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Periodontal disease measures and risk of incident peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—The association of periodontal disease with atherosclerotic cardiovascular diseases is well known, but not with peripheral artery disease (PAD). Therefore, we studied the associations of periodontal disease with incident PAD in a population-based setting.

Methods—Among 9,793 participants (aged 53–75 years) without prevalent PAD, self-reported history of periodontal disease was ascertained. Of these, 5,872 participants underwent full-mouth examinations from which periodontal status was defined using the US Centers for Disease Control and Prevention-American Academy of Periodontology (CDC-AAP) definition. We quantified the association of periodontal disease with incident PAD (defined by hospital admission diagnosis or procedures) using multivariable Cox regression models.

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Author Contributions:

LTA and KM contributed to the study concept. LTA, YM, CY, JI, and KM contributed to the statistical analysis. LTA, YM, and KM drafted the manuscript. All authors contributed to the interpretation of results and critical revision of the manuscript. All authors agree to be accountable for the individual's own contributions and have approved the final version of the manuscript.

Conflicts of interest: All authors have no conflicts of interest to report.

Results—During a median follow-up of 20.1 years, 360 participants (3.6%) developed PAD. In models accounting for potential confounders including diabetes and smoking pack-years, there was higher hazard of PAD in participants with self-reported tooth loss due to periodontal disease (hazard ratio:1.54 [95% CI:1.20–1.98], history of periodontal disease treatment (1.37 [1.05–1.80]), and periodontal disease diagnosis (1.38 [1.09–1.74]), compared to their respective counterparts. The clinical measure of periodontal disease (n=5,872) was not significantly associated with incident PAD in the fully-adjusted model (e.g.,1.53 [0.94–2.50] in CDC-AAP-defined severe periodontal disease vs. no disease).

Conclusion—We observed a modest association of self-reported periodontal disease, especially when resulting in tooth loss, with incident PAD in the general population. Nonetheless, a larger study with the clinical measure of periodontal disease is warranted.

Keywords

periodontal diseases; peripheral arterial disease; tooth loss; cohort studies

INTRODUCTION

Periodontal disease affects almost half of US adults and is the major cause of edentulism.[1–3] The association of periodontal disease with the development of atherosclerotic cardiovascular diseases (ASCVD) such as myocardial infarction and stroke is well-recognized for three decades.[4–11] The plausible pathophysiologic links between periodontal disease and ASCVD are presence of periodontal pathogens in atheromatous plaques,[9, 12–16] and an increase in systemic inflammatory components induced by periodontal disease.[1, 3, 5, 9, 17–19] Moreover, there is an indication that periodontal disease may be associated with microvascular disease, a condition known to play an important role in the pathophysiology of ASCVD.[20] Periodontal disease and ASCVD also share risk factors like diabetes and smoking.[18, 21–25] Also, some data suggest shared genetic factors between both conditions.[26]

Peripheral artery disease (PAD), often due to atherosclerosis, is a potentially life- and limb-threatening condition affecting 12–20% of US adults aged 65 years and above.[9, 12, 21] It increases cardiovascular disease mortality by three- to six-fold, adjusted for age and sex.[18, 21, 22] However, the association between periodontal disease and PAD has received lesser attention than myocardial infarction or stroke.[4, 18, 21, 23, 27] Although some studies have explored this association,[4, 9, 12, 18, 21–23, 27, 28] most were cross-sectional studies,[9, 18, 21–23, 28] had small study sample with less than 100 PAD cases,[4, 9, 18, 21, 22, 28] limited number of periodontal parameters (e.g., focusing only on tooth loss),[12] or selected study population (e.g., health professionals, veterans, or patients).[4, 9, 12, 18, 21, 22, 27]

To overcome these caveats and add to the existing body of work, we evaluated several self-reported, and clinically-assessed, measures of periodontal disease and their prospective associations with incident PAD using data from a community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study.

MATERIALS AND METHODS

Study population

The ARIC study is a prospective cohort of 15,792 participants aged 45 to 64 years at visit 1 (1987–89) from four US communities: Jackson, Mississippi; Washington County, Maryland; Minneapolis, Minnesota; and Forsyth County, North Carolina.[1, 29] Data collection has been completed for 6 subsequent visits. For our study, we used visit 4 (1996–98) as baseline, when a systematic oral health evaluation was conducted.

We conducted two sets of analysis (Supplementary Figure 1). Analysis 1 assessed the self-reported measures of periodontal disease as the exposure of interest, and Analysis 2 assessed one periodontal disease classification based on clinical oral examination. For Analysis 1, of 11,656 ARIC visit 4 participants, we excluded participants with prevalent PAD, defined by ankle-brachial index (ABI) ≤ 0.9, self-reported intermittent claudication, or leg revascularization at visit 1 or any incident PAD outcomes between visits 1 and 4 (n=511),[30] who were censored at visit 4 (n=1), non-White and non-Black participants (n=31), who had missing information on covariates of interest (n=1320), resulting in a sample of 9,793 participants. For Analysis 2, out of 9,793 participants in Analysis 1, we further excluded those who were ineligible (e.g., edentulous, had medical contraindications to dental probing, such as rheumatic heart disease or taking prednisone or immunosuppressive medication) or refused to participate in the Dental ARIC (D-ARIC) Study,[31] an ancillary ARIC study with a dedicated oral examination,[29] resulting in a sample of 5,872 participants. By design, Analysis 2 participants tended to have a healthier profile (e.g., lower prevalence of anti-hypertensive medication use and history of CVD) than those only in Analysis 1 (Supplementary Table 1). The ARIC Study was approved by the Institutional Review Board of the four field centers and the coordinating center. Written informed consent was obtained from all participants.

Assessment of periodontal disease

Self-reported periodontal disease (Analysis 1)—Periodontal history was obtained by interviewer-administered questionnaire at visit 4.[32] Participants were asked whether they had ever been told by a dentist that they had periodontal disease (yes/no). Those who answered yes, were further asked whether they had ever received periodontal disease treatment (yes/no). Additionally, participants were asked whether they had ever lost any teeth due to periodontal disease (yes/no). Although we used all three self-reported measures in Analysis 1, we selected tooth loss due to periodontal disease as our primary exposure since it represents severe periodontal disease[1, 9, 12, 18, 29, 33] and is less likely to be influenced by access to dental healthcare than the measures of periodontal disease diagnosis, and treatment. We also constructed a composite variable from these three self-reported measures: 1) no periodontal disease diagnosis; 2) periodontal disease diagnosis without treatment or tooth loss due to periodontal disease; 3) periodontal disease diagnosis with treatment but without tooth loss due to periodontal disease; and 4) periodontal disease diagnosis with tooth loss due to periodontal disease.

Clinical measure of periodontal disease (Analysis 2)—The D-ARIC examination included caries status, periodontal probing depth, cemento-enamel junction, bleeding on probing, gingival inflammation index, plaque score, presence of a tooth, and presence of a full prosthetic crown on a tooth.[34–36] Measurements were recorded at six sites per tooth on all teeth present.[1] Clinical attachment level (CAL) was calculated as a sum of periodontal probing depth and cemento-enamel junction scores.[5, 17, 29, 37] Periodontal examiners were trained as per a modified protocol from the third National Health and Nutrition Examination Survey.[38] All measurements were calibrated to a standard examiner. Percent agreement of CAL within 1 mm between each of the seven examiners and the standard examiner ranged from 83.2% to 90.2% and their intra-class correlation coefficients ranged from 0.76 to 0.90.[5]

Buccal surfaces of teeth are usually prone to the ill-effects of overzealous toothbrushing, use of a hard-bristled toothbrush, or improper brushing movements.[1] Hence, these surfaces may exhibit non-pathologic gingival recession. To address this possibility, a correction was made for the buccal surfaces exhibiting ≥3 mm CAL than their adjacent sites (mesiobuccal or distobuccal) on the same tooth. For such sites, the buccal measurement was replaced by the mesiobuccal or distobuccal measurement, whichever was higher.[1, 5]

We classified periodontal disease severity according to the US Centers for Disease Control and Prevention-American Academy of Periodontology (CDC-AAP).[39] This definition has been used in previous studies,[1, 36] as noted by a systematic review[40] and focuses on disease severity based on increasing levels of CAL and probing depth[1] to categorize individuals, which reflects history of disease.[35] The CDC-AAP definition excludes third molars and includes CAL and interproximal probing depth per tooth. The definition is: 1) None: No evidence of mild, moderate or severe periodontitis; 2) Mild: ≥2 interproximal sites with CAL ≥3 mm and ≥2 interproximal sites with probing depth ≥4 mm (not on the same tooth) or one site with probing depth ≥5 mm; 3) Moderate: ≥2 interproximal sites with CAL ≥4 mm (not on the same tooth), or ≥2 interproximal sites with probing depth ≥5 mm (not on the same tooth); 4) Severe: ≥2 interproximal sites with CAL ≥6 mm (not on the same tooth), or ≥1 interproximal sites with probing depth ≥5 mm.

Assessment of peripheral artery disease

Incident PAD was defined as hospitalization with International Classification of Diseases (ICD)-9 discharge and procedure codes as done previously[30, 41]. Participants were followed from visit 4 until the date of incident PAD, death, loss-to-follow-up, or administrative censoring on December 31, 2019, whichever came earlier.

Covariates

All covariate data were collected at visit 4 and via an interview unless specified otherwise. Demographic information (age, race, sex, and education level) was ascertained at visit 1 (age was appropriately updated at visit 4). Medical history, socioeconomic status (health insurance and total annual family income), and lifestyle factors (smoking) were assessed via standardized questionnaires. Education level was categorized as basic (less than high school), intermediate (high school graduate or vocational school), and advanced (at least some college, graduate school or professional school). Health insurance status

was dichotomized as yes/no, and total annual family income was categorized into three groups: <$12,000, $12,000 to $24,999, and >$25,000. Smoking status was dichotomized as ever (current/former) vs. never smoker. Cigarette pack-years were calculated as the number of packs smoked per day multiplied by years of smoking habit among ever smokers at visit 4. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or taking anti-hypertensive medications. Diabetes was defined as fasting blood glucose levels ≥126 mg/dL, or non-fasting blood glucose levels ≥200 mg/dL, or self-reported physician diagnosis of diabetes, or taking anti-glycemic medications. Total and high-density lipoprotein (HDL) cholesterol values were measured using automated enzymatic procedures.[30] History of CVD included prevalent coronary heart disease (CHD), stroke, or heart failure. Prevalent CHD and stroke were defined as self-reported clinical history before visit 1, or cases adjudicated by a physician panel between visits 1 and 4. Prevalent heart failure was defined as self-reported treatment or Gothenburg stage 3 at visit 1, or hospitalization with heart failure between visits 1 and visit 4.

Statistical analyses

Baseline characteristics were summarized by periodontal disease categories. For both Analysis 1 (self-reported measures of periodontal disease) and Analysis 2 (clinical measure of periodontal disease), we first estimated cumulative incidence of PAD using the Kaplan-Meier method. Subsequently, we quantified the association of periodontal disease measures with incident PAD, using Cox proportional hazards regression. Model 1 was unadjusted. Model 2 adjusted for age, sex, and race. Model 3 additionally accounted for education level, diabetes, smoking pack-years, systolic blood pressure, anti-hypertensive medication, total cholesterol, HDL cholesterol, lipid-lowering therapy, and history of CVD. For variables reflecting periodontal disease severity, we obtained p-values for trend from Cox models by modeling each periodontal variable as a discrete variable.

We conducted several sensitivity analyses. First, we stratified the study population by major demographics and clinical parameters such as age (< vs. ≥ median age [63 years in Analysis 1 and 62 years in Analysis 2]), sex, race, smoking status, diabetes, hypertension, and history of CVD. Effect measure modification by these variables was formally tested by contrasting models with and without the relevant interaction term(s) using the likelihood ratio test. Second, we adjusted for total annual family income (Model 4) or health insurance status (Model 5) as indicators of socioeconomic status instead of education level. We also ran models including all three measures of socioeconomic status (Model 6). Finally, to account for the healthier profile of Analysis 2 participants compared with Analysis 1 participants, we applied inverse probability weighting. We used the Analysis 1 cohort to estimate a propensity score of being included into the Analysis 2 cohort, using Model 3 covariates. The inverse probability of inclusion weighting was calculated using the stabilized weight (W): $W = \{Z*Pr(Z=1)÷e\} + \{(1-Z)*Pr(Z=0)÷(1-e)\}$, where Z indicates presence in Analysis 2 (Z=1 if present in Analysis 2 and Z=0 if not), e indicates the propensity score (probability of being included in Analysis 2 conditional on his or her data on Model 3 covariates), and Pr(Z=1) and Pr(Z=0) indicate the proportion being included and excluded from Analysis 2, respectively, in the overall Analysis 1 cohort.

The level of significance was set to $p<0.05$. **

RESULTS

Self-reported measures of periodontal disease and incident PAD (Analysis 1)

Among the 9,793 study participants, the mean age at baseline was 62.8 (standard deviation 5.6) years, 44.3% were men, and 20.4% were Black participants (Supplementary Table 1). There were 2,177 participants with self-reported diagnosis of periodontal disease (22.2%), 1,470 with history of periodontal disease treatment (15.0%), and 1,349 participants with tooth loss due to periodontal disease (13.7%) (Table 1). Participants with tooth loss due to periodontal disease were more likely to be Black and have worse cardiovascular risk factor profiles (i.e., higher prevalence of diabetes, hypertension, and history of CVD as well as higher pack-years of smoking) compared to those without tooth loss due to periodontal disease (Table 1). They also tended to have lower total annual family income and lower education levels. When we compared participants with history of periodontal disease treatment or diagnosis with their respective counterparts, similar results were seen only for smoking patterns, but there were no evident differences in other cardiovascular risk factors between these groups (Table 1).

Over a median follow-up of 20.1 years (interquartile interval [IQI]: 13.8, 22.0 years), there were 360 incident PAD cases (incidence rate: 2.1 per 1,000 person-year). Participants with tooth loss due to periodontal disease demonstrated a higher cumulative incidence of PAD (Figure 1A; 9.2% vs. 4.1% at ~ 24 years, respectively, $p<0.001$) compared to those without tooth loss due to periodontal disease. A similar, although less evident, difference was seen for participants with history of periodontal disease treatment vs. those without (Supplementary Figure 2A; 5.7% vs. 4.5%, respectively, $p=0.03$) and participants with periodontal disease diagnosis vs. those without (Supplementary Figure 2B; 6.1% vs. 4.3%, respectively, $p=0.002$).

In the unadjusted model (Model 1), participants with tooth loss due to periodontal disease had a hazard ratio (HR) of 2.14 (95% confidence interval [CI]: 1.68–2.73) for incident PAD, compared to those without (Table 2). The associations were attenuated but remained significant after adjustment for demographic variables (HR: 1.93 [95% CI: 1.51–2.48] in Model 2) and other potential confounders (HR: 1.54 [95% CI: 1.20–1.98] in Model 3). Similar but slightly weaker associations were seen for history of periodontal disease treatment and periodontal disease diagnosis (e.g., HR: 1.37 [95% CI: 1.05–1.80] and HR: 1.38 [95% CI: 1.09–1.74] in Model 3, respectively) (Table 2). The association of these self-reported measures of periodontal disease and incident PAD showed largely consistent results across subgroups, without any significant interactions (Supplementary Table 2). The replacement of education level by total annual family income (Model 4) or health insurance (Model 5) and the simultaneous adjustment of all of these three sociodemographic measures (Model 6) largely demonstrated similar results, although the associations were slightly attenuated (Supplementary Table 3).

** All statistical analyses and data management were performed using Stata 14.0 (StataCorp LP, College Station, TX, USA).

When we examined combined categories of self-reported measures of periodontal disease, we confirmed that those with tooth loss due to periodontal disease had an elevated hazard of incident PAD (e.g., HR: 1.70 [95% CI: 1.28–2.25] in Model 3), compared to those without periodontal disease diagnosis in all Models 1–6 (Table 3 and Supplementary Table 4). In contrast, participants with periodontal disease diagnosis or treatment without tooth loss did not demonstrate an elevated hazard of incident PAD, compared to those without periodontal disease diagnosis in any models (e.g., HR: 1.18 [95% CI: 0.70–1.99] and HR: 1.00 [95% CI: 0.66–1.53] respectively, in Model 3).

Clinical measure of periodontal disease and incident PAD (Analysis 2)

Of 5,872 participants, the mean age at baseline was 62.4 (standard deviation 5.5) years, 46.3% were men, and 17.5% were Black participants (Supplementary Table 1). According to the CDC-AAP definition of periodontal disease, participants with advancing periodontal disease severity were more likely to be male, have higher pack-years of smoking and history of CHD (Table 4). For several other characteristics, we observed a U- or an inverse U-shaped pattern across categories of periodontal disease (e.g., a higher proportion of Black participants and diabetes in categories with no, and severe periodontal disease compared to the mild periodontal disease category). The U-shaped pattern was not evident for most characteristics when we merged the two groups of no and mild periodontal disease (Supplementary Table 5).

Over a median follow-up of 21.0 years (IQI: 15.6, 22.1 years), there were 165 incident PAD cases (incidence rate: 1.5 per 1,000 person-year). According to the CDC-AAP definition, individuals with more severe forms of periodontal disease had a higher cumulative incidence of PAD in a graded fashion, with the risk separation being especially evident after 10 years of follow-up (Figure 1B; 5.4%, 4.2%, 2.0%, and 2.0% at ~24 years for severe, moderate, mild, and no periodontal disease, respectively, $p<0.001$).

In the unadjusted model (Model 1), increasing severity in CDC-AAP-defined periodontal disease was associated with incident PAD (e.g., HR: 1.78 [95% CI: 1.17–2.72] for moderate disease and HR: 2.47 [95% CI: 1.55–3.95] for severe disease vs. no disease) (Table 5). The associations were attenuated but significant in demographically-adjusted model (Model 2) for moderate disease (HR: 1.60 [95% CI: 1.04–2.46]) and for severe disease (HR: 1.97 [95% CI: 1.22–3.18]) vs. no disease. However, the association was no longer significant once we accounted for other potential confounders (Model 3). There were no significant interactions in the subgroup analyses (Supplementary Table 6). The adjustment for total annual family income (Model 4) or health insurance status (Model 5) instead of education level did not meaningfully change the results (Supplementary Table 7).

We repeated our Cox regression models with inverse probability weighting to account for the potential selection bias among those participants who attended D-ARIC and were included in Analysis 2 compared to those who did not attend. In general, similar results were observed (Supplementary Table 8).

DISCUSSION

In our full cohort of community-based biracial participants having ~24 years of follow-up, we observed a modest association of self-reported periodontal disease with incident PAD. More specifically, self-reported measures of periodontal disease (tooth loss due to periodontal disease, history of periodontal disease treatment, and periodontal disease diagnosis) demonstrated 1.37- to 1.54-fold higher hazard of incident PAD, compared to the counterparts of each self-reported measure, independent of demographic and clinical characteristics. The elevated hazard of PAD was especially evident and robust among participants with tooth loss due to periodontal disease, compared to those without tooth loss due to periodontal disease. We further demonstrated the consistent associations across major subgroups. On the other hand, the severity of periodontal disease based on objective clinical measures was generally associated with incident PAD in unadjusted and demographically-adjusted models but not in more extended models.

Our finding of a modest association of periodontal disease with subsequent risk of PAD is in line with previous studies.[4, 7, 9, 12, 18, 21–23, 27, 28] There are plausible mechanisms for this association, such as shared risk factors like diabetes and smoking.[27] However, the association remained significant even after accounting for these factors (Model 3) in Analysis 1, indicating the involvement of other mechanisms. In this context, oral inflammation may mediate this association.[27] Locally produced pro-inflammatory mediators enter the blood circulation and may trigger the chain of the atherosclerotic process, namely the recruitment of monocytes at the arterial wall, the up-regulation of endothelial adhesion molecules, and an increase in the macrophage uptake of lipids.[1, 3–5, 9, 17, 18, 28, 42] Also, periodontopathic bacteria may also contribute to atherogenesis.[5, 9, 12–16, 43, 44] Nonetheless, we observed that the association was most robust for those with severe periodontal disease leading to or requiring tooth loss, indicating that periodontal disease may need to be severe to impact PAD risk.

The weaker associations of incident PAD with clinical measure of periodontal disease (Analysis 2) than self-reported measures (Analysis 1) deserve specific discussion. Our results should not be interpreted that self-report is preferable than objectively-measured clinical periodontal parameters, which should be the gold standard for assessing periodontitis in general. Nonetheless, in this specific study, D-ARIC excluded participants who were edentulous or had contraindications to dental probing and thus selected healthier participants from the entire study population,[5] potentially biasing the results towards null, by design. Although we tried to address this bias by applying inverse probability weighting, it is possible that we could not fully address it. Also, we should keep in mind that Analysis 2 had lower statistical power compared to Analysis 1 due to a smaller number of participants.

Our study results should be interpreted in light of the following limitations. First, there might be misclassification in the self-reported measures of periodontal disease, as has been reported in a few other general populations.[45] Additionally, there is a possibility of misclassification in the CDC-AAP definition. Indeed, we observed U- or inverse U-shaped patterns of some factors such as diabetes across no, mild, moderate, and severe periodontal disease as defined by the CDC-AAP definition, which excludes third molars

from its assessment.[1] Third molars are more likely to have worse periodontal status than other regions in the mouth,[46–48] and thus the CDC-AAP definition may misclassify some participants with 'mild' periodontal disease as 'no' periodontal disease. Second, incident PAD definition was based on discharge ICD-9 codes, and thus it is possible that mild cases were under-ascertained or cases treated by practice-based physicians or small community clinics or none at all were missed.[30] Third, our study population included White and Black participants aged 53–75 years at baseline, and thus our results may not be generalizable to other age ranges or racial/ethnic groups. Finally, although we accounted for potential confounders, the possibility of residual confounding cannot be ruled out, as is true for any observational study.

On the other hand, there are a few strengths or unique aspects of our study. We evaluated multiple parameters of self-reported periodontal disease, along with a clinical definition based on a dedicated oral examination, enabling us to contrast the results between the two methods of data collection. Also, we studied both White and Black participants. Furthermore, a large population (particularly in Analysis 1) allowed us to elaborate several sensitivity analyses. Our study had a long follow-up of ~24 years. Additionally, we have employed comprehensive and sophisticated analysis (e.g., inverse probability weighting and correction for teeth exhibiting non-pathologic gingival recession) to address our study question.

Given the high prevalence of periodontal disease in adults (e.g., 47% in the US),[1–3, 5, 22] and our finding of a modest association between self-reported periodontal disease, especially with co-existing tooth loss, and incident PAD in the general population, the community and healthcare providers need to be aware of the importance of oral health. In this context, our findings suggest that a healthy periodontium, which is known to benefit not only oral health but also potentially cardiovascular health,[3, 9, 12, 19] may also play a role in vascular health of lower extremities, although this concept should be evaluated in future studies. Since the association between periodontal disease and incident PAD was somewhat explained by modifiable confounders such as diabetes and smoking, our study further supports the importance of controlling these risk factors for oral and systemic vascular health.

CONCLUSIONS

In conclusion, we observed a modest association of periodontal disease with incident PAD in the general population. The association was more robust in severe periodontal disease with tooth loss. Nonetheless, a larger study with the clinical measure of periodontal disease is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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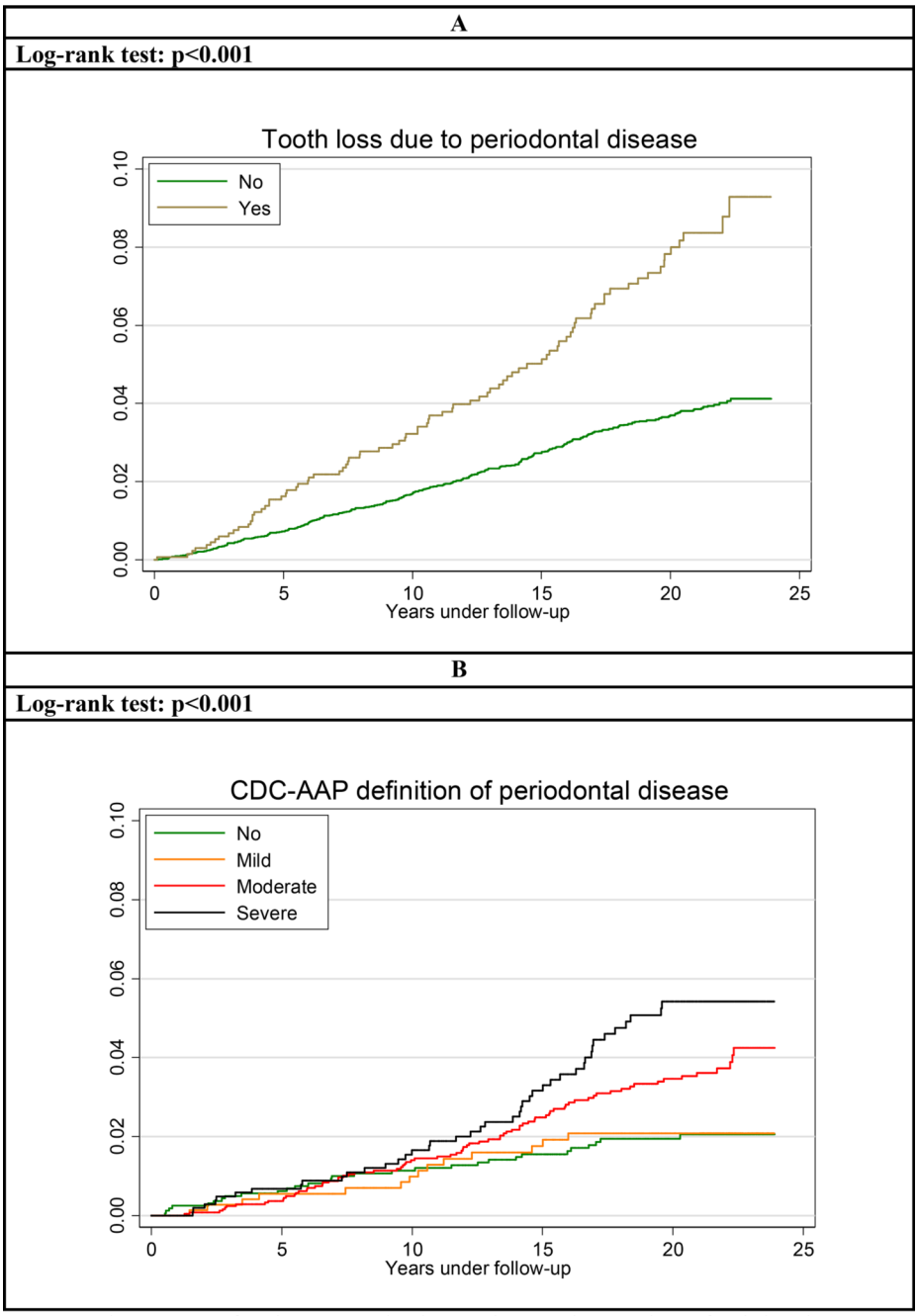
Summary describing the key finding from the study:

We observed a modest association of self-reported periodontal disease, especially when resulting in tooth loss, with incident PAD in our community-based population.



CDC-AAP, the US Centers for Disease Control and Prevention-American Academy of Periodontology

Figure 1:

Cumulative incidence of incident PAD stratified by individual measures of periodontal disease

1A: Cumulative incidence of incident PAD stratified by tooth loss due to periodontal disease

1B: Cumulative incidence of incident PAD stratified by CDC-AAP definition of periodontal disease

Table 1.

Baseline characteristics of the study population at visit 4, stratified by self-reported individual measures of periodontal disease (N=9,793)

Characteristics	Tooth loss due to periodontal disease		History of periodontal disease treatment		Periodontal disease diagnosis	
	No	Yes	No	Yes	No	Yes
N	8,444	1,349	8,323	1,470	7,616	2,177
Age, years	62.7 (5.6)	63.4 (5.6)	62.8 (5.6)	62.4 (5.7)	62.9 (5.6)	62.4 (5.7)
Male, %	44.4	43.2	44.6	42.1	44.5	43.5
Black, %	18.4	33.2	20.9	17.7	20.5	20.2
Education, %						
No or basic	16.9	27.2	19.8	10.0	19.5	14.3
Intermediate	42.7	40.8	42.6	41.5	42.5	42.0
Advanced	40.3	31.8	37.5	48.4	37.9	43.5
Health insurance, %	95.7	94.6	95.3	97.1	95.4	96.1
Total annual family income, dollars ††						
<$12000	8.7	17.7	10.7	5.7	10.2	8.7
$12000–$24999	19.8	24.8	21.3	16.3	21.2	18.1
≥$25000	71.4	57.3	67.9	77.9	68.4	73.0
Ever smoker, %	53.2	67.5	52.8	68.7	52.0	66.1
Pack-years of smoking	15.3 (23.7)	24.8 (28.4)	15.5 (23.9)	23.1 (27.3)	15.0 (23.7)	22.2 (26.7)
Diabetes, %	15.2	22.0	16.3	15.1	16.1	16.2
Systolic blood pressure, mmHg	127 (18.7)	128 (19.0)	127 (18.8)	125 (18.1)	128 (18.9)	126 (18.3)
Hypertension, %	45.8	51.6	46.8	45.7	46.7	46.5
Anti-hypertensive medication use, %	41.8	49.1	42.9	42.3	42.7	43.1
Total cholesterol, mmol/L	5.2 (0.9)	5.1 (0.9)	5.1 (0.9)	5.2 (0.9)	5.2 (0.9)	5.1 (0.9)
HDL-cholesterol, mmol/L	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)
Lipid-lowering therapy, %	13.9	16.2	14.0	15.6	13.9	15.5
History of CVD						
Coronary heart disease, %	7.6	9.9	7.9	7.6	7.9	7.9
Stroke, %	2.0	2.8	2.2	1.8	2.0	2.4
Heart failure, %	4.7	8.0	5.2	5.0	5.0	5.6

Values for categorical variables are given as percentage; values for continuous variables are given as mean (standard deviation)

CVD, cardiovascular disease; HDL-cholesterol, high-density lipoprotein-cholesterol

†† 9,392 participants have information on total annual family income

Table 2.

Hazard ratios (95% confidence interval) of incident PAD with self-reported individual measures of periodontal disease

	Tooth loss due to periodontal disease		History of periodontal disease treatment		Periodontal disease diagnosis	
	No	Yes	No	Yes	No	Yes
	N=8,444	N=1,349	N=8,323	N=1,470	N=7,616	N=2,177
Cases	275	85	291	69	257	103
Model 1	Ref.	2.14 (1.68–2.73)	Ref.	1.32 (1.01–1.71)	Ref.	1.41 (1.12–1.77)
Model 2	Ref.	1.93 (1.51–2.48)	Ref.	1.39 (1.07–1.81)	Ref.	1.46 (1.16–1.83)
Model 3	Ref.	1.54 (1.20–1.98)	Ref.	1.37 (1.05–1.80)	Ref.	1.38 (1.09–1.74)

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race

Model 3: Adjusted for age, sex, race, education level, diabetes, pack-years of smoking, systolic blood pressure, anti-hypertensive medication, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering therapy, history of cardiovascular disease

Table 3.

Hazard ratios (95% confidence interval) of incident PAD with self-reported combined measures of periodontal disease

	Periodontal disease diagnosis				
	No	**Yes**			**P-value for trend**
		No treatment and no tooth loss	**Treatment and no tooth loss**	**Tooth loss**	
	N=7,616	**N=399**	**N=803**	**N=975**	
Cases	257	15	25	63	
Model 1	Ref.	1.11 (0.66–1.87)	0.87 (0.57–1.31)	2.05 (1.56–2.70)	<0.001
Model 2	Ref.	1.16 (0.69–1.95)	0.97 (0.64–1.47)	1.96 (1.49–2.59)	<0.001
Model 3	Ref.	1.18 (0.70–1.99)	1.00 (0.66–1.53)	1.70 (1.28–2.25)	0.001

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race

Model 3: Adjusted for age, sex, race, education level, diabetes, pack-years of smoking, systolic blood pressure, anti-hypertensive medication, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering therapy, history of cardiovascular disease

Table 4.

Baseline characteristics of the study population stratified by CDC-AAP definition of periodontal disease (N=5,872)

Characteristics	CDC-AAP definition of periodontal disease			
	No	Mild	Moderate	Severe
N	1,620	732	2,474	1,046
Age, years	61.9 (5.5)	61.2 (5.3)	62.8 (5.6)	63.0 (5.5)
Male, %	31.1	40.1	50.8	63.3
Black, %	25.6	4.2	14.6	21.3
Education, %				
No or basic	12.2	6.0	13.4	17.6
Intermediate	41.5	43.4	44.2	44.4
Advanced	46.1	50.5	42.3	37.8
Health insurance, %	96.1	97.1	96.4	95.4
Total annual family income, dollars††				
<$12000	7.5	2.8	6.4	8.7
$12000–$24999	19.3	11.9	16.9	20.8
≥$25000	73.0	85.2	76.6	70.4
Ever smoker, %	40.3	43.5	56.3	70.4
Pack-years of smoking	8.7 (16.6)	9.0 (16.2)	16.3 (23.4)	24.0 (26.7)
Diabetes, %	12.3	8.6	14.5	16.2
Systolic blood pressure, mmHg	126 (18.0)	123 (16.5)	126 (18.1)	127 (18.6)
Hypertension, %	45.0	34.2	42.2	45.8
Anti-hypertensive medication use, %	40.0	31.8	37.4	37.4
Total cholesterol, mmol/L	5.2 (0.9)	5.2 (0.9)	5.2 (0.9)	5.1 (0.9)
HDL-cholesterol, mmol/L	1.3 (0.4)	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)
Lipid-lowering therapy, %	12.5	13.9	12.9	14.9
History of CVD				
Coronary heart disease, %	4.2	4.5	5.8	7.6
Stroke, %	1.3	0.4	1.9	2.2
Heart failure, %	3.7	2.1	3.5	3.8

Values for categorical variables are given as percentage; values for continuous variables are given as mean (standard deviation)

CDC-AAP, the US Centers for Disease Control and Prevention-American Academy of Periodontology; CVD, cardiovascular disease; HDL-cholesterol, high-density lipoprotein-cholesterol

†† 5,663 participants have information on total annual family income

Table 5.

Hazard ratios (95% confidence interval) of incident PAD with CDC-AAP definition of periodontal disease

	CDC-AAP definition of periodontal disease				P-value for trend
	No	Mild	Moderate	Severe	
	N=1,620	N=732	N=2,474	N=1,046	
Cases	30	14	78	43	
Model 1	Ref.	1.01 (0.53–1.90)	1.78 (1.17–2.72)	2.47 (1.55–3.95)	<0.001
Model 2	Ref.	1.17 (0.61–2.23)	1.60 (1.04–2.46)	1.97 (1.22–3.18)	0.003
Model 3	Ref.	1.31 (0.69–2.51)	1.39 (0.90–2.14)	1.53 (0.94–2.50)	0.07

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race

Model 3: Adjusted for age, sex, race, education level, diabetes, pack-years of smoking, systolic blood pressure, anti-hypertensive medication, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering therapy, history of cardiovascular disease

CDC-AAP, the US Centers for Disease Control and Prevention-American Academy of Periodontology