Title

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Journal

American Journal of Hypertension, 32(2)

ISSN

0895-7061

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Publication Date

2019-01-15

DOI

10.1093/ajh/hpy164

Peer reviewed

Association of Periodontal Disease and Edentulism With Hypertension Risk in Postmenopausal Women

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BACKGROUND
Multiple cross-sectional epidemiologic studies have suggested an association between periodontal disease and tooth loss and hypertension, but the temporality of these associations remains unclear. The objective of our study was to evaluate the association of baseline self-reported periodontal disease and edentulism with incident hypertension.

METHODS
Study participants were 36,692 postmenopausal women in the Women's Health Initiative-Observational Study who were followed annually from initial periodontal assessment (1998–2003) through 2015 (mean follow-up 8.3 years) for newly diagnosed treated hypertension. Cox proportional hazards regression with adjustment for potential confounders was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS
Edentulism was significantly associated with incident hypertension in crude (HR (95% CI) = 1.38 (1.28–1.49)) and adjusted (HR (95% CI) = 1.21 (1.11–1.30)) models. This association was stronger among those <60 years compared to ≥60 years (*P* interaction 0.04) and among those with <120 mm Hg systolic blood pressure, compared to those with ≥120 mm Hg (*P* interaction 0.004). No association was found between periodontal disease and hypertension.

CONCLUSIONS
These findings suggest that edentulous postmenopausal women may represent a group with higher risk of developing future hypertension. As such improved dental hygiene among those at risk for tooth loss as well as preventive measures among the edentulous such as closer blood pressure monitoring, dietary modification, physical activity, and weight loss may be warranted to reduce disease burden of hypertension. Further studies are needed to clarify these results and further elucidate a potential role of periodontal conditions on hypertension risk.

Keywords: blood pressure; edentulous; hypertension; mouth; periodontal diseases; postmenopause; prospective cohort study.

doi:10.1093/ajh/hpy164

Several cross-sectional epidemiologic studies have suggested that periodontal disease and/or tooth loss are positively associated with blood pressure levels and hypertension.[1–7] However, because of their design, these studies cannot account for the potential for reverse causality. Moreover, prospective studies evaluating risk of hypertension associated with baseline periodontal disease and missing teeth are few and have conflicting results.[8–10] Despite the high prevalence of hypertension and periodontal disease among postmenopausal women, few prospective studies on periodontal disease and hypertension have focused on this group.

Complete edentulism, the loss of all teeth, is the terminal stage of periodontal disease and may represent another condition predisposing for hypertension. Edentulism has been

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Initially submitted June 30, 2018; date of first revision September 16, 2018; accepted for publication November 20, 2018; online publication December 4, 2018.

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found to be associated with coronary heart disease,[11] stroke,[12] and all-cause mortality.[13] In cross-sectional epidemiologic studies, edentulism was associated with elevated systolic blood pressure (SBP),[6,7] diastolic blood pressure (DBP),[7] and prevalent hypertension.[7,14] Risk of hypertension associated with edentulism could be related to life-course health factors that either lead to or were associated with edentulism, including past history of periodontal disease. Alternatively, microbiome or diet associated with an edentulous mouth could help to promote hypertension. To the best of our knowledge, no previous studies have evaluated edentulism as a prospective risk factor for hypertension in women.

Considering the limited prospective data on periodontal disease and edentulism as risk factors for hypertension, we assessed whether periodontal disease and edentulism are associated with longitudinal hypertension risk within the Women's Health Initiative-Observational Study (WHI-OS).

METHODS

Study design and study population

The WHI-OS is a prospective cohort study of 93,676 postmenopausal women. Women aged 50–79 years were enrolled at 40 clinical sites across the United States between 1993 and 1998. The study was approved by human subjects institutional review boards at each of the participating sites, and informed consent was provided by each participant. The baseline for the present analyses was year 5 of the WHI-OS, where study participants were queried about oral health, including periodontal/gum disease and edentulism.

Of the 82,414 women who responded to the year-5 questionnaire, participants were excluded if they did not answer questions on periodontal/gum disease (n = 611, 0.74%) or edentulism (n = 423, 0.51%), or were missing follow-up data after year 5 (n = 715, 0.87%). Participants were also excluded who had prevalent hypertension at or before the year-5 questionnaire, based on self-report of a physician diagnosis of hypertension, current or past use of antihypertension medication, or measured SBP or DBP ≥140 or ≥90 mm Hg, respectively at either WHI-OS baseline or year-3 study visits (n = 42,659, 51.8%). After application of these exclusion criteria, 38,147 women remained eligible for this analysis. An additional 1,455 participants were excluded based on missing data for key variables including body mass index (BMI) (n = 63), pack-years smoking (n = 1,115), education (n = 285), or baseline SBP (n = 5). The analytic cohort consists of 36,692 women who have complete data on all information relevant to this analysis (Figure 1).

Measurement of study variables

The primary exposure variables were history of periodontal disease diagnosis and/or edentulism. Periodontal disease was assessed on the year-5 questionnaire as "Has a dentist or dental hygienist ever told you that you had periodontal or gum disease?". Edentulism was assessed using the question "Have you lost ALL your permanent teeth, both upper and lower?". Incident hypertension was the outcome variable and was assessed on annual health updates each study participant completed following study entry. Specifically, those who answered yes to the question "Since your last completed questionnaire, has a doctor or other healthcare provider prescribed for the first time pills for high blood pressure or hypertension?" were considered an incident hypertension case.

SBP and DBP were measured *via* auscultation using a conventional sphygmomanometer at WHI-OS baseline enrollment and year-3 clinic examination. Blood pressure measurements were not available at year 5, thus most recent blood pressure measurements were considered in models. Blood pressure was measured after 5 minutes of seated rest in a clinic examination room. The average of 2 measures taken at least 30 seconds apart was recorded. Additional study covariates were collected *via* questionnaire including smoking history (current status: never, former, current; total pack-years), physical activity (based on total recreational activity; metabolic equivalent-hours/week), sleep disturbance score (based on several questions regarding sleep hygiene, quality, and restedness), highest level of education, neighborhood socioeconomic status (based on several items from census tract), race/ethnicity, hormone therapy use, and comorbidities.[15–20] The Healthy Eating Index-2005 (HEI-2005), a composite dietary score based on 12 food categories, and composite variables for total intake of alcohol, caffeine, sodium, and red meat, were calculated based on WHI food frequency questionnaire.[21] Measurements of height and weight[16] were taken at the year-3 clinical examination and used for calculating BMI (kg/m^2). Medication for diabetes mellitus, anti-cholesterol agents, and multivitamin usage were recorded *via* a medication inventory.[22] In our analyses, individuals were considered to have diabetes if they either reported a physician diagnosis of diabetes or were currently taking medication for diabetes.

Statistical analyses

Data analysis was conducted using SAS, version 9.4 (SAS Institute, Cary, NC). Comparison of characteristics between those with and without hypertension was accomplished using nonparametric Wilcoxon rank-sum test for continuous variables and X^2 test of independence for categorical variables. Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) to test crude and multivariable adjusted associations between periodontal disease and edentulism, and hypertension diagnosis. Stratified analyses and interaction testing were performed with previously determined potential effect modifying variables: age, ethnicity, smoking status, BMI, alcohol intake, total physical activity, diabetes, frequency of dental visits, and baseline SBP. In stratified analysis of continuous variables (age, BMI, alcohol intake, total physical activity, and SBP), models are further adjusted for the stratifying variable within each stratum. Interaction on a multiplicative scale was tested by including variables for the factor of interest plus a cross-product term for the either periodontal disease or edentulism and the factor of interest. Wald X^2 test was used to assess the significance of the cross-product term. Potential confounding factors were each added to the crude models of periodontal disease and edentulism, and hypertension individually. Potential confounders included age, BMI, race/ethnicity, education level, smoking status, pack-years smoking, alcohol intake, dietary energy,

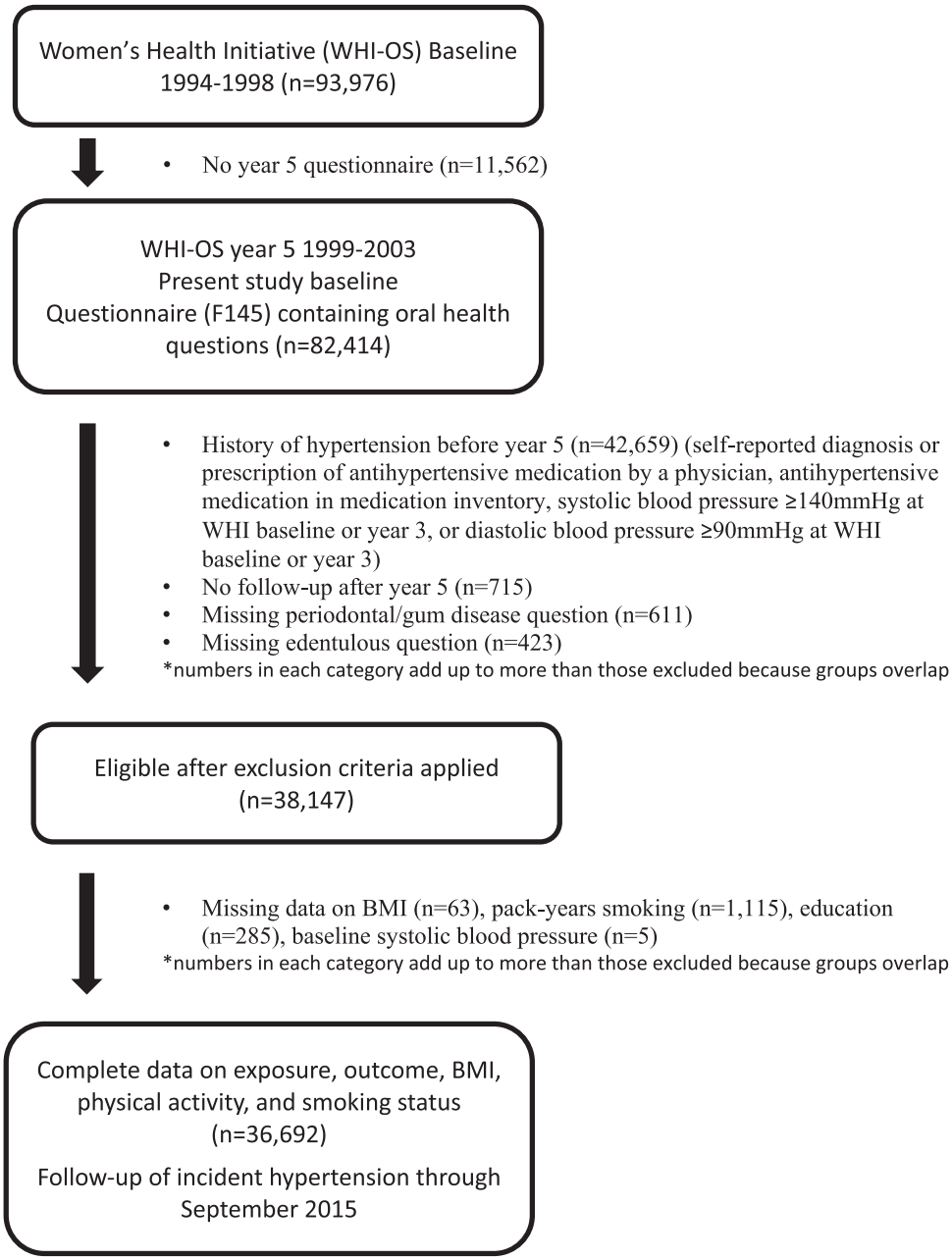

Figure 1. Study enrollment flow diagram and timeline.

HEI-2005, caffeine intake, red meat intake, dietary sodium, physical activity, sleep disturbance, hours of sleep, diabetes, cancer, heart disease, stroke, statin use, multivitamin use, and hormone therapy use. Factors were included in final multivariable adjusted model if their inclusion resulted in changes to the association between the periodontal disease or edentulism exposure and hypertension by at least 1%; however, factors showing significant interaction were not included in overall multivariable adjusted model.

To evaluate potential influence of missing data, we analyzed missing data patterns and conducted sensitivity analyses of primary models after multiple imputation by fully conditional specification. We conducted a sensitivity analysis excluding anyone with previous diagnosis of cardiovascular disease (CVD) and one excluding anyone diagnosed with hypertension or censored within the first 2 years of follow-up to minimize the possibility of reverse causation bias by baseline health status.

RESULTS

Characteristics of the 36,692 study participants comprising the analytic cohort are presented in Table 1 categorized by baseline periodontal disease and edentulism. Participants included in this study were all postmenopausal, with mean age of 67.1 (7.0). They were predominantly Caucasian

(89.3%) and mostly with at least some college education (97.3%). Approximately half the women reported never smoking (52.0%), with 43.5% former smokers and 4.5% current smokers. Baseline history of other health conditions was reported as diabetes (2.6%), heart disease (16.8%), and cancer (16.7%).

Those with periodontal disease, compared to those without periodontal disease, had higher number of pack-years smoking, but slightly lower age and SBP (Table 1). BMI values were similar between these 2 groups. Those with edentulism tended have higher age, BMI, and SBP (Table 1). Incident hypertension cases tended to have higher BMI (26.7 ± 5.2 vs. 25.6 ± 4.9 kg/m^2), higher SBP (120.1 ± 10.7 vs. 114.1 ± 11.5 mm Hg), and higher proportion of ever smokers (49.6% vs. 47.2%), but similar age (67.0 ± 7.1 vs. 67.3 ± 6.9 years). The participants were followed from year 5 (1999–2003) through September 2015 for a mean time of 8.3 (4.8) years. In that time, 12,635 (34.4%) developed incident hypertension.

Results of crude and multivariable adjusted regression models are presented in Table 2. Periodontal disease was not associated with increased risk of hypertension in crude (HR (95% CI) = 1.00 (0.96–1.04)) or multivariable adjusted models (HR (95% CI) = 0.99 (0.95–1.03)). Edentulism was significantly associated with hypertension risk in unadjusted model (HR (95% CI) = 1.38 (1.28–1.49)). On the basis of assessment of potential confounders, all multivariable adjusted models were adjusted for education, BMI, and pack-years smoking. Although age also appeared to be a confounder, because in this analysis it also appears to be an effect modifier, only age-stratified models are presented with age adjustment. The overall model with adjustment for education, BMI, and pack-years smoking demonstrates attenuated but statistically significant association between edentulism and hypertension risk (HR (95% CI) = 1.21 (1.11–1.30)). Of note, there was significant interaction with both age and baseline SBP (Table 2.) The risk of hypertension with edentulism appeared stronger in women younger than 60 years of age (*P* interaction 0.04) and those with lower SBP at baseline (*P* interaction 0.0004). In addition, a borderline significant interaction was seen between edentulism and BMI, with women in lower BMI categories having higher hypertension risk (*P* interaction 0.06). No significant interactions were seen for race, smoking status, alcohol intake, physical activity, or diabetes status (Supplementary Table 1).

In sensitivity analyses, no substantial differences in primary results were observed when restricting analyses to individuals with no CVD at baseline, when restricting to individuals with follow-up longer than 2 years, or using multiple imputation for missing covariate data (Supplementary Table 1).

DISCUSSION

In this large prospective cohort study, we observed a modest positive association between edentulism and incident hypertension risk among postmenopausal women enrolled in the WHI-OS. Specifically, edentulous women had approximately 20% higher risk of developing hypertension during follow-up compared to dentate women. We observed a null association between periodontal disease and hypertension.

Previous studies have evaluated missing teeth with respect to hypertension. In a cross-sectional study, Taguchi et al.[4] compared 67 postmenopausal women with any missing teeth (mean 5.8 teeth missing not including 3rd molars) with 31 women without missing teeth. Adjusting for BMI, total cholesterol, and low-density lipoprotein cholesterol, those with any missing teeth had 3.5 higher odds of having either SBP ≥140 mm Hg or DBP ≥90 mm Hg on at least 3 occasions in the clinic (odds ratio = 3.57, 95% CI = 1.10–11.7). Nevertheless, this study was relatively small and its cross-sectional nature could not account for potential reverse causality. Prospective studies have evaluated missing teeth and incident hypertension, although none of these looked specifically at edentulism.[8–10] Although all 3 prospective studies observed positive associations of missing teeth with hypertension, models were nonsignificant after multivariable adjustment. These nonsignificant results may reflect study of relatively young populations with limited follow-up duration,[8,9] or misclassification due to self-report of number of teeth and hypertension outcome.[10] Furthermore, none of these studies assessed this association in a substantial number of postmenopausal women. In addition, although tooth loss is a component of the path to complete edentulism, complete edentulism as a construct that may have characteristics and associated factors distinct from general tooth loss. In cross-sectional studies, edentulism has been found to be associated with increased SBP,[6,7] DBP,[7] and prevalent hypertension.[7,14] Edentulism has additionally been found to be associated with coronary heart disease,[11] stroke,[12] and all-cause mortality[13] in other cohort studies, and recently with all-cause and CVD mortality risks within the WHI-OS using the same assessment of edentulism as here.[23]

Numerous studies have reported significant positive associations between periodontal disease based on self-report or clinically measured periodontal disease status and hypertension using either cross-sectional or case–control designs.[1,3,24,25] Nevertheless, these studies are unable to exclude reverse causality as potential explanation of results. The potential role of hypertension as a risk factor in periodontal disease[26] highlights the need for prospective studies to exclude reverse causality as an explanation of results. Few studies have evaluated the association between periodontal disease and hypertension using prospective design.[8–10] Our finding of a null association between self-reported periodontal disease and hypertension is similar to what was found among older men in the Health Professionals Follow-Up Study (HPFS), which found no association between self-reported periodontal disease and incidence of hypertension by self-report among 31,543 males aged 40–75 years over 20 years of follow-up.[10] Conversely, 2 studies from Japan observed positive associations between periodontal disease based on clinical measures and incident hypertension based on measured blood pressure. The first study was among 1,150 university students mean age 18 years over 3 years follow-up and the second was among

Table 1. Characteristics of participants of Women's Health Initiative Observational Study at baseline (WHI-OS year 5)

		Periodontal/gum disease		Edentulism	
	All (*N* = 36,692)	**No (*n* = 26,773)**	**Yes (*n* = 9,919)**	**No (*n* = 34,829)**	**Yes (*n* = 1,863)**
Age (years; mean ± SD)	67.1 ± 7.0	67.3 ± 7.1*	66.7 ± 6.8*	67.0 ± 7.0*	69.7 ± 7.0*
Pack-years smoking (median IQR)	0.0 (0.0, 12.3)	0.0 (0.0, 7.5)*	1.5 (0.0, 20.0)*	0.0 (0.0, 10.0)*	5.1 (0.0, 34.5)*
Physical activity (MET-hours/week; median IQR)	11.5 (3.8, 21.8)	11.5 (3.8, 21.9)	11.3 (3.8, 21.5)	11.8 (3.8, 22.0)*	6.9 (1.5, 16.9)*
Body mass index (kg/m^2; mean ± SD)	26.0 ± 5.1	26.0 ± 5.1*	26.1 ± 5.1*	25.9 ± 5.0*	27.3 ± 5.6*
Baseline systolic blood pressure (mm Hg; mean ± SD)	116.2 ± 11.6	116.4 ± 11.6*	115.5 ± 11.6*	116.1 ± 11.6*	118.4 ± 11.2*
Baseline diastolic blood pressure (mm Hg; mean ± SD)	70.5 ± 7.7	70.5 ± 7.7	70.4 ± 7.7	70.5 ± 7.7	70.2 ± 7.9
	N (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Ethnicity					
American Indian or Alaskan Native	117 (0.3)	87 (0.3)*	30 (0.3)*	108 (0.3)*	9 (0.5)*
Asian or Pacific Islander	958 (2.6)	726 (2.7)*	232 (2.3)*	921 (2.7)*	37 (2.0)*
Black or African American	1,329 (3.6)	902 (3.4)*	427 (4.3)*	1,189 (3.4)*	140 (7.5)*
Hispanic/Latino	1,162 (3.2)	892 (3.3)*	270 (2.7)*	1,087 (3.1)*	75 (4.0)*
White (not of Hispanic origin)	32,683 (89.3)	23,847 (89.3)*	8,836 (89.3)*	31,108 (89.5)*	1,575 (84.9)*
Other	351 (1.0)	252 (0.9)*	99 (1.0)*	332 (1.0)*	19 (1.0)*
Education					
High school or less	1,006 (2.7)	4,812 (18)*	1,216 (12.3)*	5,336 (15.3)*	692 (37.1)*
College or some college	17,589 (47.9)	12,678 (47.4)*	4,641 (46.8)*	1,6437 (47.2)*	882 (47.3)*
Postgraduate	18,097 (49.3)	9,283 (34.7)*	4,062 (41.0)*	13,056 (37.5)*	289 (15.5)*
Smoking status					
Never smoked	18,989 (52.0)	14,744 (55.3)*	4,245 (43.0)*	18,282 (52.7)*	707 (38.2)*
Past smoker	15,910 (43.5)	10,916 (41.0)*	4,994 (50.6)*	14,987 (43.2)*	923 (49.9)*
Current smoker	1,634 (4.5)	996 (3.7)*	638 (6.5)*	1,415 (4.1)*	219 (11.8)*
Diabetes history					
Yes	947 (2.6)	693 (2.6)	254 (2.6)	827 (2.4)*	120 (6.4)*
Heart disease history					
Yes	6,178 (16.8)	4,451 (16.6)	1,727 (17.4)	5,759 (16.5)*	419 (22.5)*
Stroke history					
Yes	294 (0.8)	212 (0.8)	82 (0.8)	260 (0.7)*	34 (1.8)*
Statin use					
Yes	3,875 (10.6)	2,793 (10.4)	1,082 (10.9)	3,636 (10.4)*	239 (12.8)*
Multivitamin use					
Yes	25,441 (69.3)	18,618 (69.5)	6,823 (68.8)	24,307 (69.8)*	1,134 (60.9)*
Hormone therapy use					
Never	10,170 (28.4)	7,406 (28.4)*	2,764 (28.6)	9,481 (27.8)*	689 (39.2)*
Former estrogen alone	3,387 (9.5)	2,561 (9.8)*	826 (8.5)*	3,160 (9.3)*	227 (12.9)*
Current estrogen alone	6,604 (18.4)	4,924 (18.8)*	1,680 (17.4)*	6,305 (18.5)*	299 (17.0)*
Former estrogen + progesterone	7,095 (19.8)	5,125 (19.6)*	1,970 (20.4)*	6,816 (20)*	279 (15.9)*
Current estrogen + progesterone	8,545 (23.9)	6,107 (23.4)*	2,438 (25.2)*	8,283 (24.3)*	262 (14.9)*
Frequency of dental check-ups or cleanings					
<2 visits/year	8,053 (22.0)	6,627 (24.8)*	1,426 (14.4)*	6,957 (20.0)*	1,096 (59.4)*
≥2 visits/year	26,372 (71.9)	18,349 (68.6)*	8,023 (81.0)*	26,093 (74.9)*	279 (15.1)*
Whenever needed, no regular schedule	2,234 (6.1)	1,773 (6.6)*	461 (4.7)*	1,765 (5.1)*	469 (25.4)*

Abbreviations: MET, metabolic equivalent; IQR, interquartile range.

*P values statistically significant at $\alpha < 0.05$ denoted by *. P values derive from Mann–Whitney U test for continuous variables and chi-square test of independence for categorical variables.

Table 2. Cox proportional hazards models for risk of hypertension associated with baseline periodontal disease and edentulism

			Periodontal/gum disease			Edentulism		
Model	*N*	*n*, cases	*n*, Perio.	Hazard ratio (95% CI)	*P*†	*n*, Edent.	Hazard ratio (95% CI)	*P*†
Crude	36,692	12,635	9,919	1.00 (0.96–1.04)	0.9	1,863	1.38 (1.28–1.49)	<0.0001
Multivariable adjusted*	36,692	12,635	9,919	0.99 (0.95–1.03)	0.6	1,863	1.21 (1.11–1.30)	<0.0001
Stratified by age‡					0.9§			0.04§
<60	6,626	2,047	1,825	1.03 (0.94–1.14)		170	1.32 (1.03–1.71)	
60–69	17,011	5,987	4,849	0.97 (0.91–1.02)		775	1.15 (1.02–1.29)	
70–79	11,515	4,123	2,926	1.02 (0.95–1.09)		773	1.15 (1.02–1.30)	
≥80	1,540	478	319	1.03 (0.83–1.28)		145	1.15 (0.83–1.59)	
Stratified by body mass index‡					0.2§			0.06§
Underweight/normal (<25.0)	18,127	5,447	4,753	0.95 (0.90–1.01)		701	1.29 (1.13–1.48)	
Overweight (25.0–29.9)	12,239	4,525	3,467	0.99 (0.93–1.06)		669	1.23 (1.09–1.40)	
Obese (≥30)	6,326	2,663	1,699	1.05 (0.97–1.15)		493	1.07 (0.92–1.24)	
Stratified by frequency of dental visits					0.6			0.09
<2 visits/year	8,053	2,653	1,426	1.03 (0.94–1.14)		1,096	1.27 (1.14–1.42)	
≥2 visits/year	26,372	9,211	8,023	0.98 (0.94–1.03)		279	1.28 (1.07–1.54)	
Whenever needed	2,234	766	461	0.97 (0.81–1.17)		469	1.05 (0.88–1.26)	
Systolic BP (mm Hg) ‡					0.2§			0.0004§
<110	6,055	985	1,834	1.01 (0.88–1.16)		210	1.28 (0.92–1.76)	
110–119	10,491	2,800	2,881	1.03 (0.95–1.12)		474	1.25 (1.05–1.49)	
120–129	11,874	4,669	3,133	1.02 (0.96–1.09)		651	1.18 (1.04–1.34)	
130–139	8,272	4,181	2,071	1.04 (0.97–1.12)		528	0.98 (0.86–1.12)	

Abbreviations: BP, blood pressure; CI, confidence interval.

*Multivariable model adjusted for education, body mass index, and pack-years smoking. Stratified analysis conducted using multivariable adjusted model.

†*P* value based on Wald chi square for exposure term (periodontal/gum disease or edentulism) in overall models or for cross-product term in stratified analyses.

‡Models stratified by continuous variables also adjusted for stratifying variable within each strata.

§*P* value for interaction based on continuous parameterization of stratifying variable.

1,023 Japanese industrial workers mean age 37 years over 4 years follow-up. Use of self-reported periodontal disease is a limitation in our study and the HPFS that may have contributed to our null findings. A validation study in a subgroup of women in the WHI-OS demonstrated validity of self-reported periodontal disease diagnosis in older women, however some misclassification is expected.[27] An alternate potential explanations for the differential results for the periodontal disease–hypertension relationship could be related to age, as the 2 studies finding positive associations between periodontal disease and hypertension had younger populations than the studies that found null associations. It is plausible that periodontal disease could be more related to mechanisms of hypertension in younger individuals than in older individuals.

There are critical distinctions between the evaluation of periodontal disease and edentulism. In general, periodontal disease represents a disease construct consisting of inflammation and tissue damage to the periodontium, with consistent etiological factors. In contrast, edentulism represents the common end point of numerous potential causal mechanisms. In the overall population, caries are the most common cause of tooth loss, representing 40–50% of tooth loss.[28] However, in older populations such as those in this study, periodontal disease is an equivalent or perhaps stronger cause of tooth loss.[29] Low income and other socioeconomic disparities are also associated with tooth loss.[30] Furthermore, the extreme nature of missing all natural teeth may not simply represent an acute condition, but rather a response to cumulative exposures and insults to the periodontium throughout an entire lifetime, in addition to simply poor oral hygiene and dental care.

In our stratified analyses, we observed stronger positive associations between edentulism and incident hypertension among those with lower baseline blood pressure, younger age, and lower BMI at baseline. One possible explanation

is that those with prehypertension may already be on the verge of developing hypertension, such that the presence of edentulism has little impact at this point. In this scenario, edentulism or the factors underlying it may have already influenced the blood pressure regulatory process that resulted in individuals reaching blood pressure in the prehypertension range. Accordingly, it may be possible that edentulism and its antecedent factors predominantly affect blood pressure processes early in the development of hypertension but are less influential in later stages of disease progression. Regarding the particular difference in risk of hypertension associated with edentulism according to BMI, in previous studies it has been reported that smoking prevalence and intensity were higher in adults along the lower distribution of BMI[31]; however, this was not observed in our study (53.3% never smokers, mean 8.2 pack-years among those with normal BMI vs. 49.8% never smokers, mean 11.2 pack-years among those with obese BMI). Alternatively, lower BMIs could reflect individuals with occult disease,[32] which could predispose to edentulism, hypertension, or both; however, in our study we observed relatively similar risk with edentulism across underweight/normal and overweight BMI. Another possibility is that women predisposed to hypertension who also had obese BMI may have already been diagnosed with hypertension by the time they would were enrolled in our study, so they would have been a prevalent case of hypertension and thus not included in our analysis. Those with obese BMI who did not develop hypertension may have intrinsic resistance to developing hypertension, such that the presence of edentulism may not add much additional risk. It could be speculated that in women who had underweight/normal BMI or overweight BMI but are still susceptible, the added risk associated with edentulism is more appreciable. Additional work is needed to further understand this apparent interaction between BMI and edentulism in hypertension risk.

There are several possible reasons for the observed association between edentulism and hypertension. In our analyses, we adjusted for BMI before study baseline; however, one possible explanation is that edentulism could lead to changes in dietary patterns that could be associated with higher risk of hypertension. We investigated potential confounding due to dietary factors (red meat, sodium, total calories, and HEI-2005) assessed before study baseline, but inclusion of these factors in multivariable models did not impact the association between edentulism and hypertension. Nevertheless, we would not be able to discern if changes in diet or changes in BMI took place after completion of the edentulism questionnaire. In this situation, altered diet and body composition based on edentulism could contribute to the association with hypertension. We also examined potential confounding by education and neighborhood socioeconomic status that are the variables in our data set that we felt provided the best approximation of socioeconomic status, but these did not explain the observed association between edentulism and hypertension. One of the major causes of edentulism in older individuals is periodontal disease,[29] so the association between edentulism and hypertension could be mediated by inflammation, endothelial dysfunction, or oxidative stress resulting from severe past periodontal disease.[33] Another possibility is that edentulism may influence hypertension risk *via* alteration of the composition of the oral microbiome. Oral microbes contribute to vasodilation *via* participation in the nitrate cycle, which could influence hypertension risk *via* availability of nitric oxide (NO).[34] Oral microbes reduce nitrate consumed in diet to nitrite, which is subsequently converted to NO, a potent vasodilator. This represents an important source of oxygen-independent NO synthesis. In randomized controlled trials, consumption of nitrate-containing foods has been shown lower SBP,[35] a phenomenon that may be predicated on the presence of oral microbes.[36] Alternately, denture-related issues may contribute to hypertension risk. Among the edentulous, denture-related inflammation and irritation is common, which could contribute to a state of chronic low-grade inflammation.[37] Furthermore, dentures can harbor microbial flora similar to what is found in periodontal disease.[38] Higher levels of inflammation could contribute to the development or maintenance of elevated blood pressure.[39–41]

In contrast to the observed association between edentulism and hypertension, we did not observe significant association between periodontal disease and hypertension. It is possible that the question on edentulism had higher accuracy than reported history of periodontal disease, resulting in less misclassification on exposure. In a validation study within the participants of the WHI-OS, our question on periodontal disease was found to have a sensitivity of 56.2% and specificity of 78.8% when compared to severe periodontal disease based on the Centers for Disease Control and Prevention/American Academy of Periodontology definition and a sensitivity of 76.0% and specificity of 77.4% when compared to having tooth loss due to periodontal disease.[27] There are little data evaluating the validity of self-reported edentulism; however, a study of 1,501 participants found an overall good correlation between self-report and clinically evaluated number of teeth (Spearman's R 0.69).[42] As edentulism can result from periodontal disease, it is possible that the question on edentulism better represented the individuals with a past history of the most severe periodontal disease, resulting in less misclassification on exposure. There may be subsets of individuals with higher or lower risk of hypertension on the basis of factors not captured by our periodontal disease question, such as disease duration and severity, gingival inflammation, or subgingival microbiome. For instance, certain microbes associated with periodontal disease may better predict hypertension risk. In addition, missing some but not all teeth may represent an intermediate between periodontal disease and edentulism. Thus, it could be hypothesized that there is a continuum of risk of hypertension that increases with increasing number of missing teeth. In this study, we were unable to evaluate the relationship between number of missing teeth and incidence of hypertension. Future studies evaluating the risk of hypertension associated with composition of oral microbes would allow us to further understand these associations.

Strengths of this study include large sample size, extensive database that allowed for consideration of numerous potential

confounding factors, and long duration of follow-up. Potential limitations included use of self-reported periodontal disease, edentulism, and first treatment for hypertension, as well as generalizability of this study consisting of postmenopausal women. Regarding generalizability to other populations, our observed interaction between edentulism and age with regard to hypertension risk suggests that the association between edentulism and hypertension may be stronger in younger populations. Furthermore, the 2 studies that observed significant associations between periodontal disease and hypertension had study populations that were younger than those of this study.[8,9] Regarding potential generalizability to males, the difference in associations between edentulism and age that we observed suggests this association there is little data available on possible sex differences regarding the relationship between periodontal disease, edentulism, and hypertension. Two previous studies evaluating periodontal disease and hypertension included both males and females, but did not evaluate the potential for a sex difference.[8,9] In a cross-sectional study, the potential suggestion of a stronger association between periodontal disease severity and measured systolic blood pressure was identified (P interaction 0.15); however, in this study population, males were younger than females (67 vs. 70 years; $P<0.001$) so this difference could be related to age.[24] Within the HPFS, consisting of older males, there was a null association between self-reported number of teeth and self-reported incident hypertension after multivariable adjustment; however, they did not specifically evaluate edentulism.

Overall, this study found no association between periodontal disease and hypertension risk among postmenopausal women enrolled in the WHI-OS. We did observe a modest elevated risk of hypertension among postmenopausal women with complete edentulism compared to dentate women, which was stronger among those with younger age, lower BMI, and lower baseline SBP. Our findings suggest that the presence of edentulism may serve as a clinical warning sign for increased hypertension risk. Improved oral hygiene aimed at preventing edentulism as well as careful blood pressure monitoring and intervention among the edentulous may be indicated to prevent morbidity and mortality associated with hypertension.

SUPPLEMENTARY DATA

Supplementary data are available at *American Journal of Hypertension* online.

ACKNOWLEDGMENTS

J.H.G.'s time was supported in part by the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH; grant F30HL132604). The Women's Health Initiative (WHI) program was funded by the National Heart, Lung, and Blood Institute, NIH, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN 268201600003C, and HHSN268201600004C. Short list of WHI investigators Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland.

DISCLOSURE

Authors report no conflicts of interest related to this study.

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