ORIGINAL RESEARCH

History of Periodontitis Diagnosis and Edentulism as Predictors of Cardiovascular Disease, Stroke, and Mortality in Postmenopausal Women

Michael J. LaMonte, PhD, MPH; Robert J. Genco, DDS, PhD; Kathleen M. Hovey, MS; Robert B. Wallace, MD, MSc; Jo L. Freudenheim, PhD; Dominique S. Michaud, ScD; Xiaodan Mai, PhD; Lesley F. Tinker, PhD; Christian R. Salazar, PhD, MPH; Christopher A. Andrews, PhD; Wenjun Li, PhD; Charles B. Eaton, MD, MS; Lisa W. Martin, MD; Jean Wactawski-Wende, PhD

***Background*—**Few studies have reported associations between periodontitis and cardiovascular disease (CVD) risk in older women, which is the objective of the present investigation.

***Methods and Results*—**Participants were 57 001 postmenopausal women ages 55 to 89 years (mean 68 years; >85% 60 and older) who were enrolled (1993–1998) in the Women's Health Initiative Observational Study, and were without known CVD when history of periodontitis and edentulism was assessed by questionnaire at study Year-5 (1998–2003). There were 3589 incident CVD events and 3816 total deaths during a mean follow-up of 6.7 years. In multivariable analysis, periodontitis was not associated with CVD events, but was associated with higher total mortality (hazard ratio (HR)=1.12, 95% CI: 1.05–1.21). Edentulism was associated with higher age- and smoking-adjusted risks of CVD (HR=1.42, 95% CI: 1.27–1.59) and mortality (HR=1.47, 95% CI: 1.32–1.63). Further adjustment eliminated the association with CVD, but mortality remained significantly increased (HR=1.17, 95% CI: 1.02–1.33). Stratification on age, race-ethnicity, smoking, and diabetes mellitus yielded comparable results; however, edentulism was more strongly associated with CVD in women reporting ≥1 dental visit (HR=1.57) compared with <1 visit (HR 1.03, interaction *P*=0.004) annually.

***Conclusions*—**In community-dwelling older women, edentulism was associated with increased risks of CVD and total mortality, and presence of periodontitis, which is more prevalent than edentulism, was associated with 17% higher mortality rate. These findings suggest that improving periodontal condition of the general population could reduce overall mortality. **(*J Am Heart Assoc*. 2017;6:e004518. DOI: 10.1161/JAHA.116.004518.)**

Key Words: cardiovascular disease • epidemiology • mortality • periodontal disease • women's health

Periodontitis is a chronic inflammatory condition and a major cause of tooth loss in adults.[1] Moderate to severe periodontitis and edentulism are present in about 64% and 33% of US adults 60 years and older, respectively.[2,3] Periodontitis and tooth loss have been associated with higher risks of atherosclerotic cardiovascular disease (CVD)[4,5] and total mortality.[6–10] Few studies have included older adults or specifically women, and in those that have, inconsistent results were reported.[8,11–13] Further understanding the relationship of periodontitis and tooth loss with CVD risk and

From the Departments of Epidemiology and Environmental Health (M.J.L., K.M.H., J.L.F., X.M., J.W.-W.) and Oral Biology (R.J.G.), University at Buffalo, NY; Department of Epidemiology, University of Iowa, Iowa City, IA (R.B.W.); Department of Public Health and Community Medicine, Tufts University, Boston, MA (D.S.M.); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (L.F.T.); Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY (C.R.S.); Department of Ophthalmology, University of Michigan, Ann Arbor, MI (C.A.A.); Department of Preventive and Behavioral Medicine, University of Massachusetts, Worcester, MA (W.L.); Departments of Family and Preventive Medicine and Epidemiology, Brown University, Providence, RI (C.B.E.); Department of Cardiology, The George Washington University, Washington, DC (L.W.M.).

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Correspondence to: Michael J. LaMonte, PhD, MPH, Department of Epidemiology and Environmental Health, University at Buffalo, 273 Farber Hall, 3435 Main St, Buffalo, NY 14214. E-mail: malmaonte@buffalo.edu

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mortality is relevant to health and population aging. We examined these associations in a prospective cohort of older postmenopausal women.

Methods

Study Participants

Participants were women ages 50 to 79 who enrolled in the Women's Health Initiative (WHI) Observational Study (OS) at 40 US centers from 1993 through 1998 as detailed elsewhere.[14,15] History of periodontitis diagnosis was ascertained using the WHI OS Year-5 follow-up questionnaire.[16] Of the 93 676 women enrolled in the WHI OS, 70 134 were without known CVD at Year-5, and 62 335 of them responded to the Year-5 questionnaire. Women who had omitted dental health questions (n=401), were lost to follow-up after Year-5 (n=570), or missing covariable information (n=4363) were excluded, resulting in an analytic sample of 57 001. The Institutional Review Boards at participating study centers regularly reviewed and approved all study protocols. Participants provided written informed consent to all aspects of the WHI OS.

Assessment of Periodontitis and Edentulism

Periodontitis was assessed by asking "Has a dentist or dental hygienist ever told you that you had periodontal or gum disease?". Additional questions were, "During the past 3 years, how often have you gone to the dentist or dental hygienist for routine check-ups or cleaning?" and "Have you lost all of your permanent teeth (edentulism), both upper and lower?". Self-reported periodontitis diagnosis is reported accurately in this cohort. Prevalence of self-reported periodontitis diagnosis was 13%, 24%, and 56% among women grouped on standardized clinical categories of none/mild, moderate, and severe periodontitis (κ=0.27), defined by objective probing measures in a subset of 992 WHI OS participants.[16] When compared to a criterion clinical measure of tooth loss due to periodontitis, accuracy of self-reported history of periodontal/gum disease diagnosis was comparable across age groups (<65 years: Sensitivity 0.81, Specificity 0.76; ≥65 years: Sensitivity 0.74, Specificity 0.80) and level of education attained (high school: Sensitivity 0.79, Specificity 0.76; college: Sensitivity 0.76, Specificity 0.80). In a separate cohort of older adults (≥55 years) comparable in demographics to the women in the present study, reproducibility of self-reported dental conditions including gum disease and tooth extraction, across 2 administrations separated by 2 years was similarly high in those 55 to 64 years (κ=0.82), and in those ≥65 (κ=0.80); reproducibility did not differ by sex.[17] Because the history of periodontitis diagnosis was self-reported as a yes or no response, we are not able to evaluate whether risks of study outcomes differed according to severity of periodontitis (eg, moderate compared to severe disease).

Assessment of Covariables

Information on demographics, health behaviors, medical conditions, and medication use was collected using questionnaires at WHI OS entry. When available, information updated prior to Year-5 is used here. Because smoking is strongly associated with periodontitis and tooth loss,[18,19] adequate consideration of smoking is needed when evaluating relationships with CVD. Smoking status (never, former, current) and cigarettes smoked per day were assessed at baseline and updated annually. Pack-years was computed by multiplying packs smoked per day by number of years smoked. Other potential confounding factors included age (years), educational level (≤high school, college/some college, postgraduate), race/ethnicity (non-Hispanic white, black, other), body mass index (kg/m^2), waist–hip ratio, recreational physical activity (total metabolic equivalent hours per week), dietary healthy eating index, alcohol consumption (gram servings per week), age at menopause, hormone therapy use (never user, former user, current user), and history of diagnosed or treated diabetes mellitus, hypertension, or hypercholesterolemia (yes, no each). The specific measurements, procedures, and reliability of these factors have been described elsewhere.[14,15]

Ascertainment of End Points

Follow-up through December 2010 for clinical outcomes was performed annually in the WHI OS, as previously detailed.[20] The primary end point for this analysis was incident total CVD (nonfatal myocardial infarction, cardiac death, stroke, pulmonary embolism, heart failure). Coronary heart disease (myocardial infarction and cardiac death) and ischemic stroke also were evaluated separately. Events were identified on the basis of annual mailed follow-up questionnaires (response rates >95%) and, when possible, medical record review using standard case definitions.[20] Physicians blinded to exposure data adjudicated self-reported diagnoses and clinical records, which, in a WHI substudy,[21] showed good agreement for myocardial infarction (Sensitivity=80%, κ=0.64), stroke (Sensitivity=82%, κ=0.76), heart failure (Sensitivity=79%, κ=0.56), and pulmonary embolism (Sensitivity=82%, κ=0.84).

Total mortality was defined as death from any cause identified as part of routine participant follow-up that included reports from family/next of kin, obituaries, and National Death Index searches. Death certificates and hospital records were obtained and then centrally adjudicated by reviewers blinded to study component. For many out-of-hospital deaths,

documentation relied on the death certificate and the most recent relevant hospitalization before death.

Statistical Analysis

Follow-up time was computed for each participant from the date of Year-5 questionnaire completion (1998–2003) to the date of CVD diagnosis, death, loss to follow-up, or end of follow-up (September 30, 2010), for which the mean (SD) was 6.7 (2.7) years. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% CI for crude and multivariable-adjusted models. A parsimonious model-building approach was utilized to maximize statistical power and reduce the probability of bias. Adjustments started with age (years) and smoking (status and pack-years) as done in other epidemiologic studies on periodontitis,[12,22] then added dental visit frequency, history of diabetes mellitus, and other factors relevant to CVD risk. Stratified analyses and cross-product regression terms were used to evaluate whether associations varied appreciably across prespecified cohort subgroups. The proportional hazards assumption was evaluated by visual inspection of cumulative hazard plots grouped on exposures; no appreciable violations were noted. The impact of subclinical disease at baseline was evaluated by excluding the first year of follow-up; little change was noted. *P*-values are for 2-sided hypothesis tests at α=0.05.

Results

Characteristics of the cohort are shown in Table 1. Overall, the mean age was 68.1 years and the majority was non-Hispanic white with at least some college education. About half the cohort was overweight or obese and two thirds reported ever using hormone therapy. Prevalence of major CVD risk factors was 4.1%, 5.0%, 36.7%, and 11.9% for current smoking, diabetes mellitus, hypertension, and hypercholesterolemia, respectively.

The prevalence of periodontitis diagnosis was 26% (Table 1). Because of the large cohort size, many of the comparisons between women with and without periodontitis were statistically significant although differences were small. Women with periodontitis tended to be younger, more educated, consume more alcohol, and have higher frequency of dental visits and lower frequency of edentulism as compared with women without periodontitis (P<0.05, all). The only significant differences in CVD risk factors were for slightly lower frequency of hypertension and higher frequency of current smoking in women with periodontitis (P<0.05, all). Mean age at menopause was somewhat higher in those with than without periodontitis (P=0.02). Hormone therapy use was comparable between groups.

The cohort prevalence of edentulism was 5.9% (Table 1). Edentulous women were older, less educated and physically active, consumed less alcohol and a less healthy diet, visited the dentist less frequently, and had lower frequency of periodontitis compared to dentate women (P<0.001, all). CVD risk factors were significantly worse among edentulous women, with nearly 35% being obese and prevalence of current smoking, diabetes mellitus, hypertension, and hypercholesterolemia being 10.5%, 10.8%, 46.7%, and 14.5%, respectively (P<0.001, all). Edentulous women had a lower mean age at menopause and were more frequently never hormone users (P<0.001, each).

The mean time to event or censoring was 6.8 and 6.7 years in women with and without periodontitis (P<0.001), and 6.0 and 6.8 years in edentulous and dentate women (P<0.001). There were 3816 total deaths (819 CVD) and 3589 total CVD events identified. Rates and hazard ratios of study outcomes according to periodontitis and edentulous status are shown in Table 2. Crude rates (per 1000 person years) of total CVD, CHD, and stroke in women with and without periodontitis were 9.4 and 9.4 (P=0.94), 4.4 and 4.3 (P=0.93), and 2.2 and 2.1 (P=0.78), respectively. Following adjustment for age, smoking status, and pack-years, relative hazards (95% CI) for these end point comparisons were 1.01 (0.94–1.09), 1.02 (0.91–1.14), and 1.08 (0.93–1.26). Further adjustment for dental visits and diabetes mellitus, and for demographic and CVD risk factors did not materially change these associations or their lack of statistical significance.

The crude rate for total mortality was significantly higher in women with (10.5) than without (9.4, P=0.005) periodontitis. The age- and smoking-adjusted relative hazard was 1.08 (1.00–1.16, P=0.042) and was 1.12 (1.05–1.21) after further adjustment for dental visits and diabetes mellitus. This higher relative hazard associated with periodontitis persisted with additional adjustments. Crude rates of CVD mortality were 2.0 and 2.1 in those with and without periodontitis (P=0.69). CVD mortality was not associated with periodontitis in adjusted regression models.

Crude rates for total CVD (16.6 versus 9.0, P<0.001), CHD (8.1 versus 4.1, P<0.001), and stroke (2.7 versus 2.1, P=0.063) were higher in edentulous compared with dentate women. Age- and smoking-adjusted relative hazards for this comparison were significantly higher for total CVD (HR=1.42, 95% CI: 1.27–1.59) and CHD (HR=1.47, 95% CI: 1.25–1.73), but not for stroke (HR=0.97, 95% CI: 0.74–1.28). These associations were not statistically significant after further adjustment.

Edentulous women had significantly higher crude rates of total mortality (18.9 versus 9.2, P<0.001) and CVD mortality (4.5 versus 2.0, P<0.001) compared with dentate women. Age- and smoking-adjusted hazard ratios remained significantly elevated for both total mortality (HR=1.47, 95% CI:

Table 1. Characteristics of the Total Study Group and According to Periodontitis and Edentulism Status (n=57 001)

		Periodontitis			Edentulism		
	Total	Yes	No		Yes	No	
	57 001	14 847	42 154		3342	53 659	
	N (%)	N (%)	N (%)	*P* Value	N (%)	N (%)	*P* Value
Age, y							
Mean±SD	68.1±7.1	67.6±6.9	68.3±7.2	<0.001	70.2±7.0	68.0±7.1	<0.001
50 to 59	8354 (14.7)	2276 (15.3)	6078 (14.4)	<0.001	260 (7.8)	8094 (15.1)	<0.001
60 to 69	24 945 (43.8)	6936 (46.7)	18 009 (42.7)		1311 (39.2)	23 634 (44.0)	
≥70	23 702 (41.5)	5635 (38.0)	18 067 (42.9)		1771 (52.9)	21 931 (40.9)	
Ethnicity							
White	48 999 (86.0)	12 703 (85.6)	36 296 (86.1)	<0.001	2644 (79.1)	46 355 (86.4)	<0.001
Black	3589 (6.3)	1121 (7.6)	2468 (5.9)		418 (12.5)	3171 (5.9)	
Other	4413 (7.7)	1023 (6.8)	3390 (8.0)		280 (8.4)	4133 (7.7)	
Education							
≤High school diploma	10 920 (19.2)	2204 (14.8)	8716 (20.7)	<0.001	1339 (40.1)	9581 (17.9)	<0.001
College or some college	27 293 (47.9)	6931 (46.7)	20 362 (48.3)		1539 (46.1)	25 754 (48.0)	
Postgraduate	18 788 (33.0)	5712 (38.5)	13 076 (31.0)		464 (13.9)	18 324 (34.1)	
Body mass index, kg/m^2							
Mean±SD	27.1±5.7	27.2±5.7	27.1±5.6	0.134	28.8±6.3	27.0±5.6	<0.001
<25	23 471 (41.2)	6008 (40.4)	17 463 (41.4)	0.103	978 (29.3)	22 493 (41.9)	
25.0 to 29.9	19 683 (34.5)	5255 (35.4)	14 428 (34.2)		1147 (34.3)	18 536 (34.6)	
≥30	13 847 (24.3)	3584 (24.2)	10 263 (24.4)		1217 (36.4)	12 630 (23.5)	
Physical activity (MET-hr/week)							
Mean±SD	13.9±14.0	13.9±13.7	13.9±14.1	0.889	10.6±13.3	14.1±14.0	<0.001
Healthy eating index, units							
Mean±SD	69.5±10.5	69.0±10.7	69.7±10.4	<0.001	65.7±11.4	69.7±10.4	<0.001
Smoking status							
Never smoked	30 216 (53.0)	6461 (43.5)	23 755 (56.4)	<0.001	1371 (41.0)	28 845 (53.8)	<0.001
Past smoker	24 470 (42.9)	7531 (50.7)	16 939 (40.2)		1619 (48.4)	22 851 (42.6)	
Current smoker	2315 (4.1)	855 (5.8)	1460 (3.5)		352 (10.5)	1963 (3.7)	
Smoking pack-years							
Mean±SD	9.1±16.8	13.1±19.9	7.7±15.3	<0.001	17.3±23.4	8.6±16.2	<0.001
0	30 216 (53.0)	6461 (43.5)	23 755 (56.4)	<0.001	1371 (41.0)	28 845 (53.8)	<0.001
≤40	23 021 (40.4)	6753 (45.5)	16 268 (38.6)		1418 (42.4)	21 603 (40.3)	
>40	3764 (6.6)	1633 (11.0)	2131 (5.1)		553 (16.5)	3211 (6.0)	
Alcohol serving/week							
Mean±SD	2.58±5.2	3.09±5.87	2.40±4.93	<0.001	1.70±4.59	2.64±5.24	<0.001
Age at menopause							
Mean±SD	48.5±6.0	48.6±5.9	48.5±6.0	0.021	47.6±6.9	48.5±5.9	<0.001

Continued

Table 1. Continued

		Periodontitis			Edentulism		
	Total	Yes	No		Yes	No	
	57 001	14 847	42 154		3342	53 659	
	N (%)	N (%)	N (%)	*P* Value	N (%)	N (%)	*P* Value
Hormone therapy use							
Never user	16 190 (29.2)	4164 (28.8)	12 026 (29.3)	<0.001	1278 (40.6)	14 912 (28.5)	<0.001
Former user	16 043 (28.1)	4192 (28.2)	11 851 (28.1)		872 (26.1)	15 171 (28.2)	
Current user	23 207 (40.7)	6102 (41.1)	17 105 (40.6)		997 (29.8)	22 210 (41.4)	
History of treated diabetes mellitus							
Yes	2847 (5.0)	774 (5.2)	2073 (4.9)	0.155	362 (10.8)	2485 (4.6)	<0.001
History of treated hypertension							
Yes	20 940 (36.7)	5341 (36.0)	15 599 (37.0)	0.025	1561 (46.7)	19 379 (36.1)	<0.001
History of treated high cholesterol							
Yes	6766 (11.9)	1740 (11.7)	5026 (11.9)	0.510	486 (14.5)	6280 (11.7)	<0.001
Routine dental check-ups							
≥2 times per year	39 800 (69.8)	11 735 (79.0)	28 065 (66.6)	<0.001	420 (12.6)	39 380 (73.4)	<0.001
≤1 time per year	10 081 (17.6)	1748 (11.8)	8333 (19.7)		472 (14.1)	9609 (17.9)	
Whenever needed	4082 (7.2)	814 (5.5)	3268 (7.8)		899 (26.9)	3183 (5.9)	
None in past 3 years	3038 (5.3)	550 (3.7)	2488 (5.9)		1551 (46.4)	1487 (2.8)	
Edentulous							
Yes	3342 (5.9)	682 (4.6)	2660 (6.3)	<0.001			
History of periodontitis							
Yes					682 (20.4)	14 165 (26.4)	<0.001

Data coincide with, or were the most recently obtained relative to, the Year-5 periodontal disease questionnaire. Comparisons were made using χ^2 tests for proportions and independent *t* tests or Wilcoxon tests for means. MET, metabolic equivalent.

1.32–1.63) and CVD mortality (HR=1.59, 95% CI: 1.28–1.98). Fully adjusted hazard ratios were attenuated but remained statistically significant for total mortality (HR=1.17, 95% CI: 1.02–1.33) but not for CVD mortality (HR=1.07, 95% CI: 0.81–1.40).

Stratified associations are shown in Tables 3 and 4. After adjusting for age and smoking, there were no appreciable differences in magnitude or significance of associations between periodontitis and either CVD risk or total mortality across categories of age, race-ethnicity, smoking pack-years, history of diabetes mellitus, or frequency of dental visits (interaction $P>0.05$, all). There was a stronger association between edentulism and CVD among women who visited the dentist at least once per year (HR=1.57) compared with less than once per year (HR=1.03, interaction $P=0.004$). Results were similar for stratified associations between edentulism and total mortality (HR=1.63 for visits ≥1 per year; HR=1.08 for visits <1 per year; interaction $P=0.002$).

In sensitivity analysis (data not shown), in participant subsets where information was available, adjustment for self-rated health status, depression, and use of statins did not materially change the primary findings. To further explore potential diagnostic ascertainment bias, associations were stratified on finer groupings of dental visit frequency. Subgroups tended to have limited sample size. Comparable hazard ratios for total CVD and mortality were seen for periodontitis diagnosis across all levels of dental visit frequency. Higher risks of total CVD and total mortality persisted in edentulous women with more frequent dental visits, as seen in the main analysis. Lastly, we explored disease risks according to jointly classified periodontitis and edentulism exposures. Sample sizes and CVD event counts were particularly small for the exposure group in which women reported being positive for both periodontitis and edentulism (N=682; 12 strokes, 13 CVD deaths, 30 CHD cases), which limited statistical power and precision of results in this subgroup. For the total mortality outcome, for which end point counts are largest (93 deaths in those reporting "yes" to both exposure questions), results showed the highest risk in women reporting both periodontitis and edentulism.

Table 2. Rates, Hazard Ratios (HR) and 95% CI for CVD Events and Mortality According to Periodontitis and Edentulism (n=57 001)

	Periodontitis			Edentulism		
	No 42 154	Yes 14 847	*P* Value	No 53 659	Yes 3342	*P* Value
Total cardiovascular disease						
Events, no.	2640	949		3257	332	
Person-years	281 882	101 439		363 269	20 053	
Rate per 1000 person-years	9.4	9.4		9.0	16.6	
Unadjusted HR (95% CI)	1.00 (ref)	1.00 (0.93–1.07)	0.94	1.00 (ref)	1.86 (1.66–2.08)	<0.001
Model 1 adjusted HR (95% CI)	1.00 (ref)	1.01 (0.94–1.09)	0.83	1.00 (ref)	1.42 (1.27–1.59)	<0.001
Model 2 adjusted HR (95% CI)	1.00 (ref)	1.04 (0.97–1.13)	0.28	1.00 (ref)	1.09 (0.95–1.26)	0.21
Model 3 adjusted HR (95% CI)	1.00 (ref)	1.06 (0.98–1.14)	0.14	1.00 (ref)	1.07 (0.93–1.23)	0.36
Coronary heart disease*						
Events, No.	1238	450		1520	168	
Person-years	287 232	103 353		369 907	20 678	
Rate per 1000 person-years	4.3	4.4		4.1	8.1	
Unadjusted HR (95% CI)	1.00 (ref)	1.01 (0.90–1.12)	0.92	1.00 (ref)	2.02 (1.72–2.37)	<0.001
Model 1 adjusted HR (95% CI)	1.00 (ref)	1.02 (0.91–1.14)	0.72	1.00 (ref)	1.47 (1.25–1.73)	<0.001
Model 2 adjusted HR (95% CI)	1.00 (ref)	1.07 (0.96–1.19)	0.25	1.00 (ref)	1.11 (0.91–1.36)	0.30
Model 3 adjusted HR (95% CI)	1.00 (ref)	1.08 (0.97–1.20)	0.18	1.00 (ref)	1.10 (0.90–1.34)	0.36
Stroke†						
Events, no.	612	226		782	56	
Person-years	287 875	103 659		370 673	20 860	
Rate per 1000 person-years	2.1	2.2		2.1	2.7	
Unadjusted HR (95% CI)	1.00 (ref)	1.02 (0.88–1.19)	0.77	1.00 (ref)	1.29 (0.99–1.70)	0.06
Model 1 adjusted HR (95% CI)	1.00 (ref)	1.08 (0.93–1.26)	0.31	1.00 (ref)	0.97 (0.74–1.28)	0.83
Model 2 adjusted HR (95% CI)	1.00 (ref)	1.10 (0.95–1.29)	0.21	1.00 (ref)	0.77 (0.55–1.06)	0.10
Model 3 adjusted HR (95% CI)	1.00 (ref)	1.11 (0.95–1.30)	0.19	1.00 (ref)	0.77 (0.55–1.06)	0.10
Total mortality						
Deaths, no.	2726	1090		3421	395	
Person-years	288 976	104 059		372 149	20 886	
Rate per 1000 person-years	9.4	10.5		9.2	18.9	
Unadjusted HR (95% CI)	1.00 (ref)	1.11 (1.03–1.19)	0.005	1.00 (ref)	2.11 (1.90–2.34)	<0.001
Model 1 adjusted HR (95% CI)	1.00 (ref)	1.08 (1.00–1.16)	0.04	1.00 (ref)	1.47 (1.32–1.63)	<0.001
Model 2 adjusted HR (95% CI)	1.00 (ref)	1.12 (1.05–1.21)	0.002	1.00 (ref)	1.16 (1.02–1.33)	0.02
Model 3 adjusted HR (95% CI)	1.00 (ref)	1.12 (1.05–1.21)	0.002	1.00 (ref)	1.17 (1.02–1.33)	0.02
CVD mortality‡						
Deaths, no.	606	213		726	93	
Person-years	288 976	104 059		372 149	20 886	
Rate per 1000 person-years	2.1	2.0		2.0	4.5	
Unadjusted HR (95% CI)	1.00 (ref)	0.97 (0.83–1.13)	0.69	1.00 (ref)	2.36 (1.90–2.92)	<0.001
Model 1 adjusted HR (95% CI)	1.00 (ref)	1.01 (0.86–1.18)	0.95	1.00 (ref)	1.59 (1.28–1.98)	<0.001

Continued

Table 2. Continued

	Periodontitis			Edentulism		
	No 42 154	Yes 14 847	*P* Value	No 53 659	Yes 3342	*P* Value
Model 2 adjusted HR (95% CI)	1.00 (ref)	1.08 (0.92–1.27)	0.33	1.00 (ref)	1.06 (0.81–1.39)	0.67
Model 3 adjusted HR (95% CI)	1.00 (ref)	1.09 (0.93–1.28)	0.30	1.00 (ref)	1.07 (0.81–1.40)	0.64

Model 1—adjusted for age, smoking (status and pack-years). Model 2—adjusted for factors in model 1 plus dental visits and diabetes mellitus. Model 3—adjusted for factors in model 2 plus race-ethnicity, education, hypertension, high cholesterol, body mass index, physical activity, alcohol, and dietary healthy eating index. CVD indicates cardiovascular disease.
*Includes myocardial infarction or cardiac death.
†Ischemic strokes only.
‡Includes myocardial infarction, cardiac death, cerebrovascular events, pulmonary embolism, and heart failure.

Compared to women with neither exposure (referent), the multivariable adjusted HR (95% CI) was 1.46 (1.17, 1.81) among women with both exposures present; 1.12 (0.97, 1.30) for women reporting no periodontitis/yes edentulism; and was 1.11 (1.03, 1.20) for women reporting yes periodontitis/no edentulism.

Discussion

Accumulating evidence strongly suggests a biological link between periodontitis and atherosclerotic CVD, but few studies have evaluated this hypothesis in older women. In our study of postmenopausal women, 1 in 4 reported a history periodontitis diagnosis which was not associated with elevated risks of CVD events or CVD mortality. Edentulism, however, was associated with significantly higher risks of total CVD and CHD, and CVD mortality. These increased risks were robust to adjustment for confounding and were generally consistent across cohort subgroups. An association was not seen with ischemic stroke, though case counts were relatively small for this end point. Total mortality risk also was significantly higher in women with either edentulism or periodontitis even when adjusted for confounding. The association for edentulism with total CVD and mortality appeared stronger in women who reported more frequent dental visits. Because edentulism may be a more objective reflection of periodontal health than self-reported periodontitis diagnosis,[16,23] and because tooth loss at older ages occurs predominantly due to periodontitis,[1] the present findings are consistent with the hypothesis that dental inflammatory processes and resulting periodontitis may be relevant to atherosclerotic CVD risk in older adults. Additional prospective studies with objective periodontal measures and randomized CVD prevention trials that intervene on existing periodontitis are needed to confirm this hypothesis.

Positive associations with risks of CVD and mortality have been more consistently reported in studies that defined periodontitis based on clinical examination[6–9,24–26] as compared to self-report.[11–13,22,27] Because in the present study periodontitis was assessed by self-report, comparison with studies using similar methodology seems most relevant. No association between self-reported periodontitis diagnosis and CVD risks has been reported among middle-aged and older men in the Health Professionals[22] and Physician's Health[11] studies. Periodontitis prevalence was lower (12–15%) than in the present study (26%), whereas higher prevalence was seen for current smoking and diabetes mellitus, each of which are strongly associated with periodontitis and CVD. Nevertheless, age- and smoking-adjusted relative risks for total CVD or CHD were similar in the studies on men (relative risk [RR] 1.04–1.12) and the present study (HR 1.02). In the Women's Health Study,[13] follow-up on predominantly white women ages 45 and older with similar diabetes mellitus history but higher current smoking than in the present study showed significantly increased relative risks of total CVD and myocardial infarction associated with self-reported periodontitis following age adjustment (RR 1.27 and 1.34); risks that remained significantly elevated following multivariable adjustment (RR 1.04 and 1.27). In this study, however, the periodontitis exposure variable was defined as combined history of clinical diagnosis or tooth loss. Thus, it is not possible to fully compare findings with our study in which periodontitis was defined solely on history of clinical diagnosis.

Our finding of no association between periodontitis and incident stroke is similar to results of the Physician's Health Study,[11] but unlike the significant 33% greater age- and smoking-adjusted risk in the Health Professionals Follow-up Study[27] and the 28% greater age-adjusted risk in the Women's Health Study.[13] Both of these studies evaluated nonfatal stroke only, whereas in the present study combined nonfatal and fatal ischemic stroke was the end point.

As in previous studies,[12,13,27] we found that poorer self-assessed dentition status was associated with higher risks of total CVD and CHD. We observed significantly elevated age- and smoking-adjusted relative risks of comparable magnitude

Table 3. Age- and Smoking- (Status and Pack-Years) Adjusted Hazard Ratios (HR) and 95% CI of Total Cardiovascular Disease Incidence for History of Periodontitis and Edentulism According to Study Subgroups

	Events	Periodontitis HR (95% CI)*	Edentulism HR (95% CI)*
Age, y			
50 to 59 (n=8354)	176	1.14 (0.83–1.56)	1.30 (0.61–2.76)
60 to 69 (n=24 945)	1104	1.04 (0.92–1.19)	1.41 (1.13–1.76)
≥70 (n=23 702)	2309	0.98 (0.89–1.08)	1.43 (1.25–1.63)
Interaction *P* value		0.53	0.97
Race-ethnicity			
White (n=48 999)	3238	0.99 (0.92–1.08)	1.45 (1.28–1.64)
Black (n=3589)	190	1.01 (0.75–1.37)	1.21 (0.82–1.79)
Other (n=4413)	161	1.25 (0.88–1.76)	1.24 (0.72–2.15)
Interaction *P* value		0.45	0.61
Smoking pack-years			
0 (n=30 216)	1793	1.00 (0.89–1.12)	1.37 (1.14–1.65)
≤40 (n=23 021)	1444	1.06 (0.94–1.18)	1.56 (1.31–1.85)
>40 (n=3764)	352	0.99 (0.80–1.23)	1.42 (1.09–1.86)
Interaction *P* value		0.75	0.60
History of treated diabetes mellitus			
No (n=54 154)	3232	1.00 (0.93–1.08)	1.40 (1.23–1.58)
Yes (n=2847)	357	1.06 (0.84–1.34)	1.10 (0.82–1.48)
Interaction *P* value		0.62	0.15
Dental visits			
≥1 time per year	2849	1.03 (0.95–1.12)	1.57 (1.23–1.99)
<1 time per year	740	1.06 (0.89–1.27)	1.03 (0.89–1.20)
Interaction *P* value		0.76	0.004

*HR comparing women with periodontitis or edentulism to women without either condition (referent group), within stratum of each modifying factor.

Table 4. Age- and Smoking- (Status and Pack-Years) Adjusted Hazard Ratios (HR) and 95% CI of Total Mortality for History of Periodontitis and Edentulism According to Study Subgroups

	Events	Periodontitis HR (95% CI)*	Edentulism HR (95% CI)*
Age, y			
50 to 59 (n=8354)	224	1.25 (0.95–1.65)	1.53 (0.84–2.81)
60 to 69 (n=24 945)	1047	1.18 (1.03–1.34)	1.46 (1.18–1.81)
≥70 (n=23 702)	2545	1.02 (0.94–1.12)	1.47 (1.30–1.66)
Interaction *P*-value		0.12	0.99
Race-ethnicity			
White (n=48 999)	3451	1.06 (0.99–1.15)	1.44 (1.28–1.61)
Black (n=3589)	187	1.01 (0.74–1.37)	1.58 (1.11–2.26)
Other (n=4413)	178	1.48 (1.08–2.02)	1.73 (1.10–2.73)
Interaction *P*-value		0.12	0.68
Smoking pack-years			
0 (n=30 216)	1731	1.13 (1.01–1.27)	1.43 (1.19–1.72)
≤40 (n=23 021)	1597	1.08 (0.97–1.20)	1.67 (1.43–1.96)
>40 (n=3764)	506	1.06 (0.89–1.26)	1.38 (1.11–1.73)
Interaction *P*-value		0.75	0.28
History of treated diabetes mellitus			
No (n=54 154)	3521	1.07 (0.99–1.15)	1.42 (1.27–1.60)
Yes (n=2847)	295	1.23 (0.96–1.58)	1.44 (1.08–1.93)
Interaction *P*-value		0.23	0.94
Dental visits			
≥1 time per year	3005	1.10 (1.02–1.19)	1.63 (1.30–2.04)
<1 time per year	811	1.16 (0.98–1.37)	1.08 (0.93–1.24)
Interaction *P*-value		0.61	0.002

*HR comparing women with periodontitis or edentulism to women without either condition (referent group), within stratum of each modifying factor.

to those in men in the Health Professionals study[12,27] and women in the Nurse's Health Study,[12] for which the exposure was 0 to 10 teeth present (RR 1.49–2.13). Whereas stroke risk was elevated in the Health Professionals study, we did not observe greater risk among edentulous women following adjustment for age and smoking. The small number of stroke cases among edentulous women likely limited our study.

Total mortality arguably is the best measure of the impact a risk factor or disease has on population health.[28] Previous studies evaluating total mortality typically have used oral examinations to define periodontitis.[6–9,26] Higher mortality risk generally has been associated with presence and severity of periodontitis and with tooth loss, and tends to persist following adjustment for age, smoking, diabetes mellitus, and other factors. In the present study on older women, significant increases in total mortality were seen for both history of periodontitis and edentulism. Mortality risks remained elevated and of comparable magnitude within strata of selected cohort subgroups including categories of smoking pack-years and diabetes mellitus status. Our multivariable adjusted hazard ratio of 1.17 among edentulous women is comparable to that (RR 1.21) recently reported in women 80 years old who self-reported edentulism.[10] Taken together, available findings including the present study suggest that factors related to periodontitis and retaining natural teeth may have important implications for survival.

Frequency of dental visits did not modify associations of periodontitis with total- and CVD mortality, easing concern about potential diagnostic ascertainment bias. Conversely, significantly stronger associations for edentulism with both mortality end points were observed in women with more frequent compared to less frequent dental visits. The reason for this interaction is not completely clear. It is possible that edentulous women also had historically more aggressive periodontitis requiring greater utilization of dental services. We do not have measures of periodontitis severity to directly test this hypothesis, nor do we have information on reason for dental visits, which also could have provided context for this result. Although previous studies have demonstrated an inverse association between frequency of past year dental visits and total mortality in older women,[10] the joint effect of dental visits with either periodontitis or edentulism was not reported; thus, comparison with, and context for, our present findings is not possible.

Numerous biologic mechanisms support plausibility of an association between periodontitis, edentulism, and risks of CVD or mortality.[4,9,24,29,30] Prominent is systemic endotoxemia and inflammation resulting from transient bacteremia induced by subgingival bacterial leaking through ulcerated epithelium of the periodontal pocket.[30] It is reasonable to expect that with loss of all natural teeth, persistent periodontal infection is unlikely. However, edentulism is more a reflection of historical dental infection that, when present, probably contributed both to atherosclerotic disease onset and progression as well as to breakdown of the periodontium and subsequent tooth loss. Another possibility is translocation of bacteria from the oral to systemic compartment that then initiate localized inflammatory and immune responses at extraoral sites. This mechanism is thought to be relevant to atherosclerotic CVD,[29,30] particularly in light of oral microbes being found in atheromatous plaque.[31] Factors such as smoking and uncontrolled diabetes mellitus, each an antecedent for periodontitis and atherosclerosis, likely reflect common pathways shared by these diseases.[24,30] Menopausal reduction in endogenous estrogen may be another biologic pathway shared by periodontitis[32] and atherosclerotic CVD. Lastly, shared genetic susceptibility could predispose individuals to these chronic inflammatory conditions.[33]

Study strengths include the large cohort of older postmenopausal women, in whom the association of interest has been understudied, and the long follow-up and sufficient number of end point events for primary analysis and stratification by cohort subgroups. Surveillance for outcomes was conducted with a standardized approach administered nationally by the WHI program. The extensive available baseline information allowed control for several relevant confounding factors. A major limitation of this study was reliance on self-reported periodontitis and dentition status. Although some misclassification would be expected, a previously conducted validation study in a subgroup of WHI OS participants showed that older women can validly report history of periodontitis diagnosis.[16] Sensitivity and specificity determined by cross-classifying self-reported with clinically assessed periodontitis were reasonably strong for both younger and older women, and for women of differing levels of education in our study group (generally 60–80%). These are comparable to values reported between self-reported and clinically measured periodontitis in the Health Professionals Follow-up Study.[12,23,27] Based on the sensitivity and specificity values in our validation study, and as postulated by Joshipura,[27] one might expect misclassification on periodontitis history to be around 30% to 40%, which would theoretically attenuate a true relative risk for CVD of 2.0 to about 1.2 to 1.4, comparable to many of the point estimates seen in the present study. Nevertheless, the possibility of exposure misclassification should be considered when interpreting findings reported herein. The somewhat stronger and more consistent adverse findings associated with edentulism, which is a more reliable marker of periodontitis history than self-reported diagnosis, enhances confidence in the present results. Moreover, if edentulism is, in fact, a surrogate for past periodontitis, the expectation should be that women reporting exposure to both factors have the highest disease risks. Indeed, our sensitivity analysis cross-tabulating total mortality on jointly classified periodontitis and edentulism exposures supported this assertion. Because the history of periodontitis diagnosis was self-reported as a binary response (yes or no), we were unable to evaluate potential differences in associations with study outcomes based on disease severity. Moreover, understanding whether a dose–response pattern of association exists with periodontitis is of interest,

but cannot be addressed here. Reliance on a single assessment of periodontitis to predict risks of long-term disease occurrence also could be seen as a potential study limitation. However, other studies that have evaluated periodontitis exposures assessed both at baseline as well as again during follow-up have reported comparable relative risk measures for CVD incidence and mortality.[12,13,27] Although we included in multivariable models markers of socioeconomic status, the possibility for residual confounding by socioeconomic factors or by healthcare utilization is plausible.

In conclusion, among community-dwelling older postmenopausal women with no history of CVD, we observed no association between reported history of periodontitis diagnosis and incidence of atherosclerotic CVD events. We did observe significantly higher risks of CVD incidence and mortality for edentulous compared to dentate women, risks that were stronger in women reporting more frequent annual dental visits. Both self-reported periodontitis and edentulism were significantly associated with increased total mortality. The relevance of periodontitis and tooth loss as possible modifiable risk factors for CVD prevention or prolonged survival at later ages needs confirmation by other studies.

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Disclosures

None.

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History of Periodontitis Diagnosis and Edentulism as Predictors of Cardiovascular Disease, Stroke, and Mortality in Postmenopausal Women

Michael J. LaMonte, Robert J. Genco, Kathleen M. Hovey, Robert B. Wallace, Jo L. Freudenheim, Dominique S. Michaud, Xiaodan Mai, Lesley F. Tinker, Christian R. Salazar, Christopher A. Andrews, Wenjun Li, Charles B. Eaton, Lisa W. Martin and Jean Wactawski-Wende

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