J Clin Periodontol 2016; 43: 104–113 doi: 10.1111/jcpe.12502

Journal of Clinical Periodontology

Association between periodontitis and mortality in stages 3–5 chronic kidney disease: NHANES III and linked mortality study

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Sharma P, Dietrich T, Ferro CJ, Cockwell P, Chapple ILC. Association between periodontitis and mortality in stages 3–5 chronic kidney disease: NHANES III and linked mortality study. J Clin Periodontol 2016; 43: 104–113. doi: 10.1111/jcpe.12502

Abstract

Introduction: Periodontitis may add to the systemic inflammatory burden in individuals with chronic kidney disease (CKD), thereby contributing to an increased mortality rate. This study aimed to determine the association between periodontitis and mortality rate (all-cause and cardiovascular disease-related) in individuals with stage 3–5 CKD, hitherto referred to as "CKD".

Methods: Survival analysis was carried out using the Third National Health and Nutrition Examination Survey (NHANES III) and linked mortality data. Cox proportional hazards regression was employed to assess the association between periodontitis and mortality, in individuals with CKD. This association was compared with the association between mortality and traditional risk factors in CKD mortality (diabetes, hypertension and smoking).

Results: Of the 13,784 participants eligible for analysis in NHANES III, 861 (6%) had CKD. The median follow-up for this cohort was 14.3 years. Adjusting for confounders, the 10-year all-cause mortality rate for individuals with CKD increased from 32% (95% CI: 29–35%) to 41% (36–47%) with the addition of periodontitis. For diabetes, the 10-year all-cause mortality rate increased to 43% (38–49%).

Conclusion: There is a strong, association between periodontitis and increased mortality in individuals with CKD. Sources of chronic systemic inflammation (including periodontitis) may be important contributors to mortality in patients with CKD.

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Key words: chronic kidney disease; NHANES; periodontitis; survival

Accepted for publication 24 December 2015

Chronic kidney disease (CKD) affects between 8 and 13% of the global population (Jha et al. 2013) and is associated with increased morbidity and mortality. Cardiovascular disease (CVD)-related events are the main cause of mortality in patients with CKD (Go et al. 2004) and systemic inflammation is recog-

Conflict of interest and source of funding statement

The authors declare that they have no competing interests. Praveen Sharma is funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship and Charles J. Ferro is funded by an NIHR Post-Doctoral Fellowship. The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

nized as a non-traditional risk factor associated with increased risk of CVD events in such patients (Menon et al. 2005).

Severe periodontitis is the sixth most common human disease (Kassebaum et al. 2014) causing micro-ulceration of the investing sulcular and pocket lining epithelium of affected teeth. The estimated surface area of this ulcerated epithelium approximates 40 cm^2 in severe disease (Nesse et al. 2008). Consequently, individuals with periodontitis have elevated systemic markers of acute-phase (C-reactive protein/CRP, Interleukin-6/IL-6) and oxidative stress (peripheral neutrophil hyperactivity) responses. This has potential systemic consequences and co-morbid effects that have been implicated in other disease processes such as diabetes and CVD (Chapple & Genco 2013, Tonetti & VanDyke 2013).

We have reported that patients with CKD have an increase in prevalence of periodontitis compared with community dwelling adults (Sharma et al. 2014). This finding is supported by a recent systematic review, reporting an association between periodontitis and CKD in several populations with a combined odds-ratio (OR) of 1.65 (95% confidence interval/CI: 1.53–2.01) (Chambrone et al. 2013).

Successful periodontal treatment can reduce levels of systemic inflammation in patients with and without CKD (D'Aiuto et al. 2004, Vilela et al. 2011, Siribamrungwong et al. 2014, Fang et al. 2015). However, the only investigations into associations between periodontitis and mortality rates (all-cause and CVD) in patients with CKD have involved relatively small numbers of patients (ranging from 122–253 patients) on haemodialysis and with a short follow-up period (ranging from 18 months to 6 years) (Kshirsagar et al. 2009, Chen et al. 2011, de Souza et al. 2014). In epidemiological studies reporting mortality outcomes from non-CKD populations some, (Garcia et al. 1998, Xu & Lu 2011, Linden et al. 2012) but not all, (Avlund et al. 2009, Kim et al. 2013) report a significant positive association between periodontitis and an increased mortality rate.

The aim of this study was to evaluate the association between periodontitis and other traditional risk factors (diabetes, hypertension and smoking status) and mortality (all-cause and CVD) in individuals with stage 3–5 CKD, compared to those without using robust, large-scale, population-based data.

Materials and Methods

Data source

Data were derived from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994), a representative survey of the civilian, non-institutionalized US population conducted by the National Center for Health Statistics (NCHS) of the Center for Disease Control and Prevention. Details of the survey design and methodology are available elsewhere (NCHS, 2006a). Briefly, individuals were interviewed at home, then invited to a mobile examination centre (MEC) for further interviews, tests and examinations.

Assessment of periodontal health

Details of the oral health component of NHANES III are published elsewhere (Drury et al. 1996). Briefly, detailed periodontal measurements were taken from volunteers aged 13 and over. The teeth were divided into two maxillary and two mandibular halves and measurements were taken from two sites per tooth (mid-buccal and mesio-buccal) for all teeth (excluding third molars) in one randomly chosen upper and lower quadrant. These measurements included periodontal probing depth (PPD), gingival recession and bleeding on probing (BOP). Clinical attachment loss (CAL) was calculated as the sum of the recession and PPD. Individuals receiving renal replacement therapy (through dialysis or kidney transplant) were excluded from periodontal examination.

Periodontitis was defined using the 2007 CDC/AAP (Centre for Disease Control and Prevention/American Academy of Periodontology) classification (Page & Eke 2007). In addition, continuous periodontal parameters were also employed such as mean PPD, mean CAL, cumulative periodontal probing depth (C-PPD), number of teeth present and proportion of sites that bled upon probing. Cumulative PPD was calculated as the sum of the maximum probing pocket depths ≥4 mm of each tooth and as such is a surrogate measure of the potential extent of biofilm exposed connective tissues (Dietrich et al. 2008). Edentulous individuals were included in the analyses but formed a group distinct from individuals with periodontitis.

Assessment of CKD

The serum creatinine levels recorded in the NHANES III survey were recalibrated to be traceable to an isotope-derived mass spectroscopy method using the equation below (NCHS, 2006b):

$$\text{Standardized creatinine} = (0.960 \times \text{serum creatinine}) - 0.18$$

Age, sex, ethnicity and standardized serum creatinine were incorporated in the CKD Epidemiology Collaboration (CKD-EPI) equation to calculate estimated glomerular filtration rate (eGFR) (Levey et al. 2009). This equation improves mortality risk stratification in individuals with CKD compared with the Modification of Diet in renal Disease (MDRD) equation (Shafi et al. 2012). Based on an eGFR<60 ml/min/1.73 m^2, individuals were classified as having stage 3–5 CKD, hitherto referred to as "CKD".

Urinary albumin and creatinine levels were employed to calculate the albumin-creatinine ratio (ACR). Details of the laboratory assays can be found elsewhere (NCHS, 2006b). Albuminuria was classified as ACR <30 mg/g; ACR ≥ 30 mg/g and <300 mg/g; and ACR ≥ 300 mg/g.

Assessment of traditional risk factors

Individuals were classed as hypertensive if their mean (of three consecutive measurements) systolic blood pressure (BP) was ≥140 mmHg or mean diastolic BP was ≥90 mmHg.

Individuals were classed as diabetic by self-reporting (excluding gestational diabetes) or if their glycated haemoglobin (HbA1C) was ≥6.5%.

Individuals' smoking status was determined from self-reporting and

classified into current, former or never smokers (cigarettes only).

Covariate data

Data on covariates employed in the statistical analyses included information on age, sex, ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American or Other), alcohol consumption (never, not in last year, between 0–14 drinks/week, more than 14 drinks/week) and self-reported history of previous cardiovascular events (stroke, heart attack or heart failure). Pulse pressure was calculated as the difference between the mean systolic and diastolic BP. Self- reported measures of socio-economic status (household income, marital status and educational attainment) were coded as follows. Household income (less than $20,000 or $20,000 or more); marital status (married or living as married, never married, divorced or separated or widowed); educational attainment (less than high school, high school diploma or more than high school). Body mass index (BMI) was coded as a categorical variable with BMI <18.5 kg/m^2 as underweight; ≥ 18.5 kg/m^2 and <25 kg/m^2 as normal; ≥ 25 kg/m^2 and <30 kg/m^2 as overweight and ≥ 30 kg/m^2 as obese. Laboratory tests including serum cholesterol (total and high-density lipoprotein/HDL) were performed. Serum cholesterol levels were classified into binary variables (total serum cholesterol ≥ 24 mg/L or <24 mg/L and serum HDL cholesterol ≤ 3.5 mg/L or >3.5 mg/L). Physical activity was self-reported by individuals and reclassified as "recommended or more" if they reported moderate activity five or more times a week or vigorous activity three or more times a week. Physical activity was also classified as "recommended or more" if individuals reported moderate physical activity four or more times a week and vigorous activity one or more times a week or reported moderate activity three or more times a week and vigorous activity two or more times a week. Individuals' physical activity was classified as "none" if they reported no leisure time physical activities. Individuals who reported some level of physical activity but less than recommended were classed as "less than recommended" (Beddhu et al. 2009).

Mortality data

The NCHS provide mortality data for NHANES III participants up to 31st December 2006, linked by probabilistic record matching with the National Death Index (NDI). The publicly available data set contains information on the mortality status of individuals aged 17 years or older. For individuals who are classified as "assumed deceased", information is available on 113 underlying cause of death categories, based on the ninth and tenth revisions of the International Classification of Diseases (ICD-9 and ICD-10). CVD mortality was limited to cases where the underlying cause of death was coded between 53 and 75 (inclusive) (Anderson et al. 2001). Details of the linked mortality data have been published elsewhere (NCHS, 2010).

Statistical analyses

Analyses performed followed guidelines for NHANES III (NCHS, 1996), accounting for the complex survey design and sampling weights to yield estimates generalizable to the US population. Differences in categorical and continuous data were assessed for statistical significance using Pearson Chi-square, *t*-test, Fisher's exact test and analysis of variance (ANOVA) as appropriate. Cox proportional hazards (PH) regression models were fitted to evaluate the association between periodontal status, traditional risk factors (diabetes, hypertension and smoking status) and all-cause and CVD mortality, independent of potential confounders. The fully adjusted model adjusted for age, sex, ethnicity, CKD status, periodontal status, diabetic status, hypertensive status, smoking status, pulse pressure, history of CVD (heart attack or stroke or heart failure), alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity and measures of socio-economic status (household income, marital status and educational attainment). The PH assumption was tested using Schoenfeld residuals, scaled Schoenfeld residuals and graphical methods. Variables were chosen to minimize missing data. Any individuals with missing covariate data were not included in the analyses (listwise deletion). Thus out of a possible 13,784 individuals eligible for analyses, 1379 (10%) individuals were excluded due to incomplete covariate data (Table S1).

We considered the effect measure modification of mortality (all-cause and cardiovascular) in individuals with CKD according to their periodontal health status. We conducted formal tests of interaction between periodontal variables and CKD case definition by entering interaction terms in the model. Further formal tests of interactions between CKD, periodontitis or edentulism and age, gender and ethnicity were also carried out.

Analyses were carried out using Stata/IC version 12.1 (StataCorp LP, College Station, TX, USA).

Results

Description of whole population and subpopulations

We analysed data from individuals in NHANES III aged 20 years and older with complete data on serum creatinine, periodontal status and mortality follow-up ($n = 13{,}784$) and with a median follow-up time of 14.3 years (mean 13.5 years, range 1 month–18.2 years). Of the 13,794 individuals included in the analyses, 861 (6%) were classified as CKD and 12,923 as non-CKD. Individuals with CKD were more likely to be older, have different ethnic and socio-economic mix, non-smokers (never or ex- smokers), diabetic, hypertensive, with higher total serum cholesterol and lower levels of serum HDL, report lower levels of physical activity and consume less alcohol and report a history of CVD (stroke, heart attack and congestive heart failure) compared to those without CKD. Individuals with CKD were more likely to suffer from periodontitis (or be edentulous) and have fewer teeth compared to individuals without CKD. When examining continuous variables of periodontal health, patients with CKD were more likely to have a greater mean CAL and greater BOP (Table 1).

Among individuals with CKD, those with periodontitis were more likely to be older, of non-white eth-

Table 1. Demographics of study population divided by CKD and periodontal status. Values are percentages (standard error) unless stated

Characteristics	No CKD (eGFR ≥ 60 ml/min/1.73 m^2) N = 12,923			CKD (eGFR<60 ml/min/1.73 m^2) N = 861			*p*-values*	*p*-values†
	Periodontal status			Periodontal status				
	Healthy n = 10,089 (78%)	Periodontitis n = 1637 (13%)	Edentulous n = 1197 (9%)	Healthy n = 357 (41%)	Periodontitis n = 172 (20%)	Edentulous n = 332 (39%)		
Assumed deceased							<0.001	<0.001
All-cause mortality	11	35	56	70	88	87		
Cardiovascular mortality	4	14	23	39	48	44		
Mean (SE) age (years)	41 (0.2)	55 (0.4)	67 (0.4)	73 (0.6)	75 (0.7)	77 (0.5)	<0.001	0.03
Female	55 (0.4)	37 (1.2)	54 (1.4)	54 (2.6)	45 (3.8)	55 (2.7)	0.95	0.07
Ethnicity							<0.001	<0.001
Non-Hispanic White	37 (0.5)	32 (1.2)	60 (1.4)	72 (2.4)	54 (3.8)	70 (2.5)		
Non-Hispanic Black	27 (0.4)	34 (1.2)	23 (1.2)	16 (2.0)	27 (3.4)	20 (2.2)		
Mexican American	31 (0.4)	30 (1.1)	13 (1.0)	8 (1.4)	17 (2.9)	6 (1.3)		
Other	4 (0.2)	3 (0.4)	4 (0.5)	3 (1.0)	2 (1.0)	3 (1.0)		
Current Smoker	24 (0.4)	39 (1.2)	29 (1.3)	8 (1.4)	13 (2.6)	12 (1.8)	<0.001	0.03
Diabetic	6.7 (0.2)	17.7 (0.9)	20.3 (1.2)	21.4 (2.2)	29.7 (3.5)	27.1 (2.4)	<0.001	0.04
Hypertensive	16 (0.3)	33 (1.2)	44 (1.4)	54 (2.6)	65 (3.6)	59 (2.7)	<0.001	0.01
Alcohol consumption							<0.001	0.07
Never	17 (0.4)	16 (0.9)	25 (1.3)	22 (2.2)	27 (3.5)	35 (2.6)		
Not in last year	33 (0.5)	40 (1.2)	49 (1.5)	47 (2.7)	51 (3.9)	53 (2.8)		
0–14 drinks/week	44 (0.5)	36 (1.2)	22 (1.2)	31 (2.5)	20 (3.1)	11 (1.8)		
>14 drinks/week	6 (0.2)	8 (0.7)	4 (0.5)	0.6 (0.4)	1 (0.8)	1 (0.5)		
History of stroke	1.1 (0.1)	3.5 (0.5)	4.8 (0.6)	9 (1.5)	10 (2.3)	14 (1.9)	<0.001	0.75
History of heart attack	1.9 (0.1)	5.1 (0.5)	7.8 (0.8)	12 (1.7)	15 (2.8)	17 (2.0)	<0.001	0.31
History of congestive heart failure	1.5 (0.1)	3.1 (0.4)	5.1 (0.6)	9 (1.5)	15 (2.7)	11 (1.7)	<0.001	0.07
Mean (SE) eGFR (ml/min/1.73 m^2)	107 (0.2)	96 (0.5)	87 (0.4)	49 (0.5)	47 (0.9)	48 (0.5)	<0.001	0.005
Mean (SE) ACR (mg/g)	19.8 (1.3)	53.5 (10.0)	63.2 (12.5)	211 (63.6)	276 (74.2)	320 (82.7)	<0.001	0.54
Mean (SE) BMI (kg/m^2)	27.1 (0.06)	27.6 (0.15)	27.0 (0.16)	27.5 (0.27)	26.8 (0.40)	26.5 (0.27)	0.27	0.16
Total serum cholesterol (≥24 mg/L)	25 (0.4)	35 (1.2)	44 (1.4)	50 (2.6)	47 (3.8)	48 (2.8)	<0.001	0.512
HDL cholesterol (≤3.5 mg/L)	11 (0.3)	17 (0.9)	13 (1.0)	18 (2.0)	16 (2.9)	20 (2.2)	<0.001	0.767
Pulse pressure (mm Hg)	47 (0.1)	56 (0.4)	63 (0.6)	68 (1.1)	74 (1.5)	74 (1.1)	<0.001	0.002
Marital status							<0.001	0.53
Married (or living as married)	63 (0.5)	65 (1.2)	57 (1.4)	56 (2.6)	51 (3.8)	45 (2.7)		
Never married	21 (0.4)	9 (0.7)	5 (0.6)	5 (1.2)	5 (1.6)	2 (0.8)		
Divorced or separated	11 (0.3)	13 (0.8)	11 (0.9)	8 (1.4)	11 (2.4)	5 (1.2)		
Widowed	5 (0.2)	12 (0.8)	26 (1.3)	31 (2.5)	33 (3.6)	48 (2.7)		
Household income (<$20,000)	43 (0.5)	57 (1.2)	66 (1.4)	55 (2.7)	68 (3.6)	72 (2.5)	<0.001	0.004
Educational status							<0.001	<0.001
Less Than High School	33 (0.5)	54 (1.2)	63 (1.4)	40 (2.6)	62 (3.7)	75 (2.4)		
High School Diploma (including GED)	33 (0.5)	28 (1.1)	26 (1.3)	30 (2.4)	22 (3.2)	16 (2.0)		
More Than High School	34 (0.5)	18 (1.0)	11 (0.9)	30 (2.5)	16 (2.8)	9 (1.6)		
Physical activity							<0.001	0.15
None	18 (0.4)	25 (1.1)	30 (1.3)	25 (2.3)	33 (3.6)	39 (2.7)		
Less than recommended	44 (0.5)	43 (1.2)	36 (1.4)	36 (2.5)	34 (3.6)	29 (2.5)		
Recommended or more	38 (0.5)	32 (1.2)	34 (1.4)	39 (2.6)	33 (3.6)	32 (2.7)		
Mean (SE) Teeth Present	26 (0.1)	21 (0.2)	0	18 (0.4)	17 (0.5)	0	<0.001	0.10
Mean (SE) CAL (mm)	0.9 (0.008)	3.1 (0.04)	N/A	1.6 (0.06)	3.6 (0.11)	N/A	<0.001	<0.001
Mean (SE) PPD (mm)	1.5 (0.004)	2.2 (0.02)	N/A	1.4 (0.2)	1.9 (0.6)	N/A	0.77	<0.001
Mean (SE) C-PPD (mm)	1.8 (0.04)	11.4 (0.3)	N/A	1.0 (0.2)	7.1 (0.8)	N/A	0.53	<0.001
BOP	11 (0.2)	18 (0.5)	N/A	14 (1.1)	19 (1.8)	N/A	<0.001	0.015

ACR, albumin-creatinine ratio; BMI, body mass index; BOP, percentage of sites that bleed on probing; CAL, clinical attachment loss; C-PPD, cumulative probing depth; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; PPD, periodontal probing depth.

*Comparing no CKD and CKD.

†Within individuals with CKD, comparing healthy and periodontitis.

nicity, current smokers, diabetic and hypertensive and have a lower eGFR compared to periodontally healthy individuals. These individuals also had lower household incomes and educational attainments compared to periodontally healthy individuals. Periodontally healthy individuals were similar to those with periodontitis in terms of their sex, alcohol consumption, marital status, physical activity, history of CVD events and BMI (Table 1).

All-cause mortality

After adjusting for covariates, individuals with CKD had a 44% (95% CI: 28–63%) increased rate of all-cause mortality compared to those without CKD (Table 2). Individuals with periodontitis had a 36% (22–51%) increased rate of all-cause mortality compared to individuals who were periodontally healthy.

The association between periodontitis and all-cause mortality was similar between individuals with or without CKD (p-value for interaction = 0.57). Similarly, the associations between CKD and all-cause mortality did not vary by age, sex or diabetes status (p-values for interaction 0.14, 0.99 and 0.09 respectively). Furthermore, the association between periodontitis and all-cause mortality did not vary by age, gender or diabetes status (p-values for interaction 0.73, 0.51 and 0.51 respectively). In edentulous individuals, there was a significant difference in all-cause mortality by age. Edentulous individuals under the age of 65 had a significantly increased rate of all-cause mortality compared to edentulous individuals 65 years and older, hazard ratio (HR) 1.85 (1.41–2.44) and 1.18 (1.04–1.33) respectively (Tables S2, S3 and Fig. S1).

For continuous measures of periodontitis in fully adjusted models, an increased mortality rate was seen with worsening periodontal health in a dose-dependent manner. For example a 1 mm increase in mean PPD was associated with a 17% (6–28%) increase in incident rate of all-cause mortality (Table 2). Edentulousness was associated with a 32% (17–50%) increased rate of all-cause mortality compared with periodontally healthy dentate individuals.

Diabetes (HR 1.41; 1.27–1.57), hypertension (HR 1.06; 0.93–1.20) and current smoking (HR 2.12; 1.82–2.48) were associated with an increased rate of all-cause mortality although this increase was not significant for hypertension (Table 2).

The 10-year all-cause mortality for individuals with CKD (but without periodontitis or other traditional risk factors) was 32% (29–35%). Addition of periodontitis to the risk profile increased 10-year mortality to 41% (36–47%). This increase in mortality was comparable with that seen in individuals with CKD who had diabetes instead of periodontitis (43%; 38–49%). A similar cumulative effect on mortality is seen with periodontitis and other traditional risk factors (Table 3). These estimates are based on the demographic features of individuals with CKD within NHANES III (e.g. a mean age of 73 years). Estimated survival curves for individuals with CKD and different risk factor profiles is given in Fig. 1.

Cardiovascular mortality

After adjusting for covariates, individuals with CKD had a 60% (32–95%) increased rate of CVD mortality compared to those without CKD (Table 2), independent of confounders specified. Individuals with periodontitis had a 38% (16–65%) increased rate of CVD mortality compared to individuals who were periodontally healthy. The association between periodontitis and CVD

Table 2. Results from Cox proportional hazards regression analyses for all-cause and cardiovascular mortality using an age and sex-adjusted and a fully adjusted model

	Hazard Ratio (95% CI) of All-cause mortality		Hazard Ratio (95% CI) of Cardiovascular mortality	
	Age adjusted	Fully adjusted	Age adjusted	Fully adjusted
CKD	1.58 (1.39–1.80)	1.44 (1.28–1.63)	1.81 (1.55–2.14)	1.60 (1.32–1.95)
Periodontal status				
Healthy	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Periodontitis	1.78 (1.59–2.00)	1.36 (1.22–1.51)	1.79 (1.52–2.11)	1.38 (1.16–1.65)
Edentulous	1.83 (1.64–2.05)	1.32 (1.17–1.50)	1.47 (1.24–1.73)	1.05 (0.85–1.29)
Continuous periodontal variables				
Mean PPD (per mm)	1.48 (1.35–1.62)	1.17 (1.06–1.28)	1.51 (1.34–1.72)	1.21 (1.05–1.40)
Mean CAL (per mm)	1.20 (1.16–1.25)	1.09 (1.05–1.14)	1.16 (1.11–1.22)	1.05 (0.99–1.12)
C-PPD (per 10 mm)	1.29 (1.20–1.38)	1.08 (1.01–1.17)	1.35 (1.19–1.54)	1.16 (0.99–1.35)
BOP (per 10%)	1.10 (1.07–1.13)	1.05 (1.02–1.08)	1.10 (1.06–1.13)	1.05 (1.01–1.09)
Diabetes	1.85 (1.63–2.10)	1.41 (1.27–1.57)	2.00 (1.71–2.35)	1.45 (1.24–1.70)
Hypertension	1.28 (1.15–1.43)	1.06 (0.93–1.20)	1.52 (1.31–1.77)	1.32 (1.06–1.63)
Smoking status				
Never	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Former	1.41 (1.23–1.60)	1.25 (1.09–1.43)	1.32 (1.11–1.56)	1.18 (0.98–1.42)
Current	2.70 (2.35–3.09)	2.12 (1.82–2.48)	2.44 (2.05–2.91)	2.10 (1.69–2.62)

BOP, proportion of sites that bleed on probing; CAL, clinical attachment loss; CKD, chronic kidney disease; C-PPD, cumulative periodontal probing depth; PPD, periodontal probing depth.
Fully adjusted model adjusted for age, sex, ethnicity, CKD status, periodontal status, diabetic status, hypertensive status, smoking status, pulse pressure, history of CVD (heart attack or stroke or heart failure), alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity and measures of socio-economic status (household income, marital status and educational attainment).

Table 3. Ten-year all-cause mortality (percentages) of individuals with CKD by risk factors (along with the addition of periodontitis to the risk factor)

Risk factor	10-year all-cause mortality (95% CI) without periodontitis	10-year all-cause mortality (95% CI) with periodontitis
CKD	32% (29–35%)	41% (36–47%)
CKD + Diabetes	43% (38–49%)	55% (47–63%)
CKD + Hypertension	34% (29–39%)	44% (37–52%)
CKD + Smoking	58% (51–65%)	71% (62–79%)

Fully adjusted model adjusted for age, sex, ethnicity, CKD status, periodontal status, diabetic status, hypertensive status, smoking status, pulse pressure, history of CVD (heart attack or stroke or heart failure), alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity and measures of socio-economic status (household income, marital status and educational attainment).

mortality was similar between individuals with or without CKD (p-value for interaction = 0.27). The associations between CKD and CVD mortality did not vary by age, sex or diabetes status (p-values for interaction 0.39, 0.82 and 0.34 respectively). The association between periodontitis and CVD mortality did not vary by gender or diabetes status (p-values for interaction 0.77 and 0.17 respectively). There was a trend in patients with CKD and periodontitis to have an increased HR of CVD mortality if they were under the age of 65 compared with 65 and over but this was not significant. In edentulous individuals, there was a significant difference in CVD mortality by age. Edentulous individuals under the age of 65 having a significantly increased rate of CVD mortality, HR 2.03 (1.31–3.13), compared to edentulous individuals 65 years and older who had comparable rates of CVD mortality compared to periodontally healthy individuals, HR 0.89 (0.71–1.10) (Tables S4, S5 and Fig. S2).

For continuous measures of periodontal health, mean PPD and percentage of sites that bleed on probing were associated with a statistically significant increase in the rate of CVD mortality (Table 2). Edentulous and periodontally healthy dentate individuals had comparable rates of CVD mortality (Table 2).

Diabetes (HR 1.45; 1.24–1.70), hypertension (HR 1.32; 1.06–1.63) and current smoking (HR 2.10; 1.69–2.62) were associated with an increased rate of CVD mortality (Table 2).

The 10-year CVD mortality for individuals with CKD (and combinations of risk factors) highlights the similarity in the magnitude of increase in CVD mortality associated with diabetes (24%; 19–30%) compared with periodontitis (22%; 19–27%) (Table 4). Estimated CVD survival for individuals with CKD and

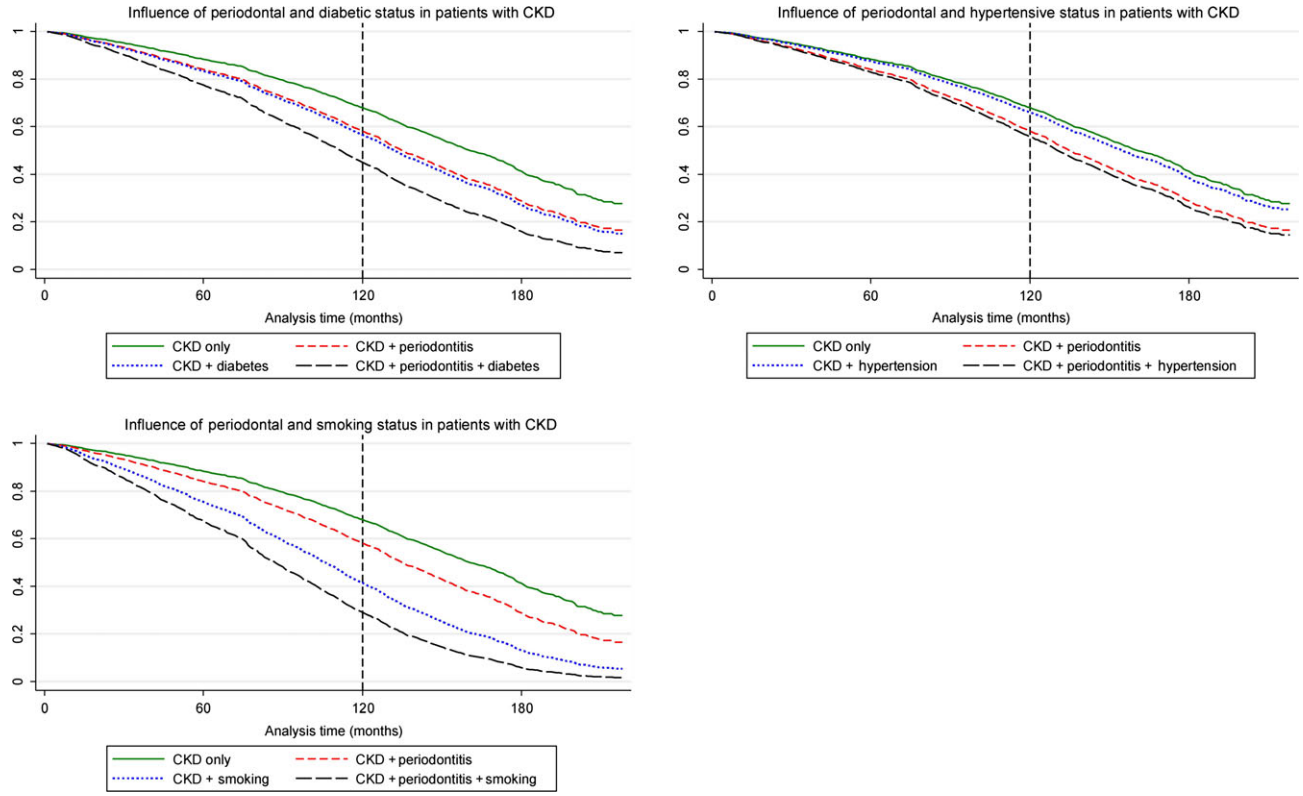

Fig. 1. For all-cause mortality. Cox proportional hazard regression graphs (adjusting for age, sex, ethnicity, pulse pressure, history of CVD, alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity, household income, marital status and educational attainment) of survival in patients with CKD stratified using periodontitis and other traditional risk factors (diabetes, hypertension and smoking). The reference lines indicate 10 year survival.

Table 4. Ten-year CVD mortality (percentages) of individuals with CKD by risk factors (along with the addition of periodontitis to the risk factor)

Risk factor	10-year CVD mortality (95% CI) without periodontitis	10-year CVD mortality (95% CI) with periodontitis
CKD	16% (14–19%)	22% (19–27%)
CKD + Diabetes	24% (19–30%)	32% (27–39%)
CKD + Hypertension	21% (16–28%)	29% (22–37%)
CKD + Smoking	33% (24–44%)	43% (32–56%)

Fully adjusted model adjusted for age, sex, ethnicity, CKD status, periodontal status, diabetic status, hypertensive status, smoking status, pulse pressure, history of CVD (heart attack or stroke or heart failure), alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity and measures of socio-economic status (household income, marital status and educational attainment).

different risk factor profiles is given in Fig. 2.

Discussion

In this large cohort, representative of the US population from which it was derived, CKD was associated with increased rates of all-cause mortality and CVD mortality, independent of periodontitis, traditional risk factors and other confounders. Periodontitis was associated with increased rates of all-cause and CVD mortality comparable with, but independent of, that associated with diabetes (Tables 2–4; Figs 1 and 2). There was an increased rate of all-cause mortality but not CVD mortality in edentulous individuals with CKD compared with periodontally healthy dentate individuals. The association between edentulousness and CVD mortality was significant in a subgroup of edentulous individuals under the age of 65. Given the high prevalence of chronic periodontitis in patients with CKD (Chambrone et al. 2013), our results suggest that periodontitis may be an important non-traditional risk factor for CVD and all-cause mortality in these patients, and interestingly contributing to the increased risk to a similar extent as diabetes.

The strengths of this study are its large population-based sampling with robust sampling methodology which allow the results from this analysis to be generalized to the US population. The detailed clinical, demographic and anthropomorphic data collected allows for many of the known covariates to be accounted for in the Cox proportional hazards regression model, generating more accurate point estimates. The length of follow-up for this study is its final strength and allows for the pragmatic assessment of long term, hard outcomes (all-cause and CVD mortality). The

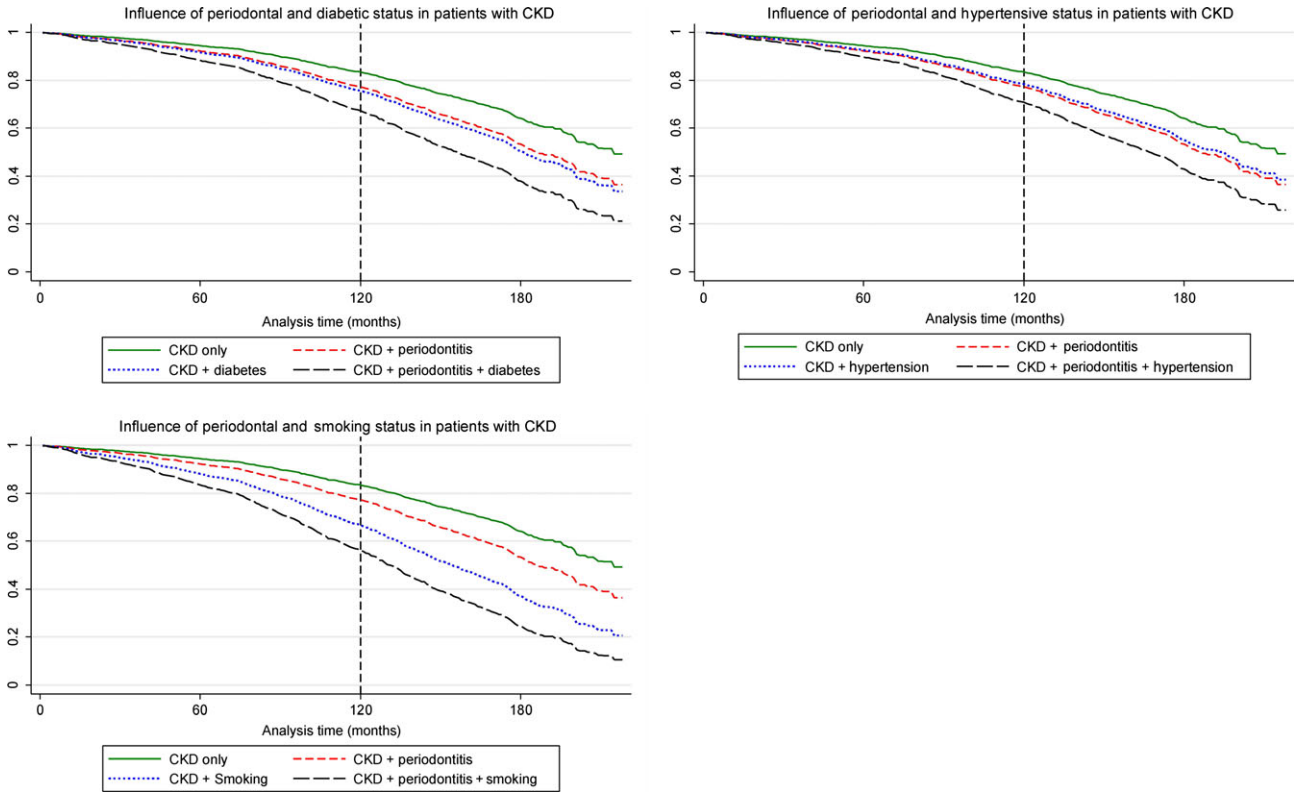

Fig. 2. For cardiovascular mortality. Cox proportional hazard regression graphs (adjusting for age, sex, ethnicity, pulse pressure, history of CVD, alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity, household income, marital status and educational attainment) of survival in patients with CKD stratified using periodontitis and other traditional risk factors (diabetes, hypertension and smoking). The reference lines indicate 10-year survival.

limitations of this study include the lack of longitudinal examination of individuals. Unfortunately, in NHANES, the longitudinal data is limited to the mortality status of patients derived from the National Death Index. Data on variables were only gathered at inception and therefore changes in variables (periodontal, diabetes, smoking status, etc) are not ascertainable. Analyses were carried out on the assumption that characteristics did not change between inception and time to death or censoring. Some individuals with periodontitis are likely to have received treatment and/or lost teeth during follow-up, resulting in disease misclassification over time. Furthermore, periodontal measurements from NHANES III are known to underestimate the prevalence of periodontitis by 13.4% (absolute) or 60% (relative) (Eke et al. 2010). The results of this study may therefore under-estimate the association between periodontitis and mortality in CKD. Also, as with any multivariable regression analysis, the issue of residual confounding from inaccurate measurement or categorization of variables or confounding from variables not included in the analysis cannot be ruled out.

Previous studies investigating the link between mortality and periodontitis in patients with CKD have done so in patients on haemodialysis (Kshirsagar et al. 2009, Chen et al. 2011, de Souza et al. 2014). Apart from the small sample sizes (122–253 patients) and shorter follow-up period (18 months to 6 years), these studies differed significantly from the present analysis as individuals receiving RRT (through chronic dialysis or a functioning kidney transplant) were not included in the present analysis (RRT was an exclusion criteria for periodontal examination in NHANES III). Hence, even though these studies demonstrate an association between periodontitis and mortality, thereby lending support to the current findings, the results cannot be directly compared.

A putative mechanism for a possible link between periodontitis and increased all-cause and CVD mortality is via the increased systemic acute-phase and oxidative stress burden. This increased burden is seen in individuals with periodontitis and CKD (Ioannidou et al. 2011) and individuals with periodontitis who do not have CKD (D'Aiuto et al. 2004, Chapple & Genco 2013). Increased systemic inflammatory and oxidative stress burdens increase the incidence of CVD events in patients with CKD (Arici & Walls 2001, Mathew et al. 2008, Li et al. 2015). This mechanism is supported by the association demonstrated here between increased risk of CVD mortality and measures of active periodontitis (periodontitis case definition, mean PPD and BOP), as opposed to measures of historical periodontitis (edentulousness and mean CAL), where there was a lack of association (Table 2). However, at least part of the association between periodontitis and CVD may also be due to common risk factors such as smoking and diabetes (Dietrich et al. 2008, Mucci et al. 2009). The increase in all-cause mortality in edentulous individuals compared to periodontally healthy dentate individuals, as reported here and also by other investigators in non-CKD cohorts (Brown 2009), may be due to several factors. Patients are rendered edentulous for a variety of reasons including periodontitis, with approximately 50% of teeth being extracted due to periodontal disease (Phipps & Stevens 1995). As approximately half of all tooth extractions are for reasons other than periodontal disease, edentulousness may act as a surrogate marker of general health attitudes and/or behaviours, limited healthcare access or other socio-economic measures (Joshipura & Ritchie 2005). This might also explain the association between edentulousness and CVD mortality in patients under the age of 65 who might have such characteristics and attitudes towards healthcare that render them edentulous before the age of 65.

The biological mechanisms underpinning the relationship between periodontitis and increased mortality in individuals with CKD form a promising area of research and may produce mechanistic targets leading to risk stratification and novel interventions. Ongoing longitudinal studies (Stringer et al. 2013) investigating large cohorts of patients with pre-dialysis CKD may provide confirmation of this association and shed light upon explanatory mechanisms. Successful treatment of periodontitis has been shown to improve surrogate markers of CVD risk, including serum markers of systemic inflammation (CRP, IL-6) (D'Aiuto et al. 2004), endothelial function as measured by flow-mediated dilatation (FMD) and endothelial-activation markers such as soluble E-selectin and von Willebrand factor (Tonetti et al. 2007). Two randomized controlled trials of periodontal interventions in patients with CKD have been carried out but limited to cohorts of haemodialysis patients. These have produced conflicting results either not demonstrating changes in inflammatory markers following periodontal intervention (Wehmeyer et al. 2013) or demonstrating that significant reductions in inflammatory markers can be achieved following periodontal therapy (Fang et al. 2015). Currently, patients with CKD are managed to strict targets concerning glycaemic control (diabetes) and control of hypertension and smoking cessation to improve outcomes. If a causal link is established between periodontitis and increased rates of adverse outcomes in CKD patients, then establishing and maintaining periodontal health may become an important part of the care pathway of patients with CKD.

Acknowledgements

The team thanks the members of the NCHS and CDC for collecting this data and making it publically available. We would also like to thank the individuals who participated in this survey.

Finally, the team would like to acknowledge the statistical input of Miss Danielle Burke (Biostatistician, School of Dentistry, University of Birmingham, UK).

Disclosures

None.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Cox PH regression graphs for all-cause mortality in individuals with periodontitis/edentulism and CKD by age category

Figure S2 Cox PH regression graphs for CVD mortality in individuals with periodontitis/edentulism and CKD by age category.

Table S1 Numbers of participants (and percentage) with missing data in variables included in statistical model.

Table S2 Exploring the interactions between CKD (stage 3–5), periodontal variables and age, gender and diabetes status for all-cause mortality.

Table S3 Hazard ratios (95% CI) and 10-year survival (95% CI) of all-cause mortality by subgroups of age (<65 years of age and ≥65 years of age).

Table S4 Exploring the interactions between CKD (stage 3–5), periodontal variables and age, gender and diabetes status for CVD mortality.

Table S5 Hazard ratios (95% CI) and 10-year survival (95% CI) of CVD mortality by subgroups of age (<65 years of age and ≥65 years of age).

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Clinical Relevance

Scientific rationale for the study: CKD prevalence and complications cannot be entirely explained by traditional risk factors such as diabetes or cardiovascular disease (CVD). Periodontitis is independently associated with CKD and contributes to the systemic inflammatory burden, therefore this study aimed to establish the association between periodontitis and mortality in patients with chronic kidney disease (CKD).

Principal findings: Periodontitis was associated with a 9% (absolute) or 28% (relative) increase in all-cause mortality at 10 years for individuals with CKD, within the limitation of this analysis. This association is of a similar magnitude, but independent of, that seen between diabetes and mortality in individuals with CKD.

Practical implications: Periodontitis may be an important predictor of mortality in patients with CKD and sources of chronic inflammation (including periodontitis) may be important contributors beyond traditional risk factors in patients with CKD.