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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.

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

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

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

27 **Results:** The prevalence of severe periodontitis combined with severe AAC was 8.49%-8.54%.
28 According to the AAC-8 and AAC-24 score classifications, patients with severe periodontitis had
29 higher odds of severe AAC [AAC-8 score ≥ 3 : (OR: 2.53; 95% CI 1.04, 6.17) and AAC-24 score >6 :
30 (OR: 3.60; 95% CI 1.48, 8.78)]. A positive association between mild-moderate periodontitis and severe
31 AAC was found only when the AAC-24 score was applied (OR: 2.25; 95% CI 1.24, 4.06). In the
32 subgroup analyses, the likelihood ratio test showed no multiplicative interaction (all P for interaction
33 > 0.05).

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

37 **Strengths and limitations of this study**

38 1. This is the first population-based cross-sectional epidemiological study to explore the link between
39 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 prevalence¹. 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 age². Periodontitis can affect the risk of systemic diseases, including cardiovascular disease (CVD)³⁻⁴, diabetes⁵, 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 sequelae⁷. As part of its strategy, the Centers for Disease Control and Prevention (CDC) is supporting and improving periodontal disease surveillance⁸.

The abdominal aorta is considered to valuable in observing early atherosclerotic calcification⁹, and its degree of calcification is closely related to the prevalence of and mortality due to CVD¹⁰. 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 disease¹¹⁻¹². 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 participants¹³. In addition, a cross-sectional study and meta-analysis suggested that periodontitis was associated with carotid calcification¹⁴⁻¹⁵, and there was radiographic evidence suggesting the possible involvement of intracranial carotid calcification¹⁶. However, other cohort studies reported inconsistent conclusions¹⁷⁻¹⁸. 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 stimuli¹⁹. Previous animal studies demonstrated that periodontitis and vascular calcification promoted each other²⁰, and the mechanisms involved were gradually revealed in subsequent studies²¹⁻²⁴.

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 calcification²⁶. 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.

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2
3 86 The NHANES 2013-2014 was a cross-sectional, nationally representative survey of the U.S.
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5 87 noninstitutionalized civilian population designed to examine demographic, socioeconomic, health, and
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7 88 nutritional information. To ensure a representative sample, complex multistage sampling was used to
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10 89 collect data, and strata were determined based on geographic location and population proportions²⁷.

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13 90 The NHANES 2013-2014 was the only cycle that also performed examinations for periodontitis
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15 91 and abdominal aortic calcification. Participants ≥ 40 years of age who received a full-mouth
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17 92 periodontal examination and participated in lateral DXA scans of the thoraco-lumbar spine were
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19 93 included in this study. In the 2013-2014 cycle of the NHANES, 10,175 participants completed the
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21 94 survey. However, in this study, individuals aged < 40 years without complete information about
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23 95 periodontitis and abdominal aortic calcification were excluded (N = 7,741). Additionally, cancer
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25 96 participants (N = 285) were excluded from the analysis. Ultimately, 2,149 participants were included
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27 97 in the analysis (Figure 1). All participants provided written informed consent to participate in
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29 98 NHANES, and the NCHS Research Ethics Review Board approved the protocol (NCHS IRB/ERB
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31 99 Protocol Number: Continuation of Protocol #2011-17). The study was designed according to the
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33 100 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for
34
35 101 reporting cross-sectional studies²⁸, and all procedures were performed in accordance with the principles
36
37 102 of the Helsinki Declaration of 1975.

38 39 40 41 42 43 44 103 **2.2. Definitions of periodontitis**

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46 104 Oral health examinations were performed by dental examiners who were licensed dentists in at
47
48 105 least one state in the U.S. During oral health assessments, a portable dental chair, lights, and
49
50 106 compressed air were provided in a mobile examination center (MEC). All dental examiners received
51
52 107 standardized training and collected reliable statistical data to objectively assess examiner agreement²⁹.

1
2 108 Six measurement points were selected for periodontal examinations (mesiobuccal, midbuccal,
3
4 109 distobuccal, mesiolingual, midlingual, and distolingual) for all teeth, with the exception of third molars.
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6 110 Indicators of periodontitis included probing depth (PD) and clinical attachment loss (AL), which are
7
8 111 important bases for the CDC/AAP classification/case definition³⁰. Accordingly, periodontitis was
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10 112 divided into mild periodontitis, moderate periodontitis and severe periodontitis, No periodontitis was
11
12 113 defined as no evidence of mild, moderate, or severe periodontitis. Because there were few data from
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14 114 those with mild periodontitis, mild periodontitis and moderate periodontitis were combined for analysis
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16 115 in our study.
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21 116 **2.3. Abdominal aortic calcification outcomes**

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23 117 AAC can be accurately identified on lateral spine images obtained by DXA and shows good
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25 118 sensitivity and specificity at lower radiation doses³¹⁻³². Those < 40 years old, pregnant, weighing over
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27 119 450 pounds, or ingesting barium within the last week were ineligible for DXA scans in this study. Both
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29 120 the AAC-24 and AAC-8 semiquantitative scoring tools were used for AAC evaluation²⁵. An
30
31 121 assessment of the length of anterior and posterior aortic wall calcification anterior to the L1 to L4
32
33 122 vertebral bodies was made using the AAC-8 score, and participants with a score of three or more were
34
35 123 considered to be at high risk for AAC. Using the L1-L4 region as a reference, the anterior and posterior
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37 124 aortic walls are divided into four segments to calculate the AAC-24 score. Depending on the degree of
38
39 125 calcification, each vertebral body can receive a score from 0 to 6, with a total possible score of 0 to 24;
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41 126 this allows a more precise assessment of abdominal aortic calcification. We categorized AAC-24 scores
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43 127 into three groups: no calcification (AAC-24 score =0), mild to moderate calcification ($6 \geq$ AAC-24
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45 128 score > 0) and severe calcification (AAC-24 score >6).
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52 129 **2.4. Covariates**

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3 130 Based on previous studies, we considered some confounding factors potentially associated with
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5 131 periodontitis and AAC in our analysis, including socioeconomic factors, behavioral factors, body mass
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7 132 index (BMI), medical history, and laboratory measurements³³⁻³⁴.

9
10 133 Information about socioeconomic factors was obtained during the home interview. The poverty
11
12 134 income ratio (PIR) was stratified into <1.3, 1.3–3.5, and >3.5, as recorded in the original survey.
13
14 135 Behavioral factors were obtained from self-reports. A never smoker is an individual who has never
15
16 136 smoked more than 100 cigarettes in their lifetime. Former smokers were defined as those who smoked
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18 137 more than 100 cigarettes in their lifetime and had quit smoking, and smokers have to smoke at least
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20 138 100 cigarettes in their lifetime and smoke some days or every day to qualify as current smokers.
21
22 139 The status of alcohol consumption was categorised as never (never drank greater than or equal to
23
24 140 12 drinks in their lifetime), former (greater than or equal to 12 drinks in 1 year and did not drink last
25
26 141 year, or did not drink last year but drank ≥ 12 drinks in their lifetime), current mild (≤ 1 drink/d for
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28 142 female or ≤ 2 drink/d for male on average over the past year), current moderate (2 drink/d for female
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30 143 or 3 drink/d for male on average over the past year), current heavy drinkers (≥ 3 drink/d for female or
31
32 144 ≥ 4 drink/d for male on average over the past year). BMI was measured at a MEC using standard
33
34 145 protocols and stratified into ≥ 30 and < 30 .

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36 146 Those participants who self-reported heart failure, angina, coronary heart disease, heart attack, or
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38 147 stroke diagnosed by a physician were classified as having CVD. The definition of hypertension was a
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40 148 diagnosis by a healthcare professional, an average blood pressure of $\geq 130/80$ mmHg or using
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42 149 hypertension medications³⁵. Diabetes was defined as a diagnosis made by a physician or
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44 150 other healthcare professional, HbA1c (%) > 6.5 , random blood glucose (mmol/l) ≥ 11.1 , or use of
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46 151 diabetes medication or insulin. As defined by the International Renal Association, chronic kidney
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48 152 disease is characterized by an estimated glomerular filtration rate < 60 mL/min/1.73 m² or a urine
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2 153 albumin–creatinine ratio of at least 30³⁶. Based on serum creatinine, the Chronic Kidney Disease
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4 154 Epidemiology Collaboration (CKD-EPI) equation was used to estimate the glomerular filtration rate³⁷.
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7 155 Laboratory data were obtained from participant serum samples that were processed in the Collaborative
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9 156 Laboratory Services, Ottumwa, Iowa, for analysis. Detailed instructions regarding specimen collection
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11 157 and processing are documented in the NHANES Laboratory Procedures Manual, and quality control
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13 158 was in accordance with standard procedures.
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17 159 **2.5. Statistical analysis**

19 160 A weight is assigned to the NHANES to compensate for the complex survey design, survey
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21 161 nonresponses, and poststratification adjustment to match the total U.S. population.. All results of this
22
23 162 study were weighted by 2-year MEC weights. In accordance with the CDC/AAP classification of
24
25 163 periodontitis, descriptive statistics were calculated to describe the characteristics of the participants.
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27 164 Continuous variables are presented as the weighted mean \pm standard deviation (SD) and were compared
28
29 165 using a one-way ANOVA, while categorical variables were compared using the Rao-Scott chi-square
30
31 166 test and are presented as weighted percentages (95% confidence interval, 95% CI). Linear regression
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33 167 was used to evaluate the association of the AAC-8 score and AAC-24 score as dependent variables
34
35 168 with periodontitis with varying degrees of severity as independent variables. Beta coefficients and 95%
36
37 169 CIs were calculated. Multivariate logistic regression analysis was performed to evaluate the correlation
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39 170 between periodontitis with varying degrees of severity and AAC with varying degrees of severity using
40
41 171 odds ratios (ORs) and 95% CIs. Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for
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43 172 the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status,
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45 173 PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in
46
47 174 Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D,
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49 175 hemoglobin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides
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51 176 (TGs). Subgroup analysis stratified by age, sex, CVD, hypertension, diabetes, and CKD was also
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3 177 conducted using stratified multivariate regression analysis, and multiplicative interactions were
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5 178 assessed using likelihood ratio tests.
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8 179 In this study, we used the MissForest³⁸ package in R software to address missing covariates. The
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10 180 algorithm can address categorical and continuous variables and shows superior performance. The
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12 181 numbers and percentages of missing covariate data are shown in Supplementary Material Table 1.
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14 182 Sensitivity analyses were performed as followed: (1) only participants with complete data were
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16 183 included, and participants with missing covariates were excluded; (2) mild and moderate periodontitis
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18 184 were not combined for analysis, and mild periodontitis was excluded; and (3) participants with CVD
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20 185 were excluded. R software (version 4.1.3) was used for all statistical analyses. It was considered
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22 186 statistically significant if the P value was less than 0.05 for all statistical tests of two-tailed.
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28 187 **2.6. Patient and public involvement**

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30 188 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination
31 189 plans of our research.
32

33 190 **3. Results**

34
35 191 Descriptive statistics of our study participants by periodontitis status according to the CDC/AAP
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37 192 case definitions are presented in Table 1. The study included 2,149 participants, representing
38
39 193 86,199,511 noninstitutionalized adults (40 years and older) in the U.S. Overall, participants had a mean
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41 194 age±SD of 54.96 ± 0.32 years; 50.46% (44.32, 56.60) were female, and 68.14% (54.20, 82.08) were
42
43 195 non-Hispanic white. The prevalence of mild-moderate periodontitis was 29.93 (25.36, 34.51) and that
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45 196 of severe periodontitis was 6.77 (5.40, 8.13). Periodontitis was more prevalent in older individuals,
46
47 197 males, those with a low educational level, those with a low PIR, and those with low insurance coverage
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49 198 than in their counterparts and showed differences among races. The prevalence of mild to moderate
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51 199 AAC and severe AAC was significantly higher in participants with periodontitis than in those without.
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55 200 In addition, we also found significant differences in smoking status, alcohol consumption status, CVD,
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201 diabetes, hypertension, CKD, albumin, total 25-hydroxyvitamin D, TGs, and HDL-C compared with
 202 participants without periodontitis (all $p < 0.05$).

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

Characters	Overall (n=2,149)	No Periodontitis (n=1,142)	Mild-Moderate periodontitis (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 high 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)	
High 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 high 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

205 Note: Values indicate the weighted mean ± SD or weighted % (95% confidence interval). P-values are weighted.

206 AAC, abdominal aortic calcification.

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

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

	Case/participants	Model 1 β (95% CI), P- value	Model 2 β (95% CI), P- value	Model 3 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) P=0.149	0.03(-0.11,0.17) P=0.643	0.02(-0.12,0.17) P=0.740
Severe periodontitis	220/2149	0.29(0.08,0.50) P=0.015	0.17(-0.07,0.41) P=0.159	0.17(-0.08,0.41) 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

215 Note: Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for the parameters in Model 1 plus insurance,
 216 education level, smoking status, alcohol consumption status, PIR, BMI, diabetes, hypertension, CVD and CKD; and
 217 Model 3 was adjusted for the parameters in Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total
 218 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. AAC: abdominal aortic calcification.

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

in the high-AAC risk group (AAC-8 score \geq 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 \geq 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

235 25-hydroxyvitamin D, hemoglobin, TC, HDL-C, and TGs. No AAC, mild–moderate AAC and Severe AAC were
 236 defined by AAC-24 score. AAC: abdominal aortic calcification.

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

243 **TABLE 4** Subgroup analysis for the association between periodontal status and risk of severe AAC (AAC-8 score
 244 ≥ 3 points).

	Periodontal status OR (95% CI), P- value			
	No periodontitis	Mild–moderate periodontitis	Severe periodontitis	P for interaction
Age				0.212
$\geq 60y$	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

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

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

265 4. Discussion

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

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3 268 (40 years and older). Our study fully considered socioeconomic status, behavioral factors and medical
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5 269 history of the participants and controlled for a wide range of confounders. Severe periodontitis was
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7 270 positively associated with severe AAC, defined by either the AAC-8 score or AAC-24 score. A positive
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10 271 association between mild to moderate periodontitis and severe AAC was found only when AAC was
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12 272 classified by the AAC-24 score. In the subgroups stratified by age; sex; and CVD, hypertension,
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14 273 diabetes, and CKD status, this association and the main results were generally consistent; the only
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16 274 difference was associated with the different severities of periodontitis, which differed in their
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19 275 associations with severe AAC in the stratified population. Linear regression evaluation of the AAC-8
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21 276 score and AAC-24 score as dependent variables and the different severities of periodontitis as
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23 277 independent variables showed no linear correlation. In the sensitivity analysis, the association remained
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26 278 significant after excluding participants with mild periodontitis and CVD. However, the association was
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28 279 no longer significant after excluding participants with missing covariates.

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31 280 To date, some epidemiological studies have suggested a close relationship between periodontitis
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33 281 and vascular calcification or CVD. A consensus report on periodontitis and CVD states that
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35 282 periodontitis is broadly associated with CVD and that the link is bidirectional; CVD drives the
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38 283 progression of periodontitis and vice versa³⁹. NHANES-based cross-sectional studies have shown an
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40 284 association between periodontitis severity and cardiovascular risk⁴, as demonstrated by the results of a
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43 285 13-year cohort study, and further studies suggest that periodontitis may be an independent risk factor
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45 286 for CVD⁴⁰. Oindrila Paul et al. reviewed the pathophysiology of periodontitis and showed that
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47 287 inflammation associated with periodontitis may be the main mechanism affecting CVD and could be
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50 288 facilitated by common risk factors⁴¹. Vascular calcification has been shown to involve soft tissue
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52 289 calcification also caused by chronic inflammatory stimuli¹⁹ and is closely related to the prevalence and
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54 290 prognosis of CVD. This may suggest that the association between periodontitis and CVD may depend
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57 291 on the severity of vascular calcification. The results of a cross-sectional Japanese population-based

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2 292 study suggest that measuring alveolar bone loss on panoramic radiographs may be an effective method
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4 293 to identify an increased risk of carotid artery calcification¹⁴. Imaging studies using cone-beam
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6 294 computed tomography have further confirmed that the development of periodontitis may cause
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9 295 calcification involving the intracranial carotid arteries¹⁶. The results from a meta-analysis that included
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11 296 12 studies also revealed a significant relationship between periodontitis and carotid artery
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13 297 calcification¹⁵. Similar to our findings, a cohort study in Chinese populations suggested that
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16 298 periodontitis was also positively associated with aortic calcification, and this association was more
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18 299 pronounced in men and in participants younger than 65 years¹³.

20
21 300 The exact mechanism of the link between periodontitis and AAC remains unclear and needs to be
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23 301 further explored. Existing mainstream views suggest that *Porphyromonas gingivalis* (*P. gingivalis*)
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25 302 infection and chronic inflammation are important bridges between periodontitis and vascular
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27 303 calcification^{19, 41-42}. Recent studies have shown that periodontal pathogens can be detected in the blood
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29 304 of patients with coronary heart disease, and it is hypothesized that periodontal pathogens can spread
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31 305 through the blood to other parts of the body, where they may enhance inflammatory processes, leading
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33 306 to the development or aggravation of atherosclerosis⁴³. Evidence from in vitro cell culture studies
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35 307 suggests that *P. gingivalis* infection accelerates phosphate-induced calcification of vascular smooth
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37 308 muscle cells²² and that *P. gingivalis* lipopolysaccharide increases alkaline phosphatase activity and
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39 309 upregulates the expression of genes involved in calcification to stimulate calcification⁴⁴. In addition, it
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41 310 has been shown that *P. gingivalis* invasiveness is enhanced after high-glucose treatment, and vascular
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43 311 calcification can be initiated by stimulating autocrine regulation of bone morphogenetic protein 4 in
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45 312 aortic smooth muscle cells²¹. *P. gingivalis* infection elicits an inflammatory response in the host, which
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47 313 is in line with the definition of periodontitis as a chronic inflammatory disease. A meta-analysis
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49 314 suggested that the diagnosis of chronic aggressive periodontitis was consistently associated with higher
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51 315 C-reactive protein and high-sensitivity C-reactive protein levels, and treatment reduced serum C-
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3 316 reactive protein levels⁴⁵. In addition, studies have observed an association between periodontitis and
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5 317 systemic inflammation, which increases with the severity of periodontal disease⁴⁶. Notably, there are
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7 318 studies revealing other possible mechanisms involved in the link between periodontitis and vascular
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10 319 calcification, including the activation of osteoprotegerin/receptor activator of nuclear factor- κ B ligand
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12 320 and endoplasmic reticulum stress-induced apoptosis²³⁻²⁴.

15 321 Our study has several important strengths. Our findings were derived from a large nationwide
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17 322 random sample survey and can be generalized to the adult noninstitutionalized population in the U.S.
18
19 323 Periodontitis and AAC were defined based on objective clinical data collected by calibrated
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21 324 professionals. In addition, this study addressed a number of known potential confounders, and sample
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23 325 weights were applied in each analysis following the NHANES guidelines to account for the complex
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25 326 survey design. However, several limitations of this study warrant attention. Given the cross-sectional
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27 327 design of the NHANES, it is difficult for us to determine causality, and further large-scale prospective
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29 328 studies are needed. In addition, we cannot exclude the possibility of residual confounding by other
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31 329 confounding factors related to oral health, which could have influenced the observed results. It is worth
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33 330 noting that only a small proportion of patients with severe periodontitis in our study had severe AAC;
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35 331 perhaps because of this, the results of the sensitivity analysis excluding patients with missing covariates
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37 332 were not robust. This also suggests that the conclusions of this study should be interpreted with caution.
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39 333 An explanation for this phenomenon is the possibility of selection bias⁴⁷. In addition, tooth loss is not
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41 334 considered in the CDC/AAP case definition of periodontitis; therefore, the prevalence of the disease
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43 335 may be underestimated³⁰. Because of the sample size, we were not able to include the new periodontal
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45 336 profile class (PPC) system to precisely classify periodontal disease because this classification method
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47 337 classifies periodontitis into seven categories: PPC-A to PPC-G⁴⁸.

55 338 **5. Conclusion**

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2 339 Our study suggests that periodontitis is associated with an increased risk of severe AAC in the
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4 340 U.S. population aged 40 years and older. The associations investigated in this study are credible due to
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6 341 their cross-sectional nature, but these findings require further large-scale prospective studies to
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8
9 342 confirm.

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24

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29 349 KK, AnA and AiA participated in the design of the study, analysis of the data and drafted the
30
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32
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48 356 **Competing interests**

51 357 None declared.
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54 358 **Patient consent for publication**

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3 359 The participants provided written informed consent to participate in the NHANES survey.
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5

6 360 **Ethics approval**

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8

9 361 The present study complied with the term of the Declaration of Helsinki and was approved by the
10
11 362 NCHS Research Ethics Review Committee (NCHS IRB/ERB Protocol Number: Continuation of
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13 363 Protocol #2011-17).
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16 364 **Data availability statement**

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19 365 This study is a secondary analysis based on a publicly available database and the raw data can be
20
21 366 found on the website: <https://www.cdc.gov/nchs/nhanes/index.htm>
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26 367 **References**

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8 9 480 **Figure legends**

10
11 481 Figure 1. Flow chart of eligible National Health and Nutrition Examination Survey (NHANES)
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13 482 participants included in this study.
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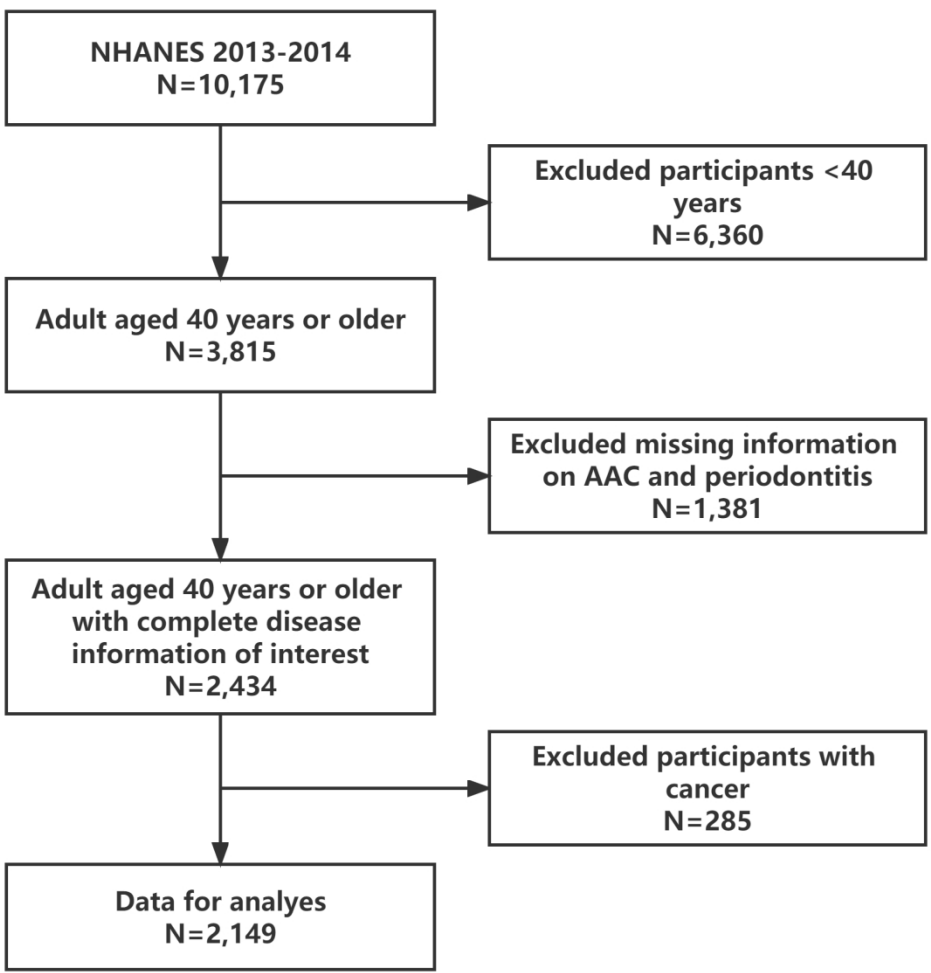


Figure 1. Flow chart of eligible National Health and Nutrition Examination Survey (NHANES) participants included in this study.

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 periodontitis (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 high 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)	
High 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 high 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 \pm 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 OR (95% CI), P- value	Model 2 OR (95% CI), P- value	Model 3 OR (95% CI), P- value
AAC-8 score \geq 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) p=0.116	1.53(0.81,2.88) p=0.171	1.56(0.83,2.92) p=0.153
Severe periodontitis	15/180	2.44(0.96,6.21) p=0.059	1.80(0.81,4.00) p=0.137	1.80(0.77,4.22) 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) p=0.439	0.71(0.50,1.02) p=0.060	0.69(0.49,0.97) p=0.033
Severe periodontitis	50/164	1.52(0.78,2.96) p=0.181	1.06(0.49,2.30) p=0.869	0.99(0.46,2.10) 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) p=0.030	1.89(1.02, 3.50) p=0.044	1.89(1.01, 3.56) p=0.048
Severe periodontitis	16/139	5.22(1.85,14.76) p=0.007	2.81(1.06, 7.42) p=0.038	2.73(0.92, 8.13) 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) p=0.018	1.82(0.98,3.39) p=0.059	1.87(0.96, 3.66) p=0.065
Severe periodontitis	16/57	2.41(0.79,7.29) p=0.103	1.85(0.78,4.38) p=0.147	1.85(0.75, 4.60) 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 OR (95% CI), P- value	Model 2 OR (95% CI), P- value	Model 3 OR (95% CI), P- value
AAC-8 score \geq 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) P=0.096	1.68(0.82,3.46) P=0.147	1.73(0.87,3.42) P=0.109
Severe periodontitis	14/220	3.12(1.17,8.36) P=0.029	2.44(1.02,6.00) P=0.046	2.44(1.01,6.05) 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) P=0.587	0.75(0.52,1.09) P=0.121	0.72(0.50,1.03) P=0.069
Severe periodontitis	50/200	1.46(0.80,2.68) P=0.184	1.05(0.52,2.11) P=0.881	0.96(0.48,1.94) 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) P=0.036	1.97(0.96,4.06) P=0.063	2.03(1.02,4.03) P=0.044
Severe periodontitis	20/170	6.02(2.44,14.86) P=0.002	3.49(1.53,7.97) P=0.006	3.48(1.42,8.54) 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) P=0.018	2.10(1.08,4.07) P=0.031	2.17(1.09, 4.32) P=0.030
Severe periodontitis	20/70	3.10(1.15,8.32) P=0.030	2.76(1.16,6.57) P=0.025	2.75(1.14, 6.63) 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 OR (95% CI), P- value	Model 2 OR (95% CI), P- value	Model 3 OR (95% CI), P- value
AAC-8 score \geq 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) P= 0.054	1.90(0.95,3.81) P=0.067	1.95(1.02,3.73) P=0.044
Severe periodontitis	14/202	3.27(1.26,8.48) P=0.022	2.18(0.88,5.45) P=0.088	2.14(0.86,5.35) 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) P=0.371	0.68(0.47,0.99) P=0.049	0.65(0.45,0.94) P=0.026
Severe periodontitis	44/187	1.33(0.70,2.51) P=0.330	0.90(0.41,1.95) P=0.774	0.83(0.38,1.81) 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) P=0.005	2.62(1.44, 4.76) P=0.004	2.71(1.49, 4.93) P=0.003
Severe periodontitis	15/158	6.00(2.47,14.57) P=0.002	3.00(1.31, 6.87) P=0.013	2.89(1.13, 7.40) 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) P=0.003	2.99(1.68, 5.32) P=0.001	3.16(1.75, 5.69) P<0.001
Severe periodontitis	15/59	3.79(1.38,10.43) P=0.017	3.82(1.42,10.27) P=0.011	3.75(1.32,10.60) 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.

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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 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 Line 2-4; 15-36
Introduction			
Background/rationale	2 ✓ introduction	Explain the scientific background and rationale for the investigation being reported	Page 3-4 Line 47-73
Objectives	3 ✓ introduction	State specific objectives, including any prespecified hypotheses	Page 4 Line 74-83
Methods			
Study design	4 ✓ data source	Present key elements of study design early in the paper	Page 5 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 Line 86-105
Participants	6 ✓ data source	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5 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 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 Line 106-162
Bias	9 ✓ statistical analysis	Describe any efforts to address potential sources of bias	Page 8-9 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 Line 163-191
Statistical methods	12 ✓ statistical analysis	(a) Describe all statistical methods, including those used to control for confounding	Page 8-9 Line 163-191
	✓ statistical analysis	(b) Describe any methods used to examine subgroups and interactions	Page 8-9 Line 163-191
	✓ statistical analysis	(c) Explain how missing data were addressed	Page 8-9
	✓ statistical analysis	(d) If applicable, describe analytical methods taking account of sampling strategy	Line 163-191
	✓ statistical analysis	(e) Describe any sensitivity analyses	Page 8-9 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 Line 86-105
	✓ data source; figure 1; supplementary table 1	(b) Give reasons for non-participation at each stage	Page 5 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 Line 196-211
	✓ supplementary table 1	(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 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 Line 242-270
Discussion			
Key results	18 ✓ discussion – 1 st paragraph	Summarise key results with reference to study objectives	Page 15 Line 272-286
Limitations	19 ✓ discussion – 4 th 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 Line 329-345
Interpretation	20 ✓ discussion – 2 th -3 th 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 Line 287-328
Generalisability	21 ✓ discussion – 4 th	Discuss the generalisability (external validity) of the study results	Page 17-18 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 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.

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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.

1
2 19 **Setting:** The National Health and Nutrition Examination Survey (2013–2014).
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5 20 **Participants:** A total of 2,149 participants aged 40 years or older who have complete information for
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7
8 21 periodontitis and AAC assessment test were included in this study.
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10
11 22 **Primary and secondary outcome measures:** AAC scores can be accurately identified on lateral spine
12
13 23 images obtained by DXA, and both the AAC-24 and AAC-8 semiquantitative scoring tools were used
14
15 24 for AAC evaluation. Linear regression analysis was used to investigate the relationship between
16
17 25 periodontitis and the AAC-8 and AAC-24 scores. Multivariate logistic regression models and reported
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19 26 odds ratios (ORs) were used to examine the relationship between periodontitis and AAC.
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23 27 **Results:** The prevalence of severe periodontitis combined with severe AAC was 8.49%-8.54%.
24
25 28 According to the AAC-8 and AAC-24 score classifications, patients with severe periodontitis had
26
27 29 higher odds of severe AAC [AAC-8 score ≥ 3 : (OR: 2.53; 95% CI 1.04, 6.17) and AAC-24 score >6 :
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29 30 (OR: 3.60; 95% CI 1.48, 8.78)]. A positive association between mild-moderate periodontitis and severe
30
31 31 AAC was found only when the AAC-24 score was applied (OR: 2.25; 95% CI 1.24, 4.06). In the
32
33 32 subgroup analyses, the likelihood ratio test showed no multiplicative interaction (all P for interaction
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35 33 > 0.05).
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40 34 **Conclusions:** The findings showed that periodontitis is associated with an increased risk of severe
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42 35 AAC in the U.S. population aged 40 years and older; this requires further large-scale prospective
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44 36 studies for confirmation.
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48 37 **Strengths and limitations of this study**

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51 38 1. A complex, multistage probability sampling approach was used to obtain a representative sample of
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53 39 individual composition to investigate the total national population.
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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 prevalence¹. 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 age². Periodontitis can affect the risk of systemic diseases, including cardiovascular disease (CVD)³⁻⁴, diabetes⁵, 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 sequelae⁷. As part of its strategy, the Centers for Disease Control and Prevention (CDC) is supporting and improving periodontal disease surveillance⁸.

1
2 60 The abdominal aorta is considered to valuable in observing early atherosclerotic calcification⁹,
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4 61 and its degree of calcification is closely related to the prevalence of and mortality due to CVD¹⁰.
5
6 62 Abdominal aortic calcification (AAC) is characterized by metabolic disorders involving minerals, such
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8 63 as calcium and phosphorus, and abnormal deposition in the vascular wall, which is common in patients
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10 64 with chronic disease¹¹⁻¹². Some epidemiological evidence suggests that periodontitis is associated with
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12 65 arterial calcification at multiple sites. A Chinese cohort study showed that periodontitis increased the
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14 66 risk of aortic calcification and was more pronounced in men and younger participants than in women
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16 67 and older participants¹³. In addition, a cross-sectional study and meta-analysis suggested that
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18 68 periodontitis was associated with carotid calcification¹⁴⁻¹⁵, and there was radiographic evidence
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20 69 suggesting the possible involvement of intracranial carotid calcification¹⁶. However, other cohort
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22 70 studies reported inconsistent conclusions¹⁷⁻¹⁸. In recent years, vascular calcification, including soft
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24 71 tissue calcification, has been recognized as an active process regulated by multiple molecular signaling
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26 72 pathways in response to chronic inflammatory stimuli¹⁹. Previous animal studies demonstrated that
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28 73 periodontitis and vascular calcification promoted each other²⁰, and the mechanisms involved were
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30 74 gradually revealed in subsequent studies²¹⁻²⁴.

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37 75 An assessment of the utility of the AAC score in a 25-year cohort study of 617 Framingham
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39 76 Heart Study participants was conducted by Kauppila et al. using lateral lumbar radiography as the
40
41 77 AAC grading tool (AAC score)²⁵. Based on the AAC score, it is possible to assess subclinical vascular
42
43 78 disease at a low cost, with predictive value for cardiovascular events and mortality independent of
44
45 79 coronary calcification²⁶. Therefore, using abdominal aortic calcification data obtained from dual-
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47 80 energy X-ray absorptiometry (DXA) in the 2013–2014 National Health and Nutrition Examination
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49 81 Survey (NHANES), the aim of this study was to investigate the relationship between periodontitis and
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51 82 AAC and propose new ideas for the prevention and management of AAC in clinical practice. We
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53 83 hypothesized that periodontitis would be associated with an increased prevalence of AAC.
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84 2. Materials and methods

85 2.1. Data source

86 The current cross-sectional study analyzed data from individuals who participated in the 2013 to
87 2014 NHANES, which was performed by the National Center for Health Statistics (NCHS) at the CDC.
88 The NHANES 2013-2014 was a cross-sectional, nationally representative survey of the U.S.
89 noninstitutionalized civilian population designed to examine demographic, socioeconomic, health, and
90 nutritional information. To ensure a representative sample, complex multistage sampling was used to
91 collect data, and strata were determined based on geographic location and population proportions²⁷.

92 The NHANES 2013-2014 was the only cycle that also performed examinations for periodontitis
93 and abdominal aortic calcification. Participants ≥ 40 years of age who received a full-mouth
94 periodontal examination and participated in lateral DXA scans of the thoraco-lumbar spine were
95 included in this study. In the 2013-2014 cycle of the NHANES, 10,175 participants completed the
96 survey. However, in this study, individuals aged < 40 years without complete information about
97 periodontitis and abdominal aortic calcification were excluded (N = 7,741). Additionally, cancer
98 participants (N = 285) were excluded from the analysis. Ultimately, 2,149 participants were included
99 in the analysis (Figure 1). All participants provided written informed consent to participate in
100 NHANES, and the NCHS Research Ethics Review Board approved the protocol (NCHS IRB/ERB
101 Protocol Number: Continuation of Protocol #2011-17). The study was designed according to the
102 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for
103 reporting cross-sectional studies²⁸, and all procedures were performed in accordance with the principles
104 of the Helsinki Declaration of 1975.

105 2.2. Definitions of periodontitis

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2 106 Oral health examinations were performed by dental examiners who were licensed dentists in at
3
4 107 least one state in the U.S. During oral health assessments, a portable dental chair, lights, and
5
6 108 compressed air were provided in a mobile examination center (MEC). All dental examiners received
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8
9 109 standardized training and collected reliable statistical data to objectively assess examiner agreement²⁹.

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12 110 Six measurement points were selected for periodontal examinations (mesiobuccal, midbuccal,
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14 111 distobuccal, mesiolingual, midlingual, and distolingual) for all teeth, with the exception of third molars.
15
16 112 Indicators of periodontitis included probing depth (PD) and clinical attachment loss (AL), which are
17
18 113 important bases for the CDC/AAP classification/case definition³⁰. Accordingly, periodontitis was
19
20 114 divided into mild periodontitis, moderate periodontitis and severe periodontitis. No periodontitis was
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22 115 defined as no evidence of mild, moderate, or severe periodontitis. Because there were few data from
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24 116 those with mild periodontitis, mild periodontitis and moderate periodontitis were combined for analysis
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28 117 in our study.

31 118 **2.3. Abdominal aortic calcification outcomes**

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34 119 AAC can be accurately identified on lateral spine images obtained by DXA and shows good
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36 120 sensitivity and specificity at lower radiation doses³¹⁻³². Those < 40 years old, pregnant, weighing over
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38 121 450 pounds, or ingesting barium within the last week were ineligible for DXA scans in this study. Both
39
40 122 the AAC-24 and AAC-8 semiquantitative scoring tools were used for AAC evaluation²⁵. An
41
42 123 assessment of the length of anterior and posterior aortic wall calcification anterior to the L1 to L4
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44 124 vertebral bodies was made using the AAC-8 score, and participants with a score of three or more were
45
46 125 considered to be at high risk for AAC. Using the L1-L4 region as a reference, the anterior and posterior
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48 126 aortic walls are divided into four segments to calculate the AAC-24 score. Depending on the degree of
49
50 127 calcification, each vertebral body can receive a score from 0 to 6, with a total possible score of 0 to 24;
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52 128 this allows a more precise assessment of abdominal aortic calcification. We categorized AAC-24 scores
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3 129 into three groups: no calcification (AAC-24 score =0), mild to moderate calcification ($6 \geq$ AAC-24
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5 130 score > 0) and severe calcification (AAC-24 score >6).
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8 131 **2.4. Covariates**

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10 132 Based on previous studies, we considered some confounding factors potentially associated with
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12 133 periodontitis and AAC in our analysis, including socioeconomic factors, behavioral factors, body mass
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14 134 index (BMI), medical history, and laboratory measurements³³⁻³⁴.
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18 135 Information about socioeconomic factors was obtained during the home interview. The poverty
19
20 136 income ratio (PIR) was stratified into <1.3 , $1.3-3.5$, and >3.5 , as recorded in the original survey.
21
22 137 Behavioral factors were obtained from self-reports. A never smoker is an individual who has never
23
24 138 smoked more than 100 cigarettes in their lifetime. Former smokers were defined as those who smoked
25
26 139 more than 100 cigarettes in their lifetime and had quit smoking, and smokers have to smoke at least
27
28 140 100 cigarettes in their lifetime and smoke some days or every day to qualify as current smokers.
29
30 141 The status of alcohol consumption was categorised as never (never drank greater than or equal to
31
32 142 12 drinks in their lifetime), former (greater than or equal to 12 drinks in 1 year and did not drink last
33
34 143 year, or did not drink last year but drank ≥ 12 drinks in their lifetime), current mild (≤ 1 drink/d for
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36 144 female or ≤ 2 drink/d for male on average over the past year), current moderate (2 drink/d for female
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38 145 or 3 drink/d for male on average over the past year), current heavy drinkers (≥ 3 drink/d for female or
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40 146 ≥ 4 drink/d for male on average over the past year). BMI was measured at a MEC using standard
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42 147 protocols and stratified into ≥ 30 and <30 .
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49 148 Those participants who self-reported heart failure, angina, coronary heart disease, heart attack, or
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51 149 stroke diagnosed by a physician were classified as having CVD. The definition of hypertension was a
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53 150 diagnosis by a healthcare professional, an average blood pressure of $\geq 130/80$ mmHg or using
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55 151 hypertension medications³⁵. Diabetes was defined as a diagnosis made by a physician or
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1
2 152 other healthcare professional, HbA1c (%) >6.5, random blood glucose (mmol/l) \geq 11.1, or use of
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4 153 diabetes medication or insulin. As defined by the International Renal Association, chronic kidney
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6 154 disease is characterized by an estimated glomerular filtration rate <60 mL/min/1.73 m² or a urine
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8
9 155 albumin–creatinine ratio of at least 30³⁶. Based on serum creatinine, the Chronic Kidney Disease
10
11 156 Epidemiology Collaboration (CKD-EPI) equation was used to estimate the glomerular filtration rate³⁷.
12
13 157 Laboratory data were obtained from participant serum samples that were processed in the Collaborative
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15
16 158 Laboratory Services, Ottumwa, Iowa, for analysis. Detailed instructions regarding specimen collection
17
18 159 and processing are documented in the NHANES Laboratory Procedures Manual, and quality control
19
20 160 was in accordance with standard procedures.

24 161 **2.5. Statistical analysis**

25
26 162 A weight is assigned to the NHANES to compensate for the complex survey design, survey
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28 163 nonresponses, and poststratification adjustment to match the total U.S. population. All results of this
29
30 164 study were weighted by 2-year MEC weights. In accordance with the CDC/AAP classification of
31
32 165 periodontitis, descriptive statistics were calculated to describe the characteristics of the participants.
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35 166 Continuous variables are presented as the weighted mean \pm standard deviation (SD) and were compared
36
37 167 using a one-way ANOVA, while categorical variables were compared using the Rao-Scott chi-square
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39
40 168 test and are presented as weighted percentages (95% confidence interval, 95% CI). Linear regression
41
42 169 was used to evaluate the association of the AAC-8 score and AAC-24 score as dependent variables
43
44 170 with periodontitis with varying degrees of severity as independent variables. Beta coefficients and 95%
45
46 171 CIs were calculated. Multivariate logistic regression analysis was performed to evaluate the correlation
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48
49 172 between periodontitis with varying degrees of severity and AAC with varying degrees of severity using
50
51 173 odds ratios (ORs) and 95% CIs. Model 1 was adjusted for age, sex, and race; Model 2 was adjusted for
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53 174 the parameters in Model 1 plus insurance, education level, smoking status, alcohol consumption status,
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56 175 PIR, BMI, diabetes, hypertension, CVD and CKD; and Model 3 was adjusted for the parameters in

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3 176 Model 2 plus albumin, serum calcium, serum phosphorus, uric acid, total 25-hydroxyvitamin D,
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5 177 hemoglobin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides
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7 178 (TGs). Subgroup analysis stratified by age, sex, CVD, hypertension, diabetes, and CKD was also
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10 179 conducted using stratified multivariate regression analysis, and multiplicative interactions were
11
12 180 assessed using likelihood ratio tests.
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14

15 181 In this study, we used the MissForest³⁸ package in R software to address missing covariates. The
16
17 182 algorithm can address categorical and continuous variables and shows superior performance. The
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19 183 numbers and percentages of missing covariate data are shown in Supplementary Material Table 1.
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21 184 Sensitivity analyses were performed as followed: (1) only participants with complete data were
22
23 185 included, and participants with missing covariates were excluded; (2) mild and moderate periodontitis
24
25 186 were not combined for analysis, and mild periodontitis was excluded; and (3) participants with CVD
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27 187 were excluded. R software (version 4.1.3) was used for all statistical analyses. It was considered
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29 188 statistically significant if the P value was less than 0.05 for all statistical tests of two-tailed.
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35 189 **2.6. Patient and public involvement**

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37 190 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination
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39 191 plans of our research.
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41

42 192 **3. Results**

43
44 193 Descriptive statistics of our study participants by periodontitis status according to the CDC/AAP
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46 194 case definitions are presented in Table 1. The study included 2,149 participants, representing
47
48 195 86,199,511 noninstitutionalized adults (40 years and older) in the U.S. Overall, participants had a mean
49
50 196 age±SD of 54.96 ± 0.32 years; 50.46% (44.32, 56.60) were female, and 68.14% (54.20, 82.08) were
51
52 197 non-Hispanic white. The prevalence of mild-moderate periodontitis was 29.93 (25.36, 34.51) and that
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54 198 of severe periodontitis was 6.77 (5.40, 8.13). Periodontitis was more prevalent in older individuals,
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199 males, those with a low educational level, those with a low PIR, and those with low insurance coverage
 200 than in their counterparts and showed differences among races. The prevalence of mild to moderate
 201 AAC and severe AAC was significantly higher in participants with periodontitis than in those without.
 202 In addition, we also found significant differences in smoking status, alcohol consumption status, CVD,
 203 diabetes, hypertension, CKD, albumin, total 25-hydroxyvitamin D, TGs, and HDL-C compared with
 204 participants without periodontitis (all $p < 0.05$).

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

Characters	Overall (n=2,149)	No Periodontitis (n=1,142)	Mild-Moderate periodontitis (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 high 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)	
High 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 high 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 β (95% CI), P- value	Model 2 β (95% CI), P- value	Model 3 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) P=0.149	0.03(-0.11,0.17) P=0.643	0.02(-0.12,0.17) P=0.740
Severe periodontitis	220/2149	0.29(0.08,0.50) P=0.015	0.17(-0.07,0.41) P=0.159	0.17(-0.08,0.41) 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			P for interaction
	No periodontitis	Mild–moderate periodontitis	Severe periodontitis	
Age				0.212
$\geq 60y$	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

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3 261 attenuated or had disappeared (Supplementary Material Table 3). When we decoupled mild-moderate
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5 262 periodontitis and excluded participants with mild periodontitis, the results of the sensitivity analysis
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7 263 were similar to those of the main analysis (Supplementary Material Table 4). It is worth mentioning
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10 264 that mild-moderate periodontitis was associated with a reduced prevalence of mild to moderate AAC
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12 265 in participants without CVD, and the association of severe periodontitis with AAC in the high-AAC
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14 266 risk group (AAC-8 scores ≥ 3 points) disappeared (Supplementary Material Table 5).

17 18 267 **4. Discussion**

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20 268 To our knowledge, this is the first population-based cross-sectional epidemiological study to
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22 269 explore the link between periodontitis and AAC in a nationally representative sample of U.S. adults
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24 270 (40 years and older). Our study fully considered socioeconomic status, behavioral factors and medical
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26 271 history of the participants and controlled for a wide range of confounders. Severe periodontitis was
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28 272 positively associated with severe AAC, defined by either the AAC-8 score or AAC-24 score. A positive
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30 273 association between mild to moderate periodontitis and severe AAC was found only when AAC was
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32 274 classified by the AAC-24 score. In the subgroups stratified by age; sex; and CVD, hypertension,
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34 275 diabetes, and CKD status, this association and the main results were generally consistent; the only
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36 276 difference was associated with the different severities of periodontitis, which differed in their
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38 277 associations with severe AAC in the stratified population. Linear regression evaluation of the AAC-8
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40 278 score and AAC-24 score as dependent variables and the different severities of periodontitis as
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42 279 independent variables showed no linear correlation. In the sensitivity analysis, the association remained
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44 280 significant after excluding participants with mild periodontitis and CVD. However, the association was
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46 281 no longer significant after excluding participants with missing covariates.
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53 282 To date, some epidemiological studies have suggested a close relationship between periodontitis
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55 283 and vascular calcification or CVD. A consensus report on periodontitis and CVD states that
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2 284 periodontitis is broadly associated with CVD and that the link is bidirectional; CVD drives the
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4 285 progression of periodontitis and vice versa³⁹. NHANES-based cross-sectional studies have shown an
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6 286 association between periodontitis severity and cardiovascular risk⁴, as demonstrated by the results of a
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8 287 13-year cohort study, and further studies suggest that periodontitis may be an independent risk factor
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10 288 for CVD⁴⁰. Oindrila Paul et al. reviewed the pathophysiology of periodontitis and showed that
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12 289 inflammation associated with periodontitis may be the main mechanism affecting CVD and could be
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14 290 facilitated by common risk factors⁴¹. Vascular calcification has been shown to involve soft tissue
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16 291 calcification also caused by chronic inflammatory stimuli¹⁹ and is closely related to the prevalence and
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18 292 prognosis of CVD. This may suggest that the association between periodontitis and CVD may depend
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20 293 on the severity of vascular calcification. The results of a cross-sectional Japanese population-based
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22 294 study suggest that measuring alveolar bone loss on panoramic radiographs may be an effective method
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24 295 to identify an increased risk of carotid artery calcification¹⁴. Imaging studies using cone-beam
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26 296 computed tomography have further confirmed that the development of periodontitis may cause
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28 297 calcification involving the intracranial carotid arteries¹⁶. The results from a meta-analysis that included
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30 298 12 studies also revealed a significant relationship between periodontitis and carotid artery
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32 299 calcification¹⁵. Similar to our findings, a cohort study in Chinese populations suggested that
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34 300 periodontitis was also positively associated with aortic calcification, and this association was more
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36 301 pronounced in men and in participants younger than 65 years¹³.
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44 302 The exact mechanism of the link between periodontitis and AAC remains unclear and needs to be
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46 303 further explored. Existing mainstream views suggest that *Porphyromonas gingivalis* (*P. gingivalis*)
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48 304 infection and chronic inflammation are important bridges between periodontitis and vascular
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50 305 calcification^{19, 41-42}. Recent studies have shown that periodontal pathogens can be detected in the blood
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52 306 of patients with coronary heart disease, and it is hypothesized that periodontal pathogens can spread
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54 307 through the blood to other parts of the body, where they may enhance inflammatory processes, leading
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3 308 to the development or aggravation of atherosclerosis⁴³. Evidence from in vitro cell culture studies
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5 309 suggests that *P. gingivalis* infection accelerates phosphate-induced calcification of vascular smooth
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7 310 muscle cells²² and that *P. gingivalis* lipopolysaccharide increases alkaline phosphatase activity and
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9 311 upregulates the expression of genes involved in calcification to stimulate calcification⁴⁴. In addition, it
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11 312 has been shown that *P. gingivalis* invasiveness is enhanced after high-glucose treatment, and vascular
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13 313 calcification can be initiated by stimulating autocrine regulation of bone morphogenetic protein 4 in
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15 314 aortic smooth muscle cells²¹. *P. gingivalis* infection elicits an inflammatory response in the host, which
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17 315 is in line with the definition of periodontitis as a chronic inflammatory disease. A meta-analysis
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19 316 suggested that the diagnosis of chronic aggressive periodontitis was consistently associated with higher
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21 317 C-reactive protein and high-sensitivity C-reactive protein levels, and treatment reduced serum C-
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23 318 reactive protein levels⁴⁵. In addition, studies have observed an association between periodontitis and
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25 319 systemic inflammation, which increases with the severity of periodontal disease⁴⁶. Notably, there are
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27 320 studies revealing other possible mechanisms involved in the link between periodontitis and vascular
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29 321 calcification, including the activation of osteoprotegerin/receptor activator of nuclear factor- κ B ligand
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31 322 and endoplasmic reticulum stress-induced apoptosis²³⁻²⁴.

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38 323 Our study has several important strengths. Our findings were derived from a large nationwide
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40 324 random sample survey and can be generalized to the adult noninstitutionalized population in the U.S.
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42 325 Periodontitis and AAC were defined based on objective clinical data collected by calibrated
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44 326 professionals. In addition, this study addressed a number of known potential confounders, and sample
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46 327 weights were applied in each analysis following the NHANES guidelines to account for the complex
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48 328 survey design. However, several limitations of this study warrant attention. Given the cross-sectional
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50 329 design of the NHANES, it is difficult for us to determine causality, and further large-scale prospective
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52 330 studies are needed. In addition, we cannot exclude the possibility of residual confounding by other
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54 331 confounding factors related to oral health, which could have influenced the observed results. It is worth
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2 332 noting that only a small proportion of patients with severe periodontitis in our study had severe AAC;
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4 333 perhaps because of this, the results of the sensitivity analysis excluding patients with missing covariates
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6 334 were not robust. This also suggests that the conclusions of this study should be interpreted with caution.
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9 335 An explanation for this phenomenon is the possibility of selection bias⁴⁷. In addition, tooth loss is not
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11 336 considered in the CDC/AAP case definition of periodontitis; therefore, the prevalence of the disease
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13 337 may be underestimated³⁰. Because of the sample size, we were not able to include the new periodontal
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15 338 profile class (PPC) system to precisely classify periodontal disease because this classification method
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17 339 classifies periodontitis into seven categories: PPC-A to PPC-G⁴⁸.

21 340 **5. Conclusion**

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23 341 Our study suggests that periodontitis is associated with an increased risk of severe AAC in the
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26 342 U.S. population aged 40 years and older. The associations investigated in this study are credible due to
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28 343 their cross-sectional nature, but these findings require further large-scale prospective studies to
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30 344 confirm.

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17 358 **Competing interests**

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21 359 None declared.
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24 360 **Patient consent for publication**

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27 361 Not applicable.
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29 362 **Ethics approval**

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33 363 The present study complied with the term of the Declaration of Helsinki and was approved by the
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35 364 NCHS Research Ethics Review Committee (NCHS IRB/ERB Protocol Number: Continuation of
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37 365 Protocol #2011-17).
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40 366 **Data availability statement**

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44 367 Data may be obtained from a third party and are not publicly available. Data described in the
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46 368 article are publicly and freely available without restriction at
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48 369 <https://www.cdc.gov/nchs/nhanes/index.htm>
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483 **Figure legends**

- 33
34 484 Figure 1. Flow chart of eligible National Health and Nutrition Examination Survey (NHANES)
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36 485 participants included in this study.
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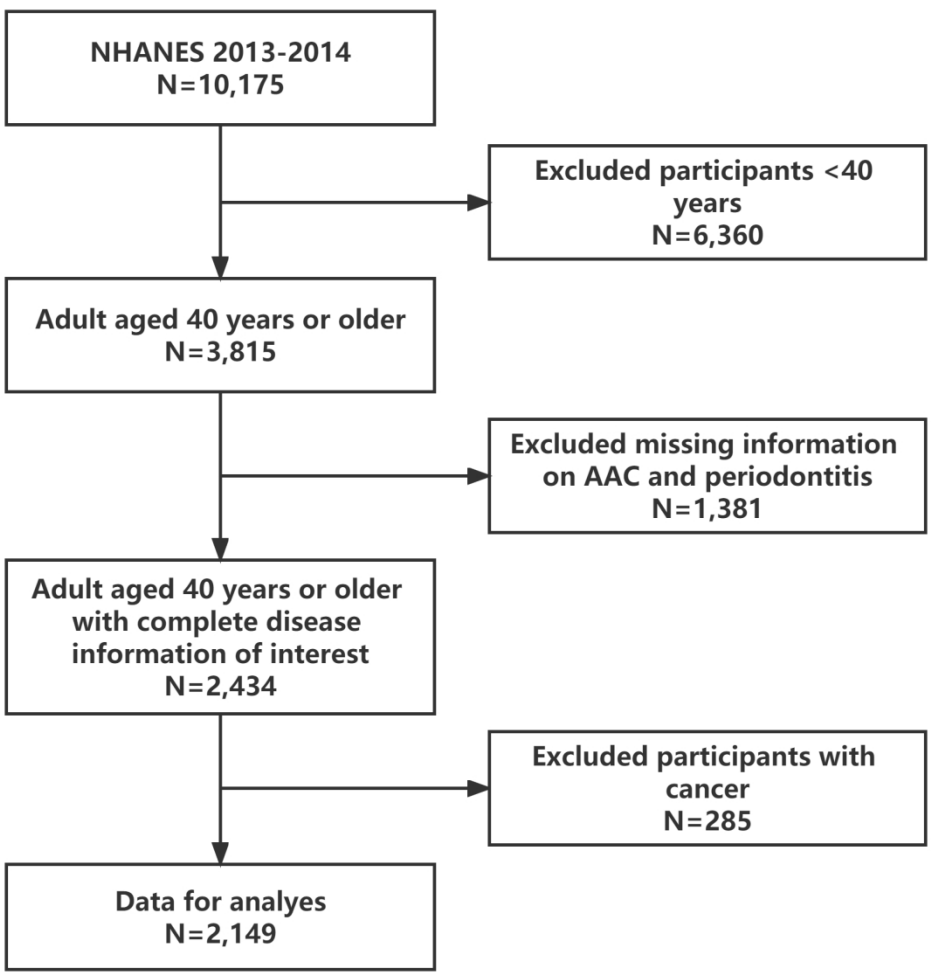


Figure 1. Flow chart of eligible National Health and Nutrition Examination Survey (NHANES) participants included in this study.

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 periodontitis (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 high 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)	
High 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 high 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 \pm 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 OR (95% CI), P- value	Model 2 OR (95% CI), P- value	Model 3 OR (95% CI), P- value
AAC-8 score \geq 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) p=0.116	1.53(0.81,2.88) p=0.171	1.56(0.83,2.92) p=0.153
Severe periodontitis	15/180	2.44(0.96,6.21) p=0.059	1.80(0.81,4.00) p=0.137	1.80(0.77,4.22) 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) p=0.439	0.71(0.50,1.02) p=0.060	0.69(0.49,0.97) p=0.033
Severe periodontitis	50/164	1.52(0.78,2.96) p=0.181	1.06(0.49,2.30) p=0.869	0.99(0.46,2.10) 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) p=0.030	1.89(1.02, 3.50) p=0.044	1.89(1.01, 3.56) p=0.048
Severe periodontitis	16/139	5.22(1.85,14.76) p=0.007	2.81(1.06, 7.42) p=0.038	2.73(0.92, 8.13) 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) p=0.018	1.82(0.98,3.39) p=0.059	1.87(0.96, 3.66) p=0.065
Severe periodontitis	16/57	2.41(0.79,7.29) p=0.103	1.85(0.78,4.38) p=0.147	1.85(0.75, 4.60) 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 OR (95% CI), P- value	Model 2 OR (95% CI), P- value	Model 3 OR (95% CI), P- value
AAC-8 score \geq 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) P=0.096	1.68(0.82,3.46) P=0.147	1.73(0.87,3.42) P=0.109
Severe periodontitis	14/220	3.12(1.17,8.36) P=0.029	2.44(1.02,6.00) P=0.046	2.44(1.01,6.05) 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) P=0.587	0.75(0.52,1.09) P=0.121	0.72(0.50,1.03) P=0.069
Severe periodontitis	50/200	1.46(0.80,2.68) P=0.184	1.05(0.52,2.11) P=0.881	0.96(0.48,1.94) 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) P=0.036	1.97(0.96,4.06) P=0.063	2.03(1.02,4.03) P=0.044
Severe periodontitis	20/170	6.02(2.44,14.86) P=0.002	3.49(1.53,7.97) P=0.006	3.48(1.42,8.54) 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) P=0.018	2.10(1.08,4.07) P=0.031	2.17(1.09, 4.32) P=0.030
Severe periodontitis	20/70	3.10(1.15,8.32) P=0.030	2.76(1.16,6.57) P=0.025	2.75(1.14, 6.63) 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 OR (95% CI), P- value	Model 2 OR (95% CI), P- value	Model 3 OR (95% CI), P- value
AAC-8 score \geq 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) P= 0.054	1.90(0.95,3.81) P=0.067	1.95(1.02,3.73) P=0.044
Severe periodontitis	14/202	3.27(1.26,8.48) P=0.022	2.18(0.88,5.45) P=0.088	2.14(0.86,5.35) 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) P=0.371	0.68(0.47,0.99) P=0.049	0.65(0.45,0.94) P=0.026
Severe periodontitis	44/187	1.33(0.70,2.51) P=0.330	0.90(0.41,1.95) P=0.774	0.83(0.38,1.81) 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) P=0.005	2.62(1.44, 4.76) P=0.004	2.71(1.49, 4.93) P=0.003
Severe periodontitis	15/158	6.00(2.47,14.57) P=0.002	3.00(1.31, 6.87) P=0.013	2.89(1.13, 7.40) 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) P=0.003	2.99(1.68, 5.32) P=0.001	3.16(1.75, 5.69) P<0.001
Severe periodontitis	15/59	3.79(1.38,10.43) P=0.017	3.82(1.42,10.27) P=0.011	3.75(1.32,10.60) 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.

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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 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 Line 2-4; 15-36
Introduction			
Background/rationale	2 ✓ introduction	Explain the scientific background and rationale for the investigation being reported	Page 3-4 Line 47-73
Objectives	3 ✓ introduction	State specific objectives, including any prespecified hypotheses	Page 4 Line 74-83
Methods			
Study design	4 ✓ data source	Present key elements of study design early in the paper	Page 5 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 Line 86-105
Participants	6 ✓ data source	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5 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 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 Line 106-162
Bias	9 ✓ statistical analysis	Describe any efforts to address potential sources of bias	Page 8-9 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 Line 163-191
Statistical methods	12 ✓ statistical analysis	(a) Describe all statistical methods, including those used to control for confounding	Page 8-9 Line 163-191
	✓ statistical analysis	(b) Describe any methods used to examine subgroups and interactions	Page 8-9 Line 163-191
	✓ statistical analysis	(c) Explain how missing data were addressed	Page 8-9
	✓ statistical analysis	(d) If applicable, describe analytical methods taking account of sampling strategy	Line 163-191
	✓ statistical analysis	(e) Describe any sensitivity analyses	Page 8-9 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 Line 86-105
	✓ data source; figure 1;supplementary table1	(b) Give reasons for non-participation at each stage	Page 5 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 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 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 Line 242-270
Discussion			
Key results	18 ✓ discussion – 1 st paragraph	Summarise key results with reference to study objectives	Page 15 Line 272-286
Limitations	19 ✓ discussion – 4 th 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 Line 329-345
Interpretation	20 ✓ discussion – 2 th -3 th 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 Line 287-328
Generalisability	21 ✓ discussion – 4 th	Discuss the generalisability (external validity) of the study results	Page 17-18 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 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.