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All-cause and cause-specific mortality in US adults with periodontal diseases: A prospective cohort study

Harriet Larvin[1] | Paris J. Baptiste[1] | Chenyi Gao[2] | Vanessa Muirhead[3] | Nikolaos Donos[3] | Sue Pavitt[2] | Jing Kang[4] | Jianhua Wu[1]

[1]Wolfson Institute of Population Health, Queen Mary University of London, London, UK

[2]School of Dentistry, University of Leeds, Leeds, UK

[3]Centre for Oral Clinical Research, Institute of Dentistry, Queen Mary University of London, London, UK

[4]Oral Biology, School of Dentistry, University of Leeds, Leeds, UK

Correspondence
Harriet Larvin, Clinical Effectiveness Group (CEG), Centre for Primary Care, Wolfson Institute of Population Health, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.
Email: h.larvin@qmul.ac.uk

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Abstract

Aim: This prospective cohort study investigated the association between periodontal diseases (PDs) and all-cause and cause-specific mortality.

Materials and Methods: We utilized adult participants recruited from six National Health and Nutrition Examination Survey cycles (1999–2014) and linked mortality data from the National Death Index up to December 2019. Baseline clinical periodontal examinations were performed by trained and calibrated examiners. All-cause and cause-specific mortality was modelled through multivariable Cox proportional hazards and Fine–Gray models to account for competing risks. All models were adjusted for demographic and lifestyle variables, clinical measurements and comorbidities.

Results: Overall, 15,030 participants were included, with a median length of follow-up of 9 years. Risk of all-cause mortality was 22% greater in people with PD than the control group (adjusted hazard ratio [HR]: 1.22, 95% confidence interval [CI]: 1.12–1.31). Risks of mortality by cardiovascular diseases (CVD), respiratory disease and diabetes were highest in participants with severe PD (CVD—sub-distribution HR [SHR]: 1.38, 95% CI: 1.16–1.64; respiratory—SHR: 1.62, 95% CI: 1.07–2.45; diabetes—SHR: 1.68, 95% CI: 1.12–2.53).

Conclusions: Severe PD is associated with all-cause and cause-specific mortality among US adults after multivariable adjustment.

KEYWORDS
Big Data, cohort study, mortality, oral health, periodontal diseases

Clinical Relevance

Scientific rationale for study: Epidemiological studies have indicated an association between periodontal disease (PD), systemic diseases and all-cause mortality. As yet, the evidence of links between PD and underlying causes of death is inconclusive.

Principal findings: The findings of this prospective cohort study demonstrated that the risks of all-cause and cause-specific mortality were greater in people with PD.

Practical implications: As such, clinicians and health researchers should consider oral health status as a potential risk factor to mortality. This study promotes the integration of oral health towards a whole-person, holistic approach to medicine to improve the understanding of a patient's full health profile.

1 | INTRODUCTION

Approximately 1.1 billion people are living with severe periodontal diseases (PDs) globally (M. X. Chen et al., 2021); up to 45% of adults in the United States have mild, moderate or severe periodontitis (Eke et al., 2020). It is widely acknowledged that PD is significantly associated with the development of non-communicable diseases, including diabetes and cardiovascular diseases (CVD) (Herrera et al., 2023). Two putative hypotheses support this oral-systemic connection: through shared inflammatory pathways, or from the systemic pathogenic repercussions of bacterial dysbiosis (Hajishengallis & Chavakis, 2021). Risk factors such as age, ethnicity and the severity of PD further increase the likelihood of co-occurring comorbidities in individuals with PD (Larvin et al., 2022a). Consequently, PD could substantially contribute to the overall healthcare burden, beyond the realm of dental care services through associated comorbidities.

A systematic review of findings from epidemiological studies suggests that people with PD have greater risks of all-cause mortality compared with those without (Romandini et al., 2021). Nevertheless, previous studies investigating cause-specific mortality have been limited by confounding and insufficient consideration of concurrent risks. This impedes the ability to draw robust inferences on the association between PD and specific causes of death (Romandini et al., 2021). Deconstructing the relationship between PD and the causes of mortality will lead to a better understanding of the oral-systemic pathological link and will address the call for comprehensive, person-centred and holistic research (Watt et al., 2019).

The National Health and Nutrition Examination Survey (NHANES) is a survey-based data resource sampled from a population in the United States (Centers for Disease Control and Prevention [CDC], 2023). The dataset comprises a rich source of information including demographics, biomarkers and medical history. The effects of oral health outcomes (including PD) on adverse health outcomes have been investigated by including clinical dental examinations in the NHANES (Dye et al., 2019). A recent study using NHANES data showed that PD may accentuate the effects of phenotypic age on subsequent risk of all-cause mortality (Liu et al., 2023). A separate study found that PD had an additive effect on the risk of all-cause mortality in NHANES participants with CVD, compared with those with CVD and do not have PD (F. Chen et al., 2023). To our knowledge, there has been no study that has explored the relationship between PD and disease-specific cause of death in NHANES participants utilizing the up-to-date linked National Death Index mortality dataset through December 2019.

This study aimed to investigate the association between PD and the risk of all-cause and cause-specific mortality using this broadly diverse US adult population.

2 | METHODS

2.1 | Study design

A longitudinal cohort study utilizing survey data from participants of the NHANES between 1999 and 2014 was used and the participants were followed up with linked mortality data from National Center for Health Statistics (NCHS) until 2019.

2.2 | Data source

This study utilized data from adult participants of the NHANES cross-sectional surveys run by CDC in the United States (CDC, 2023). The surveys are conducted biennially using stratified multistage probability sampling and data collected from self-reported questionnaires comprising demographics, socioeconomic information and medical history. There are approximately 10,000 participants within each NHANES cycle, with around half of participants also undergoing a health examination. All participants included in the NHANES must provide informed written consent and data are fully de-identified prior to external researcher access.

NHANES participants from cycles where clinical periodontal examination was also undertaken were eligible for inclusion in this study. Follow-up commenced on the date of periodontal examination (baseline) and continued until censorship (date of death; 31st December 2019 [date of the last National Death Index extraction]). Figure 1 shows the full study inclusion flow chart.

2.3 | Study exposure

The exposure for this study was the presence of PD at baseline using the definition outlined by Eke et al. (2012) for the Centers for Disease Control and Prevention and the American Academy of Periodontology. Clinical periodontal examinations were undertaken by trained and calibrated examiners during NHANES cycles 1999–2000, 2001–2002, 2003–2004, 2009–2010, 2011–2012 and 2013–2014. Full-mouth periodontal examinations occurred in cycles 2011–2014; prior cycles included partial examination only. Loss of attachment (LOA) and periodontal probing depths (PPD) were recorded for between

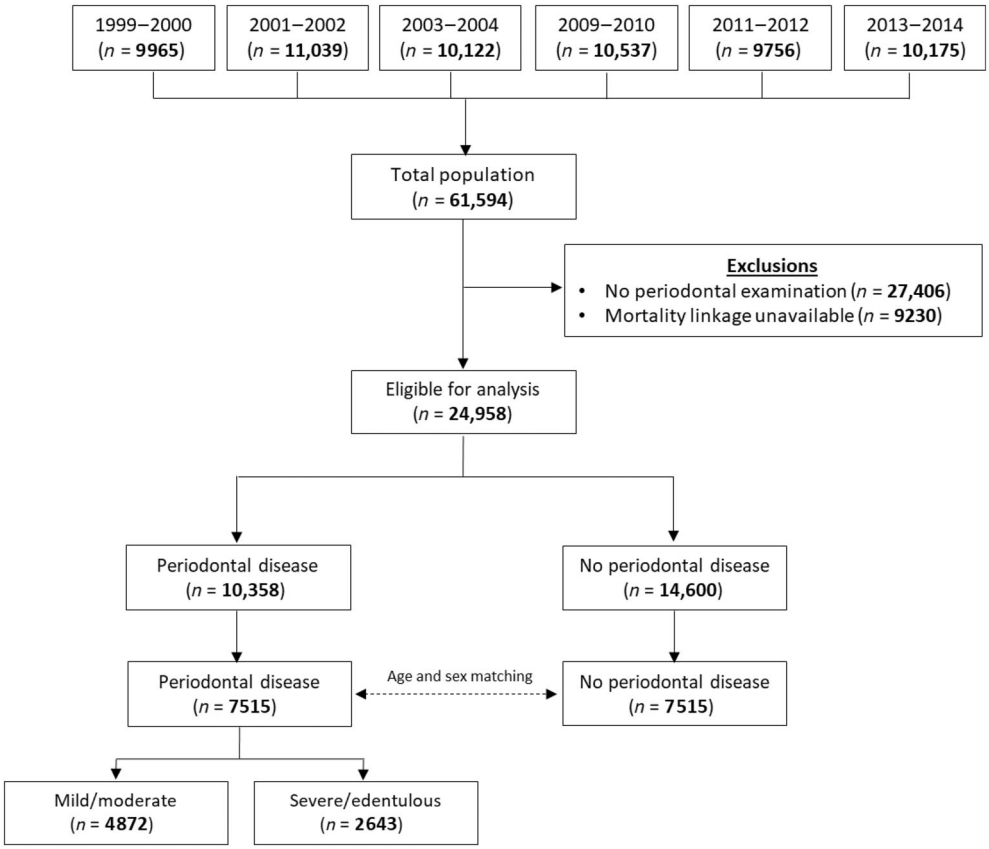

FIGURE 1 Study flow chart. Participants were exact-matched on age and sex in a 1:1 ratio.

two and six sites on each tooth - dependent on year of cycle and associated examination protocol. PD severities were classified according to the following criteria:

- Mild PD: Two or more interproximal sites with LOA ≥ 3 mm AND (2 or more interproximal sites with PPD ≥ 4 mm not on the same tooth OR 1 site with PPD ≥ 5 mm)
- Moderate PD: Two or more interproximal sites with LOA ≥ 4 mm, not on the same tooth OR 2 or more interproximal sites with PPD ≥ 5 mm not on the same tooth
- Severe PD: Two or more interproximal sites with LOA ≥ 6 mm, not on the same tooth AND 1 or more interproximal sites with PPD ≥ 5 mm.

Participants with mild, moderate or severe PD, or who were edentulous, were combined in subgroup analyses to increase the statistical power. The rationale for this was that severe cases of PD can lead to eventual tooth loss; previous studies have included missing teeth in definitions of PD to improve the accuracy of prevalence rates (Tonetti et al., 2018). Participants who had no clinical evidence of mild, moderate or severe PD were eligible for inclusion into the study as controls.

2.4 | Study outcomes

Mortality data were extracted from the 2019 Public-Use Linked mortality files provided from the National Death Index from January 1999 to December 2019. All-cause mortality was the primary outcome for this study. The secondary outcome of this study was cause-specific mortality including by CVD, malignancy, chronic lower respiratory disease, unintentional injuries (accident), cerebrovascular diseases, Alzheimer's disease, diabetes, pneumonia and influenza or renal disease. Cause-specific mortality is defined as underlying cause of death reported by NCHS in the linked mortality data. A previous validation study has shown that the National Death Index shows good validity in comparison with other national death registries (Conway et al., 2021).

2.5 | Covariates

Covariates were selected based on existing literature suggesting the risk factors of PD and associations with systemic diseases. The identified relationship between PD and covariates is demonstrated as a directed acyclic graph (DAG), created using DAGitty package for R within the supplemental file (Supplemental file 1; Textor et al., 2016).

Participant information at baseline including demographics (age, sex [male, female], ethnicity [White, Black, Hispanic, other race], household income [quintile], highest education level [high school or below, or college or above]), smoking status (current smoker, ex-smoker and non-smoker), dietary information (daily calorie intake [kcal]), alcohol intake (drinks per day, where 14 g = 1 drink) and medical history (comorbidities) were self-reported in survey responses. Household income was estimated from family income and stratified

by quintile with 1 for lower incomes and 5 representing the highest income ranges. Pack years were calculated by dividing (cigarettes per day multiplied by total years smoked) by 20. Heavy smokers were quantified as having smoked more than 25 cigarettes per day. Comorbidities were determined by responses to the question "Have you even been told by a doctor or health professional that you have *x*?", where *x* was one of the following conditions: diabetes, cancer, heart attack, coronary heart disease, congestive heart failure, angina and stroke, hypertension, arthritis, liver disease, thyroid disorder, emphysema and bronchitis. Comorbidities were categorized into binary disease groups for covariate adjustment in statistical modelling: cardiovascular (angina, coronary heart disease, congestive heart failure, heart attack, hypertension, stroke), metabolic (diabetes, liver disease, thyroid disorder), respiratory (bronchitis, emphysema) and inflammatory (arthritis) and malignancy. Physical measurements (body mass index [BMI], blood pressure) were recorded during the baseline health examination by trained health technicians.

2.6 | Statistical analysis

Baseline participant characteristics are presented as means with standard deviations (SD), or medians with interquartile ranges (IQR) for continuous variables depending on distribution of data; frequency and percentage are reported for categorical variables. We extracted age and sex for each PD case and identified participants within the control cohort with the same age/sex combination (at a 1:1 ratio) to fully balance the dataset on these covariates and minimize confounding. A summary of baseline characteristics is provided for the total study population and by exposure status; baseline characteristics prior to imputation and stratified by cycle year can be found in the Supplement file.

All-cause and cause-specific mortality was reported by cumulative incidence rate across the follow-up period, stratified by PD status. Multivariable Cox proportional hazard (PH) modelling was used to quantify the risk of all-cause mortality. Violations to proportionality for Cox PH models of all-cause mortality were tested by assessing Schoenfeld residuals, with significance level set to 0.05. Cause-specific mortality was quantified using Fine–Gray sub-distribution hazard modelling for competing risks. Fine–Gray hazard ratios (HRs) estimate the risk of a specific event (cause-specific mortality) relative to the incidence of competing risks (deaths by other causes). Cumulative incidence plots were prepared to display survival curves and rule out the possibility for violations of the PHs assumption, identified by crossover of survival curves.

All statistical models were adjusted for age, sex, BMI, ethnicity, household income quintile, history of smoking and comorbidities. While exact matching balances the data at baseline, both age (10 year age group) and sex were included as covariates in the final model, as these variables are clinically significant confounders that can influence the outcome. We compared the risk of all-cause and cause-specific mortality in PD participants with controls, as well as stratification by PD severity compared with controls. Missing data were reported in all baseline characteristic tables. Both continuous and categorical data were imputed using multiple imputation by chained equations with Gibbs sampling using the 'mice' package in R for the main analysis (van Buuren & Groothuis-Oudshoorn, 2011).

Sensitivity analyses were conducted to determine the impact of using unmatched and unimputed study cohorts on findings. We conducted additional analyses to evaluate the differences in periodontal examination of earlier and recent surveys. We compared the baseline characteristics of earlier (1999–2003) versus later cycles (2009–2014). We also refined the PD data collection of all surveys to match 1999 to 2000 for continuity. Two quadrants and two sites (excluding mid-buccal and mid-lingual) for each participant were randomly selected using R for later cycles according to the half-reduced CDC/AAP case definition, which may lead to the underestimation of PD prevalence (Tran et al., 2014). We then investigated the effect of using the half-reduced CDC/AAP case definition for PD on baseline characteristics and all-cause and cause-specific mortality. A sensitivity analysis to assess the effect of including pack years instead of smoking status as covariates in the models was also conducted. Collinearity between hypertension and diastolic/systolic blood pressure, and diabetes and fasting plasma glucose level was also investigated using correlation matrices prior to adjustment in statistical modelling.

All analyses and data processing were conducted in R version (4.0.0; R Core Team, 2022). This report conforms to STROBE guidelines.

3 | RESULTS

3.1 | Summary of study population

Overall, 24,958 participants met the eligibility criteria across six NHANES cycles (1999, 2001, 2003, 2009, 2011 and 2013). The median follow-up from periodontal examination to censor for all participants was 117 months (IQR: 81.0–198.0). After matching by age and sex, there were 7515 participants with PD (mild/moderate: 4872 [64%], severe/edentulous: 2643 [36%]) and 7515 participants without PD in the control group (Figure 1). The mean age was 54 years and 50.0% of the cohorts were females in both the any PD and control groups. Most participants were White (PD: 40.8%, controls: 52.5%) and had high school education or below (PD: 63.4%, controls: 42.9%). More participants with PD had a history of smoking (55.3%) than those in the control group (41.2%). Participants with severe PD were older on average (mean: 50.9 years, SD: 13.7) than those with mild/moderate PD (mean: 61.3 years, SD: 14.0). See Table 1 for full summary of participant characteristics.

3.2 | PD and all-cause mortality

Overall, Cox PH regression showed that the risk of all-cause mortality in participants with PD was greater than that in the control group (crude Cox PH HR: 1.67, 95% CI: 1.56–1.79). After adjustments, this risk remained 22% higher for participants with PD (adjusted Cox PH HR: 1.22, 95% CI: 1.12–1.31; Figure 2). The risk of all-cause mortality

TABLE 1 Participant characteristics of the age- and sex-matched population.

		PD		
	Controls	Any	Mild/moderate	Severe/edentulous
	7515	7515	4872	2643
Median follow-up, months (IQR)	117.0 (81.0–198.0)	113.0 (85.0–161.0)	114.0 (89.0–173.0)	109.0 (76.0–156.0)
Age, years	54.0 (14.7)	54.6 (14.6)	50.9 (13.7)	61.3 (14.0)
Sex, female	3760 (50.0%)	3760 (50.0%)	2413 (49.5%)	1347 (51.0%)
BMI	29.0 (6.3)	29.3 (6.8)	29.4 (6.8)	29.0 (6.6)
Diastolic blood pressure	72.0 (13.1)	71.5 (13.7)	72.3 (12.6)	69.9 (15.3)
Systolic blood pressure	126.2 (19.1)	128.2 (20.5)	125.5 (18.8)	133.2 (22.6)
Ethnicity				
White	3949 (52.5%)	3069 (40.8%)	1804 (37.0%)	1265 (47.9%)
Black	1294 (17.2%)	1728 (23.0%)	1108 (22.7%)	620 (23.5%)
Hispanic	1708 (22.7%)	2090 (27.8%)	1500 (30.8%)	590 (22.3%)
Other race	564 (7.5%)	628 (8.4%)	460 (9.4%)	168 (6.4%)
Education				
High school or below	3143 (41.8%)	4768 (63.4%)	2778 (57.0%)	1990 (75.3%)
College or above	4302 (57.2%)	2714 (36.1%)	2067 (42.4%)	647 (24.5%)
Household income, quintile				
5	2302 (30.6%)	1048 (13.9%)	853 (17.5%)	195 (7.4%)
4	1441 (19.2%)	1150 (15.3%)	829 (17.0%)	321 (12.1%)
3	1397 (18.6%)	1685 (22.4%)	1099 (22.6%)	586 (22.2%)
2	880 (11.7%)	1303 (17.3%)	783 (16.1%)	520 (19.7%)
1	773 (10.3%)	1446 (19.2%)	740 (15.2%)	706 (26.7%)
History of comorbidities				
Angina	171 (2.3%)	247 (3.3%)	89 (1.8%)	158 (6.0%)
Arthritis	2204 (29.3%)	2263 (30.1%)	1206 (24.8%)	1057 (40.0%)
Bronchitis	842 (11.2%)	660 (8.8%)	381 (7.8%)	279 (10.6%)
Malignancy	768 (10.2%)	681 (9.1%)	356 (7.3%)	325 (12.3%)
CHD	219 (2.9%)	281 (3.7%)	100 (2.1%)	181 (6.8%)
CHF	126 (1.7%)	274 (3.6%)	105 (2.2%)	169 (6.4%)
Diabetes	785 (10.4%)	1154 (15.4%)	606 (12.4%)	548 (20.7%)
Emphysema	78 (1.0%)	222 (3.0%)	87 (1.8%)	135 (5.1%)
Heart attack	190 (2.5%)	382 (5.1%)	144 (3.0%)	238 (9.0%)
Hypertension	2767 (36.8%)	2987 (39.7%)	1695 (34.8%)	1292 (48.9%)
Liver disease	370 (4.9%)	487 (6.5%)	262 (5.4%)	225 (8.5%)
Stroke	225 (3.0%)	319 (4.2%)	128 (2.6%)	191 (7.2%)
Thyroid disease	292 (3.9%)	305 (4.1%)	178 (3.7%)	127 (4.8%)
None	2895 (38.5%)	2720 (36.2%)	2068 (42.4%)	652 (24.7%)
History of smoking				
Non-smoker	4353 (57.9%)	3330 (44.3%)	2385 (49.0%)	945 (35.8%)
Ex-smoker	2110 (28.1%)	2000 (26.6%)	1186 (24.3%)	814 (30.8%)
Current	986 (13.1%)	2157 (28.7%)	1276 (26.2%)	881 (33.3%)
Heavy smoker (>25 cigarettes per day)	550 (3.8%)	965 (9.3%)	455 (7.1%)	510 (13.0%)

Note: Data are *N* (%) for categorical variables and mean (SD) for continuous variables, unless otherwise stated. The following variables were imputed due to missing data: education (0.8%), household income (10.7%), BMI (1.8%), systolic and diastolic blood pressure (2.9%) and history of smoking (0.6%).
Abbreviations: BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; IQR, interquartile range; *N*, number of patients; PD, periodontal disease; SD, standard deviation.

increased incrementally with PD severity, with 4% increased risk in participants with mild/moderate PD, rising to nearly 40% greater risk for severe PD compared with the control group (mild/moderate—adjusted Cox PH HR: 1.04, 95% CI: 0.95–1.15; severe—adjusted Cox PH HR: 1.37, 95% CI: 1.26–1.50; Figure 4).

Cumulative incidence curves of each cause-specific mortality by PD severity demonstrated no violation to the proportionality assumption of Fine–Gray regression (Figure 3).

3.3 | PD and CVD-related mortality

CVD-related mortality was the most commonly reported specific cause of mortality in participants with PD (*N*: 323). After accounting for the presence of competing risks (mortality by other causes) and before adjustments, PD was significantly associated with increased risk of mortality by CVD (crude sub-distribution HR [SHR]: 1.80, 95% CI: 1.57–2.07). After adjustments, the risk of mortality by CVD was approximately 20% higher in participants with any PD, relative to mortality by other causes (adjusted SHR: 1.21, 95% CI: 1.03–1.41; Figure 2). Compared with controls, the risk of CVD-related mortality was highest in participants with severe PD (adjusted SHR: 1.38, 95% CI: 1.16–1.64), while the risk in participants with mild/moderate PD specifically was not statistically significant (adjusted SHR: 0.98, 95% CI: 0.81–1.19; Figure 4).

3.4 | PD and diabetes-related mortality

Relative to death by other causes, PD was significantly associated with increased risk of diabetes-related mortality before adjustments

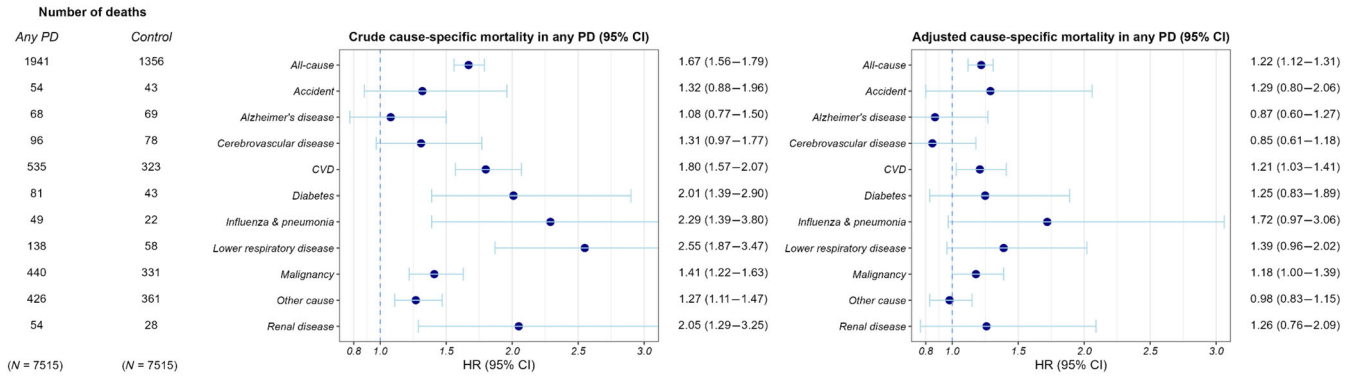

FIGURE 2 Crude and adjusted mortality by underlying cause of death in participants with periodontal disease. Adjustments were made by age, sex, body mass index, systolic and diastolic blood pressure, ethnicity, education, household income, alcohol use, daily calorie intake, history of smoking and history of comorbidities (malignancy, cardiovascular diseases, respiratory diseases, metabolic diseases and inflammatory diseases). CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; *N*, number of patients; PD, periodontal disease.

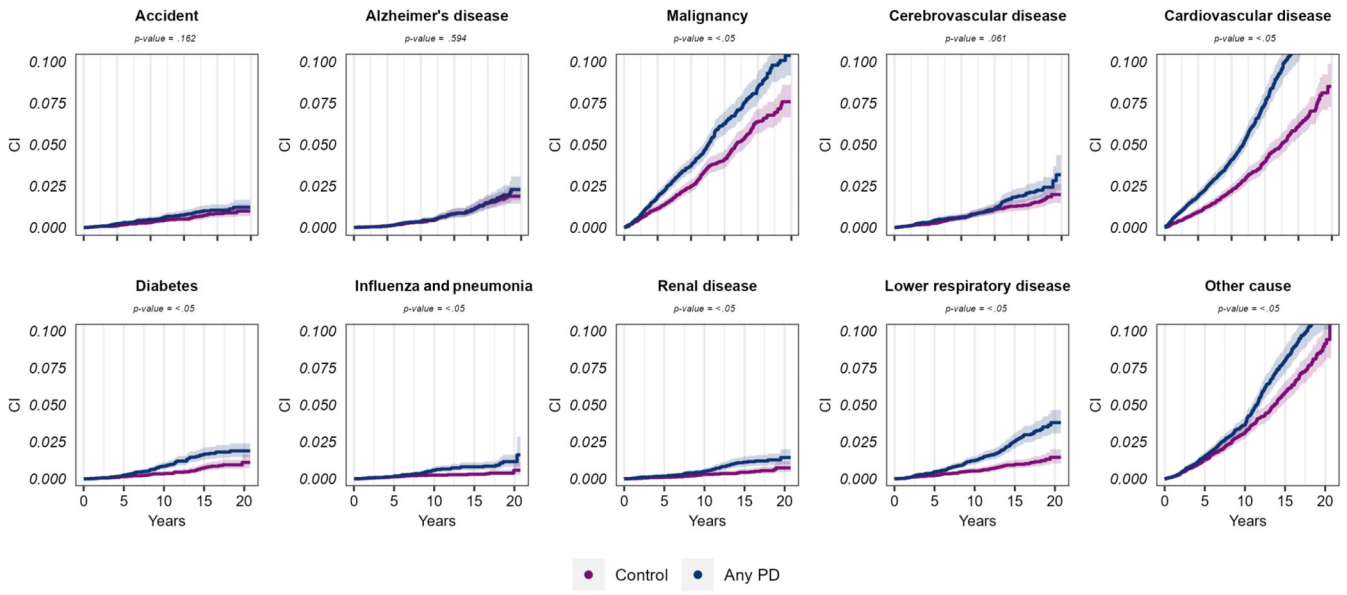

FIGURE 3 Cumulative incidence of mortality by underlying cause of death in participants with periodontal disease compared with controls. PD, periodontal disease.

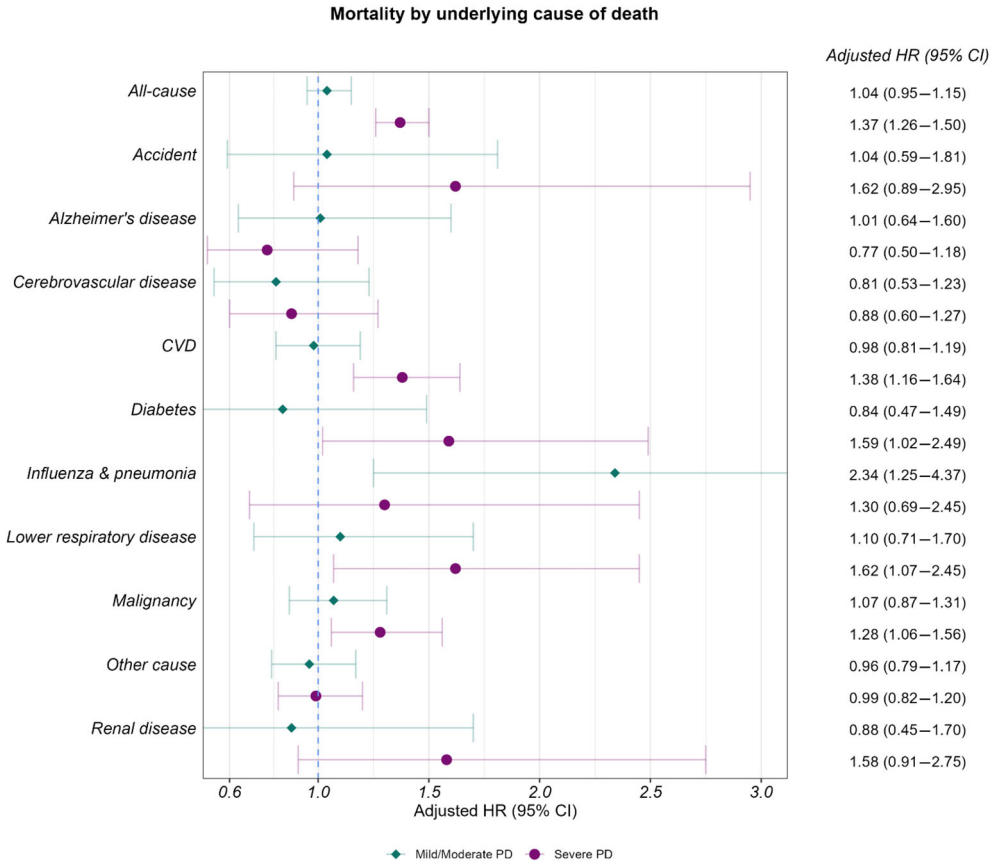

FIGURE 4 Mortality by underlying cause of death, stratified by periodontal disease severity. Adjustments were made by age, sex, body mass index, systolic and diastolic blood pressure, ethnicity, education, household income, alcohol use, daily calorie intake, history of smoking and history of comorbidities (malignancy, cardiovascular diseases, respiratory diseases, metabolic diseases and inflammatory diseases). CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; *N*, number of patients; PD, periodontal disease.

(crude SHR: 2.01, 95% CI: 1.39–2.90). The unadjusted increased risk of diabetes-related mortality in participants with any PD (crude SHR: 2.01, 95% CI: 1.39–2.90) was not significant after adjustments (adjusted SHR: 1.25, 95% CI: 0.83–1.89; Figure 2). However, participants with severe PD had a 59% greater risk of diabetes-related mortality than the control group (adjusted SHR: 1.59, 95% CI: 1.02–2.49; Figure 4).

3.5 | PD and respiratory-related mortality

Before adjustments and accounting for the presence of competing risks, PD was significantly associated with increased risk of mortality by influenza and pneumonia (crude SHR: 2.29, 95% CI: 1.39–3.80) and lower respiratory disease (crude SHR: 2.55, 95% CI: 1.87–3.47). After adjustments, the risk of mortality by lower respiratory diseases was 62% higher in participants with severe PD (adjusted SHR: 1.62, 95% CI: 1.07–2.45; Figure 4).

3.6 | PD and cancer/malignancy-related mortality

Mortality caused by cancer/malignancy was the second most commonly reported underlying cause of mortality observed in participants with PD (*N*: 331). PD was significantly associated with increased risk of malignancy-related mortality before adjustments (crude SHR: 1.41, 95% CI: 1.22–1.63; Figure 2). The risk was not higher in participants with mild/moderate PD (adjusted SHR: 1.07, 95% CI: 0.87–1.31). However, participants with severe PD/edentulous had a 28% higher risk of malignancy-related mortality compared with controls who had not yet died from malignancy-related causes (adjusted SHR: 1.28, 95% CI: 1.06–1.56; Figure 4).

3.7 | PD and other cause-specific mortality

The risks of other cause-specific mortality including Alzheimer's disease (adjusted SHR: 0.87, 95% CI: 0.60–1.27) and renal disease (adjusted SHR: 1.26, 95% CI: 0.76–2.09) were not associated with any PD compared with the control group. Participants with PD also did not have heightened risks of other unlisted causes of mortality after adjustments (adjusted SHR: 0.98, 95% CI: 0.83–1.15; Figure 2).

3.8 | Sensitivity analysis

Sensitivity analysis showed that the baseline characteristics were similar among the matched population to those prior to matching and imputation (Supplemental Table 1). Sensitivity analysis using the unmatched and complete cases only (no imputation) cohorts demonstrated no notable impact on risks of cause-specific mortality (Supplemental Figures 1 and 2). There were no noticeable differences in the

baseline characteristics of earlier NHANES cycles (1999–2003) versus later NHANES cycles (2009–2014; Supplemental Table 2). After applying random sampling of quadrant and site on later cycles to match the 1999 cycle periodontal examination protocol, participants were older (mean: 60 years) and there were fewer females (43%; Supplemental Table 3). While the all-cause death events were higher in the half-reduced CDC/AAP case definition for PD ($n = 1553$) compared with those of the main analysis ($n = 1356$), there was a similar trend in mortality, with higher risks in PD for CVD and lower respiratory diseases after adjustment (CVD-adjusted SHR: 1.25, 95% CI: 1.09–1.43; diabetes-adjusted SHR: 1.47, 95% CI: 1.02–2.10; lower respiratory disease-adjusted SHR: 1.41, 95% CI: 1.02–1.95 Supplemental Figure 3). Exclusion of edentulous participants in the severe PD category showed similar direction of effect on mortality to the main analysis (Supplemental Figure 4), while replacing smoking status for pack years also had no effect on direction or magnitude of effect estimates (Supplemental Figure 5). Including fasting plasma glucose level into hazard models also showed similar trend to the main analysis, with significant association between PD and risk of CVD-related mortality (adjusted SHR: 1.38, 95% CI: 1.11–1.72). Confidence intervals (CIs) were wider for other outcomes in this sensitivity analyses due to greater rates of missingness in the fasting plasma glucose level variable (Supplemental Figure 6).

4 | DISCUSSION

4.1 | Main findings

This study explored all-cause and cause-specific mortality in participants with PD at baseline, over an average follow-up period of approximately 9 years. The findings demonstrate a life course relationship between PD and underlying causes of death. Overall, participants with any PD had greater risk of all-cause mortality and were associated with an increased risk of CVD and lower respiratory diseases specifically. When stratified by PD severity, participants with more severe PD/edentulous had a higher risk of CVD and lower respiratory diseases cause mortality. Participants with severe PD also had higher risks of death due to diabetes and malignancy than mild/moderate PD when compared with controls.

4.2 | Comparison with previous literature

The results of this study concur with a previous systematic review of 48 cohort studies, which also showed that adults with PD had greater risks of all-cause mortality (Romandini et al., 2021). The authors speculate that PD could therefore be a risk factor for mortality itself due to a combination of risk factors shared with other non-communicable diseases, bacterial dysbiosis and chronic dysregulation of inflammatory responses (Herrera et al., 2023). A recent study using NHANES data also suggested that PD is linked to both unhealthy lifestyles (e.g., smoking) and inflammatory processes. The authors suggest that this association could accelerate ageing and increase the risks of all-cause mortality (Liu et al., 2023). For example, circulating levels of inflammatory mediators such as c-reactive protein and interleukin-6 are increased in people with PD (Yucel-Lindberg & Båge, 2013). This inflammatory stress may have a systemic, pathological effect and thereby induce ageing with increased magnitude (Michaud et al., 2013; Puzianowska-Kuźnicka et al., 2016), indirectly driving the association of PD and mortality. Consequently, findings showing associations with PD and greater risk of adverse outcomes advocate further research into how good periodontal health may improve long-term health outcomes. For example, there are suggestions that PD treatment may be linked to reduced blood pressure, lower risk of CVD outcomes and shorter hospitalization (Czesnikiewicz-Guzik et al., 2019; Michalowicz et al., 2023; Tsakos et al., 2010; Ye et al., 2022). Future research demonstrating the impact of periodontal treatment and life-long periodontal health maintenance on rates of mortality would support proposals for better integration of dental and medical health services in alleviating wider healthcare burden.

The present study utilized Fine–Gray modelling to account for competing risks in assessing cause-specific mortality. A systematic review by Romandini et al. (2021) reported heightened risks of CVD-specific mortality for people with PD, as well as for death by malignancy in edentulous cases (as a sequela of severe PD) (Romandini et al., 2021). This agrees with the findings in the present study and suggests the pathogenicity of severe PD is closely associated with adverse outcomes of CVD and cancer. Epidemiological evidence indicates that PD is associated with both CVD and cancer (Larvin, Kang, et al., 2021; Maisonneuve et al., 2017). A previous study of NHANES participants with a shorter follow-up period demonstrated that participants with PD and CVD had marginally greater risk of all-cause mortality than those with CVD and no PD. When stratified by underlying cause, there was no association with CVD or malignancy-related mortality specifically (F. Chen et al., 2023). Of note, the authors did not account for competing risks, and therefore the estimates may be biased. However, this bias would typically lead to overestimation of HRs, which does not justify the discrepancy in results. A possible explanation is that the authors did not report or adjust for comorbidities, or the temporal disease development to CVD. For example, patients with CVD are likely to live with other chronic conditions (Sison et al., 2023): there is a risk that other conditions may be cited as the final cause of death in patients with multimorbidity.

Increased risks of death by diabetes (metabolic) and respiratory-related causes in people with severe PD have also been observed in other cohort studies (Kotronia et al., 2021; Nabila et al., 2023; Wu et al., 2021). Cohort studies have shown that PD is linked to both diabetes and respiratory disease development (Larvin et al., 2022b; Yang et al., 2023). Severe PD could lead to upregulated immune responses that disrupt systemic metabolic networks, causing detrimental effects to glucose control, insulin resistance and the subsequent onset of diabetes (Blanco et al., 2021; Herrera et al., 2023). Alternatively, the link between PD and respiratory diseases could be induced by uncontrolled inflammatory responses and subsequent effects on endothelial cell and pulmonary function (Herrera et al., 2023). Recent evidence suggests that PD is associated with increased mortality following COVID-19 infection (Larvin, Wilmott, et al., 2021). While the present

study period did not cover the pandemic, the estimate for respiratory-related deaths in participants with PD could be augmented in future analyses of updated mortality data from cycles covering the pandemic period.

4.3 | Strengths and limitations

A major strength of the present study is the use of NHANES as an open access data resource, which has enabled investigation into the effect of PD on all-cause and cause-specific mortality (CDC, 2023). This study is the first of its kind to compare mortality outcomes in participants with PD using the updated linked mortality data through December 2019. Combining multiple NHANES cycles with a longer follow-up period significantly strengthens the statistical robustness compared with previous studies (F. Chen et al., 2023; Liu et al., 2023; Romandini et al., 2021). Using Fine–Gray models for competing risks also ensures that the mortality estimates of the present study are at minimal risk of overestimation by accounting for deaths by other causes. Lastly, while there are inherent risks of using observational datasets that are susceptible to residual confounding, we were able to minimize these biases by matching on age and sex and conducting multivariate modelling. The present study has some acknowledged methodological limitations. While the NHANES data resource provides a validated clinical PD classification, other variables including demographics and medical history were self-reported with risk of response/recall bias. As such, causal inferences cannot be made. In our study, self-reported medical history was used as a surrogate for clinical diagnosis of comorbidities. Recent findings suggest that the accuracy of self-reported conditions can vary dependent on condition type and participant characteristics (Sulieman et al., 2022). Ergo, there is a possibility that medical history in NHANES is underreported, and thus there may be some residual confounding in the results of the present study. There is also a possibility that some participants may have received periodontal therapy during the follow-up period. PD can be reversed with treatment and continued oral self-maintenance; some participants may not have had PD at the time of death due to treatment during follow-up, equally some controls may later acquire PD. This may cause some statistical heterogeneity; however, as controls and cases are equally likely to be affected, this should not greatly affect the overall direction of estimates. The aim of this study was to quantitatively explore mortality in PD, as such severe PD was combined with edentulism to promote statistical power (Tonetti et al., 2018). It should be noted that previous surveillance studies do not typically include edentulism in severe PD case definitions (Page & Eke, 2007), thereby our findings may not be directly comparable to previous analyses. While this could lead to overestimation (Liljestrand et al., 2015; Matsuyama et al., 2017), the sensitivity analysis excluding edentulous patients from the severe PD definition demonstrated a similar trend and direction of effect to the main analysis (Romandini et al., 2021). This trend matches the findings of previous systematic review of studies showing an increased risk of all-cause and cause-specific mortality in cohorts with PD or edentulism. Other variables reported at baseline, such as comorbidities, may have also changed during follow-up and this should also be considered when interpreting the findings. Some outcomes also had wide CIs, indicating low statistical power due to a small number of events reported; the estimates from these outcomes should therefore be interpreted with caution. To enable larger sample size and greater statistical robustness, cycle year was not used for matching. While the median follow-up time across cohorts was similar, it is possible that differing follow-up durations may have impacted the results. However, Supplemental Table 2 shows that overall participant characteristics across survey cycle years were similar, and this should have minimal impact on the interpretation of the findings.

4.4 | Future work and clinical implications

The outcomes of this study were limited to the specified causes available in the mortality dataset. As such, analysis of diagnoses within the groupings, such as coronary heart disease as CVD, specific cancers and stroke as cerebrovascular disease, was not available. To dissect the complex relationship between PD pathogenicity and cause-specific mortality, future work should explore the association with more precise diagnoses, as well as combined systemic disease diagnoses as underlying causes of death. Furthermore, research into the effect of periodontal treatment and life-long periodontal maintenance on mortality outcomes could confirm PD as a risk factor for mortality. Alongside the present findings, further studies would support calls for improved integration of dental and general healthcare research and services, ultimately lending towards the 'One Health' initiative that is supported by the World Health Organization (Colombo & Wu, 2023).

4.5 | Conclusion

Severe PD is associated with increased all-cause mortality, and compared to people without PD, those with severe cases of PD are at the greatest risk of mortality from CVD, malignancy and lower respiratory diseases. The findings of this study support the need for future intervention studies to assess the influence of periodontal interventions, or policy approaches to improving access to care, on the rate of all-cause mortality.

AUTHOR CONTRIBUTIONS

HL performed statistical analysis, interpreted results and contributed to the drafting and critical revision of the manuscript. PJB interpreted the results and contributed to the drafting and critical revision of the manuscript. CG, JK, SP and ND contributed to the drafting and critical revision of the manuscript. JW conceived and designed the study, interpreted the results and contributed to the drafting and critical revision of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in National Health and Nutrition Examination Survey (NHANES) at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

ETHICS STATEMENT

All NHANES procedures and protocols are reviewed and approved by the National Center for Health Statistics research ethics review board and participants provide written informed consent.

ORCID

Paris J. Baptiste https://orcid.org/0000-0002-2565-8525
Chenyi Gao https://orcid.org/0000-0003-1163-2751
Jing Kang https://orcid.org/0000-0002-2770-1099
Jianhua Wu https://orcid.org/0000-0001-6093-599X

REFERENCES

Blanco, C., Liñares, A., Dopico, J., Pico, A., Sobrino, T., Leira, Y., & Blanco, J. (2021). Peri-implantitis, systemic inflammation, and dyslipidemia: A cross-sectional biochemical study. *Journal of Periodontal & Implant Science*, *51*(5), 342–351.

Centers for Disease Control and Prevention (CDC). (2023). *National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

Chen, F., Song, Y., Li, W., Xu, H., Dan, H., & Chen, Q. (2023). Association between periodontitis and mortality of patients with cardiovascular diseases: A cohort study based on NHANES. *Journal of Periodontology*, *95*(2), 175–184.

Chen, M. X., Zhong, Y. J., Dong, Q. Q., Wong, H. M., & Wen, Y. F. (2021). Global, regional, and national burden of severe periodontitis, 1990–2019: An analysis of the Global Burden of Disease Study 2019. *Journal of Clinical Periodontology*, *48*(9), 1165–1188.

Colombo, A. P., & Wu, B. (2023). Aging and oral health: Biological and sociobehavioral perspectives. *Journal of Dental Research*, *102*(8), 841–843.

Conway, R. B. N., Armistead, M. G., Denney, M. J., & Smith, G. S. (2021). Validating the matching of patients in the linkage of a large hospital system's EHR with state and national death databases. *Applied Clinical Informatics*, *12*(1), 82–89.

Czesnikiewicz-Guzik, M., Osmenda, G., Siedlinski, M., Nosalski, R., Pelka, P., Nowakowski, D., Wilk, G., Mikolajczyk, T. P., Schramm-Luc, A., Furtak, A., Matusik, P., Koziol, J., Drozdz, M., Munoz-Aguilera, E., Tomaszewski, M., Evangelou, E., Caulfield, M., Grodzicki, T., D'Aiuto, F., & Guzik, T. J. (2019). Causal association between periodontitis and hypertension: Evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. *European Heart Journal*, *40*(42), 3459–3470.

Dye, B. A., Afful, J., Thornton-Evans, G., & Iafolla, T. (2019). Overview and quality assurance for the oral health component of the National Health and Nutrition Examination Survey (NHANES), 2011-2014. *BMC Oral Health*, *19*(1), 95.

Eke, P. I., Borgnakke, W. S., & Genco, R. J. (2020). Recent epidemiologic trends in periodontitis in the USA. *Periodontology 2000*, *82*(1), 257–267.

Eke, P. I., Page, R. C., Wei, L., Thornton-Evans, G., & Genco, R. J. (2012). Update of the case definitions for population-based surveillance of periodontitis. *Journal of Periodontology*, *83*(12), 1449–1454.

Hajishengallis, G., & Chavakis, T. (2021). Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. *Nature Reviews. Immunology*, *21*(7), 426–440.

Herrera, D., Sanz, M., Shapira, L., Brotons, C., Chapple, I., Frese, T., Graziani, F., Hobbs, F. D. R., Huck, O., Hummers, E., Jepsen, S., Kravtchenko, O., Madianos, P., Molina, A., Ungan, M., Vilaseca, J., Windak, A., & Vinker, S. (2023). Association between periodontal diseases and cardiovascular diseases, diabetes and respiratory diseases: Consensus report of the Joint Workshop by the European Federation of Periodontology (EFP) and the European arm of the world Organization of Family Doctors (WONCA Europe). *Journal of Clinical Periodontology*, *50*(6), 819–841.

Kotronia, E., Brown, H., Papacosta, A. O., Lennon, L. T., Weyant, R. J., Whincup, P. H., Wannamethee, S. G., & Ramsay, S. E. (2021). Oral health and all-cause, cardiovascular disease, and respiratory mortality in older people in the UK and USA. *Scientific Reports*, *11*(1), 16452.

Larvin, H., Kang, J., Aggarwal, V. R., Pavitt, S., & Wu, J. (2021). Risk of incident cardiovascular disease in people with periodontal disease: A systematic review and meta-analysis. *Clinical and Experimental Dental Research*, *7*(1), 109–122.

Larvin, H., Kang, J., Aggarwal, V. R., Pavitt, S., & Wu, J. (2022a). Systemic multimorbidity clusters in people with periodontitis. *Journal of Dental Research*, *101*(11), 1335–1342.

Larvin, H., Kang, J., Aggarwal, V. R., Pavitt, S., & Wu, J. (2022b). Periodontitis and risk of immune-mediated systemic conditions: A systematic review and meta-analysis. *Community Dentistry and Oral Epidemiology*, *51*, 705–717.

Larvin, H., Wilmott, S., Kang, J., Aggarwal, V. R., Pavitt, S., & Wu, J. (2021). Additive effect of periodontal disease and obesity on COVID-19 outcomes. *Journal of Dental Research*, *100*(11), 1228–1235.

Liljestrand, J. M., Havulinna, A. S., Paju, S., Männistö, S., Salomaa, V., & Pussinen, P. J. (2015). Missing teeth predict incident cardiovascular events, diabetes, and death. *Journal of Dental Research*, *94*(8), 1055–1062.

Liu, Y., Xu, S., Cai, Q., Chen, Y., Zhu, P., Du, M., Visser, A., & Li, A. (2023). Does periodontitis affect the association of biological aging with mortality? *Journal of Dental Research*, *102*(8), 909–918.

Maisonneuve, P., Amar, S., & Lowenfels, A. B. (2017). Periodontal disease, edentulism, and pancreatic cancer: A meta-analysis. *Annals of Oncology*, *28*(5), 985–995.

Matsuyama, Y., Aida, J., Watt, R. G., Tsuboya, T., Koyama, S., Sato, Y., Kondo, K., & Osaka, K. (2017). Dental status and compression of life expectancy with disability. *Journal of Dental Research*, *96*(9), 1006–1013.

Michalowicz, B. S., Anderson, J. P., Kottke, T. E., Dehmer, S. P., Worley, D. C., Kane, S., Basile, S., & Rindal, D. B. (2023). Periodontal treatment and subsequent clinical outcomes and medical care costs: A retrospective cohort study. *PLoS One*, *18*(8), e0290028.

Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., Cesari, M., & Nourhashemi, F. (2013). Proinflammatory cytokines, aging, and age-related diseases. *Journal of the American Medical Directors Association*, *14*(12), 877–882.

Nabila, S., Choi, J., Kim, J.-E., Hahn, S., Hwang, I.-K., Kim, T.-I., Park, H. K., & Choi, J. Y. (2023). Bidirectional associations between periodontal disease and systemic diseases: A nationwide population-based study in Korea. *Scientific Reports*, *13*(1), 14078.

Page, R. C., & Eke, P. I. (2007). Case definitions for use in population-based surveillance of periodontitis. *Journal of Periodontology*, *78*(7 Suppl), 1387–1399.

Puzianowska-Kuźnicka, M., Owczarz, M., Wieczorowska-Tobis, K., Nadrowski, P., Chudek, J., Slusarczyk, P., Skalska, A., Jonas, M., Franek, E., & Mossakowska, M. (2016). Interleukin-6 and C-reactive protein, successful aging, and mortality: The PolSenior study. *Immunity & Ageing*, *13*, 21.

R Core Team. (2022). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing.

Romandini, M., Baima, G., Antonoglou, G., Bueno, J., Figuero, E., & Sanz, M. (2021). Periodontitis, edentulism, and risk of mortality: A systematic review with meta-analyses. *Journal of Dental Research*, *100*(1), 37–49.

Sison, S. D. M., Lin, K. J., Najafzadeh, M., Ko, D., Patorno, E., Bessette, L. G., Zakoul, H., & Kim, D. H. (2023). Common non-cardiovascular multimorbidity groupings and clinical outcomes in older adults with major cardiovascular disease. *Journal of the American Geriatrics Society*, *71*, 3179–3188.

Sulieman, L., Cronin, R. M., Carroll, R. J., Natarajan, K., Marginean, K., Mapes, B., Roden, D., Harris, P., & Ramirez, A. (2022). Comparing medical history data derived from electronic health records and survey answers in the all of us research program. *Journal of the American Medical Informatics Association*, *29*(7), 1131–1141.

Textor, J., van der Zander, B., Gilthorpe, M. K., Liskiewicz, M., & Ellison, G. T. H. (2016). Robust causal inference using directed acyclic graphs: The R package 'dagitty'. *International Journal of Epidemiology*, *45*(6), 1887–1894.

Tonetti, M. S., Greenwell, H., & Kornman, K. S. (2018). Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *Journal of Periodontology*, *89*(S1), S159–S172.

Tran, D. T., Gay, I., Du, X. L., Fu, Y., Bebermeyer, R. D., Neumann, A. S., Streckfus, C., Chan, W., & Walji, M. F. (2014). Assessment of partial-mouth periodontal examination protocols for periodontitis surveillance. *Journal of Clinical Periodontology*, *41*(9), 846–852.

Tsakos, G., Sabbah, W., Hingorani, A. D., Netuveli, G., Donos, N., Watt, R. G., & D'Aiuto, F. (2010). Is periodontal inflammation associated with raised blood pressure? Evidence from a National US survey. *Journal of Hypertension*, *28*(12), 2386–2393.

van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software*, *45*(3), 1–67.

Watt, R. G., Daly, B., Allison, P., Macpherson, L. M. D., Venturelli, R., Listl, S., Weyant, R. J., Mathur, M. R., Guarnizo-Herreño, C. C., Celeste, R. K., Peres, M. A., Kearns, C., & Benzian, H. (2019). Ending the neglect of global oral health: Time for radical action. *Lancet*, *394*(10194), 261–272.

Wu, Z., O'Brien, K. M., Lawrence, K. G., Han, Y., Weinberg, C. R., Sandler, D. P., & Vogtmann, E. (2021). Associations of periodontal disease and tooth loss with all-cause and cause-specific mortality in the Sister Study. *Journal of Clinical Periodontology*, *48*(12), 1597–1604.

Yang, M., Peng, R., Li, X., Peng, J., Liu, L., & Chen, L. (2023). Association between chronic obstructive pulmonary disease and periodontal disease: A systematic review and meta-analysis. *BMJ Open*, *13*(6), e067432.

Ye, Z., Cao, Y., Miao, C., Liu, W., Dong, L., Lv, Z., Iheozor-Ejiofor, Z., & Li, C. (2022). Periodontal therapy for primary or secondary prevention of cardiovascular disease in people with periodontitis. *Cochrane Database of Systematic Reviews*, *10*(10), Cd009197.

Yucel-Lindberg, T., & Båge, T. (2013). Inflammatory mediators in the pathogenesis of periodontitis. *Expert Reviews in Molecular Medicine*, *15*, e7.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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