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Association between periodontitis and mortality in participants with metabolic dysfunction-associated steatotic liver disease: results from NHANES

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Abstract

Background It has been reported that periodontitis was a risk factor for metabolic dysfunction-associated steatotic liver disease (MASLD). The aim of this study is to investigate the impact of periodontitis on all-cause and cause-specific mortality of MASLD patients.

Methods We included 11,019 individuals with metabolic dysfunction-associated steatotic liver disease (MASLD) from the National Health and Nutrition Examination Survey. Multivariable Cox proportional hazards models were utilized to analyze the estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and cause-specific mortality among participants with different periods of periodontitis status. Additionally, we employed restricted cubic splines (RCS) curves to explore the dose-response relationship between clinical attachment level (CAL) and pocket probing depth (PPD) and mortality rates. Finally, a series of sensitivity analyses and stratification analyses were conducted to test the reliability and robustness of the results.

Results In this study, moderate to severe periodontitis significantly increased the all-cause mortality (HR 1.29, 95% CI 1.08–1.55; $P=0.003$) and cardiovascular disease (CVD)-related mortality (HR 1.41, 95% CI 1.10–1.79; $P=0.006$) among MASLD participants. However, no significant effects of different periodontal statuses on cancer mortality were observed among MASLD participants.

Conclusions A nationwide large-sample longitudinal study indicated that MASLD patients with moderate to severe periodontitis experienced significantly higher all-cause and CVD-related mortality rates compared to those with no or mild periodontitis.

Keywords Metabolic dysfunction-associated steatotic liver disease, Periodontitis, Mortality

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly named nonalcoholic fatty liver disease (NAFLD), a metabolic stress liver injury which is characterized by excessive accumulation of triglyceride accumulation in hepatocytes in the absence of alcohol and other specific reasons of liver injury. It is one of the most common causes of liver-related morbidity and mortality [1, 2, 3, 4]. The global prevalence of MASLD is estimated to be 30.2% (95% CI: 28.7–31.7%) [5]. Recently, various models have indicated that MASLD will cause enormous clinical and economic burden, as well as poor prognosis [4, 6, 7].

Over the last decades, it has been shown that the influences of MASLD is not only limited to liver, but growing evidence has indicated that MASLD is multi-system disease, affecting extra-hepatic organs and regulatory pathways. For example, it has been reported that MASLD increases the risk of type 2 diabetes mellitus (T2DM), cardiovascular (CVD) and cardiac diseases, and chronic kidney disease (CKD) [8, 9, 10]. The etiology of MASLD is diverse and the pathological mechanisms are complex. It is currently believed that inflammation, including both extrahepatic and intrahepatic factors, is a key driving force in the development of MASLD [9]. Extrahepatic factors, such as increased carbohydrate and fat intake, progressive adipose tissue dysfunction and insulin resistance could act as pro-inflammatory factors, upregulating liver inflammatory gene expression level and inducing metabolic disturbance and facilitating the development of MASLD [11, 12, 13, 14, 15]. Intrahepatic factors, oxidative stress in hepatocytes and mitochondrial dysfunction could trigger the liver inflammation and injury, and the injury further resulting the infiltration of monocytes and lymphocytes, amplifying the liver inflammation [16, 17, 18].

Periodontitis is a chronic multifactorial inflammatory condition caused by dental plaque biofilm, characterized by localized inflammation due to oral microbial infection, leading to the loss of dental supporting tissues, the formation of periodontal pockets, and bleeding of the gums [19]. Porphyromonas gingivalis (*P.g*), the key pathogen of periodontitis, can be detected in the liver tissue of about 52.5% MASLD patients, and the number of bacteria is positively correlated with the degree of liver fibrosis [20]. Another study found that *P.g* can significantly increase the inflammatory response and fibrosis degree in the liver tissue of rats, promoting the progression of MASLD [21]. Therefore, periodontitis is speculated as an important risk factor for the development and prognosis of MASLD [22, 23]. However, the association between periodontal status and mortality in adults with MASLD still remains unclear.

In this study, we aimed to explore the association between periodontitis and all-cause and cause-specific mortality of adults with MASLD.

Method

Study population

The National Health and Nutrition Examination Survey (NHANES) is a public database of health and nutrition research on U.S. populations. The design incorporates a comprehensive stratification and weighting methodology that ensures the sample is representative of the U.S. population. The study included individuals from the NHANES III (1988–1994), 1999–2004, and 2009–2014 cycles, as data on periodontitis was only available for these cycles [24]. The diagnosis of hepatic steatosis was based on the calculation of the hepatic steatosis index (HSI), which is based on the following formula: HSI = 8 × (alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ratio) + body mass index (+ 2 for female; +2 for diabetes). Hepatic steatosis was considered to be present when the HSI was > 36 [25, 26]. To ensure uniformity in the criteria, 13,468 participants aged ≥ 30 years with complete data on periodontitis and HSI > 36 were included in the subsequent analysis. Exclusion criteria included heavy alcohol consumption (2,294), hepatitis B (47), hepatitis C (94), and missing data on mortality (14), resulting in the inclusion of 11,019 participants for subsequent analysis (Fig. 1).

Evaluation of periodontitis

In mobile examination centers, data pertaining to the oral health component are recorded directly on computerized data collection forms. The NHANES included periodontal examination records from both the maxillary and mandibular quadrants. However, in order to maintain a consistent diagnosis of periodontitis across cycles, only the proximal buccal and mesiobuccal sites were selected for the subsequent analysis. Mild periodontitis was defined as ≥ 1 interproximal sites with ≥ 3 mm clinical attachment level (CAL), or ≥ 1 interproximal sites with ≥ 4 mm pocket probing depth (PPD). Moderate periodontitis was defined as ≥ 1 interproximal sites with ≥ 4 mm CAL, or ≥ 1 interproximal sites with ≥ 5 mm PPD. Severe periodontitis comprised ≥ 1 interproximal sites with ≥ 5 mm PPD, or ≥ 1 interproximal sites with CAL ≥ 6 mm (on the same site or different sites) [27]. As in previous studies [28, 29], in order to examine the possible effect of a higher prevalence of mild periodontitis on the results, we used no/mild periodontitis as the normal group

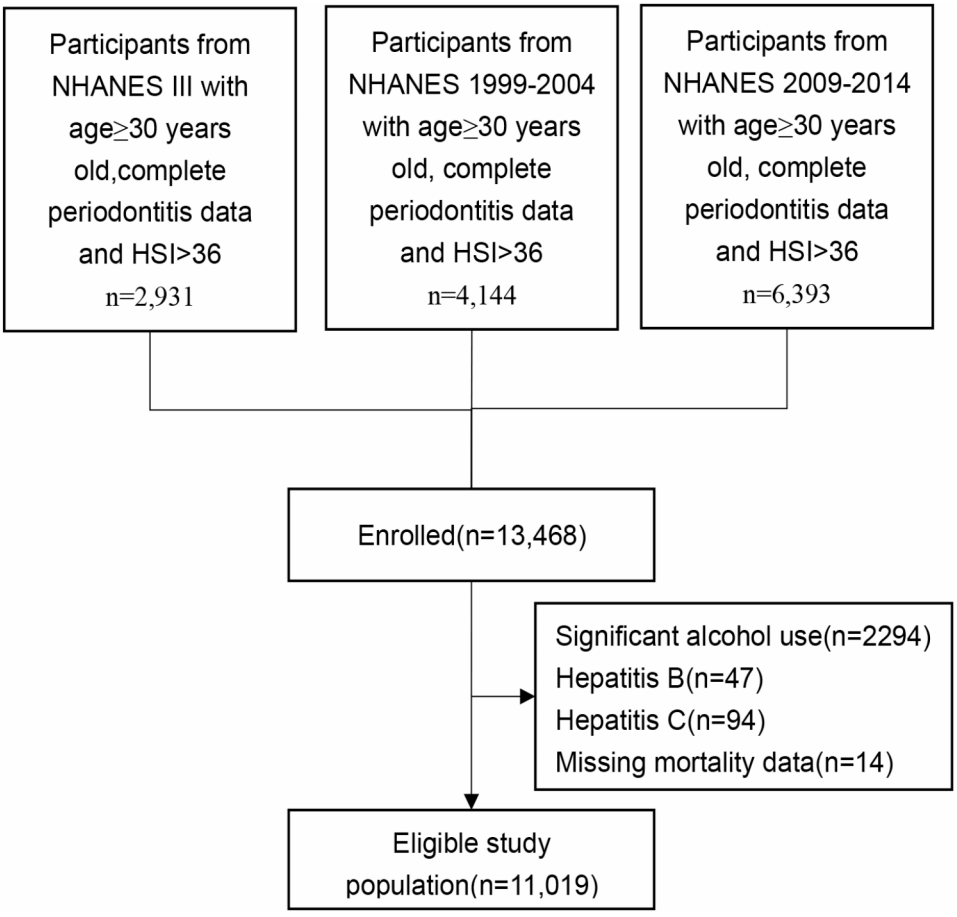

Fig. 1 Flowchart of participant selection. NHANES, National Health and Nutrition Examination Survey; HSI, Hepatic steatosis index

and moderate/severe periodontitis as the observation group.

Determination of mortality

We combined periodontitis data from NHANES III (1988–1994), 1999–2004, 2009–2014 with mortality data from the National Center for Health Statistics (NCHS) (NCHS Data Linkage-Mortality Data - Public-Use Files (cdc.gov)). Thus, this study on the relationship between periodontitis status and mortality can be considered as a prospective study [30]. Deaths from cardiovascular disease are defined as (ICD-10 codes I00-I09, I11, I13, I20-I51, and I60-I69) and deaths from cancer are defined as (ICD-10 codes C00-C97) [31].

Covariates

The identification of confounding factors was based on clinical experience and included a range of variables, including age, sex, race, socioeconomic status (SES), physical activity, smoking status, alcohol consumption, healthy eating index (HEI), and body mass index (BMI). The analysis of covariates in this study did not include alcohol consumption because the study population comprised individuals with MASLD. Therefore, those who consumed a significant amount of alcohol (defined as more than 14 drinks/week for men or more than 7 drinks/week for women) were excluded [32]. The race category was divided into four groups: non-Hispanic white, non-Hispanic Black, Hispanic, and others. Poverty income ratio, occupation, education level, and health insurance coverage were used to assess socioeconomic status (SES), which was categorized into low, medium, and high levels [33]. Physical activity was categorized as inactive, insufficient, and recommended [34]. Smoking status was categorized as never smoked, ever smoked, and currently smoked. The HEI-1995 was adapted to the NHANES (1988–1994) cycle, while the HEI-2015 was adapted to the NHANES 1999–2004 and 2009–2014 cycles [29]. BMI was defined as height divided by weight squared(kg/m^2). Obesity was defined as BMI ≥ 30 kg/m^2 [35]. Furthermore, we considered six additional covariates: estimated glomerular filtration rate (eGFR), diabetes, hypertension, cardiovascular disease, hyperlipidemia, and cancer status, among which hyperlipidemia is characterized by triglyceride levels of

≥ 150 mg/dL, total cholesterol levels of ≥ 200 mg/dL, low-density lipoprotein (LDL) levels of ≥ 130 mg/dL, or high-density lipoprotein (HDL) levels of ≤ 50 mg/dL for women and ≤ 40 mg/dL for men. Moreover, individuals who reported the use of lipid-lowering medications are also classified as having hyperlipidemia [36].

Statistical analysis

Given the intricate design encompassed by NHANES, all analyses in this study were conducted with the effect of weights taken into account. The student's t-tests was used for continuous variables and the χ2 test for categorical variables. Data were presented as weighted mean standard error (SE) for continuous variables and weighted percentages SE for categorical variables.

Firstly, a multifactorial Cox proportional risk model was employed to calculate the risk of death Hazard Ratios (HRs) and 95% confidence intervals (CIs) for all-cause and idiosyncratic mortality under different covariates [37]. We chose different models for our analysis. Model 0 was not adjusted for any covariates. Model 1 was adjusted for age, sex, and race. Model 2 was further adjusted for education level, PIR, physical activity, smoking status, HEI, and BMI based on model (1) Model 3 was further adjusted for eGFR, diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, and cancer status based on model (2) Secondly, the Weibull accelerated failure time model was employed to evaluate whether moderate to severe periodontitis reduced the expected survival time for all-cause mortality and cardiovascular disease-related mortality among participants with diabetes [38]. At last, a Kaplan-Meier survival curve was used to show all-cause mortality and cardiovascular mortality for different periodontal statuses. In addition, we used restricted cubic splines (RCS) to more intuitively reflect the dose-response relationship between periodontal status (including CAL and PPD) and all-cause and cause-specific mortality.

In order to ascertain the reliability of the results, a series of sensitivity analyses were also performed. At first, a multifactorial Cox proportional risk model analysis was performed after excluding those who died within 2 years of follow-up in order to reduce potential reverse causality bias. Second, we also verified the association between mean CAL and mean PPD with mortality. Finally, we also stratified analyses according to age (< 45 or ≥ 45 years), sex(male or female), race(non-Hispanic white, non-Hispanic Black, Hispanic, and others), education level(< high school or ≥ high school), PIR(< 1, 1 ≤ PIR ≤ 3, ≥ 3), smoking status(never smoker, former smoker, current smoker), HEI (quartiles), obesity(yes or no), hypertension(yes or no), and diabetes(yes or no). The interaction *p*-values were calculated by examining the corresponding multiplicative interaction term.

Stata 16.0 statistical analysis software (StataCorp, College Station, TX, USA) and R 4.2.1 soft-ware (http://www.R-project.org, The R Foundation, Aus-tria) were used for all analyses. A two-tailed *p* value < 0.05 indicated a statistically significant result.

Result

Demographic characteristics of participants

Table 1 displays the distribution of periodontitis characteristics in the MASLD population. A total of 11,019 MASLD populations with complete periodontitis as well as mortality data were included in this study, with a mean age of 50.85 years and 53.51% females. Compared to participants with no/mild periodontitis, those with moderate/severe periodontitis were more likely to be older (55.06 vs. 48.71, $P < 0.001$), male (53.92% vs. 42.72%, $P < 0.001$), current smokers (18.53% vs. 11.82%, $P < 0.001$), lower eGFR (87.98 vs. 92.89, $P < 0.001$), diabetes (27.29% vs. 16.40%, $P < 0.001$), hypertension (53.09% vs. 45.01%, $P < 0.001$), cardiovascular disease (9.43% vs. 5.93%, $P < 0.001$), hyperlipidemia (80.98% vs. 74.21%, $P < 0.001$), and cancer status (10.78% vs. 8.50%, $P = 0.005$). However, there was no significant difference between the two groups in terms of BMI and HEI.

Association between periodontitis status with all-cause and specific mortality

In the study, with a median follow-up of 10.58 years, there were 2,293 deaths, including 645 cardiovascular deaths and 526 cancer deaths. In the unadjusted model (model 0), the Cox proportional risk model showed that the HR was significantly higher in the moderate/severe periodontitis population than in participants with no/mild periodontitis (HR 2.19, 95% CI 1.93–2.48; $P < 0.001$); Adjusted for age, sex, and race in model 1 (HR 1.65, 95% CI 1.45–1.88; $P < 0.001$); model 2 further adjusted for SES, smoking status, physical activity, BMI, and HEI (HR 1.32, 95% CI 1.15–1.54; $P < 0.001$), model 3 adjusted in addition to model 2 for ALT, AST, eGFR, diabetes, hypertension, hyperlipidemia, cardiovascular disease, and cancer (HR 1.29, 95% CI 1.08–1.55; $P < 0.003$). Similar findings were observed for periodontitis status and cardiovascular mortality in both the unadjusted model 0 and the fully adjusted model 3. The moderate/severe periodontitis cohort exhibited a signifiantly elevated cardiovascular mortality rate compared to participants with no/mild periodontitis in model 0 (HR 2.42, 95% CI 1.91–3.06; $P < 0.001$) and in model 3 (HR 1.41, 95% CI 1.10–1.79; $P = 0.006$). However, our study identified a significant

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

Variables	Overall	Periodontal status		*P* value
		No/Mild periodontitis	Moderate/Severe periodontitis	
HSI	43.06(0.14)	43.11(0.15)	42.89(0.31)	0.411
Age, years	50.85(0.16)	48.71(0.19)	55.06(0.25)	< 0.001
Male, %	46.49(0.66)	42.72(0.83)	53.92(1.07)	< 0.001
Race/ethnicity, %				< 0.001
Non-Hispanic white	70.44(0.51)	73.07(0.62)	65.24(0.91)	
Non-Hispanic black	11.53(0.28)	10.73(0.34)	13.13(0.49)	
Hispanic	5.87(0.26)	5.46(0.32)	6.68(0.44)	
Others	12.16(0.34)	10.74(0.40)	14.95(0.64)	
SES, %				< 0.001
Low	17.53(0.71)	13.52(0.69)	23.51(0.66)	
Moderate	45.31(0.82)	43.02(0.86)	49.01(0.72)	
High	37.16(0.77)	43.46(0.75)	27.48(0.80)	
Physical activity, %				< 0.001
Inactive	48.63(0.66)	46.50(0.83)	52.82(1.08)	
Insufficient	28.12(0.59)	29.35(0.76)	25.68(0.93)	
Recommended	23.25(0.58)	24.15(0.73)	21.45(0.93)	
Smoking status				< 0.001
Never	57.08(0.66)	60.94(0.82)	49.48(1.08)	
Former	28.84(0.60)	27.24(0.75)	31.99(1.02)	
Current	14.08(0.46)	11.82(0.54)	18.53(0.86)	
HEI, %				0.521
Quartile 1	26.72(0.59)	27.09(0.76)	26.00(0.95)	
Quartile 2	27.22(0.59)	27.14(0.74)	27.37(0.97)	
Quartile 3	22.81(0.56)	22.61(0.69)	23.21(0.92)	
Quartile 4	23.25(0.55)	23.16(0.68)	23.42(0.90)	
BMI status (kg/m2), %				0.614
< 30	37.06(0.64)	37.14(0.81)	36.90(1.05)	
≥ 30	62.94(0.64)	62.86(0.81)	63.10(1.05)	
eGFR, mL/min/1.73 m2	91.24(0.26)	92.89(0.32)	87.98(0.41)	< 0.001
ALT(IU/L)	30.01(0.83)	29.71(0.47)	31.06(3.34)	0.437
AST(IU/L)	24.71(0.29)	24.90(0.36)	24.05(0.38)	0.168
GGT(IU/L)	32.02(0.65)	31.14(0.74)	35.06(1.31)	0.108
TC(mg/dL)	216.27(0.94)	209.01(1.02)	234.66(2.18)	< 0.001
HDL-c(mg/dL)	48.12(0.28)	48.35(0.32)	47.32(0.54)	< 0.001
TG(mg/dL)	167.43(3.09)	161.76(3.26)	187.01(7.79)	0.006
Uric acid(μmol/L)	332.83(1.74)	328.80(1.98)	346.73(3.59)	< 0.001
Diabetes mellitus, %	20.07(0.50)	16.40(0.58)	27.29(0.93)	< 0.001
Hypertension, %	47.74(0.66)	45.01(0.83)	53.09(1.09)	< 0.001
Hyperlipidemia, %	76.49(0.56)	74.21(0.72)	80.98(0.82)	< 0.001
CVD, %	7.11(0.32)	5.93(0.36)	9.43(0.61)	< 0.001
Cancer, %	9.27(0.38)	8.50(0.47)	10.78(0.67)	0.005

SES, socioeconomic status; HEI: health eating index; BMI: body mass index; eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease, ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; TC, total cholesterol; HDL-c: high-density lipoprotein cholesterol; TG: triglycerides

The student's t-tests was used for continuous variables and the $\chi 2$ test for categorical variables

Data were presented as weighted mean (SE) for continuous variables and weighted percentages (SE) for categorical variables

association between periodontitis status and cancer mortality in models 0, 1, and 2, but this association was not observed in the fully adjusted model 3 (HR 1.15, 95% CI 0.83–1.59; $P = 0.399$) (Table 2).

The results of the Weibull accelerated failure time model indicated that moderate to severe periodontitis shortened the expected survival time for all-cause mortality, CVD-related mortality, and cancer-related mortality in participants with MASLD (all-cause: time ratio, 0.90, CI: 0.86–0.95, $p < 0.001$; CVD-related: time ratio, 0.85, CI: 0.77–0.93, $p < 0.001$; cancer: time ratio, 0.87, CI:0.77–0.99) (Table 3).

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

Mortality	Periodontal status		*P*Value
	No/Mild periodontitis	Moderate/Severe periodontitis	
All cause			
Deaths/total	1106/6599	1187/4420	
model 0	1.00	2.19(1.93,2.48)	< 0.001
model 1	1.00	1.65(1.45,1.88)	< 0.001
model 2	1.00	1.32(1.15,1.54)	< 0.001
model 3	1.00	1.29(1.08,1.55)	0.003
CVD-related cause			
Deaths/total	294/6599	351/4420	
model 0	1.00	2.42(1.91,3.06)	< 0.001
model 1	1.00	1.82(1.42,2.34)	< 0.001
model 2	1.00	1.45(1.11,1.90)	0.005
model 3	1.00	1.41(1.10,1.79)	0.006
Cancer-related cause			
Deaths/total	255/6599	271/4420	
model 0	1.00	2.11(1.65,2.69)	< 0.001
model 1	1.00	1.59(1.24,2.04)	< 0.001
model 2	1.00	1.31(1.04,1.77)	0.042
model 3	1.00	1.15(0.83,1.59)	0.399

Model 0 was not adjusted for any covariates

Model 1 was adjusted for age, sex, and race

Model 2 was adjusted for age, sex, race, socioeconomic status, smoking status, physical activity, body mass index, and health eating index

Model 3 was adjusted for age, sex, race, socioeconomic status, smoking status, physical activity, body mass index, health eating index, ALT, AST, estimated glomerular filtration rate, diabetes, hypertension, hyperlipidemia, cardiovascular disease, and cancer

Table 3 Time ratio (95% confidence intervals) for all-cause and cause-specific mortality according to periodontitis by Weibull model

Mortality	Periodontal status		*P*Value
	No/Mild periodontitis	Moderate/Severe periodontitis	
All cause			
Deaths/total	1106/6599	1187/4420	
model 0	1.00	0.63(0.59,0.67)	< 0.001
model 1	1.00	0.79(0.74,0.83)	< 0.001
model 2	1.00	0.85(0.80,0.89)	< 0.001
model 3	1.00	0.90(0.86,0.95)	< 0.001
CVD-related cause			
Deaths/total	294/6599	351/4420	
model 0	1.00	0.59(0.53,0.66)	< 0.001
model 1	1.00	0.73(0.66,0.81)	< 0.001
model 2	1.00	0.78(0.71,0.87)	< 0.001
model 3	1.00	0.85(0.77,0.93)	< 0.001
Cancer-related cause			
Deaths/total	255/6599	271/4420	
model 0	1.00	0.62(0.54,0.70)	< 0.001
model 1	1.00	0.77(0.68,0.87)	< 0.001
model 2	1.00	0.85(0.75,0.96)	0.008
model 3	1.00	0.87(0.77,0.99)	0.028

Model 0 was not adjusted for any covariates

Model 1 was adjusted for age, sex, and race

Model 2 was adjusted for age, sex, race, socioeconomic status, smoking status, physical activity, body mass index, and health eating index

Model 3 was adjusted for age, sex, race, socioeconomic status, smoking status, physical activity, body mass index, health eating index, estimated glomerular filtration rate, diabetes, hypertension, hyperlipidemia, cardiovascular disease, and cancer

Furthermore, we conducted a Kaplan-Meier analysis to investigate the relationship between periodontitis status and all-cause (Fig. 2) and cardiovascular mortality (Fig. 3). The results revealed a statistically significant difference in mortality between the two groups, with a log-rank p value < 0.001.

Association between mean CAL/PPD and mortality

Furthermore, we conducted a separate analysis to investigate the correlation between mean CAL and mean PPD with mortality in the MASLD population. As shown in Table 4, all-cause mortality rate was found to be statistically significant in the fully adjusted model 3 for the second quartile (Q2), the third quartile (Q3), and the forth quartile (Q4) of mean CAL when compared to the first quartile (Q1) (Q2: HR 1.24; 95% CI, 1.09 – 1.50. Q3: HR 1.50; 95% CI, 1.38–1.84. Q4: HR, 1.85; 95% CI, 1.61–2.17. *P*-trend = 0.010). Similarly, in the fully adjusted model 3, a comparable relationship was observed between PPD quartiles and all-cause mortality, (Q2: HR 1.03; 95% CI, 0.93 – 1.27. Q3: HR 1.24; 95% CI, 1.21–1.59. Q4: HR, 1.31; 95% CI, 1.19–1.62. *P*-trend < 0.001). In addition, we also observed a significant increasing trend relationship between quartiles of mean CAL and PPD with cardiovascular mortality.

RCS curves were employed to illustrate the nonlinear correlation between mean CAL and mean PPD with all-cause and cardiovascular mortality. There was a nonlinear relationship between mean CAL and mean PPD with mortality (*P* for nonlinear < 0.05) (Fig. 4). The risk of all-cause and cardiovascular mortality showed a tendency to rise with increasing mean CAL and mean PPD values. To examine the link between CAL, PPD levels and mortality in MASLD participants, a Cox proportional hazards model and a two-segment Cox proportional hazards model were employed for analysis. The inflection point values of CAL for all-cause

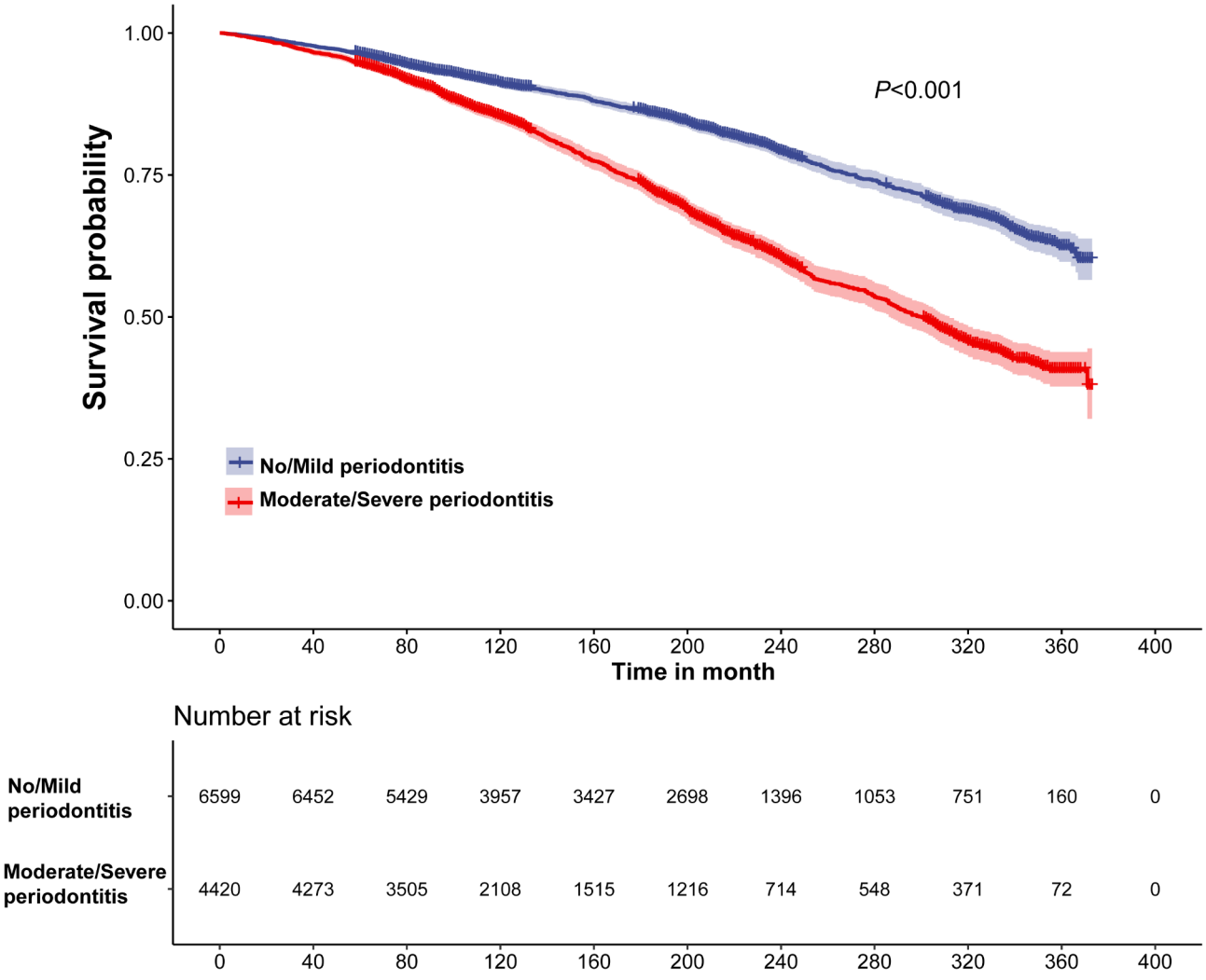

Fig. 2 The Kaplan-Meier analysis of periodontitis with all-cause survival

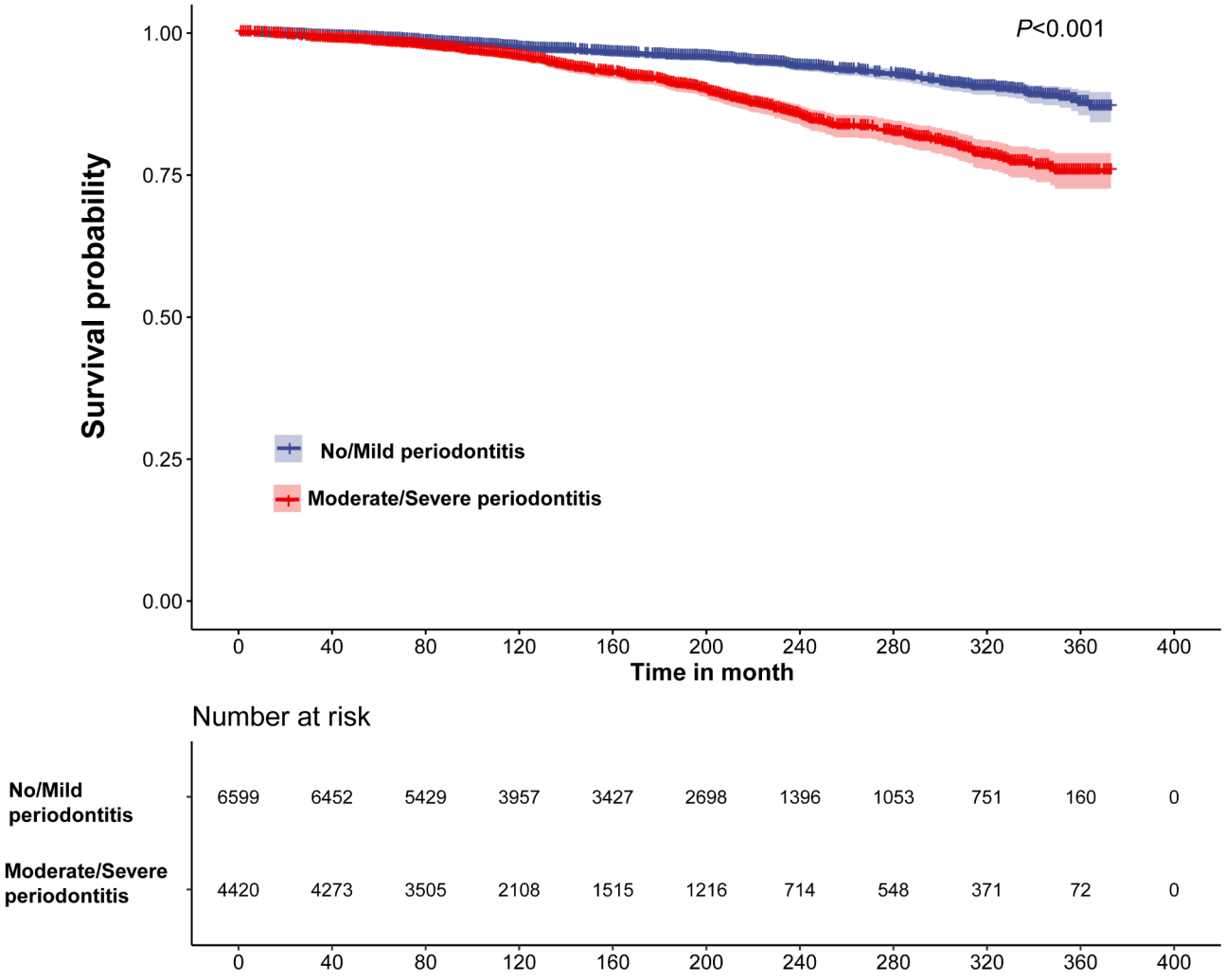

Fig. 3 The Kaplan-Meier analysis of periodontitis with cardiovascular survival

and cardiovascular mortality were both 1.42, as shown in Table 5. When CAL was below 1.42, each 1-unit increase was associated with a 2.29-fold higher risk of all-cause mortality (HR 3.29, 95% CI 2.92–3.71; $P < 0.001$) and a 2.91-fold higher risk of cardiovascular mortality (HR 3.91, 95% CI 3.09–4.94; $P < 0.001$). When CAL exceeded 1.42, each 1-unit increase was associated with a 20% higher risk of all-cause mortality (HR 1.20, 95% CI 1.16–1.24; $P < 0.001$) and a 19% higher risk of cardiovascular mortality (HR 1.19, 95% CI 1.13–1.28; $P < 0.001$). On the other hand, the inflection point value of PPD for all-cause and cardiovascular mortality risk was 1.35. When PPD was below 1.35, each 1-unit increase was associated with a 94% higher risk of all-cause mortality (HR 1.94, 95% CI 1.61–2.34; $P < 0.001$) and a 1.82-fold higher risk of cardiovascular mortality (HR 2.82, 95% CI 1.92–4.13; $P < 0.001$). When PPD exceeded 1.35, each 1-unit increase was associated with an 19% higher risk of all-cause mortality (HR 1.19, 95% CI 1.09–1.29; $P < 0.001$) and a 22% higher risk of cardiovascular mortality (HR 1.22, 95% CI 1.04–1.42; $P < 0.001$).

Sensitivity analysis

To verify the accuracy of the results, we conducted the following two sensitivity analyses. First, those participants who died within 2 years were excluded to prevent reverse causation from influencing outcomes. The results indicated that all-cause mortality (HR, 1.27; 95% CI, 1.09–1.48) and cardiovascular mortality (HR, 1.37; 95% CI, 1.18–1.59) remained significantly increased in those with moderate/severe periodontitis compared to those with no/mild periodontitis (Table 6). Second, to ascertain the stability of the results across populations, the analyses were also stratified by age (< 45 or ≥ 45 years), sex (male or female), race (non-Hispanic white, non-Hispanic Black, Hispanic, and others), education level (< high school or ≥ high school), PIR (< 1, 1 ≤ PIR ≤ 3, ≥ 3), smoking status (never smoker, ever smoker, never smoker), HEI (Q1,

Table 4 The results of the sensitivity analysis according to quintiles of mean CAL and mean PPD as outcomes of exposure

Mean CAL	Periodontal status				*P* trend
	Q1	Q2	Q3	Q4	
All cause	HR	HR(95%CI)	HR(95%CI)	HR(95%CI)	
model 0	1(Ref.)	1.72(1.49,1.98)	3.03(2.66,3.45)	4.38(3.88,4.96)	< 0.001
model 1	1(Ref.)	1.48(1.29,1.70)	2.17(1.89,2.47)	2.72(2.39,3.09)	< 0.001
model 2	1(Ref.)	1.37(1.20,1.58)	1.87(1.66,2.20)	2.25(1.99,2.58)	< 0.001
model 3	1(Ref.)	1.24(1.09,1.50)	1.50(1.38,1.84)	1.85(1.61,2.17)	0.010
CVD cause					
model 0	1(Ref.)	1.84(1.39,2.41)	3.29(2.55,4.25)	5.23(4.13,6.64)	< 0.001
model 1	1(Ref.)	1.58(1.20,2.07)	2.34(1.80,3.03	3.23(2.53,4.13)	< 0.001
model 2	1(Ref.)	1.46(1.11,1.92)	2.03(1.62,2.70)	2.72(2.06,3.55)	< 0.001
model 3	1(Ref.)	1.30(0.99,1.71)	1.57(1.19,2.05)	2.11(1.64,2.79)	0.015
Mean PPD					
All cause					
model 0	1(Ref.)	1.25(1.09,1.44)	1.79(1.57,2.05)	1.81(1.59,2.06)	< 0.001
model 1	1(Ref.)	1.26(1.09,1.45)	1.80(1.57.2.06)	1.88(1.65,2.14)	< 0.001
model 2	1(Ref.)	1.13(1.00,1.30)	1.58(1.39,1.85)	1.60(1.37,1.85)	< 0.001
model 3	1(Ref.)	1.03(0.93,1.27)	1.24(1.21,1.59)	1.31(1.19,1.62)	< 0.001
CVD cause					
model 0	1(Ref.)	1.58(1.19,2.11)	2.44(1.86,3.19)	2.47(1.89,3.22)	< 0.001
model 1	1(Ref.)	1.60(1.20,2.13)	2.46(1.88,3.23)	2.63(2.01,3.44)	< 0.001
model 2	1(Ref.)	1.44(1.06,1.93)	2.13(1.66,2.80)	2.27(1.72,2.98)	< 0.001
model 3	1(Ref.)	1.23(0.90,1.69)	1.62(1.25,2.30)	1.82(1.51,2.55)	< 0.001

Quintiles of mean CAL: Q1, < 0.71 mm; Q2, 0.71–1.21 mm; Q3, 1.21–1.75 mm; Q4, > 1.75 mm

Quintiles of mean PPD: Q1, < 0.95 mm; Q2, 0.95–1.30 mm; Q3, 1.30–1.62 mm; Q4, > 1.62 mm

Model 0 was not adjusted for any covariates

Model 1 was adjusted for age, sex, and race

Model 2 was adjusted for age, sex, race, socioeconomic status, smoking status, physical activity, body mass index, and health eating index

Model 3 was adjusted for age, sex, race, socioeconomic status, smoking status, physical activity, body mass index, health eating index, ALT, AST, estimated glomerular filtration rate, diabetes, hypertension, hyperlipidemia, cardiovascular disease, and cancer

Q2, Q3, Q4), obesity (yes or no), hypertension (yes or no), and diabetes (yes or no). The interaction *p*-values were then calculated. The *p*-values for the interactions were all > 0.05 when stratified by populations except education level in all cause mortality (Fig. 5). This suggests that the relationship between periodontitis status with all cause and cardiovascular mortality was relatively stable.

Discussion

The cohort study is conducted based on NHANES, a public database of health and nutrition research on U.S. populations, showed periodontitis was related to higher all-cause and CVD-related mortality of MASLD patients. This study indicates that moderate or severe periodontitis and higher level of CAL and PPD are related to increased risk of all-cause and CVD-related mortality, and this is the first study that report the association between periodontitis status and mortality of patients with MASLD.

Periodontitis, a common chronic inflammatory and infectious disease, is caused by oral biofilm–mediated microbial dysbiosis [39]. The biofilm components also have access to periodontal tissue and host circulation [39]. It not only causes tooth loss, but enter the circulation and exacerbate or be associated with various metabolic disorders, such as dyslipidemia, diabetes, obesity and cardiovascular disease [29, 40, 41, 42, 43]. Recently, growing evidence has suggested that periodontal disease has adverse effects on the pathophysiology of liver disease [44, 45]. In particular, it was reported that periodontal disease can negatively affect MASLD, thus inducing the progression and worsen of MASLD [42]. Whereas, it still remains unclear whether the mortality of MASLD is related to periodontitis. So this study mainly focused on the effect of periodontitis and its severity on the MASLD mortality. In consistent with the above findings, our results showed that MASLD patients with moderate or severe periodontitis did have 28% higher risk of all-cause mortality than those without or with mild periodontitis (Table 2). As is reported that MASLD is considered as the hepatic manifestation of metabolic syndrome because it is closely associated with obesity, insulin resistance, hypertension, and dyslipidemia. For example, the triglyceride glucose (TyG) index has recently

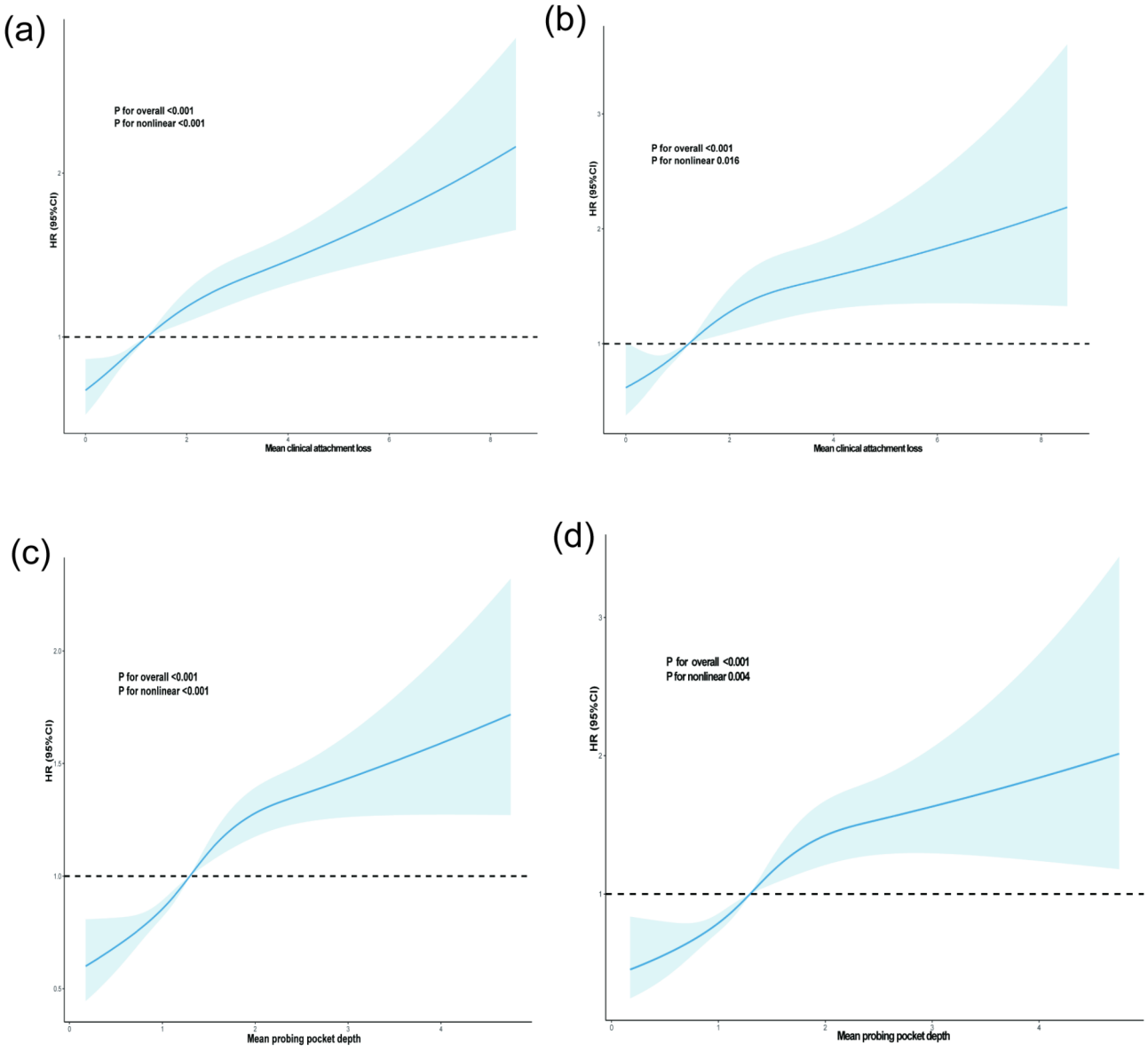

Fig. 4 Restricted cubic spline model of the relationship between Mean CAL and PPD with Mortality. (**a**) Mean CAL and all-cause mortality; (**b**) Mean CAL and cardiovascular mortality; (**c**) Mean PPD and all-cause mortality; (**d**) Mean PPD and cardiovascular mortality

emerged as a powerful marker of insulin resistance and metabolic dysfunction, both of which are key factors in the development and progression of MASLD [46, 47]. Moreover, large numbers of researches have confirmed that periodontitis can exacerbate various metabolic disorders, such as diabetes, obesity, dyslipidemia, and chronic kidney disease [48, 49]. Periodontitis-related systemic inflammation may induce to insulin resistance through elevated blood levels of adipocytokines, such as tumor necrosis factor alpha, IL-6, and leptin, which inhibit the insulin receptor and its downstream signaling [50, 51]. Clearly, there is a bidirectional three-way relationship among metabolic syndrome, MASLD, and periodontitis, centering on insulin resistance [42]. Consequently, the mutual influences among these diseases may cause a higher mortality risk in MASLD with peridontitis. Furthermore, the correlation between mean CAL and mean PPD with mortality in the MASLD population was investigated and a comparable relationship was observed between CAL and PPD quartiles and all-cause mortality, implying there may be a potential dose-response effect. These results indicate that periodontitis is strongly linked with the MASLD prognosis, and the severity of periodontitis influence the mortality of MASLD.

Notably, we found the participants with moderate/severe periodontitis were more likely to be older, male, current smokers, lower eGFR, diabetes, hypertension,

Table 5 Threshold effect analysis of CAL and PPD on mortality in MASLD participants

All-cause mortality	Adjust HR(95% CI) *P* value
CAL	
Fitting by the standard linear model	1.38 (1.35, 1.42) < 0.001
Fitting by the two-piecewise linear model	
Inflection point	1.42
< 1.42	3.29 (2.92, 3.71) < 0.001
> 1.42	1.20 (1.16, 1.24) < 0.001
P for Log-likelihood ratio	< 0.001
PPD	
Fitting by the standard linear model	1.34 (1.26, 1.42) < 0.001
Fitting by the two-piecewise linear model	
Inflection point	1.35
< 1.35	1.94 (1.61, 2.34) < 0.001
> 1.35	1.19 (1.09, 1.29) < 0.001
P for Log-likelihood ratio	< 0.001
CVD mortality	
CAL	
Fitting by the standard linear model	1.41 (1.35, 1.46) < 0.001
Fitting by the two-piecewise linear model	
Inflection point	1.42
< 1.42	3.91 (3.09, 4.94) < 0.001
> 1.42	1.19 (1.13, 1.28) < 0.001
P for Log-likelihood ratio	< 0.001
PPD	
Fitting by the standard linear model	1.45 (1.307, 1.609) < 0.001
Fitting by the two-piecewise linear model	
Inflection point	1.35
< 1.35	2.82 (1.92, 4.13) < 0.001
> 1.35	1.22 (1.04, 1.42) < 0.001
P for Log-likelihood ratio	< 0.001

The analysis was adjusted for age, sex, race, socioeconomic status, smoking status, physical activity, body mass index, health eating index, ALT, AST, estimated glomerular filtration rate, diabetes, hypertension, hyperlipidemia, cardiovascular disease, and cancer

Table 6 Association of periodontitis with mortality after exclusion of participants who died within first 2 years of follow-up

Mortality	Periodontal status		*P* Value
	No/Mild periodontitis	Moderate/Severe periodontitis	
All cause			
Deaths/total	1025/6518	1109/4342	
model 0	1.00	2.23(1.96,2.54)	< 0.001
model 1	1.00	1.68(1.46,1.92)	< 0.001
model 2	1.00	1.35(1.18,1.57)	< 0.001
model 3	1.00	1.27(1.09,1.48)	0.009
CVD-related cause			
Deaths/total	268/6518	325/4342	
model 0	1.00	2.59(2.02,3.32)	< 0.001
model 1	1.00	1.94(1.49,2.53)	< 0.001
model 2	1.00	1.58(1.20,2.09)	0.001
model 3	1.00	1.37(1.18,1.59)	0.001

Model 0 was not adjusted for any covariates

Model 1 was adjusted for age, sex, and race

Model 2 was adjusted for age, sex, race, education level, poverty income ratio, smoking status, physical activity, body mass index, and health eating index

Model 3 was adjusted for age, sex, race, socioeconomic status, smoking status, physical activity, body mass index, health eating index, ALT, AST, estimated glomerular filtration rate, diabetes, hypertension, hyperlipidemia, cardiovascular disease, and cancer

Variables	ALL-cause mortality			CVD-mortality		
	HR (95% CI)	*P*	*P* for interaction	HR (95% CI)	*P*	*P* for interaction
Age			0.873			0.663
<45 years	1.19(0.91,1.58)	0.261		1.53(0.91,2.58)	0.111	
≥45 years	1.18(1.08,1.29)	<0.001		1.30(1.09,1.54)	0.002	
Sex			0.331			0.299
Male	1.15(1.02,1.31)	0.028		1.23(0.97,1.55)	0.085	
Female	1.23(1.09,1.38)	0.001		1.43(1.14,1.79)	0.002	
Race			0.506			0.619
Non-Hispanic white	1.24(1.09,1.39)	<0.001		1.30(1.05,1.61)	0.015	
Non-Hispanic black	1.18(0.98,1.41)	0.082		1.53(1.07,2.17)	0.018	
Hispanic	1.05(0.84,1.33)	0.661		1.04(0.66,1.64)	0.877	
Others	1.24(0.95,1.60)	0.112		1.54(0.85,2.81)	0.158	
Educational level			0.007			0.607
<high school	1.08(0.97,1.21)	0.157		1.29(1.05,1.59)	0.017	
≥high school	1.36(1.19,1.56)	<0.001		1.38(1.06,1.78)	0.015	
Poverty-income ratio			0.440			0.564
low	1.21(0.99,1.48)	0.060		1.55(1.06,2.67)	0.024	
moderate	1.13(1.01,1.27)	0.048		1.21(0.96,1.51)	0.102	
high	1.34(1.14,1.58)	<0.001		1.45(1.07,1.97)	0.018	
Smoking status			0.477			0.090
Never	1.23(1.09,1.39)	0.001		1.39(1.09,1.75)	0.006	
Former	1.18(1.03,1.36)	0.017		1.51(1.15,1.98)	0.003	
Current	1.15(0.92,1.44)	0.216		0.91(0.59,1.39)	0.652	
HEI			0.184			0.781
Quartile 1	1.06(0.89,1.25)	0.541		1.49(1.08,2.06)	0.016	
Quartile 2	1.29(1.09,1.54)	0.004		1.18(0.85,1.65)	0.314	
Quartile 3	1.36(1.14,1.63)	0.001		1.51(1.08,2.12)	0.018	
Quartile 4	1.14(0.96,1.35)	0.124		1.27(0.92,1.76)	0.141	
Obesity			0.644			0.640
Yes	1.17(1.06,1.30)	0.003		1.37(1.22,1.67)	0.002	
No	1.24(1.06,1.44)	0.007		1.29(0.97,1.73)	0.085	
Hypertension			0.089			0.855
Yes	1.23(1.11,1.37)	<0.001		1.33(1.11,1.61)	0.002	
No	1.06(0.89,1.25)	0.503		1.33(0.95,1.86)	0.101	
Diabetes			0.323			0.209
Yes	1.15(1.01,1.31)	0.041		1.29(1.01,1.64)	0.039	
No	1.23(1.09,1.37)	<0.001		1.35(1.08,1.68)	0.008	
FIB-4			0.166			0.474
<1.45	1.25(1.03,1.52)	0.025		1.56(1.05,2.31)	0.027	
≥1.45	1.31(1.08,1.66)	0.029		1.77(1.19,2.61)	0.004	

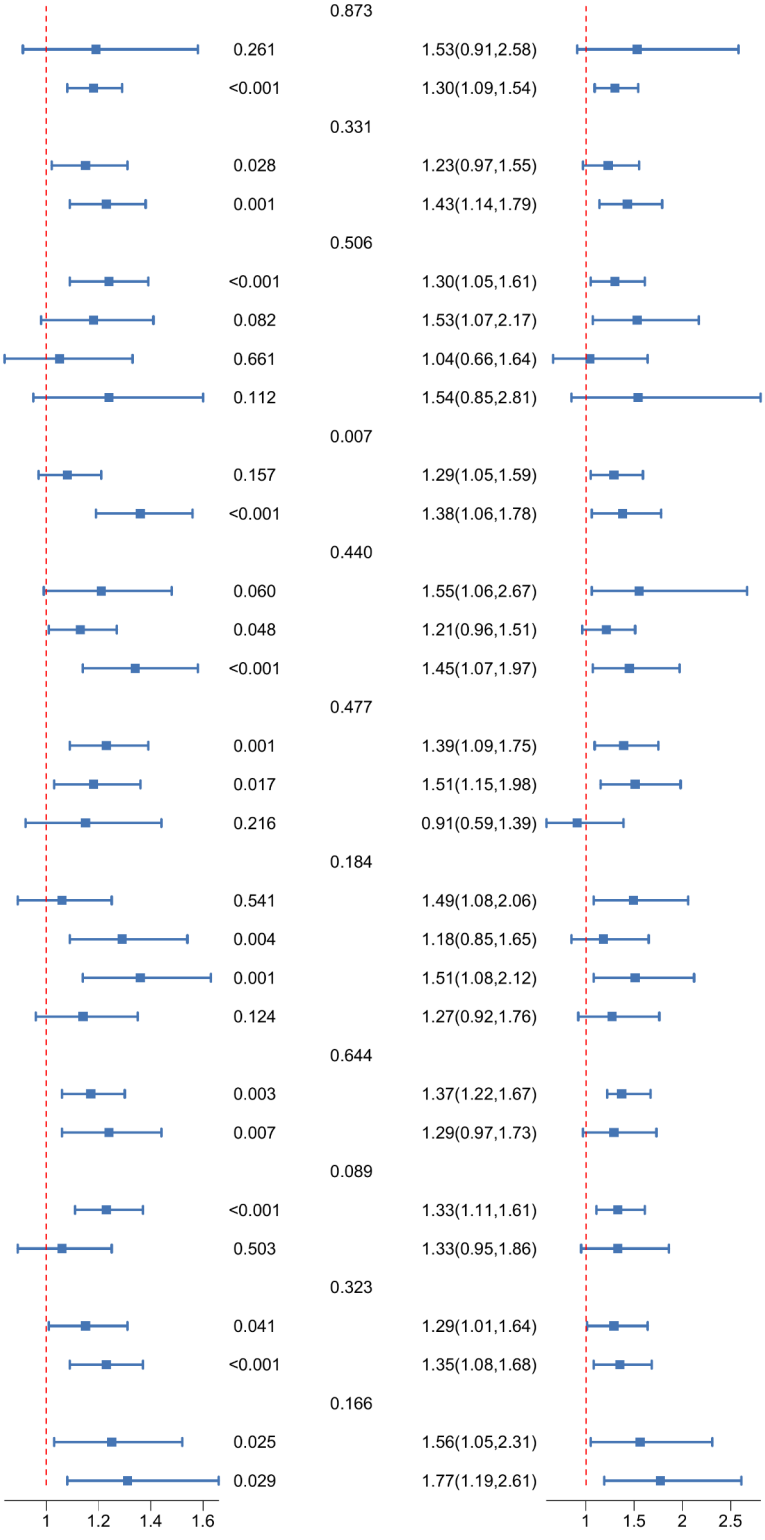

Fig. 5 Forest plots of stratified analyses of periodontitis status with all-cause and cardivascular mortality

cardiovascular disease, hyperlipidemia, and cancer status. Then we further analyzed association between periodontitis status with specific mortality induced by cardiovascular diseases or cancer in MASLD patients. Results indicated cancer-related mortality has no significant difference between patients with or without periodontitis. Though increasing evidence that cancer is driven, at least in part, by chronic infection and inflammation [52]. Interestingly, periodontitis, a common chronic oral inflammatory disease driven by exposure to biofilms, has been associated with several forms of malignancy [53]. Nerverthless, due to the diversity of cancer types and the complexity of pathogenesis, the exact association between cancer and periodontits still remains unclear and long term exploration is still needed [54]. However, results showed that CVD-related mortality was 43% higher, suggesting a remarkable mortality association between periodontitis and people with MASLD. Moreover, moderate or severe periodontitis reduces the survival probability and time for all-cause and CVD-related mortality in people with MASLD (Figs. 2 and 3), suggesting that periodontitis may be an important factor for predicting all-cause and CVD-related mortality in adults with MASLD. It has been reported that though MASLD have increased risks of end-stage liver disease, hepatocellular carcinoma, and liver-related mortality, the largest cause of death among patients with MASLD is cardiovascular disease [55]. Also, it has been reported that people with cardiovascular disease may have a higher chance of getting further complications when they have periodontitis and there was a significant association between periodontitis and increased risks cardiovascular mortality [56]. Particularly, recent statistical results show that in Europe CVD is responsible for 3.9 million deaths (45% of deaths). Therefore, people with CVD realated diseases should actively manage all their cardiovascular risk factors. Taking all these into account, MASLD patients with CVD should receive a comprehensive periodontal evaluation, including full mouth probing and bleeding scores. If no periodontitis is diagnosed initially, patients should be recommended a preventive care regime and monitored regularly (at least once a year) for changes in periodontal status. If periodontitis is diagnosed, patients should be informed that they may be at higher risk for subsequent CVD complications, and they should regularly insist on the recommended dental therapeutic, maintenance and preventive regimes. Besides, if the periodontitis is not appropriately controlled, patients should consult his/her physician timely [57].

There is multiple evidence that periodontitis may be a hazard factor for MASLD. Previous researches showed that the liver of patients with periodontitis is constantly under exposure to pathogenic factors including bacteria and their by-products, reactive oxygen species, inflammatory cytokines that released from oral cavity systemically, and these are involved in MASLD progression [42, 45]. *P. gingivalis (P.g)*, one of the periodontopathic bacteria, is strongly indicated to be involved in MASLD [58]. Yoneda et al. analyzed various periodontopathic bacteria in saliva collected from MASLD patients and found that the detection frequency of *P. g* was obviously higher in the MASLD patients than in the non-MASLD subjects [59]. In an animal study, rats were infected with *P.g* and fed with a high fat diet, results showed that infection with *P.g* aggravated the progression of MASLD, and it is believed that *P.g* and its endotoxin play a key role in the deterioration of MASLD [21]. Two possible pathways for the link between periodontitis and MASLD were proposed. On one hand, not only bacteria can colonize the liver through blood circulation, but the endotoxin and cytokines produced by bacteria can enter the circulation system, evoking and resulting in liver inflammatory immune reaction and injury [42, 60, 61]. Notabely, several signaling pathways that periodontitis may affect MASLD have been gradually been revealed. Ding indicated that P. gingivalis-derived LPS might contribute to intracellular lipid accumulation and inflammatory reaction of human hepatocellular cells HepG2 via the activation of NF-κB and JNK signaling pathways [62]. Moreover, the link between MASLD and T helper 17 (Th17) has also attracted attention in recent years. Th17 cells are a subset of T helper cells defined subsets, which primarily secrete IL-17 A. IL-17 A induces a number of proinflammatory cytokines in both immune and non-immune cells and plays a protective role against infection [63]. Interestingly, it was found that there were a large number of Th17 cells in the liver and peripheral blood of MASLD animal models and the animal studies also showed that the accumulation of Th17 cells in periodontal tissues is dependent on oral bacteria, suggesting that there may be a link among them and it is speculated that Th17 may be a key molecule for explaining the relationship between periodontal disease and NAFLD [64, 65, 66]. Besides, another pathway that periodontitis may influence MASLD is attributed to LPS/TLR4 signaling. It is reported that one of the constituents of periodontal pathogens, LPS, could combine with Toll-like receptor (TLR-2/4) and influence immune system [67]. As Kupper cells in liver express high level of TLR4, they recognize LPS quickly and generate inflammatory cytokines, chemokines and ROS, inducing a cascade of immune responses and further causing liver damage [68]. On the other hand, another mechanism is gut microbiome dysbiosis induced by enteral translocation

of periodontopathic bacteria ruptures gut wall barrier and accelerate delivery of hepatotoxins and enterobacteria to the liver through the enterohepatic circulation, further leading to hepatic exposure to bacteria, endotoxin, and bacterial metabolite through the enterohepatic circulation by portal vein system [69, 70, 71]. Consequently, by hematogenous or enteral routes, periodontitis greatly accelerating MASLD progression and may result in higher mortality of MASLD [42].

This study is the first representative study on the association between periodontitis and all-cause and CVD-related mortality in patients with MASLD. However, there are some limitations in our study should be noticed. First, data on periodontitis and MASLD was obtained at baseline the same time, which may not previously reflect the causal and mediating effects between the conditions. Second, the covariates acquired at baseline may have changed over time, which may have weakened the true association between periodontitis and mortality in people with MASLD. Third, in this study, the severity of periodontitis was classified by CAL and PPD based on quartiles of the study population, so the results are not comparable to other studies using different sorting scheme.

Conclusions

In a nationally representative sample of US adults with MASLD, we found that moderate or severe periodontitis and high levels of mean CAL and PPD are associated with an elevated risk of all-cause and CVD-related mortality among adults with MASLD in the US. Periodontitis has prognostic utility in explaining residual risk of MASLD. Further researches are needed to affirm our findings and establish causal inference.

Abbreviations

MASLD	Metabolic dysfunction associated steatotic liver disease
HRs	Hazard Ratios
CIs	Confidence Intervals
RCS	Restricted cubic Splines
CAL	Clinical Attachment Level
PPD	Pocket Probing Depth
CVD	Cardiovascular Disease
T2DM	Type 2 Diabetes Mellitus
NHANES	National Health and Nutrition Examination Survey
HSI	Hepatic Steatosis Index
NCHS	National Center for Health Statistics
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
SES	Socioeconomic Status
HEI	Healthy Eating Index
BMI	Body Mass Index
eGFR	Estimated glomerular filtration rate
SE	Standard error
TyG	Triglyceride Glucose

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Author contributions

Zhaofu Zhang: Writing– original draft, Conceptualization, Methodology, Formal analysis. Qiuyun Zheng: Methodology, Conceptualization. Yiheng Liu: Validation, Data curation. Guanhui Chen: Writing– review & editing, Conceptualization. Yiming Li: Writing– review & editing, Conceptualization, Supervision.

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Data availability

The publicly available data used in this study can be downloaded for free on NHANES website: https://wwwn.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate

The parts of this study that involved human participants, human materials, or human data were conducted in compliance with the Declaration of Helsinkiand were approved by the National Center for Health Statistics (NCHS) Ethics Review Board. The patients/participants provided written informed consent to participate in this study. Ethical address as the follow: 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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References

1. Tilg H, Adolph TE, Dudek M, Knolle P. Non-alcoholic fatty liver disease: the interplay between metabolism, microbes and immunity. Nat Metab. 2021;3(12):1596–607.
2. Paternostro R, Trauner M. Current treatment of non-alcoholic fatty liver disease. J Intern Med. 2022;292(2):190–204.
3. Schwabe RF, Tabas I, Pajvani UB. Mechanisms of fibrosis development in nonalcoholic steatohepatitis. Gastroenterology. 2020;158(7):1913–28.
4. Schuster S, Cabrera D, Arrese M, Feldstein AE. Triggering and resolution of inflammation in NASH. Nat Rev Gastroenterol Hepatol. 2018;15(6):349–64.
5. Amini-Salehi E, Letafatkar N, Norouzi N, Joukar F, Habibi A, Javid M, Sattari N, Khorasani M, Farahmand A, Tavakoli S, et al. Global prevalence of nonalcoholic fatty liver disease: an updated review Meta-Analysis comprising a population of 78 million from 38 countries. Arch Med Res. 2024;55(6):103043.
6. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;67(1):123–33.
7. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.
8. Kim GA, Lee HC, Choe J, Kim MJ, Lee MJ, Chang HS, Bae IY, Kim HK, An J, Shim JH et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. J Hepatol 2017.
9. Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, Wai-Sun Wong V, Yilmaz Y, George J, Fan J, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2019;69(6):2672–82.
10. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol. 2015;62(1 Suppl):S47–64.
11. Lastuvkova H, Faradonbeh FA, Schreiberova J, Hroch M, Mokry J, Faistova H, Nova Z, Hyspler R, Igreja Sa IC, Nachtigal P et al. Atorvastatin modulates bile

acid homeostasis in mice with Diet-Induced nonalcoholic steatohepatitis. Int J Mol Sci. 2021;22(12).
12. Civelek M, Podszun MC. Genetic factors associated with response to vitamin E treatment in NAFLD. Antioxid (Basel) 2022, 11(7).
13. Gao Y, Jiang D, Wang C, An G, Zhu L, Cui C. Comprehensive analysis of metabolic changes in male mice exposed to sodium valproate based on GC-MS analysis. Drug Des Devel Ther. 2022;16:1915–30.
14. Parthasarathy G, Revelo X, Malhi H. Pathogenesis of nonalcoholic steatohepatitis: an overview. Hepatol Commun. 2020;4(4):478–92.
15. Abdelmalek MF. Nonalcoholic fatty liver disease: another leap forward. Nat Rev Gastroenterol Hepatol. 2021;18(2):85–6.
16. Svegliati-Baroni G, Pierantonelli I, Torquato P, Marinelli R, Ferreri C, Chatgilialoglu C, Bartolini D, Galli F. Lipidomic biomarkers and mechanisms of lipotoxicity in non-alcoholic fatty liver disease. Free Radic Biol Med. 2019;144:293–309.
17. Carnagarin R, Tan K, Adams L, Matthews VB, Kiuchi MG, Marisol Lugo Gavidia L, Lambert GW, Lambert EA, Herat LY, Schlaich MP. Metabolic Dysfunction-Associated fatty liver disease (MAFLD)-A condition associated with heightened sympathetic activation. Int J Mol Sci 2021, 22(8).
18. Welch RD, Billon C, Losby M, Bedia-Diaz G, Fang Y, Avdagic A, Elgendy B, Burris TP, Griffett K. Emerging Role of Nuclear Receptors for the Treatment of NAFLD and NASH. Metabolites. 2022;12(3).
19. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci (Qassim). 2017;11(2):72–80.
20. Furusho H, Miyauchi M, Hyogo H, Inubushi T, Ao M, Ouhara K, Hisatune J, Kurihara H, Sugai M, Hayes CN, et al. Dental infection of Porphyromonas gingivalis exacerbates high fat diet-induced steatohepatitis in mice. J Gastroenterol. 2013;48(11):1259–70.
21. Kuraji R, Ito H, Fujita M, Ishiguro H, Hashimoto S, Numabe Y. Porphyromonas gingivalis induced periodontitis exacerbates progression of non-alcoholic steatohepatitis in rats. Clin Exp Dent Res. 2016;2(3):216–25.
22. Akinkugbe AA, Slade GD, Barritt AS, Cole SR, Offenbacher S, Petersmann A, Kocher T, Lerch MM, Mayerle J, Völzke H, et al. Periodontitis and Non-alcoholic fatty liver disease, a population-based cohort investigation in the study of health in Pomerania. J Clin Periodontol. 2017;44(11):1077–87.
23. Shin HS, Hong MH, Moon JY, Sim SJ. Periodontal disease could be a potential risk factor for non-alcoholic fatty liver disease: an 11-year retrospective follow-up study. Clin Oral Investig. 2022;26(8):5503–14.
24. Chen F, Song Y, Li W, Xu H, Dan H, Chen Q. Association between periodontitis and mortality of patients with cardiovascular diseases: A cohort study based on NHANES. J Periodontol. 2024;95(2):175–84.
25. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, Kim YJ, Yoon JH, Cho SH, Sung MW, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010;42(7):503–8.
26. Meffert PJ, Baumeister SE, Lerch MM, Mayerle J, Kratzer W, Völzke H. Development, external validation, and comparative assessment of a new diagnostic score for hepatic steatosis. Am J Gastroenterol. 2014;109(9):1404–14.
27. Choi SE, Sima C, Pandya A. Impact of treating oral disease on preventing vascular diseases: A Model-Based Cost-effectiveness analysis of periodontal treatment among patients with type 2 diabetes. Diabetes Care. 2020;43(3):563–71.
28. Tran DT, Gay I, Du XL, Fu Y, Bebermeyer RD, Neumann AS, Streckfus C, Chan W, Walji MF. Assessment of partial-mouth periodontal examination protocols for periodontitis surveillance. J Clin Periodontol. 2014;41(9):846–52.
29. Li W, Peng J, Shang Q, Yang D, Zhao H, Xu H. Periodontitis and the risk of all-cause and cause-specific mortality among US adults with diabetes: A population-based cohort study. J Clin Periodontol. 2024;51(3):288–98.
30. Zhang YB, Chen C, Pan XF, Guo J, Li Y, Franco OH, Liu G, Pan A. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. BMJ. 2021;373:n604.
31. Chen C, Ye Y, Zhang Y, Pan XF, Pan A. Weight change across adulthood in relation to all cause and cause specific mortality: prospective cohort study. BMJ. 2019;367:l5584.
32. Raza SA, Sokale IO, Thrift AP. Burden of high-risk phenotype of heavy alcohol consumption among obese U.S. Population: results from National health and nutrition examination survey, 1999–2020. Lancet Reg Health Am. 2023;23:100525.
33. Zhang H, Zhang L, Li J, Xiang H, Liu Y, Gao C, Sun X. The influence of life's essential 8 on the link between socioeconomic status and depression in adults: a mediation analysis. BMC Psychiatry. 2024;24(1):296.
34. Luo J, Hendryx M. Mediation analysis of social isolation and mortality by health behaviors. Prev Med. 2022;154:106881.
35. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, Coutinho T, Jensen MD, Roger VL, Singh P, et al. Normal-Weight central obesity: implications for total and cardiovascular mortality. Ann Intern Med. 2015;163(11):827–35.
36. Third Report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III) final report. Circulation. 2002;106(25):3143–421.
37. Bundy JD, Mills KT, He H, LaVeist TA, Ferdinand KC, Chen J, He J. Social determinants of health and premature death among adults in the USA from 1999 to 2018: a National cohort study. Lancet Public Health. 2023;8(6):e422–31.
38. Ku E, Amaral S, McCulloch CE, Adey DB, Li L, Johansen KL. Comparison of 2021 CKD-EPI equations for estimating Racial differences in preemptive waitlisting for kidney transplantation. Clin J Am Soc Nephrol. 2022;17(10):1515–21.
39. Zhang Y, Li Y, Yang Y, Wang Y, Cao X, Jin Y, Xu Y, Li SC, Zhou Q. Periodontal and Peri-Implant Microbiome dysbiosis is associated with alterations in the microbial community structure and local stability. Front Microbiol. 2021;12:785191.
40. Sanz M, Del Castillo AM, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, Chapple I, Dietrich T, Gotsman I, Graziani F, et al. Periodontitis and cardiovascular diseases. Consensus report. Glob Heart. 2020;15(1):1.
41. Jepsen S, Suvan J, Deschner J. The association of periodontal diseases with metabolic syndrome and obesity. Periodontol 2000. 2020;83(1):125–53.
42. Kuraji R, Sekino S, Kapila Y, Numabe Y. Periodontal disease-related nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an emerging concept of oral-liver axis. Periodontol 2000. 2021;87(1):204–40.
43. Li W, Li T, Wei Y, Chen X, Lin S, Lin L. Associations of periodontitis with risk of all-cause and cause-specific mortality among Us adults with chronic kidney disease. J Dent. 2023;138:104712.
44. Rinčić G, Gaćina P, Virović Jukić L, Rinčić N, Božić D, Badovinac A. ASSOCIATION BETWEEN PERIODONTITIS AND LIVER DISEASE. Acta Clin Croat. 2022;60(3):510–8.
45. Albuquerque-Souza E, Sahingur SE. Periodontitis, chronic liver diseases, and the emerging oral-gut-liver axis. Periodontol 2000. 2022;89(1):125–41.
46. Yin JL, Yang J, Song XJ, Qin X, Chang YJ, Chen X, Liu FH, Li YZ, Xu HL, Wei YF, et al. Triglyceride-glucose index and health outcomes: an umbrella review of systematic reviews with meta-analyses of observational studies. Cardiovasc Diabetol. 2024;23(1):177.
47. Nayak SS, Kuriyakose D, Polisetty LD, Patil AA, Ameen D, Bonu R, Shetty SP, Biswas P, Ulrich MT, Letafatkar N, et al. Diagnostic and prognostic value of triglyceride glucose index: a comprehensive evaluation of meta-analysis. Cardiovasc Diabetol. 2024;23(1):310.
48. Han DH, Lim S, Paek D, Kim HD. Periodontitis could be related factors on metabolic syndrome among Koreans: a case-control study. J Clin Periodontol. 2012;39(1):30–7.
49. Graziani F, Gennai S, Solini A, Petrini M. A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes an update of the EFP-AAP review. J Clin Periodontol. 2018;45(2):167–87.
50. Engebretson S, Chertog R, Nichols A, Hey-Hadavi J, Celenti R, Grbic J. Plasma levels of tumour necrosis factor-alpha in patients with chronic periodontitis and type 2 diabetes. J Clin Periodontol. 2007;34(1):18–24.
51. Kardeşler L, Buduneli N, Cetinkalp S, Kinane DF. Adipokines and inflammatory mediators after initial periodontal treatment in patients with type 2 diabetes and chronic periodontitis. J Periodontol. 2010;81(1):24–33.
52. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180–90.
53. Li TJ, Hao YH, Tang YL, Liang XH. Periodontal pathogens: A crucial link between periodontal diseases and oral cancer. Front Microbiol. 2022;13:919633.
54. Higham J, Scannapieco FA. Epidemiological associations between periodontitis and cancer. Periodontol 2000. 2024;96(1):74–82.
55. Tomeno W, Imajo K, Takayanagi T, Ebisawa Y, Seita K, Takimoto T, Honda K, Kobayashi T, Nogami A, Kato T et al. Complications of Non-Alcoholic fatty liver disease in extrahepatic organs. Diagnostics (Basel) 2020, 10(11).
56. Li J, Yao Y, Yin W, Feng S, Yan P, Wang L, Zhu X, Zhang K, Tian J, Wang Z, et al. Association of periodontitis with cardiovascular and all-cause mortality in hypertensive individuals: insights from a NHANES cohort study. BMC Oral Health. 2024;24(1):950.
57. Orlandi M, Graziani F, D'Aiuto F. Periodontal therapy and cardiovascular risk. Periodontol 2000. 2020;83(1):107–24.

58. Nakahara T, Hyogo H, Ono A, Nagaoki Y, Kawaoka T, Miki D, Tsuge M, Hiraga N, Hayes CN, Hiramatsu A, et al. Involvement of Porphyromonas gingivalis in the progression of non-alcoholic fatty liver disease. J Gastroenterol. 2018;53(2):269–80.
59. Yoneda M, Naka S, Nakano K, Wada K, Endo H, Mawatari H, Imajo K, Nomura R, Hokamura K, Ono M, et al. Involvement of a periodontal pathogen, Porphyromonas gingivalis on the pathogenesis of non-alcoholic fatty liver disease. BMC Gastroenterol. 2012;12:16.
60. Konkel JE, O'Boyle C, Krishnan S. Distal consequences of oral inflammation. Front Immunol. 2019;10:1403.
61. Frank RM. Bacterial penetration in the apical pocket wall of advanced human periodontitis. J Periodontal Res. 1980;15(6):563–73.
62. Ding LY, Liang LZ, Zhao YX, Yang YN, Liu F, Ding QR, Luo LJ. Porphyromonas gingivalis-derived lipopolysaccharide causes excessive hepatic lipid accumulation via activating NF-κB and JNK signaling pathways. Oral Dis. 2019;25(7):1789–97.
63. Schumann J, Stanko K, Schliesser U, Appelt C, Sawitzki B. Differences in CD44 surface expression levels and function discriminates IL-17 and IFN-γ producing helper T cells. PLoS ONE. 2015;10(7):e0132479.
64. Zhou Y, Zhang H, Yao Y, Zhang X, Guan Y, Zheng F. CD4(+) T cell activation and inflammation in NASH-related fibrosis. Front Immunol. 2022;13:967410.
65. Kini V, Mohanty I, Telang G, Vyas N. Immunopathogenesis and distinct role of Th17 in periodontitis: A review. J Oral Biosci. 2022;64(2):193–201.
66. Hatasa M, Yoshida S, Takahashi H, Tanaka K, Kubotsu Y, Ohsugi Y, Katagiri T, Iwata T, Katagiri S. Relationship between NAFLD and periodontal disease from the view of clinical and basic research, and immunological response. Int J Mol Sci 2021, 22(7).
67. Lu YC, Yeh WC, Ohashi PS. LPS/TLR4 signal transduction pathway. Cytokine. 2008;42(2):145–51.
68. Chen SN, Tan Y, Xiao XC, Li Q, Wu Q, Peng YY, Ren J, Dong ML. Deletion of TLR4 attenuates lipopolysaccharide-induced acute liver injury by inhibiting inflammation and apoptosis. Acta Pharmacol Sin. 2021;42(10):1610–9.
69. Atarashi K, Suda W, Luo C, Kawaguchi T, Motoo I, Narushima S, Kiguchi Y, Yasuma K, Watanabe E, Tanoue T, et al. Ectopic colonization of oral bacteria in the intestine drives T(H)1 cell induction and inflammation. Science. 2017;358(6361):359–65.
70. Kitamoto S, Nagao-Kitamoto H, Jiao Y, Gillilland MG 3rd, Hayashi A, Imai J, Sugihara K, Miyoshi M, Brazil JC, Kuffa P, et al. The intermucosal connection between the mouth and gut in commensal Pathobiont-Driven colitis. Cell. 2020;182(2):447–e462414.
71. Wieland A, Frank DN, Harnke B, Bambha K. Systematic review: microbial dysbiosis and nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2015;42(9):1051–63.

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