Review

Association of periodontitis and gingivitis with stroke: A systematic review and meta-analysis

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Abstract

Background. Stroke is among the leading causes of morbidity and mortality. Chronic inflammatory conditions may lead to atherosclerosis and a subsequent stroke.

Objectives. This systematic review and meta-analysis aimed to review the association of periodontitis and gingivitis with stroke.

Methods. An electronic search of PubMed, Ovid EMBASE, Ovid MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Science Citation Index, Database of Abstracts and Reviews of Effects (DARE), and various clinical trial registries was conducted to include studies published up to February 2022. Data was retrieved by 2 independent reviewers. The Stata software, v. 13, was used to conduct a meta-analysis.

Results. Thirteen studies stated an association between periodontitis, determined based on clinical attachment loss (CAL), and stroke. Meanwhile, 6 studies described an association between gingivitis, determined based on the gingival index (GI), and stroke. Out of the 6 studies on gingivitis, 5 also investigated CAL, which means the meta-analysis included 14 studies in total. The total number of participants from the included studies was 35,937, and they were all above 17 years of age. There was a significant association between periodontitis and gingivitis and stroke and its all types. There was a significant association between periodontitis and stroke and its all types in 13 studies (*ES* (effect size): 1.32; 95% *CI* (confidence interval): 1.04–1.60), and between gingivitis and all stroke types in 6 studies (*ES*: 1.17; 95% *CI*: 0.42–1.92).

Conclusions. This systematic review indicated a significant association between stroke and periodontal disease in case–control, cohort and cross-sectional studies. The findings need to be further substantiated in prospective cohort studies with an optimal sample size.

Keywords: periodontitis, stroke, bacteria, cerebrovascular disorders, gingivitis and stroke

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Introduction

Stroke is a major cause of disability and the third most common cause of mortality.[1] A "Lancet" editorial stated that "any stroke is a deplorable event, but a preventable stroke is a tragedy".[2] Furthermore, the prevalence of low-grade chronic inflammation in the adult population of industrialized countries is approx. 15–35%.[3]

There is evidence that chronic infectious diseases, including dental diseases, such as periodontitis and gingivitis, can lead to atherosclerosis, which increases the risk of stroke and coronary heart disease (CHD). In this regard, it is thought that the oral cavity acts as a perpetual source of infections and serves as a bacterial reservoir that augments systemic pathologies. Indeed, gingivitis and periodontitis are chronic inflammatory conditions of multifactorial origin that trigger a pro-inflammatory host immune response to bacterial products present in the oral cavity.

Studies on the mechanisms of periodontal and gingival inflammation suggest that microorganisms enter the bloodstream during chewing or tooth brushing via compromised tooth-supporting structures, such as the periodontal ligament and the alveolar bone, which leads to the formation of periodontal pockets or gingival recession, or both. Such microorganisms have been found in the carotid artery plaques and thrombectomy samples obtained from patients who suffered a stroke, implicating a probable association.[4] Although this association has been observed, it has certainly not been confirmed. Nonetheless, epidemiological studies (cohort, cross-sectional and case–control studies) have also demonstrated an association between periodontitis and gingivitis and a subsequent stroke of various types.[5,6] A previous systematic review and meta-analysis investigated the link between stroke and oral diseases, including periodontitis and gingivitis.[6] However, no studies have presented relevant clinical evidence regarding the abovementioned association, and there have been inconsistencies in the definitions of periodontitis and gingivitis. Therefore, the present study aimed to determine the association between the most common inflammatory conditions of the oral cavity – periodontitis and gingivitis – and stroke of various types.

Methodology

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[7]

Search strategy

An electronic search of PubMed, Ovid EMBASE, Ovid MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Science Citation Index, and Database of Abstracts and Reviews of Effects (DARE) was conducted to include articles published up to February 2022. Various clinical trial registries were also searched. All the articles retrieved during the search that studied the relationship between oral health and stroke were evaluated.

The literature search was restricted to English-language publications involving human subjects. The following combination of terms was searched: "stroke" OR "cerebrovascular disorders", (cerebrovascular disorders) AND (periodontitis), (cerebrovascular disorders) AND (gingivitis), (cerebrovascular accident) AND (gingivitis), (clinical attachment loss) AND (brain stroke), (periodontitis) AND (brain stroke), and (gingival inflammation) AND (stroke). The available secondary bibliographies were also reviewed, and a manual search of articles was undertaken as well.

The study is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under No.: CRD42021237995.

Selection criteria

For inclusion in this systematic review and meta-analysis, studies had to be cohort (retrospective or prospective), cross-sectional or case–control in design, they had to include adult human subjects, and they had to define periodontitis in terms of clinical attachment loss (CAL) and gingivitis in terms of gingival index (GI).

Studies were excluded from further analysis if they did not report risk ratios (*RR*s) or odds ratios (*OR*s), or if they were published in a language other than English. Studies not addressing the association of periodontitis or gingivitis with various types of stroke were also excluded. If the study data was published in more than one publication, then the study published later or the publication with a more detailed report was included in the analysis.

Operational definitions

Periodontitis was defined as having CAL > 3 mm and more than 30% of sites involved. Periodontitis was expressed as CAL, or as CAL and probing depth (PD).[8]

The presence of gingivitis was defined as gingival inflammation measured using GI (Löe and Silness, 1963).

The stroke diagnosis was based on definitive examinations (i.e., an ischemic or hemorrhagic lesion on brain imaging and/or on clinical examination, with a definite neurological deficit).

Outcomes

The primary outcome was the association between periodontitis or gingivitis and strokes of various types, including an ischemic stroke, a hemorrhagic stroke and transient ischemic attacks (TIAs).

The secondary outcomes included tooth loss, bleeding on probing (BoP), PD, plaque index (PI), and gingival recession.

Data collection

Two reviewers (MD and AKP) retrieved data independently from the variety of sources outlined above. All of the included articles were scrutinized, and data on the study characteristics, methods, types of observations, patients, and outcomes was retrieved from texts, tables, figures, and graphs. Any disagreement between the 2 reviewers was resolved by consensus among the authors.

Quality assessment

The quality of the included studies was assessed using the Newcastle–Ottawa Scale (Tables 1,2).[9,10]

Table 1. Methodological quality of the included studies (case–control studies[5,13,15,16,18,19,24])

Study	Selection				Comparability	Exposure			Total score
	Is case definition adequate?	representativeness of cases	selection of controls	definition of controls	comparability of cases and controls based on the design or analysis	ascertainment of exposure	no-response rate	the same method of ascertainment for cases and controls	
Hashemipour et al. 2013[5]	*	*	*	*	0	**	*	*	8
Grau et al. 2004[13]	*	*	*	*	0	*	*	*	7
Pradeep et al. 2010[15]	*	0	0	*	0	*	*	*	5
Kim et al. 2010[16]	*	*	*	*	*	*	*	*	8
Diouf et al. 2015[18]	*	*	*	*	*	*	*	*	8
Leira et al. 2016[19]	*	*	*	*	*	*	*	*	8
Ghizoni et al. 2012[24]	*	0	0	*	*	*	*	*	6

Assessment: 4 stars for selecting participants and measuring exposure; 2 stars for comparability; and 3 stars for assessing the adequacy of the outcome and the follow-up. * score 1; no * score 0 (no description).

Table 2. Methodological quality of the included studies (cohort and cross-sectional studies[11,12,14,17,20–23])

Study	Selection				Comparability	Exposure			Total score
	representativeness of the exposed cohort	selection of the non-exposed cohort	ascertainment of exposure	outcome at the initiation of the study	comparability of the cohorts based on the design or analysis	ascertainment of the outcome	Was the follow-up long enough for the outcome to occur?	adequacy of the follow-up cohorts	
Loesche et al. 1998[11]	*	*	*	*	*	*	*	*	8
Elter et al. 2003[12]	*	*	*	*	*	*	*	*	8
Lee et al. 2006[14]	*	*	*	*	*	*	*	**	9
Sen et al. 2013[17]	*	*	*	*	*	*	*	*	8
Sen et al. 2018[20]	*	*	*	*	*	*	*	*	8
Beck et al. 2018[21]	*	*	*	*	*	*	*	*	8
Mascari et al. 2021[22]	*	*	**	*	*	*	*	*	9
Söder et al. 2015[23]	*	*	*	*	*	*	*	*	8

Assessment: 4 stars for selecting participants and measuring exposure; 2 stars for comparability; and 3 stars for assessing the adequacy of the outcome and the follow-up. * score 1; no * score 0 (no description).

Statistical analysis

Statistical analysis was performed using the Stata software, v. 13 (StataCorp, College Station, USA). Based on the data extracted from individual studies, the pooled estimates of effect size (*ES*) and 95% confidence intervals (*CI*s) were calculated for the association between periodontitis or gingivitis and stroke (ischemic, hemorrhagic or TIA). These were calculated based on various study designs and according to the reported *OR*, *RR* or hazard ratio (*HR*). The pooled estimates were presented as pooled *OR*, *RR* or *HR*.

The heterogeneity amongst studies was measured using the I^2 statistics. Heterogeneity was considered significant at $I^2 > 50\%$, in which case the random-effects model was used to synthesize the data; otherwise, the fixed-effects model was used for the estimation of the pooled *ES*. A p-value <0.05 was considered statistically significant.

Results

The comprehensive search generated 678 studies, and following a review of the titles, abstracts and full texts, 36 studies were included in the final analysis. A PRISMA flow diagram for the selected articles is shown in Fig. 1.

The total number of participants from the studies included in the meta-analysis was 35,937, with all subjects aged >17 years. Tables 3 and 4 provide a summary of the characteristics of the included studies. The secondary dental parameters from the included studies are shown in Table 5.

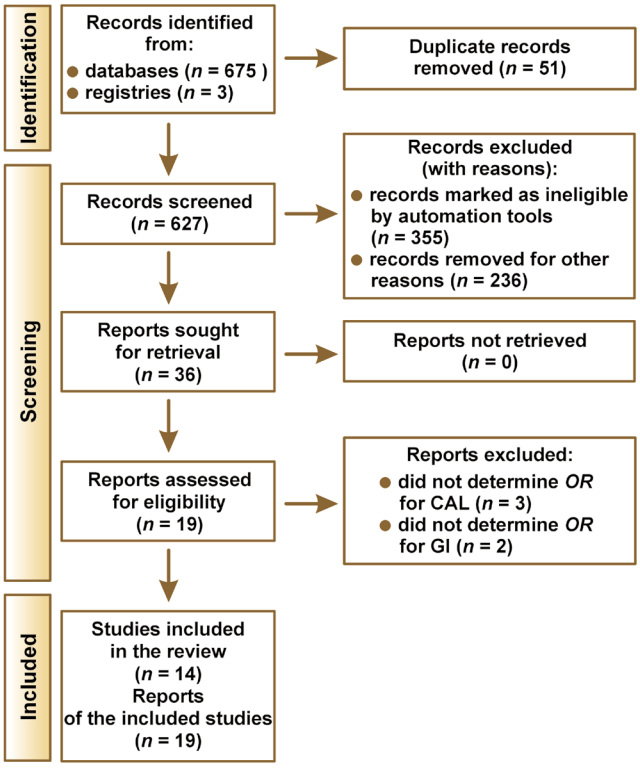

Fig. 1. Flow diagram of the study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[7]

OR – odds ratio; CAL – clinical attachment loss; GI – gingival index.

Outcome analysis

It was an inverse-variance random-effects meta-analysis.

Periodontitis and all stroke types

There was a significant association between periodontitis and stroke among patients from the various studies reviewed (*ES*: 1.32; 95% *CI*: 1.04–1.60). No significant heterogeneity was detected when reviewing the studies correlating periodontitis with stroke and its types; the inconsistency was moderate (I^2 = 30.3%) (Fig. 2).

Gingivitis and all stroke types

There was a significant association between gingivitis and stroke among patients from the various studies reviewed (*ES*: 1.17; 95% *CI*: 0.42–1.92). There was no significant heterogeneity detected between the studies on gingivitis and stroke types; the inconsistency was moderate (I^2 = 45.9%) (Fig. 3).

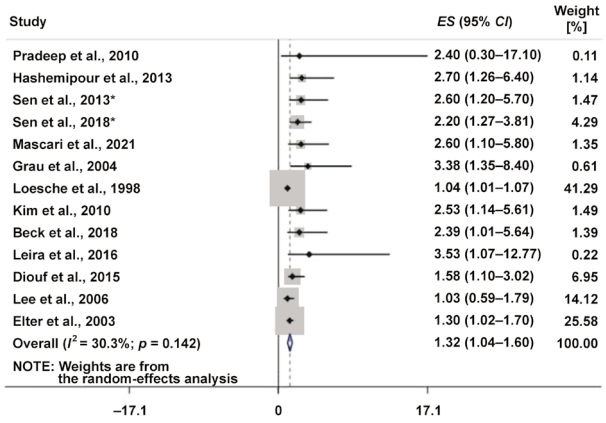

Fig. 2. Forest plots for periodontitis and stroke (all types) with the estimated risk (effect size (*ES*) (95% confidence interval (*CI*)) reported

* hazard ratio (*HR*) reported instead of *OR*.

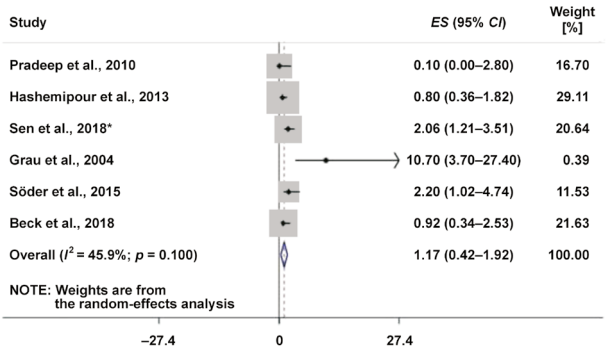

Fig. 3. Forest plots for gingivitis and stroke (all types) with the estimated risk (effect size (*ES*) (95% confidence interval (*CI*)) reported

* *HR* reported instead of *OR*.

Table 3. General characteristics of the studies included in the systematic review (periodontitis – clinical attachment loss (CAL))

No.	Study	Country	Study design	Age [years]	Number of participants		Number of males	Stroke features	Dental features	Study key points	Study analysis
					controls	cases					
1	Hashemipour et al. 2013[5]	Iran	case–control study	52	100	100	86	ischemic stroke	CAL	age, gender, smoking, diabetes, renal failure, cholesterol, TG, HT, AF, peripheral cardiovascular disease, history of stroke, BoP, GI, CAL	there is a significant relation between stroke and periodontal disease
2	Loesche et al. 1998[11]	USA	cross-sectional study	<60	401	–	–	stroke	CAL	age, race, education, ever/current smoker, alcohol, number of medications, BMI, BP, dental examination	CAL > 6 mm was significantly associated with stroke
3	Elter et al. 2003[12]	USA	cross-sectional study	–	10,906	–	–	stroke/TIA	CAL	age, gender, race, demographics, lifestyle, education, income, Medicaid, smoking, diabetes, HT, CHD, edentulism, dental examination	CAL was found to be associated with stroke/TIA
4	Grau et al. 2004[13]	Germany	case–control study	18–75	168	300	–	stroke	CAL	age, female gender, school education, profession, smoking, alcohol, diabetes, hyperlipidemia, HT, AF, CAD, PAD, previous stroke/TIA, family history of stroke, dental examination	subjects with severe periodontitis (mean CAL = 6 mm) were at a 4.3 times higher risk of cerebral ischemia (95% *CI*: 1.85–10.2) than subjects with mild periodontitis (CAL = 3 mm) or without periodontitis
5	Lee et al. 2006[14]	USA	cross-sectional study	>60	5,123	–	–	stroke	CAL	age, gender, race, ethnicity, education, income, poverty, smoking, alcohol	there is evidence of an association between cumulative periodontal disease, based on PHS, and a history of stroke
6	Pradeep et al. 2010[15]	India	case–control study	54	100	100	–	CVA or stroke	CAL	age, gender, education, smoking, diet, diabetes, serum cholesterol, HT, cardiovascular disease, previous stroke, family history of stroke, PI, GI, CAL, PD	the mean CAL values for cases were significantly higher when compared with the control group ($p < 0.05$), which clearly shows that periodontitis may be a potential risk factor for stroke
7	Kim et al. 2010[16]	South Korea	case–control study	40–79	118	214	164	hemorrhagic stroke	CAL	age, male gender, duration of education ≥9 years, income ≥1,000 USD/month, smoking, alcohol, BMI ≥ 25, diabetes, HT, cardiac disease, family history of diabetes or cardiac disease, tooth brushing >2 times/day, annual dental visit, DMFT index, CAL	the association between periodontal disease (CAL > 6 mm) and hemorrhagic stroke was significant for males
8	Sen et al. 2013[17]	USA	cohort study	54.5	40	66	–	stroke/TIA	CAL	age, gender, race, education, income, ever/current smoker, BMI, diabetes, hyperlipidemia, hypercholesterolemia, HT, AF, CAD, TIA, PI, GI, CAL, PD, NIHSS, brain MRI/CT	HPD is associated with recurrent vascular events in stroke/TIA patients
9	Diouf et al. 2015[18]	Senegal	case–control study	–	120	120	–	stroke	CAL	sociodemographic characteristics, lifestyle behaviors, HT, general history, type of stroke (ischemic or hemorrhagic), PI, PBI, CAL, PD, CPITN	periodontal disease is associated with stroke in the Senegalese population
10	Leira et al. 2016[19]	Spain	case–control study	30–80	60	62	–	LI	CAL	age, male gender, smoking, alcohol, statins, diabetes, hypercholesterolemia, HT, PAD, IHD, FMPS, FMBS, periodontitis, CAL, PD, gingival recession, missing teeth, LI in the TOAST classification, MRI, CT, carotid Doppler	severe periodontitis is strongly associated with LI
11	Sen et al. 2018[20]	USA	cohort study	54.5	40	66	–	stroke/TIA	CAL	age, gender, race, education, income, ever/current smoker, BMI, diabetes, hyperlipidemia, hypercholesterolemia, HT, AF, CAD, TIA, PI, GI, CAL, PD, NIHSS, brain MRI/CT	HPD is associated with recurrent vascular events in stroke/TIA patients
12	Beck et al. 2018[21]	USA	original study	45–64	15,792	–	–	stroke	CAL	age, gender, race, education, never/former/current smoker, BMI, diabetes/non-diabetes, HT/non-HT, TC, periodontitis, BoP, PI, GI, CAL, tooth loss	periodontitis was found to be significantly associated with stroke
13	Mascari et al. 2021[22]	USA	cross-sectional study	64	265	–	–	stroke/TIA	CAL	age, gender, race, height, smoking, pre-diabetes, diabetes, hyperlipidemia, AF, CAD, history of TIA or stroke, HbA1c	a higher prevalence of stroke due to large-artery atherosclerosis was observed in patients with periodontal disease as compared to those without periodontal disease

TIA – transient ischemic attack; CVA – cerebrovascular accident; LI – lacunar infarct; TG – triglycerides; HT – hypertension; AF – atrial fibrillation; BoP – bleeding on probing; BMI – body mass index; BP – blood pressure; CHD – coronary heart disease; CAD – coronary artery disease, PAD – peripheral artery disease; PI – plaque index; PD – probing depth; DMFT index – decayed, missing and filled teeth (permanent teeth); NIHSS – National Institutes of Health Stroke Scale; MRI – magnetic resonance imaging; CT – computed tomography; PBI – papillary bleeding index; CPITN – community periodontal index of treatment needs; IHD – ischemic heart disease; FMPS – full-mouth plaque score; FMBS – full-mouth bleeding score; TOAST – Trial of Org 10172 in Acute Stroke Treatment; TC – total; HbA1c – glycated hemoglobin; PHS – periodontal health status; HPD – high periodontal disease.

Table 4. General characteristics of the studies included in the systematic review (gingivitis – the gingival index (GI))

No.	Study	Country	Study design	Age [years]	Number of participants		Number of males	Stroke features	Dental features	Study key points	Study analysis
					controls	cases					
1	Hashemipour et al. 2013[5]	Iran	case–control study	52	100	100	86	ischemic stroke	CAL	age, gender, smoking, diabetes, renal failure, cholesterol, TG, HT, AF, peripheral cardiovascular disease, history of stroke, BoP, GI, CAL	there is a significant relation between stroke and periodontitis, but insignificant with gingivitis
2	Grau et al. 2004[13]	Germany	case–control study	18–75	168	300	–	stroke	CAL	age, female gender, school education, profession, smoking, alcohol, diabetes, hyperlipidemia, HT, AF, CAD, PAD, previous stroke/TIA, family history of stroke, dental examination	subjects with severe periodontitis (mean CAL = 6 mm) were at a 4.3 times higher risk of cerebral ischemia (95% *CI*: 1.85–10.2) than subjects with mild periodontitis (CAL = 3 mm) or without periodontitis
3	Pradeep et al. 2010[15]	India	case–control study	54	100	100	–	CVA or stroke	CAL	age, gender, education, smoking, diet, diabetes, serum cholesterol, HT, cardiovascular disease, previous stroke, family history of stroke, PI, GI, CAL, PD	the mean CAL values for cases were significantly higher when compared with the control group ($p < 0.05$), which clearly shows that periodontitis may be a potential risk factor for stroke
4	Sen et al. 2018[20]	USA	cohort study	54.5	40	66	–	stroke/TIA	CAL	age, gender, race, education, income, ever/current smoker, BMI, diabetes, hyperlipidemia, hypercholesterolemia, HT, AF, CAD, TIA, PI, GI, CAL, PD, NIHSS, brain MRI/CT	HPD is associated with recurrent vascular events in stroke/TIA patients
5	Beck et al. 2018[21]	USA	original study	45–64	15,792	–	–	stroke	CAL	age, gender, race, education, never/former/current smoker, BMI, diabetes/non-diabetes, HT/non-HT, TC, periodontitis, BoP, PI, GI, CAL, tooth loss	periodontitis was found to be significantly associated with stroke
6	Söder et al. 2015[23]	Finland	cohort study	30–40	39	1,637	838	stroke	GI	age, gender, education, income, smoking, CI, PI, GI, number of missing teeth	GI appeared to be a principal independent predictor associated with a higher risk of stroke

CI – calculus index.

Discussion

This systematic review aimed to find an association between various types of stroke and periodontitis or gingivitis. A total of 19 studies were included in the analysis, of which 13 studies were on the association of periodontitis with stroke types, and 6 were on the association between gingivitis and stroke. The results indicated an association between stroke and both periodontitis and gingivitis, with the pooled results of *ES*: 1.32; 95% *CI*: 1.04–1.60 and *ES*: 1.17; 95% *CI*: 0.42–1.92, respectively.

Out of the 13 studies on periodontitis, 4 were cross-sectional studies, 2 were cohort studies, 1 was an original study, and the remaining 6 were case–control studies. A significant association between periodontitis and stroke (all types) was found in all case–control studies. Cross-sectional and cohort studies also showed that periodontitis was linked with various types of stroke. The association between periodontitis and stroke has been studied previously, but the criteria for the evaluation of periodontitis varied across studies, which limited the generalization of study findings. Indeed, significant heterogeneity was noted among such studies, meaning that the association was not robust. This may have been due to the methodological quality of the studies. In the current systematic review, periodontitis was defined in terms of CAL, which is a better parameter for diagnosing periodontitis than either PD or alveolar bone loss.

Several studies included in this meta-analysis had limitations in terms of methodological quality, which impeded the observations of the study sample, the quality of measurements as well as blinding. In 3 of the case–control studies – by Kim et al.,[16] Diouf et al.[18] and Ghizoni et al.[24] (the study was excluded from the meta-analysis) – the misclassification bias was observed. Non-differential misclassification usually dilutes the estimate of an association, as exposure is unrelated to other variables. In such a study, the link between the periodontal status and the risk of stroke is likely to be underestimated, although overestimation is not entirely impossible. In the study by Pradeep et al., the selection bias was detected in the control subjects.[15] The study enrolled persons who had been admitted to the same department, as they were suffering from neurological diseases, such as degenerative disease, myasthenia gravis and Wilson's disease.[15] The selection bias was also detected in the study by Leira et al., along with a lack of validity of the patient history, which was assessed by interviewing the participants.[19] The selection bias was also observed in the study by Mascari et al.[22] A small sample size was observed in the study by Sen et al.[17]

Six studies explored the association between GI and stroke. One study was an original study, 2 studies were cohort, and 3 were case–control studies. No association

Table 5. Secondary dental features in the included studies

No.	Study	Country	Study design	Stroke features	Secondary dental features	Study analysis
1	Loesche et al. 1998[11]	USA	cross-sectional study	stroke	DMFT index, PD, gingival recession, presence of dentures and other prosthetic devices	PI and the oral hygiene habits relating to brushing, flossing and the frequency of having teeth cleaned by a dentist/ hygienist were significantly associated with CVA
2	Elter et al. 2003[12]	USA	cross-sectional study	stroke/TIA	edentulism	edentulism was found to be associated with stroke/TIA
3	Grau et al. 2004[13]	Germany	case–control study	stroke	dental visit <1 time/year, DMFT index, PI, bone loss	subjects with severe periodontitis (mean CAL = 6 mm) had an increased risk of cerebral ischemia; gingivitis and bone loss were found to have a strong independent association with stroke; caries, the number of missing teeth and PI were not independent risk factors
4	Lee et al. 2006[14]	USA	cross-sectional study	stroke	PHS	no statistically significant association was found between PHS and stroke
5	Pradeep et al. 2010[15]	India	case–control study	CVA or stroke	PI, PD	PD > 4.5 mm was found to be the most significant risk factor for stroke; the mean PI value was also found to be significant
6	Kim et al. 2010[16]	South Korea	case–control study	hemorrhagic stroke	tooth brushing >2 times/day, annual dental visit >1, DMFT index, number of missing teeth	stroke was not associated with the number of missing teeth, the experience of dental caries or the annual dentist visits
7	Sen et al. 2013[17]	USA	cohort study	stroke/TIA	PI, PD, tooth loss	HPD is associated with recurrent vascular events in stroke/TIA patients; no association was observed between GI and stroke; regular dental care was associated with a lower adjusted stroke risk
8	Diouf et al. 2015[18]	Senegal	case–control study	stroke	PI, PBI, PD, CPITN	periodontal disease and various periodontal parameters were significantly associated with stroke
9	Leira et al. 2016[19]	Spain	case–control study	LI	PI, PBI, PD, CPITN	FMPS, FMBS, PD, gingival recession, and missing teeth were significantly associated with LI
10	Sen et al. 2018[20]	USA	cohort study	stroke/TIA	PI, tooth loss	HPD is associated with recurrent vascular events in stroke/TIA patients
11	Beck et al. 2018[21]	USA	original study	stroke	BoP, PI, tooth loss	high gingival inflammation, tooth loss and severe tooth loss were significantly associated with diabetes, CHD, hs-CRP, and IL-6
12	Mascari et al. 2021[22]	USA	cross-sectional study	stroke/TIA	PD, gingival margin position	a higher prevalence of stroke due to large-artery atherosclerosis was observed in patients with periodontal disease as compared to those without periodontal disease
13	Söder et al. 2015[23]	Finland	cohort study	stroke	number of dental visits, CI, PI, GI, number of missing teeth	CI and GI were significantly higher in the stroke group
14	Ghizoni et al. 2012[24]	Brazil	case–control study	ischemic/ hemorrhagic stroke	BoP, PI, CAL, PD, number of missing teeth, Pg and Aa bacteria; age- and gender-matched	stroke patients had deeper pockets, and presented with increased BoP and PI values; in their pockets, increased amounts of Pg harbored

Pg – *Porphyromonas gingivalis*; Aa – *Aggregatibacter actinomycetemcomitans*; hs-CRP – high-sensitivity C-reactive protein; IL-6 – interleukin 6.

was found between gingival inflammation and the incidence of stroke in the studies by Hashemipour et al.[5] and Sen et al.[20] Meanwhile, the other 4 studies found that high gingival inflammation was associated with stroke, and concluded that gingivitis was a risk factor for various types of stroke.

Secondary outcomes studied were tooth loss, BoP, PD, PI, and gingival recession. Most studies found that increased PD and tooth loss were independent risk factors for a stroke event. Söder et al. concluded that the calculus index (CI) and GI were significantly associated with stroke.[23] Beck et al. studied cytokine levels and found C-reactive protein (CRP) and interleukin 6 (IL-6) to be higher in patients with a cardiovascular risk.[21]

The quality assessment of the cohort studies with the Newcastle–Ottawa Scale indicated that the studies provided moderate to good quality evidence. Amongst the various cohort studies, it was found that information on some other risk factors for stroke, such as body mass index (BMI), a family history and smoking, as well as some co-morbidities, e.g., inflammatory diseases,[12] was not collected. A weakness was the lack of data on certain stroke risk factors, such as hypertension, diabetes and dyslipidemia, which were not available for analysis due to the nature of the study. Furthermore, data from the oral microbiomes of subjects was not included in the study by Söder et al.[23] Some studies included in the analysis had small sample sizes,[20,23] so in those cases, drawing any conclusions may be biased.

Gingivitis and periodontitis are chronic inflammatory conditions that can result from a pro-inflammatory host immune response in reaction to pathogenic bacteria. These microorganisms enter the bloodstream during mastication, tooth brushing and minor dental procedures, resulting in transient bacteremia. Pro-inflammatory cytokines, such as IL-6 and interferons, are produced in response to endothelial activation, which is responsible for plaque rupture, platelet aggregation, thrombus formation, and thromboembolism, all of which can lead to stroke.

In a systematic review by Fernandes Fagundes et al., it was concluded that periodontitis was a significant risk factor for stroke.[6] However, there was no clear-cut definition of periodontitis, and gingival inflammation was not taken into consideration.[6] In another systematic review by Pillai et al., the relationship between oral health and stroke was studied.[25] The main aim of the study was to find a relationship between stroke and oral health. It was concluded that stroke patients had poor hygiene practices, but there was no conclusive evidence regarding gingivitis. Dental prophylaxis and various dental procedures reduced the incidence of stroke.[25]

In a systematic review, Scannapieco et al. explored the link between periodontitis, atherosclerosis, cardiovascular disease, and stroke.[26] They concluded that a lack of uniform definitions and periodontal diagnosis measures complicated the interpretation of data and results, with some studies showing a moderate association and others showing no association at all.[26]

Larvin et al. found a modest but increased risk of cardiovascular disease in periodontal patients.[27] All of the possible outcomes of cardiovascular events were measured, including infarction, coronary artery disease (CAD) and stroke, while the diagnosis of periodontal disease was both self-reported and clinically confirmed.[27]

Oral disease (gingivitis and periodontitis) has been implicated as a factor in an increased incidence of stroke. However, whether oral disease can modify stroke through the role of inflammation in atherogenesis and the physiopathology of cerebral ischemia is not clear. Many long-term studies are being conducted in this area, with some proven and unproven data available. Therefore, a consistent relationship exists between periodontal disease and stroke in terms of biological and dental knowledge, and it is appropriate to analyze each case individually.[28]

One case–control study by Ghizoni et al.[24] was included in this systematic review, but was later excluded from the meta-analysis, since the *CI* was too wide.

Future directions

The proposed future studies need to confirm the association between periodontitis and gingivitis and stroke/TIA.

The proposed study design should be a prospective cohort study. The following selection, comparability and outcome criteria should be considered:

– selection:
- representativeness of the exposed cohort,
- selection of the non-exposed cohort,
- ascertainment of exposure – 2 dentists should evaluate the dental condition, and the inter-observer agreement should be targeted at >0.8,
- outcome at the initiation of study – ensure there is no stroke/TIA at the time of enrollment,
- confounders to be included – all the known prognostic factors for stroke should be included in the study, with validated criteria;

– comparability – comparability of the cohorts based on the design or analysis;

– outcome:
- ascertainment of the outcome – clinico-radiological confirmation of the diagnosis of stroke/TIA,
- follow-up – at least 10 years, or more, of follow-up to ascertain a definite association between the dental condition and stroke,
- adequacy of the follow-up cohorts – minimal attrition of the participants from the study.

Cases to be included – patients with chronic periodontitis and gingivitis. The cases should not have evidence of other systemic illnesses or inflammatory diseases.

The microbiological evaluation of dental infection/inflammation leading to atherosclerosis and a subsequent stroke should be confirmed after the exclusion of all possible confounders. The analysis should include healthy individuals, who need to be followed up once dental infection/inflammation develops and a subsequent stroke/TIA occurs.

Conclusions

This systematic review indicated a significant association between stroke and periodontal disease in case–control, cohort and cross-sectional studies.

Ethics approval and consent to participate

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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