Association of Chronic Periodontitis on Alzheimer's Disease or Vascular Dementia

Seulggie Choi, MD, Kyuwoong Kim, BSc,* Jooyoung Chang, MD,* Sung Min Kim, BSc,* Seon Jip Kim, RDH,† Hyun-Jae Cho, DDS, PhD,† and Sang Min Park, MD, PhD, MPH*‡*

OBJECTIVES: Although chronic periodontitis has been associated with Alzheimer's disease, the effect of chronic periodontitis on vascular dementia as well as the role of lifestyle behaviors such as smoking, alcohol consumption, and physical activity in this association are still unclear.

DESIGN: Retrospective cohort study.

SETTING: Population based.

PARTICIPANTS: The study population was derived from the Korean National Health Insurance Service-Health Screening Cohort. Among 262 349 participants, diagnosis of chronic periodontitis was determined during 2003-2004.

MEASUREMENTS:
Starting from 2005, participants were followed up for overall dementia, Alzheimer's disease, and vascular dementia until 2015. Cox proportional hazards regression was used to determine the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of dementia according to chronic periodontitis.

RESULTS: Compared with nonchronic periodontitis participants, chronic periodontitis patients had elevated risk for overall dementia (aHR = 1.06; 95% CI = 1.01-1.11) and Alzheimer's disease (aHR = 1.05; 95% CI = 1.00-1.11). There was a tendency toward increased vascular dementia risk among chronic periodontitis patients (aHR = 1.10; 95% CI = 0.98-1.22). The risk-increasing effect of chronic periodontitis on dementia tended to be stronger among participants with healthy lifestyle behaviors including never-smokers and those who exercised and did not consume alcohol.

CONCLUSION: Chronic periodontitis may be associated with a higher risk of developing dementia. Future studies that investigate whether preventing chronic periodontitis may lead to reduced risk of dementia are needed. **J Am Geriatr Soc 67:1234–1239, 2019.**

Key words: chronic periodontitis; Alzheimer's disease; vascular dementia

Dementia is considered one of the leading causes for increased disability-adjusted life years among older adults.[1] It was estimated that approximately 36 million people had dementia in 2010.[2] Furthermore, the prevalence of dementia is expected to increase globally due to the rising life expectancy worldwide. According to one report using the United Nations worldwide population forecasts, it was estimated that 1 in 85 individuals will be diagnosed with Alzheimer's disease (AD) by 2050.[3] Interestingly, a 2014 study suggested that a 20% reduction of key exposures could lead to a 15.3% decrease in dementia prevalence by 2050, highlighting the importance of determining risk factors that could lead to dementia.[4] Therefore, the need is increasing to identify and manage risk factors associated with dementia. One such risk factor is chronic periodontitis (CP).

Multiple animal[5] and human[6–9] studies previously showed an association between CP and dementia. Most recently, a retrospective cohort study demonstrated that CP patients had a significantly higher risk of AD compared with those without CP.[10] However, previous studies had limitations in the relatively small sample size, no consideration of dementia outside of AD, and by the lack of consideration of important confounders such as lifestyle behaviors. Because one of the suggested mechanisms of the risk-increasing effect

From the *Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, South Korea; †Department of Preventive Dentistry and Public Oral Health, School of Dentistry and Dental Research Institute, Seoul National University, Seoul, South Korea; and the ‡Department of Family Medicine, Seoul National University Hospital, Seoul, South Korea.

Address correspondence to Hyun-Jae Cho, DDS, PhD, Department of Preventive Dentistry and Public Oral Health, School of Dentistry and Dental Research Institute, Seoul National University, 101 Daehak-ro, Jongno-gu, Seoul, South Korea; E-mail: stbluewi@snu.ac.kr; Sang Min Park, MD, PhD, MPH, Department of Family Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, South Korea; E-mail: smpark.snuh@gmail.com

DOI: 10.1111/jgs.15828

0002-8614/18/$15.00

of CP on dementia is by inducing vascular damage,[11,12] other types of dementia such as vascular dementia (VD) may be at elevated risk among CP patients. Furthermore, lifestyle behaviors such as smoking, alcohol consumption, and physical activity are all considered risk factors for both CP and dementia, and they are thus potentially important confounders that must be considered.

Therefore, further studies on the association between CP and dementia are needed using a large study population, with consideration of an extensive number of covariates, and determining the risk of other types of dementia such as VD. In this longitudinal population-based study, we determined the association of CP on AD and VD using the Korean National Health Insurance Service (NHIS) database using a wide range of covariates including smoking, alcohol consumption, and physical activity.

METHODS

Study Population

The study population was derived from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS). In South Korea, the NHIS provides mandatory health insurance covering nearly all forms of healthcare for all Korean citizens.[13] Records from inpatient and outpatient department visits including diagnosis, drug prescriptions, treatment, and surgical procedures are collected. Furthermore, the NHIS provides biannual mandatory health screening examinations for all enrollees 40 years or older.[14] The health screening examination consists of a self-reported questionnaire on health behavior, body measurements including height, weight, and blood pressure, and blood and urine tests. From this claims database, the NHIS provides a part of its data for research purposes that include information on inpatient and outpatient hospital use, drug prescriptions, death dates, and results from health screening examinations. The NHIS database was previously used for multiple epidemiological studies, and its validity is described in detail elsewhere.[14,15]

Among 313 537 participants aged 50 or older, we excluded 31 293 participants who were diagnosed with CP during 2002. Furthermore, we excluded 16 173 participants with missing values on covariates. Finally, 1942 and 1780 participants who were diagnosed with dementia or died before the index date were excluded, respectively. The final study population consisted of 262 349 participants. All participants were grouped as healthy (no CP) or diagnosed with CP during 2003-2004. Starting from January 1, 2005, the participants were followed up until date of dementia diagnosis, date of death, or December 31, 2015, whichever came first.

This study was approved by the institutional review board of Seoul National University Hospital (IRB number E-1801-019-912). The requirement for informed consent was waived because the NHIS-HEALS database is anonymized with strict confidentiality guidelines.

Key Variables

CP was defined as being diagnosed with CP according to the *International Classification of Diseases, Tenth Revision* (ICD-10 code K05.3), and having undergone at least one of the CP-related treatments.[16] The considered CP-related treatments were subgingival curettage, periodontal flap operation, gingivectomy, and odontectomy.[16] Participants who were not diagnosed with CP and did not undergo CP-related treatment were considered healthy. Dementia was defined as being prescribed with dementia-related drugs under a diagnosis for AD (ICD-10 codes F00, G30) or VD (ICD-10 code F01).[17] The considered dementia-related drugs were donepezil, galantamine, rivastigmine, and memantine.[17]

The considered covariates included age (years, continuous), sex (categorical, men and women), household income (categorical, first, second, third, and fourth quartiles), smoking status (categorical, never, past, and current smoker), alcohol consumption (categorical, none, 0-1, 1-2, 3-4, and ≥5 times per week), physical activity (categorical, none, 1-2, 3-4, 5-6, and 7 times per week), body mass index (continuous, kg/m^2), systolic blood pressure (continuous, mm Hg), fasting serum glucose (continuous, mg/dL), total cholesterol (continuous, mg/dL), and Charlson Comorbidity Index (categorical, 0, 1, 2, ≥3). Household income was derived from the insurance premium, and body mass index was calculated by dividing height in meters by weight in kilograms squared.

Statistical Analysis

Cox proportional hazard regression was used to determine the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of overall dementia, AD, and VD according to CP. Furthermore, we conducted a stratified analysis for the association of CP on dementia according to subgroups of smoking, physical activity, and alcohol consumption. Finally, a sensitivity analysis on the effect of CP on dementia after excluding participants diagnosed with dementia up to 5 years after the index date was conducted.

Statistical significance was considered at $P < .05$ in a two-sided manner. All data analyses were conducted using SAS software v.9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Table 1 shows the descriptive characteristics of the study population. Among 262 349 participants, 216 005 did not have CP and 46 344 were diagnosed with CP. The mean age for healthy and CP patients were 60.4 years (standard deviation [SD] = 7.7) and 60.2 years (SD = 7.3), respectively. The percentages of male healthy and CP patients were 49.4% and 56.8%, respectively. Compared with healthy participants, CP patients tended to have higher proportions of men, have higher household income, smoke, consume more alcohol, and exercise more.

The association of CP on overall dementia, AD, and VD is shown in Figure 1. Compared with healthy participants, CP patients had a higher risk for overall dementia (aHR = 1.06; 95% CI = 1.01-1.11; $P = .015$) and AD (aHR = 1.05; 95% CI = 1.00-1.11; $P = .042$). Similarly, CP patients tended to have increased risk for VD (aHR = 1.10; 95% CI = 0.98-1.22; $P = .088$), although it was not statistically significant. Table 2 depicts the results from a stratified analysis on the association of CP on dementia according to subgroups of smoking, physical activity, and alcohol

consumption. Compared with healthy participants, CP patients who were never-smokers (aHR = 1.06; 95% CI = 1.01-1.12), exercised (aHR = 1.09; 95% CI = 1.01-1.18), and did not consume alcohol (aHR = 1.06; 95% CI = 1.00-1.12) had a higher risk for overall dementia in their respective subgroups. Similarly, never-smokers (aHR = 1.08; 95% CI = 1.02-1.14), participants who exercised (aHR = 1.11; 95% CI = 1.02-1.21), and did not consume alcohol (aHR = 1.08; 95% CI = 1.02-1.14) had an elevated risk for AD compared with healthy participants in their respective subgroups.

Finally, Table 3 depicts the association of CP on dementia after excluding participants diagnosed with dementia up to 5 years after the index date. The risk of overall dementia after excluding participants with dementia up to 5 years after the index date tended to be preserved (aHR = 1.04; 95% CI = 0.98-1.10). Similarly, CP patients after a 5-year washout for dementia tended to have an increased risk for AD (aHR = 1.04; 95% CI = 0.98-1.10) and VD (aHR = 1.06; 95% CI = 0.92-1.21).

Table 1. Descriptive characteristics of the study population

	Healthy	Chronic periodontitis
No. of people	216 005	46 344
Age, y, mean (SD)	60.4 (7.7)	60.2 (7.3)
Sex, N (%)		
Men	106 684 (49.4)	26 342 (56.8)
Women	109 321 (50.6)	20 002 (43.2)
Household income, N (%)		
First quartile (highest)	64 213 (29.7)	15 294 (33.0)
Second quartile	61 545 (28.5)	13 421 (29.0)
Third quartile	50 088 (23.2)	9934 (21.4)
Fourth quartile (lowest)	40 159 (18.6)	7695 (16.6)
Smoking status, N (%)		
Never-smoker	158 337 (73.3)	31 261 (67.5)
Past smoker	16 795 (7.8)	4184 (9.0)
Current smoker	40 873 (18.9)	10 899 (23.5)
Alcohol consumption, times per week, N (%)		
None	139 091 (64.4)	28 144 (60.7)
0-1	25 659 (11.9)	5861 (12.7)
1-2	27 095 (12.5)	6622 (14.3)
3-4	13 008 (6.0)	3239 (7.0)
≥5	11 152 (5.2)	2478 (5.4)
Physical activity, times per week, N (%)		
None	129 145 (59.8)	25 795 (55.7)
1-2	43 470 (20.1)	10 369 (22.4)
3-4	19 060 (8.8)	4448 (9.6)
5-6	5403 (2.5)	1334 (2.9)
7	18 927 (8.8)	4398 (9.5)
Body mass index, kg/m^2, mean (SD)	24.0 (3.0)	24.2 (2.9)
Systolic blood pressure, mm Hg, mean (SD)	130.2 (18.8)	129.9 (18.3)
Fasting serum glucose, mg/dL, mean (SD)	100.0 (34.2)	102.0 (37.3)
Total cholesterol, mg/dL, mean (SD)	202.7 (38.8)	202.4 (38.9)
Charlson Comorbidity Index, N (%)		
0	68 625 (31.8)	14 342 (31.0)
1	60 534 (28.0)	12 967 (28.0)
2	41 136 (19.0)	9025 (19.5)
≥3	45 710 (21.2)	10 010 (21.6)

Abbreviation: SD = standard deviation.

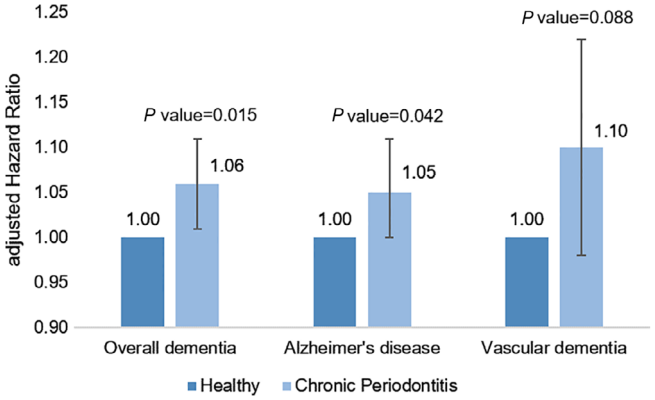

Figure 1. Hazard ratios for dementia according to chronic periodontitis Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index.

DISCUSSION

In this population-based longitudinal study, we showed that compared with participants without CP, those with CP had a 6% higher risk for dementia. This association held true after adjustments for lifestyle behaviors including smoking, alcohol consumption, and physical activity. To our knowledge, this is the first study to demonstrate that CP was associated with higher dementia risk even after adjustments for lifestyle behaviors.

A number of previous studies that have investigated the association between CP and dementia are in line with our findings. In 2009, Grabe and colleagues determined the association between number of teeth, a surrogate marker for CP, and the Mini-Mental State Examination (MMSE) scores.[6] They found a significant positive relationship between number of teeth and MMSE scores for women (β coefficient = .045; 95% CI = .011-.079).[6] Moreover, Martande and colleagues showed that clinical parameters for CP such as plaque index, gingival index, probing pocket depth, clinical attachment level, and percentage of bleeding on probing were all significantly worse among AD patients compared with those without AD.[18] In 2016, Ide and colleagues demonstrated that CP patients had significantly lower Alzheimer's Disease Assessment Scale (mean difference = 5.2; 95% CI = 1.7-8.8) and MMSE (mean difference = −1.8, 95% CI = −3.6 to −.03) scores compared with healthy participants.[19] Finally, using a claims data from Taiwan in 2017, Chen and colleagues showed that CP was associated with increased risk for AD (aHR = 1.71; 95% CI = 1.15-2.53).[10] The results from our study further add to those from previous studies by showing that CP was significantly associated with dementia even after adjustments for smoking, alcohol consumption, and physical activity.

Table 2. Stratified analysis on the association of chronic periodontitis with dementia according to subgroups

	Adjusted hazard ratio (95% confidence interval)		
	Overall dementia	Alzheimer's disease	Vascular dementia
Smoking			
Never-smoker	1.06 (1.01-1.12)	1.08 (1.02-1.14)	1.06 (0.93-1.20)
Past or current smoker	1.03 (0.93-1.13)	0.98 (0.87-1.09)	1.21 (0.98-1.49)
Physical activity			
No	1.03 (0.97-1.09)	1.02 (0.96-1.09)	1.10 (0.97-1.26)
Yes	1.09 (1.01-1.18)	1.11 (1.02-1.21)	1.07 (0.89-1.29)
Alcohol consumption			
No	1.06 (1.00-1.12)	1.08 (1.02-1.14)	1.06 (0.93-1.21)
Yes	1.04 (0.95-1.14)	0.98 (0.89-1.09)	1.19 (0.98-1.45)

Note: Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index.

Three main mechanisms may explain the association between CP and vascular or neurodegenerative disease: direct invasion of periodontopathogens, increased inflammatory markers, and induction of atherosclerotic plaques. First, upon CP, periodontopathogens may enter the systemic circulation and cross the blood-brain barrier (BBB) to invade the brain.[20] Once inside the brain, the pathogens' lipopolysaccharides may stimulate cytokine production, causing an increased inflammatory state.[12] Furthermore, certain pathogen products may induce the formation of beta amyloid and tau protein, both of which are observed in AD.[21] Second, CP may contribute to the development of dementia by inducing a systemic inflammatory state.[22] CP leads to the release of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α.[23] Such inflammatory mediators can be transported through the BBB into the brain, thus causing inflammation within the brain tissue. Upon prolonged inflammation, beta amyloid products build up, which in turn induces even more cytokine production, thus creating a feedback cycle of increasing inflammation and tissue destruction.[24] Third, CP may lead to increased atherosclerotic plaques by causing endothelial cell damage.[11] Increased atherosclerosis and damage of vascular tissue was previously shown to be associated with a heavier burden of neuritic plaques and neurofibrillary tangles, thus leading to an increased risk for dementia.[25]

A major limitation of previous studies investigating the association between CP and dementia is the lack of consideration of lifestyle behaviors such as smoking, alcohol consumption, and physical activity. For example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study depicted that a multidomain approach including healthier lifestyle behaviors is beneficial in preventing cognitive decline, and therefore lifestyle behaviors could act as important confounders in the association between CP and dementia.[26] Although the risk-increasing effect of CP on dementia was preserved regardless of smoking, alcohol consumption, and physical activity, there was a tendency toward a stronger association between CP and dementia among participants with healthy behaviors (eg, never-smokers and participants who exercise and do not consume alcohol). These findings do not necessarily

Table 3. Sensitivity analysis on the association of chronic periodontitis on dementia[a]

		Chronic periodontitis Washout period, y				
	Healthy	1	2	3	4	5
Overall dementia						
Events	10 299	2023	1950	1848	1706	1493
Person-years	2 208 610	477 303	477 122	476 764	476 126	474 946
aHR (95% CI)	1.00 (Ref.)	1.06 (1.01-1.11)	1.06 (1.01-1.11)	1.06 (1.00-1.11)	1.06 (1.00-1.12)	1.04 (0.98-1.10)
Alzheimer's disease						
Events	8989	1770	1708	1617	1503	1337
Person-years	2 212 950	478 254	478 101	477 782	477 270	476 349
aHR (95% CI)	1.00 (Ref.)	1.06 (1.01-1.12)	1.06 (1.01-1.12)	1.05 (1.00-1.11)	1.06 (1.00-1.12)	1.04 (0.98-1.10)
Vascular dementia						
Events	1850	388	373	360	328	288
Person-years	2 234 077	482 503	482 466	482 420	482 276	482 055
aHR (95% CI)	1.00 (Ref.)	1.09 (0.97-1.22)	1.09 (0.97-1.22)	1.10 (0.98-1.24)	1.11 (0.98-1.25)	1.06 (0.92-1.21)

Note: The aHR was calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index.
Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval.
[a]After excluding participants diagnosed with dementia within the first 1 to 5 years after the index date.

contradict but are rather parallel reports from previous studies because our findings do not compare dementia risk across different health behaviors, but rather the risk of dementia according to CP in participants with similar health behaviors. Due to the lack of detrimental effects of unhealthy behaviors on dementia, the risk-increasing effect of CP on dementia may have been simply more pronounced among participants with healthy behaviors. Nonetheless, the exact roles of lifestyle behaviors on the relationship between CP and dementia are unclear and merit further investigation.

Several limitations must be considered when interpreting the results from our study. First, we had limited information on a CP-related clinical index such as probing pocket depth. Additional clinical information such as probing pocket depth would have been useful in determining more accurately which participants had CP. Nonetheless, we attempted to take this into account by using a combination of diagnosis and CP-related treatment codes, an operational definition that was used in previous reports.[16] Second, we did not have access to medical chart records related to dementia but rather had to rely on diagnosis codes and drug prescription records. Nonetheless, to claim reimbursement for anti-dementia drugs from the NHIS, the following two criteria must be met: first, an MMSE score of 26 or lower and second, either a Clinical Dementia Rating of 1 or higher or a Global Deterioration Scale of 3 or higher.[17] Although this appears to enhance the reliability of the diagnosis of dementia, future studies that use chart records for a more accurate definition of dementia are needed to validate the findings of our study.

Third, we could not adjust for level of education or apolipoprotein E (APOE) e4 containing genotype, both of which may be important confounders for the relationship between CP and dementia. Nonetheless, we attempted to compensate for this by adjusting for household income that may act as a surrogate marker for education. Studies that additionally take into consideration APOE e4 containing genotype are needed. Fourth, because dementia is a slowly developing chronic neurodegenerative disorder, the entire effect of CP on dementia may not have been accurately portrayed in the 11 years of follow-up in our study. This could in part explain the small observed effect sizes in our study, which may increase upon longer follow-up durations. Therefore, future studies with longer follow-up durations are needed to validate our findings. Similarly, although the statistical significance may be in part due to the large study population, we have shown that statistical significance was maintained even after excluding dementia patients diagnosed within the first 4 years of follow-up.

Despite these limitations, a number of strengths exist. First, we considered lifestyle behavior including smoking, alcohol consumption, and physical activity, a group of covariates that were not considered in previous studies, thus enhancing the reliability of our results. Second, we also determined the association of CP on VD as well as AD. Although not significant, the tendency toward increased VD risk for CP patients was not previously shown. Third, the relatively large study population further enhances the generalizability of our results. Finally, the extensive number of covariates considered gives further weight to the reliability of the findings from our study.

In conclusion, CP appeared to be associated with increased risk for dementia even after taking into consideration lifestyle behaviors including smoking, alcohol intake, and physical activity. Future prospective studies investigating whether CP prevention and management actually lead to reduced risk of dementia are needed to validate the findings of this study.

ACKNOWLEDGMENTS

Financial Disclosure: This research was supported by the Convergence Research Program from the School of Dentistry and College of Medicine, Seoul National University (grant number 800-20170479) and the Seoul National University Hospital research fund (grant number 04-2018-0370). S. Choi, K. Kim, and S.M. Kim received grants from the BK21-Plus Education Program from the National Research Foundation of Korea.

Conflict of Interest: Nothing to report.

Author Contributions: H.J. Cho and S.M. Park had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* H.J. Cho and S.M. Park. *Acquisition of data:* S.M. Park. *Analysis and interpretation of data*: All authors. *Drafting of the manuscript:* S. Choi, H.J. Cho, and S.M. Park. *Critical revision of the manuscript:* All authors. *Statistical analysis: S. Choi. Administrative, technical, or material support:* S.M. Kim and S.J. Kim.

Sponsor's Role: Seoul National University and the National Research Foundation of Korea had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation, review, or approval of the manuscript, and decision to submit for publication.

REFERENCES

1. DALYs GBD, Collaborators H, Murray CJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet. 2015;386:2145-2191.
2. Chan KY, Wang W, Wu JJ, et al. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. Lancet. 2013;381:2016-2023.
3. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007;3:186-191.
4. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 2014;13:788-794.
5. Oue H, Miyamoto Y, Okada S, et al. Tooth loss induces memory impairment and neuronal cell loss in APP transgenic mice. Behav Brain Res. 2013; 252:318-325.
6. Grabe HJ, Schwahn C, Volzke H, et al. Tooth loss and cognitive impairment. J Clin Periodontol. 2009;36:550-557.
7. Kaye EK, Valencia A, Baba N, Spiro A 3rd, Dietrich T, Garcia RI. Tooth loss and periodontal disease predict poor cognitive function in older men. J Am Geriatr Soc. 2010;58:713-718.
8. Minn YK, Suk SH, Park H, et al. Tooth loss is associated with brain white matter change and silent infarction among adults without dementia and stroke. J Korean Med Sci. 2013;28:929-933.
9. Saito Y, Sugawara N, Yasui-Furukori N, Takahashi I, Nakaji S, Kimura H. Cognitive function and number of teeth in a community-dwelling population in Japan. Ann Gen Psychiatry. 2013;12:20.
10. Chen CK, Wu YT, Chang YC. Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. Alzheimers Res Ther. 2017;9:56.

11. Tonetti MS, D'Aiuto F, Nibali L, et al. Treatment of periodontitis and endothelial function. N Engl J Med. 2007;356:911-920.
12. Uppoor AS, Lohi HS, Nayak D. Periodontitis and Alzheimer's disease: oral systemic link still on the rise? Gerodontology. 2013;30:239-242.
13. Cheol Seong S, Kim YY, Khang YH, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol. 2017;46:799-800.
14. Seong SC, Kim YY, Park SK, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open. 2017;7:e016640.
15. Kim K, Park SM, Lee K. Weight gain after smoking cessation does not modify its protective effect on myocardial infarction and stroke: evidence from a cohort study of men. Eur Heart J. 2018;39:1523-1531.
16. Huang YF, Chang CT, Liu SP, et al. The impact of oral hygiene maintenance on the association between periodontitis and osteoporosis: a nationwide population-based cross sectional study. Medicine (Baltimore). 2016;95: e2348.
17. Jeong SM, Shin DW, Lee JE, Hyeon JH, Lee J, Kim S. Anemia is associated with incidence of dementia: a national health screening study in Korea involving 37,900 persons. Alzheimers Res Ther. 2017;9:94.
18. Martande SS, Pradeep AR, Singh SP, et al. Periodontal health condition in patients with Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2014; 29:498-502.
19. Ide M, Harris M, Stevens A, et al. Periodontitis and cognitive decline in Alzheimer's disease. PLoS One. 2016;11:e0151081.
20. Riviere GR, Riviere KH, Smith KS. Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer's disease. Oral Microbiol Immunol. 2002;17:113-118.
21. Cribbs DH, Azizeh BY, Cotman CW, LaFerla FM. Fibril formation and neurotoxicity by a herpes simplex virus glycoprotein B fragment with homology to the Alzheimer's a beta peptide. Biochemistry. 2000;39:5988-5994.
22. Abbayya K, Puthanakar NY, Naduwinmani S, Chidambar YS. Association between periodontitis and Alzheimer's disease. N Am J Med Sci. 2015;7: 241-246.
23. Gaur S, Agnihotri R. Alzheimer's disease and chronic periodontitis: is there an association? Geriatr Gerontol Int. 2015;15:391-404.
24. Griffin WS, Sheng JG, Royston MC, et al. Glial-neuronal interactions in Alzheimer's disease: the potential role of a 'cytokine cycle' in disease progression. Brain Pathol. 1998;8:65-72.
25. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's coordinating center. Neurology. 2005;64: 494-500.
26. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015;385:2255-2263.

Editor's Note

This study is interesting and timely. Consistent with a few previous reports in the literature, the authors found a modest, statistically significant association between chronic periodontitis and incident dementia in general, and with incident Alzheimer's disease (AD) in particular. There was also an association, although not statistically significant, with vascular dementia. The authors propose three main potential mechanisms for this association: direct invasion of the brain by periodontopathogens, increased inflammatory markers, and induction of atherosclerotic plaques. Shortly after this manuscript was accepted in JAGS, a new study was published in *Science Advances* (the American Association for the Advancement of Science's open-access multidisciplinary journal), suggesting a link between periodontal bacteria (*Porphyromonas gingivalis*) and AD. Although periodontal bacteria were previously implicated in the development and progression of AD, this new study implies that inhibitors of gingipain (a toxic protease released by the bacteria) may be useful in treating both *P. gingivalis* and neurodegeneration in AD. As the authors of the current study acknowledge, their data have several limitations including using coded diagnoses for dementia, lacking detail on the degree of periodontitis, and lacking data on some important potential confounders such as educational level and ApoE4 genotype. Nevertheless, this study, in combination with the recently published report on *P. gingivalis,* should make us all think more seriously about optimizing our own and our patients' oral hygiene practices and dental care, with the added potential of perhaps protecting our brain health as well.

-Joseph G. Ouslander, MD, and Mary Ganguli, MD, MPH