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Periodontitis and incidence of cerebrovascular disease in men:

Periodontitis & cerebrovascular disease in men

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Abstract

Objective—To identify associations between periodontitis and incidence of cerebrovascular disease.

Methods—We analyzed data of 1,137 dentate men in the VA Normative Aging and Dental Longitudinal Study who were followed with triennial medical/dental exams for up to 34 years (mean 24 years). We evaluated incidence of cerebrovascular events consistent with stroke or transient ischemic attack in relation to mean radiographic alveolar bone loss (a measure of periodontitis history) and cumulative periodontal probing depth (a measure of current periodontal inflammation). Cox proportional hazards models were fit controlling for age, baseline socio-economic status and time varying effects of established cardiovascular risk factors.

Results—Eighty incident cases of cerebrovascular disease occurred from 27,506 person-years. Periodontal bone loss was significantly associated with an increased hazard rate of cerebrovascular disease (HR: 3.52, 95% CI: 1.59, 7.81 comparing highest to lowest bone loss category, *p* for trend <0.001). There was a stronger effect among men aged <65 yrs (HR: 5.81, 95% CI: 1.63, 20.7) as compared to men ≥65 yrs (HR: 2.39, 95% CI: 0.91, 6.25). Periodontal probing depth was not associated with a significantly increased rate of cerebrovascular disease in the combined or age stratified analyses.

Interpretation—These results support an association between history of periodontitis - but not current periodontal inflammation - and incidence of cerebrovascular disease in men, independent of established cardiovascular risk factors, particularly among men younger than 65 years.

Keywords

Epidemiology; Risk Factors for Stroke; Transient Ischemic Attacks; Periodontal Diseases

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Introduction

The potential role of periodontitis in risk of cardiovascular disease (CVD)¹ has received growing attention in the past decade and evidence for an association of periodontitis and cerebrovascular disease has been stronger compared to other types of CVD. In general, studies have shown moderately increased risk of cerebrovascular disease in persons with periodontitis compared to those without, with the strongest association with ischemic stroke.^{2–5} However, there is considerable variation in the observed associations and differences among studies may be related to differences in the populations studied, ascertainment and classification of cerebrovascular disease and/or periodontitis, and insufficient control for important confounders.⁶

Periodontitis is clinically assessed by measuring tissue destruction at various sites of the dentition using a periodontal probe or radiographs. However, the majority of available cohort studies have utilized self reports of periodontitis or crude clinical indices not based on periodontal probing or radiographs.^{3, 5, 7} These limitations may result in substantial attenuation of relative risk estimates.⁶ Indeed, studies that utilized periodontal probing to assess periodontitis have reported stronger associations with cerebrovascular disease.^{2, 4} Definitions of periodontitis vary widely and are typically based on clinical attachment loss or bone loss (cumulative measures of loss of periodontal ligament and alveolar bone), periodontal probing depth (the depth of the gingival crevice) or on combinations of such measures.^{8, 9} ‘Standard’ definitions of periodontitis have only recently been proposed and are not yet universally accepted. Furthermore, they have been proposed for purposes of periodontal disease surveillance⁸ and for epidemiologic studies into determinants of periodontitis risk⁹ and are not necessarily suitable for studies on the potential systemic effects of periodontitis. Indeed, the definition of periodontitis which most accurately reflects true underlying exposure to systemic effects of periodontitis remains arguable.¹⁰ Both causal and non-causal pathways have been proposed to explain the observed associations between periodontitis and cerebrovascular disease,² and different exposure measures may capture these causal and non-causal pathways to varying extents.

Our aim was to evaluate the association between periodontitis and risk of cerebrovascular disease in an established longitudinal study cohort of adult men. Earlier work using this cohort suggested the presence of such an association.² The present analysis builds on 15 additional years of follow-up, capturing additional incident cerebrovascular events, and includes testing of different definitions of periodontitis. In addition, we utilized Cox proportional hazards models taking full advantage of the longitudinal study design and allowing for the time-varying effects of exposure and potential confounders. To date, this is the only prospective cohort study with clinical measures of periodontitis available.

Materials and Methods

Study population

The Veterans Affairs (VA) Normative Aging Study (NAS) is an ongoing closed panel longitudinal cohort study begun in the 1960’s with 2,280 healthy male volunteers recruited from the greater Boston area.¹¹ Subjects were not VA patients and have continued to receive their medical and dental care in the private sector. They have undergone triennial medical assessments by NAS physicians, including detailed history, physical examination, and laboratory tests. Diseases and conditions were recorded according to the 8th revision of the International Classification of Diseases (ICD-8). A subset of 1,231 NAS subject, volunteered for enrollment in its dental component, the VA Dental Longitudinal Study (DLS).¹² A trained and calibrated periodontist conducted comprehensive oral examinations triennially, including full-mouth radiographs and periodontal probing at each tooth. We have

excluded subjects who were edentulous or developed cerebrovascular disease prior to their first DLS examination (1969–1973), which was used as the baseline for the present analyses.

This study was approved by the Department of Veterans Affairs Committee on Human Studies, and procedures followed were in accordance with institutional guidelines. All subjects conferred their informed consent for participation.

Outcome assessment

Cerebrovascular disease was defined as a cerebrovascular event consistent with stroke or transient ischemic attack. Non-fatal events were ascertained in the NAS using the same criteria employed in the Framingham Heart Study, based on history and physician examination findings consistent with cerebral thrombosis (ICD-8: 432–436).¹³ Examinations were performed by a NAS internist, who also reviewed subjects' medical records as needed. Fatal events were ascertained from death certificates (ICD-8: 432–436 for primary cause of death).

Exposure assessment

A trained and calibrated periodontist performed triennial full mouth dental examinations. We used two measures of periodontitis: radiographic alveolar bone loss and periodontal probing pocket depth. Bone loss was measured on each interproximal tooth surface, in 20% increments as percent of root length and recorded on a scale of 0 to 5, using a Schei ruler superimposed on intraoral periapical radiographs (score 0: no bone loss, score 1: bone loss $\leq$ 20%, score 2: bone loss $>20\%$ and $\leq 40\%$, score 3: bone loss $>40\%$ and $\leq 60\%$, score 4: bone loss $>60\%$ and $\leq 80\%$, score 5: bone loss $>80\%$).¹⁴ More detailed descriptions of the periodontal indices used in the DLS have been previously published.^{15, 16} We computed the mean whole mouth bone loss score, calculated as the sum of all tooth measurements divided by the number of sites assessed. Maximum probing pocket depth was recorded for each tooth in categories of 0– ≤ 3 mm, >3 – <5 mm and ≥ 5 mm. A cumulative probing depth score was constructed as the sum of all probing depths >3 mm, using the mean of each category (4mm and 6mm, respectively).^{15, 16}

Other Variables

Data on covariates were taken from each triennial NAS visit, except for education, occupation and income¹⁷ for which only baseline data were available. Levels of educational attainment were categorized as some or completed high school compared to greater than a high school education. Occupation was used as a binary variable with the professional and technical category as the referent group. Income level was categorized in three categories. Marital status was dichotomized into currently married and not separated versus not married or separated. Smoking exposure was expressed using a comprehensive smoking index^{18, 19} that accounts for subjects' reports of duration of smoking, intensity and time since cessation. Body mass index (BMI) was calculated from measured weight and height. Hypertension was assessed by physician exam using mean systolic and diastolic blood pressures, measured on each arm on seated subjects using standard mercury sphygmomanometry. Total cholesterol, triglycerides, fasting glucose level, and high density lipoprotein cholesterol (determination of HDL began in 1981) were assessed from blood samples collected at each exam. Diabetes was determined by physician exam or fasting glucose ≥ 126 mg/dL, or 2 hour glucose level ≥ 200 mg/dL. Alcohol consumption was assessed using the Cornell Medical Index Health, based on daily consumption of 2 or more drinks per day. Oral hygiene was assessed using ordinal scores for plaque (0 to 3) and gingivitis (0 to 3) on each tooth and a mean score was calculated for each participant.^{15, 16} In addition, information on use of floss (yes/no) was collected at baseline.

Data analysis

Descriptive analyses were conducted for the full cohort and separately for men with or without incident cerebrovascular disease during follow-up. Crude incidence rate ratios were calculated for the full cohort and stratified by age ≥ 65 years. The relationship between periodontitis and incident cerebrovascular disease was assessed using Cox proportional hazards models with time-varying effects of the exposure updated at each dental exam. Hazard Ratios (HR) are reported as the measure of relative risk with 95% confidence intervals (CI). Person-time for each participant was calculated from their first dental exam to first diagnosis of cerebrovascular disease, death, last NAS visit for non-events or edentulism whichever occurred first.

Both age adjusted and multivariate adjusted Cox proportional hazards models were fit. Multivariate models additionally adjusted for income, education and occupation at baseline and time-varying effects of smoking, BMI, HDL, total cholesterol, triglycerides, hypertension, mean systolic blood pressure, mean diastolic blood pressure, diagnosis of diabetes, alcohol consumption and marital status. The last observation carried forward was used for triennially updated variables in the event of missing data and baseline values were used for variables only collected at baseline (i.e. education, income and occupation). Furthermore, for these variables only collected at baseline or not collected until many years after baseline (HDL cholesterol) we utilized the missing indicator method. In addition, the missing indicator method was used for a few subjects in which data on a covariate from a recent previous exam was not available and not carried forward ($<10\%$ of observations). Data for the cumulative probing depth measure was only carried forward for at most one exam cycle only if the number of teeth had not changed, therefore the number of events based on the cumulative probing depth measure is 1 less than that for the bone loss measure. Deviations from linearity were assessed using a likelihood ratio test comparing a model with a linear term to a model with indicator variables. Mean whole mouth bone loss score and cumulative probing depth were modeled as categorical and continuous variables. Linear trend for each exposure variable was assessed using the median of each category and modeling the categorical variable as ordinal. Due to prior evidence for a stronger association between periodontitis and cerebrovascular disease in younger subjects,^{3, 4, 20} we explored effect-modification by stratifying the models by age (<65 years versus ≥ 65 years). We additionally ran separate models exploring the effects of edentulousness. Further we conducted sensitivity analyses and restricted the sample to confirmed ischemic events (stroke or TIA). All models were evaluated to determine departure from the proportional hazards assumption. All analyses were performed using STATA 9.0 (StataCorp, College Station, TX, USA).

Results

After exclusion of men with prevalent cerebrovascular disease and/or those edentulous at baseline the final sample resulted in 1,137 white males contributing 27,506 person-years. The mean age at baseline was 48 years (median=48, range: 27–84). There were 80 documented incident cerebrovascular events, of which 19 were transient ischemic attacks (ICD-8: 435), 27 were confirmed ischemic events (ICD-8: 432–435) and seventeen events were fatal. Those who experienced a cerebrovascular event were slightly older and in overall poorer general health, with higher total cholesterol and more likely to be diabetic, current smokers and have fewer number of teeth (Table 1). There were no significant differences between oral hygiene characteristics at baseline of subsequent cerebrovascular events and non-events over the follow-up period.

In age adjusted analyses, there was a significant dose-dependent association between mean whole mouth bone loss score and cerebrovascular disease incidence (Table 2, linear trend:

$p < 0.001$). In the fully adjusted model, there was a significant positive association between mean whole mouth bone loss score and rate of cerebrovascular disease (p for trend: 0.001). Compared to men with mean bone loss scores ≤ 0.5 , men with mean bone loss scores > 1.5 had more than 3 times higher hazard rates of cerebrovascular disease (HR=3.52, 95% CI: 1.59–7.81, Table 2).

There was evidence for effect modification by age as the association between mean whole mouth bone loss score and cerebrovascular disease was substantially stronger among men younger than 65 years of age (Table 3). Compared to men with mean bone loss scores ≤ 0.5 , men with mean bone loss scores > 1.5 had almost 6 times higher hazard rates of cerebrovascular disease (HR=5.81, 95% CI: 1.63–20.7). In contrast to mean bone loss, there were no significant associations observed between cumulative probing depth and incident cerebrovascular disease in the full sample (Table 2) or in the age-stratified analyses (Table 3).

Additionally, we examined the effect of edentulousness on risk of cerebrovascular disease although there were limited number of events within this subgroup ($n=8$). In the multivariate analysis, edentulous men exhibited an increased rate of cerebrovascular disease compared to men with bone loss ≤ 0.5 (HR=2.56, 95% CI: 0.94–6.96). When compared to men with cumulative probing depth ≤ 4 mm, edentulousness was associated with a non-significant 19% increased risk of cerebrovascular disease (HR=1.19, 95% CI: 0.51–2.79).

In sub-analyses among confirmed ischemic events ($n=27$), there was a substantially increased rate for all categories of mean whole mouth bone loss score with stronger effects than observed in the combined cerebrovascular disease analyses. Incidence of cerebrovascular disease was significantly higher among men in the highest category of mean whole mouth bone loss score (HR: 10.3; 95% CI: 1.20–89.1) compared to men with a score ≤ 0.5 .

Discussion

We found a significant positive association between periodontal bone loss and the incidence of cerebrovascular disease (stroke and TIA), independent of important cardiovascular risk factors. The observed association was much stronger among men younger than 65 years old. We found no significant association between cumulative probing depth and incidence of cerebrovascular disease.^{2–5, 20, 21}

Several causal and non-causal pathways have been postulated to explain the observed association between periodontitis and cerebrovascular disease.² Causal pathways may involve direct and indirect effects of the periodontal infection and the inflammatory response,²² while an increased pro-inflammatory susceptibility to both atherosclerosis/thrombosis and chronic periodontitis would be an alternate, non-causal pathway. However, current epidemiologic studies are not able to differentiate between these causal and non-causal pathways, even with perfect control of all established cardiovascular risk factors. Thus, both causal and non-causal pathways may have a role in the observed associations.

Treatment of periodontitis typically results in a reduction or elimination of periodontal pockets but does not typically result in regeneration of lost bone. Hence, alveolar bone loss is a better measure of periodontitis history, while the probing depth measure we utilized in this study may better reflect current exposure to periodontal inflammation.⁸ Furthermore, the latter measure adequately accounts for the reduction in inflammatory exposure due to tooth loss.²³ Thus, one would expect cumulative probing depth to be a better clinical measure of exposure to periodontitis if the periodontal infection or inflammation itself was a causal risk factor for cerebrovascular disease. However, we found that only periodontal bone

loss was associated with the incidence of cerebrovascular disease, while cumulative probing depth was not. These results may be more consistent with a non-causal pathway, as treatment of periodontitis or tooth loss would not affect the underlying susceptibility to inflammatory diseases. However, to what extent specific clinical definitions of periodontitis reflect variations in disease susceptibility is uncertain, and it has been demonstrated that wide variations in host immune response may be present in patients with similar clinical presentation.²⁴

Other studies have also aimed to evaluate measures possibly more reflective of current infection than attachment or bone loss. Grau et al.⁴ utilized gingivitis measured shortly after acute cerebrovascular disease. They argued that the inflammatory response directly preceding the cerebrovascular event may be more important in influencing risk of an event rather than cumulative measures of disease progression. Results suggested that gingivitis was a strong independent risk factor for cerebrovascular disease in a multivariate model when adjusting for radiographic bone loss. However, since the exposure, gingivitis, was measured after the cerebrovascular event, one cannot confirm the temporal sequence. It is possible that oral hygiene may have been poor in subjects immediately following a cerebrovascular event which can lead to gingivitis within several days thereby resulting in reverse causation.

However, other studies do provide indirect evidence for a causal role of periodontitis in the pathogenesis of cerebrovascular disease via direct and indirect pathways. Firstly, several cross-sectional studies have shown periodontitis to be associated with systemic markers of inflammation, including serum CRP^{25, 26} and plasma fibrinogen.^{23, 26} In addition, several uncontrolled and controlled intervention studies suggest that periodontal treatment may reduce levels of inflammatory biomarkers such as CRP,^{27, 28} although results are equivocal.²⁹ More notably, a recent randomized controlled trial found that successful periodontal therapy improved endothelial function.⁹ Furthermore, bacterial DNA and viable periodontal pathogens have been isolated from human atheromas.^{30, 31} However, the relative importance of such causal mechanisms as compared to confounding by a common pro-inflammatory phenotype is uncertain.

We found evidence of a stronger effect of bone loss on incidence of cerebrovascular disease among younger men (<65yrs). This is consistent with other studies that have explored differences of effect by age. Wu et al.²⁰ found an increased risk of total stroke among periodontal positive NHANES I participants (RR=1.33; 95% CI: 1.07–1.66) and even stronger effect when restricted to those aged 25–54 (RR=1.57; 95% CI: 1.05–2.36), which implies that there was relevant association among older participants. Joshipura et al.³ also reported a stronger effect among younger men compared to older men in a cohort of health professionals (≤55 years RR=2.17; 95% CI: 1.22–3.84 versus >55 yrs RR=1.21; 95% CI: 0.92–1.59) when controlling for time-varying effects of potential confounders. Similarly, in a case-control study,⁴ clinical attachment loss of 4.5–≤6 mm was associated with significantly increased odds of stroke (OR=3.43; 95% CI: 1.39–8.50), among men ≤60 yrs of age whereas effect estimates were much smaller and non-significant (OR=1.71; 95% CI: 0.65–4.5) among older men. Men with a higher susceptibility to periodontitis would exhibit a given severity of periodontal destruction at an earlier age than those with a lower susceptibility to inflammatory periodontitis. Therefore, the findings of a strong significant association between periodontitis and cerebrovascular disease among younger men and a much weaker and non-significant association among older men may further support the hypothesis of a common pro-inflammatory susceptibility.

Important limitations exist with this study. The NAS and DLS began in the late 1960s prior to modern imaging technologies and we were unable to definitively exclude all cases of

hemorrhagic stroke, as we included ICD-8 codes for ‘unspecified’ events which could represent ischemic or hemorrhagic events. However, we would expect the vast majority of these events to represent ischemic events given the well established higher incidence of ischemic compared to hemorrhagic events. We have no reason to believe that hemorrhagic events were more or less likely in our study than in any other population based cohort. The potential inclusion of hemorrhagic strokes would be expected to result in an estimate of association closer to the null. Hemorrhagic stroke etiology has not been associated with infection and has not been shown to exhibit an association with periodontitis. Wu et. al.⁵ found no evidence of an association between periodontitis and hemorrhagic stroke but a significantly increased risk of cerebrovascular disease (ischemic and hemorrhagic) and an even stronger association in analyses restricted to ischemic stroke. Consistent with this, our sensitivity analysis restricted to confirmed ischemic events found a stronger association with mean whole mouth bone loss score.

However, the moderate sample size and consequently relatively small number of incident cerebrovascular events limited the precision of our estimates. This is of particular relevance for the age-stratified analyses. Thus, there remains considerable uncertainty with respect to the strength of the association between periodontitis and cerebrovascular disease among younger men and a moderate but important association among older men cannot be ruled out. Furthermore, generalizability of these results to populations other than White men is uncertain. For example, previous results by Grau et al. suggest a stronger effect of periodontitis on ischemic cerebrovascular disease among men than women.⁴

This study also has notable strengths such as its longitudinal design which allows for the establishment of the temporal sequence of exposure and disease. In addition, this study utilized clinical exposure assessment based on radiographs and periodontal probing by calibrated examiners; which would minimize potential misclassification of exposure. Furthermore, there was a long follow-up period with exposure and confounder measurement updated in approximately 3 year intervals, allowing for the time-varying effects of exposure and potential confounders. Confounding by smoking is a genuine concern given the strong association smoking exhibits with both periodontitis and cerebrovascular disease.³² However, we were able to control for the time-varying effects of smoking using a comprehensive smoking index which accounts for intensity, duration of smoking and time since cessation for former smokers.^{18, 19} Furthermore, relative to the strength of the observed associations, adjustment for established cardiovascular risk factors resulted in a moderate attenuation of estimates, suggesting no important residual confounding by established CVD risk factors.

Summary

A significant association was found between history of periodontitis as measured by alveolar bone loss and incidence of cerebrovascular disease in men, independent of established cardiovascular risk factors. Furthermore, there was evidence for a stronger association between periodontal bone loss and incidence of cerebrovascular disease among younger men (<65 years). Even if this association was predominantly non-causal, periodontitis could be an important marker of risk for cerebrovascular disease, given its relatively high prevalence and the strength of the association. Large epidemiologic studies using molecular and genetic approaches in various populations are necessary to determine the strength of the association between periodontitis and cerebrovascular disease and to elucidate its biologic basis.

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Table 1

Baseline Characteristic of Men with or without Incident Cerebrovascular Disease during Follow-up

	Overall	Non-Cerebrovascular Events	Cerebrovascular Events	P-value*
N	1,137	1,057	80	
Age	48 ± 8.8	48 ± 8.8	52 ± 7.6	<0.001
BMI	26.1 ± 3.0	26.1 ± 3.0	26.5 ± 3.2	0.35
Total Cholesterol	224.5 ± 47.3	223.9 ± 45.9	231.2 ± 62.2	0.18
HDL[†]	48.3 ± 14.0	48.7 ± 14.1	42.2 ± 11.2	0.01
Triglycerides	154 ± 85.5 Median=138	152.5 ± 82.9 Median=137	171.8 ± 113.7 Median=151.5	0.04
Hypertension	11% (130)	11% (116)	18% (14)	0.08
Systolic Blood Pressure	124 ± 15.4	123.6 ± 15.2	128.3 ± 16.1	0.01
Diastolic Blood Pressure	76.7 ± 8.9	76.6 ± 9.0	78 ± 8.2	0.17
Diabetes[‡]	6% (73)	6% (62)	14% (11)	0.01
Current Smokers	23% (265)	23% (242)	29% (23)	0.45
Alcohol Use	22% (251)	22% (230)	26% (21)	0.35
Income[§]				
≤ \$14,999	31% (341)	31% (311)	39% (30)	0.32
\$15,000 – \$24,999	50% (548)	51% (514)	44% (34)	
≥ \$25,000	18% (199)	18% (186)	17% (13)	
<High School Education	10% (117)	11% (112)	6% (5)	0.24
Professional Occupation	18% (182)	17% (166)	22% (16)	0.92
Married	92% (1,040)	92% (967)	91% (73)	0.88
Plaque Index	1.57 ± 0.51	1.57 ± 0.52	1.58 ± 0.42	0.84
Gingivitis Index	1.99 ± 0.48	1.98 ± 0.48	2.02 ± 0.48	0.42
Floss	35% (400)	36% (375)	31% (25)	0.44
Number of teeth				
>20	82% (931)	83% (872)	75% (60)	0.31
15–20	9% (101)	9% (90)	14% (11)	
10–15	4% (40)	4% (38)	3% (2)	
5–10	5% (52)	4% (45)	8% (6)	
<5	1% (13)	1% (12)	1% (1)	
Bone loss Score				
< 0.5	54% (613)	55% (611)	42% (33)	0.03
>0.5 – < 1	25% (279)	25% (278)	28% (22)	
>1 – ≤ 1.5	13% (147)	13% (144)	23% (18)	
> 1.5	8% (89)	8% (87)	8% (6)	
Cumulative Probing Depth				
0 – ≤ 4 mm	37% (414)	37% (390)	30% (24)	0.17
> 4 – ≤ 30 mm	40% (456)	40% (426)	38% (30)	
>30 mm	23% (264)	23% (239)	32% (25)	

Where appropriate, means are reported ± s.d, medians and percentages (frequency); Percentages may not sum to 100% due to rounding

* P-values for group comparisons based on t-tests for normally distributed variables, Wilcoxon rank sum test for non-normally distributed variables and Chi-square test for categorical variables.

[†] HDL – Cholesterol available beginning in 1981

[‡] Diabetes based on diagnosis by physician or elevated fasting or 2h glucose test

[§] Income at DLS baseline. Median income for a white family of 3 in 1969, DLS baseline, was \$9,59717

^{//} Education and occupation were assessed at NAS baseline.

Age and Multivariate Adjusted Hazard Ratios (HR) and 95% CIs for Incident Cerebrovascular Disease by Categories of Periodontitis

Table 2

	Median	Median # teeth	Events	IR* (95% CI) [†]	HR (95% CI) [‡]	HR (95% CI) [§]
Mean bone loss score (Schei)						
≤ 0.5	0.25	26	10	94	1.00	1.00
>0.5 – ≤ 1	0.74	24	22	269	1.83	1.88
				(0.85, 3.90)	(0.88, 4.03)	(0.79, 3.65)
>1 – ≤ 1.5	1.22	22	24	468	2.58	2.74
				(1.20, 5.56)	(1.27, 5.92)	(1.05, 4.96)
> 1.5	1.85	17	24	758	3.98	4.48
				(1.83, 8.63)	(2.05, 9.80)	(1.59, 7.81)
Continuous	0.67	24	80	296	1.88	2.06
				(1.40, 2.53)	(1.51, 2.81)	(1.33, 2.58)
Test of trend				<0.001	<0.001	0.001
Cumulative Probing depth						
0 – ≤ 4	0	24	22	241	1.00	1.00
> 4 – ≤ 30	16	24	31	291	0.92	0.92
				(0.53, 1.60)	(0.53, 1.61)	(0.51, 1.56)
>30	48	25	26	383	1.18	1.20
				(0.66, 2.10)	(0.67, 2.15)	(0.59, 1.93)
Continuous [#]	12	24	79	298	1.09	1.10
				(0.92, 1.28)	(0.93, 1.30)	(0.90, 1.27)
Test of trend				0.46	0.42	0.71

* Crude incidence rate (IR) for cerebrovascular disease (cases/10⁵ person-years)

[†] Age adjusted estimates

[‡] Adjusted for age, marital status, and baseline measures of education, occupation and income.

[§] Adjusted for age, BMI, HDL, total cholesterol, triglycerides, diagnosis of hypertension, mean systolic blood pressure, mean diastolic blood pressure, diabetes diagnosis, daily alcohol consumption, comprehensive smoking index, marital status, and baseline measures of education, occupation and income.

^{||} HR for increase in mean bone loss score by one

HR for 20mm increase in cumulative probing depth

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Table 3

Age and Multivariate Adjusted Hazard Ratios (HR) and 95% CIs for Incident Cerebrovascular Disease by Age (<65 vs. 65+)

	< 65 yrs						≥ 65 yrs					
	Median	Median # teeth	Events	IR* (95% CI) [†]	HR (95% CI) [‡]	HR (95% CI) [§]	Median	Median # teeth	Events	IR* (95% CI) [†]	HR (95% CI) [‡]	HR (95% CI) [§]
Mean bone loss score (Schei)												
≤ 0.5	0.25	27	4	43	1.00	1.00	0.33	26	6	465	1.00	1.00
> 0.5 – ≤ 1	0.73	24	9	154	3.00	3.11	0.78	24	13	555	1.11	1.15
					(0.92, 9.82)	(0.95, 10.18)					(0.42, 2.93)	(0.43, 3.02)
> 1 – ≤ 1.5	1.21	22	7	231	4.39	4.65	1.22	21	17	811	1.56	1.67
					(1.27, 15.20)	(1.34, 16.15)					(0.61, 3.98)	(0.65, 4.27)
> 1.5	1.84	18	7	366	7.13	8.10	1.88	15	17	1356	2.40	2.71
					(2.07, 24.49)	(2.34, 28.07)					(0.93, 6.17)	(1.05, 7.03)
Continuous ^{//}	0.55	25	27	134	2.53	2.74	1.00	22	53	759	1.62	1.79
					(1.55, 4.13)	(1.67, 4.51)					(1.12, 2.35)	(1.22, 2.64)
Test of trend					0.001	<0.001					0.02	0.01
Cumulative probing depth												
≤ 4	0	24	9	124	1.00	1.00	0	20	13	710	1.00	1.00
> 4 – ≤ 30	16	25	8	109	0.82	0.84	16	22	23	702	0.93	0.93
					(0.32, 2.14)	(0.32, 2.17)					(0.47, 1.85)	(0.47, 1.85)
> 30	48	25	9	181	1.28	1.33	44	24	17	940	1.15	1.16
					(0.50, 3.25)	(0.52, 3.39)					(0.55, 2.39)	(0.55, 2.42)
Continuous [#]	12	25	26	133	1.19	1.20	16	22	53	766	1.02	1.03
					(0.93, 1.51)	(0.95, 1.53)					(0.81, 1.29)	(0.82, 1.30)
Test of trend					0.53	0.48					0.61	0.59
						0.76						0.74

* Crude incidence rate (IR) for cerebrovascular disease (cases/10⁵ person-years)[†] Age adjusted estimates[‡] Adjusted for age, marital status, and baseline measures of education, occupation and income.[§] Adjusted for age, BMI, HDL, total cholesterol, triglycerides, diagnosis of hypertension, mean systolic blood pressure, mean diastolic blood pressure, diabetes diagnosis, daily alcohol consumption, comprehensive smoking index, marital status, and baseline measures of education, occupation and income.

// HR for increase in mean bone loss score by one

HR for 20mm increase in cumulative probing depth