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Association between periodontitis with the all-cause and cause specific mortality among the population with hyperlipidemia

Jiaying Xu[1†], Ruya Zhang[2†], Shanfeng Lin[3], Weiqi Li[4], Tian Li[5], Zhenning Li[3*] and Fayu Liu[3*]

Abstract

Background To explore the association between periodontitis and all-cause as well as cause-specific mortality rates in U.S. adults with hyperlipidemia.

Methods Participants were extracted from NHANES during 1988–1994, 1999–2004 and 2009–2014 periods. To assess the association between moderate-to-severe periodontitis and mortality rates for both all-cause and cause-specific mortality, hazard ratios (HRs), time ratios (TRs), and their respective 95% confidence intervals (CIs) were calculated using Cox proportional hazards and Weibull accelerated failure time (AFT) models.

Results Over a median follow-up duration of 11.83 years, 4,623 deaths of 16,848 participants were recorded. Multivariate Cox regression and AFT analyses showed moderate-to-severe periodontitis were associated with an increased risk of all-cause (HR: 1.31, 95% CI: 1.20–1.44, $P<0.001$; TR: 0.85, 95% CI: 0.80–0.90, $P<0.001$), cardiovascular disease (CVD)-related (HR: 1.36, 95% CI: 1.14–1.63, $P=0.001$; TR: 0.83, 95% CI: 0.75–0.92, $P<0.001$) and cancer-related mortality (HR: 1.35, 95% CI: 1.12–1.63, $P=0.002$; TR: 0.82, 95% CI: 0.72–0.93, $P=0.002$). Meanwhile, there was a significant upward trend in the risk of mortality with increasing severity of periodontitis (P for trend <0.001).

Conclusions Our study highlights the moderate-to-severe periodontitis is associated with an increased risk of all-cause, CVD-related and cancer-related mortality among U.S. adults with hyperlipidemia. And the mortality risk increasing alongside the severity of periodontitis.

Keywords Periodontitis, Hyperlipidemia, Mortality, Cardiovascular disease

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Introduction

Periodontitis is an oral disease characterized by inflammation and infection, which results in the destruction of periodontal tissues and can eventually lead to tooth loss [1]. An estimated 796 million people are affected by severe periodontitis (95% uncertainty interval [95% UI], 671 to 930 million) resulting, in the sixth most prevalent non-communicable human diseases [2]. People with periodontitis increased risk of various physical diseases including cardiovascular disease, diabetes mellitus (DM), certain types of cancers, and hyperlipidemia (HPL) [3, 4]. Moreover, some clinical studies have extensively documented the strong correlation between periodontitis and mortality rates in individuals suffering from systemic diseases such as diabetes mellitus, cardiovascular disease, and chronic kidney disease [5–7].

Hyperlipidemia is a common metabolic condition, which is a pathological condition featured as the derangements of lipoproteins circulating in the blood [8–10]. Hyperlipidemia have been identifed as a severe challenge in most high-income countries, its prevalence now is rapidly increasing even in low-incoming settings [11]. The rising prevalence of hyperlipidemia is largely attributed to modern lifestyles, such as poor dietary habits and insufficient physical activity, creating substantial healthcare challenges worldwide, in both developed and low-income nations [12, 13]. Notably, several studies have shown a connection between periodontitis and hyperlipidemia, implying that periodontal disease might play a fundamental role in the pathogenesis of hyperlipidemia [14–16]. A study using NHANES data indicates a significant correlation between higher serum total cholesterol levels and periodontitis [17]. Furthermore, a recent meta-analysis has demonstrated that individuals with chronic periodontitis exhibit higher plasma triglyceride and low density lipoprotein (LDL) levels compared to their healthy individuals [18]. Interestingly, treating hyperlipidemia has been found to protect against periodontal attachment loss, highlighting the potential links between oral health and lipid metabolism [19]. Nevertheless, there is barely studies explored the impact of periodontitis on the long-term survival of patients with hyperlipidemia, particularly in terms of all-cause and cause-specific mortality. Thus, our study aims to explore the association between periodontitis with the all-cause as well as cause-specific mortality of the hyperlipidemia participates, based on a large-scale, prospective, population-based cohort in the U.S.

Materials and methods

In this cohort study, we complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines specific to cohort studies. Supplementary file 1 includes detailed information on the materials and methods used.

Study population

The National Health and Nutrition Examination Survey (NHANES) utilizes a stratified, multistage probability sampling design to recruit a nationally representative estimates of health in the non-institutionalized U.S. population [20, 21]. This study analyzed data from three distinct periods (1988–1994, 1999–2004, and 2009–2014), as these intervals provided concurrent periodontal measurements and hyperlipidemia data. Participants aged over 30 years with diagnosed hyperlipidemia and available periodontal measurement data were included in the study. The criteria for hyperlipidemia were defined as having a total cholesterol level of 200 mg/dL or higher, a formal diagnosis of hyperlipidemia, or undergoing treatment for cholesterol management [21, 22]. Exclusions were made for pregnant and lactating individuals (n=228) and those unable to provide follow-up information (n=22). Ultimately, there were 16,848 participants were included in this study. Supplementary Fig. 1 provides details of the data extraction process. All supplementary tables and figures are included in Supplementary file 2.

Assessment of oral examination

Periodontitis assessment was conducted using the half-mouth method, provided by the Centers for Disease Control and Prevention in collaboration with the American Academy of Periodontology (CDC-AAP) [23]. To maintain consistent diagnostic criteria, participants were randomly chosen for the evaluation of clinical attachment loss (CAL) and periodontal probing depth (PPD) in one quadrant each of the maxilla and mandible. Measurements were specifically taken at the mesial buccal and mid buccal sites. Based on prior studies, participants were classified into two groups: those with moderate-to-severe periodontitis and those with no/mild periodontitis [7, 24–26]. Moderate-to-severe periodontitis was characterized by the presence of at least one interproximal site with a CAL of 4 mm or more, or one interproximal site with a PPD of 5 mm or more, irrespective of whether these readings were at the same or different locations. The average values of CAL and PPD were calculated to compare periodontal conditions [7, 24].

Ascertainment of participants mortality

The outcome of the current study was all-cause and cause-specific mortality (CVD-related mortality and cancer-related mortality) of the hyperlipidemia participates. Mortality data for the follow-up participates was sourced from the National Center for Health Statistics. The baseline was established at the time of participants'

periodontal examinations [27]. Person-years were computed starting from the date of the oral examination up to the date of death, loss to follow-up, or December 31, 2019, whichever came first [27]. Causes of death were checked using the ICD-10 (International Statistical Classification of Diseases, 10th revision), and pertinent ICD-10 codes were utilized to compute mortality rates for cancer and cardiovascular disease [27].

Assessment of covariates

To select the covariates, a directed acyclic graph (DAG) was utilized (Supplementary Fig. 2) [28, 29]. Eight covariates were included: age, gender, race, socioeconomic status (SES), smoking, alcohol intake (drinking status), physical activity, and nutritional status (body mass index, BMI). Additionally, further adjustments were made for comorbidities such as hypertension and diabetes. Latent class analysis was utilized to combine income, education level, occupation, and insurance into a categorical SES variable with three levels (Supplementary Table 1, Supplementary Fig. 3) [27, 28, 30, 31].

Statistical analysis

In accordance with NHANES analytical guidelines, statistical analyses were conducted taking into account complex sampling designs that incorporated weights, clustering, and stratification [27, 31]. To examine disparities between different periodontal conditions (no/mild or moderate-to-severe periodontitis) within the population, student's t-tests were applied to continuous covariates, while χ^2 tests were employed for categorical covariates [27, 31]. Kaplan-Meier (KM) curves were utilized to identify potential survival patterns between the two periodontal status groups. Total person-years were calculated without applying weights, and the median follow-up period was determined using weighted reverse KM survival curves. Univariate and multivariable Cox proportional hazard models were employed to evaluate the association of moderate-to-severe periodontitis with all-cause, CVD-related as well as cancer-related mortality in participants with hyperlipidemia [32]. To analyze the relationship between periodontitis and cause-specific mortality, competing risk models were applied. The impact of periodontitis on the survival time of participants with hyperlipidemia was assessed using Weibull accelerated failure time (AFT) models [33]. Schoenfeld residuals were utilized to test the proportional hazards assumption. Four models were established in this study: Model 1, univariate regression analysis; Model 2, which included age, SES, race, and gender; Model 3, which incorporated alcohol intake, physical activity, smoking, and nutritional status (BMI); and Model 4, which added hypertension, and diabetes. Details regarding the missing data rate and multiple imputation methods for covariates are provided in Supplementary Table 2 [5, 27]. Stratified analyses were conducted by grouping participants according to age (classified as young, < 45 years, or old, ≥ 45 years) and gender (female/male). The severity of periodontitis was used to categorize periodontal status, aiming to assess the potential association between periodontitis severity and different types of mortality in participants with hyperlipidemia [5].

To compare, further analysis was performed on the average CAL/PPD results. Initially, the association between average CAL/PPD and various mortality rates in participants with hyperlipidemia was investigated. Furthermore, average CAL and PPD were divided into quartiles (quartile 1–4) based on the complex sample, with the first quartile serving as the reference, to analyze the relationship between these quartiles and various types of mortality. Additionally, trend tests were conducted [7]. Restricted cubic spline (RCS) was used to identify potential dose-effect correlations between average CAL/PPD with all-cause and cause-specific mortality of the hyperlipidemia participants [6]. Nonlinear tests were conducted using likelihood ratio tests. Stratified analyses incorporating RCS were conducted by grouping participants according to age and gender.

To check the robust relationships between periodontitis and mortality of the hyperlipidemia participants, a sets of sensitive analyses were conducted to validate the main findings: (1) Excluding participants with less than 2 years of follow-up to minimize potential bias (n=289); (2) Excluding participants with CVD or cancer to prevent the influence of pre-existing serious diseases (n=2,894); (3) Conducting an analysis without multiple imputation; (4) Excluding participants with missing information for any covariates from the statistical analysis (n=2,958). A P-value of less than 0.05 was considered statistically significant, and statistical analyses were performed using R software (version 4.3.1, Austria).

Results

Demographic characteristics of hyperlipidemia participants

Over 244,273.1 person-years of follow-up (median follow-up of 11.8) for 16,848 unweighted participants, we recorded 4,623 all-cause deaths, 1,531 deaths related to CVD, and 1,069 cancer-related deaths. Table 1 and Supplementary Table 3 provide a summary of the baseline characteristics of participants with hyperlipidemia, classified by their periodontitis status. Participants with moderate/severe periodontitis were older (mean age 56.4±0.2 vs. 49.9±0.2, P<0.001), had a lower proportion of females (42.6% vs. 53.5%, P<0.001), were less likely to be non-Hispanic black (69.4% vs. 76.7%, P<0.001), with a higher percentage of low SES (20.9% vs. 11.5%, P<0.001), were more likely to be current smokers (26.6% vs. 15.6%,

Table 1 Baseline characteristics of participants with hyperlipidemia according to periodontal status

			Periodontal status				
	Over all		No/Mild periodontitis		Moderate/Severe periodontitis		
Characteristics	**Mean/ %***	**SE***	**Mean/ %**	**SE**	**Mean/ %**	**SE**	***P*†**
No.(Unweighted)	16848		9725		7123		
No.(Weighted)	181,668,051		62,540,697		119,127,354		
Age (years), mean	52.1	0.2	49.9	0.2	56.4	0.2	< 0.001
Age status, %							< 0.001
< 45	32.3	0.6	39.1	0.8	19.3	0.7	
[45, 65)	48.4	0.6	46.2	0.8	52.6	0.8	
≥ 65	19.2	0.4	14.6	0.5	28	0.7	
Sex, Female	49.8	0.5	53.5	0.7	42.6	1	< 0.001
Race/ ethnicity, %							< 0.001
Non-Hispanic white	74.2	1.1	76.7	1.1	69.4	1.5	
Non-Hispanic black	9	0.6	8	0.5	10.9	0.8	
Hispanic	11.8	0.9	11.1	0.8	13.1	1.1	
Other race/ ethnicity	5	0.3	4.2	0.3	6.6	0.6	
Socioeconomic Status, %							< 0.001
Low	14.8	0.5	11.5	0.5	20.9	0.9	
Medium	43.1	0.8	40.3	0.9	48.4	1	
High	42.2	1	48.2	1	30.7	1	
Smoking status, %							< 0.001
Never smoker	51.6	0.6	56.7	0.9	41.7	0.9	
Former smoker	29.1	0.6	27.7	0.7	31.6	0.8	
Current smoker	19.4	0.5	15.6	0.6	26.6	0.8	
Drinking status, %							< 0.001
Nondrinker	10.8	0.5	10.7	0.7	11	0.5	
Light/ moderate drinker	62.4	0.6	60.9	0.8	65.3	0.8	
Heavier drinker	26.8	0.6	28.4	0.8	23.7	0.8	
Physical status, %							< 0.001
Inactive	18.8	0.5	16.7	0.5	22.7	0.9	
Insufficient	41	0.7	44.2	0.9	34.9	1	
Recommended	40.2	0.7	39.1	0.8	42.3	1	
BMI, Mean	29	0.1	29.2	0.1	28.6	0.1	< 0.001
BMI status (kg/m2), %							< 0.001
< 25	26.1	0.6	24.9	0.7	28.5	0.9	
[25.0–30)	38.2	0.6	38.2	0.8	38.2	0.8	
≥ 30	35.7	0.6	37	0.8	33.3	0.8	
Comorbidities, %							
Hypertension	44.1	0.6	41	0.8	50.1	1	< 0.001
Diabetes mellitus	14.2	0.4	11.8	0.4	18.7	0.6	< 0.001
Cohort period, %							< 0.001
NHANES III	11.2	0.5	10.6	0.6	12.3	0.6	
NHANES 1999–2004	38.6	1.2	42.9	1.5	30.5	1.3	
NHANES 2009–2014	50.2	1.3	46.5	1.6	57.3	1.4	

*Normally distributed continuous variables are described as means ± SEs; Categorical variables are presented as numbers (percentages). All estimates accounted for complex survey designs.

†The t test was used for continuous variables and the χ test for categorical variables.

$P<0.001$), were less likely to be heavy drinkers (23.7% vs. 28.4%, $P<0.001$), and had a greater proportion of inactive participants (22.7% vs. 16.7%, $P<0.001$). Additionally, there was a higher prevalence of comorbidities (hypertension: 50.1% vs. 41.0%, $P<0.001$; diabetes mellitus: 18.7% vs. 11.8%, $P<0.001$).

Association between moderate-to-severe periodontitis and all kinds of mortality

A Kaplan-Meier analysis, which did not adjust for covariates, revealed that the hyperlipidemia participants with moderate-to-severe periodontitis group showed significantly higher all-cause, CVD-related as

well as cancer-related mortality when compared with no/mild periodontitis group ($P<0.001$) (Fig. 1. A-C). The absolute crude mortality rates for moderate to severe periodontitis were 20.13% for all-cause mortality (95% CI: 20.12–20.14), 6.15% for CVD-related (95% CI: 6.14–6.15), and 5.12% for cancer-related (95% CI: 5.12–5.13) (Supplementary Table 4). Additionally, even after adjusting for multivariate covariates, moderate-to-severe periodontitis was still significantly associated with an increased risk of all-cause mortality (Model 4: HR, 1.31, 95% CI: 1.20–1.44, $P<0.001$), CVD-related mortality (Model 4: HR, 1.36, 95% CI: 1.14–1.63, $P=0.001$) and cancer-related mortality (Model 4: HR, 1.35, 95% CI: 1.12–1.63, $P=0.002$) (Table 2). In line with the competing risk model, the Weibull AFT model revealed that moderate-to-severe periodontitis decreased survival time for all-cause mortality (Time ratio: 0.85, 95% CI: 0.80–0.90, $P<0.001$), CVD-related mortality (Time ratio: 0.83, 95% CI: 0.75–0.92, $P<0.001$) and cancer-related mortality among participants with hyperlipidemia (Time ratio: 0.82, 95% CI: 0.72–0.93, $P=0.002$) (Table 3).

Trend test of periodontitis and stratified analyses

Trend tests indicated that the severity of periodontitis showed an increasing trend in the risk of all-cause mortality (P for trend<0.001), CVD-related mortality (P for trend$=0.001$) and cancer-related mortality (P for trend$=0.003$) (Table 4).

The stratified analyses revealed periodontitis had stronger associations with all-cause and cause-specific mortality among participants with hyperlipidemia with the clinical characteristics of age and gender. Most HRs indicated a positive association between periodontitis and both all-cause and cause-specific mortality among participants with hyperlipidemia (Supplementary Table 5). Notably, in the subgroup under 45 years old, moderate to severe periodontitis was significantly associated with an increased risk of all-cause mortality (HR: 1.60, 95% CI: 1.45–1.76, $P<0.001$), CVD-related mortality (HR: 1.73, 95% CI: 1.45–2.07, $P<0.001$), as well as cancer-related mortality (HR: 1.55, 95% CI: 1.28–1.88, $P<0.001$).

Association between average CAL/PPD and mortality

In our analyses, after adjusting for multiple variables, both of the mean CAL and PPD were significantly associated with an increased risk of all-cause mortality (HR: 1.15, 95% CI: 1.11–1.19, $P<0.001$; HR: 1.21, 95% CI: 1.14–1.29, $P<0.001$), CVD-related mortality (HR: 1.15, 95% CI: 1.09–1.21, $P<0.001$; HR: 1.30, 95% CI: 1.17–1.45, $P<0.001$) and cancer-related mortality (HR: 1.20, 95% CI: 1.16–1.24, $P<0.001$; HR: 1.19, 95% CI: 1.04–1.36, $P=0.011$), respectively (Supplementary Table 6). Furthermore, a significant increasing trend was observed across quartiles of mean CAL and PPD for all-cause mortality (CAL: P for trend$=0.006$; PPD: P for trend$=0.025$), as well as for CVD-related mortality (CAL: P for trend$=0.025$; PPD: P for trend$=0.007$) (Supplementary

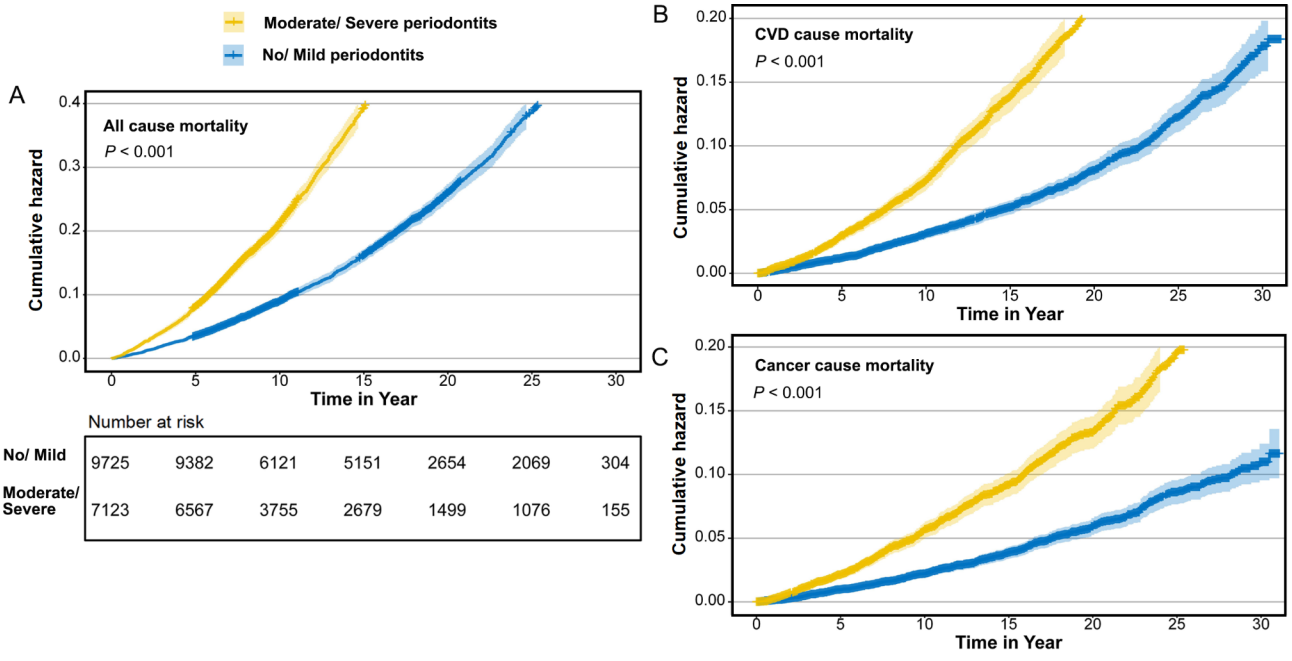

Fig. 1 Association between moderate-to-severe periodontitis and all kinds of mortality. **A**: The weighted Kaplan-Meier analysis of periodontitis with all-cause survival; **B**: The weighted Kaplan-Meier analysis of periodontitis with CVD-related survival; **C**: The weighted Kaplan-Meier analysis of periodontitis with cancer-related survival

Table 2 HR (95% CIs) for All-cause and cause-specific mortality according to periodontitis

	Periodontal status		
	No/Mild periodontitis	**Moderate/Severe periodontitis**	***P***
All cause*			
Deaths/total (Unweighted)	1971/9725	2652/7123	
Deaths/total (Weighted)	14,771,673/62,540,697	13,905,931/119,127,354	
Model 1†	1.00 [Reference]	2.43 (2.23, 2.64)	< 0.001
Model 2‡	1.00 [Reference]	1.42 (1.30, 1.56)	< 0.001
Model 3§	1.00 [Reference]	1.32 (1.21, 1.45)	< 0.001
Model 4¶	1.00 [Reference]	1.31 (1.20, 1.44)	< 0.001
CVD cause			
Deaths/total (Unweighted)	636/9725	895/7123	
Deaths/total (Weighted)	4,509,303/62,540,697	3,824,397/119,127,354	
Model 1	1.00 [Reference]	2.69 (2.33, 3.12)	< 0.001
Model 2	1.00 [Reference]	1.42 (1.20, 1.69)	< 0.001
Model 3	1.00 [Reference]	1.39 (1.17, 1.66)	< 0.001
Model 4	1.00 [Reference]	1.36 (1.14, 1.63)	0.001
Cancer cause			
Deaths/total (Unweighted)	442/9725	627/7123	
Deaths/total (Weighted)	3,758,257/62,540,697	3,628,418/119,127,354	
Model 1	1.00 [Reference]	2.33 (1.97, 2.75)	< 0.001
Model 2	1.00 [Reference]	1.52 (1.27, 1.83)	< 0.001
Model 3	1.00 [Reference]	1.34 (1.11, 1.62)	0.002
Model 4	1.00 [Reference]	1.35 (1.12, 1.63)	0.002

* All-cause mortality used Cox proportional hazards model, and Cause-specific mortality used competing risk model.

† Model 1 was univariate analysis.

‡ Model 2 included age (30–44, 45–64 or ≥ 65 years old), gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic or other races), SES (Socioeconomic Status: low, middle, high).

§ Model 3 additionally included smoking status (never smokers, former or current smokers), drinking status (nondrinker, heavier drinker, or light/moderate drinker), physical activity status (inactive, insufficient, recommended) and BMI (body measure index, normal (≤ 24.9 [kg/m2]), overweight (25.0-29.9 [kg/m2]), and obesity (≥ 30.0 [kg/m2]) based on Model 2.

¶ Model 4 was further adjusted for HTN status (hypertension, yes or no), and diabetes status (yes or no) based on Model 3.

Tables 7–8). No significant trend was found in the quartiles of mean CAL and PPD with cancer-related mortality. The multivariable-adjusted RCS analysis revealed a non-linear relationship between mean CAL and all-cause mortality (*P*-nonlinear < 0.001) as well as CVD-related mortality (*P*-nonlinear = 0.013) (Supplementary Fig. 4). No other nonlinear associations were identified through the RCS analysis.

Sensitivity analyses

To check the robustness of the main findings, several sensitive analyses were performed. First, the results remained consistent after excluding participants with less than 2 years of follow-up (Supplementary Table 9) or those with cancer/CVD (Supplementary Table 10). Similarly, the results were unaffected when multiple imputations were not performed (Supplementary Tables 11–12) or when participants with missing covariate values were excluded (Supplementary Tables 13–14). The sensitivity analysis focusing solely on hyperlipidemic participants also provided consistent results as well (Supplementary Table 15).

Discussions

In a prospective cohort study encompassing 244,273.1 person-years of follow-up in 16,848 adults with hyperlipidemia, it was observed that moderate-to-severe periodontitis and mean CAL/PPD were associated with an increased risk of all-cause, CVD-related and cancer-related mortality in the hyperlipidemia participates. Furthermore, the severity of periodontitis indices are independently associated with an increased risk of all cause mortality and cause-specific mortality among participates with hyperlipidemia. Notably, the RCS for mean CAL also revealed trends indicating an increased risk of all-cause and CVD-related mortality as mean CAL increased, implying a potential dose–response effect. To our knowledge, this study is the first to comprehensively investigate the association between periodontitis severity and mortality in adults with hyperlipidemia using such a large, population-based sample. The robustness of the sampling methodology and the extensive population base are major strengths of this study, bolstering the generalizability of the findings to the US population.

Various stratified and sensitivity analyses demonstrated a relatively stable relationship in our findings. In

Table 3 Time Ratio (95% CIs) for All-cause and cause-specific mortality according to periodontitis by Weibull model.

	Periodontal status		
	No/Mild periodontitis	**Moderate/Severe periodontitis**	**P**
All cause*			
Deaths/total (Unweighted)	1971/9725	2651/7122	
Deaths/total (Weighted)	14,765,063/62,534,087	13,905,931/119,127,354	
Model 1†	1.00 [Reference]	0.55 (0.52, 0.59)	< 0.001
Model 2‡	1.00 [Reference]	0.80 (0.76, 0.85)	< 0.001
Model 3§	1.00 [Reference]	0.84 (0.80, 0.89)	< 0.001
Model 4¶	1.00 [Reference]	0.85 (0.80, 0.90)	< 0.001
CVD cause			
Deaths/total (Unweighted)	636/9725	895/7122	
Deaths/total (Weighted)	4,509,303/62,534,087	3,824,397/119,127,354	
Model 1	1.00 [Reference]	0.51 (0.47, 0.57)	< 0.001
Model 2	1.00 [Reference]	0.81 (0.73, 0.89)	< 0.001
Model 3	1.00 [Reference]	0.82 (0.74, 0.91)	< 0.001
Model 4	1.00 [Reference]	0.83 (0.75, 0.92)	< 0.001
Cancer cause			
Deaths/total (Unweighted)	442/9725	627/7122	
Deaths/total (Weighted)	3,758,257/62,534,087	3,628,418/119,127,354	
Model 1	1.00 [Reference]	0.73 (0.65, 0.82)	< 0.001
Model 2	1.00 [Reference]	0.75 (0.66, 0.85)	< 0.001
Model 3	1.00 [Reference]	0.82 (0.72, 0.93)	0.002
Model 4	1.00 [Reference]	0.82 (0.72, 0.93)	0.002

*All-cause and Cause-specific mortality used Weibull accelerated failure time model.

† Model 1 was univariate analysis.

‡ Model 2 included age (30–44, 45–64 or ≥ 65 years old), gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic or other races), SES (Socioeconomic Status: low, middle, high).

§ Model 3 additionally included smoking status (never smokers, former or current smokers), drinking status (nondrinker, heavier drinker, or light/moderate drinker), physical activity status (inactive, insufficient, recommended) and BMI (body measure index, normal, overweight, and obesity) based on Model 2.

¶ Model 4 was further adjusted for HTN status (hypertension, yes or no), and diabetes status (yes or no) based on Model 3.

Table 4 HR (95% CIs) and P for trend for All-cause and cause-specific mortality according to status of periodontitis

Outcomes	**Events (Weighted), n/N**	**HR (95% CI)**	**P**
All cause			
No/Mild periodontitis	13,905,931/119,127,354	1.00 [Reference]	
Moderate periodontitis*	13,187,531/57,048,384	1.31 (1.20, 1.43)	< 0.001
Severe periodontitis	1,584,142/5,492,313	1.36 (1.15, 1.62)	< 0.001
P for trend		1.24 (1.16, 1.33)	< 0.001
CVD cause*			
No/Mild periodontitis	3,824,397/119,127,354	1.00 [Reference]	
Moderate periodontitis	4,059,133/57,048,384	1.37 (1.14, 1.66)	0.001
Severe periodontitis	450,170/5,492,313	1.26 (0.95, 1.66)	0.108
P for trend		1.24 (1.09, 1.41)	0.001
Cancer cause*			
No/Mild periodontitis	3,628,418/119,127,354	1.00 [Reference]	
Moderate periodontitis	3,380,280/57,048,384	1.35 (1.12, 1.63)	0.002
Severe periodontitis	377,977/5,492,313	1.32 (0.89, 1.97)	0.166
P for trend		1.25 (1.08, 1.46)	0.003

* All-cause mortality used Cox proportional hazards model, and cause-specific mortality used competing risk model. All the models were adjusted for age (30–44, 45–64 or ≥ 65 years old), gender (male and female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other races), SES (high, medium, and low level), smoking status (current smokers, former smokers, and never smokers), drinking status (nondrinkers, heavier drinkers, and light/moderate drinkers), physical activity status (inactive, insufficient, recommended), BMI (body mass index, normal, overweight, and obesity), HTN status (hypertension, yes or no), and diabetes status (yes or no).

particular, the stratified analysis revealed that moderate-to-severe periodontitis increased the risk of all cause and CVD-related mortality in younger participants (<45 years) and female. Interestingly, a study by Lee et al., using data from the Fourth Korea National Health and Nutrition Examination (KNHANES) survey, found that individuals aged 40 years or older with periodontitis did not have a significant association with dyslipidemia, despite both conditions being more prevalent in older individuals [34]. Significant association was found between periodontitis and low high-density lipoprotein (HDL) and high LDL cholesterol levels in female [35]. To validate the robustness of these findings, a series of sensitivity analyses were performed. Stable results were achieved by excluding participants with short follow-up periods, while those with cancer and cardiovascular disease diagnoses were excluded to maintain the findings' reliability. To mitigate the potential effects of multiple imputations on the results, sensitivity analyses for missing covariates were conducted. Nonetheless, our findings emphasize that the association between periodontitis and mortality in participants with hyperlipidemia warrants attention from both affected individuals and their physicians.

Previous research has rarely investigated the connection between periodontitis and mortality in adults with hyperlipidemia. However, some studies have reported an association between blood lipid levels and periodontal disease in representative populations. A recent study utilizing 2011–2012 NHANES data identified a statistically significant association between borderline to high serum total cholesterol levels and periodontitis in a combined sample of men and women [35]. Another study by Ehteshami et al. determined that increased concentrations of LDL cholesterol and triglycerides were connected to periodontal disease [36]. Additionally, several studies with relatively small sample sizes, ranging from 52 to 261 participants, did not find any association between periodontitis and hyperlipidemia [18, 37, 38]. The discrepancies in study results may be attributed to variations in study design, sample size, and the characteristics of the subjects.

Knowledge is sparse regarding mechanisms directly related to the association of periodontitis with mortality by hyperlipidemia in adults. Periodontitis has reportedly been strongly associated with systemic diseases and can cause systemic infection or systemic inflammation [39, 40]. Chronic inflammation, which commonly causes hyperlipidemia, disrupts the balance of LDL, HDL, and triglycerides, leading to dyslipidemia [18]. Moreover, periodontal disease and chronic inflammation may promote lipolysis, subsequently increasing circulating triglycerides [41]. Current evidence suggests that periodontal therapy may beneficent individuals with hyperlipidemia by decreasing the levels of TNF-α, IL-6 and CRP, suggesting the critical role of periodontal care for hyperlipidemia patients [42–44]. Furthermore, periodontal microorganisms can also trigger foam cell production, which is a characteristic features of atherosclerosis [45]. Notably, periodontal pathogens have been identified and isolated from atheromatous plaques, emphasizing the role of periodontal bacteria in atherosclerosis [44]. Additionally, periodontal infection may weaken the anti-atherogenic effect of HDL, thereby increasing the risk of cardiovascular disease [46]. Indeed, our study found an association between periodontitis and all-cause and CVD-related mortality, indicating that maintaining healthy periodontal status could potentially reduce the risk of all-cause, CVD-related, and cancer-related mortality in adults with hyperlipidemia.

Strengths and limitations

Some noteworthy strengths of the present study should be highlighted. First, to our knowledge, this is the largest and most representative investigation focusing on comprehensively evaluation the association between periodontitis with the all-cause as well as cause-specific mortality in participants with hyperlipidemia. Second, by constructing DAGs, we achieved minimal sufficient adjustment to reduce the influence of confounding factors. Third, in addition to periodontitis, we analyzed the mean CAL and PPD, exploring the non-linear association between the periodontal index and mortality among individuals with hyperlipidemia, which potentially minimizing the risk of periodontitis misclassification. Finally, we performed stratified and sensitivity analyses to confirm the robustness of our findings.

Nevertheless, our study has several limitations. First, the use of the half-mouth examination may underestimate the prevalence of periodontitis, thereby reducing the reliability of the results. Second, due to the lack of relevant radiographic information on alveolar bone, we are currently unable to use the new classification for periodontal to diagnose the periodontal status of NHANES participants. Third, data on periodontitis and hyperlipidemia were collected concurrently at baseline, which may not accurately capture causal effects. Fourth, the covariates collected at baseline might have changed over time, potentially weakening the actual association between periodontitis and mortality in hyperlipidemic participants. Fifth, although we used DAGs to identify potential confounders and added additional covariates, the subjective selection process means that residual or unknown confounding factors cannot be entirely excluded. Finally, defining hyperlipidemia using only total cholesterol level may introduce measurement bias.

Conclusion

In a nationally representative sample of U.S. adults with hyperlipidemia, our study found that moderate-to-severe periodontitis is associated with an increased risk of all-cause and cause-specific mortality, with the mortality risk increasing alongside the severity of periodontitis. These findings suggest that dental healthcare workers can play a crucial role in raising awareness among patients with periodontitis about its association with hyperlipidemia, potentially helping to mitigate mortality risk in individuals with hyperlipidemia.

Abbreviations

AFT	Accelerated failure time
BMI	Body mass index
CAL	Clinical attachment loss
CDC	Centers for Disease Control and Prevention
CIs	Confidence intervals
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DM	Diabetes mellitus
HDL	High-density lipoprotein
HEI	Healthy eating index
HPL	Hypercholesterolemia
HRs	Hazard ratios
HTN	Hypertension status
ICD-10	International Statistical Classification of Diseases, 10th revision
KM	Kaplan-Meier
LDL	Low density lipoprotein
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
PPD	Periodontal probing depth
RCS	Restricted cubic spline
SES	Socioeconomic status
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TRs	Time ratios
UI	Uncertainty interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-024-05055-2.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Jiaying Xu: Conceptualization, Writing-original draft, Writing-review & editing, Supervision. Ruya Zhang: Conceptualization, Writing-review & editing, Supervision. Shanfeng Lin: Data curation, Methodology, Writing-original draft. Weiqi Li: Data curation, Methodology, Formal analysis. Tian Li: Data curation. Zhenning Li: Writing-review & editing, Supervision. Fayu Liu: Writing-review & editing, Supervision. All authors gave final approval and agreed to be accountable for all aspects of the work.

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Data availability

The accompanying code repository at https://github.com/leescu/PD-HPL. Source data are provided with this paper and https://github.com/leescu/PD-HPL.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB) Approval. (https://www.cdc.gov/nchs/nhanes/irba98.htm)

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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