Association between periodontal disease and stroke

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Objective: **Periodontitis is a very common human infection. There is evidence that periodontitis is associated with cerebrovascular disease (CVD) and stroke. The aim of this study is to examine the relationship between periodontal disease and CVD in observational studies.**

Methods: **An electronic search of the English literature using PubMed was conducted. A meta-analysis of the studies reporting on the risk of stroke in patients with periodontitis was performed.**

Results: **Six prospective and seven retrospective studies met the inclusion criteria. Patients with both hemorrhagic and ischemic cerebrovascular events, fatal and nonfatal, were included. Definition of periodontitis was taken directly from included studies. Most studies have been adjusted for common cardiovascular risk factors. Separate statistical analysis was performed for prospective and retrospective studies. Overall adjusted risk of stroke in subjects with periodontitis was 1.47 times higher than in subjects without (95% confidence interval, 1.13-1.92;*P* = .0035) in prospective and 2.63 times (95% confidence interval, 1.59-4.33;*P* = .0002) in retrospective studies. The application of the trim and fill algorithm does not change the initial significant inference.**

Conclusions: **There is evidence that periodontitis is associated with increased risk of stroke. However, the results of this meta-analysis should be interpreted with caution because of the heterogeneity of the studies as well as the differences in periodontitis definition. (J Vasc Surg 2012;55:1178-84.)**

Gingivitis and periodontitis are among the most common human infections. It has been estimated that in the United States, at least 35% of adults aged 30 years and older have periodontitis: 22% have a mild form, and 13% have a moderate or severe form.[1] Cerebrovascular disease (CVD) is among the most prevalent causes of death and disablement in industrialized countries. Stroke is the third leading cause of death in the United States, with 60.9 deaths per 100,000 people in 2000.[2]

Periodontitis has been shown to increase the systemic inflammatory response, which has been implicated in atherosclerosis and CVD. Periodontitis results from a complex interplay between chronic bacterial infection and the inflammatory host response, leading to irreversible destruction of tooth-supporting tissues, with tooth loss as a common end point.[3] Approximately 40% of elders are edentulous.[4] Periodontitis is associated with elevated markers of inflammation[5] that are indicators of CVD and stroke risk. Tooth loss, a marker of past periodontal disease, has been related to subclinical atherosclerosis and carotid artery plaque prevalence.[6] Bacteria from periodontal pockets can enter the bloodstream during activities such as chewing or tooth brushing,[7] and periodontal pathogens were identified in carotid plaques,[8] but their role in atherogenesis is not clear.

This meta-analysis was conducted to examine the relationship between periodontal disease and CVD in observational studies. The aim was to obtain pooled estimates on the association between periodontal disease and incidence of CVD.

METHODS

A literature search was undertaken using the MEDLINE database to identify all publications on CVD and periodontitis until December 2010. The keywords used were "stroke," "cerebral ischemia," "cerebrovascular disease," and "periodontitis." Only full-length original articles were included in the analysis. The search was restricted to original studies published in English-language journals, conducted on humans. The inclusion criteria in the meta-analysis included: (1) observational studies that provided a risk estimate of CVD for patients with periodontitis; (2) cases defined as subjects with fatal or nonfatal ischemic or hemorrhagic cerebrovascular event; (3) exposure defined as periodontal diseases; (4) exposure was treated as a categorical variable.

Initial database search using the keywords "periodontitis" and "stroke" or "cerebral ischemia" or "cerebrovascular disease" revealed 146 abstracts. Twelve studies were excluded because they were published in other than English-language journals. Nine more studies were excluded because they were conducted in nonhu-

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Table I. Prospective studies included in the meta-analysis

Authors	*Study population*	*Periodontal diagnosis*	*Groups included in analysis*
Wu et al[9]	9962 adults aged 25-74 years	(1) No periodontal disease, (2) gingivitis, (3) periodontitis, and (4) edentulousness	No periodontal disease vs periodontitis (four or more teeth with pockets)
Howell et al[10]	22,037 male physicians aged 40-84 years	Self-reported periodontal disease	Presence vs absence of periodontal disease
Joshipura et al[11]	41,380 male health professionals aged 40-75 years	Self-reported periodontal disease	Presence vs absence of periodontal disease
Abnet et al[12]	29,584 adults aged 40-69 years	Loss of teeth (compared to the median number of teeth lost for subjects of the same age)	Less than or equal to vs greater than the median number of teeth lost
Beck et al[13]	1147 men	Whole mouth bone loss	Whole mouth bone loss <20% vs >20%
Jimenez et al[14]	1137 men	Mean radiographic alveolar bone loss and cumulative periodontal probing depth	Bone loss <10% vs bone loss >80%

BMI, Body mass index; *TIA,* transient ischemic attack.

Table II. Retrospective studies included in the meta-analysis

Authors	*Study population*	*Periodontal diagnosis*
Grau et al[15]	Case-control study: 303 patients with cerebrovascular ischemia, 300 population and 168 hospital controls aged 18-75 years	CAL ≥6 mm
Elter et al[16]	9415 dentate and 1491 edentulous adults	Periodontal CAL, measured at 6 sites per tooth. Number of sites with CAL 3 + mm/measured sites, X 100
Sim et al[17]	Case-control study: 265 patients with nonfatal chronic stroke and 214 controls	CAL ≥6 mm
Lee et al[18]	5123 subjects aged >60 years	Number of teeth CAL ≥2 mm and CAL ≥3 mm
Dorfer et al[19]	Case-control study: 303 consecutive patients with ischemic stroke or TIA, and 300 controls aged 18-75 years	Number of teeth, CAL ≥6 mm, radiographic bone loss, gingival index
Pradeep et al[20]	Case-control study: 100 patients and 100 controls aged 33-68 years	Plaque index, gingival index, probing pocket depth and CAL
Kim et al[21]	Case-control study: 165 patients and 214 nonstroke control subjects	CAL

BMI, Body mass index; *CAL,* clinical attachment level; *CRP,* C-reactive protein; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *TIA,* transient ischemic attack.

mans. Forty-five articles were reviews and meta-analyses. The remaining were retrieved and read. Relevant articles were manually searched for references that could be included in the meta-analysis. Finally, 13 studies met the inclusion criteria and were included in the analysis. There were six prospective[9-14] and seven retrospective studies.[15-21] Definitions of periodontitis were taken directly from the included studies. Periodontal inflammation was assessed by different parameters such as clinical attachment level (CAL), extent of attachment loss, number of teeth loss, bone loss, and self-reported presence or absence of periodontal disease. Reported results from the selected studies regarding periodontitis severity were categorized as severe or not, according to the reported measurements. In studies that periodontitis severity was categorized in more than two categories, the least and

Table I. Continued

Cerebrovascular disease	*Follow-up (years)*	*Variables controlled*	*Analysis/blinding*	*Primary outcome*
Nonhemorrhagic and hemorrhagic stroke	10	Gender, race, age, education, poverty index, diabetes, hypertension, smoking, alcohol use, BMI, cholesterol	Cox regression/no	Yes
Nonfatal stroke	12.3	Age, alcohol, smoking, hypertension, BMI, diabetes, physical activity, family history	Cox regression/ double blind	Yes
Ischemic stroke	12	Age, smoking, obesity, alcohol, exercise, family history, multivitamin use, vitamin E use, profession, hypertension, and cholesterol	Cox regression/no	Yes
Stroke death (hemorrhagic and ischemic)	5	Age, smoking, and sex	Cox regression/no	Yes
Ischemic stroke	25	Age, smoking, diabetes mellitus, hypertension, family history, education, BMI, cholesterol	Logistic regression/no	Yes
Ischemic stroke or TIA	24	Age, baseline socioeconomic status, smoking, body mass index, hypertension, hypercholesterolemia, diabetes, alcohol	Cox regression/no	Yes

Table II. Continued

Groups included in the analysis	*Cerebrovascular disease*	*Variables controlled*
Mean CAL ≥6 mm vs CAL <3 mm	Acute ischemic stroke/TIA	Age, gender, number of teeth, vascular risk factors and diseases, childhood and adult socioeconomic conditions, and lifestyle factors
0 percentage points <6.5 percentage points vs >31.4 percentage points	Ischemic or hemorrhagic stroke/TIA	Age, race, education, hypertension, smoking, diabetes, coronary heart disease, LDL, HDL, triglycerides, BMI
No presence vs presence of any CAL ≥6 mm	Nonfatal ischemic or hemorrhagic stroke	Age, gender, income, education, smoking, drinking, systemic disease, BMI, familial cardiovascular risk factors, and oral health behaviors
Subjects with <16.7% vs subjects with ≥16.7% with CAL ≥3mm	Stroke	Age, gender, race/ethnicity, educational level, poverty, income ratio, smoking, alcohol, radial pulse rate, BMI, hematocrit, total folate, plasma, fibrinogen, serum CRP, glucose, creatinine, triglycerides, total cholesterol, HDL, HDL/total cholesterol, diabetes, hypertension
CAL <3 mm vs CAL ≥6 mm	Ischemic stroke or TIA	Hypertension, diabetes, previous stroke, smoking, high lifetime alcohol consumption, atrial fibrillation, family history of stroke, and low childhood socioeconomic conditions
Probing pocket depth <3.0 mm vs ≥4.5 mm	Acute cerebrovascular ischemic attack	Age, gender, diabetes, hypertension, cholesterol, smoking, alcohol, family history of stroke, education, diet
CAL <6 mm vs CAL ≥6 mm	Hemorrhagic stroke	Age, gender, income, education, hypertension, diabetes, BMI, cardiac disease, familial hypertension history, familial diabetes history, familial cardiac disease history, smoking, and alcohol consumption

most severe category was used in the analysis. Initial reporting for each study is shown in Tables I and II. Most studies had adjusted for common cardiovascular risk factors such as age, gender, cholesterol, weight, smoking, diabetes, and hypertension. Outcome variables used were incidence of CVD. The risk ratio estimates used in these studies were the odds ratio (OR), relative risk (RR), and hazard ratio (HR).

Data analysis. A separate analysis was conducted for the prospective and retrospective studies included in this work. The relationship between periodontal disease and stroke was assessed using the RR for prospective studies and OR for retrospective studies. The estimates were log-transformed before conducting the analyses. Calculations of heterogeneity statistics (Q, I^2, t^2) showed that a random effects model should be applied. Studies were assigned weights using the inverse variance method. Sensitivity analyses were conducted to assess the impact of each study's exclusion on the pooled estimates. The corrected Kendall tau b was used to assess publication

Table III. Data provided by each prospective study and its contribution in the pooled estimate

Authors	*n*	*Periodontitis group, n (strokes)*	*No periodontitis group, n (strokes)*	*RR (95% CI)*	P	*Z*	*W*
Wu et al[9]	9962	1800 (152)	3634 (101)	2.11 (1.30-3.42)	.003	3.03	13.91%
Howell et al[10]	22,071	2653 (94)	19,384 (537)	1.01 (0.81-1.26)	.930	0.09	22.03%
Joshipura et al[11]	41,380	6613 (119)	34,767 (230)	1.33 (1.04-1.71)	.026	2.23	21.21%
Abnet et al[12]	29,584	NA	NA	1.11 (1.01-1.22)	.038	2.08	25.33%
Beck et al[13]	1147	232 (NA)	886 (NA)	2.80 (1.44-5.44)	.002	3.04	9.81%
Jimenez et al[14]	1137	89 (24)	613 (10)	3.52 (1.59-7.80)	.002	3.10	7.71%
Pooled estimate	105,281			1.48 (1.14-1.92)	.0036	2.91	100%

CI, Confidence interval; *N,* number of participants in the study; *NA,* not available; *P, P* value; *RR,* relative risk; *W,* weight; *Z, Z* test value.
Periodontitis group, n (strokes), number of patients with periodontitis included in the meta-analysis (patients with stroke).
No periodontitis group, n (strokes), number of patients without periodontitis included in the meta-analysis (patients with stroke).

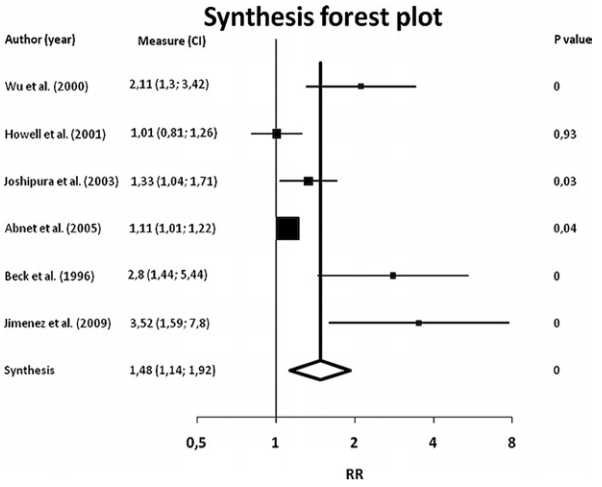

Fig 1. Prospective studies. The risk of stroke in the periodontitis group is 1.47 times (95% confidence interval [*CI*], 1.13-1.92) the risk of the nonperiodontitis group. *RR,* Relative risk.

bias and the trim and fill algorithm was used to assess dissemination bias.

RESULTS

Six prospective studies met the inclusion criteria and were included in the analysis.[9-14] The characteristics of the six prospective studies are presented in Table I. The number of participants in these studies ranged from 1,137 to 44,119. Their ages ranged from 25 to 84 years old. In all studies, adjustments for potential confounders have been performed. The most common were age, hypertension, smoking, diabetes, hyperlipidemia, and body mass index (BMI). In all studies, RR was greater than one. In five out of the six studies, the *P* value was less than .05. The analysis showed that the overall adjusted risk of stroke in subjects with periodontitis is 1.47 higher than in subjects without periodontitis (95% confidence interval [CI], 1.13-1.92; *P* = .0036; Table III; Fig 1). These estimates change to 1.12 (95% CI, 1.03-1.21) after the application of the trim and fill algorithm.

Seven retrospective studies were included in the meta-analysis.[15-21] The characteristics of these studies are presented in Table II. The number of participants in these studies ranged from 200 to 9,415. In all studies, adjustments for potential confounders have been performed. In all studies, the OR was greater than one. The analysis of the retrospective studies results in similar inference. The overall adjusted association between periodontitis and stroke is 2.63 (95% CI, 1.59-4.33; *P* = .0002; Table IV; Fig 2). This association changes to 1.50 (95% CI, 1.25-1.79) after the application of the trim and fill algorithm.

Statistical indexes used show considerable heterogeneity among retrospective but also prospective studies. Still, exclusion sensitivity shows no difference in the inference (Tables V and VI). The corrected Kendall tau b was significant in the case of the prospective studies (0.93; *P* = .008), but not in the case of retrospective studies (0.47; *P* = .13). Therefore, although publication bias cannot be excluded, in both analyzes, the trim and fill correction changes the estimates reducing the effect of periodontitis on the risk of stroke, without leading to change of the inference.

DISCUSSION

Syrjanen et al, in 1986, first suggested that chronic inflammation, including periodontitis, could be a risk factor for stroke.[22] Since then, there have been a number of studies addressing this possibility. There are common risk factors between periodontitis and stroke, including age, smoking, diabetes, hypertension, and cardiovascular disease.[11,13,20] Periodontitis is associated with elevated markers for inflammation that are themselves indicators of stroke risk; however, the epidemiologic association between periodontitis and stroke is still controversial. In this meta-analysis, periodontal diseases were associated with stroke both in prospective and retrospective studies, independent of other risk factors, socioeconomic variables, and lifestyle factors.

Chronic infections promote atherosclerosis resulting in subendothelial deposition of cholesterol, cholesterol esters, and calcium within the vessel walls. Unstable atherosclerotic plaques that are prone to rupture have a thin fibrous cap, a large lipid core, few smooth muscle cells, and are rich in macrophages.[23] Rupture of the atherosclerotic plaques releases debris and thrombi that may travel distally resulting in distal embolization and stroke. Regarding the mechanism implied in the association between periodontitis and

Table IV. Data provided by each retrospective study and its contribution in the pooled estimate of the odds ratio

Authors	*n*	*Periodontitis group, n (strokes)*	*No periodontitis group, n (strokes)*	*OR (95% CI)*	P	*Z*	*W*
Grau et al[15]	771	NA	NA	3.38 (1.36-8.43)	.009	2.61	12.99%
Elter et al[16]	9415	NA	NA	1.40 (1.09-1.79)	.007	2.68	21.66%
Sim et al[17]	479	129 (99)	233 (92)	4.30 (227-8.15)	.000	4.47	16.66%
Lee et al[18]	5123	NA	NA	1.28 (0.80-2.05)	.310	1.02	18.99%
Dorfer et al[19]	603	51 (33)	100 (39)	7.38 (2.37-22.98)	.001	3.45	10.52%
Pradeep et al[20]	200	62 (46)	35 (10)	8.50 (1.08-66.92)	.042	2.03	4.69%
Kim et al[21]	379	77 (38)	255 (80)	2.53 (1.14-5.61)	.022	2.28	14.49%
Pooled estimate	16,970			2.63 (1.60-4.34)	.00015	3.78	100%

CI, Confidence interval; *N,* number of participants in the study; *NA,* not available; *OR,* odds ratio; *P, P* value; *RR,* relative risk; *W,* weight; *Z, Z* test value.
Periodontitis group, n (strokes), number of patients with periodontitis included in the meta-analysis (patients with stroke).
No periodontitis group, n (strokes), number of patients without periodontitis included in the meta-analysis (patients with stroke).

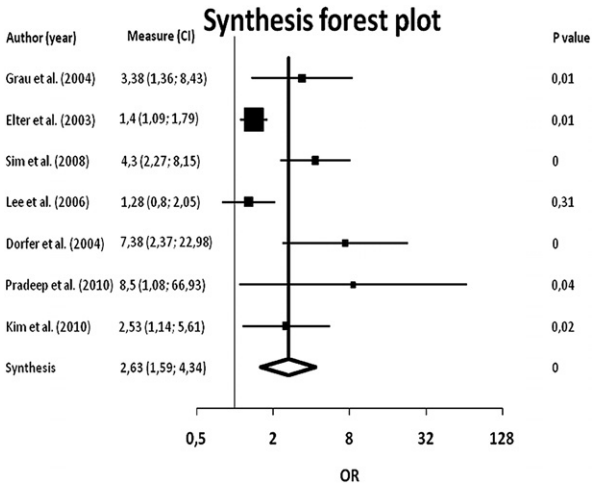

Fig 2. Retrospective studies. The odds of stroke of the periodontitis group are 2.63 (95% confidence interval [*CI*] 1.59-4.34) times the odds of the nonperiodontitis group. *OR,* Odds ratio.

Table V. Exclusion sensitivity assessment presents the changes of the estimates under the hypothesis of omitting each of the studies

Authors	*K*	*RR (95% CI)*	P	*Z*
Wu et al[9]	5	1.37 (1.05-1.78)	.018	2.36
Howell et al[10]	5	1.72 (1.21-2.45)	.003	3.01
Joshipura et al[11]	5	1.59 (1.13-2.24)	.008	2.64
Abnet et al[12]	5	1.73 (1.17-2.58)	.006	2.73
Beck et al[13]	5	1.35 (1.06-1.72)	.017	2.39
Jimenez et al[14]	5	1.34 (1.06-1.70)	.015	2.43

CI, Confidence interval; *K,* number of studies that produce the consequent estimates; *P, P* value; *RR,* relative risk; *Z, Z* test value.

Table VI. Exclusion sensitivity assessment presents the changes of the estimates under the hypothesis of omitting each of the studies

Authors	*K*	*OR (95% CI)*	P	*Z*
Grau et al[15]	6	2.54 (1.47-4.40)	.001	3.35
Elter et al[16]	6	3.18 (1.73-5.85)	.000	3.74
Sim et al[17]	6	2.29 (1.40-3.75)	.001	3.28
Lee et al[18]	6	3.23 (1.71-6.12)	.000	3.60
Dorfer et al[19]	6	2.27 (1.41-3.66)	.001	3.36
Pradeep et al[20]	6	2.47 (1.50-4.08)	.000	3.52
Kim et al[21]	6	2.70 (1.52-4.78)	.001	3.40

CI, Confidence interval; *K,* number of studies that produce the consequent estimates; *OR,* odds ratio; *P, P* value; *Z, Z* test value.

atherosclerotic plaques, three theories have been put forward: the theory of bacterial invasion assumes direct action of bacteria and their toxins on the endothelium,[24] the cytokine theory, where inflammatory mediators released by the cells of the immune system play the key role in the damage to the vascular wall endothelium,[25] and the autoimmunization theory, that emphasizes the significance of heat shock proteins (HSP65) expressed on the oral pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Actinobacillus actinomycetemcomitans.*[26] Bacterial lipopolysaccharides that pass into the blood in patients with chronic infections such as periodontitis induce production of acute-phase proteins like C-reactive protein (CRP). CRP levels in patients with periodontitis are consistently elevated compared with healthy controls.[27] Elevated levels of CRP (>2.1 mg/L) are associated with a higher incidence of acute thrombotic cardiovascular events, including stroke.[28] Acute phase proteins form deposits in damaged blood vessels and promote activation of phagocytes, which release nitrous oxide, contributing to the formation of atheromas. Chronically elevated CRP levels in patients with periodontitis exacerbate inflammatory processes in atherosclerotic plaques. Plaques with inflammation are considered unstable and prone to rupture, with increased risk for cerebrovascular events.[29]

Chronic infections presently considered as stroke risk factors mainly include periodontitis and infections with *Helicobacter pylori* and *Chlamydia pneumoniae*. Although many studies identified these infectious diseases as independent stroke risk factors, interventional trials have not been performed so far, and causality is not proven yet.[30] Chronic infectious diseases, like periodontitis, are treatable conditions, and their identification as causal contributors to

stroke risk could offer new pathways in stroke prevention. The benefit of treating periodontitis in stroke prevention is still unknown. The role of antibiotics in ischemic strokes has been investigated; however, their mechanism of action may be other than an antimicrobial effect. Minocycline, a tetracycline antibiotic, has shown anti-inflammatory, anti-apoptotic, and neuroprotective effects in many models of cerebral ischemia and neurodegenerative disease.[31] In animal models, minocycline reduced infarct size and improved neurologic outcome. To date, an early-phase clinical trial has shown minocycline to be safe and potentially effective in acute ischemic stroke, in combination with tissue plasminogen activator.[32]

There is evidence that periodontitis and chronic inflammation is associated with carotid atherosclerosis. A retrospective analysis of digital panoramic radiographic findings in pretreatment of cancer patients concluded that nearly one in four patients had calcifications in the carotid artery bifurcation area, significantly related to the calculated percentage of alveolar bone loss, which is a major finding in chronic periodontitis and results in tooth loss.[33] The Oral Infections and Vascular Disease Epidemiology Study (INVEST), found a correlation between chronic periodontitis and the presence of carotid artery plaque.[6] A total of 711 stroke-free subjects received a clinical periodontal examination. Among patients with zero to nine missing teeth, 46% had carotid artery plaque, whereas among those with more than 10 missing teeth, carotid artery plaque prevalence was 60% ($P < .05$). Interestingly, there was no difference in the findings between smokers and nonsmokers. A significant association was observed between missing teeth because of past periodontal disease and the presence of carotid artery plaque.[6] Periodontitis may induce carotid atherosclerosis and, by this mechanism, cause ischemic cerebrovascular events. However, such interaction remains to be proved.

Many of the included studies report stronger association between periodontitis and CVD in younger patients.[9,14,11,15,17] Jimenez et al found evidence of a stronger effect of bone loss on incidence of cerebrovascular disease among younger men (<65 years).[14] Wu et al found an increased risk of total stroke among periodontal-positive First National Health and Nutrition Examination Survey (NHANES I) participants aged 25 to 54 years (RR, 1.57; 95% CI, 1.05-2.36).[9] Joshipura et al also reported a stronger effect among younger men compared with older men in a cohort of health professionals (≤55 years: RR, 2.17; 95% CI, 1.22-3.84 vs >55 years: RR, 1.21; 95% CI, 0.92-1.59).[11] Grau et al found that clinical attachment loss of 4.5 mm to ≤6 mm was associated with significantly increased odds of stroke (OR, 3.43; 95% CI, 1.39-8.50) among men <60 years of age, whereas effect estimates were much smaller and nonsignificant (OR, 1.71; 95% CI, 0.65-4.5) among older men.[15]

The results of this meta-analysis should be carefully interpreted. It is a meta-analysis of observational studies. Estimated association may deviate from true, underlying relationships. It also may be due to the effect of confounding factors, the influence of biases, or both. Periodontitis is diagnosed through several different measurements. Clarity on definition of periodontitis was a major inclusion criterion and has therefore led to a relatively limited number of selected studies. In studies that periodontitis severity was categorized in more than two groups, only the least and most severe group was included in the meta-analysis. Inclusion criteria for the studies used in our analysis are quite similar with a previous meta-analysis published in 2004 by Khader et al.[34] Studies included in the previous meta-analysis and those published from 2004 to present are used in our meta-analysis. Our methods differ as we have compared the incidence of stroke between two groups, the least and most severe periodontitis. The results are similar: Khader et al reported a significant association between periodontitis and CVD (overall adjusted relative risk of CVD in patients with periodontitis compared with healthy individuals, 1.13; 95% CI, 1.01-1.27; $P = .032$).[34]

The inclusion of patients with both ischemic and hemorrhagic stroke is another limitation of this meta-analysis. In three out of the six prospective studies, only patients with ischemic stroke or transient ischemic attack are included,[11,13,14] while in two studies, both patients with ischemic and hemorrhagic stroke are included,[9,12] and in one study, no clear definition of stroke is presented.[10] Regarding the two studies with both cerebrovascular events, no adequate data for each group are provided to allow us to perform a separate statistical analysis. In one of these two latter reports, periodontitis was significantly associated with ischemic but not with hemorrhagic stroke.[9] Regarding the seven retrospective studies, in three of them, patients with ischemic events are included.[15,19,20] In two studies, both groups are included[16,17]; however, no separate data are provided. In one study, no definition of stroke is presented,[18] and one study includes only patients with hemorrhagic stroke.[21] In this latter report by Kim et al, selected control subjects from the population were matched to the valid case subjects hospitalized at the Korean National Rehabilitation Center. Periodontitis was directly evaluated by measurement of clinical attachment level and computed tomography assessment of brain imaging for hemorrhagic stroke was performed. Periodontitis is independently associated with a nonfatal hemorrhagic stroke (OR, 2.4; 95% CI, 1.1-5.5) after controlling for possible potential confounders. The association between periodontitis and hemorrhagic stroke was stronger among males, patients without diabetes mellitus, and obese patients.[21] A distinction and separate cumulative analysis for patients with ischemic and hemorrhagic cerebrovascular events cannot be performed because of the inadequate information presented in many of the studies. Even if we only include studies that provide adequate data for patients with ischemic events, the number of studies (three prospective and three retrospective) is too small to present pooled data.

Finally, another limitation is the presence of publication bias. However, the application of the trim and fill algorithm on the data suggests that this affects the estimation accuracy but does not change the interpretation of the results of our meta-analysis. Although the average risk

increase of stroke due to periodontitis cannot be precise, because of the heterogeneity of the studies as well as the differences in periodontitis definition, it appears that the increased risk of cerebrovascular events in patients with periodontitis is not to be doubted.

The establishment of such association in well-designed prospective natural history studies could have important clinical implications. Early prevention and treatment of periodontitis at a younger age may stop the development of chronic low-grade inflammation. This in combination with prompt prevention of the other atherosclerotic risk factors may all contribute in risk reduction of cardiovascular disease and, in particular, stroke.

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AUTHOR CONTRIBUTIONS

Conception and design: AG
Analysis and interpretation: GS, NR, VS, CA
Data collection: GS, VS, CA
Writing the article: GS, NR, AG
Critical revision of the article: AG
Final approval of the article: GS, NR, VS, CA, AG
Statistical analysis: GS
Obtaining funding: AG
Overall responsibility: GS, NR, VS, CA, AG

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