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Original Article

Relationship Between Periodontal and Gingival Diseases and the Risk of Stroke: A Systematic Review and Meta-Analysis

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ABSTRACT

Stroke remains one of the major global causes of disability and death, and persistent inflammatory disorders can promote atherosclerosis, thereby increasing the likelihood of stroke. This systematic review and meta-analysis aimed to evaluate the relationship between periodontal diseases—specifically periodontitis and gingivitis—and the occurrence of stroke. A comprehensive literature search was carried out in PubMed, Ovid EMBASE, Ovid MEDLINE, Web of Science, Cochrane CENTRAL, Science Citation Index, DARE, and several clinical trial registries for studies published up to February 2022. Two independent reviewers extracted the data, and meta-analysis was performed using Stata version 13. Thirteen studies identified a link between stroke and periodontitis, as measured by clinical attachment loss (CAL), while six studies demonstrated an association between stroke and gingivitis, assessed using the gingival index (GI). Five of the gingivitis studies also examined CAL, resulting in a total of 14 studies being included in the meta-analysis, encompassing 35,937 participants aged 17 years and older. A significant relationship was observed between both periodontal conditions and all stroke subtypes. Specifically, periodontitis showed a significant association with stroke across 13 studies (effect size [ES]: 1.32; 95% confidence interval [CI]: 1.04–1.60), and gingivitis demonstrated a similar trend across six studies (ES: 1.17; 95% CI: 0.42–1.92). The evidence from this systematic review and meta-analysis supports a notable correlation between stroke and periodontal disease across case–control, cohort, and cross-sectional designs. However, further large-scale, prospective cohort studies are required to confirm these findings and clarify the causal relationship.

Keywords: Gingivitis and stroke, Periodontitis, Stroke, Cerebrovascular disorders, Bacteria

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Introduction

Stroke remains a leading contributor to global disability and stands as the third primary cause of death [1]. As noted by The Lancet, "any stroke is a deplorable event, but a preventable stroke is a tragedy" [2]. Moreover, low-grade chronic inflammation affects roughly 15–35% of adults in developed nations [3].

Chronic infections, including oral conditions such as periodontitis and gingivitis, have been implicated in the development of atherosclerosis, which in turn heightens the risk of both stroke and coronary heart disease (CHD). The oral cavity may act as a continuous infectious focus and a microbial reservoir that promotes systemic inflammatory activity. Periodontitis and gingivitis are persistent inflammatory disorders of complex origin, provoking an excessive immune response to bacterial agents inhabiting the mouth.

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Research exploring the underlying mechanisms of periodontal and gingival inflammation indicates that microorganisms can enter the bloodstream through disrupted periodontal structures—such as the alveolar bone and ligament—during everyday actions like chewing or brushing. This translocation may lead to the formation of periodontal pockets or gingival recession, allowing pathogens to circulate systemically. Evidence of oral microorganisms in carotid plaques and thrombectomy samples from stroke patients suggests a potential biological link [4]. While this association has been reported, causation has not been definitively proven. Nonetheless, epidemiological investigations—including cohort, case–control, and cross-sectional designs—have consistently demonstrated correlations between periodontal inflammation and various forms of stroke [5, 6]. Although an earlier systematic review and meta-analysis examined the connection between stroke and oral diseases [6], it lacked consistent diagnostic criteria for periodontitis and gingivitis, and clinical confirmation remained limited. Therefore, this study sought to explore the relationship between the most prevalent chronic inflammatory oral conditions—periodontitis and gingivitis—and stroke across its subtypes.

Methodology

This systematic review and meta-analysis were performed following the PRISMA 2020 reporting standards [7].

Search strategy

A detailed electronic search strategy was implemented using PubMed, Ovid EMBASE, Ovid MEDLINE, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), the Science Citation Index, and the Database of Abstracts and Reviews of Effects (DARE) to locate studies published up to February 2022. Relevant clinical trial registries were also examined. All retrieved articles exploring the relationship between oral health and stroke were screened for eligibility.

Only English-language publications involving human participants were included. Search terms combined the following expressions: “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). Secondary bibliographies were also reviewed, and a manual search was performed to ensure comprehensive coverage.

This review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42021237995.

Selection criteria

Studies considered for inclusion in this systematic review and meta-analysis were required to follow a cohort (retrospective or prospective), cross-sectional, or case–control design, involve adult human participants, and provide clear diagnostic criteria for periodontitis—defined through clinical attachment loss (CAL)—and for gingivitis—assessed via the gingival index (GI). Research was excluded if it did not report effect measures such as risk ratios (RRs) or odds ratios (ORs), if it was published in a language other than English, or if it failed to evaluate the connection between periodontal inflammation and any form of stroke. When overlapping publications were identified, the most recent or the one containing the most comprehensive dataset was selected for analysis.

Operational definitions

Periodontitis was classified as CAL exceeding 3 mm affecting over 30% of the examined sites and was quantified either by CAL alone or by a combination of CAL and probing depth (PD) [8]. Gingivitis referred to gingival inflammation measured using the Löe and Silness gingival index (1963). The diagnosis of stroke was based on definitive evidence obtained from neuroimaging (identifying ischemic or hemorrhagic lesions) and/or clinical examination confirming neurological impairment.

Outcomes

The main objective of this review was to assess the relationship between periodontal diseases (periodontitis and gingivitis) and different stroke categories, including ischemic stroke, hemorrhagic stroke, and transient ischemic attacks (TIAs). Additional parameters such as tooth loss, bleeding on probing (BoP), probing depth (PD), plaque index (PI), and gingival recession were analyzed as secondary outcomes.

Data collection

Data extraction was independently conducted by two reviewers (MD and AKP) following a standardized protocol. Each included paper was thoroughly examined, and relevant data on study characteristics, methodology, participant demographics, and measured variables were compiled from text, figures, tables, and

charts. Discrepancies between the reviewers were resolved through discussion and consensus among all authors.

Quality assessment

The methodological rigor and potential bias of the selected studies were appraised using the Newcastle–Ottawa Scale, as presented in **Tables 1 and 2** [9, 10].

Table 1. Assessment of methodological quality in the included research (case–control studies [5, 11-16])

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.* [5]	*	*	*	*	0	**	*	*	8
Grau *et al.* [16]	*	*	*	*	0	*	*	*	7
Pradeep *et al.* [12]	*	0	0	*	0	*	*	*	5
Kim *et al.* [13]	*	*	*	*	*	*	*	*	8
Diouf *et al.* [14]	*	*	*	*	*	*	*	*	8
Leira *et al.* [15]	*	*	*	*	*	*	*	*	8
Ghizoni *et al.* [16]	*	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. Evaluation of methodological quality for the included cohort and cross-sectional studies [17-24]

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.* [17]	*	*	*	*	*	*	*	*	8
Elter *et al.* [18]	*	*	*	*	*	*	*	*	8
Lee *et al.* [19]	*	*	*	*	*	*	*	**	9

Sen *et al.* [20]	*	*	*	*	*	*	*	*	8
Sen *et al.* [21]	*	*	*	*	*	*	*	*	8
Beck *et al.*[22]	*	*	*	*	*	*	*	*	8
Mascari *et al.* [23]	*	*	**	*	*	*	*	*	9
Söder *et al.* [24]	*	*	*	*	*	*	*	*	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

All statistical procedures were conducted using Stata version 13 (StataCorp, College Station, USA). From the data extracted across eligible studies, pooled effect sizes (ES) along with their 95 percent confidence intervals (CIs) were computed to evaluate the association between periodontitis or gingivitis and different stroke types, including ischemic, hemorrhagic, and transient ischemic attacks (TIAs). Depending on the study design and the measures reported, the pooled analyses incorporated odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs), and the combined estimates were expressed as pooled OR, RR, or HR values.

Between-study variability was assessed using the I^2 statistic, where an I^2 value greater than 50% indicated substantial heterogeneity, prompting the use of a random-effects model; otherwise, a fixed-effects model was applied. Statistical significance was set at a p-value of less than 0.05.

Results

The database search initially identified 678 records. After screening titles, abstracts, and full texts, 36 studies met the inclusion criteria and were retained for final evaluation. The selection process is summarized in the PRISMA flow diagram presented in **Figure 1**.

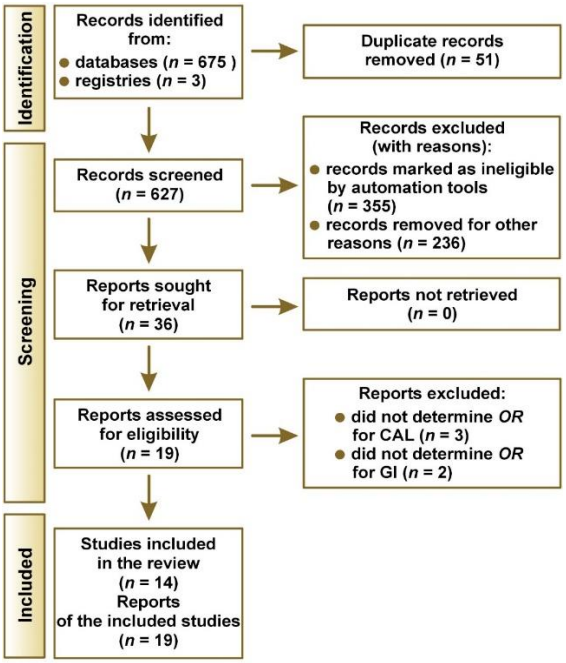

Figure 1. Study selection process illustrated according to the PRISMA 2020 guidelines [7]. OR – odds ratio; CAL – clinical attachment loss; GI – gingival index

The meta-analysis encompassed a total of 35,937 participants, all above 17 years of age. A summary of the study characteristics is provided in **Tables 3 and 4**, and the reported secondary dental outcomes are detailed in **Table 5**.

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

No.	Study	Country	Study design	Age [years]	controls	cases	Number of males	Stroke features	Dental features	Study key points	Study analysis

1	Hashemipour *et al.* [5]	Iran	case–control study	52	100	100	86	ischemic stroke	CAL	Age, sex, smoking status, diabetes, renal failure, cholesterol, triglycerides, hypertension, atrial fibrillation, peripheral vascular disease, prior stroke, bleeding on probing (BoP), gingival inflammation (GI), clinical attachment loss (CAL)	A significant association exists between stroke and periodontal disease.
2	Loesche *et al.*[17]	USA	cross-sectional study	<60	401	–	–	stroke	CAL	Age, race, education level, smoking history (ever/current), alcohol use, number of medications, body mass index (BMI), blood pressure, dental examination	Clinical attachment loss (CAL) greater than 6 mm showed a significant association with stroke.
3	Elter *et al.* [12]	USA	cross-sectional study	–	10,906	–	–	stroke/TIA	CAL	Age, sex, race, demographic factors, lifestyle habits, education, income, Medicaid coverage, smoking, diabetes, hypertension, coronary heart disease, edentulism, dental examination	Clinical attachment loss (CAL) was found to be linked with stroke or transient ischemic attack (TIA).
4	Grau *et al.* [11]	Germany	case–control study	18–75	168	300	–	stroke	CAL	Age, female sex, school education, occupation, smoking, alcohol consumption, diabetes, hyperlipidemia, hypertension, atrial fibrillation, coronary artery disease, peripheral artery disease, previous stroke or transient ischemic attack, family history of stroke, dental examination	Individuals with severe periodontitis (mean CAL = 6 mm) had a 4.3-fold greater risk of cerebral ischemia (95% CI: 1.85–10.2) compared to those with mild periodontitis (CAL = 3 mm) or no periodontitis.
5	Lee *et al.* [19]	USA	cross-sectional study	>60	5,123	–	–	stroke	CAL	Age, sex, race, ethnicity, education, income, poverty status, smoking, alcohol use	Evidence suggests a link between cumulative periodontal disease, as measured by the Periodontal Health Score (PHS), and a history of stroke.

6	Pradeep *et al.* [12]	India	case–control study	54	100	100	–	CVA or stroke	CAL	Age, sex, education, smoking, dietary habits, diabetes, serum cholesterol, hypertension, cardiovascular disease, prior stroke, family history of stroke, plaque index (PI), gingival index (GI), clinical attachment loss (CAL), probing depth (PD)	The average CAL values were significantly greater in stroke cases than in the control group ($p < 0.05$), indicating that periodontitis may be a potential risk factor for stroke.
7	Kim *et al.* [13]	South Korea	case–control study	40–79	118	214	164	hemorrhagic stroke	CAL	Age, male sex, education ≥9 years, income ≥1,000 USD/month, smoking, alcohol use, BMI ≥25, diabetes, hypertension, cardiac disease, family history of diabetes or cardiac disease, tooth brushing >2/day, annual dental visit, decayed/missing/filled teeth (DMFT), CAL	In males, periodontal disease with CAL greater than 6 mm was significantly associated with hemorrhagic stroke.
8	Sen *et al.* [20]	USA	cohort study	54.5	40	66	–	stroke/TIA	CAL	Age, sex, race, education, income, smoking status (ever/current), BMI, diabetes, hyperlipidemia, hypercholesterolemia, hypertension, atrial fibrillation, coronary artery disease, TIA, PI, GI, CAL, PD, NIH Stroke Scale (NIHSS), brain MRI/CT	High periodontal disease (HPD) is linked to recurrent vascular events in patients with stroke or TIA.
9	Diouf *et al.* [14]	Senegal	case–control study	–	120	120	–	stroke	CAL	Sociodemographic characteristics, lifestyle behaviors, hypertension, general medical history, stroke type (ischemic or hemorrhagic), PI, papillary bleeding index (PBI), CAL, PD, Community Periodontal Index of Treatment Needs (CPITN)	Periodontal disease has been found to be associated with stroke in the Senegalese population.
10	Leira *et al.* [15]	Spain	case–control study	30–80	60	62	–	LI	CAL	Age, male sex, smoking, alcohol use, statin therapy, diabetes, hypercholesterolemia, hypertension, peripheral artery disease, ischemic heart disease, full-mouth plaque score (FMPS), full-mouth bleeding score (FMBS), periodontitis, CAL, PD, gingival recession, missing teeth, lesion index (LI) in TOAST classification, MRI, CT, carotid Doppler	Severe periodontitis shows a strong association with lesion index (LI).

11	Sen *et al.* [21]	USA	cohort study	54.5	40	66	–	stroke/TIA	CAL	Age, sex, race, education, income, smoking status (ever/current), BMI, diabetes, hyperlipidemia, hypercholesterolemia, hypertension, atrial fibrillation, coronary artery disease, TIA, PI, GI, CAL, PD, NIHSS, brain MRI/CT	High periodontal disease (HPD) is correlated with recurrent vascular events in patients who have experienced stroke or TIA.
12	Beck *et al.* [22]	USA	original study	45–64	15,792	–	–	stroke	CAL	Age, sex, race, education, smoking status (never/former/current), BMI, diabetes status, hypertension status, total cholesterol, periodontitis, BoP, PI, GI, CAL, tooth loss	Periodontitis was found to have a significant association with stroke.
13	Mascari *et al.* [23]	USA	cross-sectional study	64	265	–	–	stroke/TIA	CAL	Age, sex, race, height, smoking, pre-diabetes, diabetes, hyperlipidemia, atrial fibrillation, coronary artery disease, history of TIA or stroke, HbA1c	Patients with periodontal disease exhibited a higher prevalence of stroke caused by large-artery atherosclerosis 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 Studies Included in the Systematic Review (Gingivitis – Gingival Index (GI))

No.	Study	Country	Study Design	Age [Years]	Number of Participants	Number of Males	Stroke Characteristics	Dental Characteristics	Key Study Variables	Study Findings
1	Hashemipour *et al.* [5]	Iran	Case-Control Study	52	100 controls, 100 cases	86	Ischemic stroke	CAL	Age, gender, smoking, diabetes, renal failure, cholesterol, triglycerides, hypertension, atrial fibrillation, peripheral cardiovascular disease, stroke history, BoP, GI, CAL	Periodontitis is significantly linked to stroke, but no significant association was found with gingivitis.

2	Grau *et al.* [11]	Germany	Case-Control Study	18–75	168 controls, 300 cases	–	Stroke	CAL	Age, female gender, education level, occupation, smoking, alcohol consumption, diabetes, hyperlipidemia, hypertension, atrial fibrillation, coronary artery disease, peripheral artery disease, prior stroke/TIA, dental examination	Individuals with severe periodontitis (mean CAL = 6 mm) had a 4.3-fold increased risk of cerebral ischemia (95% CI: 1.85–10.2) compared to those with mild periodontitis (CAL = 3 mm) or no periodontitis.
3	Pradeep *et al.* [12]	India	Case-Control Study	54	100 controls, 100 cases	–	CVA or stroke	CAL	Age, gender, education, smoking, diet, diabetes, serum cholesterol, hypertension, cardiovascular disease, prior stroke, family history of stroke, PI, GI, CAL, PD	Cases showed significantly higher mean CAL values compared to controls ($p < 0.05$), indicating periodontitis as a potential risk factor for stroke.
4	Sen *et al.* [21]	USA	Cohort Study	54.5	40 controls, 66 cases	–	Stroke/TIA	CAL	Age, gender, race, education, income, smoking status, BMI, diabetes, hyperlipidemia, hypercholesterolemia, hypertension, atrial fibrillation, coronary artery disease, TIA, PI, GI, CAL, PD, NIHSS, brain MRI/CT	High periodontal disease (HPD) is associated with recurrent vascular events in patients with stroke/TIA.
5	Beck *et al.* [22]	USA	Original Study	45–64	15,792 total	–	Stroke	CAL	Age, gender, race, education, smoking status, BMI, diabetes, hypertension, total cholesterol, periodontitis, BoP, PI, GI, CAL, tooth loss	Periodontitis was significantly associated with stroke.
6	Söder *et al.* [24]	Finland	Cohort Study	30–40	39 controls, 1,637 cases	838	Stroke	GI	Age, gender, education, income, smoking, calculus index, PI, GI, number of missing teeth	GI was a significant independent predictor of increased stroke risk.

Table 5. Secondary Dental Features in Reviewed Studies

No.	Study	Country	Study Design	Stroke Features	Secondary Dental Features	Study Analysis
1	Loesche *et al.* [17]	USA	Cross-sectional	Stroke	DMFT index, periodontal depth, gingival recession, use of dentures/prosthetic devices	Oral hygiene practices (brushing, flossing, frequency of professional dental cleanings) and plaque index were significantly linked to cerebrovascular accidents (CVA).
2	Elter *et al.* [18]	USA	Cross-sectional	Stroke/TIA	Edentulism	Edentulism showed a significant association with stroke or transient ischemic attack (TIA).
3	Grau *et al.* [11]	Germany	Case-control	Stroke	Dental visits <1/year, DMFT index, plaque index, bone loss	Severe periodontitis (mean CAL ≥ 6 mm) increased cerebral ischemia risk; gingivitis and bone loss had a strong independent link to stroke; caries, missing teeth, and plaque index were not independent risk factors.

4	Lee *et al.* [19]	USA	Cross-sectional	Stroke	Periodontal health status	No significant relationship was found between periodontal health status and stroke.
5	Pradeep *et al.* [12]	India	Case-control	CVA/Stroke	Plaque index, periodontal depth	Periodontal depth >4.5 mm was the most significant stroke risk factor; mean plaque index was also significant.
6	Kim *et al.* [13]	South Korea	Case-control	Hemorrhagic stroke	Tooth brushing >2/day, dental visits >1/year, DMFT index, missing teeth	Stroke was not linked to missing teeth, dental caries experience, or annual dental visits.
7	Sen *et al.* [20]	USA	Cohort	Stroke/TIA	Plaque index, periodontal depth, tooth loss	History of periodontal disease was associated with recurrent vascular events in stroke/TIA patients; no link was found between gingival inflammation and stroke; regular dental care reduced adjusted stroke risk.
8	Diouf *et al.* [14]	Senegal	Case-control	Stroke	Plaque index, periodontal bleeding index, periodontal depth, CPITN	Periodontal disease and related parameters were significantly associated with stroke.
9	Leira *et al.* [15]	Spain	Case-control	Lacunar infarction	Plaque index, periodontal bleeding index, periodontal depth, CPITN	Full-mouth plaque score, full-mouth bleeding score, periodontal depth, gingival recession, and missing teeth were significantly linked to lacunar infarction.
10	Sen *et al.* [21]	USA	Cohort	Stroke/TIA	Plaque index, tooth loss	History of periodontal disease was linked to recurrent vascular events in stroke/TIA patients.
11	Beck *et al.* [22]	USA	Original study	Stroke	Bleeding on probing, plaque index, tooth loss	High gingival inflammation, tooth loss, and severe tooth loss were significantly associated with diabetes, coronary heart disease, high-sensitivity C-reactive protein, and interleukin-6.
12	Mascari *et al.* [23]	USA	Cross-sectional	Stroke/TIA	Periodontal depth, gingival margin position	Patients with periodontal disease had a higher prevalence of stroke due to large-artery atherosclerosis compared to those without periodontal disease.
13	Söder *et al.* [24]	Finland	Cohort	Stroke	Dental visits, caries index, plaque index, gingival index, missing teeth	Caries and gingival indices were significantly elevated in the stroke group.
14	Ghizoni *et al.* [16]	Brazil	Case-control	Ischemic/hemorrhagic stroke	Bleeding on probing, plaque index, clinical attachment loss, periodontal depth, missing teeth, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans	Stroke patients had deeper periodontal pockets, higher bleeding on probing, and plaque index values; increased Porphyromonas gingivalis was found in their pockets.

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

Outcome analysis

An inverse-variance random-effects model was used for the meta-analysis.

Periodontitis and all stroke types

The analysis revealed a significant association between periodontitis and stroke across the included studies (ES: 1.32; 95 percent CI: 1.04–1.60). No significant

heterogeneity was observed among the studies examining the relationship between periodontitis and stroke or its subtypes, with a moderate level of inconsistency (I^2 = 30.3 percent) **(Figure 2)**.

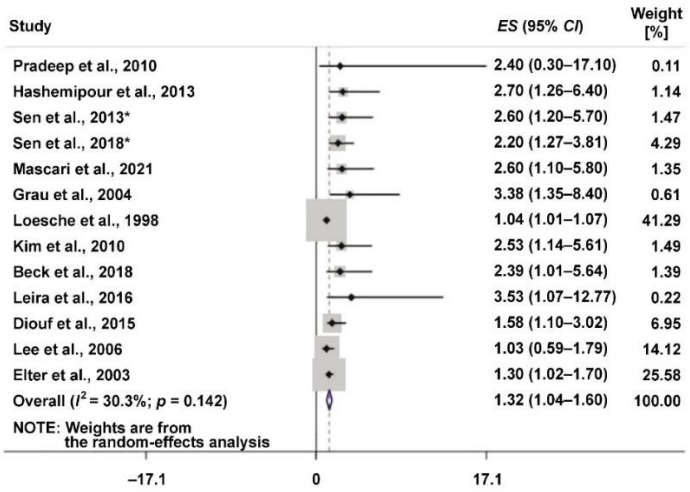

Figure 2. Forest plots depicting the association between periodontitis and all types of stroke, showing the estimated risk as effect size (ES) with 95% confidence intervals (CI); *hazard ratios (HR) were reported instead of odds ratios (OR)

Gingivitis and all stroke types

The analysis indicated a significant association between gingivitis and stroke across the reviewed studies (ES: 1.17; 95 percent CI: 0.42–1.92). No significant heterogeneity was found among the studies examining gingivitis and stroke subtypes, with a moderate level of inconsistency (I^2 = 45.9 percent) **(Figure 3).**

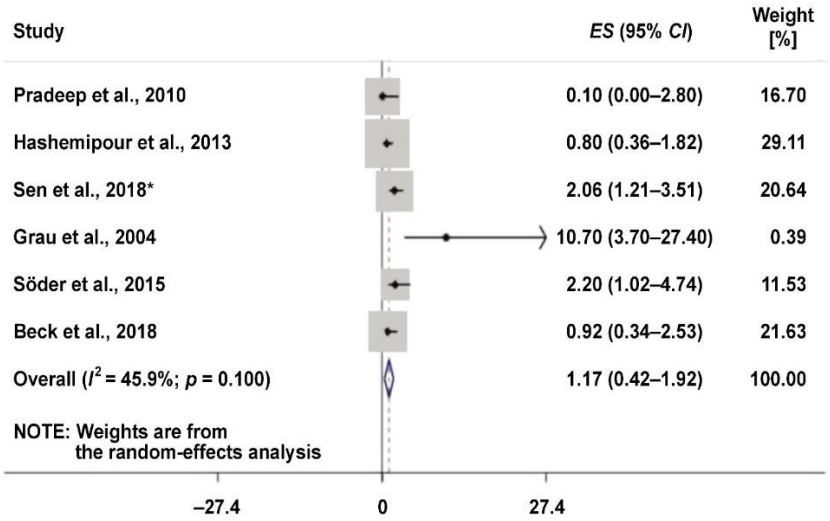

Figure 3. Forest plots illustrating the relationship between gingivitis and all types of stroke, presenting the estimated risk as effect size (ES) with 95% confidence intervals (CI); *hazard ratios (HR) were reported in place of odds ratios (OR)

Discussion

This systematic review examined the potential link between various stroke types and periodontal conditions, including periodontitis and gingivitis. A total of 19 studies were analyzed: 13 investigated the relationship between periodontitis and stroke, and 6 focused on gingivitis and stroke. Overall, the findings suggested a significant association for both conditions, with pooled effect sizes of ES: 1.32 (95% CI: 1.04–1.60) for periodontitis and ES: 1.17 (95% CI: 0.42–1.92) for gingivitis.

Among the periodontitis studies, there were 4 cross-sectional studies, 2 cohort studies, 1 original study, and 6 case–control studies. All case–control studies consistently reported a significant association between periodontitis and stroke, while cross-sectional and cohort studies also demonstrated links with various stroke subtypes. Previous research on periodontitis and stroke has shown variable results due to differences in how periodontitis was measured, which limits the comparability of findings. Notable heterogeneity was observed across studies, suggesting that the strength of the association may vary depending on study design and quality. In this review, periodontitis was primarily assessed through clinical attachment loss (CAL), which is generally considered a more accurate diagnostic indicator than probing depth or alveolar bone loss.

Several included studies had methodological limitations affecting the reliability of their findings. Misclassification bias was identified in three case–control studies by Kim *et al.* [13], Diouf *et al.* [14], and Ghizoni *et al.* [16] (the latter excluded from meta-analysis). Such non-differential misclassification tends to weaken observed associations, meaning the true relationship between periodontal disease and stroke may have been underestimated, although overestimation remains possible. Selection bias was present in the study by Pradeep *et al.* [12], where the control group comprised patients hospitalized for other neurological disorders, such as degenerative diseases, myasthenia gravis, or Wilson's disease. Leira *et al.* [15] also showed selection bias and potential inaccuracies in patient histories collected via interviews. Additional selection bias was noted in the study by Mascari *et al.* [23], and Sen *et al.* [20] was limited by a small sample size, which may have reduced statistical power.

Six studies investigated the relationship between gingival inflammation (GI) and stroke. Among these, one was an original study, two were cohort studies, and three were case–control studies. Hashemipour *et al.* [5] and Sen *et al.* [21] reported no significant association between gingival inflammation and stroke incidence. In contrast, the remaining four studies observed that higher levels of gingival inflammation were linked to stroke, suggesting that gingivitis may serve as a risk factor for various stroke types.

Secondary outcomes examined included tooth loss, bleeding on probing (BoP), probing depth (PD), plaque index (PI), and gingival recession. Most studies indicated that increased PD and tooth loss were independent risk factors for stroke events. Söder *et al.* [24] found significant associations between the calculus index (CI), GI, and stroke, while Beck *et al.* [22] reported elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6) in patients with higher cardiovascular risk.

Quality assessment of the cohort studies using the Newcastle–Ottawa Scale suggested moderate to good evidence. However, some studies lacked information on additional stroke risk factors such as body mass index (BMI), family history, smoking status, and certain co-morbidities like inflammatory diseases [18]. Furthermore, data on key risk factors including hypertension, diabetes, and dyslipidemia were unavailable due to study design limitations. Oral microbiome data were also missing from Söder *et al.* [24]. Several studies had small sample sizes [21, 24], which could introduce bias and limit the reliability of conclusions.

Gingivitis and periodontitis are chronic inflammatory conditions triggered by a pro-inflammatory host response to pathogenic bacteria. These microorganisms can enter the bloodstream during activities such as chewing, tooth brushing, or minor dental procedures, causing transient bacteremia. The ensuing endothelial activation stimulates the production of pro-inflammatory cytokines, including IL-6 and interferons, which contribute to plaque rupture, platelet aggregation, thrombus formation, and thromboembolism, ultimately increasing the risk of stroke.

Fernandes Fagundes *et al.* [6] conducted a systematic review and concluded that periodontitis represents a significant risk factor for stroke. However, inconsistencies in the definition of periodontitis and the lack of assessment of gingival inflammation were noted [6]. Similarly, Pillai *et al.* [25] reviewed the relationship between oral health and stroke, reporting that stroke patients generally exhibited poor oral hygiene, but there was insufficient evidence regarding the role of gingivitis. Their findings also suggested that dental prophylaxis and certain dental procedures may help reduce stroke incidence [25].

Scannapieco *et al.* [26] systematically reviewed the connections between periodontitis, atherosclerosis, cardiovascular disease, and stroke. They highlighted that variations in periodontal definitions and diagnostic methods complicated the interpretation of results, with some studies indicating a moderate association and others showing no clear link [26].

Larvin *et al.* [27] reported a modest but elevated risk of cardiovascular disease among patients with periodontal disease. Their analysis considered a range of cardiovascular outcomes, including infarction, coronary artery disease (CAD), and stroke, with

periodontal status assessed through both self-report and clinical confirmation [27].

Oral diseases, such as gingivitis and periodontitis, have been suggested as contributing factors to increased stroke incidence. However, the extent to which oral disease influences stroke via inflammatory processes in atherogenesis and cerebral ischemia remains uncertain. Several long-term studies are ongoing, providing both confirmed and preliminary data. Overall, there is biological and dental evidence supporting a connection between periodontal disease and stroke, emphasizing the need for individualized case evaluation [28].

One case–control study by Ghizoni *et al.* [16] was initially included in this systematic review but was later excluded from the meta-analysis due to an excessively wide confidence interval.

Future directions

Future research should aim to clarify the relationship between periodontitis, gingivitis, and stroke/TIA. Prospective cohort studies are recommended, with careful attention to the following:

– Selection:

- Representativeness of the exposed cohort
- Selection of the non-exposed cohort
- Accurate exposure assessment, ideally with two dentists evaluating dental status and inter-observer agreement exceeding 0.8
- Confirmation that participants are stroke/TIA-free at baseline
- Inclusion of all established prognostic factors for stroke, using validated criteria

– Comparability:

- Ensuring comparability between exposed and non-exposed cohorts through study design or analytical methods

– Outcome:

- Stroke/TIA diagnosis confirmed via clinical and radiological evaluation
- Long-term follow-up of at least 10 years to establish a definitive link between oral conditions and stroke
- Minimal participant loss during follow-up to maintain cohort integrity

Cases should include individuals with chronic periodontitis and gingivitis, excluding those with other systemic or inflammatory diseases. Microbiological assessment should confirm the role of dental infection or inflammation in atherosclerosis and subsequent stroke after controlling for all potential confounders. Healthy individuals should also be followed to determine whether the development of dental infection or inflammation precedes stroke or TIA.

Conclusions

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

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References

1. Kamalakannan S, Gudlavalleti AS, Murthy Gudlavalleti VS, Goenka S, Kuper H. Incidence & prevalence of stroke in India: A systematic review. Indian J Med Res. 2017;146(2):175–85. doi:10.4103/ijmr.IJMR_516_15
2. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005;366(9499):1809–20. doi:10.1016/S0140-6736(05)67728-8
3. Joshipura K. The relationship between oral conditions and ischemic stroke and peripheral vascular disease. J Am Dent Assoc. 2002;133(Suppl):23S–30S. doi:10.14219/jada.archive.2002.0373
4. Patrakka O, Pienimäki JP, Tuomisto S, Ollikainen J, Lehtimäki T, Karhunen PJ, et al. Oral Bacterial Signatures in Cerebral Thrombi of Patients With Acute Ischemic Stroke Treated With Thrombectomy. J Am Heart Assoc. 2019;8(11):e012330. doi: 10.1161/JAHA.119.012330. PMID: 31117858; PMCID: PMC6585368.
5. Hashemipour MA, Afshar AJ, Borna R, Seddighi B, Motamedi A. Gingivitis and periodontitis as a risk factor for stroke: A case–control study in the Iranian population. Dent Res J (Isfahan). 2013;10(5):613–9. PMID:24348618. PMCID:PMC3858735.
6. Fernandes Fagundes NC, Carvalho Almeida AP, Barbosa Vilhena KF, Magno MB, Maia LC, Lima RR. Periodontitis as a risk factor for stroke: A systematic review and meta-analysis. Vasc Health Risk Manag. 2019;5:519–32. doi:10.2147/VHRM.S204097
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting

systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.

8. 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):S159–72. doi:10.1002/JPER.18-0006
9. Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (updated March 2011). https://handbook-5-1.cochrane.org. Accessed April 1, 2022.
10. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al.The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed April 1, 2022.
11. 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. doi:10.1161/01.STR.0000110789.20526.9D
12. Pradeep AR, Hadge P, Raju PA, 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. doi:10.1111/j.1600-0765.2009.01220.x
13. 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. doi:10.1902/jop.2010.090614
14. Diouf M, Basse A, Ndiaye M, Cisse D, Lo CM, Faye D. Stroke and periodontal disease in Senegal: Case–control study. Public Health. 2015;129(12):1669–73. doi:10.1016/j.puhe.2015.02.033
15. Leira Y, López-Dequidt I, Arias S, Rodríguez-Yáñez M, Leira R, Sobrino T, et al. Chronic periodontitis is associated with lacunar infarct: a case-control study. Eur J Neurol. 2016 Oct;23(10):1572-9. doi: 10.1111/ene.13080. PMID: 27418418.
16. Ghizoni JS, Taveira LA, Garlet GP, Ghizoni MF, Pereira JR, Dionísio TJ, et al. Increased levels of Porphyromonas gingivalis are associated with ischemic and hemorrhagic cerebrovascular disease in humans: an in vivo study. J Appl Oral Sci. 2012 Feb;20(1):104-12. doi: 10.1590/s1678-77572012000100019. PMID: 22437687; PMCID: PMC3928781.
17. Loesche WJ, Schork A, Terpenning MS, Chen YM, Kerr C, Dominguez BL. The relationship between dental disease and cerebral vascular accident in elderly United States veterans. Ann Periodontol. 1998;3(1):161–74. doi:10.1902/annals.1998.3.1.161
18. Elter JR, Offenbacher S, Toole JF, Beck JD. Relationship of periodontal disease and edentulism to stroke/TIA. J Dent Res. 2003;82(12):998–1001. doi:10.1177/154405910308201212
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. doi: 10.1902/jop.2006.050339. PMID: 17032119.
20. Sen S, Sumner R, Hardin J, Barros S, Moss K, Beck J, et al. Periodontal disease and recurrent vascular events in stroke/transient ischemic attack patients. J Stroke Cerebrovasc Dis. 2013;22(8):1420-7. doi: 10.1016/j.jstrokecerebrovasdis.2013.06.024. Epub 2013 Jul 30. PMID: 23910516; PMCID: PMC5624802.
21. 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. doi: 10.1161/STROKEAHA.117.018990. PMID: 29335336; PMCID: PMC5780242.
22. Beck JD, Moss KL, Morelli T, Offenbacher S. Periodontal profile class is associated with prevalent diabetes, coronary heart disease, stroke, and systemic markers of C-reactive protein and interleukin-6. J Periodontol. 2018;89(2):157–65. doi:10.1002/JPER.17-0426
23. Mascari R, Vezzeti A, Orofino C, Byrd A, Hicklin D, Nichols C, et al. Periodontal Disease Association with Large-Artery Atherosclerotic Stroke. J Neurol Disord Stroke. 2021;8(1):1173. PMID: 35243483; PMCID: PMC8889900.
24. Söder B, Meurman JH, Söder PÖ. Gingival inflammation associates with stroke – a role for oral health personnel in prevention: A database study. PLoS One. 2015;10(9):e0137142. doi:10.1371/journal.pone.0137142
25. Pillai RS, Iyer K, Spin-Neto R, Kothari SF, Nielsen JF, Kothari M. Oral health and brain injury: Causal or casual relation? Cerebrovasc Dis Extra. 2018;8(1):1–15. doi:10.1159/000484989
26. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for

nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. Ann Periodontol. 2013;8(1):54–69. doi:10.1902/annals.2003.8.1.54

27. Larvin H, Kang J, Aggarwal VR, Pavitt S, Wu J. Multimorbid disease trajectories for people with periodontitis. J Clin Periodontol. 2021;48(12):1587–96. doi:10.1111/jcpe.13536
28. Dhadse P, Gattani D, Mishra R. The link between periodontal disease and cardiovascular disease: How far we have come in last two decades? J Indian Soc Periodontol. 2010;14(3):148–54. doi:10.4103/0972-124X.75908