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Periodontal profile class is associated with prevalent diabetes, coronary heart disease, stroke, and systemic markers of C-reactive protein and interleukin-6

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Abstract

Background: This paper focuses on the Periodontal Profile Class (PPC) System that may be more informative and representative of periodontitis phenotypes than current case definitions of periodontitis. This study illustrates the unique aspects of the PPC compared with other periodontal indices for studying associations between periodontal disease and prevalent systemic conditions.

Methods: We computed odds ratios and 95% confidence intervals to compare associations between periodontal disease and prevalent systemic conditions using our new PPC and two traditional indices. We used the Bayesian Information Criterion (BIC) to determine the fit of the model and the magnitude of the contribution attributable to periodontal disease beyond traditional risk factors. The Atherosclerosis Risk in Communities (ARIC) Study (1996–1998) results were compared with results from the combined National Health and Nutrition Examination Survey 2009–2014 datasets.

Results: In the ARIC Study, high gingival inflammation, tooth loss, severe tooth loss, and severe disease PPC components were significantly associated with diabetes, coronary heart disease (CHD), high-sensitivity C-reactive protein, and interleukin (IL)-6, while only severe disease was associated with stroke. Severe disease was associated with CHD using the Centers for Disease Control/American Academy of Periodontology index, and the European Periodontal index was associated with CHD and IL-6.

Conclusions: The addition of the PPC to traditional variables associated with prevalent diabetes, stroke, CHD, and systemic measures of inflammation resulted in very strong improvement of the overall models, while the traditional indices were less likely to be associated and, if present, the associations were weaker. The PPC system provides specific insight into the individuals and

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periodontal characteristics of the phenotype that are associated with systemic conditions that may be useful in designing treatment interventions.

Keywords

Diagnosis; epidemiology; gingivitis; periodontal-systemic disease interactions; periodontitis

1 | INTRODUCTION

This is one of a series of papers about the Periodontal Profile Class (PPC).[1] The PPC is a person-level measure that provides a clinical, seven-class taxonomic system for the patient's disease status. The PPC is one component of the Periodontal Profile Phenotype (P^3) that is described in another publication.[2] The potential use of PPC for patient diagnosis/study participant classification has been described elsewhere,[2] as well as risk for disease progression and tooth loss.[3] This study presents relationships to prevalent systemic diseases and conditions; it will be followed by findings on risk for incident systemic diseases.

During the last 20 years the majority of human studies of associations between periodontal disease and prevalence of systemic diseases and related conditions reported significant associations, while some studies did not. Many factors could have played a role in the inconsistency of results, such as sample size, characteristics of the groups studied, examiner differences, and the systemic condition studied. The current authors hypothesize that a major factor related to inconsistencies in study results is how the exposure, i.e., periodontal disease, is measured.

In the present study, the utility of the P^3 System is demonstrated by presenting associations between PPC with prevalent diabetes, coronary heart disease (CHD) and stroke, as well as systemic measures of high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6, adjusting for relevant confounders. This cross-sectional study compares the patterns of associations with prevalent systemic diseases and systemic inflammation for the PPC phenotype compared with two traditional indices of periodontal status. All three classification systems show some association with prevalent disease; however, the focus of the present study is on patterns of association that emerge from the PPC that can provide the clinician and researcher insight that may guide treatment decisions.

2 | MATERIALS AND METHODS

2.1 | Study samples

The Atherosclerosis Risk in Communities (ARIC) study[4] enrolled 15,792 participants within the age group of 45 to 64 years in four different United States communities (Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland). All participants provided written informed consent to a protocol that was reviewed and approved by the Institutional Review Board on research involving human subjects at the University of North Carolina and at each ARIC field center. In the current study, all participants who completed the fourth clinic visit (1996–1998) in ARIC (N = 11,656) were eligible for inclusion. Of the 11,656 ARIC participants seen at the fourth

clinical visit, study participants who did not receive a periodontal examination were excluded. These exclusions resulted in 6,793 individuals who were included in the Dental ARIC Study as well as the Latent Class Analysis (LCA)[5] that resulted in the PPC.[1]

Three additional datasets from the National Health and Nutrition Examination Survey (NHANES; 2009–2010, 2011–2012, and 2013–2014) were combined as a replication study population. The technical details of the surveys, including sampling design, periodontal data collection protocols, and data availability, are described elsewhere.[6–9] Briefly, periodontal measurements were collected for 3,750 individuals (NHANES 2009–2010), for 3,338 individuals (NHANES 2011–2012), and 3,622 individuals for (NHANES 2013–2014) for a total of 10,710. Periodontal measures were collected on six sites per tooth for all teeth present in the mouth except third molars.[10–12]

2.2 | Measurement of exposures

2.2.1 | Periodontal profile class (PPC)—The analytic approach implemented person-level LCA to identify discrete classes of individuals using seven tooth-level clinical parameters. These parameters were: ≥one site with interproximal attachment level ≥3 mm, ≥one site with probing depth (PD) ≥4 mm, extent of bleeding on probing (BOP) dichotomized at 50% (or ≥three sites per tooth), gingival inflammation (GI) index[13] (dichotomized as GI = 0 vs GI ≥1), plaque index[14] (PI; dichotomized as PI = 0 vs Pl ≥1), the presence/absence of full prosthetic crowns for each tooth, and tooth status (present vs absent).[1]

Briefly, individuals were classified into mutually exclusive latent classes based on their responses to a set of observed categoric variables, while ensuring that clinically relevant categories were maintained (see Morelli et al[1] for a more complete description). Milligan and Cooper's[15] recommendation was used for the maximum number (n) of classes, suggesting to stop when the newly added class (n + 1) is not clinically distinct from the previous number of identified classes. Additionally, it was verified that mean posterior probabilities of correct class assignment were > 0.7, which according to Nagin,[16] indicates adequate class separation and membership precision. In the first step of LCA, the person-level LCA classified individuals into seven latent classes based on 224 dichotomous variables (derived from seven tooth-level variables, using the clinical parameters referred to above for each of 32 teeth). The class membership probabilities represent the overall, unconditional proportions of individuals in each of seven latent classes. The model parameters from the first step were then used to compute the posterior probabilities (the probability of event A occurring given that event B has occurred) of each individual's membership into each class, conditional upon the values of the 224 items or as many of them as were measured for that individual.[1]

2.2.2 | CDC/AAP and European indices—The Centers for Disease Control/American Academy of Periodontology (CDC/AAP) index[17] along with the European Periodontal index[18] may be the most frequently used indices and are a step forward in creating some consistency in periodontal disease case definitions. The CDC/AAP index was developed as a three-level index and later expanded to a four-level index (healthy, mild, moderate, and

severe disease).[9] We used the four-level index because it provided more separation of the healthy and mild groups. The definitions of the levels of disease for both indices appear in Table 1. The European Index has three levels (healthy, incipient, and severe).[18]

2.3 | Prevalent diseases and conditions

The dependent variables in this study include three prevalent diseases (diabetes, CHD, and stroke) and two markers of systemic inflammation (CRP and IL-6). All prevalent, self-reported measures of disease gathered at ARIC visit 1 were updated by incident disease adjudicated by ARIC investigators during the 9 years of follow-up until the periodontal examination during visit 4. Prevalent CHD was defined as a self-reported history of a physician-diagnosed heart attack; or evidence of an old myocardial infarction by electrocardiogram based on the Minnesota codes; or a history of coronary surgery or coronary angioplasty. Stroke and/or transient ischemic attack (TIA) history was obtained by interviewer-administered questionnaire as a report of stroke or TIA diagnosed by a physician. Angina pectoris and intermittent claudication were measured using the Rose Questionnaire.[19] We classified prevalent diabetes mellitus as a non-fasting serum glucose level of ≥200 mg/dL, a fasting glucose level of ≥126 mg/dL, a self-report of physician diagnosis, or the current use of diabetes medication.[20,21]

IL-6 and CRP concentrations from once-thawed serum aliquots (frozen at −80°C from collection until December 2009) were all measured by enzyme-linked immunosorbent assay (ELISA) techniques. Spectrophotometric endpoints were determined on a plate reader* using reagent assay kits† according to manufacturers' instructions. A control software package‡ was used to fit the standard curve data using either four or five parameter-fitting algorithms to provide a best fit of the seven-point (duplicate) standard curve after subtraction of the mean reagent blank values from all measured optical densities. Standard curve concentrations ranged from 0.156 to 10 pg/mL for serum IL-6 (using the high-sensitivity antibody) and 780 to 50,000 pg/mL for CRP. Although hs-CRP was measured using ELISA (several years before development of clinical laboratory improvement amendments (CLIA)-certified nephelometry methods), the ELISA values have been validated and shown to have high agreement against the current clinical tests ($r = 0.9$, data not shown) with the advantage of having higher sensitivity for values < 3 mg/dL.

The NHANES studies[9,22] collected information on prevalent CHD and stroke by standardized questions. Responses from three questions were combined to create the CHD variable. The three questions were: Has a doctor ever told you 1) that you had coronary heart disease? 2) that you had a heart attack? or 3) that you had congestive heart failure? The response to the question, "Has a doctor ever told you that you had a stroke?" is the basis for the stroke variable.

*SpectraMax M2, Molecular Devices, Sunnyvale, CA.
†R&D Systems, Minneapolis, MN.
‡Softmax® (v.5.0.1), Molecular Devices.

2.4 | Other variables of interest

Age, sex, race, and additional vascular risk factors, such as body mass index (BMI) and lipid profile, were measured according to published methods. Fasting plasma high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, and fasting serum glucose (all mg/dL) were collected before the clinical examination. Methods for measurement of body mass index (BMI) and blood pressure have been described previously.[23,24] Hypertension was defined as having a systolic blood pressure ≥ 140 mm/hg or diastolic blood pressure ≥ 90 mm/hg or taking blood pressure-reducing medications.[23,24]

Participants were defined as never smokers, former smokers, or current smokers by interview. Education level was divided into basic(< 12 years), intermediate (12 to 16 years), or advanced (17 to 21 years), and was included to control for socioeconomic status. Age in years at visit 4 was included, and a variable representing race/ethnicity (African-American or white) and ARIC field center was designed to control for the ethnic, regional, and examiner differences in the ARIC study.

2.5 | Statistical analysis

We performed analyses to determine associations between PPC and prevalent diabetes, CHD, stroke, serum CRP, and serum IL-6 (both dichotomized at 75th percentile) for the participants of the Dental ARIC Study using logistic regression to compute odds ratios (OR) and 95% confidence intervals (CI) with adjustment for potential confounders. We compared each PPC category to the reference group (healthy) and used a similar analytic strategy for categories of the CDC/AAP and European indices and followed the same process for the NHANES study participants, except the NHANES study did not include a serum IL-6 measure. We also computed the Bayesian Information Criterion (BIC)[25] to determine the fit of the model and the magnitude of the attributable contribution that periodontal assessment provides beyond traditional risk factors. We modified the criteria to represent model “improvement” by changing the negative signs to positive signs with the interpretation that the models obtained by adding periodontal disease to the existing traditional variables in the model significantly improved the overall fit of the model. Specific levels of BIC improvement appear in Table 2.

3 | RESULTS

3.1 | Associations with prevalent systemic diseases and conditions

Distributions of prevalent CHD according to demographic, systemic health, and periodontal disease case status for ARIC and NHANES 9–14 study participants are shown in Table 1. Similar distributions for diabetes, stroke, CRP, and IL-6 are available online (see supplementary Tables S1 to S4 in online *Journal of Periodontology*). Participants in both studies who were Caucasian, male, or hypertensive had a higher CHD prevalence. Higher mean age, BMI, and triglycerides were associated with prevalent CHD as were lower mean scores for LDL, HDL, and total cholesterol. The lower LDL relationship was supported by additional analysis of ARIC medication data showing that 46% of participants with CHD used lipid-lowering medications compared with 11% without CHD.

The pattern for education level differed for the two studies with higher prevalence of CHD in those with basic levels of education in ARIC and with intermediate level in NHANES. Smoking patterns also differed with current smokers in ARIC and former smokers in NHANES having higher CHD prevalence. Participants in both studies classified by the CDC/AAP and European indices as having severe periodontitis had higher prevalence of CHD, while the pattern differed for the PPC classifications. ARIC participants who had tooth loss and severe tooth loss had higher prevalence of CHD closely followed by the high GI and severe groups. NHANES participants with severe tooth loss had the highest prevalence of CHD followed by the tooth loss, high GI, and the posterior disease groups. Overall, there appears to be a higher prevalence of CHD in the ARIC participants, who tend to be older. The variables in Table 1 were significantly related to CHD in both studies except that race and BMI were not significantly associated with CHD in the ARIC study and triglyceride level was not significant in NHANES.

Table 2 presents associations between the PPC and prevalent systemic conditions of diabetes, CHD, stroke, hs-CRP, and serum IL-6 for ARIC study participants. The number of study participants with these diseases and conditions vary and are shown at the top of each column. All models were adjusted for relevant confounders and covariates including race/center, age, sex, BMI, smoking (three levels), education, as well as lipids and other systemic conditions relevant to the disease. These models each served as a reference model for computing the BIC that permitted comparison of having periodontal disease in the model to not having periodontal disease. It can be seen that many BIC improvement scores are above 10 (very strong contribution) for the PPC classification, with the CDC/AAP and European classifications having one BIC score above 10 and many below 2.0.

For diabetes in Table 2, most categories show significant odds ratios for the PPC, while nothing was significant for the CDC/AAP and European indices. Individuals with periodontal disease who have retained most of their teeth generally are classified as having mild, high GI, posterior disease, or severe disease. Of these classes, the high GI and severe disease classes are associated with prevalent diabetes. There also are higher odds of having prevalent diabetes with both tooth loss classes and severe disease. The PPC for severe disease has the highest odds ratio (1.88) for diabetes and the entire PPC model showed the greatest BIC Improvement. All the high GI, tooth loss, severe tooth loss, and severe disease classes were significant for CHD. Only the severe disease class was significant for prevalent stroke. Individuals classified as having high GI, tooth loss, severe tooth loss, or severe disease were significantly more likely to be in the highest quartile for serum CRP and IL-6. There were no significant associations for the CDC/AAP classification, and European index associations were between CHD and IL-6 for severe disease. Cardiovascular disease is divided into CHD and stroke because they share some risk factors, but have differing mechanisms of pathogenesis. Among the European classifications, only the severe categories show significant associations with CHD, and none of the associations with stroke were significant. Several of the PPC classes are significantly associated with CHD, with high GI being the strongest followed by mild disease and the two tooth loss classes. However, severe disease was not significant. By contrast, only the PPC severe disease class was significantly associated with stroke.

The analyses shown in Table 2 appear in Table 3 for the three combined NHANES cohorts (2009–2010, 2011–2012, and 2013–2014). IL-6 information was not available in NHANES, so it is absent in this table. BIC improvement scores for having periodontal disease classifications in the models were very strong for all PPC models, but they were weaker for most CDC/AAP- and European-based models. The NHANES results in Table 3 show all PPC classifications except posterior disease were significantly associated with diabetes as were the CDC/AAP moderate and severe and the European incipient and severe categories. The PPC models show that posterior disease and severe tooth loss are the only categories associated with CHD, and only tooth loss is associated with stroke. The two tooth loss categories and posterior disease were associated with CRP. The CDC/AAP and European models were associated with CHD and CRP, but not with stroke. The models for CHD showed that moderte and severe disease were significantly associated for the CDC/AAP and that incipient and severe disesae were significant for the European index. The BIC scores for the PPC, CDC/AAP, and European models indicated that periodontitis made a very strong contribution.

4 | DISCUSSION

In Table 2 associations were compared among the CDC/AAP, European, and PPC indices with the prevalence of three systemic diseases (diabetes, CHD, and stroke) along with two markers of systemic inflammation (hs-CRP and serum IL-6) using ARIC study data. The focus was that the broader PPC representation of the periodontitis phenotype would have a higher probability of being associated with other person-level oral and systemic conditions. The PPC produced multiple statistically significant associations with the systemic diseases and conditions along with “strong and very strong” BIC scores indicating that PPC made meaningful additions to the models. The only associations with BIC scores in the “positive or strong” categories for the CDC/AAP and European indices are for prevalent CHD. The associations between severe disease and CHD is consistent with a multitude of other studies using a variety of periodontal indices, but the lack of an association between severe disease and CHD using the PPC could be important because it may indicate that the effects of high levels of tooth loss and high GI underlie traditional associations with prevalent CHD. If standard periodontal therapy will not affect the burden of having lost teeth, what might this mean for planning treatment or design of treatment studies to reduce incident CHD? High GI is significantly associated with all the systemic diseases and conditions except stroke, which shares some common risk factors, but not others. While the high GI has extensive inflammation with less attachment loss and shallower pockets, it is significantly associated with diabetes, CHD, and the systemic inflammatory markers, whereas other categories with similar levels of periodontal disease (mild, without extensive inflammation) are not associated with those conditions. The high GI class is a novel feature of the PPC, and its association with systemic diseases and inflammatory conditions provides support for the profession's reduction of inflammation as a goal of periodontal treatment.

It is interesting that the posterior disease class that is similar to the traditional definitions of moderate and incipient disease, which usually begins in the posterior dentition, is not associated with any of the prevalent diseases or inflammatory biomarkers. Individuals in the posterior disease category may have qualified for inclusion in clinical intervention studies or

randomized controlled trials to test whether treatment of periodontal disease prevents or reduces these systemic diseases or inflammatory mediators. However, given the lack of significant associations seen in Table 2, we might not expect treatment of this phenotype to affect these conditions.

Table 3 presents the same analyses conducted in Table 2 using the NHANES 2009–2014 dataset, except IL-6 scores (data not available). This replication sample was larger than the ARIC sample, had more cases, was younger, and was more likely healthier since it included study participants as young as 30 years. We conducted a second analysis for the NHANES 2009–2014 sample that was restricted to the same age range as the ARIC study participants, and the patterns of associations were similar. Table 5 (supplementary in online *Journal of Periodontology*) shows fewer PPC categories related to the systemic conditions for all three indices, but more PPC categories were significant. This could be due to the effect of age, but also to the smaller sample sizes.

A weakness of our classification system is that it does not precisely address the diagnosis of aggressive periodontitis because the ARIC sample is older. Although the ARIC and NHANES samples differ by age and, likely, health, the patterns of associations for the PPC compared with the CDC/AAP indices with prevalent diseases and conditions are very similar. The PPC models generally make stronger contributions to the models and are more likely to show a significant association with prevalent diseases and conditions than the other indices. Additionally, there are some specific patterns of interest between the PPC models for the two datasets. While periodontal disease is associated with prevalent CHD in both datasets, mild and high GI are not associated with CHD in NHANES, which could be a function of a younger NHANES sample. While only severe disease is associated with stroke in ARIC, associations with the two tooth loss classes and posterior disease in NHANES replace the association with severe disease. Thus, the PPC performs similarly in both datasets, but the strength of the associations may differ among components of PPC.

The value of teeth lost due to periodontitis or other reasons is still a question when assessing risk for disease progression and tooth loss. Also, the case status definitions used in the past have been narrowly focused when attempting to describe the periodontal phenotype. Perhaps this problem is most profound when trying to establish a relevant case type for intervention studies. Inclusion criteria for case definitions are disparate, and responders and non-responders often are thought to be attributable to inclusion criteria. For example, a patient with severe disease has many teeth at risk for disease progression and perhaps may respond better to a specific therapeutic intervention. However, certain severe tooth loss patients may have enough teeth and enough disease to qualify for a study, but they are at lower risk of progression[3] and less likely to respond to the same intervention.

The P^3 system was designed to meet the clinical utility needs of diagnosis, assigning prognosis and risk, as well as measuring clinical outcomes in response to therapy for an individual patient. The diagnostic algorithm is robust and the math has been calculated to harmonize group-level data to apply to an individual, such that a simple data entry of clinical signs by a practitioner will assign a PPC for the patient.[2] The clinical utility of the PPC as part of the P^3 system is not fully completed. Our system is web-based, and practitioners will

be able to enter patient information and receive a chart with the patient's PPC and risk scores for future tooth loss. After treatment, the practitioner can submit revised clinical information and receive a new risk score indicating changes in risk for their patient. Examples of the clinical forms are available in the supplemental figures in another publication[2] and could be part of the patient's electronic or paper dental record. The assignment of PPCs has been demonstrated to be robust using a wide range of datasets and can be used to harmonize different studies. PPC misclassification is not a significant problem, with an 85% correct assignment rate under the worst comparisons of two missing clinical indices and less than full-mouth exams.

In many trials designed to examine the potential periodontal treatment effects on systemic inflammation and/or systemic disease, criteria for subject eligibility often is predicated on having a certain minimum number of teeth with pockets and attachment loss, but these trials do not consider either a high percentage of GI-classified teeth or tooth loss. Since these data demonstrate associations with prevalent disease outcomes, it suggests the mechanistic importance of having a history of periodontal disease that results in tooth loss as a component of risk for continuing systemic inflammation and risk for systemic disease. However, the current periodontal therapy armamentarium is not able to address the effect of past inflammation implied by a tooth lost to periodontal disease. Increasingly, the evidence that the oral microbiome is highly mobile and can translocate to other tissues and persist in extraoral compartments may provide a link between the history of chronic periodontal disease leading to tooth loss and systemic diseases (for review see Han and Wang[26]). It appears that the patterns revealed by the PPC phenotype as associated with systemic conditions and systemic inflammation may be useful in designing and providing clinical interventions with the aim of influencing systemic outcomes.

5 | CONCLUSIONS

The addition of the PPC phenotype to traditional variables associated with prevalent diabetes, stroke, CHD, and systemic measures of inflammation resulted in very strong improvement of the overall risk models. The PPC appears to capture the systemic exposure component of the phenotype because it is more strongly associated with systemic markers of inflammation than comparison indices. The new high GI class that also has mild tooth loss is strongly associated with systemic inflammation, prevalent diabetes, and CHD. The components of the PPC provide some clarity as to how the phenotype may relate to systemic disease. Clinical inflammation, independent of probing measures, is also associated with prevalent disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

ARIC and NHANES: Prevalent CHD by demographics, general health, and periodontal disease case definitions

Demographic, health, and periodontal disease variables	Dental ARIC (N =6,611)		NHANES (N =10,393)		
	CHD Yes, N	CHD No, N	CHD Yes, N	CHD No, N	*P* value[a] D-ARIC/NHANES
African American	59 (4.8%)	1,166 (95.2%)	55 (2.6%)	2,077 (97.4%)	
Caucasian	306 (5.7%)	5,056 (94.3%)	158 (3.6%)	4,286 (96.4%)	0.22/ < 0.0001
Other	..	..	75 (2.0%)	3,742 (98.9%)	
Female	106 (3.0%)	3,487 (97.1%)	84 (1.6%)	5,190 (98.4%)	<0.0001/ < 0.0001
Male	261 (8.7%)	2,757 (91.4%)	204 (4.0%)	4,915 (96.0%)	
Age, years (mean [SD])	64.2 (5.6)	62.2 (5.6)	65.8 (11.7)	51.2 (14.0)	<0.0001/ < 0.0001
BMI (mean [SD])	29.0 (5.4)	28.6 (5.4)	30.6 (6.6)	29.2 (6.7)	0.12/0.0008
Diabetes	90 (9.9%)	817 (90.1%)	89 (7.1%)	1,158 (92.9%)	
No diabetes	276 (4.9%)	5,394 (95.1%)	199 (2.2%)	8,947 (97.8%)	<0.0001/ < 0.0001
Hypertensive	187 (8.5%)	2,022 (91.5%)	209 (5.6%)	3,554 (94.5%)	
Non-hypertensive	171 (3.9%)	4,204 (96.1%)	79 (1.2%)	6,536 (98.8%)	<0.0001/ < 0.0001
Current smoker	56 (6.8%)	763 (93.2%)	59 (3.1%)	1,878 (97.0%)	
Former smoker	188 (7.9%)	2,486 (93.0%)	115 (4.5%)	2,456 (95.5%)	
Never smoker	123 (4.0%)	2,986 (96.0%)	114 (1.9%)	5,766 (98.1%)	<0.0001/ < 0.0001
BMI (mean [SD])	114.7 (32.6)	122.5 (33.1)	92.4 (36.1)	113.5 (37.2)	<0.0001/ < 0.0001
Total cholesterol (mean [SD])	188.9 (35.0)	201.8 (35.9)	174.5 (42.6)	197.7 (41.4)	<0.0001/ < 0.0001
Triglyceride (mean [SD])	155.1 (92.5)	142.0 (83.7)	175.8 (118.6)	159.3 (145.9)	0.003/0.06
HDL (mean [SD])	43.1 (13.7)	51.0 (16.8)	49.1 (17.4)	53.0 (16.0)	<0.0001/ < 0.0001
Education					
Basic	69 (8.0%)	797 (92.0%)	75 (3.1%)	2,317 (96.9%)	
Intermediate	162 (5.7%)	2,694 (94.3%)	81 (3.6%)	2,146 (96.4%)	
Advanced	136 (4.7%)	2,747 (95.3%)	131 (2.3%)	5,631 (97.7%)	0.001/0.002
PPC-Health	57 (3.1%)	1,757 (96.9%)	88 (1.5%)	5,705 (98.5%)	
PPC-Mild	53 (5.2%)	973 (94.8%)	10 (1.5%)	655 (98.5%)	
PPC-High GI	43 (6.5%)	624 (93.6%)	44 (4.8%)	876 (95.2%)	
PPC-Tooth Loss	57 (7.4%)	717 (92.6%)	57 (5.1%)	1,065 (94.9%)	
PPC-Posterior Disease	57 (5.8%)	926 (94.2%)	22 (4.5%)	465 (95.5%)	
PPC-Severe Tooth Loss	68 (7.9%)	794 (92.1%)	44 (7.0%)	589 (93.1%)	
PPC-Severe Disease	32 (6.6%)	453 (93.4%)	23 (3.0%)	750 (97.0%)	<0.0001/ < 0.0001
CDC/AAP Health	31 (4.1%)	728 (95.9%)	25 (1.1%)	2,458 (99.0%)	
CDC/AAP Mild	82 (4.1%)	1,908 (95.9%)	63 (2.0%)	3,065 (98.0%)	
CDC/AAP Moderate	155 (5.7%)	2,560 (94.3%)	151 (4.2%)	3,485 (95.9%)	
CDC/AAP Severe	99 (8.6%)	1,048 (91.4%)	49 (4.3%)	1,097 (95.7%)	<0.0001/ < 0.0001
European Health	30 (3.8%)	753 (96.2%)	23 (0.9%)	2,507 (99.1%)	
European Incipient	240 (4.9%)	4,657 (95.1%)	192 (3.0%)	6,292 (97.0%)	
European Severe	97 (10.4%)	834 (89.6%)	73 (5.3%)	1,306 (94.7%)	<0.0001/ < 0.0001

ARIC, Atherosclerosis Risk in Communities; D-ARIC, Dental-ARIC; NHANES, National Health and Nutrition Examination Survey; CHD, coronary heart disease; BMI, body mass index; HDL, high-density lipoprotein; GI, gingival inflammation; CDC/AAP, Centers for Disease Control/ American Academy of Periodontology.

[a] *P* values calculated by chi-square test for categoric variables and t-test for continuous variables.

TABLE 2

Associations between three indices of periodontal disease case status and prevalent systemic conditions in dental ARIC study

Cases/Totals Case Status (N)	Diabetes 921/6,672 OR (95% CI)[a]	CHD[b] 355/6,486 OR (95% CI)[a]	Stroke[b] 87/6,218 OR (95% CI)[a]	CRP 1,378/5,510 OR (95% CI)[a]	IL-6 1,352/5,439 OR (95% CI)[a]
PPC-Health (1,845)	Ref	Ref	Ref	Ref	Ref
PPC-Mild (1,047)	1.21 (0.93-1.58)	1.22 (0.82-1.83)	1.50 (0.69-3.26)	1.20 (0.97-1.49)	**1.25 (1.01-1.55)**
PPC-High GI (694)	**1.61 (1.18-2.18)**	**1.87 (1.16-3.04)**	0.92 (0.34-2.53)	**1.36 (1.02-1.82)**	**1.39 (1.05-1.85)**
PPC-Tooth Loss (800)	**1.44 (1.09-1.89)**	**1.61 (1.07-2.41)**	1.04 (0.43-2.52)	**1.54 (1.22-1.94)**	**1.50 (1.19-1.89)**
PPC-Posterior Disease (999)	1.16 (0.89-1.53)	1.32(0.88-1.97)	0.73 (0.29-1.86)	1.18 (0.95-1.47)	**1.29 (1.01-1.61)**
PPC-Severe Tooth Loss (900)	**1.59 (1.21-2.08)**	**1.76 (1.17-2.65)**	2.08 (0.98-4.43)	**1.39 (1.10-1.76)**	**1.28 (1.01-1.62)**
PPC-Severe Disease (508)	**1.88 (1.38-2.56)**	1.56 (0.96-2.54)	**2.39 (1.01-5.64)**	**1.50 (1.11-2.02)**	**1.52 (1.15-2.03)**
Total (6,793)					
BIC Improvement[c]	20.57	10.60	12.04	16.75	15.31
CDC-Health (775)	Ref	Ref	Ref	Ref	Ref
CDC-Mild (2,035)	0.82 (0.63-1.07)	1.04 (0.66-1.64)	0.72 (0.33-1.56)	1.00 (0.80-1.24)	1.15 (0.92-1.45)
CDC-Moderate (2,799)	1.19 (0.92-1.53)	1.11 (0.73-1.71)	0.87 (0.42-1.80)	0.95 (0.77-1.18)	1.22 (0.97-1.53)
CDC-Severe (1,184)	1.21 (0.91-1.61)	1.55 (0.98-2.44)	0.99 (0.44-2.22)	1.08 (0.84-1.38)	1.25 (0.97-1.62)
Total (6,793)					
BIC Improvement‡	17.70	7.41	1.15	1.69	3.60
European-Health (749)	Ref	Ref	Ref	Ref	Ref
European-Incipient (5,021)	1.07 (0.84-1.36)	1.12 (0.74-1.70)	0.79 (0.40-1.58)	0.98 (0.80-1.19)	1.08 (0.88-1.34)
European-Severe (973)	1.20 (0.89-1.61)	**1.97 (1.23-3.14)**	1.23 (0.55-2.76)	1.11 (0.85-1.44)	**1.38 (1.06-1.79)**
Total (6,793)					
BIC Improvement[c]	1.61	16.82	2.57	1.68	7.47

[*] Odds ratios adjusted as follows: logistic regression model for Diabetes adjusted for race, age, gender, body mass index (BMI), smoking (three levels) and education (three levels); logistic regression models for Heart Attack and Stroke adjusted for race, age, gender, BMI, smoking (three levels), diabetes, hypertension, education (three levels), high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol; logistic regression models for C-reactive protein (CRP) and interleukin (IL)-6 adjusted for race, age, gender, BMI, smoking (three levels), diabetes, hypertension, and education (three levels). Bolded text identifies statistically significant odds ratios.

[b] CHD excludes Stroke cases; Stroke excludes CHD cases

NHANES, National Health and Nutrition Examination Survey; CHD, coronary heart disease; GI, gingival inflammation.

[c] Bayesian Information Criterion (BIC)

BIC Improvement Evidence for Higher BIC

0 to 2 Not worth more than a bare mention

2 to 6 Positive

6 to 10 Strong

≤ 10 Very Strong

TABLE 3

Associations between three indices of periodontal disease case status and prevalent systemic conditions in the NHANES 2009-2014 studies

Cases/Total Case Status (N)	Diabetes 1,320/10,632 OR (95% CI)[a]	CHD[b] 272/9,805 OR (95% CI)[a]	Stroke[b] 231/9,764 OR (95% CI)[a]	CRP 899/3,575 OR (95% CI)[a]
PPC-Health (5,878)	Ref	Ref	Ref	Ref
PPC-Mild (674)	**1.37 (1.06-1.77)**	0.76 (0.37-1.54)	0.85 (0.39-1.89)	1.08 (0.77-1.52)
PPC-High GI (962)	**1.36 (1.10-1.68)**	1.20 (0.78-1.83)	1.37 (0.86-2.18)	1.19 (0.85-1.67)
PPC-Tooth Loss (1,197)	**1.51 (1.25-1.82)**	1.30 (0.88-1.93)	**1.61 (1.07-2.41)**	**1.57 (1.19-2.07)**
PPC-Posterior Disease (506)	1.17 (0.87-1.58)	**2.27 (1.35-3.81)**	1.82 (0.94-3.55)	**1.75 (1.21-2.53)**
PPC-Severe Tooth Loss (693)	**1.72 (1.37-2.16)**	**1.54 (1.00-2.37)**	**2.03 (1.31-3.14)**	**1.61 (1.14-2.29)**
PPC-Severe Disease (800)	**1.28 (1.00-1.64)**	1.33 (0.80-2.22)	1.26 (0.70-2.27)	1.28 (0.93-1.76)
Total (10,710)				
BIC Improvement[c]	30.8	12.43	13.21	18.3
CDC-Health (2,521)	Ref	Ref	Ref	Ref
CDC-Mild (3,199)	1.12 (0.91-1.37)	1.26 (0.77-2.05)	1.03 (0.65-1.62)	1.21 (0.96-1.54)
CDC-Moderate (3,791)	**1.52 (1.25-1.85)**	1.45 (0.92-2.29)	1.07 (0.69-1.64)	**1.29 (1.03-1.63)**
CDC-Severe (1,199)	**1.45 (1.13-1.85)**	1.57 (0.92-2.67)	1.10 (0.65-1.88)	**1.58 (1.16-2.15)**
Total (10,710)				
BIC Improvement[c]	24.9	3.52	0.17	9.0
European-Health (2,563)	Ref	Ref	Ref	Ref
European-Incipient (6,681)	**1.32 (1.09-1.59)**	1.43 (0.90-2.26)	1.15 (0.75-1.78)	1.21 (0.98-1.48)
European-Severe (1,466)	**1.53 (1.21-1.94)**	1.57 (0.93-2.65)	1.39 (0.84-2.32)	**1.77 (1.32-2.39)**
Total (10,710)				
BIC Improvement[c]	13.2	3.11	1.87	14.4

NHANES, National Health and Nutrition Examination Survey; CHD, coronary heart disease; GI, gingival inflammation.

[a]Odds ratios adjusted as follows: logistic regression model for Diabetes adjusted for race, age, gender, body mass index (BMI), smoking (three levels) and education (three levels); logistic regression models for Heart Attack and Stroke adjusted for race, age, gender, BMI, smoking (three levels), diabetes, hypertension, education (three levels), high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol; logistic regression models for C-reactive protein (CRP) and interleukin (IL)-6 adjusted for race, age, gender, BMI, smoking (three levels), diabetes, hypertension, and education (three levels). Bold text indicates statistically significant odds ratios. CRP was only measured at one exam cycle.

[b]CHD excludes Stroke cases; stroke excludes CHD cases.

[c]Bayesian Information Criterion (BIC) (see chart end of Table 2).