

# ASSOCIATION OF PERIODONTITIS WITH ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN ADULTS WITH END-STAGE KIDNEY DISEASE: A MULTINATIONAL COHORT STUDY

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**Background** Periodontitis is associated with cardiovascular mortality in the general population and patients with chronic disease including diabetes, but whether periodontitis is predictive of mortality among adults with chronic kidney disease has not been previously reported<sup>1</sup>. Based on the paucity of robust prognostic data for periodontitis in the setting of kidney failure, the ongoing trials of periodontal interventions, and the need to prioritize candidate interventions to improve outcomes in this population, the ORAL diseases in hemodialysis study<sup>2</sup> (ORAL-D) was conducted to estimate the association of periodontitis with survival and to determine whether the observed risks of increased mortality with periodontal inflammation seen in the general population are different among people with end-stage kidney disease treated with hemodialysis.

**Methods** The ORAL-D study was the first large, multinational cohort study of oral health in adult hemodialysis patients in Europe and Argentina recruited between 2010-2012. 4205 participants underwent a standardized oral examination conducted by a dentist trained in periodontology. At baseline and periodontitis was assessed using the World Health Organization Community Periodontal Index. Participants were matched 1:1 on their propensity score for moderate to severe periodontitis. Risks of all-cause and cardiovascular mortality was the main outcome measure. A random-effects Cox proportional hazards model was fitted with shared frailty to account for clustering of mortality risk within countries. To assess the robustness of the findings and to limit the impact of tooth loss on the results causing misclassification of periodontitis severity as low or absent, sensitivities analyses were conducted omitting participants with fewer than 12 natural teeth using the propensity matched cohort.

**Results** Among the 3338 dentate participants, 1355 (40.6%) had moderate to severe periodontitis. Participants with moderate or severe periodontitis were older, more likely to be men, were more often married, unemployed or retired, had higher serum albumin levels, and had survived longer with dialysis for longer (Table 1). There were large differences in periodontal characteristics among participants based on their periodontal status (Table 2). Overall survival and cardiovascular specific survival was longer among patients with periodontitis than in those without periodontitis for both the entire cohort and in the matched groups (Figure 1). In the entire unmatched cohort, moderate to severe periodontitis showed no association with all-cause (hazard ratio 0.92, 95% confidence interval 0.75 to 1.11) or cardiovascular (0.83, 0.63 to 1.09) mortality (Table 3). After using propensity score methods to generate a matched cohort of participants with periodontitis similar to those with less severe periodontal disease, periodontitis was associated with a lower risk of all-cause (9.1 per 100 person years v 13.0, hazard ratio 0.74, 95% confidence interval 0.61 to 0.90) and cardiovascular (4.3 per 100 person years v 6.9, 0.67, 0.51 to 0.88) mortality. These associations were consistent among participants with 12 or more natural teeth and when accounting for competing causes of cardiovascular death.

**Table 1 Baseline characteristics of study participants according to periodontal status in matched and unmatched cohorts**

Variables	Full cohort			After propensity score matching		
	None or mild periodontitis (n=1983)	Moderate to severe periodontitis (n=1355)	Standardized difference*	None or mild periodontitis (n=1355)	Moderate to severe periodontitis (n=1355)	Standardized difference*
<b>Demographics</b>						
Age (years) <sup>†</sup>	57.3 (16.3)	61.7 (14.5)	0.23	61.8 (14.5)	61.7 (14.5)	0.005
Country						
Argentina	1306 (65.8)	177 (13.1)	0.99	846 (62.4)	177 (13.1)	0.91
France	28 (1.4)	11 (0.8)	0.05	27 (2.0)	11 (0.8)	0.08
Hungary	162 (8.2)	235 (17.4)	-0.20	141 (10.4)	235 (17.4)	-0.17
Italy	97 (4.9)	312 (23.0)	-0.49	89 (6.6)	312 (23.0)	-0.42
Poland	200 (10.1)	39 (2.9)	0.22	159 (11.8)	39 (2.9)	0.19
Portugal	149 (7.5)	464 (34.2)	-0.36	131 (9.7)	464 (34.2)	-0.35
Spain	9 (0.2)	119 (8.8)	-0.42	7 (0.2)	119 (8.8)	-0.42
Men <sup>‡</sup>	1118 (56.3)	852 (62.9)	-0.10	836 (61.9)	852 (62.9)	-0.02
European race	1899 (96.4)	1244 (91.9)	0.17	1297 (95.7)	1244 (91.9)	0.13
<b>Sociodemographic characteristics</b>						
Current or former smoker <sup>§</sup>	381 (19.2)	408 (30.4)	-0.06	352 (26.0)	408 (30.4)	-0.15
Married	859 (43.3)	835 (61.6)	-0.12	583 (43.2)	835 (61.6)	-0.12
Secondary education	462 (23.3)	460 (34.0)	-0.02	331 (24.7)	460 (34.0)	-0.03
Employed	218 (11.0)	142 (10.7)	0.12	149 (11.0)	142 (10.7)	0.09
Family income above domestic average <sup>¶</sup>	132 (7.4)	106 (8.2)	-0.02	98 (7.4)	106 (8.2)	-0.02
<b>Comorbid medical conditions</b>						
Myocardial infarction	112 (5.6)	138 (10.3)	-0.09	95 (7.1)	138 (10.3)	-0.04
Stroke	88 (4.4)	125 (9.2)	-0.12	70 (5.1)	125 (9.2)	-0.12
Diabetes mellitus	338 (16.9)	335 (24.8)	0.02	238 (17.6)	335 (24.8)	0.005
<b>Laboratory variables</b>						
Serum albumin (g/L)	3.7 (0.4)	3.9 (0.4)	-0.41	3.7 (0.4)	3.9 (0.4)	-0.41
Serum phosphorus (mg/dL)	5.0 (1.5)	4.6 (0.5)	0.16	4.6 (1.5)	4.6 (0.5)	0.00
Serum calcium (mg/dL)	8.8 (0.8)	8.8 (0.8)	0	8.8 (0.8)	8.8 (0.8)	0
Hemoglobin (g/dL)	11.0 (1.4)	11.1 (1.3)	-0.12	11.1 (1.4)	11.1 (1.3)	-0.08
<b>Dialysis characteristics</b>						
Time treated with dialysis (months) <sup>‡</sup>	75.1 (54.9)	84.6 (66.4)	-0.13	82.5 (59.1)	84.6 (66.4)	-0.07
Kt/V	1.7 (0.3)	1.7 (0.3)	0	1.6 (0.3)	1.7 (0.3)	-0.27
Mean arterial pressure (mmHg)	89.0 (13.7)	91.7 (13.7)	-0.18	88.8 (13.5)	91.7 (13.7)	-0.02
<b>Oral health practices and dental health</b>						
Number of teeth <sup>‡</sup>	18.5 (9.4)	17.1 (8.3)	-0.05	18.5 (9.2)	17.1 (8.3)	-0.03
Number of decayed, missing, filled teeth	19.4 (8.9)	19.1 (8.1)	0.02	19.3 (8.8)	19.1 (8.1)	0.01
Use of dental floss	153 (7.8)	115 (8.6)	-0.02	90 (6.7)	115 (8.6)	-0.06
Brushing teeth twice or more often per day	1332 (67.1)	854 (64.2)	0.05	874 (65.2)	854 (64.2)	0.05

Data are expressed as mean (SD) or number (%). Kt/V refers to the clearance of urea and is a measure of the amount of dialysis received. Proportions do not always correspond to overall numbers of participants due to missing data.

**Table 2 Baseline periodontal characteristics defined by the World Health Organization Community Periodontal Index in unmatched and matched cohorts**

Variables	Full cohort			After propensity score matching		
	None or mild periodontitis (n=1983)	Moderate to severe periodontitis (n=1355)	Standardized difference*	None or mild periodontitis (n=1355)	Moderate to severe periodontitis (n=1355)	Standardized difference*
Periodontal probing depth, mm	0.68 (0.38)	1.53 (0.70)	-1.36	0.70 (0.38)	1.53 (0.70)	-1.33
Clinical attachment loss, mm	2.03 (1.56)	3.15 (1.55)	-0.59	2.12 (1.55)	3.15 (1.55)	-0.54
Distance between cementum-enamel junction and free gingival margin, mm	1.35 (1.49)	1.62 (1.49)	-0.15	1.42 (1.50)	1.62 (1.49)	-0.11
Bleeding on probing, % sites per person	11.1 (22.3)	20.7 (27.4)	-0.26	12.7 (21.7)	20.7 (27.4)	-0.28

Data are mean (SD). \*Standardized differences of 0.2, 0.5 and 0.8 can be considered to represent small, medium and large differences, respectively. These differences do not denote statistical significance. †The periodontal pocket depth measurements were made at three sites on the vestibular and lingual aspects of each tooth and the periodontal probing depth (PPD) score was calculated as a mean value divided by the number of sites examined. The Bleeding on Probing (BOP) index evaluated the buccal, lingual, mesial and distal sulci of all teeth based on the tendency to bleed after a standard stimulus. The four surfaces of each tooth were tested to provide a maximum total of 48 sites and the index is the percentage of sites positive for bleeding on probing for each participant. The Clinical Attachment Loss score was calculated as the sum of the mean PPD (sum of all values divided by the number of sites examined (6 per tooth)) and the mean (free gingival margin [GJ]-cementum-enamel junction [CEJ]) (sum of all values divided by the number of sites examined (2 per tooth)).

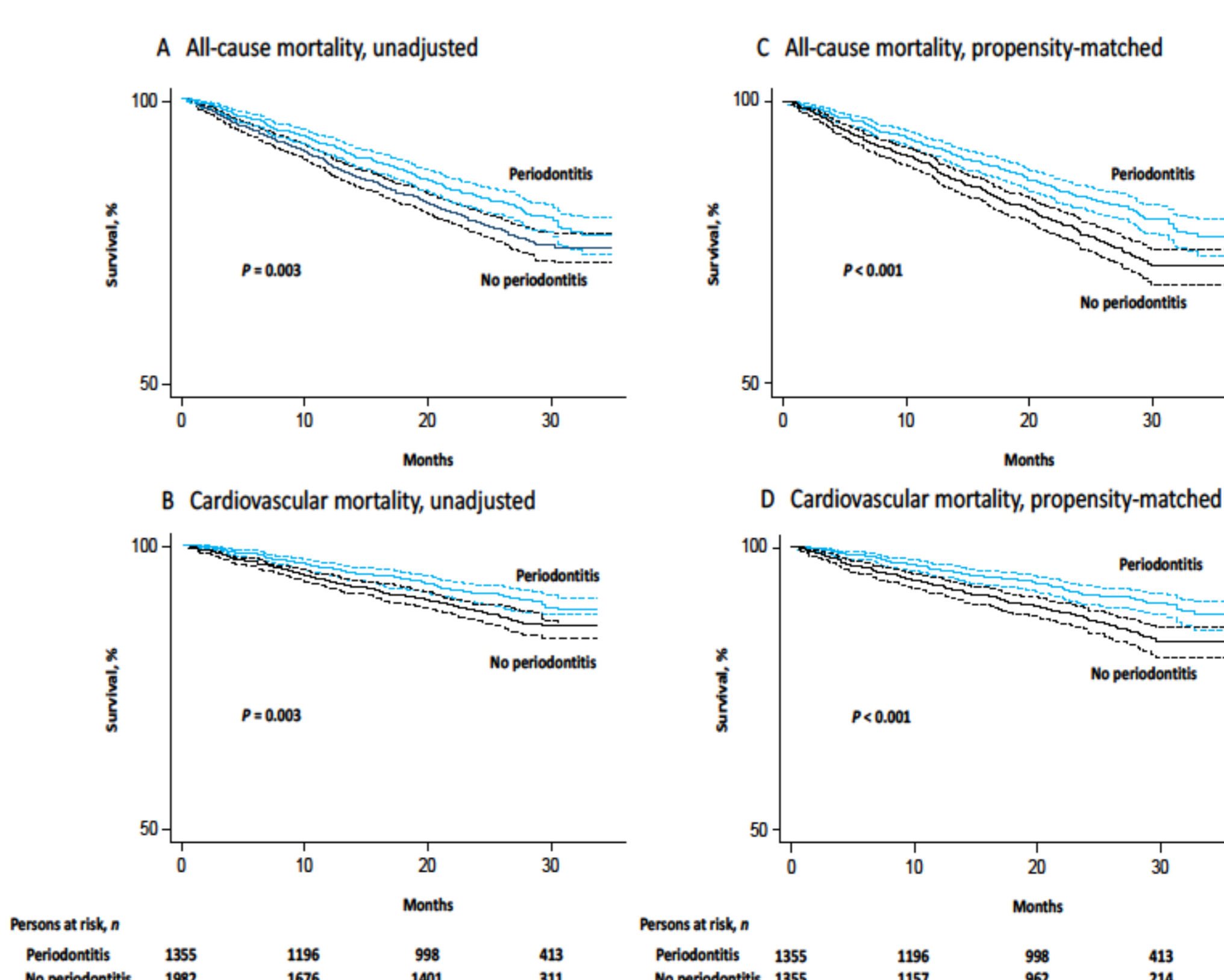
**Table 3 Mortality outcomes with moderate to severe periodontitis in unmatched and matched cohorts**

	Number of participants included in analyses	No (events per 100 person years)		Hazard ratio (95% CI)
		Moderate to severe periodontitis	No or mild periodontitis	
<b>All-cause mortality</b>				
Whole cohort	3338	242 (9.1)	408 (11.7)	0.92 (0.75 to 1.11)
Propensity-weighted	3338	242 (9.1)	408 (11.7)	0.83 (0.68 to 1.00)
Propensity-matched	2710	242 (9.1)	314 (11.0)	0.74 (0.61 to 0.90)
<b>Cardiovascular mortality</b>				
Whole cohort	3338	113 (4.3)	212 (6.1)	0.83 (0.63 to 1.09)
Propensity-weighted	3338	113 (4.3)	212 (6.1)	0.76 (0.58 to 1.00)
Propensity-matched	2710	113 (4.3)	167 (6.9)	0.67 (0.51 to 0.88)

Hazard ratios are reported for moderate to severe periodontitis (no or mild periodontitis is the reference group). CI denotes confidence interval. †Hazard ratios are controlled for age, sex, income, smoking, serum phosphorus, myocardial infarction, diabetes mellitus, mean arterial pressure, time on dialysis and number of teeth using a Cox proportional hazards regression model. ‡Clustering by country was accounted for by random effects Cox proportional hazards regression fitted using a shared frailty model.

**Conclusion** In contrast to the general population, periodontitis is not associated with risks of mortality in adults treated with hemodialysis. This finding of reverse epidemiology for periodontal disease and mortality outcomes in dialysis patients does not support the prioritization of trials evaluating periodontal treatment in this treatment setting.

**Figure 1 Kaplan-Meier survival plots (time until all-cause or cardiovascular death) for periodontitis in unmatched (left side) and matched (right side) samples**



References: 1. Ruospo M, Palmer SC, Craig JC, Gentile G, Johnson DW, Ford PJ, 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):364-75. 2. Strippoli GF, Palmer SC, Ruospo M, Natale P, Saglimbene V, Craig JC, 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.

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