi, M., Suvan, J., . . . Group, T. (2018). Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. *The lancet. Diabetes & endocrinology, 6*(12), 954-965. doi:https://dx.doi.org/10.1016/S2213-8587(18)30038-X

D'Aiuto, F., Orlandi, M., & Gunsolley, J. C. (2013). Evidence that periodontal treatment improves biomarkers and CVD outcomes. *J Periodontol, 84*(4 Suppl), S85-s105. doi:10.1902/jop.2013.134007

Deanfield, J. E., Halcox, J. P., & Rabelink, T. J. (2007). Endothelial function and dysfunction: testing and clinical relevance. *Circulation, 115*(10), 1285-1295. doi:10.1161/circulationaha.106.652859

Deepti, Tewari, S., Narula, S. C., Singhal, S. R., & Sharma, R. K. (2017). Effect of Non-Surgical Periodontal Therapy Along With Myo-Inositol on High-Sensitivity C-Reactive Protein and Insulin Resistance in Women With Polycystic Ovary Syndrome and Chronic Periodontitis: A Randomized Controlled Trial. *Journal of periodontology, 88*(10), 999-1011. doi:https://dx.doi.org/10.1902/jop.2017.170121

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Control Clin Trials, 7*(3), 177-188. doi:10.1016/0197-2456(86)90046-2

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ., 315*(7109), 629-634. doi: 610.1136/bmj.1315.7109.1629.

Engebretson, S. P., Hyman, L. G., Michalowicz, B. S., Schoenfeld, E. R., Gelato, M. C., Hou, W., . . . et al. (2013). The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. *JAMA, 310*(23), 2523-2532. doi:10.1001/jama.2013.282431

Fang, F., Wu, B., Qu, Q., Gao, J., Yan, W., Huang, X., . . . et al. (2015). The clinical response and systemic effects of non-surgical periodontal therapy in end-stage renal disease patients: a 6-month randomized controlled clinical trial. *Journal of clinical periodontology, 42*(6), 537-546. doi:10.1111/jcpe.12411

Festa, A., D'Agostino, R., Jr., Howard, G., Mykkänen, L., Tracy, R. P., & Haffner, S. M. (2000). Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation, 102*(1), 42-47. doi:10.1161/01.cir.102.1.42

Freitas, C. O., Gomes-Filho, I. S., Naves, R. C., Nogueira Filho Gda, R., Cruz, S. S., Santos, C. A., . . . Barbosa, M. D. (2012). Influence of periodontal therapy on C-reactive protein level: a systematic review and meta-analysis. *J Appl Oral Sci, 20*(1), 1-8. doi:10.1590/s1678-77572012000100002

Fu, Y. W., Li, X. X., Xu, H. Z., Gong, Y. Q., & Yang, Y. (2016). Effects of periodontal therapy on serum lipid profile and proinflammatory cytokines in patients with hyperlipidemia: a randomized controlled trial. *Clinical oral investigations, 20*(6), 1263-1269. doi:http://dx.doi.org/10.1007/s00784-015-1621-2

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., . . . Slavich, G. M. (2019). Chronic inflammation in the etiology of disease across the life span. *Nat Med, 25*(12), 1822-1832. doi:10.1038/s41591-019-0675-0

GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet, 396*(10258), 1204-1222. doi:10.1016/s0140-6736(20)30925-9

Geisinger, M. L., Michalowicz, B. S., Hou, W., Schoenfeld, E., Gelato, M., Engebretson, S. P., . . . Hyman, L. (2016). Systemic Inflammatory Biomarkers and Their Association With Periodontal and Diabetes-Related Factors in the Diabetes and Periodontal Therapy Trial, A Randomized Controlled Trial. *Journal of periodontology, 87*(8), 900-913. doi:https://dx.doi.org/10.1902/jop.2016.150727

Genco, R. J., & Sanz, M. (2020). Clinical and public health implications of periodontal and systemic diseases: An overview. *Periodontol 2000, 83*(1), 7-13. doi:10.1111/prd.12344

Grubbs, V., Garcia, F., Vittinghoff, E., Jue, B. L., Ryder, M., Lovett, D. H., . . . Powe, N. R. (2020). Nonsurgical Periodontal Therapy in CKD: Findings of the Kidney and Periodontal Disease (KAPD) Pilot Randomized Controlled Trial. *Kidney Medicine, 2*(1), 49-58. doi:http://dx.doi.org/10.1016/j.xkme.2019.09.005

Hada, D. S., Garg, S., Ramteke, G. B., & Ratre, M. S. (2015). Effect of Non-Surgical Periodontal Treatment on Clinical and Biochemical Risk Markers of Cardiovascular

Disease: A Randomized Trial. *Journal of periodontology, 86*(11), 1201-1211. doi:https://dx.doi.org/10.1902/jop.2015.150249

Higashi, Y., Goto, C., Hidaka, T., Soga, J., Nakamura, S., Fujii, Y., . . . Taguchi, A. (2009). Oral infection-inflammatory pathway, periodontitis, is a risk factor for endothelial dysfunction in patients with coronary artery disease. *Atherosclerosis, 206*(2), 604-610. doi:https://dx.doi.org/10.1016/j.atherosclerosis.2009.03.037

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557-560. doi:10.1136/bmj.327.7414.557

Hobdell, M., Petersen, P. E., Clarkson, J., & Johnson, N. (2003). Global goals for oral health 2020. *Int Dent J., 53*(5), 285-288. doi: 210.1111/j.1875-1595x.2003.tb00761.x.

Iheozor-Ejiofor, Z., Middleton, P., Esposito, M., & Glenny, A. M. (2017). Treating periodontal disease for preventing adverse birth outcomes in pregnant women. *Cochrane Database Syst Rev, 6*(6), Cd005297. doi:10.1002/14651858.CD005297.pub3

Ioannidou, E., Malekzadeh, T., & Dongari-Bagtzoglou, A. (2006). Effect of periodontal treatment on serum C-reactive protein levels: a systematic review and meta-analysis. *J Periodontol, 77*(10), 1635-1642. doi:10.1902/jop.2006.050443

Jeffcoat, M., Parry, S., Sammel, M., Clothier, B., Catlin, A., & Macones, G. (2011). Periodontal infection and preterm birth: successful periodontal therapy reduces the risk of preterm birth. *BJOG : an international journal of obstetrics and gynaecology, 118*(2), 250-256. doi:https://dx.doi.org/10.1111/j.1471-0528.2010.02713.x

Jeffcoat, M. K., Hauth, J. C., Geurs, N. C., Reddy, M. S., Cliver, S. P., Hodgkins, P. M., & Goldenberg, R. L. (2003). Periodontal disease and preterm birth: results of a pilot intervention study. *Journal of periodontology, 74*(8), 1214-1218.

Johnson, C. L., Paulose-Ram, R., Ogden, C. L., Carroll, M. D., Kruszon-Moran, D., Dohrmann, S. M., & Curtin, L. R. (2013). National health and nutrition examination survey: analytic guidelines, 1999-2010. *Vital Health Stat 2*(161), 1-24.

Jüni, P., Holenstein, F., Sterne, J., Bartlett, C., & Egger, M. (2002). Direction and impact of language bias in meta-analyses of controlled trials: empirical study. *Int J Epidemiol, 31*(1), 115-123. doi:10.1093/ije/31.1.115

Kapellas, K., Maple-Brown, L. J., Jamieson, L. M., Do, L. G., O'Dea, K., Brown, A., . . . et al. (2014). Effect of periodontal therapy on arterial structure and function among aboriginal australians: a randomized, controlled trial. *Hypertension (dallas, tex. : 1979), 64*(4), 702-708. doi:10.1161/HYPERTENSIONAHA.114.03359

Kassebaum, N. J., Bernabé, E., Dahiya, M., Bhandari, B., Murray, C. J., & Marcenes, W. (2014). Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. *J Dent Res, 93*(11), 1045-1053. doi:10.1177/0022034514552491

Kassebaum, N. J., Smith, A. G. C., Bernabé, E., Fleming, T. D., Reynolds, A. E., Vos, T., . . . Marcenes, W. (2017). Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990-2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. *J Dent Res, 96*(4), 380-387. doi:10.1177/0022034517693566

Katagiri, S., Nitta, H., Nagasawa, T., Uchimura, I., Izumiyama, H., Inagaki, K., . . . Izumi, Y. (2009). Multi-center intervention study on glycohemoglobin (HbA1c) and serum, high-sensitivity CRP (hs-CRP) after local anti-infectious periodontal treatment in type 2 diabetic patients with periodontal disease. *Diabetes research and clinical practice, 83*(3), 308-315. doi:https://dx.doi.org/10.1016/j.diabres.2008.10.016

Kaur, P. K., Narula, S. C., Rajput, R., K Sharma, R., & Tewari, S. (2015). Periodontal and glycemic effects of nonsurgical periodontal therapy in patients with type 2 diabetes stratified by baseline HbA1c. *Journal of oral science, 57*(3), 201-211. doi:https://dx.doi.org/10.2334/josnusd.57.201

Khairnar, M. S., Pawar, B. R., Marawar, P. P., & Khairnar, D. M. (2015). Estimation of changes in C-reactive protein level and pregnancy outcome after nonsurgical supportive periodontal therapy in women affected with periodontitis in a rural set up

of India. *Contemporary clinical dentistry, 6*(Suppl 1), S5-S11. doi:https://dx.doi.org/10.4103/0976-237X.152930

Koromantzos, P. A., Makrilakis, K., Dereka, X., Katsilambros, N., Vrotsos, I. A., & Madianos, P. N. (2011). A randomized, controlled trial on the effect of non-surgical periodontal therapy in patients with type 2 diabetes. Part I: effect on periodontal status and glycaemic control. *Journal of clinical periodontology, 38*(2), 142-147. doi:https://dx.doi.org/10.1111/j.1600-051X.2010.01652.x

Koromantzos, P. A., Makrilakis, K., Dereka, X., Offenbacher, S., Katsilambros, N., Vrotsos, I. A., & Madianos, P. N. (2012). Effect of non-surgical periodontal therapy on C-reactive protein, oxidative stress, and matrix metalloproteinase (MMP)-9 and MMP-2 levels in patients with type 2 diabetes: a randomized controlled study. *Journal of periodontology, 83*(1), 3-10. doi:https://dx.doi.org/10.1902/jop.2011.110148

Li, Y., Zhong, X., Cheng, G., Zhao, C., Zhang, L., Hong, Y., . . . Wang, Z. (2017). Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. *Atherosclerosis, 259*, 75-82. doi:10.1016/j.atherosclerosis.2017.02.003

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., . . . Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ, 339*, b2700. doi:10.1136/bmj.b2700

Lobo, M. G., Schmidt, M. M., Lopes, R. D., Dipp, T., Feijo, I. P., Schmidt, K. E. S., . . . Quadros, A. S. (2020). Treating periodontal disease in patients with myocardial infarction: A randomized clinical trial. *European journal of internal medicine, 71*, 76-80. doi:https://dx.doi.org/10.1016/j.ejim.2019.08.012

Lopez, N. J., Quintero, A., Casanova, P. A., Ibieta, C. I., Baelum, V., & Lopez, R. (2012). Effects of periodontal therapy on systemic markers of inflammation in patients with metabolic syndrome: a controlled clinical trial. *Journal of periodontology, 83*(3), 267-278. doi:https://dx.doi.org/10.1902/jop.2011.110227

López, N. J., Smith, P. C., & Gutierrez, J. (2002). Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. *Journal of periodontology, 73*(8), 911-924. doi:10.1902/jop.2002.73.8.911

Macones, G. A., Parry, S., Nelson, D. B., Strauss, J. F., Ludmir, J., Cohen, A. W., . . . et al. (2010). Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: results from the Periodontal Infections and Prematurity Study (PIPS). *American journal of obstetrics and gynecology, 202*(2), 147.e141-148. doi:10.1016/j.ajog.2009.10.892

Masi, S., Orlandi, M., Parkar, M., Bhowruth, D., Kingston, I., O'Rourke, C., . . . et al. (2018). Mitochondrial oxidative stress, endothelial function and metabolic control in patients with type II diabetes and periodontitis: a randomised controlled clinical trial. *International journal of cardiology, 271*, 263-268. doi:10.1016/j.ijcard.2018.05.019

Matei, A., Saccone, G., Vogel, J. P., & Armson, A. B. (2019). Primary and secondary prevention of preterm birth: a review of systematic reviews and ongoing randomized controlled trials. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 236*, 224-239. doi:https://doi.org/10.1016/j.ejogrb.2018.12.022

Mauri-Obradors, E., Merlos, A., Estrugo-Devesa, A., Jane-Salas, E., Lopez-Lopez, J., & Vinas, M. (2018). Benefits of non-surgical periodontal treatment in patients with type 2 diabetes mellitus and chronic periodontitis: A randomized controlled trial. *Journal of clinical periodontology, 45*(3), 345-353. doi:https://dx.doi.org/10.1111/jcpe.12858

Mendall, M. A., Patel, P., Ballam, L., Strachan, D., & Northfield, T. C. (1996). C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *BMJ, 312*(7038), 1061-1065. doi:10.1136/bmj.312.7038.1061

Michalowicz, B. S., Hodges, J. S., DiAngelis, A. J., Lupo, V. R., Novak, M. J., Ferguson, J. E., . . . Tschida, P. A. (2006). Treatment of periodontal disease and the risk of preterm birth. *New England Journal of Medicine, 355*(18), 1885-1894.

Mizuno, H., Ekuni, D., Maruyama, T., Kataoka, K., Yoneda, T., Fukuhara, D., . . . Morita, M. (2017). The effects of non-surgical periodontal treatment on glycemic control,

oxidative stress balance and quality of life in patients with type 2 diabetes: A randomized clinical trial. *PloS one, 12*(11), e0188171. doi:https://dx.doi.org/10.1371/journal.pone.0188171

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med, 6*(7), e1000097. doi:10.1371/journal.pmed.1000097

Monsarrat, P., Blaizot, A., Kémoun, P., Ravaud, P., Nabet, C., Sixou, M., & Vergnes, J. N. (2016). Clinical research activity in periodontal medicine: a systematic mapping of trial registers. *J Clin Periodontol, 43*(5), 390-400. doi:10.1111/jcpe.12534

Newnham, J. P., Newnham, I. A., Ball, C. M., Wright, M., Pennell, C. E., Swain, J., & Doherty, D. A. (2009). Treatment of periodontal disease during pregnancy: a randomized controlled trial. *Obstetrics and gynecology, 114*(6), 1239-1248. doi:https://dx.doi.org/10.1097/AOG.0b013e3181c15b40

Offenbacher, S., Beck, J. D., Jared, H. L., Mauriello, S. M., Mendoza, L. C., Couper, D. J., . . . et al. (2009). Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. *Obstetrics and gynecology, 114*(3), 551-559. doi:10.1097/AOG.0b013e3181b1341f

Offenbacher, S., Beck, J. D., Moss, K., Mendoza, L., Paquette, D. W., Barrow, D. A., . . . et al. (2009). Results from the Periodontitis and Vascular Events (PAVE) Study: a pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. *Journal of periodontology, 80*(2), 190-201. doi:10.1902/jop.2009.080007

Offenbacher, S., Lin, D. M., Strauss, R., McKaig, R., Irving, J., Barros, S. P., . . . Beck, J. D. (2006). Effects of periodontal therapy during pregnancy on periodontal status, biologic parameters, and pregnancy outcomes: A pilot study. *Journal of Periodontology, 77*(12), 2011-2024. doi:10.1902/jop.2006.060047

Oliveira, A. M. S. D., de Oliveira, P. A. D., Cota, L. O. M., Magalhaes, C. S., Moreira, A. N., & Costa, F. O. (2011). Periodontal therapy and risk for adverse pregnancy outcomes. *Clinical oral investigations, 15*(5), 609-615. doi:https://dx.doi.org/10.1007/s00784-010-0424-8

Paraskevas, S., Huizinga, J. D., & Loos, B. G. (2008). A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. *J Clin Periodontol, 35*(4), 277-290. doi:10.1111/j.1600-051X.2007.01173.x

Pinho, N., Oliveira, R. D., Novaes, A. B., & Voltarelli, J. C. (2009). Relationship between periodontitis and rheumatoid arthritis and the effect of non-surgical periodontal treatment. *Brazilian dental journal, 20*(5), 355-364. doi:10.1590/s0103-64402009000500001

Pirie, M., Linden, G., & Irwin, C. (2013). Intrapregnancy non-surgical periodontal treatment and pregnancy outcome: a randomized controlled trial. *Journal of periodontology, 84*(10), 1391-1400. doi:https://dx.doi.org/10.1902/jop.2012.120572

Radnai, M., Pál, A., Novák, T., Urbán, E., Eller, J., & Gorzó, I. (2009). Benefits of periodontal therapy when preterm birth threatens. *Journal of dental research, 88*(3), 280-284. doi:10.1177/0022034508330229

Reddy, B. V., Tanneeru, S., & Chava, V. K. (2014). The effect of phase-I periodontal therapy on pregnancy outcome in chronic periodontitis patients. *Journal of obstetrics and gynaecology, 34*(1), 29-32. doi:10.3109/01443615.2013.829029

Ridker, P. M., Everett, B. M., Thuren, T., MacFadyen, J. G., Chang, W. H., Ballantyne, C., . . . Glynn, R. J. (2017). Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med, 377*(12), 1119-1131. doi:10.1056/NEJMoa1707914

Sadatmansouri, S., Sedighpoor, N., & Aghaloo, M. (2006). Effects of periodontal treatment phase I on birth term and birth weight. *Journal of the Indian Society of Pedodontics and Preventive Dentistry, 24*(1), 23-26.

Sanz, M., & Kornman, K. (2013). Periodontitis and adverse pregnancy outcomes: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol, 84*(4 Suppl), S164-169. doi:10.1902/jop.2013.1340016

Schnabel, R. B., Yin, X., Larson, M. G., Yamamoto, J. F., Fontes, J. D., Kathiresan, S., . . . Benjamin, E. J. (2013). Multiple inflammatory biomarkers in relation to cardiovascular events and mortality in the community. *Arterioscler Thromb Vasc Biol, 33*(7), 1728-1733. doi:10.1161/atvbaha.112.301174

Singh-Manoux, A., Shipley, M. J., Bell, J. A., Canonico, M., Elbaz, A., & Kivimäki, M. (2017). Association between inflammatory biomarkers and all-cause, cardiovascular and cancer-related mortality. *Cmaj, 189*(10), E384-e390. doi:10.1503/cmaj.160313

Smits, K. P. J., Listl, S., Plachokova, A. S., Van der Galien, O., & Kalmus, O. (2020). Effect of periodontal treatment on diabetes-related healthcare costs: a retrospective study. *BMJ open diabetes research & care, 8*(1). doi:10.1136/bmjdrc-2020-001666

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., . . . Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ, 366*, l4898. doi:10.1136/bmj.l4898

Tarannum, F., & Faizuddin, M. (2007). Effect of periodontal therapy on pregnancy outcome in women affected by periodontitis. *Journal of periodontology, 78*(11), 2095-2103.

Tonetti, M. S., D'Aiuto, F., Nibali, L., Donald, A., Storry, C., Parkar, M., . . . Deanfield, J. (2007). Treatment of periodontitis and endothelial function. *New England Journal of Medicine, 356*(9), 911-920.

Tonetti, M. S., & Van Dyke, T. E. (2013). Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol, 84*(4 Suppl), S24-29. doi:10.1902/jop.2013.1340019

United Nations. (2011). Political Declaration of the High-Level Meeting of the General Assembly on the Prevention and Control of Non-Communicable Diseases. Retrieved from https://digitallibrary.un.org/record/710899#record-files-collapse-header

Van Dyke, T. E., Bartold, P. M., & Reynolds, E. C. (2020). The Nexus Between Periodontal Inflammation and Dysbiosis. *Frontiers in immunology, 11*, 511-511. doi:10.3389/fimmu.2020.00511

Vivares-Builes, A. M., Rangel-Rincón, L. J., Botero, J. E., & Agudelo-Suárez, A. A. (2018). Gaps in Knowledge About the Association Between Maternal Periodontitis and Adverse Obstetric Outcomes: An Umbrella Review. *Journal of Evidence Based Dental Practice, 18*(1), 1-27. doi:https://doi.org/10.1016/j.jebdp.2017.07.006

Wang, Y., Liu, H. N., Zhen, Z., Pelekos, G., Wu, M. Z., Chen, Y., . . . Jin, L. (2020). A randomized controlled trial of the effects of non-surgical periodontal therapy on cardiac function assessed by echocardiography in type 2 diabetic patients. *Journal of Clinical Periodontology, 47*(6), 726-736.

Wang, Y., Liu, H. N., Zhen, Z., Yiu, K. H., Tse, H. F., Pelekos, G., . . . Jin, L. (2017). Periodontal treatment modulates gene expression of endothelial progenitor cells in diabetic patients. *Journal of clinical periodontology, 44*(12), 1253-1263. doi:https://dx.doi.org/10.1111/jcpe.12806

Wehmeyer, M. M., Kshirsagar, A. V., Barros, S. P., Beck, J. D., Moss, K. L., Preisser, J. S., & Offenbacher, S. (2013). A randomized controlled trial of intensive periodontal therapy on metabolic and inflammatory markers in patients With ESRD: results of an exploratory study. *American journal of kidney diseases, 61*(3), 450-458. doi:10.1053/j.ajkd.2012.10.021

Wensley, F., Gao, P., Burgess, S., Kaptoge, S., Di Angelantonio, E., Shah, T., . . . Danesh, J. (2011). Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data. *BMJ, 342*, d548. doi:10.1136/bmj.d548

WHO. (2016). World health statistics 2016: monitoring health for the SDGs sustainable development goals: World Health Organization. Retrieved from https://www.who.int/gho/publications/world_health_statistics/2016/EN_WHS2016_TOC.pdf

WHO. (2021). Noncommunicable diseases -Key facts. Retrieved from https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

Wu, Y., Chen, L., Wei, B., Luo, K., & Yan, F. H. (2015). Effect of Non-Surgical Periodontal Treatment on Visfatin Concentrations in Serum and Gingival Crevicular Fluid of Patients With Chronic Periodontitis and Type 2 Diabetes Mellitus. *Journal of Periodontology, 86*(6), 795-800. doi:10.1902/jop.2015.140476

Xu, Y., Arora, R. C., Hiebert, B. M., Lerner, B., Szwajcer, A., McDonald, K., . . . Tangri, N. (2014). Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging, 15*(7), 736-746. doi:10.1093/ehjci/jet256

Zhang, H. H., Li, C. Z., Shang, S. H., & Luo, Z. X. (2013). Scaling and root planing with enhanced root planing on healthcare for type 2 diabetes mellitus: A randomized controlled clinical trial. *Journal of Dental Sciences, 8*(3), 272-280. doi:10.1016/j.jds.2012.10.009

Zhou, Q. B., Xia, W. H., Ren, J., Yu, B. B., Tong, X. Z., Chen, Y. B., . . . et al. (2017). Effect of Intensive Periodontal Therapy on Blood Pressure and Endothelial Microparticles in Patients With Prehypertension and Periodontitis: a Randomized Controlled Trial. *Journal of periodontology, 88*(8), 711-722. doi:10.1902/jop.2017.160447

Zhou, X., Han, J., Liu, Z., Song, Y., Wang, Z., & Sun, Z. (2014). Effects of periodontal treatment on lung function and exacerbation frequency in patients with chronic obstructive pulmonary disease and chronic periodontitis: a 2-year pilot randomized controlled trial. *Journal of clinical periodontology, 41*(6), 564-572. doi:https://dx.doi.org/10.1111/jcpe.12247

Table 1. PICOS Criteria

P	Population	patients with severe periodontitis (stages III or IV or equivalent) in good general health or with a noncommunicable disease or with pregnancy
I	Intervention	professionally rendered periodontal therapy comprising supra and subgingival nonsurgical or surgical procedures with or without adjunctive therapies
C	Comparison	no treatment, professionally rendered supragingival therapy, patient performed oral hygiene alone, or placebo treatment
O	Outcome	systemic biomarkers or outcomes indicative of systemic health according to the disease condition, and quality of life
S	Study Design	randomised controlled trials with a minimum of 6 months follow-up with the exception of pregnancy outcomes (shorter follow-up)

Table 2. PICOS 1 (Healthy Participants) Meta-analysis Results

Outcome	No. Studies	Total N	Effect Estimate 6M SMD	P value	I^2	P value Heterogeneity
hs-CRP	2	227	-0.51 (-1.38, 0.37)	p = 0.256	90.20%	p = 0.001
IL-6	3	336	-0.56 (-1.41, 0.30)	p = 0.201	92.80%	p < 0.001
Total cholesterol	2	216	-0.15 (-0.43, 0.12)	p = 0.269	0.00%	p = 0.927
HDL cholesterol	2	216	-0.72 (-2.34, 0.90)	p = 0.383	96.80%	p < 0.001
LDL cholesterol	2	216	-0.22 (-0.49, 0.05)	p = 0.109	0.00%	p = 0.799
Triglycerides	2	216	-0.41 (-1.33, 0.52)	p = 0.393	91.20%	p = 0.001
SBP	2	225	-1.14 (-3.36, 1.07)	p = 0.311	98.10%	p < 0.001
DBP	2	225	-0.69 (-2.13, 0.75)	p = 0.346	96.20%	p < 0.001

hs-CRP, High-sensitivity C-reactive Protein; IL-6, Interleukin-6; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; 6M, 6 Months; I^2, I^2 index; SMD, standardized mean difference.

Table 3. PICOS 2 (Participants with NCDs) Meta-analysis Results

Outcome	No. Studies	Total N	Effect Estimate 6M SMD	P value	I^2	P value Heterogeneity
hs-CRP	15	1210	-0.56 (-0.88, -0.25)	**p < 0.001**	82.60%	**p < 0.001**
TNF-α	3	424	-0.12 (-0.31, 0.07)	p = 0.231	0.00%	p = 0.969
IL-6	5	490	-0.43 (-0.90, 0.05)	p = 0.078	82.00%	p < 0.001
ESR	2	94	-1.18 (-2.40, 0.04)	p = 0.058	85.40%	p = 0.009
HbA1c	11	1278	-0.03 (-0.14, 0.08)	p = 0.580	0.%	p = 0.510
FPG	6	640	-1.33 (-2.41, -0.24)	**p = 0.016**	96.80%	**p < 0.001**
TC	8	700	-0.11 (-0.29, 0.08)	p = 0.250	28.60%	p = 0.200
HDL cholesterol	19	737	0.05 (-0.36, 0.47)	p = 0.806	86.10%	p < 0.001
LDL cholesterol	9	737	0.06 (-0.10, 0.22)	p = 0.445	10.60%	p = 0.347
TG	9	737	-0.00 (-0.18, 0.17)	p = 0.968	26.20%	p = 0.211
VLDL	2	106	-0.01 (-0.85, 0.86)	p = 0.988	79.50%	p = 0.027
FMD	2	312	0.31 (0.07, 0.55)	**p = 0.012**	2.90%	p = 0.310
BMI	5	476	-0.09 (-0.27, 0.09)	p = 0.334	0%.	p = 0.746
SBP	4	405	0.02 (-0.17, 0.22)	p = 0.826	0%	p = 0.935
DBP	4	405	0.29 (0.10, 0.49)	**p = 0.003**	0%	p = 0.537
Pulse	2	103	0.14 (-0.53, 0.82)	p = 0.680	66.4%	p = 0.085
sCR	3	378	-0.13 (-0.50, 0.76)	p = 0.675	85.6%	p = 0.001
Albumin	2	140	1.35 (-0.22, 2.92)	p = 0.092	92.50%	p < 0.001

hs-CRP, High-sensitivity C-reactive Protein; TNF-α, Tumour Necrosis Factor-α; IL-6, Interleukin-6; ESR, Erythrocyte Sedimentation Rate; HbA1c, Glycohemoglobin A1c; FPG, Fasting Plasma Glucose; TC, Total Cholesterol; HDL, High-Density

Lipoprotein; LDL, Low-Density Lipoprotein; TG, Triglycerides; VLDL, Very Low Density Lipoprotein; FMD, Flow mediated dilation; BMI, Body Max Index, SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure, Serum Creatinine; 6M, 6 Months; I^2, I^2 index; SMD, standardized mean difference.

Table 4. PICO 1 & 2 Combined (participants with and without NCDs) Meta-analysis Results

Outcome	No. Studies	Total N	Effect Estimate 6M SMD	P value	I^2	P value Heterogeneity
hs-CRP	16	1437	-0.55 (-0.84, -0.27)	**p < 0.001**	82.40%	**p < 0.001**
TNF-α	5	671	-0.27 (-0.58, 0.05)	p = 0.093	66.30%	p = 0.031
IL-6	9	992	-0.48 (-0.88, -0.08)	**p = 0.020**	86.50%	**p < 0.001**
FPG	7	760	-1.09 (-1.96, -0.21)	**p = 0.015**	96.20%	**p < 0.001**
TC	11	974	-0.11 (-0.25, 0.04)	p = 0.143	10.30%	p = 0.347
HDL cholesterol	12	1010	-0.09 (-0.55, 0.36)	p = 0.681	91.10%	p < 0.001
LDL cholesterol	11	1010	-0.00 (-0.15, 0.14)	p = 0.988	17.80%	p = 0.275
TG	11	1010	-0.10 (-0.32, 0.12)	p = 0.388	63.80%	p = 0.002
FMD	3	432	0.39 (0.14, 0.63)	**p = 0.002**	26.30%	p = 0.258
BMI	6	588	-0.09 (0.25, 0.070)	p = 0.287	0%	p= 0.856
SBP	6	672	-0.35 (-1.02, 0.32)	p =0.30	93.4%	p = 0.000
DBP	6	672	-0.06 (-0.62, 0.49)	p = 0.822	90.8%	p =0.000

hs-CRP, High-sensitivity C-reactive Protein; TNF-α, Tumour Necrosis Factor-α; IL-6, Interleukin-6; HDL, FPG, Fasting Plasma Glucose; TC, Total Cholesterol; High-Density Lipoprotein; LDL, Low-Density Lipoprotein; TG, Triglycerides; FMD, Flow mediated dilation; BMI, Body Max Index, SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; 6M, 6 Months; I^2, I^2 index; SMD, standardized mean difference.

Table 5. PICO 3 (Pregnancy Outcomes) Meta-analysis Results

Outcome	No. Studies	Total N	Effect Estimate RR/SMD*	P value	I^2	P value Heterogeneity
Preterm birth <37 weeks	14	5975	0.77 (0.60, 0.98)	**p = 0.036**	67.1%	**p < 0.001**
Preterm birth <35 weeks	4	3197	0.89 (0.74, 1.07)	p = 0.201	0.0%	p = 0.425
Preterm birth <32 weeks	2	2629	0.83 (0.41, 1.67)	p = 0.602	55.3%	p = 0.135
Low birth weight <2500	11	4573	0.77 (0.57, 1.02)	p = 0.064	57.2%	p = 0.009
Low birth weight <1500	3	3385	1.02 (0.52, 2.00)	p = 0.148	47.6%	p = 0.148
Preterm low birth weight	3	729	0.39 (0.12, 1.28)	p = 0.119	82.1%	p = 0.004
Pre-eclampsia	4	4111	1.00 (0.77, 1.31)	p = 0.988	6.4%	p = 0.361
Small for gestational age	2	2629	0.90 (0.71, 1.13)	p = 0353	15.1%	p = 0.278
Stillbirth	6	4812	0.64 (0.36, 1.14)	p = 0.131	0.0%	p = 0.500
Perinatal loss	8	5412	0.85 (0.55, 1.32)	p = 0.475	14.1%	p = 0.319
Gestational age at delivery	3	399	0.35 (-0.23, 0.93)*	p = 0.241	15.1%	p = 0.278
CRP (baseline)	2	167	-0.04 (-0.35, 0.27)*	p = 0.790	4.6%	p = 0.306
CRP (post-partum)	2	153	-0.61 (-1.84, 0.61)*	p = 0.327	92.1%	p < 0.001
Birthweight	6	1592	0.14 (-0.17, 0.45)*	p = 0.371	81.6%	p < 0.001

SMD*, Standardized Mean Difference; CRP, C-reactive Protein; I^2, I^2 index; RR, Risk Ratio.

Figure 1. Search results PRISMA flow-chart