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REVIEW

Periodontitis is associated with hypertension: a systematic review and meta-analysis

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Abstract

Recent evidence suggests a link between periodontitis (PD) and hypertension, but the nature of this association remains unclear. The overall aim of this review was to critically appraise the evidence linking these two common disorders. Systematic search was conducted for studies published up to December 2018. Prevalence of hypertension in patients with PD (moderate/severe groups) vs. those without PD (non-PD) was the primary outcome. Additional outcomes included adjusted mean difference in systolic (SBP) and diastolic (DBP) blood pressure (BP) levels in PD vs. non-PD, assessment of biomarkers in PD and hypertension, and BP changes after periodontal therapy. From 81 studies selected, 40 were included in quantitative meta-analyses. Diagnoses of moderate-severe PD [odds ratio (OR) = 1.22; 95% confidence interval (CI): 1.10–1.35] and severe PD (OR = 1.49; 95% CI: 1.09–2.05) were associated with hypertension. Prospective studies confirmed PD diagnosis increased likelihood of hypertension occurrence (OR = 1.68; 95% CI: 0.85–3.35). Patients with PD exhibited higher mean SBP [weighted mean difference (WMD) of 4.49 mmHg; 95% CI: 2.88–6.11] and DBP (2.03 mmHg; 95% CI: 1.25–2.81) when compared with non-PD. Lastly, only 5 out of 12 interventional studies confirmed a reduction in BP following periodontal therapy, ranging from 3 to 12.5 mmHg of SBP and from 0 to 10 mmHg of DBP. PD is associated with increased odds of hypertension (SORT C) and higher SBP/DBP levels. The evidence suggesting that PD therapy could reduce BP is inconclusive. Although additional research is warranted on this association, these results suggest that oral health assessment and management of PD could not only improve oral/overall health and quality of life but also be of relevance in the management of patients with hypertension.

Keyword Hypertension • Periodontitis • Blood pressure • Inflammation • Periodontal diseases • Oral health • Periodontal therapy

1. Introduction

Hypertension, defined as values ≥140 mmHg systolic blood pressure (SBP) and/or ≥90 mmHg diastolic blood pressure (DBP), is the most prevalent of all cardiovascular diseases (CVDs).[1] Almost 45% of the worldwide population is affected and the estimate increases steeping with age.[2] The incidence of adverse cardiovascular (CV) events such as stroke, myocardial infarction, sudden death, heart failure, and peripheral artery disease as well as of end-stage renal disease is strongly associated with hypertension.[3,4] According to the World Health Organization (WHO) report in 2014, hypertension accounts for 51% of deaths from stroke and 45% of overall CV mortality and this is true at all ages and in all ethnic groups.[2] Blood pressure values are an important predictor of cardiovascular risk.[5,6] Despite available treatments, essential hypertension remains poorly controlled with high rates of no treatment and under-treatment.[7] Hence, it is still one of the major modifiable risk factor for CVDs that requires urgent management.[8] Hypertension is a complex multifactorial disease with no simple mechanism entirely explaining the blood pressure rise.[9] Endothelial dysfunction (as manifested by changes in endothelin and nitric oxide), oxidative stress, and inflammation are

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implicated in the development of hypertension. Despite a prominent role of the immune system being observed in experimental models[10] and clinical studies[11] studying the onset of hypertension, the exact mechanisms initiating these responses remain unclear.[12]

Periodontitis is a chronic multifactorial inflammatory disease caused by a dysbiotic microflora and resulting in progressive destruction of the dental surrounding tissues and leading to tooth loss. It is associated with masticatory dysfunction and negative impact on the patient's quality of life.[13] It is estimated that periodontitis affects over 50% of the worldwide population and its severe form is considered the 6th most prevalent disease of humankind.[14,15] Periodontitis is a major public health problem that considerably increases morbidity and costs of oral healthcare.[16,17] There is consistent observational evidence that periodontitis is associated with an increased risk for future CVDs independent of traditional risk factors such as smoking and obesity.[17,18] The interplay between the bacterial burden and host response is the most plausible biological mechanism linking periodontitis to a number of chronic systemic diseases, such as diabetes mellitus, CVDs, and neurological diseases such as Alzheimer.[17,19,20] An ulcerated epithelial lining of the gingival pocket, subsequent to a local inflammatory response to the dental biofilm could amount to a sizeable area in patients with generalized periodontitis.[21] These patients often present with systemic inflammation and endothelial dysfunction,[22] which improves following successful periodontal treatment.[23]

Several studies appear to support a relationship between severe periodontitis and hypertension.[24–27] Limited evidence also suggests that successful periodontal treatment could improve arterial blood pressure.[28,29] However, little is still known about the direction and nature of the association between these two conditions. The overall aim was to conduct a robust critical appraisal of the evidence on the relationship between periodontitis and hypertension. Specific research questions were designed based on the following PECO outline: *Population*: Individuals >16 years old; *Exposure*: Presence of periodontitis with/without treatment; *Comparison*: Individuals with no periodontitis; *Outcome(s)*: Any measure of prevalence and/or levels of hypertension and/or changes in blood pressure following periodontal therapy. In this analysis we addressed several key questions:

- Are patients with periodontitis more likely to have hypertension (compared to those without periodontitis)?
- Is the degree of hypertension influenced by the severity and/or extent of periodontitis (linear association)?
- Is the mean SBP/DBP higher in patients with periodontitis vs. those without periodontitis?
- Does periodontal therapy modify the levels of blood pressure?

2. Methods

The systematic review protocol was registered in PROSPERO on 28/11/2017 with ID: CRD42017081455. A PRISMA statement is attached to follow the reporting of this systematic review (Supplementary material online, *Appendix S1*).

2.1 Primary and secondary outcomes

The primary outcome of this systematic review was odds ratio (OR)/relative risk (RR) and confidence interval (CI) for hypertension in individuals with periodontitis.

The secondary outcomes included prevalence of hypertension in patients with periodontitis vs. patients without periodontitis as well as prevalence of periodontitis in patients with or without hypertension; reports of mean SBP/DBP levels in periodontally healthy and diseased patients; systemic biomarkers associated with periodontitis and hypertension and changes in BP measurements following periodontal therapy.

2.2 Inclusion/exclusion criteria

To obtain an estimate of the association between periodontitis and hypertension, inclusion criteria were set to be broad and inclusive. Prospective and retrospective studies were included (randomized controlled trials, controlled clinical trials, cohort studies, case–control studies, and cross-sectional studies). Eligibility criteria included individuals from age 16 years onwards, with periodontitis (chronic and/or aggressive forms) considered as the exposure. Manuscripts including information related to primary and secondary outcomes were included.

Case report, case series and reviews, and animal studies were excluded. Individuals under 16 years old and pregnant women were also excluded. Lastly, studies that did not have any reports of the primary or secondary outcomes were disqualified.

2.3 Search methods for identification of studies

Five electronic databases were searched up to 10 December 2018 with no year restrictions [Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (OVID), EMBASE, Web of Science and Latin American & Caribbean Health Sciences Literature (LILACS)]. The search included no language restrictions and attempts were made to translate non-English language manuscripts (if this was not possible then the relevant evidence was excluded). In addition, SIGLE database was examined for relevant unpublished trials. Performed detailed search strategies deemed appropriate for each database using a combination of controlled vocabulary (MeSH terms and free text terms). All terms are available in the Supplementary material online, *Appendix S2 Table*).

MeSH terms in all trees and subheadings: 'periodontal diseases', 'periodontics', 'hypertension', 'blood pressure'.

Keywords: 'periodont$', 'gingiv$', '((blood or bleed$) adj4 prob$)', '(ging$adj disease)', 'hypertens$', '((elevat$or high$or rais$) adj3 (diastolic or systolic or arterial or blood) adj pressure)', 'bloodpressure'.

Hand searching of bibliographies of papers and review articles retrieved articles not found through other search methods.

2.4 Data management

The eligibility assessment of titles and abstracts (when available) of all reports identified were independently screened by two reviewers based on inclusion/exclusion criteria (E.M.A. and J.S.). If agreement could not be reached, the study was moved to the next stage and inclusion was based on full text screening. Full reports were obtained and assessed independently and in duplicate (E.M.A. and J.S.) for studies seeming to meet the inclusion criteria or for which insufficient information in the title and abstract precluded to make a clear decision. Disagreements were resolved by discussion and if necessary, a third reviewer was consulted (F.D.). When authors were not reporting on an effect estimate they were contacted to request additional information. Excel sheets were created to document information regarding decision for included and excluded articles. Kappa statistic was used to assess the agreement between the reviewers based on full text screening.

The main categories of data grouped according to study design and reported in evidence tables were study characteristics data; population; exposure (case definition for periodontitis); outcome (case definition for hypertension); effect (OR/RR with CI); and publication conclusions.

Regarding the exposure, multiple case definitions for periodontitis were found. A lack of consistent case definitions contributed to the difficultly in assessment and interpretation of the data retrieved. In order to collate studies looking at similar definitions, results were therefore grouped using two case definition thresholds: confident and non-confident case definition of periodontitis based on the following criteria (adapted from a previously reported definition).[30]

2.4.1 Confident case definition of periodontitis

The following criteria were considered as a confident case definition for periodontitis: generalized chronic periodontitis (at least 30% sites with CAL ≥ 4 mm)[31]; at least two sites on different teeth with clinical attachment level (CAL) 6 mm and at least one site with probing pocket depth (PPD) 4 mm (CDC/AAP periodontitis definition)[32]; presence of proximal attachment loss of >3 mm in two or more non-adjacent teeth (sensitive definition) or presence of proximal attachment loss of >5 mm in >30% of teeth present[33]; at least five sites with CAL ≥ 6 mm.[34]

2.4.2 Non-confident case definition of periodontitis

For non-confident case definition the following reported criteria were considered: community periodontal index (CPI) score 3/4 in at least one quadrant; 'Alveolar bone loss' without other measurements of PPD/CAL; unclear diagnostic criteria for periodontitis.

2.4.3 Definition of hypertension

Regarding the outcome, hypertension was defined as SBP ≥140 mmHg/DBP ≥90 mmHg or the use of anti-hypertensive medications.[1,2] However, reports of BP levels and other cases definitions were also documented for, such as self-reported hypertension and other thresholds (high normal/pre-hypertension).

2.5 Assessment of bias individual studies

Quality assessment of all included studies was undertaken independently and in duplicate by two reviewers as part of the data extraction process. For bias assessment of randomized controlled trials, non-randomized studies of interventions, and observational studies we used the revised Cochrane tool (ROB-2.0 tool),[35] the ROBINS-I tool,[36] and the Newcastle–Ottawa (NOS) tool,[37] respectively.

2.6 Data synthesis

Descriptive statistics were performed to summarize the evidence retrieved and to determine the quantity of data, checking further for study variations in terms of study characteristics and results. This assisted in confirming the suitability of further synthesis methods.

Meta-analysis A was conducted and referred to the following primary outcome: ORs for hypertension among people with or without a diagnosis of periodontitis. The ORs with adjustment for the confounding variables (i.e. age, gender, smoking, socioeconomic status, systemic disease, medication, body mass index, etc.) was chosen with hypertension as the dependent variable and periodontitis as the independent variable. Pooled estimates of OR and corresponding 95% confidence intervals were calculated for dichotomous data. In presence of significant heterogeneity ($P < 0.1$), the pooled estimates of effects were calculated using random effects models rather than fixed effects models. Meta-analysis B referred to the secondary outcome (mean SBP/DBP). The pooled mean SBP/DBP difference and 95% confidence intervals were estimated for continuous data. RevMan® 5.3 and JMP® 13.0.0 were used for all the statistical analyses.

To evaluate whether the methodological quality of the included studies influenced the direction or the magnitude of the results, we performed a separate sensitivity analysis by study design and either disease severity or case definition (*Figures 2* and *3C* and Supplementary material online, *Appendix S5*).

2.7 Publication bias

Possible publication bias was assessed for studies included in the different meta-analyses A and B using the methods described by Begg *et al.* and Egger *et al.*[38,39]

2.8 Heterogeneity

The significance of any discrepancies in the estimates from different trials was assessed by means of Cochran's test for heterogeneity and the I^2 statistic. As alluded above, sensitivity analyses were also planned to explore, quantify, and control for sources of heterogeneity between studies.

2.9 Strength of recommendation

The quality and strength of the evidence was assessed with The SORT (Strength of Recommendation Taxonomy). The authors discussed the outcomes of the systematic review, pertinent sources of evidence, clinical recommendations, and future areas requiring research.[40]

3. Results

The electronic search from combination of all databases identified 5574 potentially relevant articles after removal of duplicates, resulting in 182 publications eligible for full text screening. Eighty-one publications met inclusion criteria (*Figure 1*). The evidence tables created according to study design, included the main study characteristics (Supplementary material online, *Appendix S3*). The studies included in the systematic review have been conducted in 26 different countries from all continents involving a large variety of different populations. Reviewers (E.M.A. and J.S.) achieved an almost perfect agreement with 97.24%; Cohen's *k*: 0.94.

A variety of case definition of periodontitis was identified (as shown in evidence tables, Supplementary material online, *Appendix S3*). For hypertension diagnosis, the studies generally reported more uniformed criteria based on levels of SBP ≥140mmHg and/or DBP ≥90 mmHg or use of anti-hypertensive medication.[41] Nevertheless, some studies reported lower cut offs for hypertension (i.e. SBP ≥130mmHg and/or DBP ≥85 mmHg)[42] or hypertension prevalence was based on medical records, self-report, or national classification codes for disease. Similarly, different methods for measuring blood pressure were described in the studies included (Supplementary material online, *Appendix S3*). For additional or missing data, of all the authors contacted, only three provided additional information regarding the direction of the association and/or mean SBP/DBP following periodontal therapy.[43–45]

Study quality for observational studies as assessed by the Newcastle–Ottawa scale varied across the studies, ranging from a score of 3/9 to 9/9 (Supplementary material online, *Appendix S4*). The assessment revealed several potential sources of bias including the adequacy of case definition for cases and controls, the representativeness of the cases, no appropriate description of the sample size calculation, lack of adjustment for potential confounders or inappropriate statistical test. The assessment of randomized controlled trials with the Rob 2.0 tool revealed a low (five studies) to high (two studies) risk of bias for the studies included (Supplementary material online, *Appendix S4*). The main reasons for high risk of bias in randomized controlled trials arose from the randomization

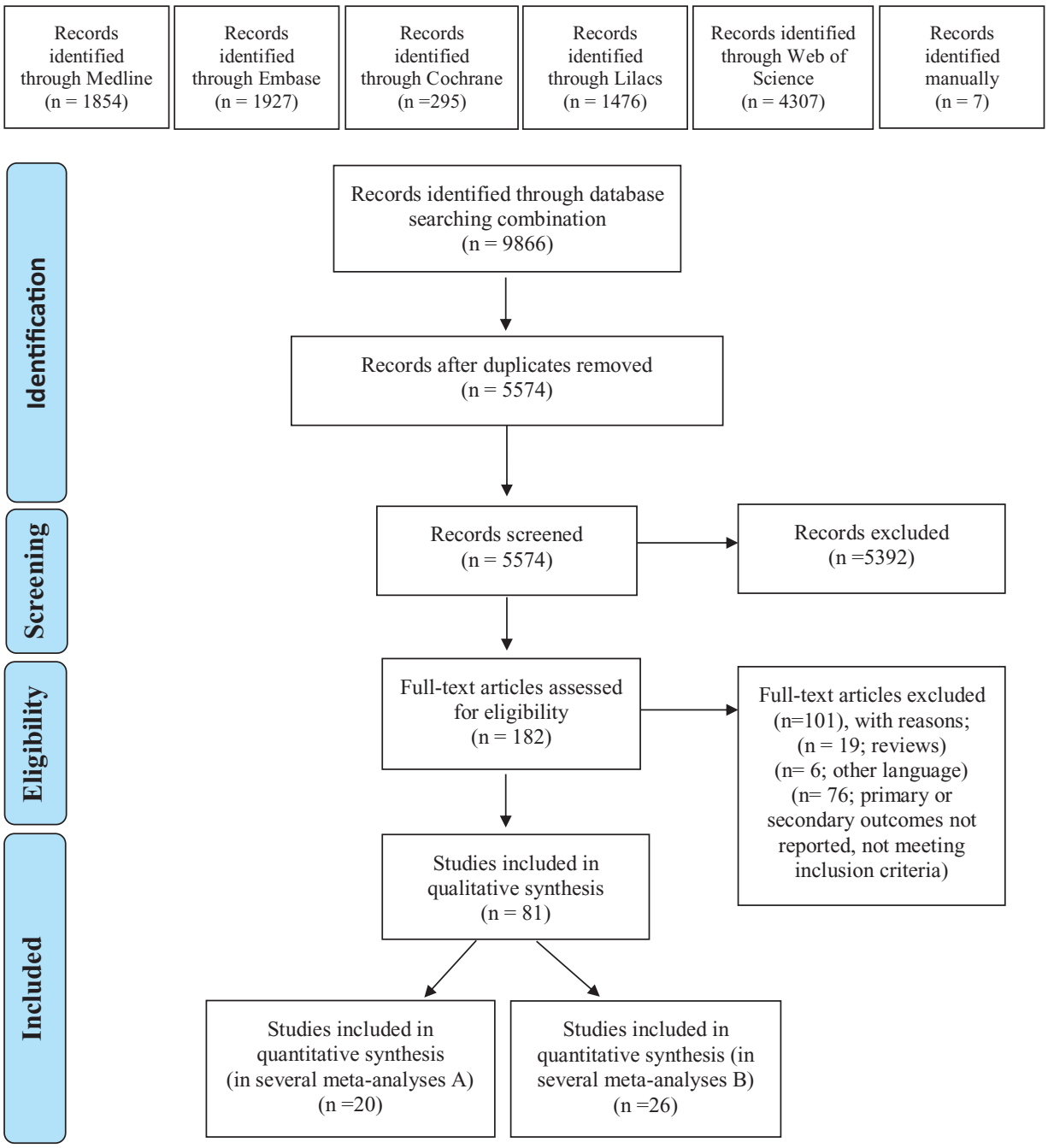

Figure 1 PRISMA flowchart. Flowchart of the study selection process. A systematic review yielded 9866 reports. After removal of duplicates and the application of inclusion and exclusion criteria, 46 studies were included in two different meta-analyses. PubMed, Embase, Cochrane, Lilacs, Web of Science, and manual search strategies are illustrated in Supplementary material online, *Appendices S1 and S2*.

process, blinding of participants and personnel. Study quality for non-randomized trials revealed moderate and serious risk of bias for the two studies assessed with the Robinson I tool (Supplementary material online, *Appendix S4*).

3.1 Primary outcome

Twenty studies included in five meta-analyses (A) of cohort, cross-sectional and case–control studies (*Figures 2* and *3C* and Supplementary material online, *Appendix S5*) compared the odds of having hypertension if an individual had periodontitis vs. periodontally healthy individuals using a periodontal case definition as the exposure measure.

Statistically significant heterogeneity was confirmed with a τ^2 test (ranging from 0.32 to 0.03), χ^2 test ranging from (ranging from <0.00001 to 0.008), and I2 test (ranging from 63% to 92%) for the different analyses completed. Due to this level of heterogeneity observed in the studies, random effect meta-analysis was performed.

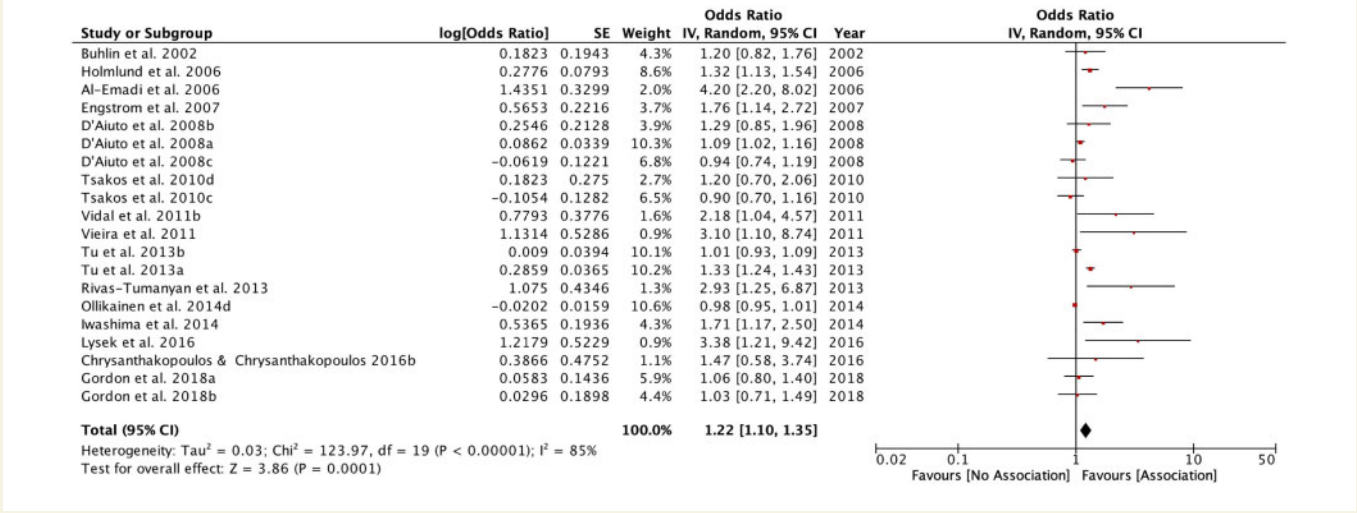

Figure 2 Association between periodontitis (moderate to severe combined diagnosis) and hypertension (cross-sectional and case–control studies). Summary Forrest plot for odds ratio of hypertension in relation to periodontitis diagnosis in cross-sectional and case–control studies (moderate to severe combined diagnosis). The random effects model was used and the relative size of the data markers indicates the weight of the sample size from each study. CI, confidence interval; IV, inverse variance; SE, standard error.

Odds ratios ranged from 0.90 to 4.20 for all studies, depending on case definition applied, severity of periodontitis and adjustment of the models. Precision of the estimates in the studies varied considerably as appreciated in the varying span of the confidence intervals. Two studies[24,46] reported ORs for moderate to severe periodontitis separately and one study[47] reported OR for men and women also separately, therefore these different ORs were included independently.

The analysis of three cohort studies predicted the occurrence of hypertension (OR = 1.68; 95% CI: 0.85–3.35), but this was not statistically significant ($P = 0.14$) (Supplementary material online, *Appendix S5*). Three studies were excluded from this meta-analysis due to one of them reported RR[48] and the other two appeared to be duplicated data.[45,49] Diagnosis of moderate-severe periodontitis in 15 cross-sectional and case–control studies was associated with higher odds of hypertension (1.22, 95% CI: 1.10–1.35), which was statistically significant ($P = 0.0001$) (*Figure 2*). A meta-analysis of eight cross-sectional and case–control studies confirmed that patients with severe periodontitis had increased odds (1.49, 95% CI: 1.09–2.50; $P = 0.01$) of diagnosis of hypertension (*Figure 3A*). Additionally, meta-analyses of studies according to confident vs. non-confident case definitions of periodontitis were performed. Seven studies with confident definition of periodontitis confirmed higher odds of hypertension (1.53, 95% CI: 1.11–2.10; $P = 0.009$) compared to a meta-analysis of eight studies with a non-confident definition of periodontitis (1.33, 95% CI: 1.14–1.55; $P = 0.003$) (*Figure 3B* and *C*).

3.2 Secondary outcomes

3.2.1 Prevalence

Thirty studies reported prevalence of hypertension in patients with periodontitis vs. patients without periodontitis or gingivitis (Supplementary material online, *Appendix S6*). Twenty-five of these studies showed a higher prevalence of hypertension in patients with a diagnosis of periodontitis (range = 7–77%) vs. those without periodontitis (range = 4–70%) and one study only confirmed higher prevalence in men.[50] These findings were not confirmed in four studies.[51–54] In addition, a consistent increased prevalence of periodontitis in patients with hypertension (range = 29–61%) vs. those without hypertension (range = 17–39%) was reported in all the seven publications that included this outcome (Supplementary material online, *Appendix S6*).

3.2.2 Mean blood pressure (observational evidence)

Thirty-one studies reported average mean SBP/DBP in patients with (range SBP = 113–172/DBP = 66–101 mmHg) and without periodontitis (range SBP = 109–143/DBP = 65–94 mmHg) (Supplementary material online, *Appendix S7*). The meta-analysis B, of mean SBP/DBP of 26 studies was performed resulting in statistically significant heterogeneity, confirmed with a Tau-squared test (ranging from 14.38 to 2.92), χ^2 test ranging from (<0.00001), and I2 test (ranging from 96 to 98%). Patients with periodontitis exhibited higher SBP [weighted mean difference (WMD) of 4.49 mmHg, 95% CI: 2.88–6.11; $P < 0.00001$] and DBP (WMD of 2.03 mmHg, 95% CI: 1.25–2.81; $P < 0.00001$) when compared with patients without periodontitis (*Figures 4* and *5*).

3.2.3 Systemic biomarkers

Three studies were included in the review as reporting changes in systemic biomarkers associated with hypertension and periodontitis.[55–57] One study analysed serum levels of neutrophilic enzymes in 95 patients.[55] They included a test group of patients with hypertension and periodontitis and two control groups: a healthy group (without periodontitis or hypertension) and a hypertensive group. The authors observed that circulating levels of matrix metalloproteinases (MMP)-8, MMP-9, myeloperoxidase and neutrophil elastase (NE) were increased in patients with hypertension and periodontitis but not in the controls. Another study examining the gingival crevicular fluid levels in patients with hypertension (21 patients) and without hypertension (26 patients) measuring levels of 8-isoprostane, interleukin (IL)-1B, monocyte chemoattractant protein (MCP)-1, tumour necrosis factor (TNF)α, C-reactive protein (CRP), and MMP-8.[56] They reported that independent of hypertension present or absent, an increased level of these biomarkers was

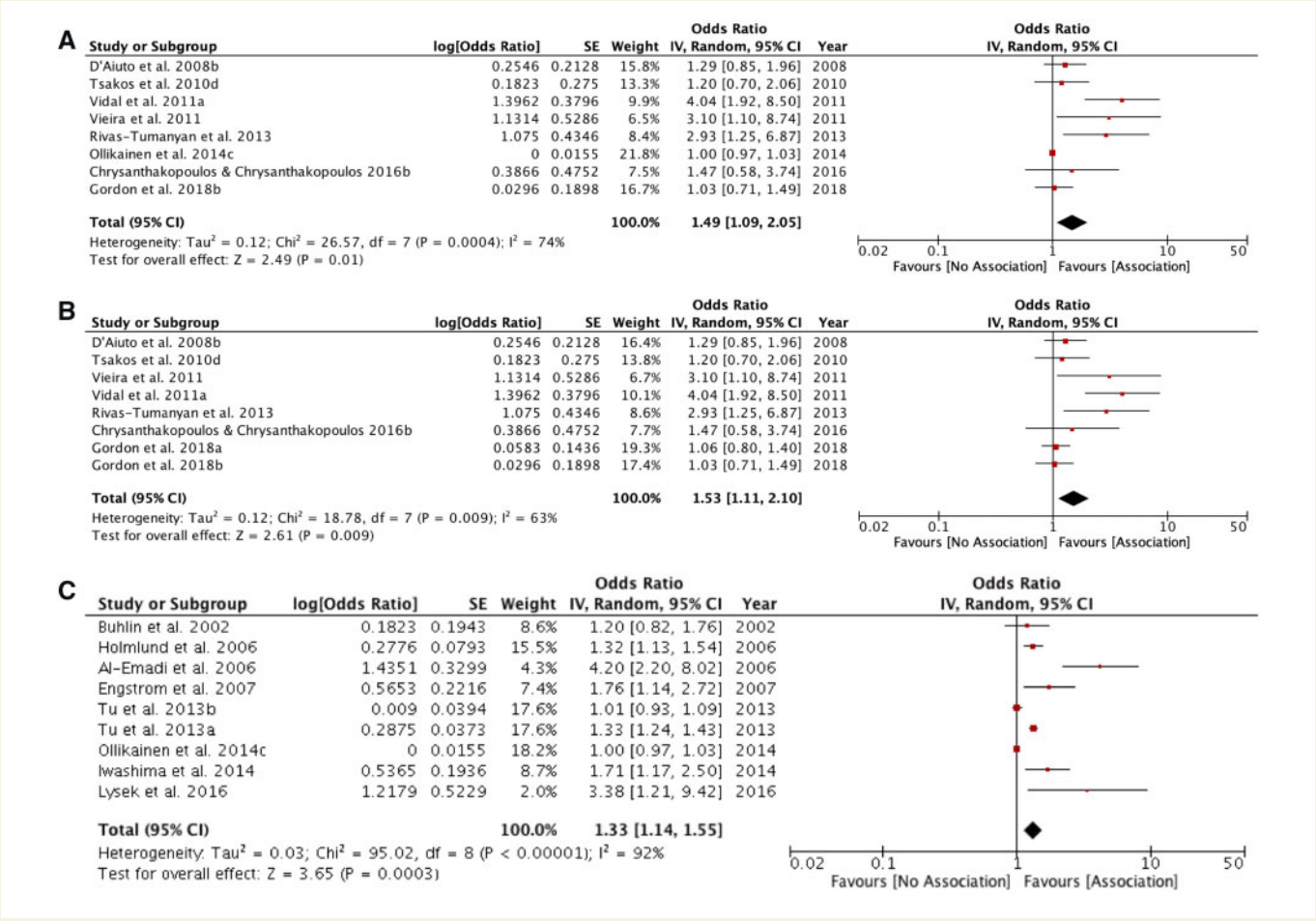

Figure 3 (*A–C*) Association between periodontitis (severe, confident, and non-confident diagnosis) and hypertension. Subgroup analysis Forrest plots for odds ratio of hypertension in relation to periodontitis status in cross-sectional and case–control studies. (*A*) Severe periodontitis only group adjusted. (*B*) Analysis adjusted for confident definition of periodontitis as described in methods. (*C*) Analysis adjusted for non-confident definition of periodontitis as described in methods. The random effects model was used and the relative size of the data markers indicates the weight of the sample size from each study. CI, confidence interval; IV, inverse variance; SE, standard error.

observed when patients had periodontal pockets. In addition, patients with hypertension presented with almost twice as much periodontal clinical attachment loss (CAL) as controls (Mean + SEM in HTN = 0.87 ± 0.13 vs. non-HTN = 0.49 ± 0.11). Albush *et al.*[57] assessed levels of vascular thrombotic markers in 40 hypertensive patients with periodontitis. Platelet count, fibrinogen, Von Willebrand factor antigen (vWF:Ag), and D-Dimer levels increased after 48 h of treatment (scaling of the teeth including subgingival root debridement for half of the patients and surgical periodontal therapy for the other 20) and decreased after 6 weeks ($P < 0.05$), with no significant differences between groups ($P > 0.05$). Acute increase in endothelial-activation markers including E-selectin, vWF, haemoglobin and haematocrit, D-dimer levels, and neutrophils counts was also reported 24 h following periodontal therapy in several publications.[22,44,58] Reductions in inflammatory biomarkers were observed in 11 interventional studies following periodontal therapy.[22,28,29,44,59–65]

3.2.4 Mean blood pressure (interventional evidence)

The search located 12 interventional clinical trials reporting the effect of periodontal therapy on blood pressure either as a primary[65] or secondary outcome (the remaining 11 studies) (see Supplementary material online, *Appendix S3* for a detailed description of the studies and treatment modalities). Eight studies were RCTs, three were non-RCT, and one was a pilot study. These studies comprised a varied sample of individuals, including people medically healthy in six studies[22,28,44,58,59,62] pre-hypertension,[65] refractory hypertension,[29] hypertension,[59] metabolic syndrome,[63] coronary artery disease,[60] and Type 2 diabetes.[64] Five of the 12 interventional studies included in the analysis confirmed a reduction in SBP following periodontal therapy (range = 3–12.5 mmHg), and an inconsistent reduction of DBP (range = 0–10 mmHg).[28,29,61,64,65] Six studies reported no changes in blood pressure measures following non-surgical and/or surgical periodontal therapy[44,58–60,62,63], however only two studies out of these six reported actual blood pressure values[59,60] and one author provided values upon request[44]. One study[22] reported an increase in blood pressure in the test group 1 day after periodontal therapy.

3.3 Publication bias

Study publication bias was examined using funnel plots for both meta-analyses A and B (Supplementary material online, *Appendix S8*). Egger's

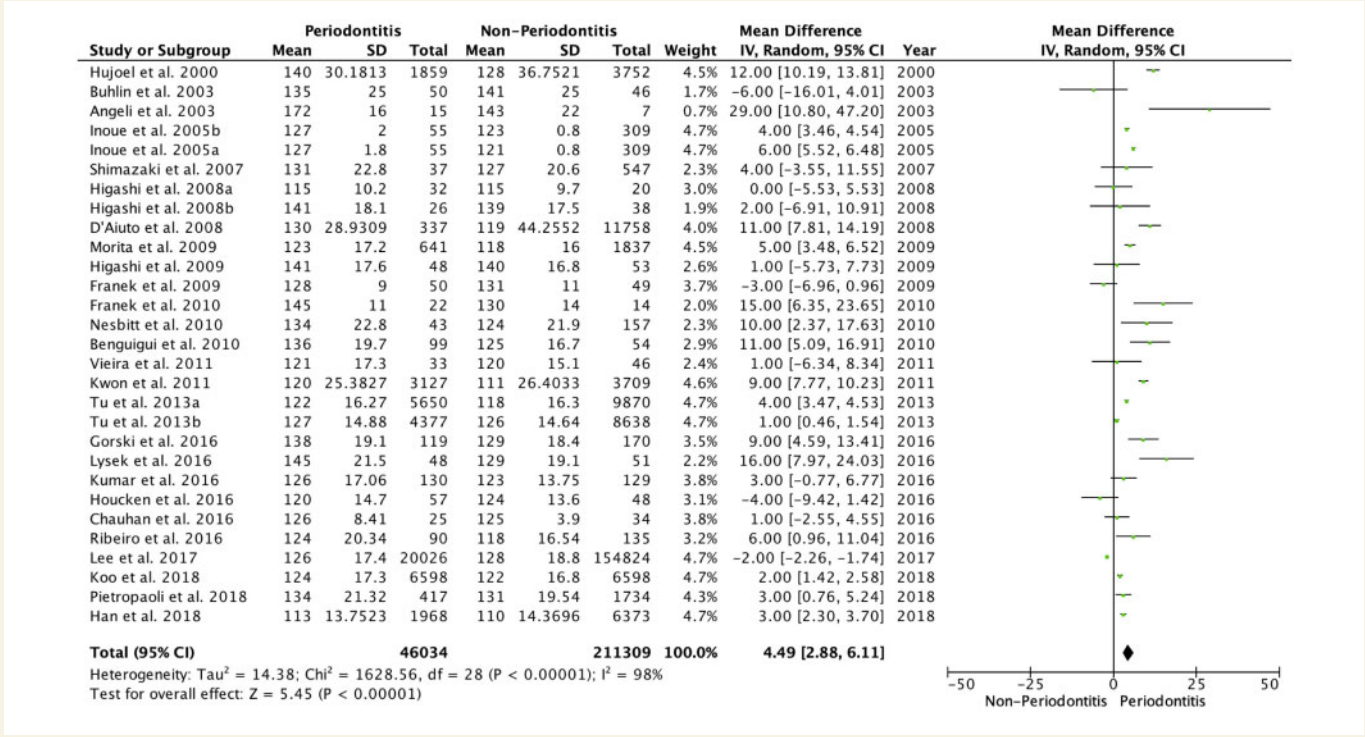

Figure 4 Periodontitis effect on systolic blood pressure (SBP). Summary Forrest plot for change in SBP in relation to periodontitis status in cross-sectional and case–control studies. The random effects model was used, weighted mean difference (WMD) reported and the relative size of the data markers indicates the weight of the sample size from each study. SE, standard error; IV, inverse variance; CI, confidence intervals.

test was only calculated for the meta-analyses A of moderate to severe periodontitis (Supplementary material online, *Appendix S8*). Visual assessment of the Funnel of moderate to severe periodontitis revealed studies were slightly skewed to the right, which was confirmed with the Egger's test showing a statistically significant difference ($P = 0.0054$); publication bias was therefore suspected in this analysis. Nevertheless, all the other funnel plots for meta-analyses A displayed symmetrical appearance. Similarly, visual assessment of the Funnel plots for mean SBP and DBP analysis revealed symmetrical appearance. Egger's test estimated for meta-analyses B revealed a not statistically significant result ($P = 0.5582$) for the mean SBP meta-analysis and a statistically significant difference ($P = 0.0224$) for the mean DBP meta-analysis. On this basis, publication bias was suspected in the mean DBP meta-analysis.

3.4 Reporting on strength of recommendation

The quality, quantity, and consistency of the evidence from observational and interventional studies on the relationship between periodontitis and hypertension were thoroughly assessed for a SORT recommendation. Accordingly, we conclude that diagnosis and treatment of periodontitis is positively associated with hypertension (SORT C).[40]

4. Discussion

The results of this systematic review support a positive association between periodontitis and hypertension. Based on the quantitative analyses of all studies included, patients with moderate to severe periodontitis have greater (20%) odds of having hypertension when compared to patients without periodontitis. In addition, a positive linear association was observed, confirming that the more severe periodontitis is, the higher the likelihood (49%) of having hypertension. This finding was further corroborated, when the studies with a confident case definition for periodontitis were analysed, confirming even greater odds (50%) of diagnosis of hypertension were found. The magnitude of association between periodontitis and hypertension reported in this review (OR 1.22–1.53) is in agreement with that recently reported.[27] In this recent review, however, Martin-Cabezas *et al.* included observational studies without specifying the exposure and outcome of the analysis. In the current systematic review, we also included three cohort studies[66–68] confirming a temporal association between periodontitis and incidence of hypertension although this was not statistically significant and we excluded a number of studies in this analysis in order to avoid bias due to suspected duplication of data.

This systematic review also confirmed an increased prevalence of periodontitis in patients with hypertension (as defined by SBP ≥140 and DBP ≥90 mmHg). Clinical and experimental evidence suggest that this direction of the association could be mediated through hypertension causing microcirculatory changes in of the gingival tissue leading to ischaemia, increased inflammation, and/or altered microbial composition of the dental biofilm.[25,69,70] This finding combined with the increased prevalence of hypertension in patients with periodontitis could be even more significant within the context of the new revised guidelines issued by the AHA for the definition of hypertension.[71] A reduced threshold of SBP/DBP for the case definition of hypertension was expressed (Stage 1 as SBP = 130–139/DBP = 80–89 mmHg, and Stage 2 agreeing to Stages 1

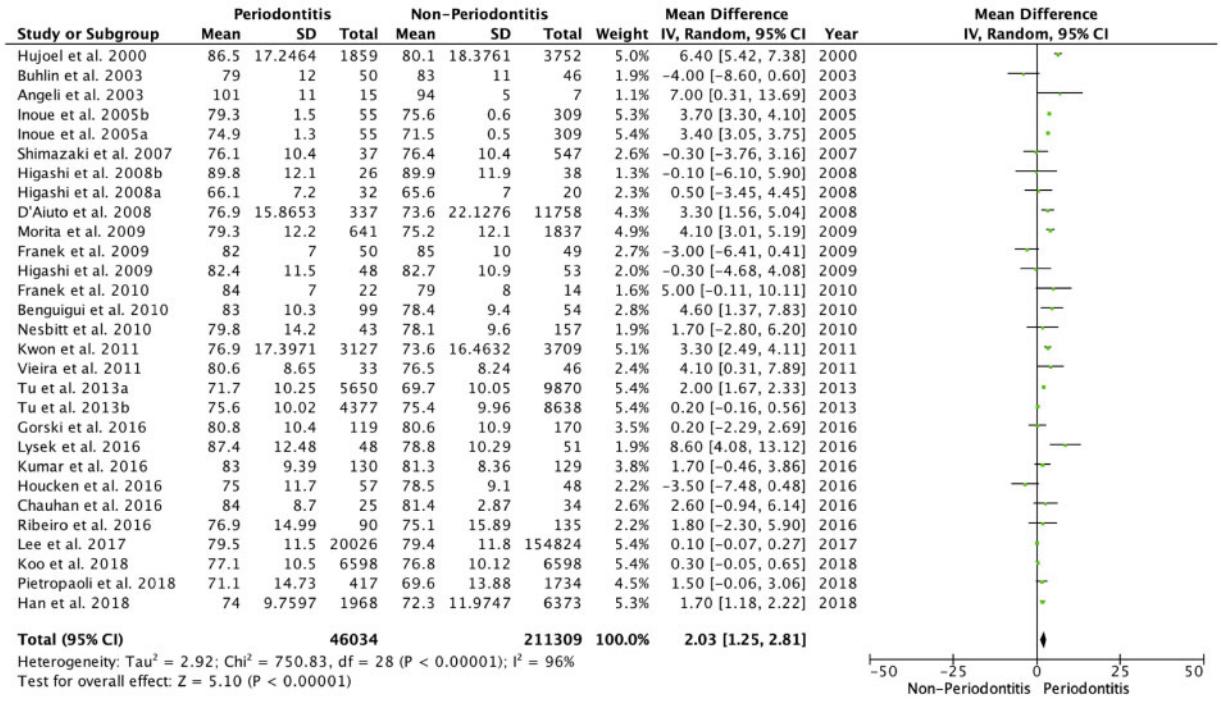

Figure 5 Periodontitis effect on diastolic blood pressure (DBP). Summary Forrest plot for change in DBP in relation to periodontitis status in cross-sectional and case–control studies. The random effects model was used, WMD reported and the relative size of the data markers indicates the weight of the sample size from each study. SE, standard error; IV, inverse variance; CI, confidence intervals.

and 2 in the JNC 7 report; i.e. SBP ≥ 140/DBP ≥ 90 mmHg), which has been reported in a recent cross-sectional study to double the prevalence estimates of hypertension in countries like China and USA.[72] This could result in even greater odds of hypertension in patients with periodontitis and vice versa. Future research should consider the impact of these thresholds for case definition of hypertension in terms of increased prevalence and treatment thereof.

In this systematic review, for the first time, we attempted to provide an estimate of the mean arterial BP in patients with periodontitis vs. controls. Very interestingly, more than 80% of the included studies reporting levels of blood pressure showed consistently increased levels of systolic and diastolic BP in patients with periodontitis. Further, the exploratory meta-analysis B revealed that patients with periodontitis showed a higher WMD of 4.49 mmHg of SBP and of 2.03 mmHg of DBP. If confirmed in long-term longitudinal studies, periodontitis could represent a novel modifiable risk factor for hypertension at the same strength of diabetes and smoking.[73,74] However, as periodontitis, diabetes and hypertension share common risk factors (such as aging, smoking, and disadvantageous socioeconomic status, among others), residual confounding could affect the magnitude of these associations. It is important to state that this association could also be driven by an association between arterial blood pressure changes and other undetected sources/chronic infections. Further research in identifying the interplay between triggers/bacterial burdens in each individual and their relative contribution on blood pressure is needed.

Raised arterial blood pressure observed in periodontitis could also explain the moderate but consistent higher risk of CV events (i.e. MI and stroke) reported by several investigators in patients with periodontitis when compared to controls.[17] Indeed, an average increase of 5 mmHg of SBP has been consistently associated with a 25% increased mortality from ischaemic heart disease and stroke.[75] These assumptions should all be interpreted with caution because of the high heterogeneity observed in the reported scientific evidence. In particular, varying case definitions of periodontitis and hypertension could have undermined the validity of these observations. Nevertheless, due to the high prevalence of both conditions, the clinical implications for public health systems could be very significant.

This systematic review also confirmed a potential positive effect of treating periodontal inflammation on arterial blood pressure. Inconclusive findings were identified in the selected studies, with only 5 out of 12 intervention trials showing a reduction of SBP/DBP in patients with periodontitis.

Only one RCT was designed to address the question whether non-surgical periodontal therapy could result in reduced arterial BP levels.[65] These authors assessed changes in blood pressure as their primary outcome following non-surgical periodontal therapy. They included 107 pre-hypertensive participants and reported an absolute difference of SBP = 12.57 mmHg 95% CI: 10.45–14.69, $P < 0.05$ and of DBP = 9.65 mmHg 95% CI: 7.06–12.24, $P < 0.05$ after periodontal therapy. As treatment of hypertension has been repeatedly advocated as a key intervention to improve general health, quality of life, and reduce CV complications,[76] periodontitis treatment could represent a novel non-pharmacological therapy to prevent/help manage hypertension. A meta-analysis of RCTs quantified a reduction of 25–30% of coronary heart disease events such as stroke and heart failure with a 10 mmHg reduction in SBP or a 5 mmHg reduction in DBP following anti-hypertensive drug

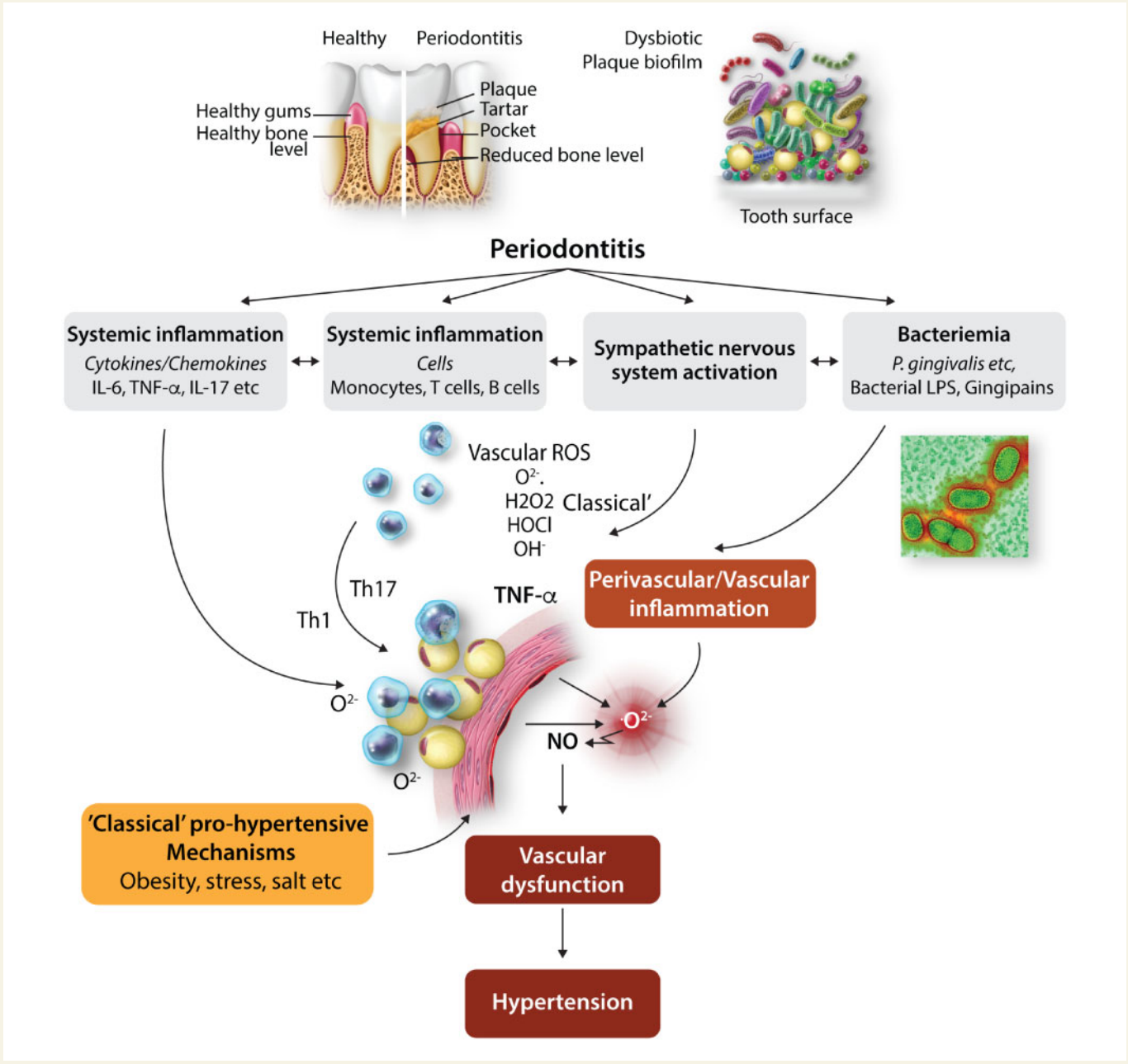

Figure 6 Some pathways through which periodontitis could lead to hypertension and vascular dysfunction. Potential mechanisms causally linking periodontitis with hypertension and vascular dysfunction. NO, nitric oxide; O_2^-, S, superoxide; Th, T-helper cells; ROS, reactive oxygen species.

therapy.[77] Future research should address the hypothesis of the treatment of periodontitis could achieve similar reduction in arterial BP and CV outcomes.

The identification of periodontitis as a possible risk factor for hypertension could be explained by a number of plausible mechanisms (*Figure 6*). Firstly, periodontitis is associated with systemic inflammation, mediators of which, including CRP, IL-6; TNF-α can all affect endothelial function. Clinical evidence suggests periodontitis affects systemic endothelial function and in turn this could impact on hypertension. Our group previously demonstrated that treatment of severe periodontitis improves endothelial function by reduction in systemic inflammation in patients with and without other comorbidities like diabetes.[22,64] Secondly, some reports suggest possible direct effects of oral microbiota related bacteraemia in mediating vascular dysfunction as well. Emerging experimental animal evidence indicates that an immune response to a common periodontal pathogen: *Porphyromonas gingivalis* (*Pg*) results in elevation of BP, vascular inflammation, and endothelial dysfunction.[78] Another possibility may be that cells, including T cells, B cells, and monocyte/macrophages, primed in inflamed periodontium may be more prone to chemotactic recruitment to perivascular adipose tissue and adventitia, a step that has been shown to precede development of vascular dysfunction, hypertension, and atherosclerosis.[79,80] This review therefore raises an important question regarding the causal nature of the association between periodontitis and hypertension.

4.1 Strengths and weaknesses

This systematic review was designed to comprehensively investigate the possible role of periodontitis as a possible novel risk factor for hypertension. A number of limitations however should be highlighted starting with the limited value of systematic reviews of observational studies for ascertaining causality.[81] Moreover, observational studies have intrinsic biases (mostly selection and information bias), hence the results of this systematic review should be interpreted within the context of the methodology used. Nevertheless, this review was broad and inclusive of not only observational but also interventional studies. Besides, because of the link between periodontitis and cardiometabolic risk factors,[17,82] this review also included data from observational studies on MetS and CVD but the authors acknowledge that some of the data may have been missed due to the difficulties in identifying the outcomes within the published reports. Moreover, studies looking at hypertension have inherent problem of the effect of blood pressure measurement technique on the outcome as well as variable degree of reporting of actual criteria of hypertension. Therefore, we have focused on a clear definition of hypertension based mainly on blood pressure values and anti-hypertensive medications. With the exception of a single study[29] most studies have used office rather than ambulatory blood pressure; our quantitative analysis of the effect of periodontitis on blood pressure values adds to the strength of the selected evidence. This study was a pilot intervention trial including only 26 patients with refractory hypertension and periodontitis and the effects of non-surgical periodontal therapy on both systolic and diastolic blood pressure were of greater magnitude of those reported in the other intervention studies. We urge caution in interpreting these results especially in view of the limited sample size and inclusion criteria adopted by the authors.[29] Future intervention trials should all be designed according to appropriate power calculation to determine sample size and include ambulatory blood pressure levels.

One of challenges encountered was to establish the direction of association when studies were included in the quantitative analyses (i.e. dependent and independent variables in the model). This was mainly due to unclear description in the published manuscripts. When a consensus could not be achieved among the reviewers (E.M.A. and J.S.), a third author was consulted (F.D.) or attempts were made to contact the authors for clarification.[43] Another important limitation of this systematic review is the high level of heterogeneity in the case definitions for both, periodontitis and hypertension.[34,83] To overcome this, data were further analysed according to an arbitrary level of confidence in a given case definition of periodontitis. In fact, when an arbitrary confident diagnosis was confirmed, the observed magnitude of association between periodontitis and hypertension was greater. The lack of consistent measures of case definition and severity of periodontitis in the retrieved evidence did not allow for a relevant analysis of extent and severity of periodontitis with all endpoints of blood pressure. We hope in the future reporting of periodontitis is more consistent and allow for such analyses. Lastly, it has been reported that anti-hypertensives such as calcium channel blockers can cause gingival enlargement in 6.3–83% of patients,[84] which should not be confounded with periodontitis.

5. Conclusions

Periodontitis could be associated with increased risk of hypertension in a linear fashion. Further, management of periodontitis could impact on the management of hypertension. Our findings highlight the potential to improve CV outcomes by addressing poor oral health in the general population. Longer and larger studies are needed however to determine whether periodontal treatment benefit patients in terms of CV health, ultimately resulting in reduced morbidity and mortality.

Translational implications

- To raise awareness of the association between periodontitis and hypertension.
- Patients with periodontitis should be informed by oral health professionals of the risk of developing hypertension.
- Oral health advice should be given to all patients with hypertension.
- Prevention and management of periodontitis improves oral/overall health and quality of life and could prevent/improve hypertension.
- Larger observational studies should include internationally recognized case definitions for periodontitis and hypertension.
- Larger and long-term RCTs with reduction of blood pressure as primary outcome should be performed.
- Patient reported outcome measures relevant to hypertension and periodontitis should be included within future study designs.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

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