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Association Between Serum Albumin and Periodontitis Across Disease Subgroups: A Cross-Sectional Study

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ABSTRACT

Purpose: This study examines the association between serum albumin (sALB) levels and periodontitis severity, focusing on subgroup differences and nonlinear relationships. It extends previous findings, which were limited to chronic kidney disease (CKD) patients.

Materials and methods: This cross-sectional study utilized data from 8352 participants in the NHANES 2009 to 2014 survey cycles. sALB and periodontitis were the exposure and outcome variables. Logistic regression models and restricted cubic spline curves were used to investigate the relationship between the two. Additionally, subgroup and interaction analyses were conducted to assess the stability of the findings. All statistical analyses considered the complex survey design.

Results: A significant negative association was observed between sALB and periodontitis status (aOR 0.94, 95% confidence intervals: 0.93-0.96, *P* value <.001). The strength of this association may be influenced by participants' gender, CKD status, and hypertension status. Among participants with sALB levels below 35 g/L (defined as hypoalbuminemia), no significant association with periodontitis was observed, even in those with CKD. Restricted cubic spline analysis demonstrated an inverted U-shaped relationship between sALB levels and periodontitis, with a threshold effect at 38 g/L. Above this inflection point, higher sALB levels were significantly associated with a lower prevalence of periodontitis ($P < .001$).

Conclusions: ALB levels were inversely associated with moderate and severe periodontitis, with an inverted U-shaped relationship observed in this study. The differences among subgroups warrant further research.

Clinical relevance: Maintaining appropriate sALB levels may be beneficial for periodontal health. Further research is needed to confirm its role in periodontitis prevention and treatment.

Introduction

Periodontitis, an inflammatory disease, affects approximately 11% of the global population in its severe form.[1] Its onset is intricate, attributable to a multitude of factors. Subgingival plaque biofilms penetrate the periodontal tissues, provoking a host immune reaction that leads to inflammation. This process culminates in the irreversible and progressive loss of the alveolar bone and periodontal ligament integrity.[2] Clinical presentations of periodontitis encompass gingival inflammation, periodontal pocketing, alveolar bone resorption, and dental mobility.[3] The loss of periodontal support is related to decreased chewing function and negatively affects oral health-related quality of life.[4] Beyond oral health implications, periodontitis is linked to systemic diseases such as Alzheimer's, cardiovascular diseases, diabetes, insulin resistance, and chronic kidney disease (CKD).[5,6] This complex disease pathogenesis and its impact underscore the importance of identifying biomarkers capable of

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modulating periodontal tissue destruction. Among these factors, certain biomarkers have drawn attention for their potential role in driving disease progression. For instance, growth differentiation factor-15 and glutathione peroxidase-1 have been identified as biomarkers that can influence the progression of periodontitis and predict treatment outcomes.[7]

Albumin, the most abundant plasma protein, plays a pivotal role in plasma osmolarity regulation, fluid balance maintenance, molecular transport, and immune modulation.[8] It also serves as a critical nonenzymatic antioxidant, protecting against oxidative stress.[9] Clinically, serum albumin (sALB) serves as a critical biomarker for assessing systemic health conditions, including infections, shock, cerebral oedema, liver cirrhosis, and hypoalbuminemia.[10] In adults, the normal range of sALB is 35 to 50 g/L, and levels below 35 g/L are defined as hypoalbuminemia.[11] Hypoalbuminemia is an independent prognostic indicator in the general population and various diseases, including cardiovascular diseases, cirrhosis, nephrotic syndrome, and colorectal cancer.[12-14] However, its relationship with periodontitis remains unclear.

Previous research has suggested a link between sALB levels and oral health. *Porphyromonas gingivalis* (Pg), a key periodontal pathogen, has been identified as a significant contributor to the development of periodontal diseases.[2] A recent study showed that sALB exhibits substantial antibacterial activity, which inhibits Pg growth primarily through inducing programmed cell death.[15] In addition to direct antibacterial action, glycated albumin accumulation could stimulate the proinflammatory response in human gingival fibroblasts against Pg.[16] Furthermore, as sALB is closely linked to coagulation pathways, it has drawn attention for its potential role in periodontal treatment, particularly in the context of anticoagulant therapy.[17] In haemodialysis patients, sALB is negatively correlated with pocket depth, an indicator of periodontal disease severity. Although hypoalbuminemia has been reported as an independent risk factor for periodontitis in advanced CKD patients, its statistical results remained questionable.[18]

The relationship between sALB and periodontitis has yet to be studied in the general population and other disease subgroups. Existing evidence is limited, particularly in determining whether this association is linear or nonlinear. These gaps in knowledge underscore the need for a more nuanced understanding of how sALB levels relate to periodontitis. To address this, our study aims to examine the association between sALB levels and periodontitis, with a specific focus on identifying subgroup differences and clarifying the nature of this relationship. We hypothesize that a nonlinear relationship exists between sALB levels and periodontitis prevalence and that this association varies significantly across population subgroups with different systemic comorbidities.

Methods

Study population

This cross-sectional study is based on the National Health and Nutrition Examination Survey (NHANES) conducted between 2009 and 2014. NHANES is a research program aimed at assessing the nutritional status and its association with health outcomes among adults and children in the United States. This survey encompasses interviews and physical examinations. The NHANES interview covers demographics, socioeconomic factors, dietary habits, and health-related questions. The National Centers for Disease Control (CDC) and the National Center for Health Statistics (NCHS) Research Ethics Review Committee approved the study protocol, and written informed consent was obtained from all participants. Detailed information is available on the CDC's official website (https://www.cdc.gov/nchs/nhanes/index.htm).

As shown in Figure 1, the 2009 to 2014 NHANES dataset initially included 30,468 participants. After applying the inclusion and exclusion criteria, 8352 participants were retained for the final analysis. The following exclusion criteria were applied to determine final subjects: (1) participants aged below 30 years; (2) missing data on sALB or periodontal examination data; (3) absence of covariate data, including education level, marital status, alcohol intake, smoking status, hypertension (HNT), alanine aminotransferase, and CKD. The detailed flowchart of participant selection is presented in Figure 1. This study design followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

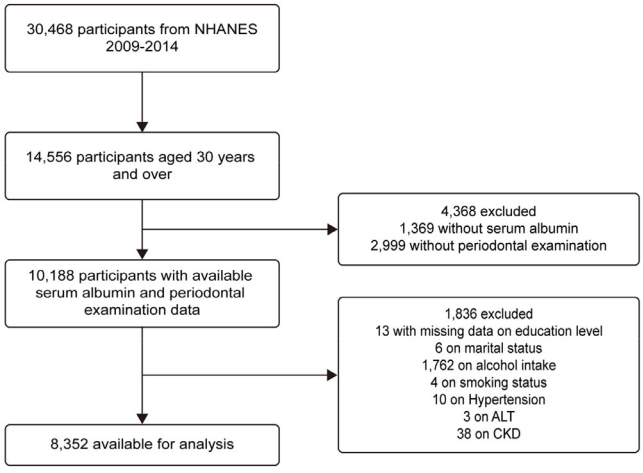

Fig. 1 – Flowchart of participant selection from the 2009 to 2014 National Health and Nutrition Examination Survey (NHANES).

sALB levels

sALB levels were considered as the exposure factor in this study. The NHANES survey utilizes bromocresol purple reagent DxC800 to measure sALB concentrations. Please refer to the laboratory technique papers for more information on the analytical methods and operational steps. sALB levels (g/L) were extracted from the 'LBDSALSI' entry in the BIOPRO project. Additionally, participants were classified into two groups based on clinical recommendations: those with hypoalbuminemia (sALB < 35 g/L) and those without.

Periodontitis status

The prespecified outcome measure for periodontitis was determined based on the Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC-AAP) criteria. Specifically, severe periodontitis was defined as: (1) the presence of ≥2 interproximal sites with clinical attachment loss (CAL) ≥6 mm (on nonadjacent teeth), and (2) ≥1 interproximal site with probing depth (PD) ≥5 mm; moderate periodontitis required either: (1) ≥2 interproximal sites with CAL ≥4 mm (nonadjacent teeth), or (2) ≥2 interproximal sites with PD ≥5 mm (nonadjacent teeth). Participants not meeting these thresholds were classified as having no/mild periodontitis (full operational definitions provided in Table 1).[19] Periodontal examination data was extracted from the OHXDEN project. Participants were categorized into two groups based on disease severity: no/mild periodontitis and moderate/severe periodontitis. This classification has been widely adopted in previous studies on periodontitis and systemic health associations.[20-23]

Covariates

Based on a literature review and clinical practice guidelines, we prespecified covariates for the statistical model.[2,24] Sociodemographic characteristics included age (<60 years, ≥60 years), sex (male and female), and race (Mexican Americans, other Hispanics, non-Hispanic whites, non-Hispanic blacks, and other races). Education level was categorized into three levels (<high school, high school, and >high school). Marital status was divided into two groups (married/living with partners and other). Income levels were divided into three levels (<1.3, 1.3-3.5, >3.5). Lifestyle characteristics encompassed alcohol intake and smoking status. Alcohol intake was categorized into four categories: never drinking, former drinking, current light/moderate drinking, and current heavy drinking.[25] Smokers were divided into three groups: never smokers, current smokers, and former smokers.[26] Their definition criteria are detailed in Supplementary Table 1.

Health status characteristics included body mass index (BMI), HTN, and diabetes. BMI was categorized into three groups: underweight or normal (<25 kg/m^2), overweight (≥25-<30 kg/m^2), and obese (≥30 kg/m^2). Participants were considered to have any HNT if their average systolic blood pressure (SBP) was ≥130 mmHg, or their average diastolic blood pressure (DBP) was ≥80 mmHg, or if they were currently taking prescription medication for HNT.[27] Diabetes was diagnosed based on the following criteria: (1) self-reported diagnosis, (2) use of insulin or hypoglycaemic medications, (3) haemoglobin A1c level exceeding 6.5%, or (4) fasting plasma glucose level exceeding 126 mg/dL.[28] These health status characteristics were identified as essential covariates in the analysis of the relationship between sALB and periodontitis status.

Considering the close association between sALB and liver and kidney function, alanine aminotransferase concentrations and CKD were included as covariates in our analysis. According to the Kidney Disease: Improving Global Outcomes 2021 Clinical Practice Guideline, CKD is defined as an estimated glomerular filtration rate ≤60 mL/min/1.73 m^2 or urine albumin/creatinine ratio ≥30 mg/g.[29] As shown in Supplementary Table 1, estimated glomerular filtration rate was calculated using the formula recently recommended by the National Kidney Foundation and the American Society of Nephrology Task Force (ASN-NKF), excluding racial factors.[30] By incorporating these markers, we aim to provide a more comprehensive understanding of the relationship.

Statistical methods

Continuous variables were presented as mean values along with and their standard deviation if they followed a normal distribution. If the variables did not follow a normal distribution, they were presented as median values along with their interquartile range. Categorical variables were expressed as counts (percentages). Variance tests and chi-square tests were used to compare differences between groups. Logistic regression models assessed the association between sALB and periodontitis status, calculating odds ratios (OR) and 95% confidence intervals (CI). The choice of logistic regression was based on its widespread application in NHANES-based periodontitis research, ensuring comparability with prior studies.[20-23] Model 1 did not adjust for any covariates, Model 2 adjusted for demographic characteristics, and Model 3 adjusted for all covariates. Following the official NHANES guidelines, the weights were adjusted by dividing the original weights by the number of cycles when combining data from

Table 1 – The Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC-AAP) criteria to define periodontitis.

Disease status	Clinical attachment loss (CAL)		Probing death (PD)
Severe periodontitis	≥2 interproximal sites with CAL ≥ 6 mm (not on same tooth)	AND	≥1 interproximal site with PD ≥ 5 mm
Moderate periodontitis	≥2 interproximal sites with CAL ≥ 4 mm (not on same tooth)	OR	≥2 interproximal sites with PD ≥ 5 mm (not on same tooth)
No or mild periodontitis	No evidence of mild, moderate, or severe periodontitis		

three survey cycles. Weight adjustment adhered to the minimum sample weight principle to ensure the representativeness and robustness of the results. Statistical analyses comprehensively considered the complex survey design, encompassing baseline data analysis, logistic regression, and subgroup analysis.

Additionally, sALB was categorized into quartiles and included in the three models, with the lowest quartile as the reference. Restricted cubic spline (RCS) analysis and recursive algorithm were used to assess nonlinear relationships between sALB and periodontitis status (the recommended nodes number: 4). Risk factors for periodontitis encompass old age, low socioeconomic status, smoking, alcohol consumption, diabetes, obesity, and inadequate oral hygiene practices at home.[2] Furthermore, sex and age can influence albumin metabolism and periodontal health, and chronic

Table 2 – Baseline characteristics of participants stratified by periodontitis status.

Characteristics	Total N (weighted %)	No/mild N (weighted %)	Moderate/severe N (weighted %)	P value
Sample, N	8352	4642	3710	
Weighted sample	185844617	119209196	66635421	
Age category				<.001
<60	5721 (73.8)	3605 (80.2)	2116 (62.2)	
≥60	2631 (26.2)	1037 (19.8)	1594 (37.8)	
Gender				<.001
Male	4079 (49.2)	1937 (44.0)	2142 (58.6)	
Female	4273 (50.8)	2705 (56.0)	1568 (41.4)	
Race				<.001
Mexican American	1187 (7.7)	525 (5.8)	662 (11.1)	
Other Hispanic	836 (5.2)	460 (4.8)	376 (6.0)	
Non-Hispanic White	3710 (70.1)	2348 (75.0)	1362 (61.2)	
Non-Hispanic Black	1651 (10.6)	752 (8.4)	899 (14.5)	
Other Race	968 (6.5)	557 (6.1)	411 (7.4)	
Education level				<.001
<High school	739 (4.5)	238 (2.4)	501 (8.2)	
Completed high school	2850 (30.0)	1280 (24.1)	1570 (40.8)	
>High school	4763 (65.5)	3124 (73.5)	1639 (51.0)	
Marital status				<.001
Married/living with partner	5459 (70.1)	3167 (73.4)	2292 (64.3)	
Widowed/divorced/others	2893 (29.9)	1475 (26.6)	1418 (35.7)	
PIR				<.001
<1.3	2071 (15.8)	886 (11.5)	1185 (23.6)	
1.3-3.5	2740 (32.4)	1435 (29.6)	1305 (37.2)	
>3.5	3541 (51.8)	2321 (58.9)	1220 (39.2)	
Alcohol intake				.005
Never	1277 (11.4)	629 (10.2)	648 (13.4)	
Former	575 (5.6)	287 (5.1)	288 (6.5)	
Current light/moderate	3404 (43.9)	1975 (45.7)	1429 (40.7)	
Current heavy	3096 (39.2)	1751 (39.0)	1345 (39.5)	
Smoking status				<.001
Never	4837 (58.2)	3020 (64.9)	1817 (46.2)	
Former	1981 (25.3)	1016 (23.5)	965 (28.5)	
Current	1534 (16.5)	606 (11.6)	928 (25.4)	
BMI category				.246
Underweight/normal	2226 (26.7)	1274 (27.2)	952 (25.9)	
Overweight	2891 (35.7)	1609 (36.2)	1282 (34.8)	
Obese	3235 (37.6)	1759 (36.6)	1476 (39.3)	
ALT (U/L)	26.15 ± 0.48	25.70 ± 0.59	26.96 ± 1.01	.051
CKD				<.001
No	7140 (88.5)	4147 (91.3)	2993 (83.7)	
Yes	1212 (11.5)	495 (8.7)	717 (16.3)	
Hypertension				<.001
No	4720 (60.0)	2942 (65.1)	1778 (51.0)	
Yes	3632 (40.0)	1700 (35.0)	1932 (49.0)	
Diabetes				<.001
No	6972 (87.0)	4095 (90.3)	2877 (81.0)	
Yes	1380 (13.0)	547 (9.7)	833 (19.0)	
Serum albumin (g/L)	42.69 ± 0.13	42.90 ± 0.15	42.33 ± 0.17	<.001

Data are mean (SD) for continuous variables with normal distribution, median (IQR) for continuous variables with abnormal distribution, and N (%) for category variables.

ALT, alanine aminotransferase; BMI, body mass index; CKD, chronic kidney disease; PIR, personal income ratio.

conditions are closely associated with systemic inflammation and nutritional status, potentially further modulating this relationship. The association between sALB and periodontitis may be affected by the aforementioned factors, hence we chose the following subgroups for our analysis. Subgroup analyses were performed for gender (male, female), age groups (<60 years, ≥60 years), race/ethnicity (White, Black, Hispanic, Mexican American, Other), socioeconomic status (low, high), lifestyle factors (no adverse behaviours, adverse behaviours), and disease status (no, yes). The purpose of these analyses was to assess whether the associations observed in the overall sample were consistent across different population groups. Interaction effects were evaluated on a multiplicative scale. Multiplicative interactions were assessed in the weighted logistic regression model by incorporating interaction terms, and their significance was determined using Wald tests. Additive interaction effects were evaluated using the interactionR package, and the delta method was applied to calculate CI.

In the adjusted models, we accounted for potential confounders, including HNT and diabetes. However, given their potential role as mediators, a sensitivity analysis was conducted by excluding these variables to examine the robustness of the associations. Additionally, a mediation analysis was performed to investigate the indirect effects of sALB on periodontitis mediated through HNT or diabetes. Given the high prevalence of moderate/severe periodontitis, we conducted a sensitivity analysis using Poisson regression with robust variance estimation to address potential overestimation of OR in logistic regression. Poisson regression provides prevalence ratios instead of ORs, which may better reflect the associations between sALB and periodontitis.[31] All data analyses were performed using R software (version 4.3.3), with R packages including 'compareGroups', 'jstable', 'ggrcs', and 'Mediation', among others. Unless otherwise stated, a *P* value of <.05 was considered statistically significant.

Results

Baseline characteristics of participants

The study enrolled 30,468 participants from NHANES from 2009 to 2014. After applying the inclusion and exclusion criteria, statistical analyses were conducted on a final sample of 8352 individuals, representing a weighted population of 185,844,617. The characteristics of the included population stratified by periodontitis status are presented in Table 2. Among these participants (26.2% ≥60 years, 49.2% male), 55.8% (weighted) were diagnosed with no or mild periodontitis, while the remaining 44.2% (weighted) exhibited moderate or severe periodontitis. Individuals with moderate/severe periodontitis were more likely to be elderly, male, Mexican-American, or non-Hispanic black compared to those with no/mild periodontitis. Additionally, they tended to have lower levels of education and income, higher rates of smoking, and a higher prevalence of CKD, HTN, and diabetes. Notably, for the two groups, the mean value of sALB was 42.90 and 42.33, respectively (*P* value <.001).

Association between albumin and periodontitis

The association between sALB levels and periodontitis status is shown in Figure 2A. A significant negative correlation was observed between them. In Model 1, without any adjustment, a significant association was observed (OR 0.94, 95% CI: 0.93-0.96). In Model 2, after adjusting for age, gender, and race, the negative association also persisted (OR 0.93, 95%

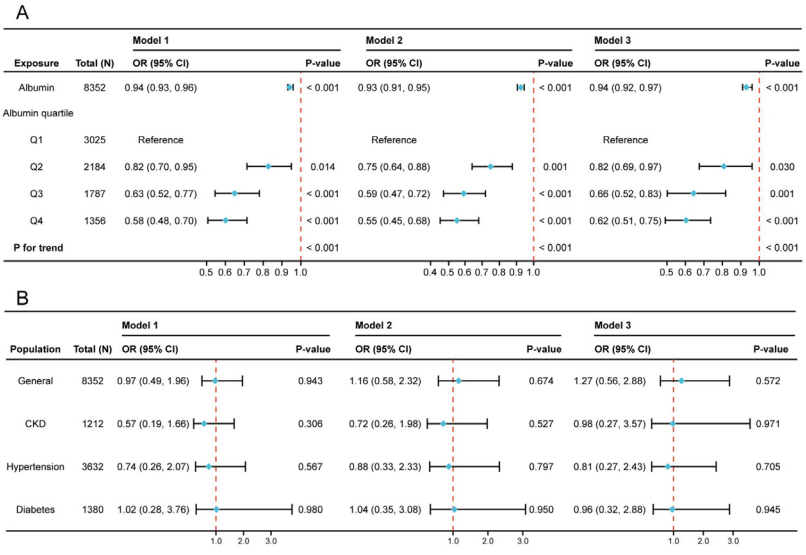

Fig. 2 – Relationship between serum albumin and periodontitis status based on logistic regression models. (A) Association between albumin levels and periodontitis status. (B) Association between hypoalbuminemia and periodontitis status in general and disease populations. Results are present as odds ratio (OR), 95% confidence intervals (CI), and *P* value; Model 1, adjusted for none; Model 2, adjusted for age, gender, and race; Model 3, adjusted for age, gender, race, education level, marital status, PIR, alcohol intake, smoking status, BMI, ALT, CKD, hypertension, and diabetes.

CI: 0.91-0.95). Model 3, which included all adjustments, still confirmed the sustained negative association (OR 0.94, 95% CI: 0.92-0.97). To gain deeper insights into the relationship, we categorized albumin into quartiles. In the fully adjusted Model 3, individuals in the highest albumin quartile exhibited a reduced likelihood of moderate/severe periodontitis compared to those in the lowest quartile (OR 0.62, 95% CI: 0.51-0.75). This indicated a stable negative association between high albumin levels and periodontitis. The trend analysis across all models was statistically significant (*P* value <.001). In addition, we divided participants into hypoalbuminemia and nonhypoalbuminemia groups according to clinical guidelines (sALB < 35 g/L). Hypoalbuminemia was not associated with periodontitis status, either in the CKD, HTN, and diabetes subgroups (Figure 2B).

Subgroup analysis and interaction tests

As shown in Figure 3, a subgroup analysis was conducted to assess the robustness of the association between albumin levels and periodontitis status. The results demonstrated a consistent negative association across most subgroups, suggesting the reliability of this association. Notably, the association seemed to disappear in patients with CKD or diabetes (*P* value = .418; *P* value = .135). Furthermore, interaction tests were performed to evaluate the impact of various covariates. The results of the multiplicative interaction analysis indicated that gender, CKD, and HNT significantly modified the strength of the albumin-periodontitis association. Similarly, the results of the additive interaction analysis suggested that this association differs significantly by gender. Obesity may

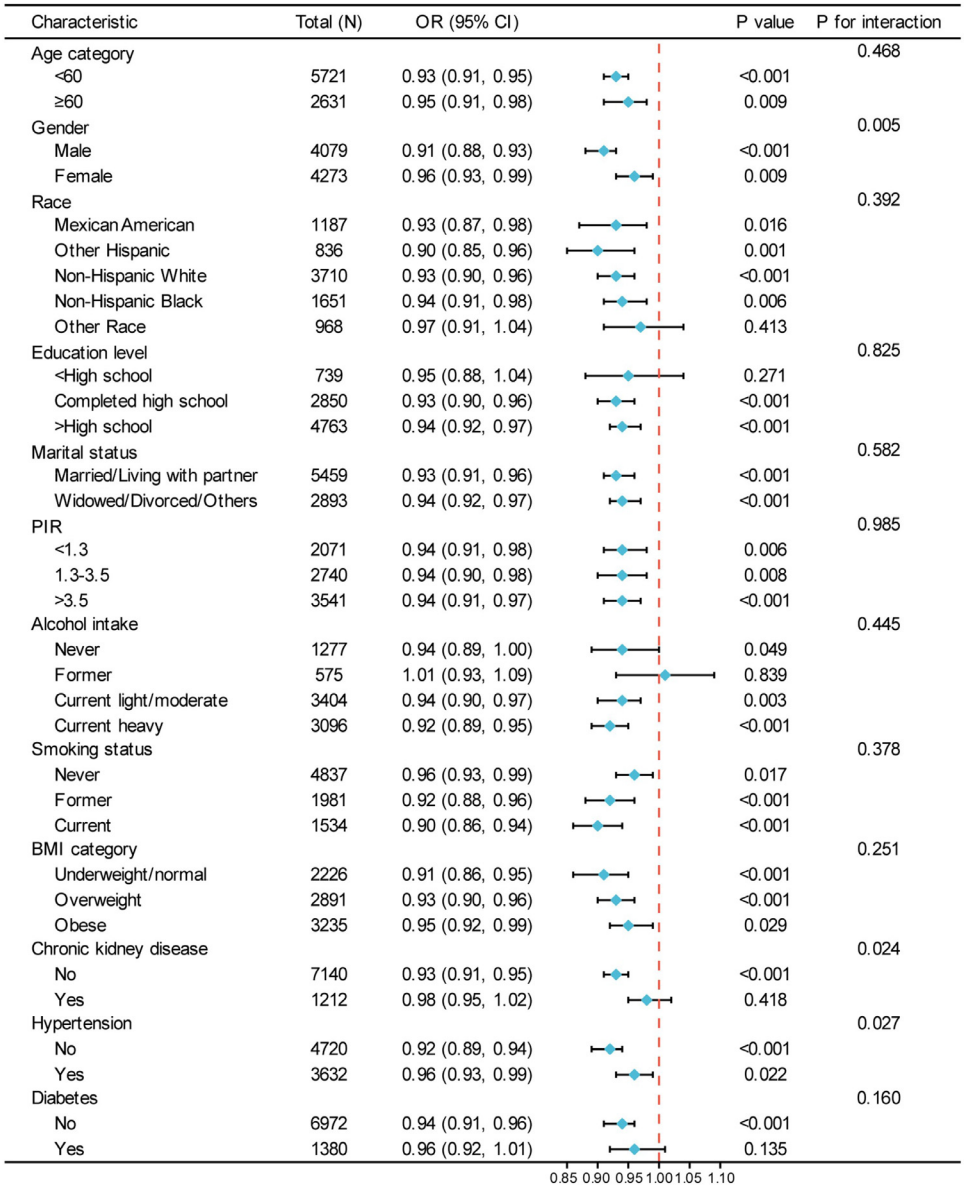

Fig. 3 – Logistic regression analyses were performed to investigate the association between albumin and periodontitis, stratifying by age, gender, race, education level, marital status, PIR, alcohol intake, smoking status, BMI, chronic kidney disease, hypertension, and diabetes.

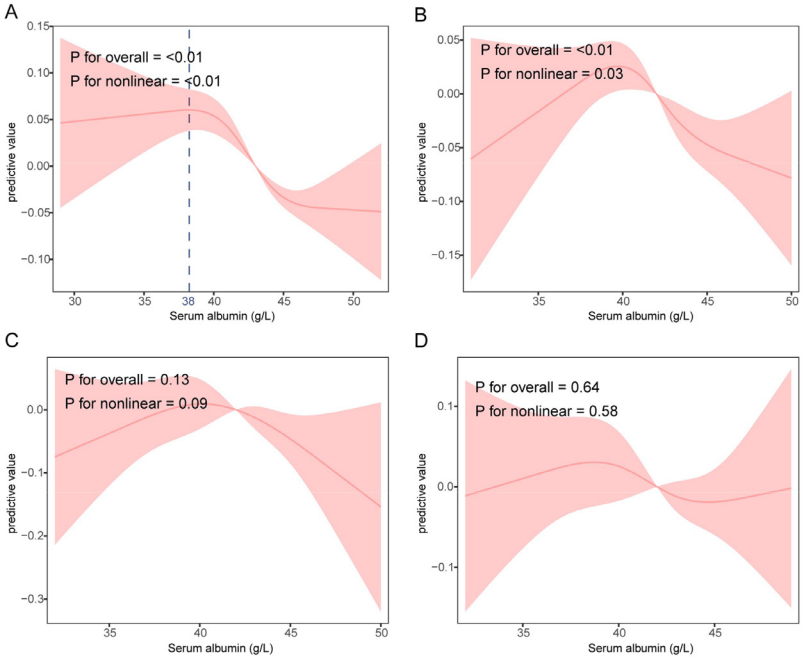

Fig. 4 – Association between albumin levels and periodontitis status: analysis across general population (A), hypertension subgroup (B), diabetes subgroup (C), and chronic kidney disease subgroup (D). Adjusted for all covariates using weighted logistic regression.

amplify the relationship, while CKD and HNT may further strengthen it. In contrast, smoking may attenuate the interaction, though the nonsignificant synergy index warrants cautious interpretation (Supplementary Table 2).

The detection of nonlinear relationships

RCS and smooth curve fitting were utilized to model the nonlinear relationship between albumin levels and periodontitis status. As depicted in Figure 4A, the fully adjusted smoothed plots revealed an inverse U-shaped association. We also employed the standard and two-piecewise linear regression models to fit the association between albumin levels and periodontitis status (detailed in Table 3). The log-likelihood ratio test demonstrated that the two-piecewise linear regression provided a better fit to the data (*P* value <.001). Notably, the inflection point in the nonlinear association corresponded to an albumin level of 38 g/L. On the left side of the inflection point, the OR was 1.047 (95%CI: 0.921-1.190), and the *P* value was .488, indicating no significant association. However, on the right side of the inflection point, albumin levels were negatively associated with periodontitis status (OR 0.938, 95%CI: 0.914-0.963, *P* value <.001). Furthermore, as albumin levels exceeded 38 g/L, the OR exhibited a downward trend.

Table 3 – Threshold effect analysis of serum albumin on periodontitis.

	OR (95% CI)	*P* value
Fitting model by standard linear regression	0.945 (0.924-0.966)	<.001
Fitting model by two-piecewise linear regression		
Inflection point (K)	38	
<K segment	1.047 (0.921-1.190)	.488
>K segment	0.938 (0.914-0.963)	<.001
P for likelihood ratio test		<.001

95% CI, 95% confidence interval; OR, odds ratio.

RCS analysis of disease subgroups showed a significant nonlinear relationship between sALB levels and periodontitis among participants with HNT (Figure 4B). As shown in Figure 4C, although the overall association between sALB and periodontitis in the diabetes population was not significant, a significant nonlinear trend was observed. Among CKD patients, serum sALB showed no association with periodontitis (Figure 4D). These further suggested that the impact of sALB on periodontitis varies among individuals with different disease backgrounds. In addition, we categorized the participants into two groups based on the disease occurrence: a group without periodontitis (*N* = 4245) and a periodontitis group (*N* = 4107). The RCS and threshold analysis results were consistent with the aforementioned findings. An inverted U-shaped nonlinear relationship was observed between sALB levels and periodontitis occurrence (Supplementary Figure 1). The periodontitis occurrence was determined based on the presence or absence of the disease.

Sensitive analyses

Sensitivity analysis excluding HNT and diabetes showed consistent associations between sALB and periodontitis (OR 0.94, 95% CI: 0.92-0.96, Supplementary Table 3). Mediation analysis revealed varing proportions of mediation effects for HNT and

diabetes in the relationship between sALB and periodontitis (Supplementary Table 4). HNT showed a weak mediation effect, accounting for 0.28% of the total effect, and was not significant (P = 0.5). In contrast, diabetes accounted for 2.45% of the total effect and demonstrated a significant mediation effect. The direct effect of sALB remained significant, indicating that its influence on periodontitis was primarily through a direct pathway. The results from Poisson regression with robust variance estimation confirmed the robustness of our findings (Supplementary Table 5). The association between sALB levels and periodontitis remained significant (prevalence ratio 0.97, 95% CI: 0.96-0.98, $P < .001$), consistent with the logistic regression results. In the subgroup analysis (Supplementary Table 6), the negative association was generally observed across different demographic and clinical subgroups, with slight variations in effect size.

Discussion

It is the first study to reveal an inverted U-shaped association between sALB and periodontitis based on large population. By defining periodontitis as a prespecified outcome, this study provides robust evidence of a significant inverse association between sALB levels and periodontal health outcomes. After fully adjusting for covariates, sALB levels were negatively associated with an increased probability of periodontitis. The association remained significant in most subgroups. At relatively high levels, higher sALB concentrations were associated with a reduced likelihood of moderate/severe periodontitis. Therefore, it is important to maintain appropriate sALB levels, as deficient levels may bring no benefits for preventing and treating periodontitis. Notably, hypoalbuminemia was not associated with periodontitis status (including CKD, HNT, and diabetes subgroups).

Periodontitis is a common oral disease that seriously impacts health-related quality of life, especially functional and aesthetic aspects.[32] The factors associated with periodontitis have been the subject of extensive research. For example, growth differentiation factor-15 and C-reactive protein, as inflammatory biomarkers, deepen our understanding of periodontitis pathophysiology and offer potential tools for assessing treatment efficacy and prognosis.[7] We believe that monitoring and managing sALB levels could enhance periodontal health management, particularly for individuals at risk of systemic inflammation. Previous studies have also investigated the association between sALB and periodontitis among the general population or those with CKD. A clinical trial revealed a significant negative correlation between sALB levels and chronic periodontitis. There was a substantial association between reduced sALB and increased CAL.[33] Periodontitis patients exhibited lower sALB levels than those with gingivitis, indicating a potential role for albumin depletion in progressing from gingivitis to periodontitis.[34] Despite the variability in confounding factors and sample sizes across studies, our research and the above findings consistently indicate a negative correlation between sALB and the development of periodontitis. Chen et al. discovered that among 253 CKD patients, those with severe periodontitis exhibited lower albumin levels, and the sALB level was independently associated with the periodontitis severity.[35] A further study suggested that hypoalbuminemia increases the risk of periodontitis among haemodialysis patients.[18]

However, our study found that hypoalbuminemia was not associated with periodontitis status. Hypoalbuminemia was not related to periodontitis in the general populations and disease subgroups (including CKD patients). These may be due to the following reasons. (1) Most of these cross-sectional studies were conducted in participants with CKD or haemodialysis, while ours was conducted in the general population with a larger sample size. Notably, in this study, the group with hypoalbuminemia made up only 1.01% of the total participants. (2) We included appropriate covariates reflecting a natural clinical practice setting. In addition to demographic characteristics, lifestyle-correlated factors and health-status-related variables exist. This will help control potential bias. (3) sALB is usually used as a biomarker of the nutritional status of haemodialysis patients. Poor nutritional status in advanced CKD patients may contribute to hypoalbuminemia and decreased resistance to periodontal pathogens.[36] There appears to be no direct association between hypoalbuminia and periodontitis development. (4) There is an inverted U-shaped association between sALB levels and periodontitis. The inflection point of the nonlinear curve is 38 g/L, which is different from the clinical diagnostic criteria for hypoalbuminemia (sALB < 35 g/L).

Our findings indicate a significant inverse association between sALB levels and periodontitis severity. While the exact mechanisms remain unclear, previous studies have suggested that sALB may influence periodontal health through pathways involving oxidative stress and inflammation, which are known drivers of disease progression. The mechanism of sALB affecting periodontitis status may be accomplished by its antioxidant, anti-inflammatory, and molecular transport effects.[8] The oxidative stress environment is the basis of chronic periodontitis, and the generation of reactive oxygen species can increase CAL.[37] Free radicals are the end products of mitochondrial respiratory bursts in polymorphic neutrophils. Excess free radicals and reduced antioxidant status promote inflammation and osteoclastogenesis, ultimately leading to bone loss in periodontitis patients. sALB is an important nonenzymatic antioxidant with free radical scavenging properties. It contains rich thiol groups, accounting for over 80% of the total thiol in plasma, scavenging active oxygen species and active nitrogen.[9] Decreased albumin levels can lead to oxidative stress dysregulation, while elevated markers of oxidative stress and reduced antioxidant capacity are detected in chronic periodontitis patients. Therefore, supplemental antioxidants may be a viable option to prevent and treat periodontitis. These mechanisms may also play a role in improving functional and aesthetic outcomes in periodontitis patients, contributing to better overall life quality. Additionally, albumin levels reflect a patient's nutritional status and liver function, both essential to the coagulation process. This is particularly significant for anticoagulation therapy, as it is closely linked to the success of invasive dental procedures. Maintaining adequate albumin levels is essential for effective blood clotting and proper healing after the procedure.[17]

In addition, sALB has the ability to bind proinflammatory substances and inflammatory mediators, such as lipopolysaccharides (LPS), a surface component of bacteria.[10] Albumin may participate in the LPS presentation and promote the decomposition of LPS-lipid polymers. Pg, a gram-negative oral anaerobic bacteria, is considered to be an important pathogen of periodontal disease. A recent study has reported that Pg can undergo programmed cell death when cultured on a substrate supplemented with human sALB.[15] Furthermore, glycated albumin can exacerbate the inflammatory response of gingival fibroblasts to LPS from Pg in diabetic patients.[16] These suggest that sALB may play a role in regulating the antibacterial inflammation of periodontal tissue. Periodontitis is associated with various molecules and metabolites, including nitric oxide, free fatty acids, and bilirubin. Nitric oxide plays a crucial role in the pathogenesis of periodontal disease by regulating certain cytokines.[38] Supplementation of Omega-3 fatty acids exhibits beneficial effects in treating periodontitis, reducing PD and CAL.[39] Elevated serum bilirubin concentrations are associated with a reduced risk of severe periodontitis, even among never-smokers.[40] In a community-based study, higher total bilirubin levels were negatively associated with PD.[39] sALB serves as a carrier and transporter of these molecules and may indirectly regulate the periodontitis progression.[24]

Interaction analyses identified sex, obesity, CKD, and HNT as modifiers of the albumin-periodontitis association. Hormonal regulation of both albumin metabolism and periodontal inflammation may explain observed sex differences, with estrogen notably counteracting albumin-mediated disease progression via its anti-inflammatory mechanisms.[24,41] In obesity, chronic adipose inflammation interacts with hypoalbuminemia to disrupt immune balance, exacerbating periodontal tissue damage through amplified cytokine signaling.[42] CKD-related uremic toxins and periodontal pathogens may weaken antioxidant capacity and drive systemic inflammation, forming a bidirectional link between renal dysfunction and oral health deterioration.[43] Meanwhile, HNT-associated vascular dysfunction may further compromise endothelial protection, facilitating microbial invasion and periodontal breakdown.[24,44] These findings indicate that albumin's role in periodontitis varies with systemic conditions that influence inflammation, metabolism, and vascular integrity. Subgroups with noncalculable synergy indices underscore the need for larger studies to clarify social determinants of interactions. Future research should prioritize stratified sampling to validate these effect modifications across diverse populations.

This study was a large cross-sectional study of the association between sALB levels and periodontitis status. First, it included 8352 participants, providing good statistical power for association analyses. Weighted analysis enhances the national representativeness of the findings, but the exclusion of missing samples may introduce bias, warranting caution in result interpretation and generalization. Secondly, we employed RCS and recursive algorithms to identify possible nonlinear relationships and threshold effects. Contrary to previous studies, our research indicated that hypoalbuminemia is unrelated to periodontitis. This study highlights the relevance of sALB levels in understanding periodontitis in patients with hypoalbuminemia or CKD. ALB concentration is a simple and routine laboratory test, which may provide effective guidance information for some periodontitis patients.

However, there are some limitations to this work. Firstly, this study cannot conclusively establish a causal relationship between sALB and periodontitis status. Although logistic regression was used in accordance with prior studies, Poisson regression with robust variance estimation were applied in sensitivity analyses, confirming the robustness of our findings. Additional longitudinal studies are required to clarify this association. Second, despite including multiple confounding factors from prior studies and clinical experience and employing subgroup analysis to mitigate potential bias, residual confounding factors may still affect the final results. Third, the study participants were sampled from the US population, limiting the overall representation of the general population. Fourth, considering the dual roles of HNT and diabetes as both covariates and mediators, we conducted additional sensitivity analyses. Excluding these variables from the analysis further validated the robustness of the study findings. The indirect effect of sALB through diabetes contributed 2.45% to the total effect. These results reveal the complexity of the association, highlighting the need for further research into its underlying mechanisms. Finally, to prevent periodontitis in specific populations, the clinical significance of this association needs further investigation.

Conclusions

We found a negative correlation between albumin levels and moderate/severe periodontitis. For the prevention and treatment of periodontitis, the disease subgroup differences may require appropriate clarification. While this study does not establish causality, it highlights the need for personalized periodontal treatment strategies that account for sALB levels as indicators of nutritional and inflammatory status. Future work will focus on validating our conclusions in high-quality prospective studies and further exploring the underlying mechanisms of this association.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Author contributions

All authors have made substantial contributions to the conception and design of the study. Junwei Xiang has been involved in the study design, data analysis, and manuscript draft. Yuhang Cai (co-first author) has been involved in data collection and data analysis. Qingping Yu and Zhongqing Zhu contributed to data interpretation. Ran Chen and Yuanyin Wang contributed to drafting the manuscript, revising the manuscript critically, and giving final approval of the version to be published.

Ethics statement and consent to participate

The survey was granted approval by the National Center for Health Statistics (NCHS) Research Ethics Review Board. Written informed consent was obtained from all participants. Given that the data used in this analysis is publicly available and deidentified, the requirement for approval from the NCHS Research Ethics Review Board was waived. All methodologies were conducted in compliance with the relevant guidelines and regulations, including the Declaration of Helsinki.

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Data availability

The data that support the findings of this study are available in NHANES at: https://www.cdc.gov/nchs/nhanes/index.htm.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.identj.2025.03.017.

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