

Periodontal Disease and Risk of Cerebrovascular Disease

The First National Health and Nutrition Examination Survey and Its Follow-up Study

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Background: Periodontal disease has been found to be a potential risk factor for coronary heart disease. However, its association with cerebrovascular accidents (CVAs) is much less studied.

Methods: This study examines the association between periodontal disease and CVA. The study cohort comprises 9962 adults aged 25 to 74 years who participated in the First National Health and Nutrition Examination Survey and its follow-up study. Baseline periodontal status was categorized into (1) no periodontal disease, (2) gingivitis, (3) periodontitis, and (4) edentulousness. All CVAs (*International Classification of Diseases, Ninth Revision [ICD-9]*, codes 430-438) were ascertained by hospital records for nonfatal events and death certificates for fatal events. The first CVA, nonfatal or fatal, was used to define incidence. Relative risks were estimated by hazard ratios from the Cox proportional hazard model with adjustment for several demographic variables and well-established cardiovascular risk factors. Weights were used to generate risk estimates.

Results: Periodontitis is a significant risk factor for total CVA and, in particular, nonhemorrhagic stroke (ICD-9, 433-434 and 436-438). Compared with no periodontal disease, the relative risks (95% confidence intervals) for incident nonhemorrhagic stroke were 1.24 (0.74-2.08) for gingivitis, 2.11 (1.30-3.42) for periodontitis, and 1.41 (0.96-2.06) for edentulousness. For total CVA, the results were 1.02 (0.70-1.48) for gingivitis, 1.66 (1.15-2.39) for periodontitis, and 1.23 (0.91-1.66) for edentulousness. Increased relative risks for total CVA and nonhemorrhagic stroke associated with periodontitis were also seen in white men, white women, and African Americans. Similar results were found for fatal CVA.

Conclusion: Periodontal disease is an important risk factor for total CVA and, in particular, nonhemorrhagic stroke.

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THE ROLE of infection in the etiology of atherosclerosis and the development of cardiovascular disease has recently received considerable attention.¹ Periodontal disease, one of the most common human infections, has been found to be a risk factor for coronary heart disease in a number of studies.²⁻⁹ However, the association between periodontal disease and the risk for cerebrovascular accident (CVA) is much less studied. The purpose of this study was to examine the association between baseline periodontal status and subsequent incidence and mortality of CVA in a representative sample of US adults.

study sample of 9962 participants, 62.0% were women; 16.8%, African Americans; and 36.7%, current smokers at baseline. The mean age for the whole sample was 48.31 years; mean BMI, 25.7 kg/m²; and mean serum total cholesterol level, 5.68 mmol/L (219.77 mg/dL). The baseline weighted prevalence rates for periodontal disease were gingivitis, 25.3%; periodontitis, 16.8%; and edentulousness, 16.8%.

For the study cohort as a whole, total person-years of follow-up were 158 294.05 for incident and 161 065.13 for fatal CVAs (**Table 2**). During the follow-up period, there were 803 incident CVAs, including 596 nonhemorrhagic strokes, 91 hemorrhagic strokes, and 116 transient cerebral ischemic events (ICD-9 435). Fatal CVAs totaled 282, including 230 nonhemorrhagic and 52 hemorrhagic strokes. The incidence rates per

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RESULTS

Characteristics of the study cohort are given in **Table 1**. Among the unweighted

METHODS

DATA AND STUDY SAMPLE

Data from the First National Health and Nutrition Examination Survey (NHANES I)¹⁰ and its Epidemiologic Follow-up Study (NHEFS)¹¹⁻¹⁴ were analyzed; NHANES I was a cross-sectional study of a representative sample of the US noninstitutionalized civilian population aged 1 to 74 years.¹⁰ The study was conducted during the years 1971 through 1974 and augmented by an additional national sample in 1974 and 1975. The survey included a standardized medical examination and questionnaires that covered various health-related topics. The dental examination was conducted only during the years 1971 through 1974.

The baseline cohort for the NHEFS consists of the 14 407 adults aged 25 to 74 years who were examined from 1971 through 1975 as part of NHANES I. Follow-up surveys or waves of NHEFS were conducted from 1982 through 1984, 1986, 1987, and 1992.¹¹⁻¹⁴ The 1982 through 1984 follow-up included all participants in the baseline sample (n = 14 407), and approximately 93% (n = 13 383) of the cohort was successfully traced. The 1986 follow-up was conducted for the members of the cohort aged 55 to 74 years at baseline and known to be alive at the previous follow-up (n = 3980). The 1987 follow-up was conducted for the entire nondeceased NHEFS cohort (n = 11 750), and the 1992 follow-up included 11 195 participants who were not deceased in the previous surveys. The basic design of each NHEFS survey consisted of the following: (1) tracing subjects or their proxies to a current address; (2) acquiring death certificates for deceased subjects; (3) performing in-depth interviews with the subjects or their proxies for surviving subjects; and (4) obtaining hospital and nursing home records. The present study is based on the follow-up through 1992.

The NHANES I sample included a total of 20 729 persons aged 25 to 74 years, 14 407 (70%) of whom completed a medical examination and 11 348 of whom (those examined at survey locations 1-65) received dental examinations. Persons who reported ever having a heart attack, heart failure, stroke, or cancer at baseline (n = 888) or with missing data of study variables (n = 498; unweighted mean age, 52.03 years; 57.5% women) were then excluded, leaving a final sample of 9962 persons for this study.

VARIABLES OF INTEREST

The outcome variables used in this analysis are incident and fatal events of CVA that occurred during the follow-up

period of NHEFS. The *International Classification of Diseases, Ninth Revision (ICD-9)* codes 430 through 438 were used for total CVA, ICD-9 433 through 434 and 436 through 438 for nonhemorrhagic stroke, and ICD-9 430 through 432 for hemorrhagic stroke. Incident cases of CVA met at least 1 of the following criteria: (1) a death certificate with cause of death due to CVA or (2) one or more hospital/nursing home stays during the follow-up period with discharge diagnosis of CVA. The date of incidence was defined as one of the following: (1) date of the first hospital/nursing home admission with a discharge diagnosis of CVA or (2) date of death for CVA if there were no records of hospital/nursing home stay for CVA.

The hospital/nursing home admission for CVA was ascertained by the Health Care Facility Stay data collected at each follow-up survey. During the interviews, respondents were asked to report all overnight facility stays since the baseline survey or prior interview. In addition to the interviews, data on facility stays were gathered from the death certificate or by tracing sources and other hospital abstracts. All reported facilities were then contacted by mail and asked to review the subject's medical records and abstract information on exact dates of admission, discharge, and diagnoses onto standard abstract forms. Discharge diagnoses were coded according to the ICD-9. The first discharge diagnosis was used to define the cause of the corresponding admission.

Fatal events of CVA were ascertained based on the Tracing and Mortality data from each follow-up survey. Information was based on death certificates and includes vital status, date last known alive, date of death, and underlying causes of death coded according to the ICD-9.

Periodontal status measured at baseline is the exposure variable of interest. The dental examiners in NHANES I were carefully trained to follow a set of standards. The standards/guidelines were used to help narrow the range of examiner variability by eliminating many borderline or questionable conditions that were frequently a source of disagreement.¹⁵

Each individual tooth was assessed for the extent of gingival inflammation, presence or absence of periodontal pockets, and firmness of teeth in their sockets. Specifically, the criteria for assessing each tooth were the following:

- No periodontal disease—there was neither overt gingival inflammation nor loss of function due to destruction of supporting tissues.
- Mild gingivitis—there was an overt area of inflammation in the free gingivae, but the area did not circumscribe the tooth.

1000 person-years of follow-up were 5.1 for total CVA, 3.8 for nonhemorrhagic stroke, and 0.6 for hemorrhagic stroke. The mortality rates per 1000 person-years were 1.8 for total CVA, 1.4 for nonhemorrhagic stroke, and 0.3 for hemorrhagic stroke. Poorer periodontal status was associated with increased incidence and mortality for all CVA outcomes. For example, the age-adjusted incidence rates for total CVA per 1000 years of follow-up were 4.7 for participants with no periodontal disease, 5.2 for those with gingivitis, 7.0 for those with periodontitis, and 7.2 for those who were edentulous.

After adjustment for a number of demographic variables and several well-established risk factors for cardiovascular disease, periodontitis was significantly associated with an increased risk for total CVA and nonhemorrhagic stroke, but not for hemorrhagic stroke (**Table 3**). Compared with no periodontal disease, RRs (95% CIs) of incident CVA were 1.02 (0.70-1.48) for gingivitis, 1.66 (1.15-2.39) for periodontitis, and 1.23 (0.91-1.66) for edentulousness; RRs (95% CI) of incident nonhemorrhagic stroke were 1.24 (0.74-2.08), 2.11 (1.30-3.42), and 1.41 (0.96-2.06), respectively. Estimates of RR for edentulousness were

- Gingivitis—inflammation completely circumscribed the tooth, but there was no apparent break in the epithelial attachment.
- Gingivitis with pocket formation—the epithelial attachment had been broken and there was a pocket, not merely a deepened gingival crevice, due to swelling in the free gingivae. There was no interference with normal masticatory function; the tooth was firm in its socket and had not drifted.
- Advanced destruction with loss of masticatory function—the tooth might be loose, have drifted, or sound dull on percussion with a metallic instrument.

Based on the assessments of all individual teeth in the mouth, periodontal status for each participant was grouped into one of the following categories: (1) no periodontal disease (no teeth with periodontal disease, or not more than 1 tooth with mild gingivitis if 20 or more teeth were examined); (2) gingivitis (at least 1 tooth with mild gingivitis or a worse condition that did not fit the category for either no periodontal disease or periodontitis); (3) periodontitis (4 or more teeth with overt pockets or worse conditions); and (4) edentulousness (both arches edentulous or all teeth were roots). The same definition for baseline periodontal status was used in a previous study on the association between periodontal status and the risk for coronary heart disease.²

A number of baseline variables were used to control for possible confounding. These variables included age, race, sex, years of schooling, family income level (poverty index),¹⁶ smoking status, diabetes status, hypertension, alcohol use, serum total cholesterol levels, and body mass index (BMI) (weight in kilograms divided by height in meters squared). All covariates were ascertained at the baseline survey; however, smoking information was collected only for a subsample of the cohort at baseline (n=6913). For the remaining persons (n=7502), smoking status at baseline was derived from questions posed in the 1982 through 1984 follow-up interviews on lifetime smoking history or imputed history. The validity of this approach has been documented.^{17,18}

Self-reported medical histories of diabetes and hypertension were ascertained by positive responses to the questions “Has a doctor ever told you that you had any of the following conditions? High blood pressure? Diabetes?” A yes to either condition was followed in turn by the question “Do you still have it?” Self-reported frequency of alcohol drinking during the past year at baseline was coded as (1) none, (2) once per month, (3) 2 to 4 times per month, and (4) 2 to 6 times per week, and (5)

every day. The BMI was calculated from the weight and height determined at the baseline survey. Serum total cholesterol levels were measured in the Centers for Disease Control and Prevention (CDC) Lipid Standardization Laboratory using a semiautomated version of the Abell-Kendall method.¹⁹

STATISTICAL ANALYSIS

Descriptive statistics including frequencies, means, SDs of the covariates, various levels of periodontal disease, and the outcome events of interest were examined to show the characteristics of the study sample. The time of follow-up was determined as (1) the time interval between the date of medical examination at baseline and the date the event occurred for a participant with an outcome event of interest or (2) the time interval between the date of medical/dental examination at baseline and the date last known alive for a person without the outcome event. The CVA incidence and mortality rates per 1000 person-years of follow-up were calculated for participants with various levels of periodontal status at baseline. Age-adjusted incidence or mortality rate for each level of periodontal status was obtained by the direct method using the total study sample as the standard population.²⁰ Three age groups (25-44, 45-64, and 65-74 years) were used in calculation of the age-adjusted rates.

Multivariate analyses were conducted using the Cox proportional hazard model.^{20,21} In each model, the occurrence of the event to be examined was defined as a failure. Participants who did not have the events of interest were considered to be censored. For example, in the analysis of CVA mortality, the failure was death due to CVA, and the censor was still alive at last contact or death caused by something other than CVA. Hazard ratios from the Cox proportional hazard models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs) after adjustment for all covariates of interest. In order to take NHANES I design features into account, SUDAAN statistical software²² and the weights for sample locations 1 through 65 were used in the analyses. Cox proportional hazard analyses for total CVA, nonhemorrhagic stroke, and hemorrhagic stroke were performed for the sample as a whole. The multivariate analyses for total CVA and nonhemorrhagic stroke were also performed separately for white men, white women, and African Americans. Owing to limited numbers of outcome events, analyses for hemorrhagic stroke were not performed separately for the sex- or race-specific groups.

weaker than those for periodontitis and did not reach statistical significance except for fatal nonhemorrhagic stroke. There was a slight difference in risk estimates for the different outcome measurements, ie, RRs for total CVA and nonhemorrhagic stroke associated with periodontal disease tended to be larger for fatal events than for incident events. The association between periodontal status and risk for hemorrhagic stroke was not significant.

Results of multivariate analyses stratified by race and sex in whites are given in **Table 4**. For incident CVA, an increased risk with periodontitis was sig-

nificant for African Americans and marginally significant for white men and white women. For fatal CVA, the association tended to be stronger. For incident nonhemorrhagic stroke, a significant increased risk with periodontitis was found in white men and white women. Compared with incident nonhemorrhagic stroke, point estimates of RR associated with periodontal disease are much larger for fatal nonhemorrhagic stroke, especially in white men and African Americans. For example, for white men, the RR (95% CI) of fatal nonhemorrhagic stroke was 5.59 (1.60-19.47) for gingivitis, 6.55 (2.19-19.62) for periodonti-

tis, and 4.35 (1.58-12.00) for edentulousness, compared with no periodontal disease.

COMMENTS

We found that periodontal disease was a significant risk factor for CVA in this prospective study of a representative sample of US adults. Specifically, periodontitis was associated with an increased risk for total CVA and nonhemorrhagic stroke but not for hemorrhagic stroke. The finding of an increased risk for total CVA and nonhemorrhagic stroke associated with peri-

odontitis was quite consistent for whites and African Americans.

Our findings are consistent with several previous studies.^{3,23,24} In a prospective study, Beck and colleagues³ found that periodontal bone loss was associated with an increased risk for stroke: 1147 participants with periodontal assessments at baseline were followed for an average of 18 years; RRs were 2.8 for stroke comparing periodontal bone loss with no bone loss after adjusting for a number of potential confounders.

In a case-control study, Syrjanen et al²³ reported poorer dental status in people with cerebral infarction than in healthy controls. In 40 patients with cerebral infarction younger than 50 years and matched by age and sex with 40 randomly selected community controls, those with cerebral infarction had poorer periodontal status as measured by gingival bleeding on probing, subgingival calculus, suppuration in the gingival pocket, and an index reflecting periapical lesions, third-degree caries lesions, vertical bone pockets, and radiolucent lesions in furcation areas.

In a more recent study, Grau et al²⁴ investigated 166 patients with cerebrovascular ischemia, including 130 with brain infarction and 36 with transient cerebral ischemia. The 166 patients were matched by age and sex with 166 hospital controls. Dental status was measured by a total dental index that reflected caries, periapical lesions, periodontitis, and other dental lesions, and that divided participants into 2 categories. Participants with brain infarction and transient cerebral ischemia were analyzed together, and the odds ratio (95% CI) was 2.60 (1.18-5.70) for poor dental status compared with healthy dental status. Further analyses indicated that the increased risk for CVA was associated with periodontitis and periapical lesions but not caries.

The association between periodontal disease and CVA has several possible pathophysiologic links. Periodontitis represents a systemic burden of bacteria, endotoxin, and other bacterial products.²⁵⁻²⁷ Bacterial challenge could induce an abundant production of proinflammatory cyto-

Table 1. Baseline Characteristics of the Study Sample of 9962 Participants in the First National Health and Nutrition Examination Survey and Its Epidemiologic Follow-up Study

Characteristic	Unweighted*	Weighted†
	Percentage	
Female	62.0	53.4
Black	16.8	9.7
Diabetes	3.4	2.6
Hypertension	14.7	11.8
Drinker	71.0	78.6
Smoker	36.7	40.6
Ex-smoker	15.4	17.1
Gingivitis‡	23.5	25.3
Periodontitis§	18.1	16.8
Edentulousness	21.9	16.8
	Mean (SD)	
Age, y	48.31 (15.77)	45.26
Years of schooling	10.64 (3.61)	11.45
Body mass index, kg/m ²	25.65 (5.18)	25.61
Poverty index	2.58 (1.70)	2.97
Serum total cholesterol, mmol/L [mg/dL]	5.68 [219.77] (1.27 [49.02])	219.78

* Summary statistics calculated without weighting.

† Summary statistics calculated with application of the weights for sample locations 1 through 65 provided in the data set.

‡ Gingivitis indicates gingival inflammation or pocket formation.

§ Periodontitis indicates 4 or more teeth with pockets.

|| Edentulousness indicates no teeth or all teeth were roots.

Table 2. Incidence and Mortality of Cerebrovascular Disease by Baseline Periodontal Status in the First National Health and Nutrition Examination Survey and Its Epidemiologic Follow-up Study*

	n	Person-years of Follow-up	Cerebrovascular Disease			Nonhemorrhagic Stroke			Hemorrhagic Stroke		
			Events, No.	Rate	Rate ^a	Events, No.	Rate	Rate ^a	Events, No.	Rate	Rate ^a
Incident Events											
No disease	3634	62 907.57	158	2.5	4.7	101	1.6	3.2	22	0.3	0.5
Gingivitis	2346	39 276.28	121	3.1	5.2	89	2.3	4.0	12	0.3	0.5
Periodontitis	1800	26 311.33	194	7.4	7.0	152	5.8	5.4	27	1.0	1.0
Edentulousness	2182	29 798.87	330	11.1	7.2	254	8.5	5.4	30	1.0	0.7
Total	9962	158 294.05	803	5.1		596	3.8		91	0.6	
Fatal Events											
No disease	3634	63 528.09	48	0.8	1.6	38	0.6	1.4	10	0.2	0.2
Gingivitis	2346	39 761.70	39	1.0	1.7	31	0.8	1.4	8	0.2	0.3
Periodontitis	1800	26 907.24	74	2.8	2.6	57	2.1	2.0	17	0.6	0.6
Edentulousness	2182	30 868.10	121	3.9	2.3	104	3.4	1.9	17	0.6	0.4
Total	9962	161 065.13	282	1.8		230	1.4		52	0.3	

* n Indicates sample size at baseline; Rate, incidence or mortality per 1000 person-years of follow-up; Rate^a, age-adjusted incidence or mortality using the age distribution of the total sample as reference; cerebrovascular disease, defined by International Classification of Diseases, Ninth Revision (ICD-9) codes 430 through 438; nonhemorrhagic stroke defined by ICD-9 codes 433 through 434 and 436 through 438; hemorrhagic stroke, defined by ICD-9 codes 430 through 432; gingivitis, overt gingival inflammation or pocket formation; and periodontitis, 4 or more teeth with overt pocket formation.

kines, cause inflammatory cell proliferation into large arteries, and stimulate hepatic synthesis of clotting factors (eg, fibrinogen), and thus contribute to atherogenesis and thromboembolic events.^{1,3,28-31} In addition, several periodontal pathogens can induce platelet aggregation and may thus be thrombogenic when entering the systemic circulation as in periodontitis.³² Furthermore, bacterial lipopolysaccharides may attack arterial lining and damage the endothelial cells.^{33,34} Periodontal bacteria have been found in the atheromatous plaques of stroke sufferers.³⁵ Peri-

odontal infection also can influence well-established cardiovascular risk factors such as lipids, fibrinogen, and C-reactive protein modifying those factors toward a profile that is more atherogenic.³⁶ The association between periodontitis and an increased risk for nonhemorrhagic stroke found in this study may well fit with the hypothesized pathophysiologic links.

The present study has several strengths. First, it is based on a sample that represents the US adult population; thus, it has good external validity compared with other studies in which study samples were restricted to local populations or clinical settings. As such, its relevant public health impact at the national level can be estimated directly.

Second, the association between periodontal status and the risk for CVA and nonhemorrhagic stroke has been addressed for white women and for African Americans in this study. As found in white men, periodontal disease may also be an important risk factor for total CVA and, in particular, nonhemorrhagic stroke in these subgroups.

The prospective feature of the study has secured the temporal sequence of a possible association. That is, cerebrovascular events ought to occur subsequent to the presence of periodontal disease, as the consequences of periodontal infection. The periodontal assessments in this study were performed before the occurrence of the outcome event, and thus, there should be little if any bias in the assessment of periodontal health that related to the outcome measurements. Selection bias should also have been low because of the high rate of follow-up.

Statistical analyses were performed with adjustment for a number of potential confounders. The design features by which the data were collected were also taken into account. Demographic variables such as age, sex, educational level, income, and well-established car-

Table 3. Relative Risk (95% Confidence Interval) of Cerebrovascular Disease by Baseline Periodontal Status in the First National Health and Nutrition Examination Survey (NHANES I) and Its Epidemiologic Follow-up Study*

	Cerebrovascular Disease	Nonhemorrhagic Stroke	Hemorrhagic Stroke
Incident Events			
No disease	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Gingivitis	1.02 (0.70-1.48)	1.24 (0.74-2.08)	0.67 (0.19-2.31)
Periodontitis	1.66 (1.15-2.39)	2.11 (1.30-3.42)	1.22 (0.53-2.83)
Edentulousness	1.23 (0.91-1.66)	1.41 (0.96-2.06)	0.61 (0.28-1.34)
Fatal Events			
No disease	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Gingivitis	1.09 (0.60-1.97)	1.71 (0.86-3.39)	0.41 (0.09-1.88)
Periodontitis	2.14 (1.16-3.93)	2.90 (1.49-5.62)	1.12 (0.32-3.89)
Edentulousness	1.34 (0.76-2.37)	2.12 (1.14-3.95)	0.47 (0.14-1.51)

*All data are adjusted for NHANES I design features and baseline information on sex, race, age, education, poverty index, diabetes status, hypertension, smoking status, average alcohol use, body mass index, and serum cholesterol using SUDAAN statistical software²² and Cox's proportional hazard model. Unless otherwise indicated, data are relative risk (95% confidence interval). Cerebrovascular disease defined by International Classification of Diseases, Ninth Revision (ICD-9) codes 430 through 438; nonhemorrhagic stroke defined by ICD-9 codes 433 through 434 and 436 through 438; hemorrhagic stroke defined by ICD-9 codes 430 through 432; gingivitis, overt gingival inflammation or pocket formation; and periodontitis, 4 or more teeth with overt pocket formation.

Table 4. Relative Risks of Incident and Fatal Cerebrovascular Disease by Baseline Periodontal Status, Stratified by Sex or Race, in the First National Health and Nutrition Examination Survey (NHANES I) and Its Epidemiologic Follow-up Study*

	Total Cerebrovascular Disease (ICD-9 Codes 430-438)		Nonhemorrhagic Stroke (ICD-9 Codes 433-434, 436-438)	
	Incident Event	Fatal Event	Incident Event	Fatal Event
White men (n = 3139)				
No disease	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Gingivitis	1.02 (0.53-1.95)	1.32 (0.31-5.69)	1.56 (0.70-3.48)	5.59 (1.60-19.47)
Periodontitis	1.80 (0.98-3.29)	2.36 (0.69-8.04)	2.58 (1.20-5.56)	6.55 (2.19-19.62)
Edentulousness	1.44 (0.86-2.42)	1.33 (0.35-4.49)	1.83 (0.93-3.60)	4.35 (1.58-12.00)
White women (n = 6174)				
No disease	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Gingivitis	0.92 (0.51-1.67)	0.78 (0.28-2.23)	0.94 (0.46-1.91)	0.64 (0.24-1.72)
Periodontitis	1.44 (0.92-2.24)	1.96 (0.98-3.91)	1.99 (1.12-3.55)	2.32 (0.96-5.65)
Edentulousness	1.17 (0.78-1.75)	1.35 (0.65-2.79)	1.25 (0.79-2.00)	1.69 (0.68-4.16)
African Americans (n = 1669)				
No disease	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Gingivitis	1.56 (0.65-3.74)	2.05 (0.59-7.10)	1.23 (0.52-2.86)	2.61 (0.47-14.51)
Periodontitis	2.20 (1.03-4.74)	3.82 (1.08-13.6)	1.88 (0.79-4.49)	3.83 (0.65-22.57)
Edentulousness	1.08 (0.43-2.71)	2.38 (0.85-6.64)	1.05 (0.37-2.96)	3.15 (0.78-12.70)

*Adjusted for NHANES I design features and baseline information on sex and race (if applicable), age, education, poverty index, diabetes status, hypertension, smoking status, average alcohol use, body mass index, and serum cholesterol using SUDAAN statistical software²² and the Cox proportional hazard model. Unless otherwise indicated, data are relative risk (RR) (95% confidence interval [CI]). ICD9 indicates International Classification of Diseases, Ninth Revision; gingivitis, overt gingival inflammation or pocket formation; periodontitis, 4 or more teeth with overt pocket formation.

diovascular risk factors such as cigarette smoking, diabetes status, BMI, and serum total cholesterol level were included in the analyses to control for possible confounding. The design features such as stratification and clustering in collecting data were adjusted for using proper statistical techniques. These techniques helped to reduce bias in generating national estimates.

This study has several limitations. Periodontal status was assessed according to a standardized protocol, but the assessments were quite crude compared with assessments used in more recent studies such as NHANES III. Misclassification of periodontal disease status is therefore likely in the present study, though it is likely to be nondifferential, since the outcome events occurred after periodontal status was already determined. Nondifferential misclassification usually dilutes the estimate of an association. As such, this study is likely to underestimate the association between periodontal status and the risk for CVA, although overestimation is not completely impossible.

Causal microorganisms per se were not measured in this study. Although periodontal disease (as defined in this study) might reflect the exposure to harmful microorganisms, the underlying cause for periodontal disease, and the presumed causal factor linking periodontal disease to CVA, we were not able to sufficiently test the role of specific microorganisms in this study. Thus, although we found an association between poor periodontal status and elevated risk for CVA, further studies are needed to confirm the possible role of specific harmful microorganisms in this association.

Periodontal status was measured only at the baseline survey. Changes in periodontal status over follow-up are not taken into account. It is expected that those who had no periodontal disease at one time might develop the disease later. Thus, the nondisease group, the referents, might include those who developed periodontal disease during the follow-up period. In addition, the periodontal disease status, especially acute periodontal inflammation, for those who already had the disease might progress during the course of follow-up, or regress if properly treated. Since there are no available data to measure change in periodontal status over time, the observed association between periodontal status and CVA might be biased, possibly in the direction toward the null.

Periodontal status is associated with socioeconomic status and health-risk lifestyle or behaviors. These factors may influence cerebrovascular risk through mechanisms in which periodontal status is not involved, thereby confounding the observed association between periodontal status and the risk for CVA if not properly adjusted for in the analysis. In this study, a number of variables including educational level, family income, alcohol and tobacco use, and BMI were adjusted for using multivariate analyses. The analyses also indicate that the relative risk of CVA tends to be higher for periodontitis than for edentulousness, which supports the hypothesis of periodontal pathogens as possible causes for the association. However, unknown factors not included in the analysis are still potential confounders in the observed association.

Cerebrovascular events were determined according to medical records or death certificates. The first step in collecting information from medical records was the participants' recall of medical service use, and if participants with periodontal disease were less likely to use medical service, their incident CVAs would be more likely to be missed. Thus, the effect of periodontal disease would be underestimated. This may explain why the association between periodontal status and fatal events of total CVA and nonhemorrhagic stroke were stronger than that between periodontal status and the incident events.

In conclusion, this prospective study suggests that periodontitis is significantly associated with risk of developing CVA and, in particular, nonhemorrhagic stroke. While a conclusive statement about cause-effect relationship cannot be made at this time, the consistency of the findings in different racial groups and the strength of the association warrant further examination of the potentially important association between 2 chronic conditions highly prevalent in the adult population.

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