Original Contribution

Periodontal Disease, Regular Dental Care Use, and Incident Ischemic Stroke

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Background and Purpose—Periodontal disease is independently associated with cardiovascular disease. Identification of periodontal disease as a risk factor for incident ischemic stroke raises the possibility that regular dental care utilization may reduce the stroke risk.

Methods—In the ARIC (Atherosclerosis Risk in Communities) study, pattern of dental visits were classified as regular or episodic dental care users. In the ancillary dental ARIC study, selected subjects from ARIC underwent fullmouth periodontal measurements collected at 6 sites per tooth and classified into 7 periodontal profile classes (PPCs).

Results—In the ARIC study 10 362 stroke-free participants, 584 participants had incident ischemic strokes over a 15-year period. In the dental ARIC study, 6736 dentate subjects were assessed for periodontal disease status using PPC with a total of 299 incident ischemic strokes over the 15-year period. The 7 levels of PPC showed a trend toward an increased stroke risk (χ^2 trend $P<0.0001$); the incidence rate for ischemic stroke/1000-person years was 1.29 for PPC-A (health), 2.82 for PPC-B, 4.80 for PPC-C, 3.81 for PPC-D, 3.50 for PPC-E, 4.78 for PPC-F, and 5.03 for PPC-G (severe periodontal disease). Periodontal disease was significantly associated with cardioembolic (hazard ratio, 2.6; 95% confidence interval, 1.2–5.6) and thrombotic (hazard ratio, 2.2; 95% confidence interval, 1.3–3.8) stroke subtypes. Regular dental care utilization was associated with lower adjusted stroke risk (hazard ratio, 0.77; 95% confidence interval, 0.63–0.94).

Conclusions—We confirm an independent association between periodontal disease and incident stroke risk, particularly cardioembolic and thrombotic stroke subtype. Further, we report that regular dental care utilization may lower this risk for stroke. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.018990.)**

Key Words: atherosclerosis ■ dental care ■ gingivitis ■ risk factors ■ stroke

Periodontal disease is a chronic inflammatory disease caused by bacterial colonization that affects the soft and hard structures that support the teeth.[1] The prevalence of periodontal disease is high, with gingivitis or periodontitis affecting up to 90% of the population worldwide. According to recent findings from the Centers for Disease Control and Prevention, half of Americans aged 30 or older have periodontitis, the more advanced form of periodontal disease.[2] Periodontitis is associated with an increase in systemic inflammation markers, through chronic low-grade exposure to Gram-negative bacteria.[3,4] The contribute of periodontitis to ischemic stroke risk may be indirectly mediated by inflammatory mechanisms.[5] Observational studies have shown that poor periodontal health status is associated with an increased stroke risk.[6–10] Poor oral hygiene is a major contributor to periodontal disease and thus a potentially modifiable stroke risk factor. An increase in tooth brushing frequency decreases the concentrations of systemic inflammatory markers levels in the serum.[11] A population based Taiwanese study found that dental prophylaxis or periodontal disease treatment could reduce the incidence of ischemic stroke.[12,13] However, similar data are lacking in the predominantly biracial US population.

Recent reports suggest a rise in the global burden of stroke.[14] Post hoc analyses of prospective–longitudinal and smaller case–control studies have reported an association between periodontal disease and incident stroke.[7] These studies suggest that stroke has a stronger association with periodontal disease than coronary artery disease.[15] Periodontal disease was found to increase the risk stroke by nearly 3-fold in a combined analysis of 2 prospective studies.[16] A more recent meta-analysis of 2 cohort studies found that periodontal disease increased the risk of incident ischemic strokes by 1.6-fold.[17] Recently, a case–control study confirmed the independent graded association between the severity of periodontal disease and prevalent stroke.[18] If causal, these associations would be of great importance because of the potential that periodontal disease treatment could reduce the stroke risk.

Received August 4, 2017; final revision received November 13, 2017; accepted November 29, 2017.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.018990/-/DC1.

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Individual studies have limitations, including the use of many differing definitions of periodontal disease, consideration of potential cofounders such as socioeconomic status, and low statistical power. Additionally, these studies underestimate the prevalence of periodontal disease.[19] Recently, we applied a latent class analysis to identify discrete classes of individuals that are discriminated by tooth-level clinical parameters to define 7 distinct periodontal profile classes (PPC A-G) ranging from health to severe periodontal disease status,[20] validated in 3 large cohorts. We applied the PPCs using latent class analysis to provide robust periodontal clinical definitions that reflect disease patterns in the population at a subject and tooth level. We examined the relationship between periodontal disease and stroke, as well as the ischemic stroke subtypes.

Methods

Study Population

The cohort of the ARIC (Atherosclerosis Risk in Communities) study recruited in 1987 to 1989 with an aim of studying the causes of atherosclerosis and clinical sequelae.[21] The study enrolled 15 792 participants within the age group of 45 to 64 identified by probability sampling in a biracial cohort from 4 US communities. In addition to follow-up visits every 3 years, participants have been contacted annually by telephone and queried about hospitalizations. The institutional review boards of all participating institutions approved the study and all participants provided written informed consent. All participants, white or blacks, who completed the fourth clinic visit (1996–1998) in ARIC (n=11 656), were included in the current study. We excluded those participants (n=1294) with prevalent stroke or a first ischemic stroke event that occurred before fourth clinical visit. Thus, 10 362 remaining participants were included for dental care utilization analysis.

Dental ARIC, an ancillary study of the ARIC, was conducted at the fourth clinic visit. Data collection included a comprehensive dental examination, questionnaire, and sample collection. Study participants who were edentulous, those with medical contraindication for periodontal examination, those with dental implants only, and those refusing dental examination were excluded.[21] Of the 6793 dental ARIC participants that underwent periodontal examination at the fourth visit, a total of 6736 participants without prior stroke were included for distinct PPC analysis.[20] The ARIC Investigators are willing to share the data used in this article with a researcher for the purposes of reproducing the results, subject to completion of a data use agreement ensuring appropriate protection of the confidentiality of ARIC participants' data.

Assessment of Dental Care Utilization

The pattern of dental care utilization or dental visits was classified by patient-reported responses to the dental history form questionnaire administered at the fourth clinical ARIC study by trained personnel (1996–1998). Participant dental care utilization was classified as regular use (those who sought routine dental care ≥1× a year) or episodic (only when in discomfort, something needed to be fixed, never, or did not receive regular dental care).

Assessment of PPC

The analytic approach implemented person-level latent class analysis to identify discrete classes of individuals was based on 7 tooth-level clinical parameters, including ≥1 site with interproximal attachment level ≥3 mm, ≥1 site with probing depth ≥4 mm, extent of bleeding on probing (dichotomized at 50% or ≥3 sites per tooth), gingival inflammation index, 14 (dichotomized as gingival inflammation index=0 versus gingival inflammation index ≥1), plaque index, 15 (dichotomized as plaque index=0 versus plaque index ≥1), the presence/absence of full prosthetic crowns for each tooth, and tooth status presence (present versus absent).[20]

The latent class analysis was conducted to capture the distribution of periodontal disease with diagnoses ranging from health to severe disease within each person-level subgroup. This tooth-level analysis enabled us to refine the individual tooth status within each PPC for risk assessment modeling by including patterns of disease and missing teeth. By definition, they were classified as PPC-A or periodontal health, PPC-B or mild periodontal disease, PPC-C or high gingival index score, PPC-D or tooth loss, PPC-E or posterior periodontal disease, PPC-F or severe tooth loss, and PPC-G or severe periodontal disease. PPC-A through G indicated higher grades of periodontal disease. This is an important refinement in the definition of periodontal disease as the majority of tooth loss in subjects over the age of 35 is attributable to periodontal disease, and yet, as teeth are lost because of disease the current status of periodontal disease improves using conventional classifications. Thus, the PPC is a data-driven agnostic classification system that uses no a priori assumptions of disease parameters to create 7 different classes of disease that follow a gradient in terms of attachment loss, but not necessarily a gradient in clinical inflammation (ie, gingival index and bleeding scores).[20]

Adjudication of Stroke Subtypes

Physicians reviewed hospitalization records and stroke diagnoses were made based on a computer algorithm, with any differences adjudicated by a second physician reviewer. All events occurring between the fourth visit (1996–1998) and December 2012 were included as verified ischemic strokes. The study considered incident ischemic strokes and the subjects were censored at the time of the event (recurrent strokes not considered in the analysis). According to criteria adopted from the National Survey of Stroke subtype classification, ischemic strokes were then further classified according to pathogenic subtype as thrombotic brain infarction, lacunar infarction, cardioembolic stroke, or other/undetermined cause.[22,23] Infarct distribution patterns on neuroimaging were not considered per the algorithm.

Other Variables of Interest

Age, sex, race, and additional vascular risk factors such as body mass index (BMI), waist:hip ratio, and lipid profile were assessed according to published methods during the fourth ARIC visit (1996–1998).[24] A race–center variable representing race/ethnicity (black or white) and ARIC field center was designed to control for the ethnic, regional, and examiner differences in the ARIC cohort.[21] Hypertension was defined as the average of 2 blood pressure readings at the visit (systolic blood pressure 140 mm HG or higher and diastolic blood pressure 90 mm Hg or higher) or on hypertension medication. Diabetes mellitus was measured by a visit-based definition and an interview-based definition. Visit-based diabetes mellitus was defined according to serum glucose measurements (fasting blood glucose >126 mg/dL or >200 mg/dL if not fasting), a self-reported physician diagnosis of diabetes mellitus, or on medication. Participants reported their 3-level education status (basic<11 years, intermediate=12–16 years, or advanced>17 years), smoking status, and alcohol use.[25]

Statistical Analysis

Cox proportional hazards models were used to assess crude and adjusted hazard ratio (HR) and 95% confidence interval (CI) to analyze the association among subjects with periodontal disease and incidence of ischemic stroke, in comparison with those with periodontal health. Similar comparisons were made between regular and episodic dental care users. In both analyses, HR was adjusted for race/center, age, sex, BMI, hypertension, diabetes mellitus, LDL (low-density lipoprotein) level, smoking (3 levels), pack years, and educational level (3 levels). Kaplan–Meier survival curve and HR analysis were used to evaluate the incidence of each ischemic stroke subtypes in periodontal disease when compared with periodontal health. All data were analyzed using SAS version 9.4 (SAS institute Inc, Cary, NC).

Results

In the dental ARIC study, during the fourth ARIC visit (1996–1998), a subset of 6736 dentate subjects (mean age±SD=62.3±5.6, 55% female, 81% white, and 19% black) were assessed for periodontal disease. The subjects excluded from this cohort had a higher rate of stroke (prior stroke, 18.5%; edentulous, 7.6%; those with other exclusions, 9.0%) compared with those included and completed the dental assessment (4.4%). Baseline characteristics of the dental cohort of the ARIC study population, stratified by PPC-A-G on visit 4, are shown in Table 1. Participants with higher PPC classes (B through G) were similar in age compared with PPC-A (health). They included a higher proportion of subjects who were of the male sex and the black race. Participants with higher PPC classes (B through G) also had a slightly higher BMI, waist:hip ratio, and higher proportions of hypertension, and diabetes mellitus, compared with PPC-A. They also had fewer years of education and were less likely to be current or former alcohol users. The PPC classes (C through G) were more likely to be former and current smokers compared with PPC class A and B. The fasting lipid profiles were similar across the groups. Baseline characteristics of the ARIC study population, divided by dental care utilization, are shown in Table 2. The regular dental care users included a higher proportion of female and white subjects compared with the episodic dental care users. They also had a slightly lower BMI, waist:hip ratio, and lower proportions of

Table 1. Selected Characteristics of the Study Participants, According to PPC*

	Periodontal Disease Class at Baseline						
Value	PPC-A (n=1837)	PPC-B (n=1036)	PPC-C (n=689)	PPC-D (n=793)	PPC-E (n=993)	PPC-F (n=890)	PPC-G (n=498)
Age, y	61.7±5.5	62.3±5.8	61.5±5.5	63.7±5.6	62.8±5.6	63.0±5.5	61.8±5.7
Sex, %							
Female	66.5	47.2	55.4	54.9	44.6	56.9	38.4
Male	33.5	52.8	44.6	45.1	55.4	43.1	61.6
Race, %							
Black	3.4	3.2	72.3	18.2	1.6	34.2	45.8
White	96.6	96.8	27.7	81.8	98.4	65.8	54.2
Body mass index†	27.4±4.8	28.3±4.9	30.4±6.2	28.9±5.3	28.2±5.0	29.7±6.1	29.5±5.9
Waist:hip ratio	0.92±0.08	0.95±0.07	0.94±0.07	0.96±0.07	0.95±0.07	0.96±0.07	0.96±0.07
Hypertension, %	26.0	32.1	47.4	38.3	28.1	40.0	41.1
Diabetes mellitus, %	8.4	12.1	21.7	15.7	10.9	18.7	21.7
Education, %							
Basic	5.4	8.1	23.8	16.4	5.7	28.5	23.3
Intermediate	41.8	45.3	32.2	48.5	44.7	47.3	39.0
Advanced	52.8	46.6	44.0	35.1	49.6	24.2	37.8
Smoking, %							
Never	54.6	55.2	51.0	41.2	36.4	35.8	46.8
Former	38.7	38.6	36.2	42.5	46.9	42.9	37.7
Current	6.8	6.2	12.8	16.3	16.7	21.3	15.6
Alcohol, %							
Never	16.0	18.8	29.7	23.8	8.4	25.0	24.1
Former	21.0	25.0	34.6	28.6	21.0	35.0	32.8
Current	16.0	18.8	29.7	23.8	8.4	25.0	24.1
Cholesterol, mg/dL	203.5±34.6	200.5±35.5	199.0±37.5	199.4±36.7	201.2±35.2	202.1±37.1	198.5±37.8
LDL	120.7±32.2	121.6±31.9	121.9±35.2	121.3±33.2	123.3±32.4	124.2±34.8	124.5±33.8
HDL	54.1±17.0	48.5±16.2	52.1±17.2	48.1±15.6	49.5±16.9	48.8±16.1	48.3±15.7
Triglycerides, mg/dL							
Median	125	130	104	127	125	126	110
25th–75th percentile	89–174	93–186	77–144	92–179	90–171	92–177	80–150

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and PPC, periodontal profile class.

*Plus–minus values are means±SD.

†Body mass index=weight (kilogram)/height (meter^2).

Table 2. Selected Characteristics of the Study Participants, According to Frequency of Dental Care Utilization

Value	Dental Care Utilization	
	Regular Dental Care User (n=6670)	Episodic Dental Care User (n=3692)
Age, y	62.7±5.6	63.0±5.7
Sex, %		
Female	57.8	52.9
Male	42.2	47.1
Race, %		
Black	8.5	39.3
White	91.5	60.7
Body mass index†	28.1±5.1	29.9±6.2
Waist:hip ratio	0.94±0.07	0.96±0.07
Hypertension, %	33.0	44.3
Diabetes mellitus, %	11.9	23.3
Education, %		
Basic	8.5	34.4
Intermediate	43.5	41.7
Advanced	48.0	23.9
Smoking, %		
Never	47.7	40.8
Former	41.3	39.4
Current	11.0	19.8
Alcohol, %		
Never	17.1	26.5
Former	24.7	37.5
Current	58.2	35.0
Periodontal status		
PPC-A	34.4	7.8
PPC-B	17.7	9.1
PPC-C	6.7	19.8
PPC-D	11.6	12.3
PPC-E	17.7	6.8
PPC-F	7.4	28.9
PPC-G	4.5	15.4

PPC indicates periodontal profile class.
*Plus–minus values are means±SD.
†Body mass index=weight (kilogram)/height (meter^2).

hypertension and diabetes mellitus. Additionally, they had more years of education and were more likely to be current or former alcohol users. The regular dental care users were less likely to be former and current smokers compared with the episodic dental care users. The fasting lipid profiles were similar across the groups (not shown). The regular dental care users had a higher proportion of low PPC grades compared with the episodic dental care users suggesting that regular dental care utilization was associated with lower burden of periodontal disease.

In the dental ARIC study, during the fourth ARIC visit (1996–1998), a subset of 6736 dentate subjects (mean age±SD=62.3±5.6, 55% female, 81% white, and 19% black) were assessed for periodontal disease. A total of 299 incident ischemic strokes occurred over a median of 15-year follow-up period. The retention of ARIC participants during the follow-up period was high (>90%). Compared with the reference healthy group without periodontal disease (PPC-A), mild periodontal disease or PPC-B (crude HR, 2.19; 95% CI, 1.39–3.46), high gingival index score or PPC-C (crude HR, 3.75; 95% CI, 2.40–5.85), tooth loss or PPC-D (crude HR, 2.97; 95% CI, 1.89–4.68), posterior disease or PPC-E (crude HR, 2.74; 95% CI, 1.76–4.25), severe tooth loss or PPC-F (crude HR, 3.74; 95% CI, 2.45–5.73), and severe periodontal disease or PPC-G (crude HR, 3.93; 95% CI, 2.44–6.35), had a higher risk for incident ischemic stroke depicted in Figure 1. After adjustment for race/center, age, sex, BMI, hypertension, diabetes mellitus, LDL level, smoking (3 levels), pack years, and education (3 levels), mild periodontal disease or PPC-B (adjusted HR, 1.86; 95% CI, 1.16–2.97), high gingival index score or PPC-C(adjusted HR, 2.06; 95% CI, 1.21–3.51), tooth loss or PPC-D (adjusted HR, 2.03; 95% CI, 1.26–3.26), posterior disease or PPC-E (adjusted HR, 2.22; 95% CI, 1.41–3.50), severe tooth loss or PPC-F (adjusted HR, 2.08; 95% CI, 1.29–3.35), and severe periodontal disease or PPC-G (adjusted HR, 2.20; 95% CI, 1.27–3.81), had a higher risk for incident ischemic stroke. The incidence rate for ischemic stroke/1000-person years was 1.29 (95% CI, 0.92–1.81) for PPC-A, 2.82 (95% CI, 2.08–3.83) for PPC-B, 4.80 (95% CI, 3.59–6.43) for PPC-C, 3.81 (95% CI, 2.80–5.17) for PPC-D, 3.50 (95% CI, 2.64–4.65) for PPC-E, 4.78 (95% CI, 3.69–6.20) for PPD-F, and 5.03 (95% CI, 3.57–7.07) for PPC-G. The PPC-incident stroke association is depicted in a Kaplan–Meier plot in the online-only Data Supplement. The 7 levels of PPC showed a trend toward graded association with incident ischemic stroke (χ^2 trend P value <0.0001).

As shown in Figure 1B, all forms of periodontal disease which are characterized by inflammatory changes are at significantly greater risk than health using this 7-level classification. The inflammatory characteristics differ among the 6 disease classes, but are listed in order of increased mean interproximal attachment loss. The figure in the online-only Data Supplement, the incident events are stratified by PPC and the highest rate of events was seen among PPC-C (gingival inflammation) and PPC-G (severe disease) which are the most inflamed classes.[21] Thus, inflammation plays a critical role in defining the risk for incident events as compared with PPC-A (health). What emerges from this investigation is that high gingival inflammation in the absence of severe periodontal disease (PPC-C) and the highly inflamed severe periodontitis class (PPC-G) are at higher risk than those with mild, moderate, or posterior disease patterns (all have less inflamed periodontal tissues). These data emphasize the importance of inflammation rather than just the level of attachment as being the main determinant of risk.

In the main ARIC cohort during the fourth ARIC visit (1996–1998), a total of 11 656 participants (mean age±SD=62.8±5.6, 56% female, 78% white, and 22% black) were assessed for dental care utilization. Over a 15-year follow-up period, a

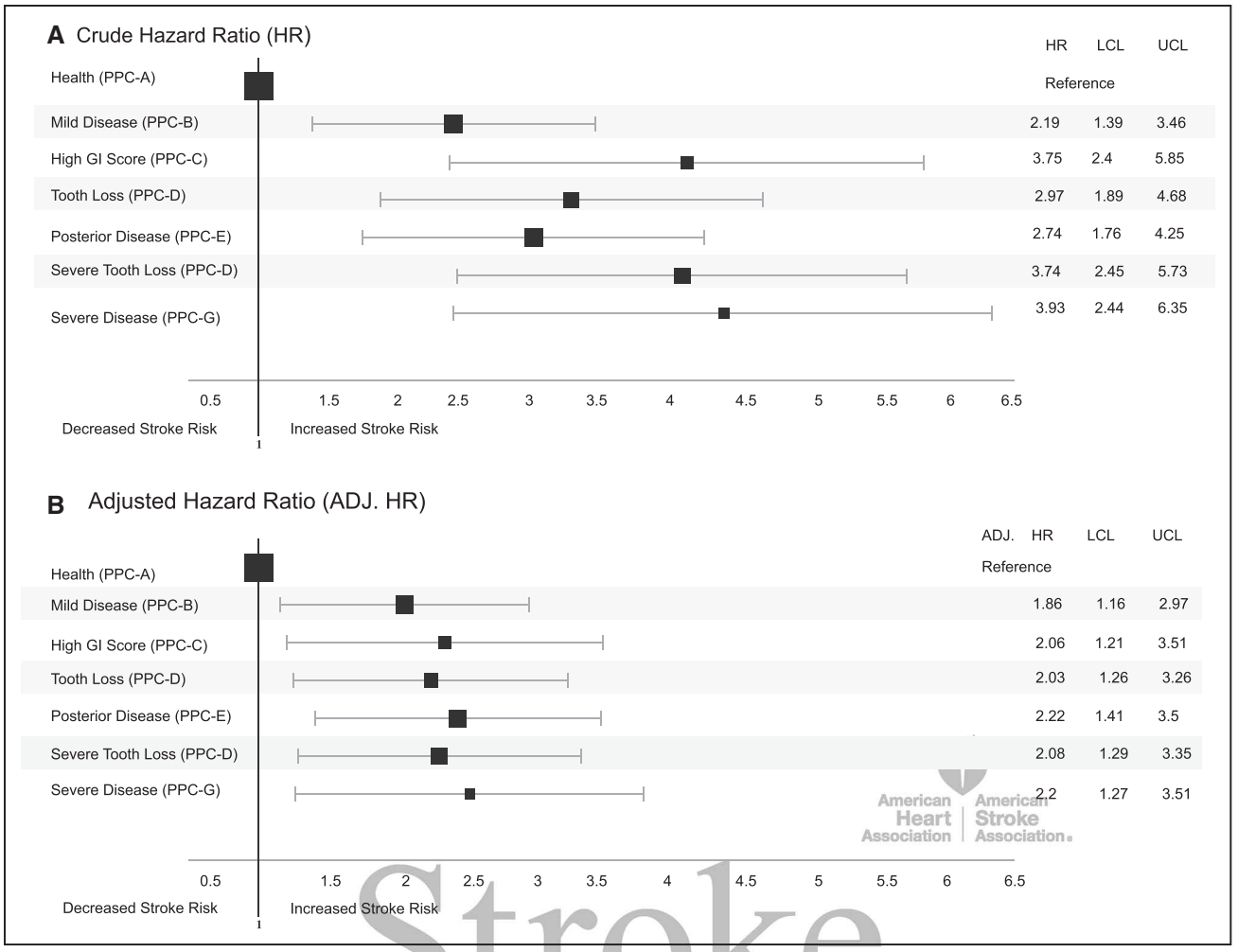

Figure 1. Risk for incident ischemic stroke in the dental ARIC (Atherosclerosis Risk in Communities) cohort depicted as crude (**A**) and adjusted (**B**) hazard ratios (HRs) for the various classes of periodontal disease periodontal profile classes (PPC)-A or reference healthy group without periodontal disease, PPC-B or mild periodontal disease, PPC-C or high gingival index (GI) score, PPC-D or tooth loss, PPC-E or posterior disease, PPC-F or severe tooth loss, and PPC-G or severe periodontal disease. In (**B**) HRs are adjusted for race/center, age, sex, body mass index, hypertension, diabetes mellitus, low-density lipoprotein level, smoking (3 levels), pack years, education (3 levels). LCL indicates lower confidence level; and UCL, upper confidence level.

total of 584 participants had incident ischemic stroke events. Compared with a reference group of episodic dental care users, regular dental care users had a lower risk for ischemic stroke (crude HR, 0.52; 95% CI, 0.44–0.61). After adjustment for race/center, age, sex, BMI, hypertension, diabetes mellitus, LDL level, smoking, and education, regular dental care use continued to be associated with lower rates of ischemic stroke (adjusted HR, 0.77; 95% CI, 0.63–0.94), as seen in Figure 2.

Among the 299 incident ischemic strokes in the dental cohort, 79 were cardioembolic, 140 thrombotic, 61 lacunar, and 19 other/undetermined cause (were excluded). Among the 3 major stroke subtypes, there was a significant increased hazard of cardioembolic (HR, 2.6; 95% CI, 1.2–5.6) and thrombotic (HR, 2.2; 95% CI, 1.3–3.8), but not of lacunar strokes (HR, 1.3; 95% CI, 0.6–2.8) among study participants with periodontal disease (PPC B-G) compared with those with periodontal health (PPC-A). The association of overall ischemic stroke as well as thrombotic, cardioembolic, or lacunar subtype of stroke and periodontal disease is demonstrated in Figure 3.

Discussion

Periodontal disease is highly prevalent among adults worldwide and is an important public health problem. Assessment of risk profiles for periodontal disease in adults in the United States show male sex, current cigarette smoking, and diabetes mellitus are important risk factors for periodontal disease.[26] These findings could enhance recognizable target populations for viable interventions to enhance periodontal health of adults, who may likewise be at an increased risk of ischemic stroke. Our findings show that periodontal disease is an independent risk factor for incident ischemic stroke. It is significant that the high gingival inflammation group, including gingivitis and mild periodontitis but also highly inflamed, likewise had an increased risk of ischemic stroke. Moreover, we report a trend toward a graded association between periodontal disease and incident ischemic stroke. Individual studies, including post hoc analyses of prospective–longitudinal studies and case–control studies, have reported an association between periodontal disease and incident stroke.[7] It is possible that an increased risk of thrombotic stroke may be secondary to atherothrombosis

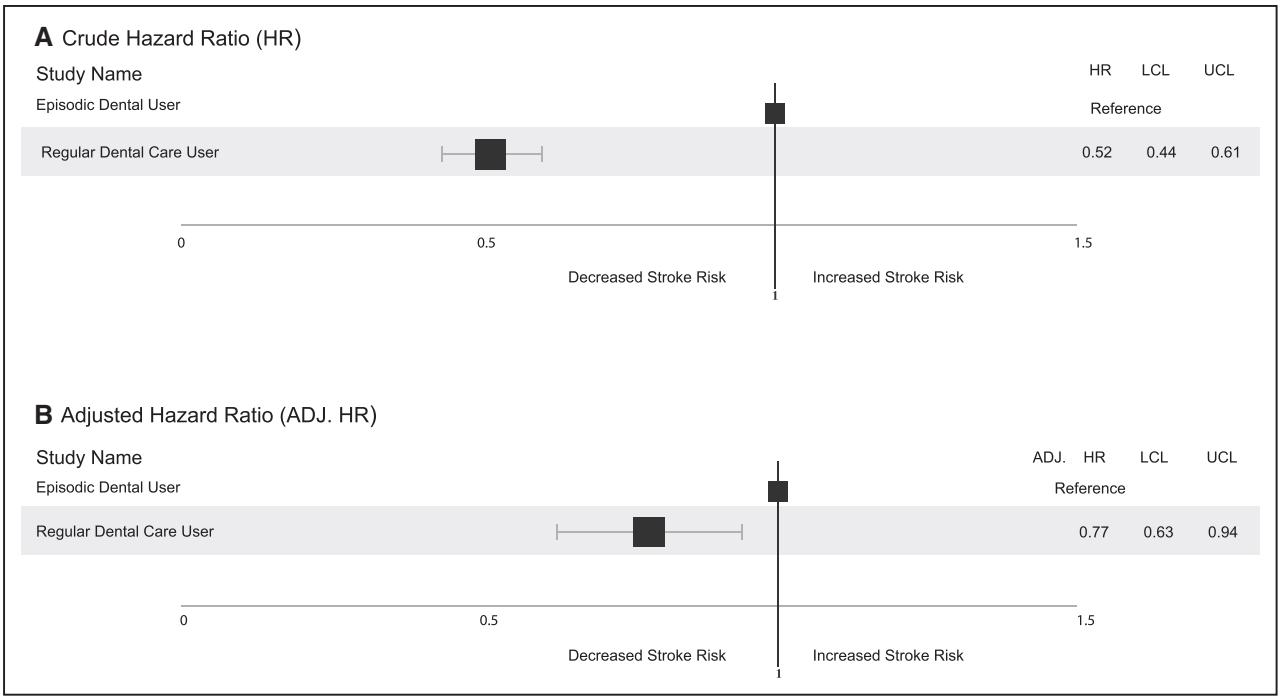

Figure 2. Risk reduction in incident ischemic stroke in the main ARIC (Atherosclerosis Risk in Communities) cohort depicted as crude (**A**) and adjusted (**B**) hazards ratio (HRs) for episodic and regular (reference group for comparison) dental care users, determined at visit 4. In (**B**) HRs is adjusted for race/center, age, sex, body mass index, hypertension, diabetes mellitus, low-density lipoprotein level, smoking (3 levels), pack years, education (3 levels).

in the cervicocerebral vasculature. The periodontal disease-cardioembolic stroke association may be because of coronary artery disease or atrial fibrillation related to periodontal disease induced inflammation. Contrary to findings noted in prior case–control studies, periodontal disease was not independently associated with lacunar strokes.[27,28] Possible factors attributable to this difference may be risk factors for lacunar stroke such as age, hypertension, diabetes mellitus, and low socioeconomic status, were adjusted for in our final HRs model. The periodontal disease-stroke association, if causal, would be of great importance because of the potential that periodontal treatment could reduce the stroke risk.

Dental care is essential for maintaining good oral health, preventing periodontal disease, and identifying symptoms of systemic conditions that might first manifest in the mouth.[29] During 2013, ≈42% of the US population reported having a dental visit[30] with socioeconomic factors serving as a major determinant for not using regular dental care.[31] A population-based, nationwide study in Taiwan identified periodontal disease as an important risk factor for incident ischemic stroke and showed that periodontal treatment lowered risk of stroke, significantly among young adults.[13] To our knowledge, this would be the first US study to report the independent role of regular dental care in prevention of incident ischemic stroke in a relatively elderly population. This is further validated by the fact that dental care was associated with lower burden of periodontal disease.

Important limitations of this study include the reliance on single periodontal disease assessment, a limited number of incident stroke subtypes, and owing to the observational nature of our investigation, the possibility of residual confounding cannot be eliminated. Socioeconomic factors such as access to care, income, and healthcare behaviors may be potential confounders. However, we adjusted for education levels that in these data serve as a surrogate for the socioeconomic status. Despite these potential limitations, this effort is one of the largest, US-based community studies of periodontal disease, dental care utilization, and ischemic stroke. Subjects excluded raise the possibility of selection bias. However, as noted these subjects had a higher rate of incident ischemic stroke compared with those included, suggesting that they are unlikely to negatively influence the study results. Major strengths of this ARIC ancillary study were the use of comprehensive periodontal assessment classified into validated class, adjudication of incident ischemic stroke, stroke subtypes, and rigorous measurement of confounders.

Evidence from randomized controlled trials has established that intensive periodontal treatment improves systemic inflammation, high blood pressure, improves lipid profile,[32] and endothelial dysfunction.[33] Therefore, the treatment of probing depth could plausibly reduce stroke incidence. To the best of our knowledge, this hypothesis has not been tested in a randomized clinical trial. The effect of probing depth treatment on recurrent vascular events in stroke/transient ischemic attack patients is currently being investigated in PREMIERS trial (Periodontal Treatment to Eliminate Minority Inequality and Rural Disparities in Stroke; URL: http://www.clinicaltrials.gov. Unique identifier: NCT02541032). Results may further help verify if periodontal treatment may reduce stroke risk.

Acknowledgments

All authors contributed to the study concept and design, data analysis, interpretation, article preparation, and critical revision of the article for important intellectual content.

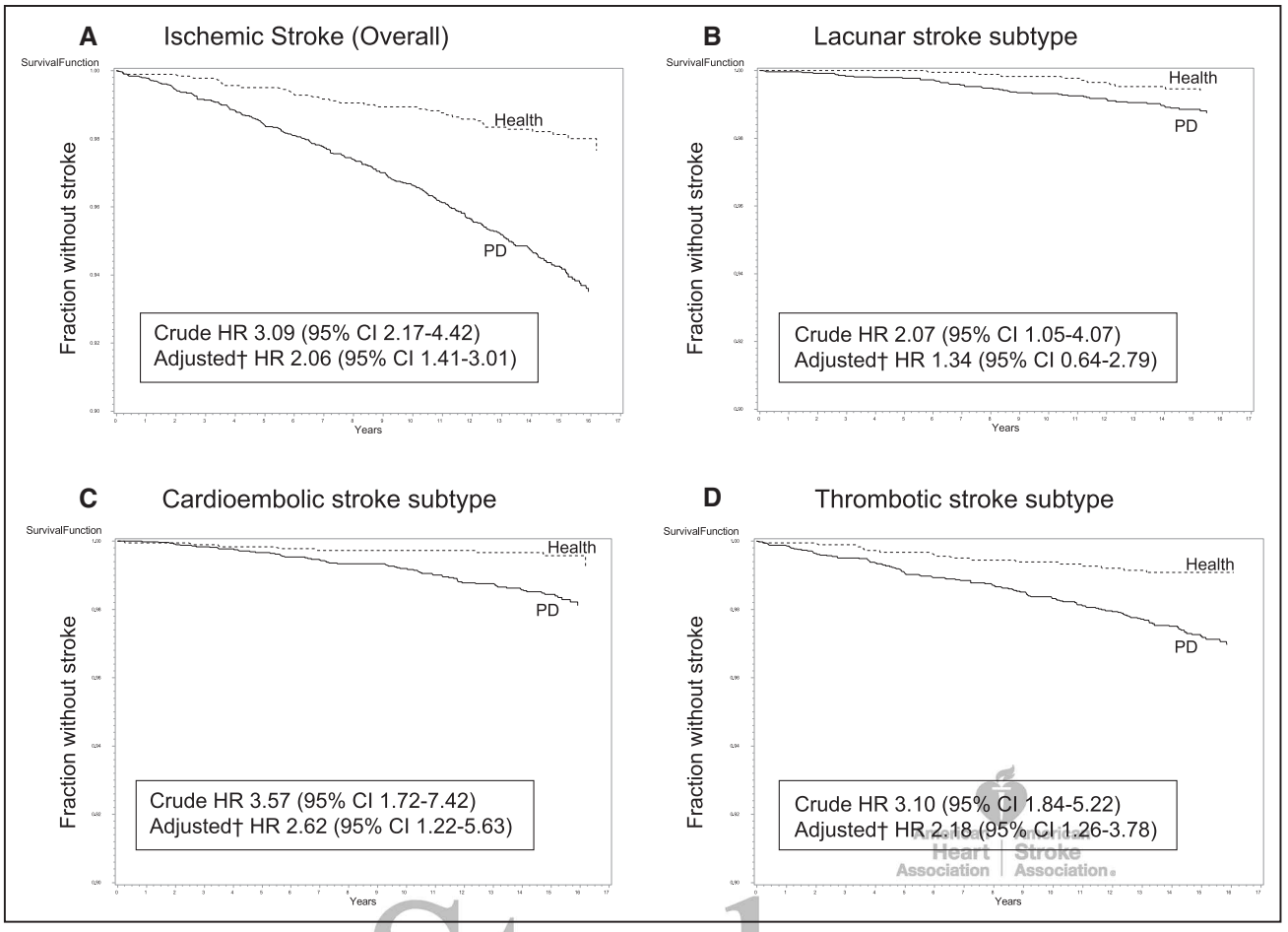

Figure 3. Kaplan–Meier curves depicting 15 years' outcome of (**A**) incident ischemic stroke (overall), (**B**) lacunar, (**C**) cardioembolic, and (**D**) thrombotic stroke subtypes. Inset: crude hazard ratios (HRs) for ischemic stroke (overall) and stroke subtypes. HRs adjusted for race/center, age, sex, body mass index, hypertension, diabetes mellitus, low-density lipoprotein level, smoking (3 levels), pack years, education (3 levels).

Sources of Funding

The ARIC (Atherosclerosis Risk in Communities) study is performed as a collaborative study supported by the National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The dental ARIC study was supported by the National Institute of Dental and Craniofacial Research grant R01DE 11551.

Disclosures

K. Moss, Dr Beck, and S. Offenbacher are seeking intellectual property protection for the periodontal profile class concept. Dr Gottesman serves as an Associate Editor of the American Academy of Neurology. The other authors report no conflicts.

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Stroke
Journal of the American Heart Association

Periodontal Disease, Regular Dental Care Use, and Incident Ischemic Stroke

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Stroke. published online January 15, 2018;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

ONLINE SUPPLEMENTAL-DATA:

Individuals were classified into mutually exclusive latent classes based on their responses to a set of observed categorical variables. Both the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used to determine the optimal number of latent classes while maintaining clinically relevant categories. We used Milligan and Cooper's [1] recommendation for the maximum number (n) of classes, suggesting stopping when the newly added class (n+1) is not clinically distinct from the previous number (n) of identified classes. Additionally, we verified that mean posterior probabilities of correct class assignment were >0.7, which according to Nagin [2] indicates adequate class separation and membership precision. In the first step of LCA, the person-level LCA was used to classify individuals into seven latent classes based on 224 dichotomous variables (derived from 7 tooth-level variables, using the clinical parameters referred to above for each of 32 teeth). The class membership probabilities represent the overall, proportions of individuals in each of seven latent classes or periodontal profiles classes. Posterior probabilities, the probability of event A occurring given that event B occurred, of each individual's membership into each class (conditional upon the 224 items, or as many of them as were observed for that individual) were computed using the model parameters from the first step. [3] The seven levels of PPC show a trend towards an increased stroke risk. Incident strokes based on the periodontal profile classes (PPC) over 15 years are depicted in the Kaplan Meier curve (Supplemental Figure).

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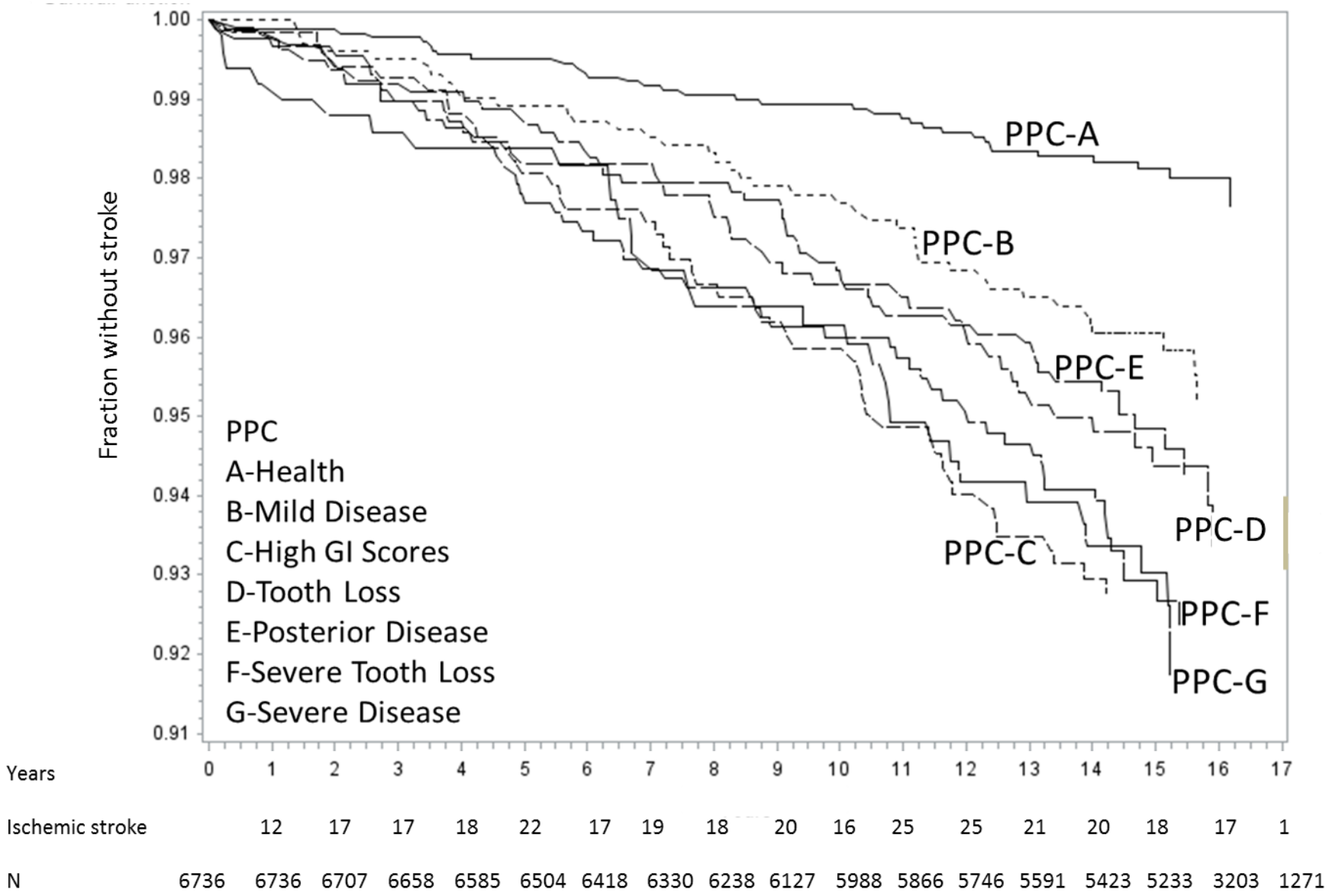
Supplemental Figure



Supplemental Figure: By 15 years, the primary outcome (incident ischemic stroke) had occurred in 34 (1.9%) out of 1831 with PPC-A, 41(4.0%) out of 1032 with PPC-B, 45(6.5%) out of 699 with PPC-C, 41(5.2%) out of 787 with PPC-D, 48(4.9%) out of 990 with PPC-E, 57(6.4%) out of 889 with PPD-F and 33(6.7%) out of 493 with PPC-G. The numbers at risk were the numbers of patients who were alive without an event and still being followed at the beginning of each time point.