Journal of Clinical Neuroscience 90 (2021) 233–237

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical study

Number of teeth is independently associated with ischemic stroke: A case-control study

Thayana Salgado de Souza Leao [a,b], Aline Veloso Zanoni [a], Raiane Franzon [a], Gustavo Henrique Tomasi [c], Lucas Piccoli Conzatti [c], Luiz Carlos Porcelo Marrone [c], Mark Allan Reynolds [b], Maximiliano Schünke Gomes [a,d,*]

[a] Graduate Program in Dentistry, School of Health and Life Sciences, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[b] Department of Advanced Oral Sciences and Therapeutics, University of Maryland School of Dentistry, Baltimore, MD 21201, United States
[c] Department of Neurology, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[d] Medical and Dental Center of the Military Police of Rio Grande do Sul, Brazil

ARTICLE INFO

Article history:
Received 2 January 2021
Accepted 27 May 2021

Keywords:
Ischemic stroke
Oral health
Tooth loss
Risk factors
Epidemiology

ABSTRACT

Poor oral health has been suggested as a potential risk factor for the occurrence of cardiovascular events. The present study aimed to test the hypothesis that the number of permanent natural teeth (NT) is independently associated with the occurrence of ischemic stroke (IS) or transient ischemic attack (TIA) in a southern Brazilian population. This case-control study enrolled 458 subjects, 229 hospital patients diagnosed with IS or TIA (cases) and 229 patients with no history of cardiovascular disease (controls). NT was assessed through a head and neck multidetector computed tomography angiography (MDCTA) and panoramic radiographs. The participants were matched by age and sex. Sociodemographic and medical confounding variables were obtained from the hospital charts and through a structured questionnaire. Multivariate logistic regression analysis were carried out to estimate the association between NT and the occurrence of IS or TIA. The mean age was 58.37 ± 10.75 years, with 46.7% males. Adjusted analyses showed an independent association between IS or TIA and hypertension (OR = 6.34, 95%CI = 3.93–10.24), smoking (OR = 4.70, 95%CI = 2.76–7.99) and NT (lower quartile: ≤7 teeth) (OR = 5.59, 95%CI = 2.88–10.86). The number of permanent natural teeth was inversely and independently associated with the occurrence of IS or TIA in this population. Present findings suggest a gradient effect on the association between oral health and IS.

1. Introduction

Stroke is one of the main causes of death worldwide, with nearly 15 million new fatal or non-fatal events each year [1]. The incidence of stroke is expected to increase, considering the global population ageing [2]. The etiology of stroke include both genetic and environmental factors, and the main risk factors are age, high blood pressure, smoking, diabetes, dyslipidemia, and obesity [3]. Nevertheless, the traditional risk factors for cardiovascular diseases (CVD) cannot explain all the clinical and epidemiological features of the occurrence of stroke. Novel risk factors for CVD are under investigation, especially those related to biomarkers of inflammation and oxidative stress [4].

Accumulating evidence has suggested that chronic oral inflammatory diseases (OID) may be associated with vascular events, such as atherosclerosis [5] ischemic stroke (IS) [6] and myocardial infarction [7]. The most prevalent oral disease worldwide are caries and periodontitis [8], and untreated caries may lead to endodontic infection with consequent apical periodontitis (AP) [9]. Both periodontitis and AP are chronic OID caused by a complex microbiota, especially gram-negative bacteria, which affects teeth and the supporting tissues [10]. Consistent findings suggest that chronic OID may contribute to a systemic immune response not confined to the local oral site, leading to increased systemic inflammation with a potential role in the global vascular risk [11].

Previous reviews have addressed the biologic plausibility and possible pathogenic mechanisms linking OID, atherogenesis, and CVD [5,12,13]. The potential biological plausibility relating OID and atherosclerotic CVD have been described through three main

* Corresponding author at: 6681 Av. Ipiranga, prédio 6, CEP: 90619900 Porto Alegre, RS, Brazil.
E-mail addresses: thayana.leao@pucrs.br (Thayana Salgado de Souza Leao), mreynolds@umaryland.edu (M.A. Reynolds), maximiliano.gomes@pucrs.br (M.S. Gomes).

https://doi.org/10.1016/j.jocn.2021.05.059
0967-5868/

routes: a) the occurrence of transitory bacteremia resulting from the oral cavity; b) the vascular dissemination of toxins and byproducts from oral microorganisms; c) the low-grade systemic inflammatory response and oxidative stress resulting from the presence of chronic OID. The main pathogenic mechanisms are based on the possible role of oral microflora and their toxins in the occurrence of endothelial dysfunction, favoring the development of initial atherosclerotic lesions. It is also suggested that oral microorganisms may contribute to the increase in the thickness of atheromatous plaques, since many studies have identified the presence of oral microorganisms within vascular lesions. Finally, it has also been described that oral microflora can contribute to the modulation and maturation of atheroma, facilitating the rupture and consequent vascular thrombosis [5,12,13].

The number of permanent natural teeth (NT) has been evaluated in several epidemiologic studies as a strong surrogate of the individual's previous history of OID [14,15] since the main causes of tooth extraction are caries, AP and/or periodontitis [8,16]. Previous studies evaluated the association between NT and stroke [17,18]. However, a possible gradient effect in the association between the burden of oral diseases, NT and CVD remains unclear [19]. In addition, the previous studies on this topic were carried out in samples from developed countries [20,21] which limits the extrapolation of the results to populations with different socioeconomic and cultural aspects. Thus, the aim of this study was to test the hypothesis that NT is independently associated with the occurrence of IS or transient ischemic attack (TIA) in a southern Brazilian population.

2. Methodology

2.1. Ethical issues

The research protocol was approved by the Ethics and Research Committee of the Pontifical Catholic University of Rio Grande do Sul (CAAE#66511417.4.1001.5336). All patients signed an informed consent form authorizing the use of the data and images for research purposes. Before the analyses, all data were de-identified to protect the patient's anonymity.

2.2. Study design and sample selection

This observational case-control study conforms to the STROBE guidelines. A previous sample size calculation was carried out based on the results of a previous study [22] considering a mean NT among cases and controls of 15.14 ± 9.43 and 19.19 ± 8.30, respectively, with α = 5% and a power of 90%, resulting in at least 114 subjects per group to identify significant differences.

A total of 458 adult individuals of any age and sex were enrolled in this study (229 cases and 229 age and sex matched controls), in the period between March 2015 to February 2018. All consecutive patients from the Neurological Department of the São Lucas Hospital (SLH) of the Pontifical Catholic University of Rio Grande do Sul (PUCRS), Brazil, diagnosed with IS or TIA, and who had a head and neck multidetector computed tomography angiography (MDCTA) and a magnetic resonance imaging (MRI) of the brain, were included in the study as cases. Control individuals were recruited from the Dental Clinics of the School of Health and Life Sciences (SHS) of the same institution, PUCRS, Brazil, and who had recent panoramic radiographs, with no previous history of CVD, IS or TIA Fig. 1.

2.3. Main exposure

The number of permanet natural teeth (NT) was evaluated by a trained dentist, who was blinded to all the other variables. In case patients, NT was assessed using the MDCTA images, with bone filter application [15]; in the control group NT was measured using panoramic radiographs. Impacted teeth and deciduous teeth were not assessed. After the data collection, NT was classified in four categories: NT $\geq$ 24; NT $\leq$ 23 & NT $\geq$ 18 ; NT $\leq$ 17 & NT $\geq$ 8; NT $\leq$ 7. These cutoffs were established according to a balanced distribution of NT (quartiles) in this sample.

2.4. Assessment of covariates

Potential sociodemographic (age and sex) and medical (hypertension, diabetes, dyslipidemia, smoking, and body mass index (BMI)) confounders were assessed in both groups. In the case group, the data were collected from the hospital patients' charts. Hypertension was defined as systolic blood pressure (SBP) $\geq$130 mm Hg or diastolic blood pressure (DBP) $\geq$80 mm Hg, and/or anti-hypertensive drug therapy [23]. The BMI was calculated by the nutrition department, dividing the weight by the height squared [24]. Diabetes Mellitus was defined as the use of insulin or hypoglycemic medication, or fasting plasma glucose $\geq$ 100 mg/dl, or a history of diagnosed diabetes [25]. Dyslipidemia was defined as a total cholesterol >200 and/or LDL > 130 and/or triglycerides >200. Smoking was assessed as current, former, or never smoker. For the control group, trained interviewers used a structured questionnaire proposed by Brazilian Cardiology Society [26] to screen the history of previous cardiovascular disease and associated risk factors, assessing the same sociodemographic and medical variables.

2.5. Main outcome

Cerebral ischemia was defined according to the World Health Organization criteria [27]. The diagnosis of IS was performed in patients with an acute ischemic lesion in the brain and/or neurological deficits lasting >24 h (n = 174). The TIA was attributed for patients with neurological deficit <24 h without new ischemic lesions (n = 55). The ischemic nature was confirmed by a brain image and confirmed by a neurologist specialized in the stroke field.

2.6. Statistical analysis

Descriptive statistics (mean, N and %) related to case and control groups was performed. The normality of the distribution of variables was determined by using the Shapiro-Wilk test. The numerical variables with non-normal distribution were compared by using the Mann-Witney *U* test. Chi-square (x^2) test was performed to analyze the qualitative variables. Bivariate and multivariate logistic regression analyses were carried out to estimate the association (odds ratio (OR)) between NT and IS or TIA. All covariates associated with IS or TIA in the bivariate analysis with a p-value <0.25 were considered potential confounders and were included in the multivariate model, where the value for rejection of the null hypothesis was set at 5%. The statistical analyses were carried out using SPSS v.26 (IBM, Chicago, USA).

3. Results

The characteristics of the sample (N/%) in relation to the case and control groups are expressed in Table 1. The mean age in the case and control groups were 58. 38 ± 10.73 and 58.36 ± 10.78

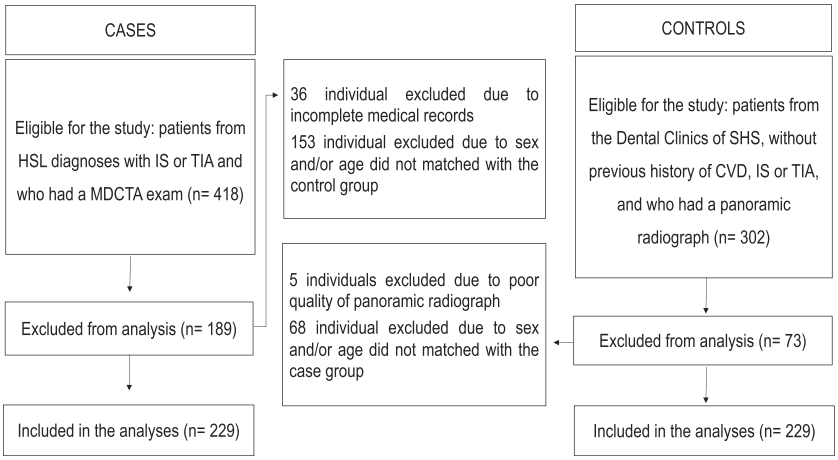

Fig. 1. Flowchart of the study sample.

Table 1
Socio-demographic, medical and dental characteristic of the sample in relation to the case (IS or TIA) and control groups. N = 458.

Variables	Control (n = 229) N (%)	Case (n = 229) N (%)	*p*-value
Socio-demographic			
Age (mean ± sd)	58.36 ± 10.78	58.38 ± 10.73	0.99[a]
Age (≥60 y)	113 (50.4)	111 (49.6)	0.85[b]
Male	107 (50)	107 (50)	1.00[b]
Medical			
BMI > 25	136 (47.7)	149 (52.3)	0.13[b]
Hypertension	78 (30.8)	175 (69.2)	<0.01[b]
Diabetes Mellitus	35 (44.3)	44 (55.7)	0.73[b]
Smoking (current or former)	37 (27.6)	97 (72.4)	<0.01[b]
Dyslipidemia	5 (55.6)	4 (44.4)	0.73[b]
Dental			
Number of teeth (mean ± sd)	18.53 ± 8.02	11.78 ± 10.06	<0.01[a]

a = Mann-Witney *U* test; b = Chi-square test; BMI = body mass index; NT = number of teeth.

respectively, and both groups had 50% of male participants. There was no difference in age and sex between study groups ($p > 0.05$). The case group presented higher levels of hypertension and smoking ($p < 0.01$). The mean number of teeth among participants in the control group was higher than the case group (18.53 ± 8.02 versus 11.78 ± 10.06).

The univariate regression analyses reveled a significant association between the occurrence of IS or TIA and hyperthension (OR = 6.27, 95%CI = 4.16–9.45), smoking (current or former) (OR = 3.81, 95%CI = 2.45–5.91), NT ≤ 17 & NT ≥ 8 (OR = 2.04, 95%CI = 1.17–3.54) and NT ≤ 7 (OR = 7.98, 95%CI = 4.45–14.29) (Table 2). The final multivariate regression model, adjusted for BMI, hypertension, smoking and NT, revealed a significant and independent association between hypertension (OR = 6.34, 95%CI = 3.93–10.24), smoking (current or former) (OR = 4.70, 95%CI = 2.76–7.99) and the lower quertile of NT ≤ 7 (OR = 5.59, 95%CI = 2.88–10.86) and the ocurrence of IS or TIA (Table 2).

4. Discussion

Present findings support the hypothesis that the number of permanent natural teeth is inversely and independently associated with the occurrence of IS or TIA. This study is novel in confirming the relation between poor oral health and adverse cerebrovascular events in a southern Brazilian population. Noteworthy, a gradient effect was clearly detected on the association between NT and IS or TIA. Thus, present results reinforce that oral health may be an additional risk indicator for stroke, parallel to the major known risk factors which include older age, smoking, ethnicity, hypertension, diabetes, and obesity [3].

The worldwide main causes of tooth extraction are dental caries with pulpal involvement and periodontitis [16] making NT a strong surrogate of previous history of OID. The biologic plausibility that launches NT as an emerging risk factor for the occurrence of atherosclerotic and ischemic events is related to the entry of oral pathogens in the bloodstream during transient bacteremia, which may play a role in the development and maturation of atheroma plaques [28]. Oral bacteria have been identified in atheroma plaques, suggesting that periodontopathic micro-organisms might be metabolically active within the wall of arteries, under the atherosclerotic lesions [29–31]. In addition, OID has the potential

Table 2
Unadjusted and adjusted regression analyses on the association between socio-demographic, medical and dental variables and IS or TIA. N = 458.

Variables	Unadjusted Model 95% CI		Adjusted Model* 95% CI	
	OR	*p-value*	OR	*p-value*
BMI (>25)	1.34 (0.91–1.96)	0.13	1.32 (0.81–2.16)	0.25
Hypertension	**6.27 (4.16–9.45)**	**<0.001**	**6.34 (3.93–10.24)**	**<0.001**
Diabetes Mellitus	1.31 (0.81–2.14)	0.26	–	–
Smoking (current or former)	**3.81 (2.45–5.91)**	**<0.001**	**4.70 (2.76–7.99)**	**<0.001**
Number of teeth (NT ≤ 23 & NT ≥ 18)	1.41 (0.81–2.46)	0.22	1.05 (0.55–2.00)	0.86
(NT ≤ 17 & NT ≥ 8)	**2.04 (1.17–3.54)**	**0.01**	1.51 (0.80–2.87)	0.20
(NT ≤ 7)	**7.98 (4.45–14.29)**	**<0.001**	**5.59 (2.88–10.86)**	**<0.001**

BMI = body mass index; NT = number of teeth; * The adjusted model was adjusted for BMI, hypertension, smoking, and NT. # Dyslipidemia was not included in the OR analysis due the low number of participants.

to elevate different pro-inflammatory mediators, which may contribute to endothelial dysfunction [32].

Similar to the present findings, previous studies reported a significant association between NT and IS [17,33]. In addition, the longitudinal study by Wu *et al.* [34] analyzed data from the first national health and nutrition examination survey in the US, and revealed an independent association between periodontitis and IS (OR = 2.11, 95%CI = 1.30–3.42). However, this association was not present between periodontists and hemorrhagic stroke (OR = 1.22, 95%CI = 0.53–2.83).

In the present study, only patients diagnosed with IS or TIA were selected. Individuals presenting other cerebrovascular events, such as hemorrhagic stroke, were excluded. The possible pathophysiological mechanisms for the association between oral health and hemorrhagic stroke events are controversial, since it occurs mainly due to an arteriovenous malformation or rupture of an aneurysm [35] with no atherosclerotic origin. Interestingly, one previous case-control study carried out in a Korean population [36] found an independent association between periodontists and hemorrhagic stroke (OR = 2.5, 95% CI = 1.1–5.6).

Grau *et al.* [22] conducted a case-control study in a Germanic population, and found an independent association between NT and IS in the comparison between cases (patients with IS or TIA) and population control groups. When the analyses were carried out between the case and the hospital control group – which was not matched for age and sex – then the results were not significant. Taken together, it emphasizes the relevance of age and sex matching in case-control studies, especially when evaluating non-communicable diseases such as IS, where age is a strong confounding factor.

Previous *meta*-analysis evaluating the dose–response between tooth loss and risk of cardiovascular disease and stroke has highlighted that increasing tooth loss (per 2 increments) was associated with a 3% increment of stroke risk [14]. This inverse association between NT and the occurrence if IS or TIA was confirmed in the present study, since the fewer teeth the participant presented, the strengthened was the association. This biological gradient effect increases the likelihood that this association may be causal, according to the Hill's causation criteria [37]. Nevertheless, no causal inference can be raised by the present findings, considering the nature of the observational study design.

Some methodological strengths and limitations of the present study must be clarified. One strength of this study is related to the accuracy of the diagnoses of IS or TIA, performed in a university hospital which is a reference in neurological diseases. All the included cases had both a MDCTA and a MRI. The MDCTA was used for the neurologic diagnosis, as well as to determine the NT. Some previous studies [38,39] assessed the NT through self- report, which may provide some inaccurate results.

An important limitation of this study was the assessment of the confounding factors in the control group. Even though other studies used this same methodology [40,41] self- reported variables are prone to some level of error, especially the lack of information related to the history of systemic diseases such as hypertension, diabetes mellitus, and dyslipidemia. However, epidemiologic evidence supports the validity of self- reported health measures, especially hypertension [42] height and weight [43]. Moreover, in the present study hypertension was analysed as a dichotomic variable, defined according to recent criteria using stage 1 hypertension as SBP $\geq$ 130 mm Hg or DBP $\geq$ 80 mm Hg, and/or anti-hypertensive drug therapy [23]. We acknowledge the limitation of using Stage 1 hypertension as the cutoff for this variable, and we recognize that the independent association between the NT and stroke could be modified if different thresholds such as SBP 140/150 or above were used for hypertension. Finally, residual confounding by factors not adjusted (e.g. alcohol consumption, level of education and ethnicity) may be a further inherent limitation.

Despite NT is epidemiologically accepted as a surrogate of the history of OID, future research should assess whether the burden of OID is also associated with IS. For an accurate diagnosis of periodontitis and AP, both clinical and image exams are necessary. Computer tomography presents the highest accuracy results for identifying oral diseases such as periodontal bone loss or AP [44]. However, in this study tomography examinations were available only for participants in the case group, so unfortunately no oral data other than NT was assessed in the present study.

The number of remaining teeth has a positive impact in the quality of life and self-esteem [45]. Dental health is related to food intake and diet quality, and performs a crucial role in nutrition quality [46]. In addition, poor oral health may increase the systemic inflammation, resulting in endothelial damage and favouring the occurrence of cardiovascular disease [47]. However, to date, the pathophysiological link between OID and adverse cerebrovascular events is not totally clear. Results from the present case-control study encourage future interventional studies to evaluate the possible impact of the treatment of OID on IS risk.

5. Conclusion

The number of permanent natural teeth was inversely and independently associated with the occurrence of IS or TIA in this southern Brazilian population. Present findings suggest a gradient effect on the association between oral health and IS.

Declaration of Competing Interest

The authors deny any conflict of interest related to this study. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil– Finance Code 001.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2021.05.059.

References

[1] Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18(5):439–58. https://doi.org/10.1016/S1474-4422(19)30034-1.

[2] Béjot Y, Bailly H, Graber M, Garnier L, Laville A, Dubourget L, et al. Impact of the ageing population on the burden of stroke: the dijon stroke registry. Neuroepidemiology 2019;52(1–20):78–85. https://doi.org/10.1159/000492820.

[3] Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45(7):2160–236. https://doi.org/10.1161/STR.0000000000000024.

[4] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105(9):1135–43. https://doi.org/10.1161/hc0902.104353.

[5] Schenkein HA, Papapanou PN, Genco R, Sanz M. Mechanisms underlying the association between periodontitis and atherosclerotic disease. Periodontology 2020;83(1):90–106. https://doi.org/10.1111/prd.12304.

[6] Leira Y, Seoane J, Blanco M, Rodríguez-Yáñez M, Takkouche B, Blanco J, et al. Association between periodontitis and ischemic stroke: a systematic review and meta-analysis. Eur J Epidemiol 2017;32(1):43–53. https://doi.org/10.1007/s10654-016-0170-6.

[7] Lysek RP, Szafraniec K, Polak M, Jankowski P, Micek A, Wolfshaut-Wolak R, et al. Relationship between past myocardial infarction, periodontal disease and Porphyromonas gingivalis serum antibodies: a case-control study. Cardiol J 2018;25(3):386–92. https://doi.org/10.5603/CJ.a2017.0015.

[8] Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, et al., 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. 2017;96(4):380-7. 10.1177/0022034517693566.
[9] Eriksen HM, Berset GP, Hansen BF, Bjertness E. Changes in endodontic status 1973–1993 among 35-year-olds in Oslo, Norway. Int Endod J 1995;28 (3):129–32. https://doi.org/10.1111/j.1365-2591.1995.tb00286.x.
[10] Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4(1):1–6. https://doi.org/10.1902/annals.1999.4.1.1.
[11] Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?. Circulation 2012;125 (20):2520–44. https://doi.org/10.1161/CIR.0b013e31825719f3.
[12] Cotti E, Mercuro G. Apical periodontitis and cardiovascular diseases: previous findings and ongoing research. Int Endod J 2015;48(10):926–32. https://doi.org/10.1111/iej.12506.
[13] Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. J Periodontol 2013;84:S51–69. https://doi.org/10.1111/jcpe.12060.
[14] Cheng F, Zhang M, Wang Q, Xu H, Dong X, Gao Z, et al., Tooth loss and risk of cardiovascular disease and stroke: A dose-response meta analysis of prospective cohort studies.PLoS One. 2018;13(3):e0194563. https://doi.org/10.1371/journal.pone.0194563.
[15] Leao TS, Tomasi G, Ibrahim MS, Conzatti L, Marrone LP, Reynolds MA, et al. Tooth loss is associated with atherosclerosis and a poorer functional outcome among stroke patients. Clin Oral Invest 2020;24(12):4541–8. https://doi.org/10.1007/s00784-020-03319-z.
[16] Caldas AF, Marcenes W, Sheiham A. Reasons for tooth extraction in a Brazilian population. Int Dent J 2000;50(5):267–73. https://doi.org/10.1111/j.1875-595x.2000.tb00564.x.
[17] Liljestrand JM, Havulinna AS, Paju S, Mannisto S, Salomaa V, Pussinen PJ. Missing teeth predict incident cardiovascular events, diabetes, and death. J Dent Res 2015;94(8):1055–62. https://doi.org/10.1177/0022034515586352.
[18] Joshy G, Arora M, Korda RJ, Chalmers J, Banks E. Is poor oral health a risk marker for incident cardiovascular disease hospitalisation and all-cause mortality? findings from 172 630 participants from the prospective 45 and Up Study.BMJ Open. 2016;6(8):e012386. 10.1136/bmjopen-2016-012386.
[19] Lee HJ, Garcia RI, Janket SJ, Jones JA, Mascarenhas AK, Scott TE, et al. The association between cumulative periodontal disease and stroke history in older adults. J Periodontol 2006;77(10):1744–54. https://doi.org/10.1902/jop.2006.050339.
[20] Sen S, Giamberardino LD, Moss K, Morelli T, Rosamond WD, Gottesman RF, et al. Periodontal disease, regular dental care use, and incident ischemic stroke. Stroke 2018;49(2):355–62. https://doi.org/10.1161/STROKEAHA.117.018990.
[21] Hansen GM, Egeberg A, Holmstrup P, Hansen PR. Relation of periodontitis to risk of cardiovascular and all-cause mortality (from a Danish nationwide cohort study). Am J Cardiol 2016;118(4):489–93. https://doi.org/10.1016/j.amjcard.2016.05.036.
[22] Grau AJ, Becher H, Ziegler CM, Lichy C, Buggle F, Kaiser C, et al. Periodontal disease as a risk factor for ischemic stroke. Stroke 2004;35(2):496–501. https://doi.org/10.1161/01.STR.0000110789.20526.9D.
[23] Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71(6):1269–324. https://doi.org/10.1161/HYP.0000000000000066.
[24] Deurenberg P, Weststrate JA, Seidell JC. Body mass index as a measure of body fatness: age-and sex-specific prediction formulas. Br J Nutr 1991;65 (2):105–14. https://doi.org/10.1079/bjn19910073.
[25] American DA. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Supplement 1):S81–90. https://doi.org/10.2337/dc14-S081.
[26] Cardiologia SBd. Questionário para fatores de risco cardiovasculares file:///C:/Users/16190836/Downloads/questionario-do-entrevistador.pdf2004.
[27] Lindsay P, Furie KL, Davis SM, Donnan GA, Norrving B. World Stroke Organization global stroke services guidelines and action plan. Int J Stroke 2014;9(Suppl A 100):4–13. https://doi.org/10.1111/ijs.12371.
[28] Kebschull M, Demmer RT, Papapanou PN. "Gum bug, leave my heart alone!"–epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. J Dent Res 2010;89(9):879–902. https://doi.org/10.1177/0022034510375281.
[29] Cavrini F, Sambri V, Moter A, Servidio D, Marangoni A, Montebugnoli L, et al. Molecular detection of Treponema denticola and Porphyromonas gingivalis in carotid and aortic atheromatous plaques by FISH: report of two cases. J Med Microbiol 2005;54(Pt 1):93–6. https://doi.org/10.1099/jmm.0.45845-0.
[30] Nakano K, Inaba H, Nomura R, Nemoto H, Takeda M, Yoshioka H, et al. Detection of cariogenic Streptococcus mutans in extirpated heart valve and atheromatous plaque specimens. J Clin Microbiol 2006;44(9):3313–7. https://doi.org/10.1128/JCM.00377-06.
[31] Gaetti-Jardim E, Marcelino SL, Feitosa ACR, Romito GA, Avila-Campos MJ. Quantitative detection of periodontopathic bacteria in atherosclerotic plaques from coronary arteries. J Med Microbiol 2009;58(Pt 12):1568–75. https://doi.org/10.1099/jmm.0.013383-0.
[32] Gomes MS, Blattner TC, Sant'Ana Filho M, Grecca FS, Hugo FN, Fouad AF, et al. Can apical periodontitis modify systemic levels of inflammatory markers? a systematic review and meta-analysis. J Endodontics 2013;39(10):1205–17. https://doi.org/10.1016/j.joen.2013.06.014.
[33] Dorfer CE, Becher H, Ziegler CM, Kaiser C, Lutz R, Jorss D, et al. The association of gingivitis and periodontitis with ischemic stroke. J Clin Periodontol 2004;31 (5):396–401. https://doi.org/10.1111/j.1600-051x.2004.00579.x.
[34] Wu T, Trevisan M, Genco RJ, Dorn JP, Falkner KL, Sempos CT. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. Arch Intern Med 2000;160(18):2749–55. https://doi.org/10.1001/archinte.160.18.2749.
[35] An SJ, Kim TJ, Yoon B-W. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. J Stroke 2017;19(1):3–10. https://doi.org/10.5853/jos.2016.00864.
[36] Kim HD, Sim SJ, Moon JY, Hong YC, Han DH. Association between periodontitis and hemorrhagic stroke among Koreans: a case-control study. J Periodontol 2010;81(5):658–65. https://doi.org/10.1902/jop.2010.090614.
[37] Hill AB. The environment and disease: association or causation?. J R Soc Med 2015;108(1):32–7. https://doi.org/10.1177/0141076814562718.
[38] LaMonte MJ, Genco RJ, Hovey KM, Wallace RB, Freudenheim JL, Michaud DS, et al. History of periodontitis diagnosis and edentulism as predictors of cardiovascular disease, stroke, and mortality in postmenopausal women. J Am Heart Assoc 2017;6(4):. https://doi.org/10.1161/JAHA.116.004518e004518.
[39] Munoz-Torres FJ, Mukamal KJ, Pai JK, Willett W, Joshipura KJ. Relationship between tooth loss and peripheral arterial disease among women. J Clin Periodontol 2017;44(10):989–95. https://doi.org/10.1111/jcpe.12787.
[40] Pradeep AR, Hadge P, Arjun Raju P, Shetty SR, Shareef K, Guruprasad CN. Periodontitis as a risk factor for cerebrovascular accident: a case-control study in the Indian population. J Periodontal Res 2010;45(2):223–8. https://doi.org/10.1111/j.1600-0765.2009.01220.x.
[41] Sim SJ, Kim HD, Moon JY, Zavras AI, Zdanowicz J, Jang SJ, et al. Periodontitis and the risk for non-fatal stroke in Korean adults. J Periodontol 2008;79 (9):1652–8. https://doi.org/10.1902/jop.2008.080015.
[42] Tormo MJ, Navarro C, Chirlaque MD, Barber X. Validation of self diagnosis of high blood pressure in a sample of the Spanish EPIC cohort: overall agreement and predictive values. J. Epidemiol. Commun. Health 2000;54(3):221–6. https://doi.org/10.1136/jech.54.3.221.
[43] Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC–Oxford participants. Public Health Nutr 2002;5(4):561–5. https://doi.org/10.1079/PHN2001322.
[44] Estrela C, Bueno MR, Leles CR, Azevedo B, Azevedo JR. Accuracy of cone beam computed tomography and panoramic and periapical radiography for detection of apical periodontitis. J. Endodontics 2008;34(3):273–9. https://doi.org/10.1016/j.joen.2007.11.023.
[45] Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NHJ. Tooth loss and oral health-related quality of life: a systematic review and meta-analysis. Health Quality Life Outcomes 2010;8(1):126. https://doi.org/10.1186/1477-7525-8-126.
[46] Zhu Y, Hollis JH. Tooth loss and its association with dietary intake and diet quality in American adults. J Dent 2014;42(11):1428–35. https://doi.org/10.1016/j.jdent.2014.08.012.
[47] Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. J Dent Res 1996;75(9):1631–6. https://doi.org/10.1177/00220345960750090301.