Hypertension

PERIODONTITIS

Association Between Periodontitis and Blood Pressure Highlighted in Systemically Healthy Individuals

Results From a Nested Case-Control Study

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ABSTRACT: Recent evidence suggests hypertension and periodontitis are closely linked but limited data is available on the nature of the association. We aimed to investigate the relationship between periodontitis and mean arterial blood pressure in a sample of otherwise systemically healthy individuals. A case-control study including 250 cases (participants with periodontitis) and 250 controls (without periodontitis) was designed from a register of clinical trials conducted between 2000 and 2018 in a university setting. Cases were age, sex, and body mass index balanced with controls. Linear, logistic regression, and mediation models were planned to test the association between various periodontal measures and arterial blood pressure. We further investigated the role of systemic inflammation assessed by hs-CRP (high-sensitivity C-reactive protein) and white cell counts. Cases presented with 3.36 mm Hg (95% CI, 0.91–5.82, *P*=0.007) higher mean systolic blood pressure and 2.16 mm Hg (95% CI, 0.24–4.08, *P*=0.027) higher diastolic blood pressure than controls. Diagnosis of periodontitis was associated with mean systolic blood pressure (β=3.46±1.25, *P*=0.005) and greater odds of systolic blood pressure ≥140 mm Hg (odds ratio, 2.3 [95% CI, 1.15–4.60], *P*=0.018) independent of common cardiovascular risk factors. Similar findings were observed when continuous measures of periodontal status were modeled against systolic blood pressure. Measures of systemic inflammation although elevated in periodontitis were not found to be mediators of the association between periodontitis and arterial blood pressure values. Periodontitis is linked to higher systolic blood pressure in otherwise healthy individuals. Promotion of periodontal and systemic health strategies in the dental and medical setting could help reduce the burden of hypertension and its complications. **(*Hypertension*. 2021;77:1765–1774. DOI: 10.1161/HYPERTENSIONAHA.120.16790.)** • **Data Supplement**

Key Words: blood pressure ■ cardiovascular diseases ■ hypertension ■ inflammation ■ periodontitis

Elevated arterial blood pressure (BP) increases the risk of complications from cardiovascular diseases (CVD), such as stroke and myocardial infarction, with >7.6 million deaths accounted for every year and 143 million disability-adjusted life-years.[1] It is estimated that >30% of the overall population suffers from hypertension, and this estimate increases with age.[2] A 15% to 50% of individuals, however, are unaware they are affected by hypertension,[3] whereas many of those with a established diagnosis fail to achieve an optimal BP control despite their prescribed medications.[2] The burden and cost of hypertension remain high for any given society. Inflammation is considered an important driver of vascular dysfunction and implicated in the development and progression of hypertension.[4,5]

Periodontitis is a common inflammatory disease caused by a dysbiotic biofilm and affecting the soft and hard tissues around teeth.[6] It is a chronic disease, usually spanning over decades of an individual's life and is characterized by gingival inflammation with associated alveolar bone loss which, if not arrested, will ultimately lead to tooth loss. Almost 750 million people (aged 15–99 years) worldwide present with moderate to severe symptoms of periodontitis[7]; plus the disease

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Novelty and Significance

What Is New?

- The link between periodontitis and high blood pressure was confirmed in systemically healthy individuals.

What Is Relevant?

- Individuals with periodontitis but otherwise healthy presented with higher mean systolic blood pressure/diastolic blood pressure and odds of systolic blood pressure >140 mm Hg.
- Bleeding gums was associated with higher mean systolic blood pressure.
- Undetected hypertension was a common finding among the participants in this study.

Summary

The risk of elevated blood pressure was highlighted in systemically healthy patients with periodontitis. Oral health professionals could play a crucial role in assisting in the screening and management of hypertension.

Nonstandard Abbreviations and Acronyms

BMI	body max index
BP	blood pressure
CVD	cardiovascular diseases
DBP	diastolic BP
FMBS	full-mouth gingival bleeding
HDL	high-density lipoprotein
Hs-CRP	high-sensitivity C-reactive protein
IL	interleukin
LDL	low-density lipoprotein
PPD	probing pocket depths
SBP	systolic BP
TNF	tumor necrosis factor
WBC	white blood cell counts

is linked to social inequality and it negatively affects patients' quality of life.[8]

Recent evidence suggests a possible causal link between periodontitis and hypertension.[9] Patients with periodontitis often present with higher arterial BP values and a 30% to 70% higher chance to also present with hypertension,[10] especially when there is active gingival inflammation (ie, with gingival bleeding).[11] Longitudinal and large interventional studies confirming the nature of this association and the exact pathogenetic mechanisms are scarce.

The aim of this study was to investigate the association between diagnosis of severe periodontitis and arterial BP in a sample of otherwise healthy participants (without a confirmed diagnosis of hypertension). The primary objective was to assess office BP values in patients with periodontitis (cases) compared with controls (participants without periodontitis) and whether a linear relationship exists between measures of periodontitis extent/severity with BP values and whether basic measures of systemic inflammation mediate any association. Furthermore, the prevalence of undiagnosed hypertension between cases and controls was explored.

MATERIAL AND METHODS

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

Study Design and Population

A nested case-control study was designed, including participants recruited at the University College London Eastman Dental Institute between the years 2001 and 2018. All participants provided written informed consent at the time of study participation including use of data for future analyses. Seventeen clinical trials with the same inclusion criteria (severe periodontitis) or control (no periodontitis) and full-mouth periodontal assessment and arterial BP measurements (same recording protocol) were screened for inclusion in this analysis. This study was approved by the local UCL Research Ethics Committee (Project ID: 16989/001).

Sample Inclusion Criteria

Cases were individuals ≥18 years old who had been diagnosed with generalized severe periodontitis (defined as ≥50% of the teeth with probing pocket depths [PPD] of ≥5 mm and ≥30% marginal alveolar bone loss) and referred to the periodontal unit for management of their condition.[12] All participants were otherwise systemically healthy (no other systemic condition, as per medical history assessment/interview) and had not undertaken periodontal therapy within 6 months of the specific study assessment.

Controls were individuals ≥18 years old attending the same hospital without a diagnosis of periodontitis (recruited from other dental units but with no active dental infections) who were equally systemically healthy (no other systemic condition, as per medical history assessment/interview).

Sample Exclusion Criteria

Possible participants were excluded from this study if presenting with any of the following: (1) active infectious diseases, such as hepatitis, HIV, or tuberculosis, (2) any confirmed systemic diseases including diabetes, kidney, liver, cardiovascular diseases, hypertension, cancer, or on any chronic medication,

(3) pregnant or breastfeeding, and (4) taking nonsteroidal anti-inflammatory drugs on a regular basis or taking antibiotics within 3 months of assessment.

Periodontal Examination

Periodontal assessment used a standardized protocol carried out by calibrated examiners, as previously described.[12] Baseline data on full-mouth periodontal assessment was retrieved for all participants. Case definition of periodontitis was confirmed against the latest validated classification.[6] The full-mouth dental plaque and full-mouth gingival bleeding (FMBS) scores were recorded and the following thresholds for localized (FMBS 10%–29%) and generalized gingival bleeding (FMBS >30%) were adopted. Periodontitis case definition was of generalized severe/stage III/IV periodontitis.[6] Continuous measures of severity and extent of periodontitis were created as follows: (1) the extent of periodontal pockets with PPD of ≥4 mm, ≥5 mm, ≥6 mm (number and percentage of sites) and (2) extent of loss of periodontal attachment levels (clinical attachment level) of ≥3 mm, ≥4 mm, ≥5 mm, ≥6 mm (number and percentage of sites).

BP Assessment

Office BP measurements were obtained following a standardized protocol using an Omron device M5-1 (HEM-757A-E) by a trained person and recorded in triplicate for each participant, as previously described.[13] The patients were advised not to exercise, smoke, or consume any caffeine during the 30 minutes before their appointment. Upon arrival, the measurements were recorded after the patients were seated for 5 min and relaxed, with the back resting on the chair and the arm on a desk at the level of the right atrium. Average of the systolic and diastolic arterial pressure (systolic BP [SBP] and diastolic BP [DBP]) readings taken to the nearest value were obtained and used as continuous variables. Unconfirmed hypertension diagnosis was evaluated applying diagnostic thresholds of the US (values of SBP ≥130 mm Hg or DBP ≥80 mm Hg) and European (values of SBP ≥140 mm Hg or DBP ≥90 mm Hg) guidelines.[14,15]

Additional Variables

Socio-demographics information (age, sex, ethnicity), health lifestyle behavior (smoking, physical activity [frequency of weekly sessions of being active through walking, cycling, sports, and recreation]), and family history of cardiovascular diseases (whether or not any family member had heart or vascular disease) were retrieved from the medical history questionnaires. Anthropometric measurements (body max index: BMI) were collected by trained staff using a standard protocol.[12] Fasting venous blood samples were collected and analyzed for white blood cell (WBC) counts, hs-CRP (high-sensitivity C-reactive protein), total cholesterol, LDL and HDL (low- and high-density lipoprotein), glucose and triglycerides using standard biochemistry procedures and as previously described.[12]

Statistical Analysis

A sample size calculation confirmed that a minimum of 248 participants per group was required to detect a difference of 3.5 mm Hg in mean SBP between cases and controls, with an SD of 12 mm Hg, to achieve a power of at least 90% assuming an alpha of 0.05.

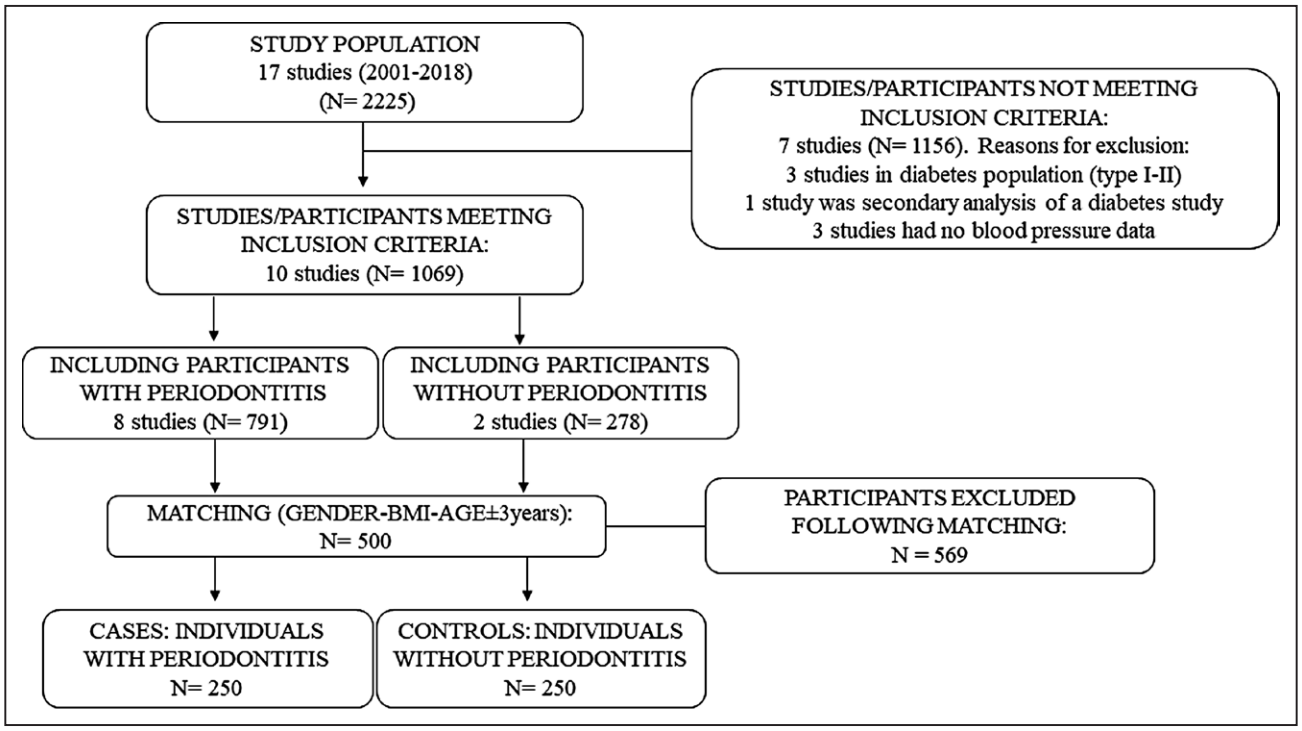

Figure. Study flow chart diagram.

Cases and controls were balanced based on age ±3years, sex, and BMI (Figure).[16] All data were checked for errors, entered in a single dataset, and analyzed using SPSS (version 25), STATA (version 15), and R Software (version 3.5.2). Descriptive statistics (comparisons between continuous variables used independent *t* test/Mann-Whitney and between categorical variables used χ^2 test) was used to compare general variables and arterial BP levels between cases and controls. Multivariate linear regression analysis was performed to investigate potential associations between (1) periodontitis (categorical and continuous definitions) or systemic markers of inflammation (ie, hs-CRP and WBC) as exposures and mean SBP and DBP as outcomes, (2) periodontitis (exposure) and systemic markers of inflammation (outcome). Age, BMI, sex, ethnicity, smoking, physical activity, and family history of CVD were used as confounders in each model. Similarly, multivariate logistic regression analysis was carried out to test the odds of the following categorical outcome variables: (1) SBP≥140, (2) SBP≥130, (3) DBP≥90, (4) DBP≥80 mm Hg, and undiagnosed hypertension defined as (5) per European guidelines[14] (SBP/DBP≥140/90 mmHg) and (6) as per US guidelines[15] (SBP/DBP≥130/80 mmHg) in relation to the different exposure variables, that is, periodontitis diagnosis (categorical yes/no), hs-CRP, and WBC. β coefficients and odds ratios with 95% CIs were calculated in unadjusted (model 1) and adjusted models including age, BMI, sex, ethnicity, smoking, physical activity, and family history of CVD (model 2). A *P* value of ≤0.05 was considered statistically significant. Mediation analyses of systemic inflammatory markers were performed if a positive association between CRP or WBC variables with periodontitis and SBP/DBP were found in linear/logistic regression models. Two different and prespecified routes were used; direct (route 1) and indirect (route 2) mediation effects with their 95% CI were estimated: route 1: periodontitis (exposure)→hypertension (outcome). Route 2: periodontitis (exposure)→WBC or hs-CRP (mediators)→hypertension (outcome).

RESULTS

Sample median age [interquartile range] was 35 [12] years with no substantial differences observed between cases (35 [9] years) and controls (34 [14] years; *P*=0.345). Similar sex (*P*=0.929) and BMI (*P*=0.209) distributions were confirmed between cases and controls. Higher number of current smokers, with predominant Black/Afro-Caribbean participants, reporting less physical activity and a higher percentage of family history of CVD were observed in cases when compared with controls. Participants with periodontitis exhibited increased glucose, LDL, CRP, and WBC levels but lower HDL values when compared with controls (all, *P*<0.01; Table 1).

Higher mean differences in SBP (3.36 mmHg [95% CI, 0.91–5.82], *P*=0.007) and DBP (2.02 mm Hg [95% CI, 0.24–4.08], *P*<0.027) were observed in cases when compared with controls.

A 14% of cases presented with SBP≥140 mm Hg versus a 7% of the controls (*P*=0.021). Similarly, >43% of the cases presented with DBP≥80 mm Hg versus 34% of the controls (*P*=0.035). The percentages of cases with SBP≥130 mm Hg or DBP≥90 mm Hg were greater than for the controls but not statistically significant (Table 1). Overall a 15.6% of the whole study participants presented with values of SBP/DBP in the range of hypertension (European definition): 17.2% of the cases and 14% of the controls (*P*=0.324) and a 45.6% (American definition): almost 50% of cases and a 41.6% of controls (*P*=0.073; Table 1).

Linear regression analysis confirmed an association between case definition of periodontitis (categorical) and higher mean SBP after adjusting for common risk factors (β±SE=3.46±1.25, *P*=0.005, model 2) and to DBP (β±SE=2.16±0.98, *P*=0.027, model 1; Table 2). Greater severity of periodontitis as assessed by mean clinical attachment level, PPD, and FMBS were associated with higher mean SBP (models 1 and 2) and with higher mean DBP (model 1; Table 2). A similar linear association between different thresholds of periodontal lesions (PPD thresholds) and SBP (models 1 and 2) were noted but for different threshold of clinical attachment level, this was only seen in model 1 (Table 2). Periodontitis (categorical and continuous variables) was associated with higher CRP (model 1) and WBC (model 1 and 2) levels (Table 2). Similarly, periodontitis (categorical) was associated with higher odds of SBP≥140 mm Hg (odds ratio, 1.98 [95% CI, 1.10–3.65], *P*=0.023, model 1; odds ratio, 2.31 [95% CI, 1.17–4.67], *P*=0.018, model 2) and DBP≥80 mm Hg (odds ratio, 1.47 [95% CI, 1.03–2.12], *P*=0.035, model 1; Table 3). No significant association was found with SBP≥130 mm Hg, DBP≥90 mm Hg, or Hypertension definition according to European or American guidelines.

When CRP and WBC were modeled as exposure variables, no associations were observed with SBP or DBP (Tables 2 and 3). Lastly, an association between SBP and increasing FMBS irrespective of periodontal diagnosis was observed in the multivariate fitted model for SBP according to bleeding status (Table 4). Participants with generalized bleeding presented with a 5 mm Hg greater SBP than those with healthy gums (95%CI, 8.22–1.91, *P*=0.002; Table 4).

Mediation analyses confirmed that WBC did not act as a mediator of the association between periodontitis (categorical) and SBP (continuous) in either in the unadjusted (β±SE=−0.00±1.21; *P*=0.994) or the fully adjusted (*β*±SE=−0.03±0.21; *P*=0.900) models (route 2; Tables S1 and S2 in the Data Supplement). Similar results were observed when the model was replicated for continuous periodontal (FMBS, clinical attachment level, PPD) and categorical BP (SBP≥140 mm Hg) variables.

DISCUSSION

The results of this study showed that systemically healthy individuals with periodontitis (cases) presented with higher mean SBP and DBP than participants without

Table 1. Main Characteristics of Participants

Variables	Overall (500)	Controls (Non-periodontitis; 250)	Cases (Periodontitis; 250)	*P* value
Categorical N (%)				
Sex (%female)*	263 (52.6)	132 (52.8)	131 (52.4)	0.929
Smoking				
Non-smoker	290 (58.0)	175 (70.0)	115 (46.0)	<0.001
Current smoker	96 (19.2)	34 (13.6)	62 (24.8)	<0.001
Ex-smoker	114 (22.8)	41 (16.4)	73 (29.2)	<0.001
Ethnicity				
White	299 (59.8)	177 (70.8)	122 (40.8)	<0.001
Asian	94 (18.8)	44 (17.6)	50 (20.0)	<0.001
Black-African	47 (9.4)	16 (6.4)	31 (12.4)	<0.001
Black-Caribbean	41 (8.2)	8 (3.2)	33 (13.2)	<0.001
Other	19 (3.8)	5 (2.0)	14 (5.6)	<0.001
Physical activity				
Daily	62 (12.4)	39 (15.6)	23 (9.2)	<0.001
> twice a week	178 (35.6)	118 (47.2)	60 (24.0)	<0.001
Once a week	63 (12.6)	30 (12.0)	33 (13.2)	<0.001
< once a week	27 (5.4)	4 (1.6)	23 (9.2)	<0.001
Never/rarely	170 (34.0)	59 (23.6)	111 (44.4)	<0.001
Family history of CVD	156 (31.2)	67 (26.8)	89 (35.6)	0.034
SBP≥140 mm Hg	54 (10.8)	19 (7.6)	35 (14.0)	0.021
DBP≥90 mm Hg	57 (11.4)	28 (11.2)	29 (11.6)	0.888
SBP≥130 mm Hg	138 (27.6)	65 (47.1)	73 (52.9)	0.424
DBP≥80 mm Hg	195 (39.0)	86 (34.4)	109 (43.6)	0.035
Hypertension definition (European guidelines)	78 (15.6)	35 (14.0)	43 (17.2)	0.324
Hypertension definition (American guidelines)	228 (45.6)	104 (41.6)	124 (49.6)	0.073
Localized gingivitis (FMBS 10%–29%)	176 (35.2)	143 (57.2)	33 (13.2)	<0.001
Generalized gingivitis (FMBS≥30)	252 (50.4)	40 (16.0)	212 (84.8)	<0.001
Continuous: mean (SD) or median [IQR]				
Age, y*	35 [12]	34 [14]	35 [9]	0.345
BMI, kg/m²*	24.01 [5.11]	23.75 [4.92]	24.42 [5.18]	0.209
SBP, mm Hg	122.39 (14.05)	120.70 (12.59)	124.07 (14.33)	0.007
DBP, mm Hg	77.02 (10.9)	75.94 (10.76)	78.10 (11.10)	0.027
Glucose, mmol/L	1.4 [2.09]	1.2 [1.1]	1.6 [3.30]	<0.001
Total cholesterol, mmol/L	5.05 [1.30]	5.01 [1.30]	5.10 [1.21]	0.091
HDL, mmol/L	1.56 (0.43)	1.64 (0.42)	1.49 (0.44)	<0.001
LDL, mmol/L	2.96 (0.83)	2.83 (0.84)	3.09 (0.79)	<0.001
Triglycerides, mmol/L	1.3 [1.49]	1.2 [1.10]	1.3 [2.10]	0.133
Hs-CRP, mg/L	1.7 [2.39]	1.38 [2.47]	1.86 [2.37]	0.008
WBC, 1000/μL	5.93 [2.20]	5.58 [1.99]	6.36 (2.26)	<0.001
PPD	2.56 [1.95]	1.99 [0.43]	3.94 [1.24]	<0.001
CAL	2.74 [2.24]	2.02 [0.47]	4.26 [1.52]	<0.001
FMBS	30.65 [26.74]	15.45 [15.27]	53.66 (33.37]	<0.001
FMPS	50.28 [39.38]	49.15 [40.78]	51.11 [39.43]	0.166

BMI indicates body mass index; CAL, clinical attachment level; CVD, cardiovascular diseases; DBP, diastolic blood pressure; FMBS, full-mouth gingival bleeding score; FMPS, full-mouth dental plaque score; HDL, high-density lipoprotein; Hs-CRP, high-sensitive C-reactive protein; IQR, Interquartile range; LDL, low-density lipoprotein; PPD, probing pocket depth; SBP, systolic blood pressure; and WBC, white blood cells.

*Cases and controls groups balanced according to age, sex, and BMI.

Table 2. Linear Regression Models of SBP, DBP and hs-CRP, WBC According to Various Indices of Periodontitis or Systemic Inflammation

Linear regression models				
	SBP		DBP	
Exposure: periodontitis	Model 1 β±SE	Model 2 β±SE	Model 1 β±SE	Model 2 β±SE
Categorical variable				
Cases vs controls (perio vs non perio)	3.36±1.25*	3.46±1.25*	2.16±0.98†	1.48±1.04
Continuous variables				
CAL (mean)	1.51±0.42‡	0.89±0.42†	0.69±0.33†	0.14±0.35
No. of sites with CAL ≥3 mm	0.03±0.01*	0.02±0.01	0.02±0.01	0.0002±0.01
No. of sites with CAL ≥4 mm	0.04±0.01*	0.02±0.01	0.02±0.01	0.004±0.01
No. of sites with CAL ≥5 mm	0.04±0.01*	0.02±0.01	0.02±0.01	0.006±0.01
No. of sites with CAL ≥6 mm	0.06±0.02*	0.03±0.02	0.03±0.02	0.004±0.01
% of sites with CAL ≥3 mm	0.06±0.02*	0.03±0.02	0.02±0.02	-0.006±0.01
% of sites with CAL ≥4 mm	0.06±0.02*	0.03±0.02	0.03±0.02	0.003±0.02
% of sites with CAL ≥5 mm	0.07±0.02*	0.04±0.02	0.03±0.02	0.01±0.02
% of sites with CAL ≥6 mm	0.10±0.03*	0.05±0.03	0.04±0.03	0.01±0.02
PPD (mean)	1.86±0.52‡	1.51±0.5*	0.81±0.41†	0.32±0.44
No. of sites with PPD ≥4 mm	0.04±0.01*	0.03±0.01†	0.02±0.01	0.008±0.01
No. of sites with PPD ≥5 mm	0.05±0.02*	0.04±0.02†	0.02±0.01	0.01±0.01
No. of sites with PPD ≥6 mm	0.08±0.02*	0.06±0.02*	0.03±0.02	0.01±0.02
% of sites with PPD ≥4 mm	0.07±0.02*	0.05±0.02†	0.03±0.02	0.01±0.02
% of sites with PPD ≥5 mm	0.07±0.03*	0.06±0.03†	0.03±0.02	0.01±0.02
% of sites with PPD ≥6 mm	0.12±0.04*	0.10±0.04*	0.05±0.03	0.02±0.03
FMBS (mean)	0.09±0.02‡	0.07±0.02*	0.04±0.02†	0.02±0.02
Exposure: systemic inflammation	SBP		DBP	
	Model 1 β±SE	Model 2 β±SE	Model 1 β±SE	Model 2 β±SE
Hs-CRP	0.22±0.19	0.18±0.17	0.24±0.15	0.21±0.14
WBC	0.17±0.38	0.61±0.34	0.25±0.30	0.44±0.28
Exposure: periodontitis	Hs-CRP (log hs-CRP)		WBC (log WBC)	
	Model 1 β±SE	Model 2 β±SE	Model 1 β±SE	Model 2 β±SE
Categorical variable				
Cases vs controls (perio vs nonperio)	0.24±0.08*	0.01±0.09	0.08±0.23‡	0.08±0.02*
Continuous variables				
CAL (mean)	0.083±0.029*	0.040±0.032	0.022±0.008*	0.023±0.008*
PPD (mean)	0.112±0.036*	0.05±0.04	0.031±0.01*	0.029±0.01*
FMBS (mean)	0.004±0.002†	0.002±0.002	0.002±0.000‡	0.001±0.000*

Model 1: Unadjusted. Model 2: age, BMI, sex, ethnicity, smoking, physical activity, family history of CVD. B indicates beta coefficient; CAL, clinical attachment level; DBP, diastolic blood pressure; FMBS, full-mouth gingival bleeding score; Hs-CRP, high-sensitive C-reactive protein; PPD, probing pocket depth; SBP, systolic blood pressure; and WBC, white blood cells.

*$P<0.01$.

†$P<0.05$.

‡$P<0.001$.

periodontitis (controls). Cases presented with more than twice higher likelihood of SBP≥140 mm Hg and almost 50% higher odds of DBP≥80 mm Hg than the controls.

A recent systematic review confirmed a 4.5 mm Hg SBP and 2.5 mm Hg DBP greater arterial BP values in the general population (including participants with and without other comorbidities).[10] In a previously reported age- and sex-matched case-control study looking at the association of periodontitis, systemic inflammation, and endothelial function, greater differences in SBP (7 mm Hg) and CRP (1.3 mg/L) levels between the cases and controls were observed.[17]

Elevated BP remains the main risk factor for heart failure, atrial fibrillation, chronic kidney disease, heart valve diseases, aortic syndromes, and dementia, in addition to coronary heart disease and stroke.[18] It is now

Table 3. Multiple Logistic Regression Models of SBP≥140 mm Hg, DBP≥90 mm Hg, SBP≥130 mm Hg, DBP≥80 mm Hg and Hypertension Definitions according to Periodontitis Diagnosis, hs-CRP and WBC

Multiple logistic models			
Exposure: periodontitis	SBP≥140 mm Hg	DBP≥90 mm Hg	Hypertension definition (European)
Model 1 OR (95% CI)	1.98 (1.10–3.65)*	1.05 (0.59–1.81)	1.28 (0.78–2.08)
Model 2 OR (95% CI)	2.31 (1.17–4.67)*	1.05 (0.55–1.98)	1.24 (0.71–2.18)
Exposure: Hs-CRP			
Model 1 OR (95% CI)	0.98 (0.89–1.08)	0.97 (0.88–1.08)	0.97 (0.88–1.05)
Model 2 OR (95% CI)	0.95 (0.84–1.06)	0.97 (0.86–1.09)	0.95 (0.85–1.05)
Exposure: WBC			
Model 1 OR (95% CI)	1.00 (0.84–1.18)	0.92 (0.78–1.10)	0.97 (0.84–1.13)
Model 2 OR (95% CI)	1.05 (0.87–1.27)	0.97 (0.80–1.17)	1.02 (0.87–1.20)
Exposure: periodontitis	SBP≥130 mm Hg	DBP≥80 mm Hg	Hypertension definition (American)
Model 1 OR (95% CI)	1.17 (1.17–1.73)	1.47 (1.03–2.12)*	1.38 (0.97–1.96)
Model 2 OR (95% CI)	1.26 (0.78–2.00)	1.20 (0.78–1.84)	1.23 (0.81–1.88)
Exposure: Hs-CRP			
Model 1 OR (95% CI)	1.02 (0.96–1.08)	1.06 (0.99–1.12)	1.06 (0.99–1.13)
Model 2 OR (95% CI)	1.02 (0.96–1.08)	1.06 (0.99–1.12)	1.06 (0.99–1.27)
Exposure: WBC			
Model 1 OR (95% CI)	1.00 (0.89–1.13)	1.04 (0.93–1.16)	1.03 (0.93–1.15)
Model 2 OR (95% CI)	1.06 (0.93–1.21)	1.08 (0.96–1.22)	1.09 (0.97–1.23)

Model 1: unadjusted. Model 2: age, BMI, sex, ethnicity, smoking, physical activity, family history of CVD. BMI indicates body mass index; CVD, cardiovascular diseases; DBP, diastolic blood pressure; Hs-CRP, high-sensitive C-reactive protein; OR, odds ratio; SBP, systolic blood pressure; and WBC, white blood cells.

*$P<0.01$.

†$P<0.05$.

‡$P<0.001$.

understood that biologically normal BP levels are lower than what previously fell within a normal range.[15] The observed differences of SBP/DBP between cases and control in this study could be clinically relevant and might represent an overlooked mechanism linking periodontitis with increased future CVD risk.[19]

In agreement with previous studies,[20,21] this study showed that irrespective of periodontal status, bleeding gums was associated with SBP. Similarly, a more recent secondary analysis of NHANES (III also reported a 2.6 mm Hg higher mean SBP for gingivitis, also independently associated with 40% greater odds of high/uncontrolled BP.[11] Bleeding gums, the earliest sign of periodontal diseases, has also been linked to increased systemic biomarkers and vascular changes.[22,23] Self-report of bleeding gums is an easy measure of periodontal inflammation for both patients and clinicians and it could represent a valuable parameter in routine BP screening protocols.

Several mechanisms underlying the links between gingival diseases and hypertension have been proposed with dysbiotic subgingival microbiome triggering low-grade systemic inflammation and oxidative stress representing the main pathways.[24] Periodontitis patients express not only increased local and systemic inflammatory markers, such as CRP, TNF (tumor necrosis

Table 4. Multivariate Fitted SBP According to Bleeding Status

Bleeding status (irrespective of periodontitis)	N (%)	SBP Mean (SD)	Multiple comparisons ΔSBP (95% CI) *P* value		
			Gingival health	Localized bleeding	Generalized bleeding
Gingival health (FMBS<10%)	72 (14.4)	118.71 (11.23)	…		
Localized bleeding (10%>FMBS≤30%)	176 (35.2)	121.92 (14.68)	3.21 (6.61–0.20) *P*=0.065	…	
Generalized bleeding (FMBS≥30%)	252 (50.4)	123.77 (14.16)	5.06 (8.22–1.91) *P*=0.002	1.85 (4.65–0.94) *P*=0.192	…

ΔSBP indicates mean difference in SBP; FMBS, Full-mouth gingival bleeding score; and SBP, systolic blood pressure.

factor)-α, neutrophilic enzymes, WBC, and disparity in T-cell subtypes, but also neutrophil dysfunction, which are all mechanisms resulting in vascular changes and endothelial dysfunction.[19,25,26] The presence of periodontal pathogens has been linked to hypertension in epidemiological studies.[27] Preclinical evidence originated by experimental animal models, including immunizations with *Porphyromonas gingivalis* lysate and lipopolysaccharide-endotoxin from other gram-negative bacteria, caused prolonged T-cell activation and elicited increased levels of CRP, TNF-α, and IL (interleukin)-1β, resulting in increased BP.[28] Interaction between oral-gut microbiome can also contribute to amplification of inflammation and metabolic changes.[29] Recent evidence implicates oral bacteria in the nitrate-nitrite-nitric oxide (NO) pathway and pathogenesis of hypertension,[30] with high concentrations of nitrite-reductase bacteria increasing systemic NO and having an effect of lowering SBP.[31]

In the current study, hs-CRP/WBC as a proxy of systemic inflammation was associated with periodontitis but not with SBP/DBP. Additionally, WBC did not show a mediation effect between periodontitis and BP. These results are in partial disagreement with a recent analysis of cross-sectional data, based on national health surveys in US and Korea, where a 2% to 7% mediating effect of WBC and CRP was observed when examining the association between periodontitis and hypertension.[32] A possible explanation for these differences relates to an overall younger population of this study sample (35 years old) versus 51 and 46 years old in the American and Korean populations, and possibly due to the systemically healthy status of this sample, when compared with representative samples of those populations, including systemic conditions. Nevertheless, an association of arterial BP with both continuous and categorical measures of periodontitis in younger and systemically healthy individuals strengthens the evidence in favor of a causal association between the two diseases.[24]

A recent Mendelian Randomization analysis and results from a short-term pilot randomized controlled clinical trial on periodontal treatment of resistant hypertensive patients corroborate these findings.[9] Single nucleotide polymorphisms in genes *SIGLEC5, DEFA1A3, MTND1P5,* and *LOC107984137* loci in Genome-wide association studies (GWAS) linked to periodontitis, and BP phenotype were discovered and a noticeable reduction in SBP/DBP, endothelial function as well as inflammatory cytokines and activated T-cell subsets was observed 2 months following the treatment. Similarly, another randomized controlled clinical trial with 6 months follow-up on a prehypertensive population also observed a significant reduction in SBP/DBP following nonsurgical periodontal treatment.[33] Oral health promotion strategies such as tooth brushing twice daily has demonstrated very effective not only in managing and preventing most common oral conditions[34] but also in providing a powerful and affordable tool for hypertension control.[35] Notably, a 14% reduction in cardiovascular events has been observed with a 4.4 mm Hg reduction in SBP.[36] Preliminary evidence suggests that periodontal treatment in patients with type 2 diabetes, a common comorbidity, could result in substantial long-term reduction of medical-related costs for healthcare systems.[37] Thus, given the importance of nonpharmacological and pharmacological BP-lowering strategies in decreasing CVD risk and mortality,[38] larger multicenter randomized controlled clinical trials and health-economic analyses are warranted to further investigate the benefits of periodontal treatments on BP prevention and control.

Elevated BP is usually asymptomatic and best detected in screening programs or opportunistic measurements of BP, which confirm that a worryingly high number of individuals (>50%) is unaware of a possible diagnosis of hypertension.[39] The presented study confirmed that a 15% to 45% of the sample could exhibit undetected hypertension (depending on whether a European or US guideline definition was used), with 54% to 55% of these having periodontitis. In a recent cross-sectional study on the association of periodontitis and hypertension, a 15.9% of the study sample presented with undiagnosed high BP (based on a single office measurement), of which a 62.5% had periodontitis.[40] These data confirm that programs of hypertension screening in the dental settings should not be underestimated.

Although this study improves the understanding of the association between periodontitis and arterial BP, it is recognized some limitations exist. The study design and analysis may have introduced some bias namely through selection and assessment biases.[41] Furthermore, in this study we did not account for other factors that might have impacted BP, such as abdominal obesity, salt intake, use of anti-inflammatory drugs, hormone treatments, or stress as well as additional oral diseases (ie, caries). Future analyses should focus on existing or new epidemiological evidence (longitudinal studies) where all possible confounders are appropriately considered. Nevertheless, this study benefits from a robust research methodology in assessing the exposure (periodontitis) and outcome (BP), and sufficient statistical power could have counteracted some of the limitations.[42] Furthermore, using a balanced study design through matching for common confounders of arterial BP facilitated analysis of comparable groups.[43]

Conclusions

This study expands current knowledge on the association between periodontitis and elevated BP, pointing at the importance of this link in the generally healthy population. Oral health professionals could play a pivotal role in helping the medical community detecting and tackling the burden and consequences of hypertension.

Perspectives

Periodontal treatments could be well-tolerated novel nonpharmacological interventions for the management of hypertension. Particularly so when patients are informed that periodontal treatment could be beneficial not only for their oral health but also for their general health and wellbeing in return. Thus, future directions and broad implications of this work will involve liaison of dental and medical health professionals with the following objectives:

1. Raising awareness of the increased risk for high BP among individuals with periodontal diseases.
2. Implementing hypertension screening systems by dental professionals and prompt referral to general practitioners.
3. Implementing periodontal disease screening systems by medical professionals and referral to dental practitioners.
4. Providing advice for common risk factors: Healthy diet, smoking cessation, promoting physical activity, alcohol reduction, and diabetes management.
5. Early diagnosis and management of gingivitis and periodontitis. Effective prevention and treatment of these conditions is very cost-effective and has shown an effect in reduction of systemic markers of inflammation and improvement in endothelial function.
6. Future research will involve larger multicenter randomized controlled clinical trials to test the effects on periodontal treatment on BP levels.

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REFERENCES

1. Forouzanfar MH, Afshin A, Alexander LT; GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388:1659–1724. doi: 10.1016/S0140-6736(16)31679-8
2. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 Countries. *Circulation.* 2016;134:441–450. doi: 10.1161/CIRCULATIONAHA.115.018912
3. Scholes S, Conolly A, Mindell JS. Income-based inequalities in hypertension and in undiagnosed hypertension: analysis of Health Survey for England data. *J Hypertens.* 2020;38:912–924. doi: 10.1097/HJH.0000000000002350
4. Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. *Nat Rev Immunol.* 2019;19:517–532. doi: 10.1038/s41577-019-0160-5
5. Jayedi A, Rahimi K, Bautista LE, Nazarzadeh M, Zargar MS, Shab-Bidar S. Inflammation markers and risk of developing hypertension: a meta-analysis of cohort studies. *Heart.* 2019;105:686–692. doi: 10.1136/heartjnl-2018-314216
6. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. *J Periodontol.* 2018;89(suppl 1):S159–S172. doi: 10.1002/JPER.18-0006
7. Frencken JE, Sharma P, Stenhouse L, Green D, Laverty D, Dietrich T. Global epidemiology of dental caries and severe periodontitis - a comprehensive review. *J Clin Periodontol.* 2017;44(suppl 18):S94–S105. doi: 10.1111/jcpe.12677
8. Ferreira MC, Dias-Pereira AC, Branco-de-Almeida LS, Martins CC, Paiva SM. Impact of periodontal disease on quality of life: a systematic review. *J Periodontal Res.* 2017;52:651–665. doi: 10.1111/jre.12436
9. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalski R, Pelka P, Nowakowski D, Wilk G, Mikolajczyk TP, Schramm-Luc A, Furtak A, et al. Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. *Eur Heart J.* 2019;40:3459–3470. doi: 10.1093/eurheartj/ehz646
10. Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F. Periodontitis is associated with hypertension: a systematic review and meta-analysis. *Cardiovasc Res.* 2020;116:28–39. doi: 10.1093/cvr/cvz201
11. Pietropaoli D, Monaco A, D'Aiuto F, Muñoz Aguilera E, Ortu E, Giannoni M, Czesnikiewicz-Guzik M, Guzik TJ, Ferri C, Del Pinto R. Active gingival inflammation is linked to hypertension. *J Hypertens.* 2020;38:2018–2027. doi: 10.1097/HJH.0000000000002514
12. D'Aiuto F, Parkar M, Nibali L, Suvan J, Lessem J, Tonetti MS. Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial. *Am Heart J.* 2006;151:977–984. doi: 10.1016/j.ahj.2005.06.018
13. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, Myers MG, Ogedegbe G, Schwartz JE, Townsend RR, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. *Hypertension.* 2019;73:e35–e66. doi: 10.1161/HYP.0000000000000087
14. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339
15. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018;71:e127–e248. doi: 10.1016/j.jacc.2017.11.006
16. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet.* 2002;359:248–252. doi: 10.1016/S0140-6736(02)07451-2
17. Amar S, Gokce N, Morgan S, Loukideli M, Van Dyke TE, Vita JA. Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arterioscler Thromb Vasc Biol.* 2003;23:1245–1249. doi: 10.1161/01.ATV.0000078603.90302.4A
18. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. *Hypertension.* 2020;75:285–292. doi: 10.1161/HYPERTENSIONAHA.119.14240
19. Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, Chapple I, Dietrich T, Gotsman I, Graziani F, et al. Periodontitis and cardiovascular diseases: consensus report. *J Clin Periodontol.* 2020;47:268–288. doi: 10.1111/jcpe.13189

20. Pietropaoli D, Del Pinto R, Ferri C, Marzo G, Giannoni M, Ortu E, Monaco A. Association between periodontal inflammation and hypertension using periodontal inflamed surface area and bleeding on probing. *J Clin Periodontol.* 2020;47:160–172. doi: 10.1111/jcpe.13216
21. Tsakos G, Sabbah W, Hingorani AD, Netuveli G, Donos N, Watt RG, D'Aiuto F. Is periodontal inflammation associated with raised blood pressure? Evidence from a National US survey. *J Hypertens.* 2010;28:2386–2393. doi: 10.1097/HJH.0b013e32833e0fe1
22. Demmer RT, Papapanou PN, Jacobs DR Jr, Desvarieux M. Bleeding on probing differentially relates to bacterial profiles: the oral Infections and vascular disease epidemiology study. *J Clin Periodontol.* 2008;35:479–486. doi: 10.1111/j.1600-051X.2008.01232.x
23. Bokhari SA, Khan AA, Butt AK, Hanif M, Izhar M, Tatakis DN, Ashfaq M. Periodontitis in coronary heart disease patients: strong association between bleeding on probing and systemic biomarkers. *J Clin Periodontol.* 2014;41:1048–1054. doi: 10.1111/jcpe.12284
24. Del Pinto R, Pietropaoli D, Munoz-Aguilera E, D'Aiuto F, Czesnikiewicz-Guzik M, Monaco A, Guzik TJ, Ferri C. Periodontitis and hypertension: is the association causal? *High Blood Press Cardiovasc Prev.* 2020;27:281–289. doi: 10.1007/s40292-020-00392-z
25. Czesnikiewicz-Guzik M, Nosalski R, Mikolajczyk TP, Vidler F, Dohnal T, Dembowska E, Graham D, Harrison DG, Guzik TJ. Th1-type immune responses to Porphyromonas gingivalis antigens exacerbate angiotensin II-dependent hypertension and vascular dysfunction. *Br J Pharmacol.* 2019;176:1922–1931.
26. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. *N Engl J Med.* 2007;356:911–920. doi: 10.1056/NEJMoa063186
27. Desvarieux M, Demmer RT, Jacobs DR Jr, Rundek T, Boden-Albala B, Sacco RL, Papapanou PN. Periodontal bacteria and hypertension: the oral infections and vascular disease epidemiology study (INVEST). *J Hypertens.* 2010;28:1413–1421. doi: 10.1097/HJH.0b013e328338cd36
28. Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, Hasan AA, Amar S. Inflammation, immunity, and infection in atherothrombosis: JACC review topic of the week. *J Am Coll Cardiol.* 2018;72:2071–2081. doi: 10.1016/j.jacc.2018.08.1043
29. Arimatsu K, Yamada H, Miyazawa H, Minagawa T, Nakajima M, Ryder MI, Gotoh K, Motooka D, Nakamura S, Iida T, et al. Oral pathobiont induces systemic inflammation and metabolic changes associated with alteration of gut microbiota. *Sci Rep.* 2014;4:4828. doi: 10.1038/srep04828
30. Goh CE, Trinh P, Colombo PC, Genkinger JM, Mathema B, Uhlemann AC, LeDuc C, Leibel R, Rosenbaum M, Paster BJ, et al. Association between nitrate-reducing oral bacteria and cardiometabolic outcomes: results from ORIGINS. *J Am Heart Assoc.* 2019;8:e013324. doi: 10.1161/JAHA.119.013324
31. Tribble GD, Angelov N, Weltman R, Wang BY, Eswaran SV, Gay IC, Parthasarathy K, Dao DV, Richardson KN, Ismail NM, et al. Frequency of tongue cleaning impacts the human tongue microbiome composition and enterosalivary circulation of nitrate. *Front Cell Infect Microbiol.* 2019;9:39. doi: 10.3389/fcimb.2019.00039
32. Muñoz Aguilera E, Leira Y, Miró Catalina Q, Orlandi M, Czesnikiewicz-Guzik M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F. Is systemic inflammation a missing link between periodontitis and hypertension? Results from two large population-based surveys. *J Intern Med.* 2020. doi: 10.1111/joim.13180
33. Zhou QB, Xia WH, Ren J, Yu BB, Tong XZ, Chen YB, Chen S, Feng L, Dai J, Tao J, et al. Effect of intensive periodontal therapy on blood pressure and endothelial microparticles in patients with prehypertension and periodontitis: a randomized controlled trial. *J Periodontol.* 2017;88:711–722. doi: 10.1902/jop.2017.160447
34. Jepsen S, Blanco J, Buchalla W, Carvalho JC, Dietrich T, Dörfer C, Eaton KA, Figuero E, Frencken JE, Graziani F, et al. Prevention and control of dental caries and periodontal diseases at individual and population level: consensus report of group 3 of joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. *J Clin Periodontol.* 2017;44(suppl 18):S85–S93. doi: 10.1111/jcpe.12687
35. Choi HM, Han K, Park YG, Park JB. Associations among oral hygiene behavior and hypertension prevalence and control: the 2008 to 2010 Korea National health and nutrition examination survey. *J Periodontol.* 2015;86:866–873. doi: 10.1902/jop.2015.150025
36. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* 2009;338:b1665. doi: 10.1136/bmj.b1665
37. Smits KP, Listl S, Plachokova AS, Van der Galien O, Kalmus O. Effect of periodontal treatment on diabetes-related healthcare costs: a retrospective study. *BMJ Open Diabetes Res Care.* 2020;8:e001666.
38. Mahmood S, Shah KU, Khan TM, Nawaz S, Rashid H, Baqar SWA, Kamran S. Non-pharmacological management of hypertension: in the light of current research. *Ir J Med Sci.* 2019;188:437–452. doi: 10.1007/s11845-018-1889-8
39. Lindholt JS, Søgaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. *Lancet.* 2017;390:2256–2265. doi: 10.1016/S0140-6736(17)32250-X
40. Machado V, Aguilera EM, Botelho J, Basit Hussain S, Leira Y, Proença L, D'Aiuto F, João Mendes J. Association between periodontitis and high blood pressure: results from the study of periodontal health in Almada-Seixal (SoPHiAS). *J Clin Med.* 2020;9:1585.
41. Sedgwick P. Nested case-control studies: advantages and disadvantages. *BMJ : British Medical Journal.* 2014;348:g1532.
42. Gauderman WJ. Sample size requirements for matched case-control studies of gene-environment interaction. *Stat Med.* 2002;21:35–50. doi: 10.1002/sim.973
43. Pearce N. Analysis of matched case-control studies. *BMJ.* 2016;352:i969.