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Original Investigation

Dental Health and Mortality in People With End-Stage Kidney Disease Treated With Hemodialysis: A Multinational Cohort Study

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Background: Dental disease is more extensive in adults with chronic kidney disease, but whether dental health and behaviors are associated with survival in the setting of hemodialysis is unknown.

Study Design: Prospective multinational cohort.

Setting & Participants: 4,205 adults treated with long-term hemodialysis, 2010 to 2012 (Oral Diseases in Hemodialysis [ORAL-D] Study).

Predictors: Dental health as assessed by a standardized dental examination using World Health Organization guidelines and personal oral care, including edentulousness; decayed, missing, and filled teeth index; teeth brushing and flossing; and dental health consultation.

Outcomes: All-cause and cardiovascular mortality at 12 months after dental assessment.

Measurements: Multivariable-adjusted Cox proportional hazards regression models fitted with shared frailty to account for clustering of mortality risk within countries.

Results: During a mean follow-up of 22.1 months, 942 deaths occurred, including 477 cardiovascular deaths. Edentulousness (adjusted HR, 1.29; 95% CI, 1.10-1.51) and decayed, missing, or filled teeth score $\geq$ 14 (adjusted HR, 1.70; 95% CI, 1.33-2.17) were associated with early all-cause mortality, while dental flossing, using mouthwash, brushing teeth daily, spending at least 2 minutes on oral hygiene daily, changing a toothbrush at least every 3 months, and visiting a dentist within the past 6 months (adjusted HRs of 0.52 [95% CI, 0.32-0.85], 0.79 [95% CI, 0.64-0.97], 0.76 [95% CI, 0.58-0.99], 0.84 [95% CI, 0.71-0.99], 0.79 [95% CI, 0.65-0.95], and 0.79 [95% CI, 0.65-0.96], respectively) were associated with better survival. Results for cardiovascular mortality were similar.

Limitations: Convenience sample of clinics.

Conclusions: In adults treated with hemodialysis, poorer dental health was associated with early death, whereas preventive dental health practices were associated with longer survival.

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INDEX WORDS: Renal failure; end-stage kidney disease; hemodialysis; oral health; oral hygeine; dental disease; all-cause mortality; cardiovascular mortality; modifiable risk factor; ORAL-D (Oral Diseases in Hemodialysis) Study.

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Chronic kidney disease (CKD) is responsible for approximately 12 billion years of life lost to premature mortality or lived with disability each year.[1] Patients with end-stage kidney disease treated with dialysis have a particularly heavy burden of severe symptoms[2] and can expect to live for only 4 to 5 years on average.[3,4] Despite decades of research, no treatment strategies have been shown to improve critical health outcomes, such as mortality, in people with end-stage kidney disease.

Oral health represents a potential determinant of health outcomes in people with end-stage kidney disease. Dental conditions such as caries, tooth loss, and poor oral hygiene are nearly universal worldwide, particularly affecting disadvantaged populations,[5,6] and are associated with excess mortality, including cardiovascular and cancer-related deaths.[7-9] Adults who have CKD have more severe oral disease than the general adult population,[10] yet infrequently use dental services.[11] Oral disease is associated with inflammation and malnutrition, which may accelerate cardiovascular disease in the setting of dialysis treatment, and therefore represents a putative etiology for cardiovascular events in the context of kidney failure.[12,13]

To our knowledge, the Oral Diseases in Hemodialysis (ORAL-D) Study[14] is the first cohort study to investigate whether oral disease using standardized assessments of dental disease and preventative dental health practices are associated with early death independent of existing cardiovascular disease and other sociodemographic factors.

METHODS

Study Population and Data Source

The ORAL-D Study included consecutive adults 18 years or older who had been treated with long-term hemodialysis within a convenience sample of clinics operated by a single dialysis provider in Europe (France, Hungary, Italy, Poland, Portugal, and Spain) and South America (Argentina).[14] We enrolled participants from July 2010 to February 2012. Patients were not enrolled if they had cognitive impairment sufficient to preclude consent or they preferred not to participate.

Demographic, clinical, laboratory, and dialysis-related data were obtained from linked databases using a unique identification code. All participants underwent a standardized oral examination by a dentist trained in periodontology, according to World Health Organization (WHO) guidelines.[15] All dentists participated in a teleconference to calibrate the protocol before examining patients. All participants anonymously completed questionnaires about self-reported dental care practices.[16] The exposures in analyses were edentulousness (complete absence of teeth), extent of dental disease (decayed, missing, or filled teeth), brushing teeth, dental flossing, use of mouthwash, frequency of changing toothbrush, time spent each day on oral hygiene, age of first visit to a dental practitioner, and time elapsed since the most recent dental visit.

Data for total and cause-specific mortality were obtained from a centralized database in which changes to patient status were updated by managing clinicians on a monthly basis. Cardiovascular death was adjudicated by participants' treating clinicians, who were unaware of dental exposures. Deaths were classified as due to cardiovascular causes when they were a sudden death or death attributed to acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema, congestive cardiac failure, or cerebrovascular accident, including intracranial hemorrhage, ischemic brain damage including anoxic encephalopathy, or mesenteric infarction or ischemia of the bowel. The primary outcome defined a priori was all-cause mortality and the secondary outcome was death due to cardiovascular causes. Patients who withdrew from the study, underwent kidney transplantation, were lost to follow-up, or survived were censored.

Ethics Approval

We received ethics approval for the ORAL-D Study from the following responsible local human research ethics committees: Comitè de Protection des Personnes Sud-Mediterranèe II (France), Komisja Bioetyczna, Slaskiego Uniwersytetu Medycznego W Katowicach (Poland), CE da Diaverum Portugal (Portugal), Comite Etico de Investigacion Clinica (CEIC) de la Fundaction Puigvert and Agencia Valenciana de Salud, Departament de Salut Valencia (Spain), and Szegedi Tudomanyegyetem, Szent-Gyorgyi albert klinikai kozpont, and Regionalis human orvosbiologiai kutatasetikai bizottsaga (Hungary). Ethics approval was not required in Italy or Argentina. The study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc). $P < 0.05$ was considered statistically significant.

Dental disease characteristics and health care practices were considered as time-fixed binary variables throughout the follow-up period. In all participants, we did analyses for extent of edentulousness and the decayed, missing, or filled teeth index; in dentate participants, we did analyses for brushing teeth, using mouthwash or dental floss, frequency of changing a toothbrush, time spent on oral hygiene, age of starting dental care, and time elapsed since last dental checkup. We also considered analyses for the number of decayed, missing, or filled teeth as a categorical variable according to the WHO classification and as a continuous exposure variable. In survival analyses, we included participants who had complete data for all oral health exposure variables (n = 4,054 participants overall, including n = 3,243 dentate participants).

Event rates for study outcomes were calculated for each dental exposure category, reporting Kaplan-Meier estimates. Time-to-event cumulative incidence Kaplan-Meier curves were plotted across dental exposure variables. Because there was heterogeneity in risks of survival (all-cause and cardiovascular mortality) among countries ($P < 0.001$), we then applied random-effects Cox proportional hazard models fitted using shared frailty to account for within-country clustering of mortality risk to estimate associations among dental status, oral hygiene and dental care variables, and risk of early all-cause and cardiovascular mortality. We used a lognormal distribution in the frailty model. In multivariable-adjusted models, we controlled for the following baseline factors: age, sex, race, smoking history, self-reported family income, prior myocardial infarction, diabetes, dialysis vintage, and mean arterial blood pressure, hemoglobin, and serum phosphorus values. The proportional hazards assumption in all Cox models was assessed by fitting log (time)-dependent covariates in the multivariable model and checking graphically by plotting Schoenfeld residuals, but no variable violated the proportionality assumption. We did not impute missing data.

In sensitivity analyses, we considered competing risks for death attributable to cardiovascular causes from other causes of death.

Table 1. Demographic, Socioeconomic, Clinical, and Dialysis Characteristics of Participants

	Overall (N = 4,205)	Dentate (n = 3,338)	Edentulous (n = 867)
Demographics			
Age, y	61.6 ± 15.6	59.1 ± 15.8	71.1 ± 10.7
Country			
Italy	593 (14.1)	409 (12.3)	184 (21.2)
Spain	189 (4.5)	122 (3.7)	67 (7.7)
France	48 (1.1)	39 (1.2)	9 (1.0)
Portugal	762 (18.1)	633 (19.0)	129 (14.9)
Poland	319 (7.6)	239 (7.2)	80 (9.2)
Hungary	550 (13.1)	415 (12.4)	135 (15.6)
Argentina	1,744 (41.5)	1,481 (44.4)	263 (30.3)
Male sex	2,426 (57.7)	1,968 (59.0)	458 (52.8)
European	3,987 (94.8)	3,145 (94.6)	842 (97.1)
Ever smoker	1,029 (33.4)	789 (32.9)	240 (35.3)
Socioeconomic characteristics			
Married	2,161 (55.0)	1,694 (54.0)	467 (58.8)
Secondary education	1,139 (38.1)	926 (39.9)	213 (32.1)
Employed	387 (12.8)	366 (15.5)	21 (3.1)
Family income > domestic average	313 (8.0)	238 (7.7)	75 (9.2)
Comorbid conditions at baseline			
Myocardial infarction	348 (12.5)	250 (11.6)	98 (16.1)
Stroke	287 (10.3)	213 (9.8)	74 (12.2)
Diabetes mellitus	933 (32.0)	673 (29.9)	260 (39.5)
Laboratory variables			
Serum albumin, g/L	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.4
Serum phosphorus, mg/dL	4.6 ± 1.5	4.7 ± 1.5	4.3 ± 1.3
Serum calcium, mg/dL	8.8 ± 0.8	8.7 ± 0.8	8.8 ± 0.8
Hemoglobin, g/dL	11.1 ± 1.3	11.1 ± 1.4	11.2 ± 1.3
Dialysis variables			
Dialysis vintage, mo	60 [38-98]	62 [39-100]	56 [36-90]
Kt/V[a]	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.3
Urea reduction ratio	0.8 ± 0.06	0.8 ± 0.06	0.8 ± 0.06
Mean arterial pressure, mm Hg	90.0 ± 13.5	90.2 ± 13.7	89.3 ± 12.9

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229. Proportions do not always correspond to overall numbers of participants due to missing data. Missing data, with number of participants with missing data (percentage) for each reported variable: age, 0 (0%); sex, 0 (0%); country, 0 (0%); race, 0 (0%); smoking history, overall, 1,129 (26.8%), dentate, 941 (28.2%), edentulous, 188 (21.7%); marital status, overall, 273 (6.5%), dentate, 199 (6.0%), edentulous, 74 (8.5%); education, overall, 1,218 (29.0%), dentate, 1,015 (30.4%), edentulous, 203 (23.4%); employment, overall, 1,178 (28.0%), dentate, 981 (29.4%), edentulous, 197 (22.7%); income, overall, 304 (7.2%), dentate, 256 (7.7%), edentulous, 48 (5.5%); myocardial infarction, overall, 1,435 (34.1%), dentate, 1,175 (35.2%), edentulous, 260 (30.0%); stroke, overall, 1,435 (34.1%), dentate, 1,175 (35.2%), edentulous, 260 (30.0%); diabetes, overall, 1,293 (30.8%), dentate, 1,085 (32.5%), edentulous, 208 (24.0%); serum albumin, overall, 896 (21.3%), dentate, 697 (20.9%), edentulous, 199 (23.0%); serum phosphorus, overall, 450 (10.7%), dentate, 359 (10.8%), edentulous, 91 (10.5%); serum calcium, overall, 444 (10.6%), dentate, 354 (10.6%), edentulous, 90 (10.4%); hemoglobin, overall, 446 (10.6%), dentate, 357 (10.7%), edentulous, 89 (10.3%); dialysis vintage, 0 (0%); Kt/V, overall, 498 (11.8%), dentate, 405 (12.1%), edentulous, 93 (10.7%); urea reduction ratio, overall, 498 (11.8%), dentate, 405 (12.1%), edentulous, 93 (10.7%); mean arterial pressure, overall, 423 (10.1%), dentate, 339 (10.2%), edentulous, 84 (9.7%).

[a]Kt/V refers to clearance of urea and is a measure of amount of dialysis received.

We considered the event of interest (cardiovascular death) and other competing events (such as death related to infection) as events and then calculated the Kaplan-Meier estimate of overall events. To assess the effect of including edentulous patients in the survival analyses for the extent of decayed, missing, or filled teeth, we additionally performed analyses excluding edentulous patients. Finally, we included first-order interaction terms with combinations of all independent predictors introduced into the multivariable model one at a time to assess heterogeneity of associations across different population subgroups.

RESULTS

Participant Characteristics

Of 4,726 patients eligible in the dialysis network, 521 (11.0%) were subsequently excluded because they did not receive the dental component of their oral examination (n = 113) or lacked data for centralized registry linkages (n = 408), leaving 4,205 participants in the analyses. Information about demographic,

Table 2. Baseline Dental Characteristics, Oral Hygiene Habits, and Dental Care Practices

Parameter	Value
Dental health in all, N = 4,205	
Edentulous	867 (20.6)
No. of teeth	16.8 ± 9.0
Decayed, missing, filled teeth index[a]	19.3 ± 8.6
Decayed, missing, or filled teeth index ≥ 14[a]	3,234 (77.5)
Oral hygiene practices in dentate patients	
Use of dental floss	268/3,283 (8.2)
Use of mouthwash	1,216/3,282 (37.0)
Brushing teeth daily	3,002/3,281 (91.5)
Oral hygiene ≥2 min daily	2,036/3,268 (62.3)
Change toothbrush every 3 mo or less	1,222/3,259 (37.5)
Dental care practices in dentate patients	
Age of first dental visit < 30 y	2,024/3,277 (61.8)
Time elapsed since last dental visit < 6 mo	983/3,284 (29.9)

Note: Values are given as number (percentage), mean ± standard deviation, or no. of participants with exposure/total no. of participants included in analyses (percentage).

[a]The decayed, missing, and filled teeth index is categorized according to World Health Organization criteria as very low, <5; low, 5-8.9; moderate, 9-13.9; and high, ≥14.

clinical, and oral health characteristics for participants excluded from the analyses are provided in Tables S1 and S2 (available as online supplementary material). Table 1 displays baseline characteristics of included participants according to the presence or complete absence of teeth (edentulousness), and dental characteristics and care practices are shown in Table 2. Mean age of the cohort was 62 ± 16 (standard deviation) years, and 58% of participants were men.

Dental Characteristics of Study Participants

Overall, 867 (20.6%) participants were edentulous. Edentulous patients were older, were more often female, had lower levels of education and employment, and more frequently had cardiovascular comorbid conditions. Dentate patients had 16.8 teeth on average, with more than two-thirds demonstrating extensive dental disease (14 or more decayed, missing, or filled teeth). Fewer than 10% used dental floss, about one-third used mouthwash, most brushed their teeth at least daily, about one-third changed their toothbrush at least every 3 months, and approximately two-thirds spent 2 minutes or more daily on oral hygiene. Most had visited a dentist before the age of 30 years and about one-third had consulted a dental practitioner within the previous 6 months.

Association of Dental Health and Behaviors With Survival

Mean follow-up was 22.1 (range, 1.3-36.2) months. In total, there were 942 deaths, including 477 cardiovascular deaths, during 7,737 person-years of follow-up (overall mortality rate, 122/1,000 person-years). Figures 1 and 2 show survival curves for each dental characteristic during the course of follow-up. The proportion of patients who died was higher with edentulousness and dental disease. In addition, fewer patients who had more frequent oral hygiene care and dental practitioner consultation died. The estimated proportion of participants who died (total and cardiovascular-related mortality) at 1, 2, and 3 years of follow-up according to the presence of oral disease or oral health practice is shown in Table 3. The proportion of patients who died was similar regardless of age at first dental consultation.

Table 4 shows adjusted hazard ratios (HRs) for mortality by dental health measures. In adjusted analyses, edentulousness (adjusted HR, 1.29; 95% confidence interval [CI], 1.10-1.51) and extensive dental disease (≥14 decayed, missing, or filled teeth: HR, 1.70; 95% CI, 1.33-2.17) were associated with increased mortality, while dental flossing, using mouthwash, brushing teeth daily, spending 2 minutes or more on oral hygiene, changing a toothbrush at least every 3 months, and visiting a dentist within the past 6 months were all associated with longer survival (adjusted HRs of 0.52 [95% CI, 0.32-0.85], 0.79 [95% CI, 0.64-0.97], 0.76 [95% CI, 0.58-0.99], 0.84 [95% CI, 0.71-0.99], 0.79 [95% CI, 0.65-0.95], and 0.79 [95% CI, 0.65-0.96], respectively). Similar results were obtained for associations with cardiovascular death, except for brushing teeth daily, which was not associated with lesser hazard of cardiovascular death. The age at which patients had first consulted a dental practitioner was not associated with either all-cause or cardiovascular mortality.

The decayed, missing, or filled teeth index showed a dose-response relationship with all-cause and cardiovascular mortality (Fig 3). For participants who had 1 or more teeth, there was a linear association between the number of decayed, missing, or filled teeth at baseline and risk of death. The adjusted mortality risk increased by 2.8% for each additional decayed, missing, or filled tooth (95% CI, 1.7%-4.0%), and the adjusted cardiovascular risk increased by 3.3% (95% CI, 1.7%-5.0%).

Sensitivity Analyses

Similar results were found for the association between dental disease and mortality when analyses were restricted to dentate patients only. In dentate patients, having 14 or more decayed, missing, or filled teeth was associated with increased adjusted risks of all-cause mortality (HR, 1.54; 95% CI, 1.22-1.95) and cardiovascular mortality (HR, 1.64; 95% CI, 1.16-2.33). Analyses for the association of the

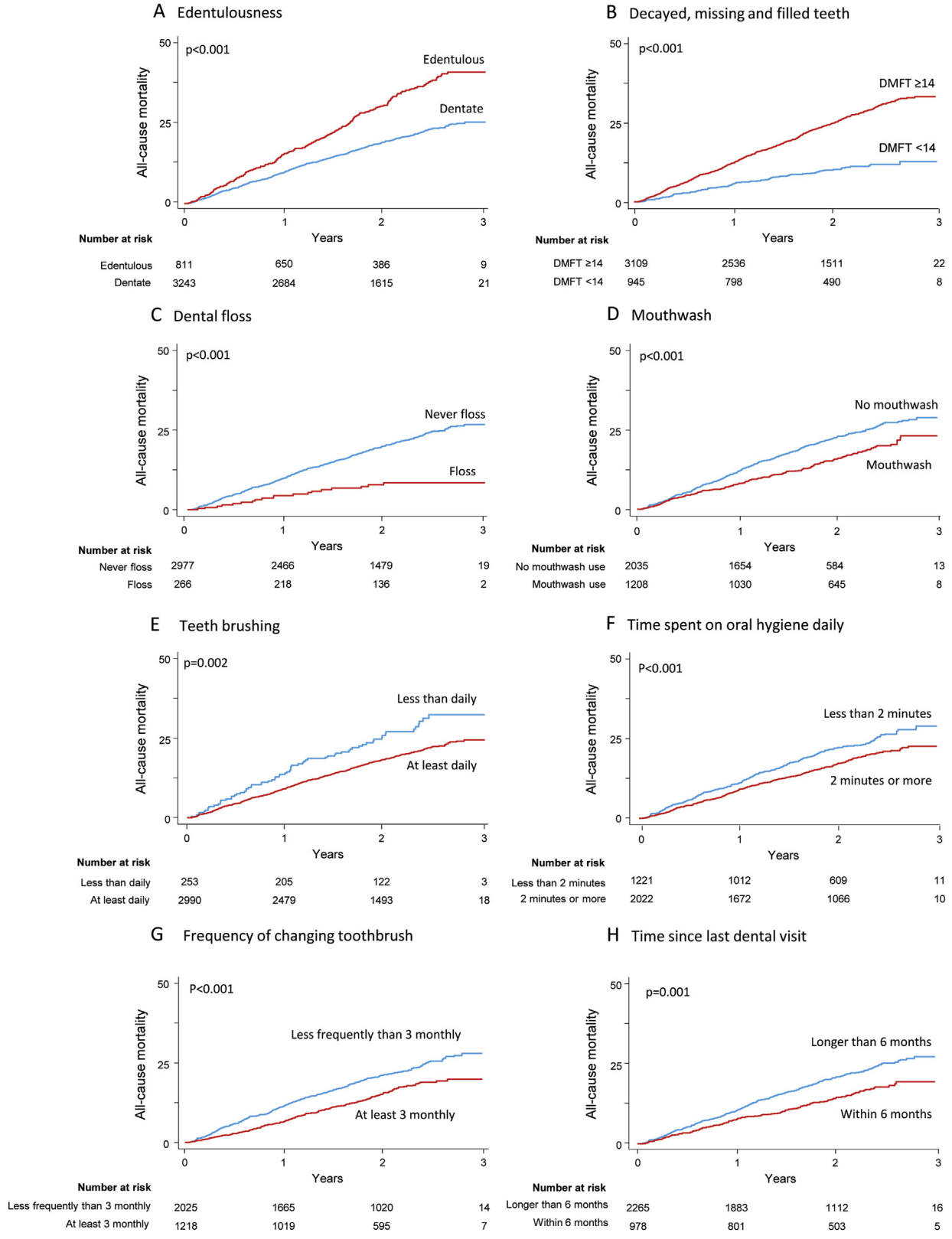

Figure 1. Cumulative incidence of all-cause mortality for each dental health measure. The decayed, missing, and filled teeth index (DMFT) is dichotomized according to World Health Organization criteria as very low to moderate, <14, and high, ≥14.[27] All 4,205 participants were included in the survival analyses for edentulousness and the DMFT and 3,338 dentate participants were included in survival analyses for oral hygiene and dental care practices.

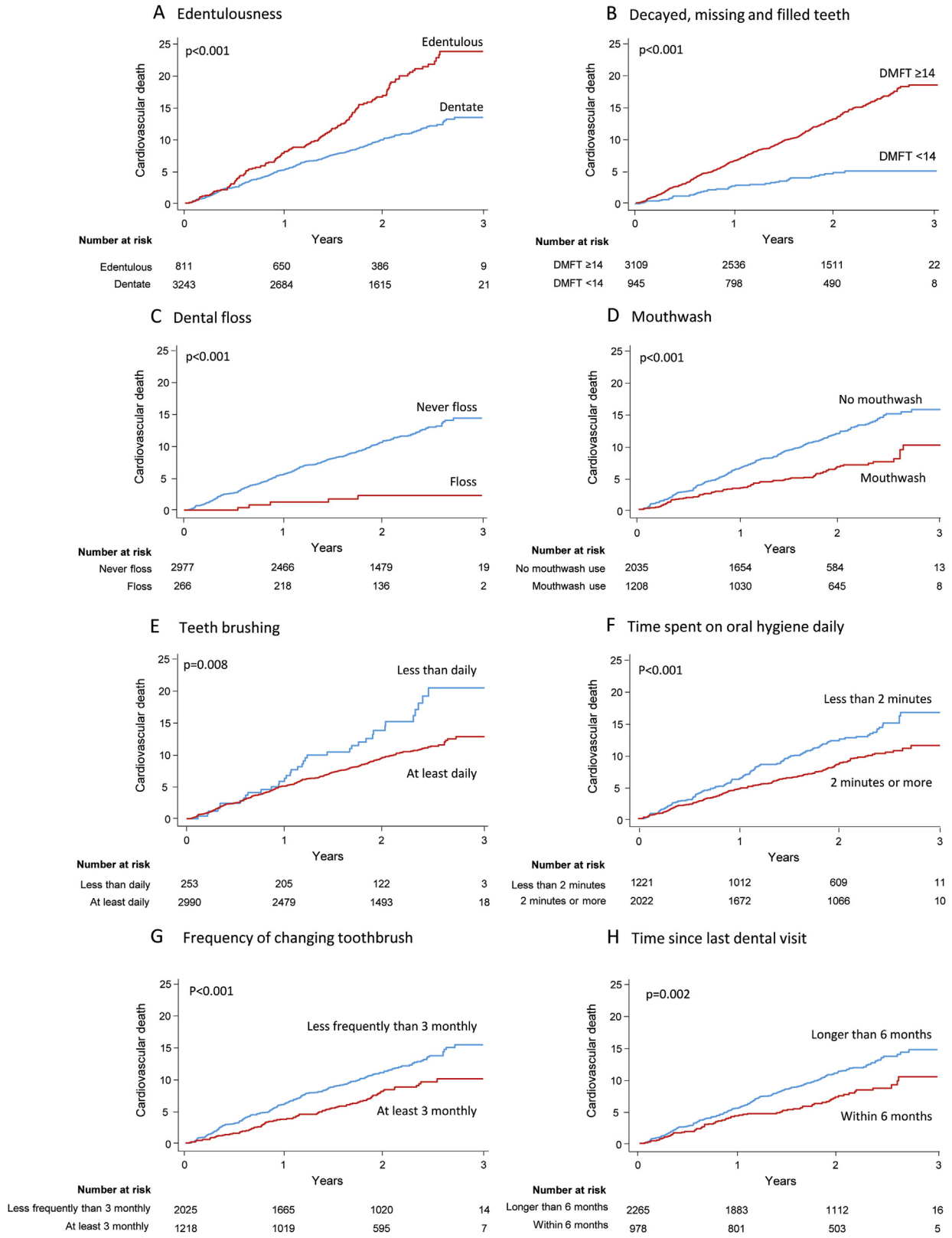

Figure 2. Cumulative incidence of cardiovascular mortality for each dental health measure. The decayed, missing, and filled teeth index (DMFT) is dichotomized according to World Health Organization criteria as very low to moderate, <14, and high, ≥14.[27] All 4,205 participants were included in the survival analyses for edentulousness and the DMFT and 3,338 dentate participants were included in survival analyses for oral hygiene and dental care practices.

Table 3. Kaplan-Meier Estimates for Total and Cardiovascular Mortality After 1, 2, and 3 Years of Follow-up, Stratified by Oral Disease or Health Practice

	1 Year		2 Years		3 Years	
	Exposure	No Exposure	Exposure	No Exposure	Exposure	No Exposure
All-cause mortality						
Edentulousness	15.6 (13.2-18.3)	9.8 (8.8-10.8)	30.7 (27.5-34.2)	19.1 (17.8-20.7)	40.9 (36.9-45.3)	25.4 (23.3-27.6)
Decayed, missing, filled teeth index	12.4 (11.3-13.6)	5.9 (4.5-7.7)	24.8 (23.3-26.5)	10.3 (8.3-12.6)	33.1 (30.9-35.4)	12.8 (10.1-16.1)
Use of dental floss	4.5 (2.5-7.9)	10.2 (9.1-11.3)	8.5 (5.4-13.0)	20.0 (18.5-21.6)	8.5 (5.4-13.0)	26.7 (24.5-29.1)
Use of mouthwash	7.5 (6.1-9.1)	11.0 (9.7-12.5)	15.1 (13.0-17.4)	21.5 (20.0-23.5)	22.1 (18.7-26.0)	27.4 (24.9-30.2)
Brushing teeth daily	9.3 (8.3-10.4)	14.2 (10.4-19.2)	18.5 (17.0-20.0)	26.1 (20.9-32.4)	24.8 (22.6-27.1)	32.8 (26.4-40.2)
Oral hygiene ≥2 min daily	8.9 (7.7-10.2)	11.1 (9.4-13.0)	17.1 (15.4-19.0)	22.2 (19.9-24.9)	22.9 (20.5-25.5)	29.3 (25.7-33.4)
Change toothbrush every 3 mo or less	6.6 (5.3-8.2)	11.5 (10.2-13.0)	15.3 (13.2-17.6)	21.3 (19.5-23.3)	20.1 (17.4-23.3)	28.3 (25.6-31.3)
Age of first dental visit < 30 y	9.0 (7.6-10.7)	10.2 (8.9-11.7)	18.2 (16.1-20.4)	19.8 (17.9-21.8)	25.4 (22.1-29.1)	25.1 (22.7-27.8)
Last dental visit within 6 mo	7.7 (6.1-9.6)	10.6 (9.3-11.9)	14.5 (12.3-17.1)	21.0 (19.3-22.8)	19.8 (16.7-23.4)	27.8 (25.2-30.7)
Cardiovascular mortality						
Edentulousness	8.2 (6.5-10.4)	5.3 (4.5-6.1)	17.1 (14.5-20.2)	10.1 (9.0-11.3)	24.4 (20.5-28.3)	13.6 (12.0-15.5)
Decayed, missing, filled teeth index	6.8 (5.9-7.7)	2.9 (2.0-4.3)	13.4 (12.2-14.8)	5.1 (3.8-7.0)	18.8 (16.9-20.8)	5.4 (4.0-7.3)
Use of dental floss	1.3 (0.4-3.9)	5.6 (4.8-6.5)	2.3 (1.0-5.5)	10.7 (9.6-12.0)	2.3 (1.0-5.5)	14.6 (12.9-16.6)
Use of mouthwash	3.3 (2.4-4.5)	6.4 (5.4-7.6)	6.8 (5.4-8.6)	12.0 (10.6-13.7)	10.2 (7.5-13.8)	15.9 (13.8-18.1)
Brushing teeth daily	5.2 (4.4-6.1)	6.4 (3.9-10.5)	9.7 (8.6-11.0)	14.1 (10.0-19.6)	13.0 (11.3-15.0)	20.8 (15.1-28.3)
Oral hygiene ≥2 min daily	4.7 (3.8-5.8)	6.2 (5.0-7.8)	8.6 (7.4-10.1)	12.4 (10.6-14.6)	11.6 (9.8-13.8)	16.9 (14.0-20.3)
Change toothbrush every 3 mo or less	3.8 (2.8-5.1)	6.2 (5.2-7.3)	8.2 (6.6-10.1)	11.2 (9.8-12.8)	10.2 (8.2-12.7)	15.6 (13.4-18.2)
Age of first dental visit < 30 y	4.5 (3.5-5.8)	5.9 (4.8-7.1)	10.2 (8.6-12.1)	10.0 (8.6-11.5)	14.5 (12.0-17.5)	12.9 (10.9-15.2)
Last dental visit within 6 mo	4.4 (3.3-6.0)	5.7 (4.8-6.7)	7.4 (5.8-9.5)	11.2 (9.9-12.7)	10.7 (8.1-14.0)	14.9 (12.9-17.2)

Note: Values are percentages and are given as estimate (95% confidence interval).

decayed, missing, and filled teeth index with cardiovascular mortality when considering competing risks from other causes of death showed similar results, with an adjusted incidence of death of 21.0% in patients with a decayed, missing, and filled teeth index score ≥ 14 compared with 12.2% in those with fewer decayed, missing, or filled teeth (adjusted HR, 1.75).

The only significant interaction term was age. Adjusted associations of edentulousness with all-cause mortality (P for interaction = 0.001) and cardiovascular mortality (P for interaction < 0.001) were stronger in adults younger than 60 years (HRs of 1.74 [95% CI, 1.15-2.62] and 2.48 [95% CI, 1.47-4.17]) than for older adults (HRs of 1.33 [95% CI, 1.15-1.55] and 1.29 [95% CI, 1.05-1.60]). Similarly, associations of the decayed, missing, and filled teeth index with all-cause mortality (P for interaction = 0.04) and cardiovascular mortality (P for interaction = 0.07) were somewhat stronger in adults younger than 60 years (HRs of 2.50 [95% CI, 1.71-3.64] and 2.82 [95% CI, 1.56-5.10]) than for older adults (HRs of 1.56 [95% CI, 1.18-2.05] and 1.58 [95% CI, 1.07-2.33]).

DISCUSSION

This study suggests that dental health status and behaviors influence the risk of death in people treated with hemodialysis independent of other risk factors, including income and comorbid conditions. Tooth loss and extensive dental disease were associated with increased risks of all-cause and cardiovascular mortality, and the extent of decayed, missing, or filled teeth showed a dose-response relationship with early mortality. Dental care behaviors, particularly the use of dental floss or mouthwash, but also daily teeth brushing, spending time on oral hygiene each day, more frequent dental visits, and changing a toothbrush more often, were associated with better survival. Dental disease at a younger age appeared more strongly linked to mortality outcomes. These associations between survival and dental health were observed across several countries in Europe and Argentina and were independent of measured sociodemographic and clinical factors.

Table 4. Dental Health, Oral Hygiene Habits, and Dental Care Practice Variables Associated With All-Cause and Cardiovascular Mortality in Adults With End-Stage Kidney Disease

	Death From Any Cause	Death From Cardiovascular Event
Edentulousness	1.29 (1.10-1.51)	1.28 (1.02-1.60)
Decayed, missing, filled teeth index ≥ 14[a]	1.70 (1.33-2.17)	1.81 (1.26-2.59)
Use of dental floss	0.52 (0.32-0.85)	0.25 (0.09-0.68)
Use of mouthwash	0.79 (0.64-0.97)	0.60 (0.44-0.82)
Brushing teeth daily	0.76 (0.58-0.99)	0.74 (0.52-1.07)
Oral hygiene ≥ 2 min daily	0.84 (0.71-0.99)	0.72 (0.57-0.92)
Change toothbrush every 3 mo or less	0.79 (0.65-0.95)	0.73 (0.56-0.95)
Age of first dental visit < 30 y	0.95 (0.79-1.15)	1.00 (0.77-1.30)
Last dental visit within 6 mo	0.79 (0.65-0.96)	0.73 (0.55-0.97)

Note: Values are given as adjusted hazard ratio (95% confidence interval). The analyses were stratified by country and adjusted for age, sex, race (European vs non-European), smoking history (ever smoker vs nonsmoker), income (above average vs below average), medical history (diabetes, myocardial infarction), dialysis vintage, and mean arterial blood pressure, serum phosphorus, and hemoglobin values. All participants with recorded data for all exposure variables (n = 4,054/4,205) were included in the survival analyses for edentulousness and the decayed, missing, and filled teeth index and all dentate participants with complete exposure data (n = 3,243/3,338) were included in survival analyses for oral hygiene and dental care practices.

[a]The decayed, missing, and filled teeth index is dichotomized according to World Health Organization criteria as very low to moderate, <14, and high, ≥14.[27]

To our knowledge, there has never been a comprehensive study to assess linkages between dental care practices with survival in dialysis patients. In a recent systematic review, existing evidence for associations between oral health and survival in patients with CKD was rare and limited to the assessment of mortality associated with periodontitis in the setting of dialysis.[10] In 2 small studies involving dialysis patients, periodontitis was associated with increased malnutrition and systemic inflammation,[17] and moderate to severe periodontitis may predict all-cause mortality.[18,19]

While our findings are consistent with studies in the general population showing associations between tooth loss and oral hygiene with mortality and cause-specific death, including cardiovascular disease and cancer, independent of socioeconomic disadvantage,[7,9,20-22] extrapolation of observational findings from the general population to the dialysis setting is not always appropriate. For example, higher blood pressure[23] and serum cholesterol[24] levels are paradoxically associated with better survival in the setting of advanced kidney disease, and drugs that reduce cardiovascular events in the general population, such as statin therapy and antiplatelet agents, may have smaller or no beneficial effects for dialysis patients.[25,26] Accordingly, the findings in this study do not simply confirm data from other populations, but represent new and testable hypotheses for improving outcomes for people with CKD. To date, these interventions have not been tested.

Despite growing and consistent evidence within general and chronic disease populations that dental health is associated with risks of total and cardiovascular death and that oral hygiene and dental care practices, particularly dental flossing, are associated with better survival, large trials evaluating the effects of dental practices and oral hygiene care on patient-centered outcomes are lacking. This is particularly striking given the very high population burden of oral diseases across most global regions.[27] A systematic review based on generally low-quality evidence has shown that dental health education may have small positive but poorly sustained effects on plaque accumulation and no impact on caries burden, but beneficial effects on dental knowledge.[28] Three trials have shown that routine scale and polish care in adults may have little or no effect on gingivitis[29] and a trial of nonsurgical periodontal treatment for periodontitis in people who had diabetes[30] was discontinued prematurely because of futility. Notably, no dental trials have specifically examined treatment effects on mortality or cardiovascular end points and none are available in the CKD population, as suggested might be appropriate based on the findings in this study.

The potential benefit of dental health interventions on survival, cardiovascular events, and quality of life might be greater in adults with CKD than for other settings due to the more severe spectrum of oral disease,[31,32] lower use of dental care practices,[11] and substantially poorer survival. Accumulated dental plaque drives neutrophil-based inflammation and may stimulate cytokine responses within gingival epithelium.[33,34] Additional causal pathways linking oral bacteria to systematic inflammation have been proposed, including bacteremia secondary to oral bacteria, circulating oral microbial toxins, and metastatic immunologic responses to oral microorganisms (reviewed in[35]). Accordingly, it is plausible that dental care and oral hygiene interventions might modify the measurable systemic inflammatory response and malnutrition that is associated with dental plaque accumulation and gingivitis,[17] which might contribute directly to accelerated cardiovascular disease in adults with CKD through nontraditional mechanisms.[36]

While the findings of our study suggest that dental health and oral hygiene practices represent a testable risk factor for health in the dialysis setting,

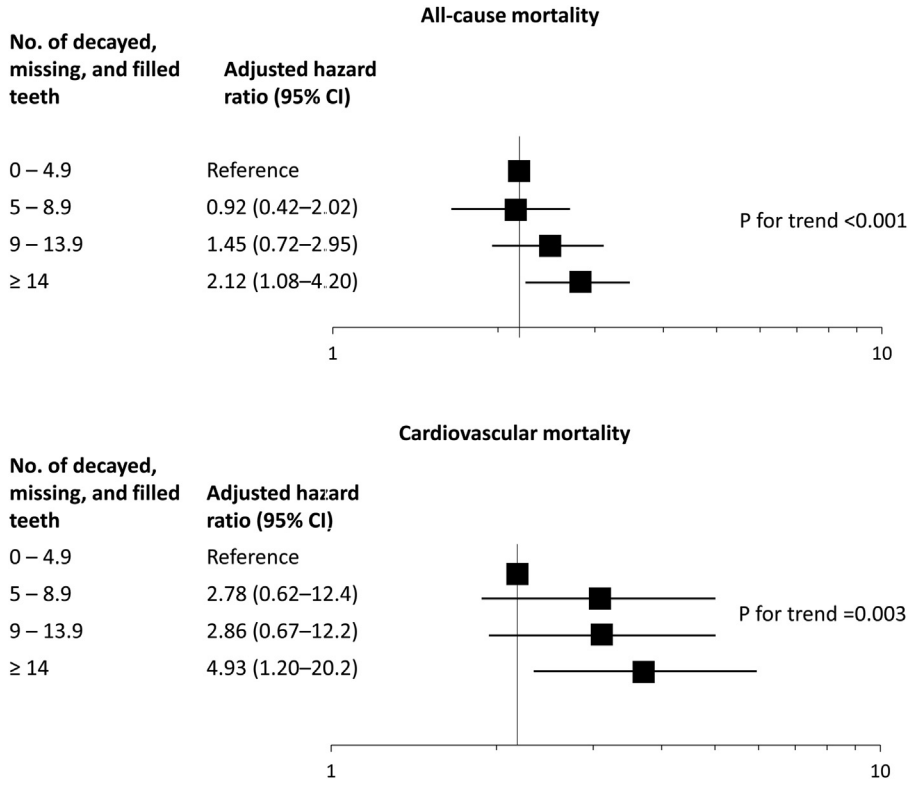

Figure 3. Multivariable adjusted hazard ratios for cardiovascular mortality for World Health Organization categories of decayed, missing, and filled teeth index. The maximum number of decayed missing and filled teeth was 32, including the third molars. The decayed, missing, and filled teeth index is dichotomized according to World Health Organization criteria as very low to moderate, <14, and high, ≥14.[27] A larger number of affected teeth indicates more extensive dental disease. Abbreviation: CI, confidence interval.

the observational nature of this study means that it is hypothesis generating at best. Large pragmatic trials to evaluate the effects of dental health practices on survival are required before appropriate policy and guideline responses can be generated. Based on previous trial evidence that oral hygiene education had nonsustained effects on dental health behaviors[28] and that periodontal treatment might be ineffective for modifying surrogate outcomes in diabetes,[30] the effects of regular funded dental consultation integrated into care of CKD and end-stage kidney disease on survival and patient-centered outcomes might be the most appropriate tested strategy, particularly involving younger patients. Understanding patient experiences and barriers to dental care in this population might also aid the design of a workable intervention that aligns with patients' values to increase patient acceptability and uptake.[37]

The limitations of the current study need to be considered when interpreting the findings. First, patients were from various European countries and Argentina, which may have different causal factors linking dental exposures to mortality; however, random-effects analyses were fitted using a shared frailty model to account for within-country clustering. Second, although a broad range of social and clinical factors were able to be accounted for, residual confounding in the analyses is still possible. For example, adjustment for access to dental care or exposure to fluoridation was not able to be undertaken. Other potential unmeasured confounders include general receptiveness to health advice, health literacy, and socioeconomic factors. Third, while an association between age of first dental consultation and mortality outcome was not observed, the question may not have sufficiently assessed whether patients had dental checkups during childhood, which might have been most relevant to lifetime risk of tooth loss and therefore mortality. Finally, assessment was based on a single dental examination measured after the occurrence of end-stage kidney disease and therefore could not inform understanding of the relative contributions of dental health through childhood and earlier adulthood to risks of mortality in end-stage kidney disease. The potential impact of the duration of exposure to dental disease in the earlier stages of CKD was hinted at by the interaction between dental health and age, suggesting that younger patients who may have experienced more severe dental pathology earlier in life are more at risk of adverse events associated with dental disease.

Tooth loss and dental disease were associated with total and cardiovascular mortality, while oral hygiene practices and more frequent dental care were associated with better survival in patients with end-stage kidney disease treated with hemodialysis. Randomized trials of dental interventions in the setting of CKD are warranted.

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SUPPLEMENTARY MATERIAL

Table S1: Baseline characteristics of participants without dental data available.

Table S2: Baseline dental characteristics, hygiene habits, and care practices in participants excluded from full analyses.

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REFERENCES

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-2223.

2. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. *Adv Chronic Kidney Dis*. 2007;14(1):82-99.

3. Finn WF, Joy MS, Webster I, Gill M. Long-term treatment with lanthanum carbonate (Fosrenol) is safe and effective in haemodialysis patients [abstract W434]. *Nephrol Dial Transplant*. 2003;18(suppl 4):685.

4. US Renal Data System. *USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013.

5. Locker D. *Concepts of Oral Health, Disease and the Quality of Life*. Chapel Hill, NC: University of North Carolina, Dental Ecology; 1997.

6. Petersen P. The World Oral Health Report 2003: continuous improvement of oral health in the 21st century—the approach of the WHO Global Oral Health Programme. *Community Dent Oral Epidemiol*. 2003;31(suppl 1):3-24.

7. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. *BMJ*. 1993;306(6879):688-691.

8. Jansson L, Lavseted S, Frithiof L. Relationship between oral health and mortality rate. *J Clin Periodontol*. 2002;29(11):1029-1034.

9. Söder B, Yakob M, Meurman JH, Andersson LC, Söder P-Ö. The association of dental plaque with cancer mortality in Sweden. A longitudinal study. *BMJ Open*. 2012;2(3).

10. Ruospo M, Palmer SC, Craig JC, et al. Prevalence and severity of oral disease in adults with chronic kidney disease: a systematic review of observational studies. *Nephrol Dial Transplant*. 2014;29(2):364-375.

11. Grubbs V, Plantinga LC, Tuot DS, Powe NR. Chronic kidney disease and use of dental services in a United States public healthcare system: a retrospective cohort study. *BMC Nephrol*. 2012;13:16.

12. Beck JD, Slade G, Offenbacher S. Oral disease, cardiovascular disease and systemic inflammation. *Periodontol 2000*. 2000;23:110-120.

13. Moynihan PJ. The role of diet and nutrition in the etiology and prevention of oral diseases. *Bull World Health Organ*. 2005;83(9):694-699.

14. Strippoli GF, Palmer SC, Ruospo M, et al. Oral disease in adults treated with hemodialysis: prevalence, predictors, and association with mortality and adverse cardiovascular events: the rationale and design of the Oral Diseases in Hemodialysis (ORAL-D) study, a prospective, multinational, longitudinal, observational, cohort study. *BMC Nephrol*. 2013;14:90.

15. World Health Organization. *Oral Health Surveys: Basic Methods*. 4th ed. Geneva, Switzerland: WHO; 1997.

16. Al-Shammari KF, Al-Ansari JM, Al-Khabbaz AK, Dashti A, Honkala EJ. Self-reported oral hygiene habits and oral health problems of Kuwaiti adults. *Med Princ Pract*. 2007;16(1):15-21.

17. Chen LP, Chiang CK, Chan CP, Hung KY, Huang CS. Does periodontitis reflect inflammation and malnutrition status in hemodialysis patients? *Am J Kidney Dis*. 2006;47(5):815-822.

18. Kshirsagar AV, Craig RG, Moss KL, et al. Periodontal disease adversely affects the survival of patients with end-stage renal disease. *Kidney Int*. 2009;75(7):746-751.

19. Chen LP, Chiang CK, Peng YS, et al. Relationship between periodontal disease and mortality in patients treated with maintenance hemodialysis. *Am J Kidney Dis*. 2011;57(2):276-282.

20. Holmlund A, Holm G, Lind L. Number of teeth as a predictor of cardiovascular mortality in a cohort of 7,674 subjects followed for 12 years. *J Periodontol*. 2010;81(6):870-876.

21. Watt RG, Tsakos G, de Oliveira C, Hamer M. Tooth loss and cardiovascular disease mortality risk—results from the Scottish Health Survey. *PLoS One*. 2012;7(2):e30797.

22. Cabrera C, Hakeberg M, Ahlqwist M, et al. Can the relation between tooth loss and chronic disease be explained by socioeconomic status? A 24-year follow-up from the population study of women in Gothenburg, Sweden. *Eur J Epidemiol*. 2005;20(3):229-236.

23. Zager PG, Nikolic J, Brown RH, et al. "U" curve association of blood pressure and mortality in hemodialysis patients. *Kidney Int*. 1998;54(2):561-569.

24. Kilpatrick RD, McAllister CJ, Kovesdy CP, Derose SF, Kopple JD, Kalantar-Zadeh K. Association between serum lipids and survival in hemodialysis patients and impact of race. *J Am Soc Nephrol*. 2007;18(1):293-303.

25. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(4):263-275.

26. Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156(6):445-459.

27. Petersen P, Bourgeois D, Ogawa H, Estupinan-Day S, Ndiaye C. The global burden of oral diseases and risks to oral health. *Bull World Health Organ*. 2005;83:661-669.

28. Kay EJ, Locker D. Is dental health education effective? A systematic review of current evidence. *Community Dent Oral Epidemiol*. 1996;24(4):231-235.

29. Worthington HV, Clarkson JE, Bryan G, Beirne PV. Routine scale and polish for periodontal health in adults. *Cochrane Database Syst Rev*. 2013;11:CD004625.

30. Engebretson SP, Hyman LG, Michalowicz BS, et al. The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. *JAMA*. 2013;310(23):2523-2532.

31. Thorman R, Neovius M, Hylander B. Clinical findings in oral health during progression of chronic kidney disease to end-stage renal disease in a Swedish population. *Scand J Urol Nephrol*. 2009;43(2):154-159.

32. Fisher MA, Taylor GW, Shelton BJ, et al. Periodontal disease and other nontraditional risk factors for CKD. *Am J Kidney Dis*. 2008;51(1):45-52.

33. Krisanaprakornkit S, Kimball JR, Weinberg A, Darveau RP, Bainbridge BW, Dale BA. Inducible expression of human beta-defensin 2 by Fusobacterium nucleatum in oral epithelial cells: multiple signaling pathways and role of commensal bacteria in innate immunity and the epithelial barrier. *Infect Immun*. 2000;68(5):2907-2915.

34. Sandros J, Karlsson C, Lappin DF, Madianos PN, Kinane DF, Papapanou PN. Cytokine responses of oral epithelial cells to Porphyromonas gingivalis infection. *J Dent Res*. 2000;79(10):1808-1814.

35. Thoden van Velzen SK, Abraham-Inpijn L, Moorer WR. Plaque and systemic disease: a reappraisal of the focal infection concept. *J Clin Periodontol*. 1984;11(4):209-220.

36. Terrier N, Senecal L, Dupuy AM, et al. Association between novel indices of malnutrition-inflammation complex syndrome and cardiovascular disease in hemodialysis patients. *Hemodial Int*. 2005;9(2):159-168.

37. Thomas J, Harden A, Oakley A, et al. Integrating qualitative research with trials in systematic reviews. *BMJ*. 2004;328(7446):1010-1012.