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# The title page

# Unraveling the link between periodontitis and abdominal aortic calcification in the U.S. adult population: A cross-sectional study based on the NHANES 2013-2014

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## Abstract

**Objective:** We aimed to explore the association between periodontitis and abdominal aortic calcification (AAC) among a nationally representative sample of U.S. adults.

**Design:** Cross- sectional study.

**Setting:** The National Health and Nutrition Examination Survey (2013–2014).

**Participants:** A total of 2,149 participants aged 40 years or older who have complete information for periodontitis and AAC assessment test were included in this study.

**Primary and secondary outcome measures:** AAC scores can be accurately identified on lateral spine images obtained by DXA, and both the AAC-24 and AAC-8 semiquantitative scoring tools were used for AAC evaluation. Linear regression analysis was used to investigate the relationship between periodontitis and the AAC-8 and AAC-24 scores. Multivariate logistic regression models and reported odds ratios (ORs) were used to examine the relationship between periodontitis and AAC.

**Results:** The prevalence of severe periodontitis combined with severe AAC was 8.49%-8.54%. According to the AAC-8 and AAC-24 score classifications, patients with severe periodontitis had higher odds of severe AAC [AAC-8 score ≥ 3: (OR: 2.53; 95% CI 1.04, 6.17) and AAC-24 score >6: (OR: 3.60; 95% CI 1.48, 8.78)]. A positive association between mild-moderate periodontitis and severe AAC was found only when the AAC-24 score was applied (OR: 2.25; 95% CI 1.24, 4.06). In the subgroup analyses, the likelihood ratio test showed no multiplicative interaction (all P for interaction > 0.05).

**Conclusions:** The findings showed that periodontitis is associated with an increased risk of severe AAC in the U.S. population aged 40 years and older; this requires further large-scale prospective studies for confirmation.

## Strengths and limitations of this study

1. This is the first population-based cross-sectional epidemiological study to explore the link between periodontitis and AAC in a nationally representative sample of U.S. adults (40 years and older).

2. Our study fully considered socioeconomic status, behavioral factors and medical history of the participants and controlled for a wide range of confounders.

3. Given the cross-sectional design of the NHANES, it is difficult for us to determine causality, and further large-scale prospective studies are needed

4. Because of the sample size, we were not able to include the new periodontal profile class (PPC) system to precisely classify periodontal disease

# Text

## 1. Introduction

Periodontitis has become a global public health challenge and imposes serious burdens on society and health services. There have been approximately 1.1 billion prevalent cases of severe periodontitis worldwide over the past 30 years, an increase of 8.44% in age-standardized prevalence[1]. Forty-six percent of American adults aged 30 years and older have periodontitis, 8.9% of whom have severe periodontitis, which is positively associated with increasing age[2]. Periodontitis can affect the risk of systemic diseases, including cardiovascular disease (CVD)[3-4], diabetes[5], and chronic kidney disease (CKD)[6], through mechanisms such as periodontal microbial damage and inflammatory cascades, and this relationship may be causal and bidirectional. Deaths due to all causes and cause-specific causes are associated with periodontitis and its sequelae[7]. As part of its strategy, the Centers for Disease Control and Prevention (CDC) is supporting and improving periodontal disease surveillance[8].

The abdominal aorta is considered to valuable in observing early atherosclerotic calcification[9], and its degree of calcification is closely related to the prevalence of and mortality due to CVD[10]. Abdominal aortic calcification (AAC) is characterized by metabolic disorders involving minerals, such as calcium and phosphorus, and abnormal deposition in the vascular wall, which is common in patients

with chronic disease[11-12]. Some epidemiological evidence suggests that periodontitis is associated with arterial calcification at multiple sites. A Chinese cohort study showed that periodontitis increased the risk of aortic calcification and was more pronounced in men and younger participants than in women and older participants[13]. In addition, a cross-sectional study and meta-analysis suggested that periodontitis was associated with carotid calcification[14-15], and there was radiographic evidence suggesting the possible involvement of intracranial carotid calcification[16]. However, other cohort studies reported inconsistent conclusions[17-18]. In recent years, vascular calcification, including soft tissue calcification, has been recognized as an active process regulated by multiple molecular signaling pathways in response to chronic inflammatory stimuli[19]. Previous animal studies demonstrated that periodontitis and vascular calcification promoted each other[20], and the mechanisms involved were gradually revealed in subsequent studies[21-24].

An assessment of the utility of the AAC score in a 25-year cohort study of 617 Framingham Heart Study participants was conducted by Kauppila et al. using lateral lumbar radiography as the AAC grading tool (AAC score)[25]. Based on the AAC score, it is possible to assess subclinical vascular disease at a low cost, with predictive value for cardiovascular events and mortality independent of coronary calcification[26]. Therefore, using abdominal aortic calcification data obtained from dual-energy X-ray absorptiometry (DXA) in the 2013–2014 National Health and Nutrition Examination Survey (NHANES), the aim of this study was to investigate the relationship between periodontitis and AAC and propose new ideas for the prevention and management of AAC in clinical practice. We hypothesized that periodontitis would be associated with an increased prevalence of AAC.

## 2. Materials and methods

### 2.1. Data source

The current cross-sectional study analyzed data from individuals who participated in the 2013 to 2014 NHANES, which was performed by the National Center for Health Statistics (NCHS) at the CDC.

The NHANES 2013-2014 was a cross-sectional, nationally representative survey of the U.S. noninstitutionalized civilian population designed to examine demographic, socioeconomic, health, and nutritional information. To ensure a representative sample, complex multistage sampling was used to collect data, and strata were determined based on geographic location and population proportions[27].

The NHANES 2013-2014 was the only cycle that also performed examinations for periodontitis and abdominal aortic calcification. Participants ≥ 40 years of age who received a full-mouth periodontal examination and participated in lateral DXA scans of the thoraco-lumbar spine were included in this study. In the 2013-2014 cycle of the NHANES, 10,175 participants completed the survey. However, in this study, individuals aged < 40 years without complete information about periodontitis and abdominal aortic calcification were excluded (N = 7,741). Additionally, cancer participants (N = 285) were excluded from the analysis. Ultimately, 2,149 participants were included in the analysis (Figure 1). All participants provided written informed consent to participate in NHANES, and the NCHS Research Ethics Review Board approved the protocol (NCHS IRB/ERB Protocol Number: Continuation of Protocol #2011-17). The study was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting cross-sectional studies[28], and all procedures were performed in accordance with the principles of the Helsinki Declaration of 1975.

### 2.2. Definitions of periodontitis

Oral health examinations were performed by dental examiners who were licensed dentists in at least one state in the U.S. During oral health assessments, a portable dental chair, lights, and compressed air were provided in a mobile examination center (MEC). All dental examiners received standardized training and collected reliable statistical data to objectively assess examiner agreement[29].

Six measurement points were selected for periodontal examinations (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual) for all teeth, with the exception of third molars. Indicators of periodontitis included probing depth (PD) and clinical attachment loss (AL), which are important bases for the CDC/AAP classification/case definition[30]. Accordingly, periodontitis was divided into mild periodontitis, moderate periodontitis and severe periodontitis, No periodontitis was defined as no evidence of mild, moderate, or severe periodontitis. Because there were few data from those with mild periodontitis, mild periodontitis and moderate periodontitis were combined for analysis in our study.

### 2.3. Abdominal aortic calcification outcomes

AAC can be accurately identified on lateral spine images obtained by DXA and shows good sensitivity and specificity at lower radiation doses[31-32]. Those < 40 years old, pregnant, weighing over 450 pounds, or ingesting barium within the last week were ineligible for DXA scans in this study. Both the AAC-24 and AAC-8 semiquantitative scoring tools were used for AAC evaluation[25]. An assessment of the length of anterior and posterior aortic wall calcification anterior to the L1 to L4 vertebral bodies was made using the AAC-8 score, and participants with a score of three or more were considered to be at high risk for AAC. Using the L1-L4 region as a reference, the anterior and posterior aortic walls are divided into four segments to calculate the AAC-24 score. Depending on the degree of calcification, each vertebral body can receive a score from 0 to 6, with a total possible score of 0 to 24; this allows a more precise assessment of abdominal aortic calcification. We categorized AAC-24 scores into three groups: no calcification (AAC-24 score =0), mild to moderate calcification (6 ≥ AAC-24 score > 0) and severe calcification (AAC-24 score >6).

### 2.4. Covariates

Based on previous studies, we considered some confounding factors potentially associated with periodontitis and AAC in our analysis, including socioeconomic factors, behavioral factors , body mass index (BMI), medical history, and laboratory measurements[33-34].

Information about socioeconomic factors was obtained during the home interview. The poverty income ratio (PIR) was stratified into <1.3, 1.3–3.5, and >3.5, as recorded in the original survey. Behavioral factors were obtained from self-reports. A never smoker is an individual who has never smoked more than 100 cigarettes in their lifetime. Former smokers were defined as those who smoked more than 100 cigarettes in their lifetime and had quit smoking, and smokers have to smoke at least 100 cigarettes in their lifetime and smoke some days or every day to qualify as current smokers. The status of alcohol consumption was categorised as never (never drank greater than or equal to 12 drinks in their lifetime), former (greater than or equal to 12 drinks in 1 year and did not drink last year, or did not drink last year but drank ≥12 drinks in their lifetime), current mild (≤1 drink/d for female or ≤2 drink/d for male on average over the past year), current moderate (2 drink/d for female or 3 drink/d for male on average over the past year), current heavy drinkers (≥3 drink/d for female or ≥4 drink/d for male on average over the past year). BMI was measured at a MEC using standard protocols and stratified into ≥30 and <30.

Those participants who self-reported heart failure, angina, coronary heart disease, heart attack, or stroke diagnosed by a physician were classified as having CVD. The definition of hypertension was a diagnosis by a healthcare professional, an average blood pressure of ≥ 130/80 mmHg or using hypertension medications[35]. Diabetes was defined as a diagnosis made by a physician or other healthcare professional, HbA1c (%) >6.5, random blood glucose (mmol/l) ≥11.1, or use of diabetes medication or insulin. As defined by the International Renal Association, chronic kidney disease is characterized by an estimated glomerular filtration rate <60 mL/min/1.73 $m^2$ or a urine

albumin–creatinine ratio of at least 30[36]. Based on serum creatinine, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate the glomerular filtration rate[37]. Laboratory data were obtained from participant serum samples that were processed in the Collaborative Laboratory Services, Ottumwa, Iowa, for analysis. Detailed instructions regarding specimen collection and processing are documented in the NHANES Laboratory Procedures Manual, and quality control was in accordance with standard procedures.

### 2.5. Statistical analysis

A weight is assigned to the NHANES to compensate for the complex survey design, survey nonresponses, and poststratification adjustment to match the total U.S. population.. All results of this study were weighted by 2-year MEC weights. In accordance with the CDC/AAP classification of periodontitis, descriptive statistics were calculated to describe the characteristics of the participants. Continuous variables are presented as the weighted mean ± standard deviation (SD) and were compared using a one-way ANOVA, while categorical variables were compared using the Rao-Scott chi-square test and are presented as weighted percentages (95% confidence interval, 95% CI). Linear regression was used to evaluate the association of the AAC-8 score and AAC-24 score as dependent variables with periodontitis with varying degrees of severity as independent variables. Beta coefficients and 95% CIs were calculated. Multivariate logistic regression analysis was performed to evaluate the correlation between periodontitis with varying degrees of severity and AAC with varying degrees of severity using odds ratios (ORs) and 95% CIs. Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs). Subgroup analysis stratified by age, sex, CVD, hypertension, diabetes, and CKD was also

conducted using stratified multivariate regression analysis, and multiplicative interactions were assessed using likelihood ratio tests.

In this study, we used the MissForest[38] package in R software to address missing covariates. The algorithm can address categorical and continuous variables and shows superior performance. The numbers and percentages of missing covariate data are shown in Supplementary Material Table 1. Sensitivity analyses were performed as followed: (1) only participants with complete data were included, and participants with missing covariates were excluded; (2) mild and moderate periodontitis were not combined for analysis, and mild periodontitis was excluded; and (3) participants with CVD were excluded. R software (version 4.1.3) was used for all statistical analyses. It was considered statistically significant if the P value was less than 0.05 for all statistical tests of two-tailed.

### 2.6. Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## 3. Results

Descriptive statistics of our study participants by periodontitis status according to the CDC/AAP case definitions are presented in Table 1. The study included 2,149 participants, representing 86,199,511 noninstitutionalized adults (40 years and older) in the U.S. Overall, participants had a mean age±SD of 54.96 ± 0.32 years; 50.46% (44.32, 56.60) were female, and 68.14% (54.20, 82.08) were non-Hispanic white. The prevalence of mild-moderate periodontitis was 29.93 (25.36, 34.51) and that of severe periodontitis was 6.77 (5.40, 8.13). Periodontitis was more prevalent in older individuals, males, those with a low educational level, those with a low PIR, and those with low insurance coverage than in their counterparts and showed differences among races. The prevalence of mild to moderate AAC and severe AAC was significantly higher in participants with periodontitis than in those without. In addition, we also found significant differences in smoking status, alcohol consumption status, CVD,

diabetes, hypertension, CKD, albumin, total 25-hydroxyvitamin D, TGs, and HDL-C compared with participants without periodontitis (all $p < 0.05$).

**TABLE 1** General characteristics of included participants (n = 2,149) according to the periodontal status in the NHANES 2013–2014.

| Characters | Overall (n=2,149) | No Periodontitis (n=1,142) | Mild-Moderate periodontitisc (n=787) | Severe periodontitis (n=220) | P-value |
|---|---|---|---|---|---|
| **Age, year** | 54.96±0.32 | 53.84±0.47 | 57.13±0.52 | 55.78±0.73 | 0.001 |
| **Gender** | | | | | < 0.001 |
| Male | 49.54 (42.66-56.42) | 44.26 (40.95-47.57) | 56.17 (52.43-59.91) | 69.60 (62.25-76.96) | |
| Female | 50.46 (44.32,56.60) | 55.74 (52.43-59.05) | 43.83 (40.09-47.57) | 30.40 (23.04-37.75) | |
| **Race** | | | | | < 0.001 |
| Mexican American | 7.98 ( 4.63-11.32) | 5.51 (2.88-8.15) | 12.60 (6.75-18.46) | 10.53 (4.02-17.05) | |
| Non-Hispanic Black | 10.53 ( 8.69-12.36) | 7.38 ( 5.67-9.09) | 14.16 ( 9.15-19.17) | 23.88 (15.54-32.23) | |
| Non-Hispanic White | 68.14 (54.20-82.08) | 74.71 (69.73-79.70) | 57.60 (46.77-68.43) | 53.28 (42.62-63.94) | |
| Other Hispanic | 5.22 ( 3.48- 6.95) | 4.38 (2.56-6.20) | 6.79 (4.13-9.44) | 6.09 (2.77-9.41) | |
| Other race or multi-racial | 8.14 ( 6.55- 9.74) | 8.02 (6.44-9.60) | 8.85 (6.07-11.63) | 6.21 (4.11-8.31) | |
| **Education** | | | | | < 0.001 |
| Less than hight school | 14.88 (12.36-17.39) | 9.09 ( 6.59-11.59) | 22.21 (17.08-27.35) | 36.60 (27.56-45.64) | |
| Hight school | 20.80 (17.18-24.43) | 16.38 (13.54-19.21) | 27.28 (22.81-31.75) | 33.56 (26.94-40.19) | |
| Above hight school | 64.32 (52.71-75.93) | 74.54 (70.84-78.23) | 50.51 (44.66-56.35) | 29.84 (20.31-39.37) | |
| **Poverty-income ratio** | | | | | < 0.001 |
| < 1.3 | 16.84 (12.82-20.86) | 10.14 ( 7.11-13.16) | 27.38 (21.64-33.13) | 32.91 (20.83-44.99) | |
| 1.3-3.5 | 34.58 (30.67-38.50) | 29.18 (25.57-32.80) | 43.20 (38.79-47.62) | 46.98 (36.21-57.75) | |
| > 3.5 | 48.58 (38.30-58.85) | 60.68 (55.49-65.87) | 29.41 (23.79-35.03) | 20.11 (10.19-30.04) | |
| **Insurance coverage** | 84.99 (72.54-97.45) | 91.46 (88.41-94.50) | 76.37 (72.89-79.85) | 62.68 (55.51-69.85) | < 0.001 |
| **Body mass index (kg/m2)** | | | | | 0.053 |
| < 30 | 64.10 (54.77-73.44) | 66.54 (63.36-69.72) | 59.50 (53.18-65.82) | 61.67 (53.95-69.39) | |
| ≥ 30 | 35.90 (31.24-40.56) | 33.46 (30.28-36.64) | 40.50 (34.18-46.82) | 38.33 (30.61-46.05) | |
| **Smoking status** | | | | | < 0.001 |
| Now | 16.07 (13.82-18.31) | 10.48 ( 8.12-12.83) | 21.91 (18.01-25.81) | 42.48 (33.91-51.05) | |
| Former | 25.38 (20.70-30.06) | 23.00 (20.09-25.92) | 31.13 (25.05-37.20) | 22.22 (13.02-31.43) | |
| Never | 58.55 (50.16-66.94) | 66.52 (62.55-70.48) | 46.96 (42.06-51.87) | 35.30 (25.73-44.86) | |
| **Alcohol consumption status** | | | | | 0.004 |
| Never | 11.48 ( 8.45-14.51) | 11.22 ( 7.14-15.29) | 12.77 (10.23-15.30) | 8.23 ( 4.19-12.27) | |
| Former | 14.23 (11.41-17.06) | 11.54 ( 9.13-13.95) | 18.94 (15.82-22.05) | 18.63 (12.99-24.26) | |
| Mild | 40.28 (33.73-46.83) | 43.77 (39.36-48.18) | 34.64 (29.89-39.39) | 32.56 (24.85-40.26) | |
| Moderate | 18.10 (14.08-22.11) | 18.98 (16.05-21.92) | 16.60 (11.73-21.47) | 16.44 ( 9.60-23.28) | |
| Heavy | 15.91 (13.83-18.00) | 14.49 (12.30-16.68) | 17.06 (13.06-21.06) | 24.15 (16.68-31.61) | |
| **Cardiovascular diseases** | 7.43 ( 5.89-8.97) | 5.95 (4.53-7.38) | 10.68 (7.93-13.43) | 6.88 (3.11-10.65) | 0.004 |
| **Hypertension** | 56.64 (50.33-62.94) | 52.31 (48.43-56.19) | 63.24 (59.08-67.39) | 67.92 (61.80-74.05) | < 0.001 |
| **Diabetes** | 14.06 (12.22-15.91) | 10.83 ( 8.78-12.87) | 21.13 (18.83-23.43) | 13.04 ( 7.94-18.15) | < 0.001 |
| **Chronic kidney disease** | 14.66 (12.77-16.55) | 12.21 (10.24-14.19) | 19.73 (17.14-22.31) | 15.13 (10.15-20.11) | < 0.001 |
| **AAC-8 score** | | | | | 0.001 |
| < 3 | 94.86 (83.16-100.00) | 96.68 (95.23-98.13) | 91.78 (89.31-94.25) | 91.51 (86.26-96.76) | |
| ≥ 3 | 5.14 ( 3.60-6.68) | 3.32 (1.87-4.77) | 8.22 (5.75-10.69) | 8.49 (3.24-13.74) | |
| **AAC-24 score** | | | | | < 0.001 |
| 0 | 75.67 (64.85-86.49) | 77.77 (74.00-81.53) | 73.24(67.18-79.30) | 66.81(59.03-74.58) | |
| 1-6 | 19.55 (15.84-23.26) | 19.38 (15.83-22.93) | 18.75(14.07-23.43) | 24.65(17.37-31.93) | |
| > 6 | 4.78 ( 3.66-5.90) | 2.85 (1.95-3.76) | 8.01(5.59-10.42) | 8.54(4.04-13.04) | |
| **Laboratory measurements** | | | | | |
| Albumin (g/dL) | 4.27±0.01 | 4.30±0.01 | 4.21±0.02 | 4.20±0.02 | < 0.001 |
| Serum calcium (mg/dL) | 9.45±0.01 | 9.45±0.01 | 9.43±0.02 | 9.45±0.03 | 0.414 |
| Serum phosphorus (mg/dL) | 3.79±0.02 | 3.81±0.03 | 3.75±0.02 | 3.78±0.04 | 0.083 |
| Uric acid (mg/dL) | 5.37±0.03 | 5.29±0.03 | 5.53±0.08 | 5.42±0.13 | 0.063 |
| Total 25-hydroxyvitamin D (nmol/L) | 73.44±1.18 | 76.90±1.44 | 68.78±1.58 | 61.71±2.42 | < 0.001 |
| Hemoglobin (g/dL) | 14.19±0.04 | 14.15±0.04 | 14.20±0.08 | 14.42±0.11 | 0.097 |

| | | | | | |
|---|---|---|---|---|---|
| Total cholesterol (mg/dL) | 196.56±0.99 | 195.79±1.15 | 197.98±2.45 | 197.48±3.31 | 0.722 |
| High-density lipoprotein cholesterol (mg/dL) | 54.67±0.60 | 56.42±0.73 | 51.79±0.70 | 50.99±1.19 | < 0.001 |
| Triglycerides (mg/dL) | 162.83±3.69 | 152.54± 3.39 | 182.64± 9.60 | 171.49±13.54 | 0.015 |

Note: Values indicate the weighted mean ± SD or weighted % (95% confidence interval). P-values are weighted. AAC, abdominal aortic calcification.

Table 2 shows the relationships between periodontitis and the AAC-8 score and AAC-24 score in the linear regression analysis. In Model 1, which was adjusted for age, sex, and race, severe periodontitis showed a significant positive correlation with the AAC-8 (β: 0.29; 95% CI 0.08, 0.50) and AAC-24 (β: 0.80; 95% CI 0.25, 1.34) scores compared with no periodontitis. However, the association disappeared in the subsequent models adjusted for additional covariates. In addition, no correlation was found between mild-moderate periodontitis and the AAC-8 score or AAC-24 score.

**TABLE 2** Weighted linear regression coefficients (β) and 95% confidence intervals for periodontal status and AAC score : The United States, 2013 to 2014

| | Case/participants | Model 1<br>β (95% CI), P- value | Model 2<br>β (95% CI), P- value | Model 3<br>β (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score** | | | | |
| No periodontitis | 1142/2149 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 787/2149 | 0.11(-0.05,0.28)<br>P=0.149 | 0.03(-0.11,0.17)<br>P=0.643 | 0.02(-0.12,0.17)<br>P=0.740 |
| Severe periodontitis | 220/2149 | **0.29( 0.08,0.50)**<br>**P=0.015** | 0.17(-0.07,0.41)<br>P=0.159 | 0.17(-0.08,0.41)<br>P=0.173 |
| **AAC-24 score** | | | | |
| No periodontitis | 1142/2149 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 787/2149 | 0.34(-0.10,0.78)<br>P=0.110 | 0.15(-0.22,0.52)<br>P=0.393 | 0.14(-0.26,0.54)<br>P=0.472 |
| Severe periodontitis | 220/2149 | **0.80( 0.25,1.34)**<br>**P=0.011** | 0.57(-0.01,1.14)<br>P=0.052 | 0.58(-0.02,1.17)<br>P=0.056 |

Note: Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. AAC: abdominal aortic calcification.

Table 3 presents the association between periodontitis and AAC based on the multivariate logistic regression analysis. In fully adjusted Model 3, severe periodontitis was positively associated with AAC

in the high-AAC risk group (AAC-8 score ≥ 3 points) (OR: 2.53; 95% CI 1.04, 6.17) compared with the low-AAC risk group (AAC-8 score < 3 points). The degree of periodontitis and AAC as defined by the more refined AAC-24 score were further analyzed. Mild-moderate and severe periodontitis were associated with an increased prevalence of severe AAC (OR: 2.25; 95% CI 1.24, 4.06 and OR: 3.60; 95% CI 1.48, 8.78) relative to participants without AAC. Furthermore, this association remained when participants with mild-moderate AAC were replaced with a reference population; mild-moderate and severe periodontitis were associated with severe AAC (OR: 2.28; 95% CI 1.28, 4.06 and OR: 2.93; 95% CI 1.28, 6.69). In addition, no correlation was found between periodontitis and mild-moderate AAC.

**TABLE 3** Weighted multiple logistic regression coefficients (ORs) and 95% confidence intervals for the association between periodontal status with AAC group: The United States, 2013 to 2014

| | Case/participants | Model 1<br>OR (95% CI), P- value | Model 2<br>OR (95% CI), P- value | Model 3<br>OR (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score ≥ 3 points versus AAC-8 score < 3 points** | | | | |
| No periodontitis | 46/1142 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 66/787 | **2.07(1.01,4.22)**<br>**P=0.047** | 1.79(0.95,3.38)<br>P=0.069 | 1.84(1.00,3.40)<br>P=0.051 |
| Severe periodontitis | 19/220 | **3.20(1.22,8.40)**<br>**P=0.025** | **2.53(1.05,6.11)**<br>**P=0.040** | **2.53(1.04,6.17)**<br>**P=0.043** |
| **Mild–moderate AAC versus no AAC** | | | | |
| No periodontitis | 224/1102 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 144/723 | 0.89(0.58,1.38)<br>P=0.561 | 0.76(0.53,1.08)<br>P=0.113 | 0.72(0.51,1.02)<br>P=0.061 |
| Severe periodontitis | 50/200 | 1.46(0.79,2.68)<br>P=0.185 | 1.05(0.52,2.10)<br>P=0.886 | 0.96(0.48,1.93)<br>P=0.914 |
| **Severe AAC versus no AAC** | | | | |
| No periodontitis | 40/918 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 64/643 | **2.57(1.35, 4.89)**<br>**P=0.010** | **2.19(1.23,3.89)**<br>**P=0.011** | **2.25(1.24,4.06)**<br>**P=0.011** |
| Severe periodontitis | 20/170 | **6.13(2.55,14.72)**<br>**P=0.002** | **3.62(1.63,8.06)**<br>**P=0.004** | **3.60(1.48,8.78)**<br>**P=0.008** |
| **Severe AAC versus mild–moderate AAC** | | | | |
| No periodontitis | 40/264 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 64/208 | **2.59(1.49,4.52)**<br>**P=0.005** | **2.20(1.27,3.80)**<br>**P=0.008** | **2.28(1.28, 4.06)**<br>**P=0.008** |
| Severe periodontitis | 20/70 | **3.16(1.21,8.22)**<br>**P=0.025** | **2.89(1.27,6.60)**<br>**P=0.015** | **2.93(1.28, 6.69)**<br>**P=0.014** |

Note: Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total

25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. No AAC, mild–moderate AAC and Severe AAC were defined by AAC-24 score. AAC: abdominal aortic calcification.

In the subgroup analysis (Table 4), we investigated the association between periodontitis and severe AAC based on an AAC-8 score ≥ 3. We found that the likelihood ratio test for multiplicative interactions was not statistically significant for age, sex, CVD, hypertension, diabetes, or CKD after adjustment for potential confounders (P interaction > 0.05). Thus, we did not find any substantial evidence to demonstrate systematic differences in associations between different subpopulations in the population, indicating that our main results were stable.

**TABLE 4** Subgroup analysis for the association between periodontal status and risk of severe AAC (AAC-8 score ≥ 3 points).

| | **Periodontal status OR (95% CI), P- value** | | | |
|---|---|---|---|---|
| | No periodontitis | Mild–moderate periodontitis | Severe periodontitis | P for interaction |
| **Age** | | | | 0.212 |
| ≥60y | Reference | 1.90(0.88,4.11) P=0.096 | **5.66(1.15,27.92) P=0.035** | |
| <60y | Reference | 3.44(0.83,14.15) P=0.083 | 1.58(0.24,10.43) P=0.611 | |
| **Gender** | | | | 0.207 |
| Male | Reference | 1.90(0.55,6.56) P=0.285 | **4.40(1.09,17.85) P=0.039** | |
| Female | Reference | **2.37(1.42,3.93) P=0.003** | 0.92(0.29,2.94) P=0.876 | |
| **Cardiovascular diseases** | | | | 0.381 |
| Yes | Reference | 1.61(0.31,8.35) P=0.548 | NA* | |
| No | Reference | **1.95(1.02,3.73) P=0.044** | 2.14(0.86,5.35) P=0.096 | |
| **Diabetes** | | | | 0.837 |
| Yes | Reference | **4.00(1.49,10.69) P=0.009** | **9.64(1.45,64.16)* P=0.022** | |
| No | Reference | 1.51(0.67,3.40) P=0.293 | 2.21(0.76,6.44) P=0.136 | |
| **Hypertension** | | | | 0.085 |
| Yes | Reference | 1.81(0.88, 3.74) P=0.099 | **3.39(1.35, 8.56) P=0.013** | |
| No | Reference | **3.27(1.08, 9.91) P=0.037** | 0.73(0.08, 6.72) P=0.767 | |
| **Chronic kidney disease** | | | | 0.501 |
| Yes | Reference | **2.20(1.15, 4.21) P=0.021** | 1.57(0.22, 11.17) P=0.630 | |
| No | Reference | 1.81(0.79, 4.12) | **2.98(1.21, 7.34)** | |

| | | |
|---|---|---|
| | P=0.147 | **P=0.020** |

Note: All presented covariates were adjusted (as Model 3) except the corresponding stratification variable. *Wide CI and no production OR are due to the small sample size for this comparison.

In the primary study, we imputed missing covariates (the proportions of all missing variables were less than 5.00% except for the PIR, at 8.19%) using the MissForest package. The random forest analysis had a seed number of 500 and completed data imputation after eight iterations. Model performance indicators normalized root mean squared error computed (NRMSE) was 0.578 and proportion of falsely classified (PFC) was 0.336. In the sensitivity analysis, we excluded participants with missing covariates, and we included 1,818 individuals with complete data in the subsequent analyses. The baseline distribution of participant characteristics did not differ significantly from that in the previously included population, but it was worth mentioning that the prevalence of severe AAC with severe periodontitis have decreased by approximately 1% (Supplementary Material Table 2). Further logistic regression analysis showed, our result regarding the association of periodontitis and AAC differed from that in the primary analysis. In Model 3, only mild-moderate periodontitis was associated with an increased risk of severe AAC (OR: 1.89; 95% CI 1.01, 3.56), and the remaining associations were attenuated or had disappeared (Supplementary Material Table 3). When we decoupled mild-moderate periodontitis and excluded participants with mild periodontitis, the results of the sensitivity analysis were similar to those of the main analysis (Supplementary Material Table 4). It is worth mentioning that mild-moderate periodontitis was associated with a reduced prevalence of mild to moderate AAC in participants without CVD, and the association of severe periodontitis with AAC in the high-AAC risk group (AAC-8 scores ≥ 3 points) disappeared (Supplementary Material Table 5).

## 4. Discussion

To our knowledge, this is the first population-based cross-sectional epidemiological study to explore the link between periodontitis and AAC in a nationally representative sample of U.S. adults

(40 years and older). Our study fully considered socioeconomic status, behavioral factors and medical history of the participants and controlled for a wide range of confounders. Severe periodontitis was positively associated with severe AAC, defined by either the AAC-8 score or AAC-24 score. A positive association between mild to moderate periodontitis and severe AAC was found only when AAC was classified by the AAC-24 score. In the subgroups stratified by age; sex; and CVD, hypertension, diabetes, and CKD status, this association and the main results were generally consistent; the only difference was associated with the different severities of periodontitis, which differed in their associations with severe AAC in the stratified population. Linear regression evaluation of the AAC-8 score and AAC-24 score as dependent variables and the different severities of periodontitis as independent variables showed no linear correlation. In the sensitivity analysis, the association remained significant after excluding participants with mild periodontitis and CVD. However, the association was no longer significant after excluding participants with missing covariates.

To date, some epidemiological studies have suggested a close relationship between periodontitis and vascular calcification or CVD. A consensus report on periodontitis and CVD states that periodontitis is broadly associated with CVD and that the link is bidirectional; CVD drives the progression of periodontitis and vice versa[39]. NHANES-based cross-sectional studies have shown an association between periodontitis severity and cardiovascular risk[4], as demonstrated by the results of a 13-year cohort study, and further studies suggest that periodontitis may be an independent risk factor for CVD[40]. Oindrila Paul et al. reviewed the pathophysiology of periodontitis and showed that inflammation associated with periodontitis may be the main mechanism affecting CVD and could be facilitated by common risk factors[41]. Vascular calcification has been shown to involve soft tissue calcification also caused by chronic inflammatory stimuli[19] and is closely related to the prevalence and prognosis of CVD. This may suggest that the association between periodontitis and CVD may depend on the severity of vascular calcification. The results of a cross-sectional Japanese population-based

study suggest that measuring alveolar bone loss on panoramic radiographs may be an effective method to identify an increased risk of carotid artery calcification[14]. Imaging studies using cone-beam computed tomography have further confirmed that the development of periodontitis may cause calcification involving the intracranial carotid arteries[16]. The results from a meta-analysis that included 12 studies also revealed a significant relationship between periodontitis and carotid artery calcification[15]. Similar to our findings, a cohort study in Chinese populations suggested that periodontitis was also positively associated with aortic calcification, and this association was more pronounced in men and in participants younger than 65 years[13].

The exact mechanism of the link between periodontitis and AAC remains unclear and needs to be further explored. Existing mainstream views suggest that *Porphyromonas gingivalis* (*P. gingivalis*) infection and chronic inflammation are important bridges between periodontitis and vascular calcification[19, 41-42]. Recent studies have shown that periodontal pathogens can be detected in the blood of patients with coronary heart disease, and it is hypothesized that periodontal pathogens can spread through the blood to other parts of the body, where they may enhance inflammatory processes, leading to the development or aggravation of atherosclerosis[43]. Evidence from in vitro cell culture studies suggests that *P. gingivalis* infection accelerates phosphate-induced calcification of vascular smooth muscle cells[22] and that *P. gingivalis* lipopolysaccharide increases alkaline phosphatase activity and upregulates the expression of genes involved in calcification to stimulate calcification[44]. In addition, it has been shown that *P. gingivalis* invasiveness is enhanced after high-glucose treatment, and vascular calcification can be initiated by stimulating autocrine regulation of bone morphogenetic protein 4 in aortic smooth muscle cells[21]. *P. gingivalis* infection elicits an inflammatory response in the host, which is in line with the definition of periodontitis as a chronic inflammatory disease. A meta-analysis suggested that the diagnosis of chronic aggressive periodontitis was consistently associated with higher C-reactive protein and high-sensitivity C-reactive protein levels, and treatment reduced serum C-

reactive protein levels[45]. In addition, studies have observed an association between periodontitis and systemic inflammation, which increases with the severity of periodontal disease[46]. Notably, there are studies revealing other possible mechanisms involved in the link between periodontitis and vascular calcification, including the activation of osteoprotegerin/receptor activator of nuclear factor-κB ligand and endoplasmic reticulum stress-induced apoptosis[23-24].

Our study has several important strengths. Our findings were derived from a large nationwide random sample survey and can be generalized to the adult noninstitutionalized population in the U.S. Periodontitis and AAC were defined based on objective clinical data collected by calibrated professionals. In addition, this study addressed a number of known potential confounders, and sample weights were applied in each analysis following the NHANES guidelines to account for the complex survey design. However, several limitations of this study warrant attention. Given the cross-sectional design of the NHANES, it is difficult for us to determine causality, and further large-scale prospective studies are needed. In addition, we cannot exclude the possibility of residual confounding by other confounding factors related to oral health, which could have influenced the observed results. It is worth noting that only a small proportion of patients with severe periodontitis in our study had severe AAC; perhaps because of this, the results of the sensitivity analysis excluding patients with missing covariates were not robust. This also suggests that the conclusions of this study should be interpreted with caution. An explanation for this phenomenon is the possibility of selection bias[47]. In addition, tooth loss is not considered in the CDC/AAP case definition of periodontitis; therefore, the prevalence of the disease may be underestimated[30]. Because of the sample size, we were not able to include the new periodontal profile class (PPC) system to precisely classify periodontal disease because this classification method classifies periodontitis into seven categories: PPC-A to PPC-G[48].

## 5. Conclusion

Our study suggests that periodontitis is associated with an increased risk of severe AAC in the U.S. population aged 40 years and older. The associations investigated in this study are credible due to their cross-sectional nature, but these findings require further large-scale prospective studies to confirm.

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**Contributors**

KK, AnA and AiA participated in the design of the study, analysis of the data and drafted the manuscript or revised it for important content. RR collected and organized data. XM and Y-TM contributed to the conception and design of the manuscript as well as reviewing critical modifications for important intellectual content.

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**Competing interests**

None declared.

**Patient consent for publication**

The participants provided written informed consent to participate in the NHANES survey.

**Ethics approval**

The present study complied with the term of the Declaration of Helsinki and was approved by the NCHS Research Ethics Review Committee (NCHS IRB/ERB Protocol Number: Continuation of Protocol #2011-17).

**Data availability statement**

This study is a secondary analysis based on a publicly available database and the raw data can be found on the website: https://www.cdc.gov/nchs/nhanes/index.htm

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# Figure legends

Figure 1. Flow chart of eligible National Health and Nutrition Examination Survey (NHANES) participants included in this study.

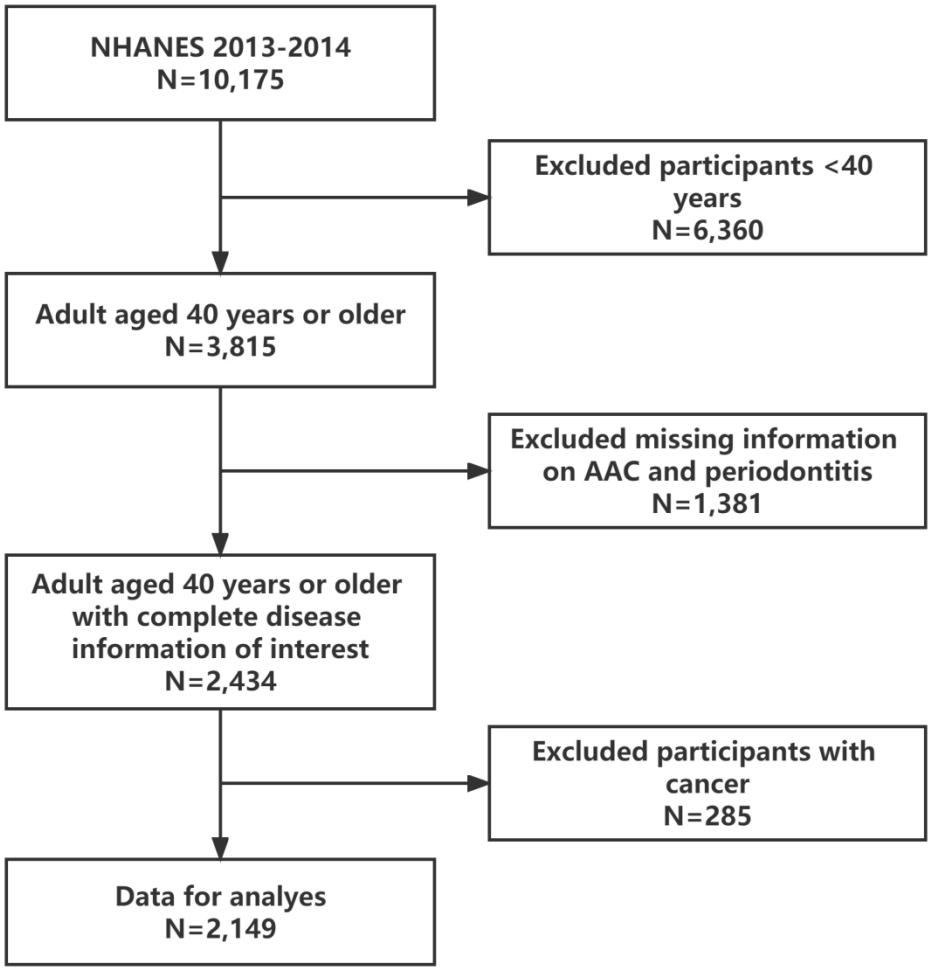


Figure 1. Flow chart of eligible National Health and Nutrition Examination Survey (NHANES) participants included in this study.

655x679mm (72 x 72 DPI)

# Supplementary Material

**TABLE 1** The numbers and percentages of missing covariate data

| Covariate | Numbers | Percentages (%) |
|---|---|---|
| Education | 1 | 0.05 |
| Poverty-income ratio | 176 | 8.19 |
| Body mass index | 6 | 0.28 |
| Smoking status | 2 | 0.09 |
| Alcohol consumption status | 97 | 4.51 |
| Cardiovascular diseases | 1 | 0.05 |
| Chronic kidney disease | 52 | 2.42 |
| Albumin | 58 | 2.70 |
| Serum calcium | 72 | 3.35 |
| Serum phosphorus | 59 | 2.75 |
| Uric acid | 60 | 2.79 |
| Total 25-hydroxyvitamin D | 49 | 2.28 |
| Hemoglobin | 38 | 1.77 |
| Total cholesterol | 53 | 2.47 |
| High-density lipoprotein cholesterol | 53 | 2.47 |
| Triglycerides | 60 | 2.79 |

**TABLE 2** General characteristics of included participants (n = 1,818) according to the periodontal status in the NHANES 2013–2014 (excluded participants with missing covariates).

| Characters | Overall (n=1,818) | No Periodontitis (n=977) | Mild-Moderate periodontitisc (n=661) | Severe periodontitis (n=180) | P-value |
|---|---|---|---|---|---|
| **Age, year** | 55.19±0.33 | 54.01±0.46 | 57.70±0.57 | 55.36±0.69 | < 0.001 |
| **Gender** | | | | | < 0.001 |
| Male | 50.34 (43.00-57.67) | 45.25 (41.74-48.75) | 57.01 (52.84-61.19) | 69.00 (60.78-77.22) | |
| Female | 49.66 (43.17-56.16) | 54.75 (51.25-58.26) | 42.99 (38.81-47.16) | 31.00 (22.78-39.22) | |
| **Race** | | | | | < 0.001 |
| Mexican American | 7.64 ( 4.29-10.99) | 5.37 (2.90- 7.83) | 12.37 (6.12-18.62) | 8.40 (2.34-14.45) | |
| Non-Hispanic Black | 9.81 ( 8.10-11.53) | 7.07 ( 5.36- 8.78) | 12.69 ( 8.36-17.02) | 23.04 (14.37-31.72) | |
| Non-Hispanic White | 69.93 (55.21-84.66) | 75.53 (70.47-80.58) | 60.66 (49.90-71.41) | 57.80 (45.71-69.90) | |
| Other Hispanic | 4.87 ( 3.34- 6.40) | 4.10 (2.37-5.83) | 6.45 (3.97-8.92) | 5.27 (1.70-8.84) | |
| Other race or multi-racial | 7.74 ( 6.20- 9.28) | 7.94 (6.34- 9.54) | 7.83 (4.98-10.68) | 5.48 (2.78- 8.18) | |
| **Education** | | | | | < 0.001 |
| Less than hight school | 13.49 (10.82-16.16) | 7.91 ( 5.25-10.56) | 20.34 (14.62-26.06) | 36.09 (26.10-46.08) | |
| Hight school | 21.25 (16.88-25.62) | 16.12 (12.81-19.42) | 29.19 (23.88-34.51) | 34.89 (27.67-42.12) | |
| Above hight school | 65.26 (52.75-77.76) | 75.98 (71.61-80.34) | 50.47 (44.14-56.80) | 29.02 (17.31-40.72) | |
| **Poverty-income ratio** | | | | | < 0.001 |
| < 1.3 | 17.53 (12.79-22.26) | 10.69 ( 7.03-14.35) | 28.23 (21.62-34.84) | 35.11 (21.93-48.30) | |
| 1.3-3.5 | 32.60 (28.53-36.67) | 26.79 (22.77-30.80) | 42.48 (37.54-47.42) | 44.16 (33.74-54.59) | |
| > 3.5 | 49.88 (38.79-60.96) | 62.52 (56.61-68.44) | 29.29 (23.25-35.33) | 20.73 ( 9.98-31.48) | |
| **Insurance coverage** | 85.84 (72.59-99.10) | 92.31 (89.14-95.48) | 77.09 (73.42-80.77) | 63.27 (55.48-71.07) | < 0.001 |
| **Body mass index (kg/m2)** | | | | | 0.051 |
| < 30 | 63.56 (53.32-73.81) | 66.24 (62.27-70.22) | 58.38 (52.44-64.31) | 60.96 (51.39-70.54) | |
| ≥ 30 | 36.44 (31.69-41.18) | 33.76 (29.78-37.73) | 41.62 (35.69-47.56) | 39.04 (29.46-48.61) | |
| **Smoking status** | | | | | < 0.001 |
| Now | 16.29 (13.83-18.75) | 10.56 ( 7.95-13.16) | 22.14 (18.08-26.19) | 44.56 (34.80-54.33) | |
| Former | 25.66 (20.34-30.98) | 22.66 (19.38-25.94) | 32.94 (26.12-39.75) | 22.22 (12.52-31.92) | |
| Never | 58.05 (49.27-66.83) | 66.79 (62.21-71.36) | 44.93 (39.88-49.98) | 33.22 (22.02-44.41) | |
| **Alcohol consumption status** | | | | | 0.018 |
| Never | 10.71 ( 7.52-13.90) | 10.61 (6.27-14.94) | 11.70 (9.07-14.33) | 7.42 (3.00-11.83) | |
| Former | 14.43 (11.55-17.31) | 11.67 ( 9.23-14.11) | 19.33 (16.24-22.41) | 19.08 (13.23-24.92) | |
| Mild | 40.15 (32.54-47.76) | 43.22 (37.75-48.68) | 35.28 (29.93-40.63) | 32.53 (24.03-41.03) | |
| Moderate | 18.73 (14.49-22.97) | 19.72 (16.57-22.87) | 17.18 (11.48-22.88) | 16.25 ( 8.35-24.15) | |
| Heavy | 15.98 (13.25-18.70) | 14.79 (11.82-17.77) | 16.51 (11.81-21.21) | 24.73 (16.17-33.29) | |
| **Cardiovascular diseases** | 7.82 ( 6.33- 9.32) | 6.24 (5.05- 7.44) | 11.38 (8.50-14.26) | 7.24 (2.99-11.48) | 0.003 |
| **Hypertension** | 56.45 (49.84-63.06) | 52.01 (47.49-56.52) | 63.21 (58.69-67.74) | 68.69 (63.15-74.24) | < 0.001 |
| **Diabetes** | 14.17 (11.92-16.43) | 10.97 ( 9.01-12.93) | 21.37 (18.55-24.19) | 12.97 ( 7.27-18.67) | < 0.001 |
| **Chronic kidney disease** | 14.93 (12.73-17.13) | 12.57 (10.40-14.75) | 19.74 (16.90-22.59) | 16.15 (10.83-21.47) | < 0.001 |
| **AAC-8 score** | | | | | 0.005 |
| < 3 | 94.75 (82.27-107.22) | 96.32 (94.70-97.94) | 91.82 (89.49-94.15) | 92.69 (88.05-97.32) | |
| ≥ 3 | 5.25 ( 3.65- 6.86) | 3.68 (2.06- 5.30) | 8.18 (5.85-10.51) | 7.31 (2.68-11.95) | |
| **AAC-24 score** | | | | | 0.004 |
| 0 | 75.38 (64.00-86.75) | 77.23 (73.37-81.09) | 73.27 (67.34-79.21) | 67.15 (58.31-76.00) | |
| 1-6 | 19.79 (15.77-23.82) | 19.62 (15.94-23.31) | 18.85 (14.06-23.64) | 25.48 (17.29-33.67) | |
| > 6 | 4.83 ( 3.85- 5.81) | 3.15 (2.14- 4.16) | 7.88 (5.61-10.15) | 7.37 (2.91-11.83) | |
| **Laboratory measurements** | | | | | |
| Albumin (g/dL) | 4.27±0.01 | 4.29±0.02 | 4.22±0.02 | 4.20±0.03 | 0.001 |
| Serum calcium (mg/dL) | 9.45±0.01 | 9.45±0.01 | 9.43±0.02 | 9.47±0.03 | 0.573 |
| Serum phosphorus (mg/dL) | 3.79±0.02 | 3.81±0.03 | 3.74±0.02 | 3.77±0.03 | 0.096 |
| Uric acid (mg/dL) | 5.37±0.04 | 5.29±0.04 | 5.54±0.10 | 5.45±0.14 | 0.126 |
| Total 25-hydroxyvitamin D (nmol/L) | 73.21±1.48 | 76.57±1.85 | 68.88±1.87 | 60.62±2.46 | < 0.001 |
| Hemoglobin (g/dL) | 14.21±0.04 | 14.17±0.04 | 14.23±0.09 | 14.44±0.12 | 0.114 |
| Total cholesterol (mg/dL) | 195.97±1.04 | 195.69±1.29 | 196.00±1.97 | 198.53±3.98 | 0.828 |
| High-density lipoprotein cholesterol (mg/dL) | 54.62±0.70 | 56.58±0.85 | 51.33±0.75 | 50.60±1.43 | < 0.001 |
| Triglycerides (mg/dL) | 160.21±3.40 | 152.06± 4.25 | 174.33± 4.71 | 175.34±16.35 | 0.011 |

Values indicate the weighted mean ± SD or weighted % (95% confidence interval). P-values are weighted. AAC, abdominal aortic calcification

**TABLE 3** Weighted multiple logistic regression coefficients (ORs) and 95% confidence intervals for the association between periodontal status with AAC group: The United States, 2013 to 2014 (exclude participants with missing covariates)

| | Case/participants | Model 1<br>OR (95% CI), P- value | Model 2<br>OR (95% CI), P- value | Model 3<br>OR (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score ≥ 3 points versus AAC-8 score < 3 points** | | | | |
| No periodontitis | 44/977 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 57/661 | 1.72(0.84,3.54)<br>p=0.116 | 1.53(0.81,2.88)<br>p=0.171 | 1.56(0.83,2.92)<br>p=0.153 |
| Severe periodontitis | 15/180 | 2.44(0.96,6.21)<br>p=0.059 | 1.80(0.81,4.00)<br>p=0.137 | 1.80(0.77,4.22)<br>p=0.160 |
| **Mild–moderate AAC versus no AAC** | | | | |
| No periodontitis | 224/939 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 144/607 | 0.87(0.58,1.31)<br>p=0.439 | 0.71(0.50,1.02)<br>p=0.060 | 0.69(0.49,0.97)<br>p=0.033 |
| Severe periodontitis | 50/164 | 1.52(0.78,2.96)<br>p=0.181 | 1.06(0.49,2.30)<br>p=0.869 | 0.99(0.46,2.10)<br>p=0.972 |
| **Severe AAC versus no AAC** | | | | |
| No periodontitis | 38/784 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 54/538 | **2.11(1.10, 4.05)**<br>**p=0.030** | **1.89(1.02, 3.50)**<br>**p=0.044** | **1.89(1.01, 3.56)**<br>**p=0.048** |
| Severe periodontitis | 16/139 | **5.22(1.85,14.76)**<br>**p=0.007** | **2.81(1.06, 7.42)**<br>**p=0.038** | 2.73(0.92, 8.13)<br>p=0.068 |
| **Severe AAC versus mild–moderate AAC** | | | | |
| No periodontitis | 38/231 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 54/177 | **2.20(1.20,4.04)**<br>**p=0.018** | 1.82(0.98,3.39)<br>p=0.059 | 1.87(0.96, 3.66)<br>p=0.065 |
| Severe periodontitis | 16/57 | 2.41(0.79,7.29)<br>p=0.103 | 1.85(0.78,4.38)<br>p=0.147 | 1.85(0.75, 4.60)<br>p=0.168 |

Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. No AAC, mild–moderate AAC and Severe AAC were defined by AAC-24 score. AAC: abdominal aortic calcification.

**TABLE 4** Weighted multiple logistic regression coefficients (ORs) and 95% confidence intervals for the association between periodontal status (exclude participants with mild periodontitis) with AAC group: The United States, 2013 to 2014

| | Case/participants | Model 1<br>OR (95% CI), P- value | Model 2<br>OR (95% CI), P- value | Model 3<br>OR (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score ≥ 3 points versus AAC-8 score < 3 points** | | | | |
| No periodontitis | 34/1142 | Reference | Reference | Reference |
| Moderate periodontitis | 53/773 | 1.94(0.86,4.40)<br>P=0.096 | 1.68(0.82,3.46)<br>P=0.147 | 1.73(0.87,3.42)<br>P=0.109 |
| Severe periodontitis | 14/220 | **3.12(1.17,8.36)**<br>**P=0.029** | **2.44(1.02,6.00)**<br>**P=0.046** | **2.44(1.01,6.05)**<br>**P=0.048** |
| **Mild–moderate AAC versus no AAC** | | | | |
| No periodontitis | 224/1102 | Reference | Reference | Reference |
| Moderate periodontitis | 141/711 | 0.90(0.57,1.41)<br>P=0.587 | 0.75(0.52,1.09)<br>P=0.121 | 0.72(0.50,1.03)<br>P=0.069 |
| Severe periodontitis | 50/200 | 1.46(0.80,2.68)<br>P=0.184 | 1.05(0.52,2.11)<br>P=0.881 | 0.96(0.48,1.94)<br>P=0.906 |
| **Severe AAC versus no AAC** | | | | |
| No periodontitis | 40/918 | Reference | Reference | Reference |
| Moderate periodontitis | 62/632 | **2.37(1.07, 5.22)**<br>**P=0.036** | 1.97(0.96,4.06)<br>P=0.063 | **2.03(1.02,4.03)**<br>**P=0.044** |
| Severe periodontitis | 20/170 | **6.02(2.44,14.86)**<br>**P=0.002** | **3.49(1.53,7.97)**<br>**P=0.006** | **3.48(1.42,8.54)**<br>**P=0.010** |
| **Severe AAC versus mild–moderate AAC** | | | | |
| No periodontitis | 40/264 | Reference | Reference | Reference |
| Moderate periodontitis | 62/203 | **2.47(1.23,4.96)**<br>**P=0.018** | **2.10(1.08,4.07)**<br>**P=0.031** | **2.17(1.09, 4.32)**<br>**P=0.030** |
| Severe periodontitis | 20/70 | **3.10(1.15,8.32)**<br>**P=0.030** | **2.76(1.16,6.57)**<br>**P=0.025** | **2.75(1.14, 6.63)**<br>**P=0.027** |

Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. No AAC, mild–moderate AAC and Severe AAC were defined by AAC-24 score. AAC: abdominal aortic calcification.

**TABLE 5** Weighted multiple logistic regression coefficients (ORs) and 95% confidence intervals for the association between periodontal status with AAC group: The United States, 2013 to 2014 (exclude participants with cardiovascular diseases)

| | Case/participants | Model 1<br>OR (95% CI), P- value | Model 2<br>OR (95% CI), P- value | Model 3<br>OR (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score ≥ 3 points versus AAC-8 score < 3 points** | | | | |
| No periodontitis | 34/1066 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 53/692 | 2.25(0.98,5.17)<br>P= 0.054 | 1.90(0.95,3.81)<br>P=0.067 | **1.95(1.02,3.73)**<br>**P=0.044** |
| Severe periodontitis | 14/202 | **3.27(1.26,8.48)**<br>**P=0.022** | 2.18(0.88,5.45)<br>P=0.088 | 2.14(0.86,5.35)<br>P=0.096 |
| **Mild–moderate AAC versus no AAC** | | | | |
| No periodontitis | 208/1038 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 118/639 | 0.83(0.52,1.32)<br>P=0.371 | **0.68(0.47,0.99)**<br>**P=0.049** | **0.65(0.45,0.94)**<br>**P=0.026** |
| Severe periodontitis | 44/187 | 1.33(0.70,2.51)<br>P=0.330 | 0.90(0.41,1.95)<br>P=0.774 | 0.83(0.38,1.81)<br>P=0.618 |
| **Severe AAC versus no AAC** | | | | |
| No periodontitis | 28/858 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 53/574 | **3.17(1.61, 6.26)**<br>**P=0.005** | **2.62(1.44, 4.76)**<br>**P=0.004** | **2.71(1.49, 4.93)**<br>**P=0.003** |
| Severe periodontitis | 15/158 | **6.00(2.47,14.57)**<br>**P=0.002** | **3.00(1.31, 6.87)**<br>**P=0.013** | **2.89(1.13, 7.40)**<br>**P=0.029** |
| **Severe AAC versus mild–moderate AAC** | | | | |
| No periodontitis | 28/236 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 53/171 | **3.17(1.73, 5.80)**<br>**P=0.003** | **2.99(1.68, 5.32)**<br>**P=0.001** | **3.16(1.75, 5.69)**<br>**P<0.001** |
| Severe periodontitis | 15/59 | **3.79(1.38,10.43)**<br>**P=0.017** | **3.82(1.42,10.27)**<br>**P=0.011** | **3.75(1.32,10.60)**<br>**P=0.016** |

Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. No AAC, mild–moderate AAC and Severe AAC were defined by AAC-24 score. AAC: abdominal aortic calcification.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

| | Item No | Recommendation | Page number and Line number |
|---|---|---|---|
| **Title and abstract** | 1 ✓title+abstract | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1-2<br>Line 2-4; 15-36 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 1-2<br>Line 2-4; 15-36 |
| **Introduction** | | | |
| Background/rationale | 2 ✓ introduction | Explain the scientific background and rationale for the investigation being reported | Page 3-4<br>Line 47-73 |
| Objectives | 3 ✓ introduction | State specific objectives, including any prespecified hypotheses | Page 4<br>Line 74-83 |
| **Methods** | | | |
| Study design | 4 ✓ data source | Present key elements of study design early in the paper | Page 5<br>Line 86-105 |
| Setting | 5 ✓ data source | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 5<br>Line 86-105 |
| Participants | 6 ✓ data source | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | Page 5<br>Line 86-105 |
| Variables | 7 ✓ definitions of periodontitis; abdominal aortic calcification outcomes; covariates | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 5-8<br>Line 106-162 |
| Data sources/ measurement | 8* ✓ definitions of periodontitis; abdominal aortic calcification outcomes; covariates | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Page 5-8<br>Line 106-162 |
| Bias | 9 ✓ statistical analysis | Describe any efforts to address potential sources of bias | Page 8-9<br>Line 163-191 |
| Study size | 10 ✓ data source; | Explain how the study size was arrived at | Page 5 |

| | | | |
|---|---|---|---|
| | figure 1; | | Line 86-105 |
| Quantitative variables | 11 ✓ statistical analysis | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 8-9<br>Line 163-191 |
| Statistical methods | 12 ✓ statistical analysis | (*a*) Describe all statistical methods, including those used to control for confounding | Page 8-9<br>Line 163-191 |
| | ✓ statistical analysis | (*b*) Describe any methods used to examine subgroups and interactions | Page 8-9<br>Line 163-191 |
| | ✓ statistical analysis | (*c*) Explain how missing data were addressed | Page 8-9<br>Line 163-191 |
| | ✓ statistical analysis | | |
| | ✓ statistical analysis | (*d*) If applicable, describe analytical methods taking account of sampling strategy | Page 8-9<br>Line 163-191 |
| | | (*e*) Describe any sensitivity analyses | Page 8-9<br>Line 163-191 |
| **Results** | | | |
| Participants | 13* ✓ data source; figure 1 | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 5<br>Line 86-105 |
| | ✓ data source; figure 1;supplementary table1 | (b) Give reasons for non-participation at each stage | Page 5<br>Line 86-105 |
| | ✓figure 1 | (c) Consider use of a flow diagram | - |
| Descriptive data | 14* ✓ table 1 | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Page 9-11<br>Line 196-211 |
| | ✓supplementary table1 | (b) Indicate number of participants with missing data for each variable of interest | - |
| Outcome data | 15* ✓ Table 1 to 4 | Report numbers of outcome events or summary measures | - |
| Main results | 16 ✓ table 2; table 3; Table 4; | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and | - |

| | | | |
|---|---|---|---|
| | | why they were included | |
| | ✓ covariates | (*b*) Report category boundaries when continuous variables were categorized | Page 7-8<br>Line 133-162 |
| | × this study does not involve | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | - |
| Other analyses | 17 ✓ results | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Page 13-15<br>Line 242-270 |
| **Discussion** | | | |
| Key results | 18 ✓ discussion – 1nd paragraph | Summarise key results with reference to study objectives | Page 15<br>Line 272-286 |
| Limitations | 19 ✓ discussion – 4th paragraph | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Page 17-18<br>Line 329-345 |
| Interpretation | 20 ✓ discussion – 2th-3th paragraphs | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Page 15-17<br>Line 287-328 |
| Generalisability | 21 ✓ discussion – 4th | Discuss the generalisability (external validity) of the study results | Page 17-18<br>Line 329-345 |
| **Other information** | | | |
| Funding | 22 ✓ | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 19<br>Line 362-363 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Unraveling the link between periodontitis and abdominal aortic calcification in the U.S. adult population: A cross-sectional study based on the NHANES 2013-2014

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| | |

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# The title page

# Unraveling the link between periodontitis and abdominal aortic calcification in the U.S. adult population: A cross-sectional study based on the NHANES 2013-2014

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**Equal contributions:** *These authors have contributed equally to this work and share first authorship

**Word count:** 3,603**; Number of figures:** 1**; Number of tables:** 4**; Number of references:** 48**.**

## Abstract

**Objective:** We aimed to explore the association between periodontitis and abdominal aortic calcification (AAC) among a nationally representative sample of U.S. adults.

**Design:** Cross- sectional study.

**Setting:** The National Health and Nutrition Examination Survey (2013–2014).

**Participants:** A total of 2,149 participants aged 40 years or older who have complete information for periodontitis and AAC assessment test were included in this study.

**Primary and secondary outcome measures:** AAC scores can be accurately identified on lateral spine images obtained by DXA, and both the AAC-24 and AAC-8 semiquantitative scoring tools were used for AAC evaluation. Linear regression analysis was used to investigate the relationship between periodontitis and the AAC-8 and AAC-24 scores. Multivariate logistic regression models and reported odds ratios (ORs) were used to examine the relationship between periodontitis and AAC.

**Results:** The prevalence of severe periodontitis combined with severe AAC was 8.49%-8.54%. According to the AAC-8 and AAC-24 score classifications, patients with severe periodontitis had higher odds of severe AAC [AAC-8 score ≥ 3: (OR: 2.53; 95% CI 1.04, 6.17) and AAC-24 score >6: (OR: 3.60; 95% CI 1.48, 8.78)]. A positive association between mild-moderate periodontitis and severe AAC was found only when the AAC-24 score was applied (OR: 2.25; 95% CI 1.24, 4.06). In the subgroup analyses, the likelihood ratio test showed no multiplicative interaction (all P for interaction > 0.05).

**Conclusions:** The findings showed that periodontitis is associated with an increased risk of severe AAC in the U.S. population aged 40 years and older; this requires further large-scale prospective studies for confirmation.

## Strengths and limitations of this study

1. A complex, multistage probability sampling approach was used to obtain a representative sample of individual composition to investigate the total national population.

2. Our study fully considered socioeconomic status, behavioral factors and medical history of the participants and controlled for a wide range of confounders.

3. Periodontitis and abdominal aortic calcification were defined based on objective clinical data collected by calibrated professionals.

4. Given the cross-sectional design of the NHANES, it is difficult for us to determine causality, and further large-scale prospective studies are needed.

5. Because of the sample size, we were not able to include the new periodontal profile class (PPC) system to precisely classify periodontal disease.

# Text

## 1. Introduction

Periodontitis has become a global public health challenge and imposes serious burdens on society and health services. There have been approximately 1.1 billion prevalent cases of severe periodontitis worldwide over the past 30 years, an increase of 8.44% in age-standardized prevalence[1]. Forty-six percent of American adults aged 30 years and older have periodontitis, 8.9% of whom have severe periodontitis, which is positively associated with increasing age[2]. Periodontitis can affect the risk of systemic diseases, including cardiovascular disease (CVD)[3-4], diabetes[5], and chronic kidney disease (CKD)[6], through mechanisms such as periodontal microbial damage and inflammatory cascades, and this relationship may be causal and bidirectional. Deaths due to all causes and cause-specific causes are associated with periodontitis and its sequelae[7]. As part of its strategy, the Centers for Disease Control and Prevention (CDC) is supporting and improving periodontal disease surveillance[8].

The abdominal aorta is considered to valuable in observing early atherosclerotic calcification[9], and its degree of calcification is closely related to the prevalence of and mortality due to CVD[10]. Abdominal aortic calcification (AAC) is characterized by metabolic disorders involving minerals, such as calcium and phosphorus, and abnormal deposition in the vascular wall, which is common in patients with chronic disease[11-12]. Some epidemiological evidence suggests that periodontitis is associated with arterial calcification at multiple sites. A Chinese cohort study showed that periodontitis increased the risk of aortic calcification and was more pronounced in men and younger participants than in women and older participants[13]. In addition, a cross-sectional study and meta-analysis suggested that periodontitis was associated with carotid calcification[14-15], and there was radiographic evidence suggesting the possible involvement of intracranial carotid calcification[16]. However, other cohort studies reported inconsistent conclusions[17-18]. In recent years, vascular calcification, including soft tissue calcification, has been recognized as an active process regulated by multiple molecular signaling pathways in response to chronic inflammatory stimuli[19]. Previous animal studies demonstrated that periodontitis and vascular calcification promoted each other[20], and the mechanisms involved were gradually revealed in subsequent studies[21-24].

An assessment of the utility of the AAC score in a 25-year cohort study of 617 Framingham Heart Study participants was conducted by Kauppila et al. using lateral lumbar radiography as the AAC grading tool (AAC score)[25]. Based on the AAC score, it is possible to assess subclinical vascular disease at a low cost, with predictive value for cardiovascular events and mortality independent of coronary calcification[26]. Therefore, using abdominal aortic calcification data obtained from dual-energy X-ray absorptiometry (DXA) in the 2013–2014 National Health and Nutrition Examination Survey (NHANES), the aim of this study was to investigate the relationship between periodontitis and AAC and propose new ideas for the prevention and management of AAC in clinical practice. We hypothesized that periodontitis would be associated with an increased prevalence of AAC.

## 2. Materials and methods

### 2.1. Data source

The current cross-sectional study analyzed data from individuals who participated in the 2013 to 2014 NHANES, which was performed by the National Center for Health Statistics (NCHS) at the CDC. The NHANES 2013-2014 was a cross-sectional, nationally representative survey of the U.S. noninstitutionalized civilian population designed to examine demographic, socioeconomic, health, and nutritional information. To ensure a representative sample, complex multistage sampling was used to collect data, and strata were determined based on geographic location and population proportions[27].

The NHANES 2013-2014 was the only cycle that also performed examinations for periodontitis and abdominal aortic calcification. Participants ≥ 40 years of age who received a full-mouth periodontal examination and participated in lateral DXA scans of the thoraco-lumbar spine were included in this study. In the 2013-2014 cycle of the NHANES, 10,175 participants completed the survey. However, in this study, individuals aged < 40 years without complete information about periodontitis and abdominal aortic calcification were excluded (N = 7,741). Additionally, cancer participants (N = 285) were excluded from the analysis. Ultimately, 2,149 participants were included in the analysis (Figure 1). All participants provided written informed consent to participate in NHANES, and the NCHS Research Ethics Review Board approved the protocol (NCHS IRB/ERB Protocol Number: Continuation of Protocol #2011-17). The study was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting cross-sectional studies[28], and all procedures were performed in accordance with the principles of the Helsinki Declaration of 1975.

### 2.2. Definitions of periodontitis

Oral health examinations were performed by dental examiners who were licensed dentists in at least one state in the U.S. During oral health assessments, a portable dental chair, lights, and compressed air were provided in a mobile examination center (MEC). All dental examiners received standardized training and collected reliable statistical data to objectively assess examiner agreement[29].

Six measurement points were selected for periodontal examinations (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual) for all teeth, with the exception of third molars. Indicators of periodontitis included probing depth (PD) and clinical attachment loss (AL), which are important bases for the CDC/AAP classification/case definition[30]. Accordingly, periodontitis was divided into mild periodontitis, moderate periodontitis and severe periodontitis, No periodontitis was defined as no evidence of mild, moderate, or severe periodontitis. Because there were few data from those with mild periodontitis, mild periodontitis and moderate periodontitis were combined for analysis in our study.

### 2.3. Abdominal aortic calcification outcomes

AAC can be accurately identified on lateral spine images obtained by DXA and shows good sensitivity and specificity at lower radiation doses[31-32]. Those < 40 years old, pregnant, weighing over 450 pounds, or ingesting barium within the last week were ineligible for DXA scans in this study. Both the AAC-24 and AAC-8 semiquantitative scoring tools were used for AAC evaluation[25]. An assessment of the length of anterior and posterior aortic wall calcification anterior to the L1 to L4 vertebral bodies was made using the AAC-8 score, and participants with a score of three or more were considered to be at high risk for AAC. Using the L1-L4 region as a reference, the anterior and posterior aortic walls are divided into four segments to calculate the AAC-24 score. Depending on the degree of calcification, each vertebral body can receive a score from 0 to 6, with a total possible score of 0 to 24; this allows a more precise assessment of abdominal aortic calcification. We categorized AAC-24 scores

into three groups: no calcification (AAC-24 score =0), mild to moderate calcification (6 ≥ AAC-24 score > 0) and severe calcification (AAC-24 score >6).

### 2.4. Covariates

Based on previous studies, we considered some confounding factors potentially associated with periodontitis and AAC in our analysis, including socioeconomic factors, behavioral factors , body mass index (BMI), medical history, and laboratory measurements[33-34].

Information about socioeconomic factors was obtained during the home interview. The poverty income ratio (PIR) was stratified into <1.3, 1.3–3.5, and >3.5, as recorded in the original survey. Behavioral factors were obtained from self-reports. A never smoker is an individual who has never smoked more than 100 cigarettes in their lifetime. Former smokers were defined as those who smoked more than 100 cigarettes in their lifetime and had quit smoking, and smokers have to smoke at least 100 cigarettes in their lifetime and smoke some days or every day to qualify as current smokers. The status of alcohol consumption was categorised as never (never drank greater than or equal to 12 drinks in their lifetime), former (greater than or equal to 12 drinks in 1 year and did not drink last year, or did not drink last year but drank ≥12 drinks in their lifetime), current mild (≤1 drink/d for female or ≤2 drink/d for male on average over the past year), current moderate (2 drink/d for female or 3 drink/d for male on average over the past year), current heavy drinkers (≥3 drink/d for female or ≥4 drink/d for male on average over the past year). BMI was measured at a MEC using standard protocols and stratified into ≥30 and <30.

Those participants who self-reported heart failure, angina, coronary heart disease, heart attack, or stroke diagnosed by a physician were classified as having CVD. The definition of hypertension was a diagnosis by a healthcare professional, an average blood pressure of ≥ 130/80 mmHg or using hypertension medications[35]. Diabetes was defined as a diagnosis made by a physician or

other healthcare professional, HbA1c (%) >6.5, random blood glucose (mmol/l) ≥11.1, or use of diabetes medication or insulin. As defined by the International Renal Association, chronic kidney disease is characterized by an estimated glomerular filtration rate <60 mL/min/1.73 $m^2$ or a urine albumin–creatinine ratio of at least 30[36]. Based on serum creatinine, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate the glomerular filtration rate[37]. Laboratory data were obtained from participant serum samples that were processed in the Collaborative Laboratory Services, Ottumwa, Iowa, for analysis. Detailed instructions regarding specimen collection and processing are documented in the NHANES Laboratory Procedures Manual, and quality control was in accordance with standard procedures.

### 2.5. Statistical analysis

A weight is assigned to the NHANES to compensate for the complex survey design, survey nonresponses, and poststratification adjustment to match the total U.S. population. All results of this study were weighted by 2-year MEC weights. In accordance with the CDC/AAP classification of periodontitis, descriptive statistics were calculated to describe the characteristics of the participants. Continuous variables are presented as the weighted mean ± standard deviation (SD) and were compared using a one-way ANOVA, while categorical variables were compared using the Rao-Scott chi-square test and are presented as weighted percentages (95% confidence interval, 95% CI). Linear regression was used to evaluate the association of the AAC-8 score and AAC-24 score as dependent variables with periodontitis with varying degrees of severity as independent variables. Beta coefficients and 95% CIs were calculated. Multivariate logistic regression analysis was performed to evaluate the correlation between periodontitis with varying degrees of severity and AAC with varying degrees of severity using odds ratios (ORs) and 95% CIs. Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in

Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs). Subgroup analysis stratified by age, sex, CVD, hypertension, diabetes, and CKD was also conducted using stratified multivariate regression analysis, and multiplicative interactions were assessed using likelihood ratio tests.

In this study, we used the MissForest[38] package in R software to address missing covariates. The algorithm can address categorical and continuous variables and shows superior performance. The numbers and percentages of missing covariate data are shown in Supplementary Material Table 1. Sensitivity analyses were performed as followed: (1) only participants with complete data were included, and participants with missing covariates were excluded; (2) mild and moderate periodontitis were not combined for analysis, and mild periodontitis was excluded; and (3) participants with CVD were excluded. R software (version 4.1.3) was used for all statistical analyses. It was considered statistically significant if the P value was less than 0.05 for all statistical tests of two-tailed.

### 2.6. Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## 3. Results

Descriptive statistics of our study participants by periodontitis status according to the CDC/AAP case definitions are presented in Table 1. The study included 2,149 participants, representing 86,199,511 noninstitutionalized adults (40 years and older) in the U.S. Overall, participants had a mean age±SD of 54.96 ± 0.32 years; 50.46% (44.32, 56.60) were female, and 68.14% (54.20, 82.08) were non-Hispanic white. The prevalence of mild-moderate periodontitis was 29.93 (25.36, 34.51) and that of severe periodontitis was 6.77 (5.40, 8.13). Periodontitis was more prevalent in older individuals,

males, those with a low educational level, those with a low PIR, and those with low insurance coverage than in their counterparts and showed differences among races. The prevalence of mild to moderate AAC and severe AAC was significantly higher in participants with periodontitis than in those without. In addition, we also found significant differences in smoking status, alcohol consumption status, CVD, diabetes, hypertension, CKD, albumin, total 25-hydroxyvitamin D, TGs, and HDL-C compared with participants without periodontitis (all $p < 0.05$).

**TABLE 1** General characteristics of included participants (n = 2,149) according to the periodontal status in the NHANES 2013–2014.

| Characters | Overall (n=2,149) | No Periodontitis (n=1,142) | Mild-Moderate periodontitisc (n=787) | Severe periodontitis (n=220) | P-value |
|---|---|---|---|---|---|
| **Age, year** | 54.96±0.32 | 53.84±0.47 | 57.13±0.52 | 55.78±0.73 | 0.001 |
| **Gender** | | | | | < 0.001 |
| Male | 49.54 (42.66-56.42) | 44.26 (40.95-47.57) | 56.17 (52.43-59.91) | 69.60 (62.25-76.96) | |
| Female | 50.46 (44.32,56.60) | 55.74 (52.43-59.05) | 43.83 (40.09-47.57) | 30.40 (23.04-37.75) | |
| **Race** | | | | | < 0.001 |
| Mexican American | 7.98 ( 4.63-11.32) | 5.51 (2.88-8.15) | 12.60 (6.75-18.46) | 10.53 (4.02-17.05) | |
| Non-Hispanic Black | 10.53 ( 8.69-12.36) | 7.38 ( 5.67-9.09) | 14.16 ( 9.15-19.17) | 23.88 (15.54-32.23) | |
| Non-Hispanic White | 68.14 (54.20-82.08) | 74.71 (69.73-79.70) | 57.60 (46.77-68.43) | 53.28 (42.62-63.94) | |
| Other Hispanic | 5.22 ( 3.48- 6.95) | 4.38 (2.56-6.20) | 6.79 (4.13-9.44) | 6.09 (2.77-9.41) | |
| Other race or multi-racial | 8.14 ( 6.55- 9.74) | 8.02 (6.44-9.60) | 8.85 (6.07-11.63) | 6.21 (4.11-8.31) | |
| **Education** | | | | | < 0.001 |
| Less than hight school | 14.88 (12.36-17.39) | 9.09 ( 6.59-11.59) | 22.21 (17.08-27.35) | 36.60 (27.56-45.64) | |
| Hight school | 20.80 (17.18-24.43) | 16.38 (13.54-19.21) | 27.28 (22.81-31.75) | 33.56 (26.94-40.19) | |
| Above hight school | 64.32 (52.71-75.93) | 74.54 (70.84-78.23) | 50.51 (44.66-56.35) | 29.84 (20.31-39.37) | |
| **Poverty-income ratio** | | | | | < 0.001 |
| < 1.3 | 16.84 (12.82-20.86) | 10.14 ( 7.11-13.16) | 27.38 (21.64-33.13) | 32.91 (20.83-44.99) | |
| 1.3-3.5 | 34.58 (30.67-38.50) | 29.18 (25.57-32.80) | 43.20 (38.79-47.62) | 46.98 (36.21-57.75) | |
| > 3.5 | 48.58 (38.30-58.85) | 60.68 (55.49-65.87) | 29.41 (23.79-35.03) | 20.11 (10.19-30.04) | |
| **Insurance coverage** | 84.99 (72.54-97.45) | 91.46 (88.41-94.50) | 76.37 (72.89-79.85) | 62.68 (55.51-69.85) | < 0.001 |
| **Body mass index (kg/m$^2$)** | | | | | 0.053 |
| < 30 | 64.10 (54.77-73.44) | 66.54 (63.36-69.72) | 59.50 (53.18-65.82) | 61.67 (53.95-69.39) | |
| ≥ 30 | 35.90 (31.24-40.56) | 33.46 (30.28-36.64) | 40.50 (34.18-46.82) | 38.33 (30.61-46.05) | |
| **Smoking status** | | | | | < 0.001 |
| Now | 16.07 (13.82-18.31) | 10.48 ( 8.12-12.83) | 21.91 (18.01-25.81) | 42.48 (33.91-51.05) | |
| Former | 25.38 (20.70-30.06) | 23.00 (20.09-25.92) | 31.13 (25.05-37.20) | 22.22 (13.02-31.43) | |
| Never | 58.55 (50.16-66.94) | 66.52 (62.55-70.48) | 46.96 (42.06-51.87) | 35.30 (25.73-44.86) | |
| **Alcohol consumption status** | | | | | 0.004 |
| Never | 11.48 ( 8.45-14.51) | 11.22 ( 7.14-15.29) | 12.77 (10.23-15.30) | 8.23 ( 4.19-12.27) | |
| Former | 14.23 (11.41-17.06) | 11.54 ( 9.13-13.95) | 18.94 (15.82-22.05) | 18.63 (12.99-24.26) | |
| Mild | 40.28 (33.73-46.83) | 43.77 (39.36-48.18) | 34.64 (29.89-39.39) | 32.56 (24.85-40.26) | |
| Moderate | 18.10 (14.08-22.11) | 18.98 (16.05-21.92) | 16.60 (11.73-21.47) | 16.44 ( 9.60-23.28) | |
| Heavy | 15.91 (13.83-18.00) | 14.49 (12.30-16.68) | 17.06 (13.06-21.06) | 24.15 (16.68-31.61) | |
| **Cardiovascular diseases** | 7.43 ( 5.89-8.97) | 5.95 (4.53-7.38) | 10.68 (7.93-13.43) | 6.88 (3.11-10.65) | 0.004 |
| **Hypertension** | 56.64 (50.33-62.94) | 52.31 (48.43-56.19) | 63.24 (59.08-67.39) | 67.92 (61.80-74.05) | < 0.001 |
| **Diabetes** | 14.06 (12.22-15.91) | 10.83 ( 8.78-12.87) | 21.13 (18.83-23.43) | 13.04 ( 7.94-18.15) | < 0.001 |
| **Chronic kidney disease** | 14.66 (12.77-16.55) | 12.21 (10.24-14.19) | 19.73 (17.14-22.31) | 15.13 (10.15-20.11) | < 0.001 |

| | | | | | |
|---|---|---|---|---|---|
| **AAC-8 score** | | | | | 0.001 |
| < 3 | 94.86 (83.16-100.00) | 96.68 (95.23-98.13) | 91.78 (89.31-94.25) | 91.51 (86.26-96.76) | |
| ≥ 3 | 5.14 ( 3.60-6.68) | 3.32 (1.87-4.77) | 8.22 (5.75-10.69) | 8.49 (3.24-13.74) | |
| **AAC-24 score** | | | | | < 0.001 |
| 0 | 75.67 (64.85-86.49) | 77.77 (74.00-81.53) | 73.24(67.18-79.30) | 66.81(59.03-74.58) | |
| 1-6 | 19.55 (15.84-23.26) | 19.38 (15.83-22.93) | 18.75(14.07-23.43) | 24.65(17.37-31.93) | |
| > 6 | 4.78 ( 3.66-5.90) | 2.85 (1.95-3.76) | 8.01(5.59-10.42) | 8.54(4.04-13.04) | |
| **Laboratory measurements** | | | | | |
| Albumin (g/dL) | 4.27±0.01 | 4.30±0.01 | 4.21±0.02 | 4.20±0.02 | < 0.001 |
| Serum calcium (mg/dL) | 9.45±0.01 | 9.45±0.01 | 9.43±0.02 | 9.45±0.03 | 0.414 |
| Serum phosphorus (mg/dL) | 3.79±0.02 | 3.81±0.03 | 3.75±0.02 | 3.78±0.04 | 0.083 |
| Uric acid (mg/dL) | 5.37±0.03 | 5.29±0.03 | 5.53±0.08 | 5.42±0.13 | 0.063 |
| Total 25-hydroxyvitamin D (nmol/L) | 73.44±1.18 | 76.90±1.44 | 68.78±1.58 | 61.71±2.42 | < 0.001 |
| Hemoglobin (g/dL) | 14.19±0.04 | 14.15±0.04 | 14.20±0.08 | 14.42±0.11 | 0.097 |
| Total cholesterol (mg/dL) | 196.56±0.99 | 195.79±1.15 | 197.98±2.45 | 197.48±3.31 | 0.722 |
| High-density lipoprotein cholesterol (mg/dL) | 54.67±0.60 | 56.42±0.73 | 51.79±0.70 | 50.99±1.19 | < 0.001 |
| Triglycerides (mg/dL) | 162.83±3.69 | 152.54± 3.39 | 182.64± 9.60 | 171.49±13.54 | 0.015 |

Note: Values indicate the weighted mean ± SD or weighted % (95% confidence interval). P-values are weighted. AAC, abdominal aortic calcification.

Table 2 shows the relationships between periodontitis and the AAC-8 score and AAC-24 score in the linear regression analysis. In Model 1, which was adjusted for age, sex, and race, severe periodontitis showed a significant positive correlation with the AAC-8 (β: 0.29; 95% CI 0.08, 0.50) and AAC-24 (β: 0.80; 95% CI 0.25, 1.34) scores compared with no periodontitis. However, the association disappeared in the subsequent models adjusted for additional covariates. In addition, no correlation was found between mild-moderate periodontitis and the AAC-8 score or AAC-24 score.

**TABLE 2** Weighted linear regression coefficients (β) and 95% confidence intervals for periodontal status and AAC score : The United States, 2013 to 2014

| | Case/participants | Model 1<br>β (95% CI), P- value | Model 2<br>β (95% CI), P- value | Model 3<br>β (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score** | | | | |
| No periodontitis | 1142/2149 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 787/2149 | 0.11(-0.05,0.28)<br>P=0.149 | 0.03(-0.11,0.17)<br>P=0.643 | 0.02(-0.12,0.17)<br>P=0.740 |
| Severe periodontitis | 220/2149 | **0.29( 0.08,0.50)<br>P=0.015** | 0.17(-0.07,0.41)<br>P=0.159 | 0.17(-0.08,0.41)<br>P=0.173 |
| **AAC-24 score** | | | | |
| No periodontitis | 1142/2149 | Reference | Reference | Reference |

| | | | | |
|---|---|---|---|---|
| Mild–moderate periodontitis | 787/2149 | 0.34(-0.10,0.78) P=0.110 | 0.15(-0.22,0.52) P=0.393 | 0.14(-0.26,0.54) P=0.472 |
| Severe periodontitis | 220/2149 | **0.80( 0.25,1.34) P=0.011** | 0.57(-0.01,1.14) P=0.052 | 0.58(-0.02,1.17) P=0.056 |

Note: Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. AAC: abdominal aortic calcification.

Table 3 presents the association between periodontitis and AAC based on the multivariate logistic regression analysis. In fully adjusted Model 3, severe periodontitis was positively associated with AAC in the high-AAC risk group (AAC-8 score ≥ 3 points) (OR: 2.53; 95% CI 1.04, 6.17) compared with the low-AAC risk group (AAC-8 score < 3 points). The degree of periodontitis and AAC as defined by the more refined AAC-24 score were further analyzed. Mild-moderate and severe periodontitis were associated with an increased prevalence of severe AAC (OR: 2.25; 95% CI 1.24, 4.06 and OR: 3.60; 95% CI 1.48, 8.78) relative to participants without AAC. Furthermore, this association remained when participants with mild-moderate AAC were replaced with a reference population; mild-moderate and severe periodontitis were associated with severe AAC (OR: 2.28; 95% CI 1.28, 4.06 and OR: 2.93; 95% CI 1.28, 6.69). In addition, no correlation was found between periodontitis and mild-moderate AAC.

**TABLE 3** Weighted multiple logistic regression coefficients (ORs) and 95% confidence intervals for the association between periodontal status with AAC group: The United States, 2013 to 2014

| | Case/participants | Model 1 OR (95% CI), P- value | Model 2 OR (95% CI), P- value | Model 3 OR (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score ≥ 3 points versus AAC-8 score < 3 points** | | | | |
| No periodontitis | 46/1142 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 66/787 | **2.07(1.01,4.22) P=0.047** | 1.79(0.95,3.38) P=0.069 | 1.84(1.00,3.40) P=0.051 |
| Severe periodontitis | 19/220 | **3.20(1.22,8.40) P=0.025** | **2.53(1.05,6.11) P=0.040** | **2.53(1.04,6.17) P=0.043** |
| **Mild–moderate AAC versus no AAC** | | | | |
| No periodontitis | 224/1102 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 144/723 | 0.89(0.58,1.38) P=0.561 | 0.76(0.53,1.08) P=0.113 | 0.72(0.51,1.02) P=0.061 |

| | | | | |
|---|---|---|---|---|
| Severe periodontitis | 50/200 | 1.46(0.79,2.68) P=0.185 | 1.05(0.52,2.10) P=0.886 | 0.96(0.48,1.93) P=0.914 |
| **Severe AAC versus no AAC** | | | | |
| No periodontitis | 40/918 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 64/643 | **2.57(1.35, 4.89) P=0.010** | **2.19(1.23,3.89) P=0.011** | **2.25(1.24,4.06) P=0.011** |
| Severe periodontitis | 20/170 | **6.13(2.55,14.72) P=0.002** | **3.62(1.63,8.06) P=0.004** | **3.60(1.48,8.78) P=0.008** |
| **Severe AAC versus mild–moderate AAC** | | | | |
| No periodontitis | 40/264 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 64/208 | **2.59(1.49,4.52) P=0.005** | **2.20(1.27,3.80) P=0.008** | **2.28(1.28, 4.06) P=0.008** |
| Severe periodontitis | 20/70 | **3.16(1.21,8.22) P=0.025** | **2.89(1.27,6.60) P=0.015** | **2.93(1.28, 6.69) P=0.014** |

Note: Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. No AAC, mild–moderate AAC and severe AAC were defined by AAC-24 score. AAC: abdominal aortic calcification.

In the subgroup analysis (Table 4), we investigated the association between periodontitis and severe AAC based on an AAC-8 score ≥ 3. We found that the likelihood ratio test for multiplicative interactions was not statistically significant for age, sex, CVD, hypertension, diabetes, or CKD after adjustment for potential confounders (P interaction > 0.05). Thus, we did not find any substantial evidence to demonstrate systematic differences in associations between different subpopulations in the population, indicating that our main results were stable.

**TABLE 4** Subgroup analysis for the association between periodontal status and risk of severe AAC (AAC-8 score ≥ 3 points).

| | **Periodontal status OR (95% CI), P- value** | | | |
|---|---|---|---|---|
| | No periodontitis | Mild–moderate periodontitis | Severe periodontitis | P for interaction |
| **Age** | | | | 0.212 |
| ≥60y | Reference | 1.90(0.88,4.11) P=0.096 | **5.66(1.15,27.92) P=0.035** | |
| <60y | Reference | 3.44(0.83,14.15) P=0.083 | 1.58(0.24,10.43) P=0.611 | |

| | | | | |
|---|---|---|---|---|
| **Gender** | | | | 0.207 |
| Male | Reference | 1.90(0.55,6.56) P=0.285 | **4.40(1.09,17.85) P=0.039** | |
| Female | Reference | **2.37(1.42,3.93) P=0.003** | 0.92(0.29,2.94) P=0.876 | |
| **Cardiovascular diseases** | | | | 0.381 |
| Yes | Reference | 1.61(0.31,8.35) P=0.548 | NA* | |
| No | Reference | **1.95(1.02,3.73) P=0.044** | 2.14(0.86,5.35) P=0.096 | |
| **Diabetes** | | | | 0.837 |
| Yes | Reference | **4.00(1.49,10.69) P=0.009** | **9.64(1.45,64.16)* P=0.022** | |
| No | Reference | 1.51(0.67,3.40) P=0.293 | 2.21(0.76,6.44) P=0.136 | |
| **Hypertension** | | | | 0.085 |
| Yes | Reference | 1.81(0.88, 3.74) P=0.099 | **3.39(1.35, 8.56) P=0.013** | |
| No | Reference | **3.27(1.08, 9.91) P=0.037** | 0.73(0.08, 6.72) P=0.767 | |
| **Chronic kidney disease** | | | | 0.501 |
| Yes | Reference | **2.20(1.15, 4.21) P=0.021** | 1.57(0.22, 11.17) P=0.630 | |
| No | Reference | 1.81(0.79, 4.12) P=0.147 | **2.98(1.21, 7.34) P=0.020** | |

Note: All presented covariates were adjusted (as Model 3) except the corresponding stratification variable. *Wide CI and no production OR are due to the small sample size for this comparison.

In the primary study, we imputed missing covariates (the proportions of all missing variables were less than 5.00% except for the PIR, at 8.19%) using the MissForest package. The random forest analysis had a seed number of 500 and completed data imputation after eight iterations. Model performance indicators normalized root mean squared error computed (NRMSE) was 0.578 and proportion of falsely classified (PFC) was 0.336. In the sensitivity analysis, we excluded participants with missing covariates, and we included 1,818 individuals with complete data in the subsequent analyses. The baseline distribution of participant characteristics did not differ significantly from that in the previously included population, but it was worth mentioning that the prevalence of severe AAC with severe periodontitis have decreased by approximately 1% (Supplementary Material Table 2). Further logistic regression analysis showed, our result regarding the association of periodontitis and AAC differed from that in the primary analysis. In Model 3, only mild-moderate periodontitis was associated with an increased risk of severe AAC (OR: 1.89; 95% CI 1.01, 3.56), and the remaining associations were

attenuated or had disappeared (Supplementary Material Table 3). When we decoupled mild-moderate periodontitis and excluded participants with mild periodontitis, the results of the sensitivity analysis were similar to those of the main analysis (Supplementary Material Table 4). It is worth mentioning that mild-moderate periodontitis was associated with a reduced prevalence of mild to moderate AAC in participants without CVD, and the association of severe periodontitis with AAC in the high-AAC risk group (AAC-8 scores ≥ 3 points) disappeared (Supplementary Material Table 5).

## 4. Discussion

To our knowledge, this is the first population-based cross-sectional epidemiological study to explore the link between periodontitis and AAC in a nationally representative sample of U.S. adults (40 years and older). Our study fully considered socioeconomic status, behavioral factors and medical history of the participants and controlled for a wide range of confounders. Severe periodontitis was positively associated with severe AAC, defined by either the AAC-8 score or AAC-24 score. A positive association between mild to moderate periodontitis and severe AAC was found only when AAC was classified by the AAC-24 score. In the subgroups stratified by age; sex; and CVD, hypertension, diabetes, and CKD status, this association and the main results were generally consistent; the only difference was associated with the different severities of periodontitis, which differed in their associations with severe AAC in the stratified population. Linear regression evaluation of the AAC-8 score and AAC-24 score as dependent variables and the different severities of periodontitis as independent variables showed no linear correlation. In the sensitivity analysis, the association remained significant after excluding participants with mild periodontitis and CVD. However, the association was no longer significant after excluding participants with missing covariates.

To date, some epidemiological studies have suggested a close relationship between periodontitis and vascular calcification or CVD. A consensus report on periodontitis and CVD states that

periodontitis is broadly associated with CVD and that the link is bidirectional; CVD drives the progression of periodontitis and vice versa[39]. NHANES-based cross-sectional studies have shown an association between periodontitis severity and cardiovascular risk[4], as demonstrated by the results of a 13-year cohort study, and further studies suggest that periodontitis may be an independent risk factor for CVD[40]. Oindrila Paul et al. reviewed the pathophysiology of periodontitis and showed that inflammation associated with periodontitis may be the main mechanism affecting CVD and could be facilitated by common risk factors[41]. Vascular calcification has been shown to involve soft tissue calcification also caused by chronic inflammatory stimuli[19] and is closely related to the prevalence and prognosis of CVD. This may suggest that the association between periodontitis and CVD may depend on the severity of vascular calcification. The results of a cross-sectional Japanese population-based study suggest that measuring alveolar bone loss on panoramic radiographs may be an effective method to identify an increased risk of carotid artery calcification[14]. Imaging studies using cone-beam computed tomography have further confirmed that the development of periodontitis may cause calcification involving the intracranial carotid arteries[16]. The results from a meta-analysis that included 12 studies also revealed a significant relationship between periodontitis and carotid artery calcification[15]. Similar to our findings, a cohort study in Chinese populations suggested that periodontitis was also positively associated with aortic calcification, and this association was more pronounced in men and in participants younger than 65 years[13].

The exact mechanism of the link between periodontitis and AAC remains unclear and needs to be further explored. Existing mainstream views suggest that *Porphyromonas gingivalis* (*P. gingivalis*) infection and chronic inflammation are important bridges between periodontitis and vascular calcification[19, 41-42]. Recent studies have shown that periodontal pathogens can be detected in the blood of patients with coronary heart disease, and it is hypothesized that periodontal pathogens can spread through the blood to other parts of the body, where they may enhance inflammatory processes, leading

to the development or aggravation of atherosclerosis[43]. Evidence from in vitro cell culture studies suggests that *P. gingivalis* infection accelerates phosphate-induced calcification of vascular smooth muscle cells[22] and that *P. gingivalis* lipopolysaccharide increases alkaline phosphatase activity and upregulates the expression of genes involved in calcification to stimulate calcification[44]. In addition, it has been shown that *P. gingivalis* invasiveness is enhanced after high-glucose treatment, and vascular calcification can be initiated by stimulating autocrine regulation of bone morphogenetic protein 4 in aortic smooth muscle cells[21]. *P. gingivalis* infection elicits an inflammatory response in the host, which is in line with the definition of periodontitis as a chronic inflammatory disease. A meta-analysis suggested that the diagnosis of chronic aggressive periodontitis was consistently associated with higher C-reactive protein and high-sensitivity C-reactive protein levels, and treatment reduced serum C-reactive protein levels[45]. In addition, studies have observed an association between periodontitis and systemic inflammation, which increases with the severity of periodontal disease[46]. Notably, there are studies revealing other possible mechanisms involved in the link between periodontitis and vascular calcification, including the activation of osteoprotegerin/receptor activator of nuclear factor-κB ligand and endoplasmic reticulum stress-induced apoptosis[23-24].

Our study has several important strengths. Our findings were derived from a large nationwide random sample survey and can be generalized to the adult noninstitutionalized population in the U.S. Periodontitis and AAC were defined based on objective clinical data collected by calibrated professionals. In addition, this study addressed a number of known potential confounders, and sample weights were applied in each analysis following the NHANES guidelines to account for the complex survey design. However, several limitations of this study warrant attention. Given the cross-sectional design of the NHANES, it is difficult for us to determine causality, and further large-scale prospective studies are needed. In addition, we cannot exclude the possibility of residual confounding by other confounding factors related to oral health, which could have influenced the observed results. It is worth

noting that only a small proportion of patients with severe periodontitis in our study had severe AAC; perhaps because of this, the results of the sensitivity analysis excluding patients with missing covariates were not robust. This also suggests that the conclusions of this study should be interpreted with caution. An explanation for this phenomenon is the possibility of selection bias[47]. In addition, tooth loss is not considered in the CDC/AAP case definition of periodontitis; therefore, the prevalence of the disease may be underestimated[30]. Because of the sample size, we were not able to include the new periodontal profile class (PPC) system to precisely classify periodontal disease because this classification method classifies periodontitis into seven categories: PPC-A to PPC-G[48].

## 5. Conclusion

Our study suggests that periodontitis is associated with an increased risk of severe AAC in the U.S. population aged 40 years and older. The associations investigated in this study are credible due to their cross-sectional nature, but these findings require further large-scale prospective studies to confirm.

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## Contributors

KK, AnA and AiA participated in the design of the study, analysis of the data and drafted the manuscript or revised it for important content. RR collected and organized data. XM and Y-TM

contributed to the conception and design of the manuscript as well as reviewing critical modifications for important intellectual content.

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**Competing interests**

None declared.

**Patient consent for publication**

Not applicable.

**Ethics approval**

The present study complied with the term of the Declaration of Helsinki and was approved by the NCHS Research Ethics Review Committee (NCHS IRB/ERB Protocol Number: Continuation of Protocol #2011-17).

**Data availability statement**

Data may be obtained from a third party and are not publicly available. Data described in the article are publicly and freely available without restriction at https://www.cdc.gov/nchs/nhanes/index.htm

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## Figure legends

Figure 1. Flow chart of eligible National Health and Nutrition Examination Survey (NHANES) participants included in this study.

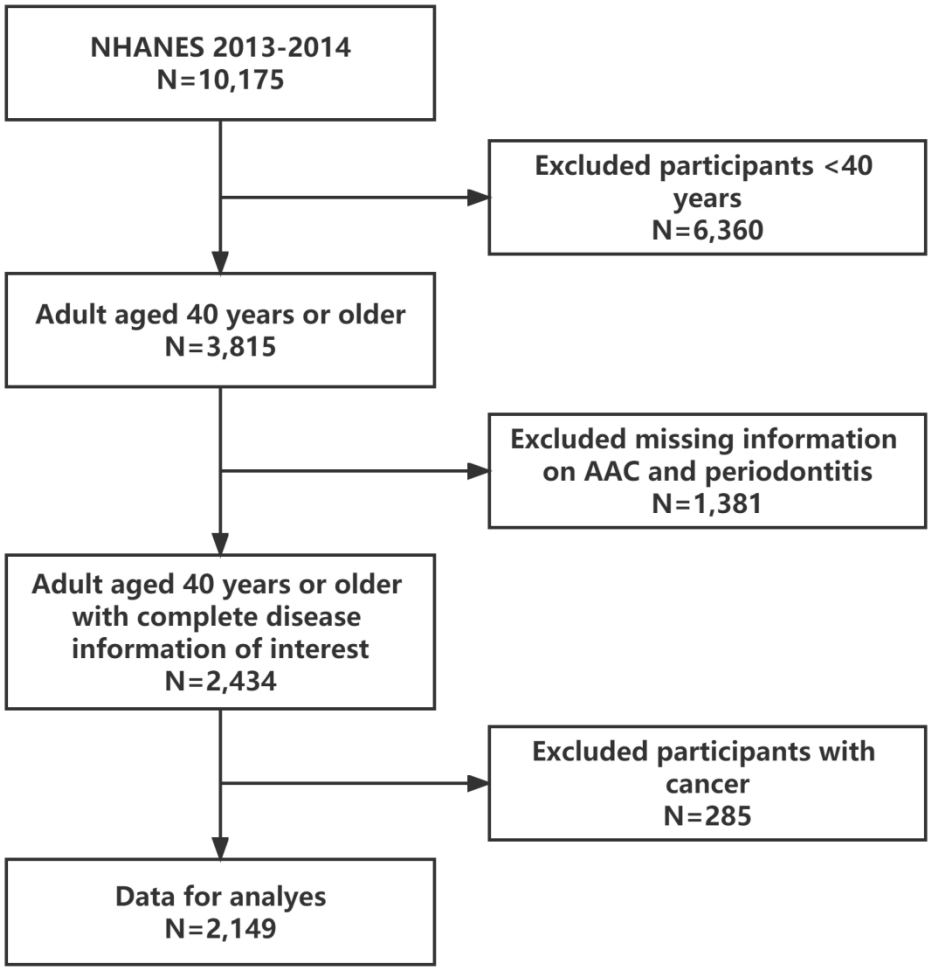


Figure 1. Flow chart of eligible National Health and Nutrition Examination Survey (NHANES) participants included in this study.

655x679mm (72 x 72 DPI)

# Supplementary Material

**TABLE 1** The numbers and percentages of missing covariate data

| Covariate | Numbers | Percentages (%) |
|---|---|---|
| Education | 1 | 0.05 |
| Poverty-income ratio | 176 | 8.19 |
| Body mass index | 6 | 0.28 |
| Smoking status | 2 | 0.09 |
| Alcohol consumption status | 97 | 4.51 |
| Cardiovascular diseases | 1 | 0.05 |
| Chronic kidney disease | 52 | 2.42 |
| Albumin | 58 | 2.70 |
| Serum calcium | 72 | 3.35 |
| Serum phosphorus | 59 | 2.75 |
| Uric acid | 60 | 2.79 |
| Total 25-hydroxyvitamin D | 49 | 2.28 |
| Hemoglobin | 38 | 1.77 |
| Total cholesterol | 53 | 2.47 |
| High-density lipoprotein cholesterol | 53 | 2.47 |
| Triglycerides | 60 | 2.79 |

**TABLE 2** General characteristics of included participants (n = 1,818) according to the periodontal status in the NHANES 2013–2014 (excluded participants with missing covariates).

| Characters | Overall (n=1,818) | No Periodontitis (n=977) | Mild-Moderate periodontitisc (n=661) | Severe periodontitis (n=180) | P-value |
|---|---|---|---|---|---|
| **Age, year** | 55.19±0.33 | 54.01±0.46 | 57.70±0.57 | 55.36±0.69 | < 0.001 |
| **Gender** | | | | | < 0.001 |
| Male | 50.34 (43.00-57.67) | 45.25 (41.74-48.75) | 57.01 (52.84-61.19) | 69.00 (60.78-77.22) | |
| Female | 49.66 (43.17-56.16) | 54.75 (51.25-58.26) | 42.99 (38.81-47.16) | 31.00 (22.78-39.22) | |
| **Race** | | | | | < 0.001 |
| Mexican American | 7.64 ( 4.29-10.99) | 5.37 (2.90- 7.83) | 12.37 (6.12-18.62) | 8.40 (2.34-14.45) | |
| Non-Hispanic Black | 9.81 ( 8.10-11.53) | 7.07 ( 5.36- 8.78) | 12.69 ( 8.36-17.02) | 23.04 (14.37-31.72) | |
| Non-Hispanic White | 69.93 (55.21-84.66) | 75.53 (70.47-80.58) | 60.66 (49.90-71.41) | 57.80 (45.71-69.90) | |
| Other Hispanic | 4.87 ( 3.34- 6.40) | 4.10 (2.37-5.83) | 6.45 (3.97-8.92) | 5.27 (1.70-8.84) | |
| Other race or multi-racial | 7.74 ( 6.20- 9.28) | 7.94 (6.34- 9.54) | 7.83 (4.98-10.68) | 5.48 (2.78- 8.18) | |
| **Education** | | | | | < 0.001 |
| Less than hight school | 13.49 (10.82-16.16) | 7.91 ( 5.25-10.56) | 20.34 (14.62-26.06) | 36.09 (26.10-46.08) | |
| Hight school | 21.25 (16.88-25.62) | 16.12 (12.81-19.42) | 29.19 (23.88-34.51) | 34.89 (27.67-42.12) | |
| Above hight school | 65.26 (52.75-77.76) | 75.98 (71.61-80.34) | 50.47 (44.14-56.80) | 29.02 (17.31-40.72) | |
| **Poverty-income ratio** | | | | | < 0.001 |
| < 1.3 | 17.53 (12.79-22.26) | 10.69 ( 7.03-14.35) | 28.23 (21.62-34.84) | 35.11 (21.93-48.30) | |
| 1.3-3.5 | 32.60 (28.53-36.67) | 26.79 (22.77-30.80) | 42.48 (37.54-47.42) | 44.16 (33.74-54.59) | |
| > 3.5 | 49.88 (38.79-60.96) | 62.52 (56.61-68.44) | 29.29 (23.25-35.33) | 20.73 ( 9.98-31.48) | |
| **Insurance coverage** | 85.84 (72.59-99.10) | 92.31 (89.14-95.48) | 77.09 (73.42-80.77) | 63.27 (55.48-71.07) | < 0.001 |
| **Body mass index (kg/m2)** | | | | | 0.051 |
| < 30 | 63.56 (53.32-73.81) | 66.24 (62.27-70.22) | 58.38 (52.44-64.31) | 60.96 (51.39-70.54) | |
| ≥ 30 | 36.44 (31.69-41.18) | 33.76 (29.78-37.73) | 41.62 (35.69-47.56) | 39.04 (29.46-48.61) | |
| **Smoking status** | | | | | < 0.001 |
| Now | 16.29 (13.83-18.75) | 10.56 ( 7.95-13.16) | 22.14 (18.08-26.19) | 44.56 (34.80-54.33) | |
| Former | 25.66 (20.34-30.98) | 22.66 (19.38-25.94) | 32.94 (26.12-39.75) | 22.22 (12.52-31.92) | |
| Never | 58.05 (49.27-66.83) | 66.79 (62.21-71.36) | 44.93 (39.88-49.98) | 33.22 (22.02-44.41) | |
| **Alcohol consumption status** | | | | | 0.018 |
| Never | 10.71 ( 7.52-13.90) | 10.61 (6.27-14.94) | 11.70 (9.07-14.33) | 7.42 (3.00-11.83) | |
| Former | 14.43 (11.55-17.31) | 11.67 ( 9.23-14.11) | 19.33 (16.24-22.41) | 19.08 (13.23-24.92) | |
| Mild | 40.15 (32.54-47.76) | 43.22 (37.75-48.68) | 35.28 (29.93-40.63) | 32.53 (24.03-41.03) | |
| Moderate | 18.73 (14.49-22.97) | 19.72 (16.57-22.87) | 17.18 (11.48-22.88) | 16.25 ( 8.35-24.15) | |
| Heavy | 15.98 (13.25-18.70) | 14.79 (11.82-17.77) | 16.51 (11.81-21.21) | 24.73 (16.17-33.29) | |
| **Cardiovascular diseases** | 7.82 ( 6.33- 9.32) | 6.24 (5.05- 7.44) | 11.38 (8.50-14.26) | 7.24 (2.99-11.48) | 0.003 |
| **Hypertension** | 56.45 (49.84-63.06) | 52.01 (47.49-56.52) | 63.21 (58.69-67.74) | 68.69 (63.15-74.24) | < 0.001 |
| **Diabetes** | 14.17 (11.92-16.43) | 10.97 ( 9.01-12.93) | 21.37 (18.55-24.19) | 12.97 ( 7.27-18.67) | < 0.001 |
| **Chronic kidney disease** | 14.93 (12.73-17.13) | 12.57 (10.40-14.75) | 19.74 (16.90-22.59) | 16.15 (10.83-21.47) | < 0.001 |
| **AAC-8 score** | | | | | 0.005 |
| < 3 | 94.75 (82.27-107.22) | 96.32 (94.70-97.94) | 91.82 (89.49-94.15) | 92.69 (88.05-97.32) | |
| ≥ 3 | 5.25 ( 3.65- 6.86) | 3.68 (2.06- 5.30) | 8.18 (5.85-10.51) | 7.31 (2.68-11.95) | |
| **AAC-24 score** | | | | | 0.004 |
| 0 | 75.38 (64.00-86.75) | 77.23 (73.37-81.09) | 73.27 (67.34-79.21) | 67.15 (58.31-76.00) | |
| 1-6 | 19.79 (15.77-23.82) | 19.62 (15.94-23.31) | 18.85 (14.06-23.64) | 25.48 (17.29-33.67) | |
| > 6 | 4.83 ( 3.85- 5.81) | 3.15 (2.14- 4.16) | 7.88 (5.61-10.15) | 7.37 (2.91-11.83) | |
| **Laboratory measurements** | | | | | |
| Albumin (g/dL) | 4.27±0.01 | 4.29±0.02 | 4.22±0.02 | 4.20±0.03 | 0.001 |
| Serum calcium (mg/dL) | 9.45±0.01 | 9.45±0.01 | 9.43±0.02 | 9.47±0.03 | 0.573 |
| Serum phosphorus (mg/dL) | 3.79±0.02 | 3.81±0.03 | 3.74±0.02 | 3.77±0.03 | 0.096 |
| Uric acid (mg/dL) | 5.37±0.04 | 5.29±0.04 | 5.54±0.10 | 5.45±0.14 | 0.126 |
| Total 25-hydroxyvitamin D (nmol/L) | 73.21±1.48 | 76.57±1.85 | 68.88±1.87 | 60.62±2.46 | < 0.001 |
| Hemoglobin (g/dL) | 14.21±0.04 | 14.17±0.04 | 14.23±0.09 | 14.44±0.12 | 0.114 |
| Total cholesterol (mg/dL) | 195.97±1.04 | 195.69±1.29 | 196.00±1.97 | 198.53±3.98 | 0.828 |
| High-density lipoprotein cholesterol (mg/dL) | 54.62±0.70 | 56.58±0.85 | 51.33±0.75 | 50.60±1.43 | < 0.001 |
| Triglycerides (mg/dL) | 160.21±3.40 | 152.06± 4.25 | 174.33± 4.71 | 175.34±16.35 | 0.011 |

Values indicate the weighted mean ± SD or weighted % (95% confidence interval). P-values are weighted. AAC, abdominal aortic calcification

**TABLE 3** Weighted multiple logistic regression coefficients (ORs) and 95% confidence intervals for the association between periodontal status with AAC group: The United States, 2013 to 2014 (exclude participants with missing covariates)

| | Case/participants | Model 1<br>OR (95% CI), P- value | Model 2<br>OR (95% CI), P- value | Model 3<br>OR (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score ≥ 3 points versus AAC-8 score < 3 points** | | | | |
| No periodontitis | 44/977 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 57/661 | 1.72(0.84,3.54)<br>p=0.116 | 1.53(0.81,2.88)<br>p=0.171 | 1.56(0.83,2.92)<br>p=0.153 |
| Severe periodontitis | 15/180 | 2.44(0.96,6.21)<br>p=0.059 | 1.80(0.81,4.00)<br>p=0.137 | 1.80(0.77,4.22)<br>p=0.160 |
| **Mild–moderate AAC versus no AAC** | | | | |
| No periodontitis | 224/939 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 144/607 | 0.87(0.58,1.31)<br>p=0.439 | 0.71(0.50,1.02)<br>p=0.060 | 0.69(0.49,0.97)<br>p=0.033 |
| Severe periodontitis | 50/164 | 1.52(0.78,2.96)<br>p=0.181 | 1.06(0.49,2.30)<br>p=0.869 | 0.99(0.46,2.10)<br>p=0.972 |
| **Severe AAC versus no AAC** | | | | |
| No periodontitis | 38/784 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 54/538 | **2.11(1.10, 4.05)**<br>**p=0.030** | **1.89(1.02, 3.50)**<br>**p=0.044** | **1.89(1.01, 3.56)**<br>**p=0.048** |
| Severe periodontitis | 16/139 | **5.22(1.85,14.76)**<br>**p=0.007** | **2.81(1.06, 7.42)**<br>**p=0.038** | 2.73(0.92, 8.13)<br>p=0.068 |
| **Severe AAC versus mild–moderate AAC** | | | | |
| No periodontitis | 38/231 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 54/177 | **2.20(1.20,4.04)**<br>**p=0.018** | 1.82(0.98,3.39)<br>p=0.059 | 1.87(0.96, 3.66)<br>p=0.065 |
| Severe periodontitis | 16/57 | 2.41(0.79,7.29)<br>p=0.103 | 1.85(0.78,4.38)<br>p=0.147 | 1.85(0.75, 4.60)<br>p=0.168 |

Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. No AAC, mild–moderate AAC and Severe AAC were defined by AAC-24 score. AAC: abdominal aortic calcification.

**TABLE 4** Weighted multiple logistic regression coefficients (ORs) and 95% confidence intervals for the association between periodontal status (exclude participants with mild periodontitis) with AAC group: The United States, 2013 to 2014

| | Case/participants | Model 1<br>OR (95% CI), P- value | Model 2<br>OR (95% CI), P- value | Model 3<br>OR (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score ≥ 3 points versus AAC-8 score < 3 points** | | | | |
| No periodontitis | 34/1142 | Reference | Reference | Reference |
| Moderate periodontitis | 53/773 | 1.94(0.86,4.40)<br>P=0.096 | 1.68(0.82,3.46)<br>P=0.147 | 1.73(0.87,3.42)<br>P=0.109 |
| Severe periodontitis | 14/220 | **3.12(1.17,8.36)**<br>**P=0.029** | **2.44(1.02,6.00)**<br>**P=0.046** | **2.44(1.01,6.05)**<br>**P=0.048** |
| **Mild–moderate AAC versus no AAC** | | | | |
| No periodontitis | 224/1102 | Reference | Reference | Reference |
| Moderate periodontitis | 141/711 | 0.90(0.57,1.41)<br>P=0.587 | 0.75(0.52,1.09)<br>P=0.121 | 0.72(0.50,1.03)<br>P=0.069 |
| Severe periodontitis | 50/200 | 1.46(0.80,2.68)<br>P=0.184 | 1.05(0.52,2.11)<br>P=0.881 | 0.96(0.48,1.94)<br>P=0.906 |
| **Severe AAC versus no AAC** | | | | |
| No periodontitis | 40/918 | Reference | Reference | Reference |
| Moderate periodontitis | 62/632 | **2.37(1.07, 5.22)**<br>**P=0.036** | 1.97(0.96,4.06)<br>P=0.063 | **2.03(1.02,4.03)**<br>**P=0.044** |
| Severe periodontitis | 20/170 | **6.02(2.44,14.86)**<br>**P=0.002** | **3.49(1.53,7.97)**<br>**P=0.006** | **3.48(1.42,8.54)**<br>**P=0.010** |
| **Severe AAC versus mild–moderate AAC** | | | | |
| No periodontitis | 40/264 | Reference | Reference | Reference |
| Moderate periodontitis | 62/203 | **2.47(1.23,4.96)**<br>**P=0.018** | **2.10(1.08,4.07)**<br>**P=0.031** | **2.17(1.09, 4.32)**<br>**P=0.030** |
| Severe periodontitis | 20/70 | **3.10(1.15,8.32)**<br>**P=0.030** | **2.76(1.16,6.57)**<br>**P=0.025** | **2.75(1.14, 6.63)**<br>**P=0.027** |

Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. No AAC, mild–moderate AAC and Severe AAC were defined by AAC-24 score. AAC: abdominal aortic calcification.

**TABLE 5** Weighted multiple logistic regression coefficients (ORs) and 95% confidence intervals for the association between periodontal status with AAC group: The United States, 2013 to 2014 (exclude participants with cardiovascular diseases)

| | Case/participants | Model 1<br>OR (95% CI), P- value | Model 2<br>OR (95% CI), P- value | Model 3<br>OR (95% CI), P- value |
|---|---|---|---|---|
| **AAC-8 score ≥ 3 points versus AAC-8 score < 3 points** | | | | |
| No periodontitis | 34/1066 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 53/692 | 2.25(0.98,5.17)<br>P= 0.054 | 1.90(0.95,3.81)<br>P=0.067 | **1.95(1.02,3.73)**<br>**P=0.044** |
| Severe periodontitis | 14/202 | **3.27(1.26,8.48)**<br>**P=0.022** | 2.18(0.88,5.45)<br>P=0.088 | 2.14(0.86,5.35)<br>P=0.096 |
| **Mild–moderate AAC versus no AAC** | | | | |
| No periodontitis | 208/1038 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 118/639 | 0.83(0.52,1.32)<br>P=0.371 | **0.68(0.47,0.99)**<br>**P=0.049** | **0.65(0.45,0.94)**<br>**P=0.026** |
| Severe periodontitis | 44/187 | 1.33(0.70,2.51)<br>P=0.330 | 0.90(0.41,1.95)<br>P=0.774 | 0.83(0.38,1.81)<br>P=0.618 |
| **Severe AAC versus no AAC** | | | | |
| No periodontitis | 28/858 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 53/574 | **3.17(1.61, 6.26)**<br>**P=0.005** | **2.62(1.44, 4.76)**<br>**P=0.004** | **2.71(1.49, 4.93)**<br>**P=0.003** |
| Severe periodontitis | 15/158 | **6.00(2.47,14.57)**<br>**P=0.002** | **3.00(1.31, 6.87)**<br>**P=0.013** | **2.89(1.13, 7.40)**<br>**P=0.029** |
| **Severe AAC versus mild–moderate AAC** | | | | |
| No periodontitis | 28/236 | Reference | Reference | Reference |
| Mild–moderate periodontitis | 53/171 | **3.17(1.73, 5.80)**<br>**P=0.003** | **2.99(1.68, 5.32)**<br>**P=0.001** | **3.16(1.75, 5.69)**<br>**P<0.001** |
| Severe periodontitis | 15/59 | **3.79(1.38,10.43)**<br>**P=0.017** | **3.82(1.42,10.27)**<br>**P=0.011** | **3.75(1.32,10.60)**<br>**P=0.016** |

Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension and CKD; and Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. No AAC, mild–moderate AAC and Severe AAC were defined by AAC-24 score. AAC: abdominal aortic calcification.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

| | Item No | Recommendation | Page number and Line number |
|---|---|---|---|
| **Title and abstract** | 1 ✓title+abstract | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1-2<br>Line 2-4; 15-36 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 1-2<br>Line 2-4; 15-36 |
| **Introduction** | | | |
| Background/rationale | 2 ✓ introduction | Explain the scientific background and rationale for the investigation being reported | Page 3-4<br>Line 47-73 |
| Objectives | 3 ✓ introduction | State specific objectives, including any prespecified hypotheses | Page 4<br>Line 74-83 |
| **Methods** | | | |
| Study design | 4 ✓ data source | Present key elements of study design early in the paper | Page 5<br>Line 86-105 |
| Setting | 5 ✓ data source | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 5<br>Line 86-105 |
| Participants | 6 ✓ data source | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | Page 5<br>Line 86-105 |
| Variables | 7 ✓ definitions of periodontitis; abdominal aortic calcification outcomes; covariates | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 5-8<br>Line 106-162 |
| Data sources/ measurement | 8* ✓ definitions of periodontitis; abdominal aortic calcification outcomes; covariates | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Page 5-8<br>Line 106-162 |
| Bias | 9 ✓ statistical analysis | Describe any efforts to address potential sources of bias | Page 8-9<br>Line 163-191 |
| Study size | 10 ✓ data source; | Explain how the study size was arrived at | Page 5 |

| | | | |
|---|---|---|---|
| | figure 1; | | Line 86-105 |
| Quantitative variables | 11 ✓ statistical analysis | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 8-9<br>Line 163-191 |
| Statistical methods | 12 ✓ statistical analysis | (*a*) Describe all statistical methods, including those used to control for confounding | Page 8-9<br>Line 163-191 |
| | ✓ statistical analysis | (*b*) Describe any methods used to examine subgroups and interactions | Page 8-9<br>Line 163-191 |
| | ✓ statistical analysis | (*c*) Explain how missing data were addressed | Page 8-9<br>Line 163-191 |
| | ✓ statistical analysis | | |
| | ✓ statistical analysis | (*d*) If applicable, describe analytical methods taking account of sampling strategy | Page 8-9<br>Line 163-191 |
| | | (*e*) Describe any sensitivity analyses | Page 8-9<br>Line 163-191 |
| **Results** | | | |
| Participants | 13* ✓ data source; figure 1 | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 5<br>Line 86-105 |
| | ✓ data source; figure 1;supplementary table1 | (b) Give reasons for non-participation at each stage | Page 5<br>Line 86-105 |
| | ✓figure 1 | (c) Consider use of a flow diagram | - |
| Descriptive data | 14* ✓ table 1 | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Page 9-11<br>Line 196-211 |
| | ✓supplementary table1 | (b) Indicate number of participants with missing data for each variable of interest | - |
| Outcome data | 15* ✓ Table 1 to 4 | Report numbers of outcome events or summary measures | - |
| Main results | 16 ✓ table 2; table 3; Table 4; | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and | - |

| | | | |
|---|---|---|---|
| | | why they were included | |
| | ✓ covariates | (*b*) Report category boundaries when continuous variables were categorized | Page 7-8<br>Line 133-162 |
| | × this study does not involve | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | - |
| Other analyses | 17 ✓ results | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Page 13-15<br>Line 242-270 |
| **Discussion** | | | |
| Key results | 18 ✓ discussion – 1nd paragraph | Summarise key results with reference to study objectives | Page 15<br>Line 272-286 |
| Limitations | 19 ✓ discussion – 4th paragraph | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Page 17-18<br>Line 329-345 |
| Interpretation | 20 ✓ discussion – 2th-3th paragraphs | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Page 15-17<br>Line 287-328 |
| Generalisability | 21 ✓ discussion – 4th | Discuss the generalisability (external validity) of the study results | Page 17-18<br>Line 329-345 |
| **Other information** | | | |
| Funding | 22 ✓ | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 19<br>Line 362-363 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.