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Severe periodontitis with tooth loss as a modifiable risk factor for the development of Alzheimer, vascular, and mixed dementia: National Health Insurance Service-National Health Screening Retrospective Cohort 2002–2015

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ABSTRACT

Purpose: The purpose of this study was to evaluate severe periodontitis with tooth loss as a modifiable risk factor for Alzheimer dementia (AD), vascular dementia (VaD), and mixed dementia (MD) using the National Health Insurance Service-National Health Screening Retrospective Cohort database with long-term follow-up over 14 years.
Methods: Multivariate Cox hazards regression analysis was applied to a longitudinal retrospective database, which was updated in 2018, to evaluate the association between severe periodontitis with few remaining teeth and dementia after adjusting for potential risk factors, including sociodemographic factors and comorbid diseases.
Results: Among 514,866 individuals in South Korea, 237,940 (46.2%) participants satisfying the inclusion criteria were selected. A total of 10,115 age- and sex-matched participants with severe periodontitis and 10,115 periodontally healthy participants were randomly selected and evenly assigned. The results showed that the risks of AD (hazard ratio [HR], 1.08), VaD (HR, 1.24), and MD (HR, 1.16) were significantly higher in patients with severe periodontitis with 1–9 remaining teeth after adjustment for sociodemographic factors, anthropomorphic measurements, lifestyle factors, and comorbidities.
Conclusions: Severe periodontitis with few remaining teeth (1–9) may be considered a modifiable risk factor for the development of AD, VaD, and MD in Korean adults.

Keywords: Alzheimer disease; Cohort studies; Periodontal diseases; Periodontitis; Vascular dementia

INTRODUCTION

Dementia is a condition that involves damage to cerebral neurons by progressive, degenerative, and cerebrovascular diseases, resulting in declining language skills, declining judgment, memory loss, and behavioral changes [1,2]. Approximately 10% of elderly

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No potential conflict of interest relevant to this article was reported.

people aged 65 years or older are reported to have Alzheimer dementia (AD); as such, AD is the most common form of dementia, accounting for 60%–80% of all dementia cases [3]. Approximately half of these patients have only AD, whereas in the other half of patients, AD is accompanied by vascular dementia (VaD) or another type of dementia [3].

The brains of AD patients present with extraneuronal plaques formed by the buildup of the amyloid β-peptide (Aβ) protein, as well as intraneuronal tau tangles, which are abnormal tangled bundles of the phosphorylated tau (P-tau) protein [4,5]. The known major risk factors for AD are traumatic brain injury, age, family history, education level, the apolipoprotein E ε4 allele, cardiovascular disease, hypertension, and diabetes mellitus [6].

VaD is the second most common form of dementia after AD, accounting for approximately 10% of all dementia cases. VaD is caused by brain injury resulting from cerebral hemorrhage, vascular obstruction, or stroke. VaD is strongly affected by the patient's stroke history and age, and 20%–25% of patients who experience a stroke develop VaD within 3 months [7]. Mixed dementia (MD) refers to dementia with multiple etiologies [8]. Previously, a diagnosis of AD was often excluded in patients with a history of VaD, but reports from around the world have recently revealed that 50% or more of AD cases are concurrent with other etiologies [3,9].

Periodontitis is a chronic inflammatory disease occurring in the alveolar bone and the soft tissue supporting the dentition [10]. This condition leads to elevated levels of endovascular inflammatory mediators, which in turn increase the risk of systemic inflammatory diseases, such as diabetes mellitus, coronary artery disease, rheumatoid arthritis, erectile dysfunction, osteoporosis, and systemic cancers [11-14]. Age is a major risk factor for dementia, irrespective of etiology, and the condition typically occurs in elderly patients. These patients experience difficulties managing their oral hygiene because of decreased motor and cognitive ability, and several epidemiological studies have reported that the risk and severity of periodontitis are higher in patients with dementia than in patients without it [15,16].

The various anaerobic Gram-negative bacteria that cause periodontitis can also directly infiltrate the central nervous system and may affect the development or progression of AD [17]. In addition, some studies have already reported a close association of periodontitis with cardiovascular and cerebrovascular diseases, which are in turn closely related to the onset of VaD [18-20]. To our knowledge, despite this steady interest, few studies have examined the association between dementia and periodontitis with and without tooth loss [21,22]. Therefore, the purpose of this study was to evaluate severe periodontitis with tooth loss as a modifiable risk factor for AD, VaD, and MD based on a retrospective analysis of a large population-level dataset.

MATERIALS AND METHODS

Data source and study population

In 2014, the National Health Insurance Service built the National Health Insurance Service-National Health Screening Retrospective Cohort (NHIS-HEALS) anonymized database for research and policy evaluation purposes. This database was updated in 2018. The NHIS-HEALS database consists of a simple random sample of 514,866 participants (representing 10% of the total population of South Korea), which was extracted from the 5.15 million registered people aged 40 to 79 years old at the end of December 2003. After the exclusion

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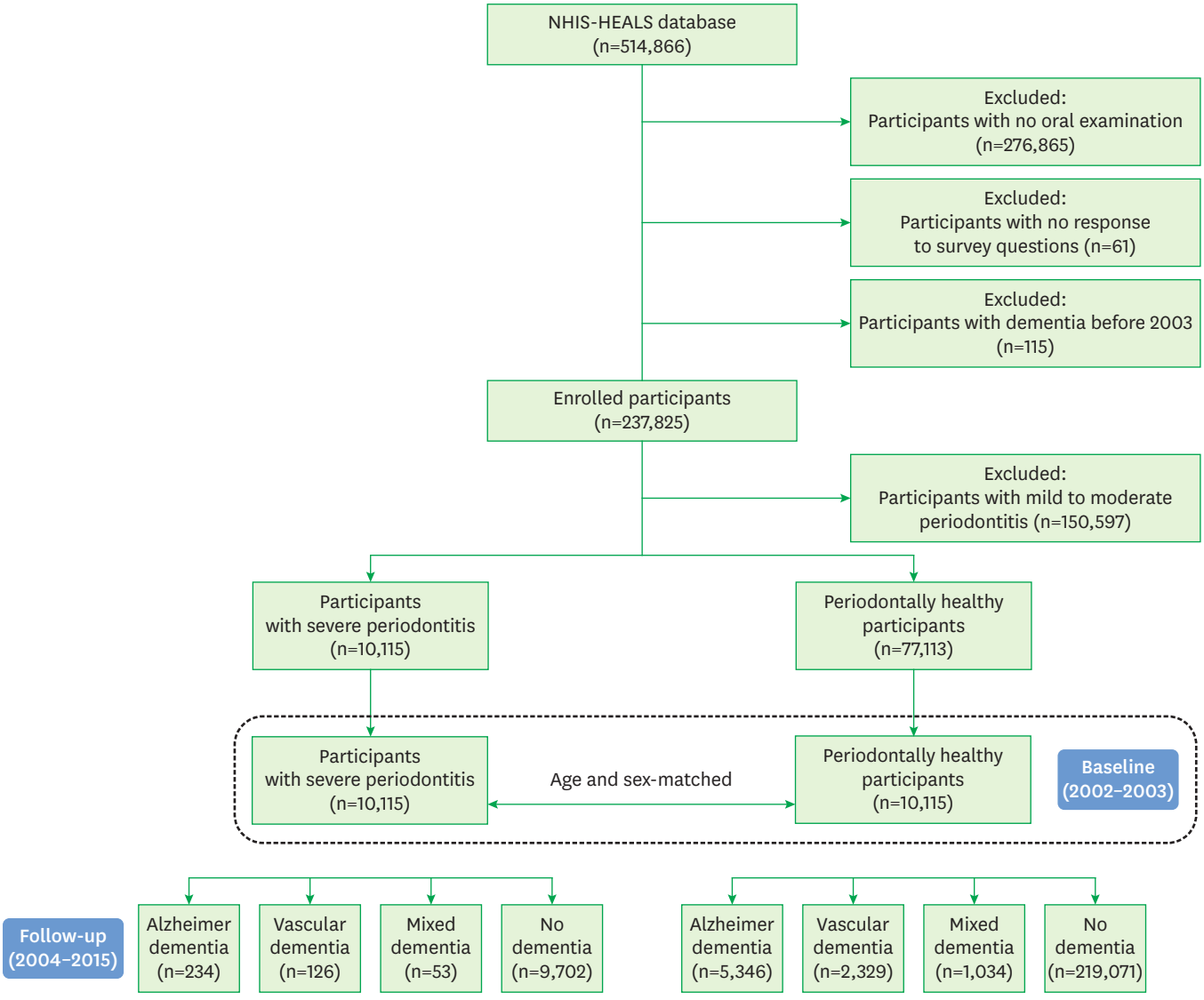

Figure 1. Flowchart of the inclusion and exclusion steps.
NHIS-HEALS, National Health Insurance Service-National Health Screening Retrospective Cohort.

of 276,865 participants with missing oral health examination data; 61 participants with missing responses to survey questions; 115 participants with AD, VaD, or MD recorded at the baseline general health examinations in 2002 and 2003; and 150,597 participants with mild to moderate periodontitis, the remaining 77,113 participants satisfying the inclusion criteria were selected. Finally, 10,115 participants with severe periodontitis and 10,115 age- and sex-matched periodontally healthy participants were randomly selected, evenly assigned, and followed until December 2015 (Figure 1).

Ethics statement

This observational study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (www.strobe-statement.org) and approved by the Institutional Review Board of Daejeon Dental Hospital at Wonkwang University (approval No. W1708/001–001).

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Diagnosis of periodontitis with tooth loss

After the baseline full-mouth oral health examinations in 2002 and 2003, the date of the first diagnosis of severe periodontitis was defined as the index date (baseline). Severe periodontitis was defined as periodontitis requiring surgical intervention. The necessity for surgical intervention was determined by the dentist through the assessment of clinical parameters such as signs of gingival inflammation, the degree of tooth loss, and the severity of calculus deposits. The numbers of remaining teeth and missing teeth were recorded for the entire dental arch of each participant during baseline oral health examinations in 2002 and 2003. Then, based on the number of remaining teeth, participants were classified into 3 groups (1–9, 10–19, and 20–28 teeth). Congenitally missing teeth and teeth with severe caries, with high mobility (including vertical movement), and with anomalies that were indications for extraction were excluded from the count of remaining teeth.

Diagnosis of dementia

Participants who had been diagnosed with dementia at the baseline general health examinations in 2002 and 2003 were excluded. AD (Korean Classification of Disease, 7th edition [KCD-7] codes F00.X) and VaD (KCD-7 codes F01.X) were identified and diagnosed by a neurologist and psychiatrist at a private or general hospital according to the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association during the follow-up period from 2004 to 2015 [23]. In addition, MD was defined as the co-diagnosis of AD and VaD [24].

Covariate variables

The potential confounding factors involving sociodemographic and economic information (sex, age, household income, and insurance status), anthropometric (body mass index [BMI]) and blood laboratory (total cholesterol level) measurements, lifestyle factors (smoking status, drinking status, and frequency of physical activity), and comorbid disease (hypertension [KCD-7 codes I10 and I15] and diabetes mellitus [KCD-7 codes E10–E14]) were obtained from the NHIS-HEALS database at the baseline general health examinations in 2002 and 2003.

Statistical analysis

The primary endpoint was a diagnosis of AD, VaD, or MD. All participants in the current study were followed up from the baseline examination until the first dementia diagnosis, death, emigration, withdrawal from the NHIS, or December 31, 2015. Distributions of sociodemographic factors, anthropomorphic measurements, lifestyle factors, and comorbidities (including sex, age, household income, insurance status, BMI, total cholesterol, smoking and drinking status, frequency of physical activity, remaining teeth, and hypertension and diabetes mellitus) at baseline were compared using chi-square and logistic regression analyses. Using Cox proportional regression analysis, adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. All analyses were conducted using the SAS statistical analysis software program (version 9.4; SAS Institute, Cary, NC, USA), and $P<0.05$ was considered to indicate statistical significance.

RESULTS

Baseline characteristics

The enrolled participants consisted of 14,474 men (71.5%) and 5,756 women (28.5%). Of the participants, at baseline, 9,388 (46.4%) were aged from 40 to 49 years, 7,030 (34.8%)

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were in the first quintile of household income, 14,491 (71.6%) were registered with the NHIS as employees, 7,391 (36.5%) were obese (BMI ≥25 kg/m^2), and 17,190 (85.0%) had normal cholesterol (≤240 mg/dL). Smoking and drinking status, frequency of physical activity, number of remaining teeth, and comorbidities were also investigated in both the participants with severe periodontitis and the periodontally healthy participants (Table 1).

Table 1. Baseline characteristics of participants according to the presence or absence of severe periodontitis

Variable	Participants with severe periodontitis (n=10,115)		Periodontally healthy participants (n=10,115)		*P*[a]
	Total No.	%	Total No.	%	
Sex					0.987
Male	7,237	71.5	7,237	71.5	
Female	2,878	28.5	2,878	28.5	
Age group (yr)					1.000
40–49	4,694	46.4	4,694	46.4	
50–59	3,301	32.6	3,301	32.6	
60–69	1,690	16.7	1,690	16.7	
70–79	430	4.3	430	4.3	
Household income[b]					**<0.001**
First quintile	3,495	34.6	3,535	34.9	
Second quintile	1,350	13.3	1,305	12.9	
Third quintile	1,563	15.5	1,457	14.4	
Fourth quintile	2,179	21.5	2,063	20.4	
Fifth quintile	1,528	15.1	1,755	17.4	
Insurance status					**<0.001**
MAP	2	0.0	10	0.1	
NHIS (self-employed)	2,733	27.0	2,994	29.6	
NHIS (employee)	7,380	73.0	7,111	70.3	
Body mass index (kg/m^2)					0.363
<18.5 (underweight)	205	2.0	213	2.1	
18.5–23 (normal)	3,359	33.2	3,459	34.2	
23–25 (overweight)	2,801	27.7	2,802	27.7	
≥25 (obese)	3,750	37.1	3,641	36.0	
Total cholesterol (mg/dL)					0.375
≤240 (normal)	8,572	84.7	8,618	85.2	
>240 (abnormal)	1,543	15.3	1,497	14.8	
Smoking status					**<0.001**
Non-smoker	5,254	51.9	6,342	62.7	
Former smoker	1,206	11.9	1,082	10.7	
Current smoker	3,655	36.1	2,691	26.6	
Drinking status					**<0.001**
None	1,751	17.3	5,118	50.6	
1–3 times/week	4,438	43.9	3,753	37.1	
4–7 times/week	3,926	38.8	1,244	12.3	
Physical activity					**<0.001**
None	4,831	47.8	5,149	50.9	
1–3 times/week	4,173	41.3	3,945	39.0	
4–7 times/week	1,111	11.0	1,021	10.1	
Remaining teeth					**<0.001**
1–9	4,592	45.4	5,215	51.6	
10–19	3,232	32.0	2,678	26.5	
20–28	2,291	22.6	2,222	22.0	
Comorbid disease					
Hypertension (yes)	5,245	51.9	4,966	49.1	**<0.001**
Diabetes mellitus (yes)	2,938	29.0	2,660	26.3	**<0.001**

Boldface denotes statistically significant values (P<0.05).
MAP: Medical Aid Program, NHIS: National Health Insurance Service.
[a]*P*-values were calculated using the chi-square test; [b]Participants were divided into 5 quintiles, with the MAP group classified in the first quintile.

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Table 2. HRs for dementia with severe periodontitis according to the number of remaining teeth

Variables	No. of remaining teeth					
	1–9		10–19		20–28	
	No. (%)	*P*	No. (%)	*P*	No. (%)	*P*
Alzheimer dementia						
Yes	42 (17.9)		16 (6.8)		176 (75.2)	
Crude HR (95% CI)	1.05 (0.90–1.21)	0.114	0.91 (0.64–1.31)	0.637	0.85 (0.50–1.46)	0.566
Adjusted HR (95% CI)[a]	1.08 (1.01–1.14)	**0.022**	0.92 (0.77–1.08)	0.322	0.70 (0.66–0.74)	0.361
Vascular dementia						
Yes	16 (12.7)		8 (6.3)		102 (81.0)	
Crude HR (95% CI)	1.13 (1.01–1.27)	**0.019**	1.06 (0.92–1.23)	0.377	1.04 (0.90–1.20)	0.588
Adjusted HR (95% CI)[a]	1.24 (1.16–1.32)	**<0.001**	1.08 (1.01–1.16)	**0.016**	1.04 (0.90–1.21)	0.533
Mixed dementia						
Yes	7 (13.2)		8 (15.1)		38 (71.7)	
Crude HR (95% CI)	1.12 (1.04–1.20)	**0.001**	1.04 (1.02–1.09)	**0.040**	1.08 (0.93–1.25)	0.302
Adjusted HR (95% CI)[a]	1.16 (1.09–1.24)	**<0.001**	1.00 (0.95–1.06)	0.140	1.05 (0.90–1.21)	0.514

Boldface denotes statistically significant values ($P<0.05$).
HR: hazard ratio, CI: confidence interval.
[a]Adjusted for sociodemographic, anthropomorphic, and lifestyle factors (sex, age, household income, insurance status, body mass index, total cholesterol, smoking and drinking status, and frequency of physical activity) and comorbidities (hypertension and diabetes mellitus).

Association between severe periodontitis and dementia

AD, VaD, and MD all showed significant associations with severe periodontitis with 1–9 remaining teeth (Table 2). The crude HR for AD among these participants was 1.08 (95% CI, 1.01–1.14; $P=0.022$). For VaD, the crude HR was 1.13 (95% CI, 1.01–1.27; $P=0.019$), and the adjusted HR was 1.24 (95% CI, 1.16–1.32; $P<0.001$). For MD, the crude HR was 1.12 (95% CI, 1.04–1.20; $P=0.001$), and the adjusted HR was 1.16 (95% CI, 1.09–1.24; $P<0.001$).

DISCUSSION

For statistical analysis of the NHIS-HEALS data, which were updated and newly released in 2018, we conducted multivariate analyses with adjustment for various sociodemographic factors, anthropomorphic measurements, lifestyle factors, and comorbidities that are known risk factors for or indicators of dementia. We found that a diagnosis of severe periodontitis with few remaining teeth (1–9) was significantly associated with relatively high risks of AD, VaD, and MD.

Several previous studies have reported an association between tooth loss and cognitive impairment [25-28]. Impaired masticatory function caused by tooth loss leads to decreases in cerebral blood supply, cerebral cortical activity, and the concentration of oxygen in the blood. Lower masticatory efficiency also leads to inappropriate nutritional intake, which can increase the risk of dementia [25,26]. Moreover, peri-radicular mechanoreceptors convey spatial information to the brain during mastication, helping to maintain neuronal activity. After tooth loss, this function decreases, which can result in reduced brain activity [26]. This evidence validates that severe periodontitis, which is considered to be the most common cause of tooth loss in the elderly, increases the risk of dementia.

Recent studies have demonstrated that periodontitis affects the development and/or progression of several types of dementia, including AD and VaD [21,22]. In one of those studies, after adjusting for the various sociodemographic and medical risk factors in the multivariate analysis, chronic periodontitis was found to be significantly associated with an increased risk of developing dementia (overall dementia: HR, 1.06; 95% CI, 1.01–1.11; AD: HR, 1.05; 95% CI, 1.00–1.11; VaD: HR, 1.10; 95% CI, 0.98–1.22) [21]. Another study by Yoo et

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al. [22], which included 209,806 participants aged ≥60 years, showed that participants with tooth loss had a higher risk of developing dementia than those without tooth loss (odds ratio, 1.18; 95% CI, 1.14–1.21). The findings that VaD is more closely associated with periodontitis than other types of dementia and that the risk of dementia increases with tooth loss are consistent with the results of this study.

Severe periodontitis causes elevated levels of inflammatory proteins, such as C-reactive protein, interleukin (IL)-1β, IL-6, prostaglandin E2, and tumor necrosis factor alpha, and these immune/inflammatory reactions can affect the development and progression of various systemic diseases [29,30]. Similarly, plasma from AD patients also shows increased levels of inflammatory markers, and this relationship remains consistent even after adjustment for confounding factors such as age, sex, and education level [31]. The circulation of systemic inflammatory proteins induced by periodontitis activates the central nervous system, particularly glial cells in the brain. This leads to the production of the amyloid β-peptide 1–42 (Aβ 42) and P-tau proteins, which form intra- and extra-neuronal plaques and increase the risks of neurodegeneration and AD [17].

A previous study demonstrated that *Prevotella intermedia* and *Fusobacterium nucleatum*, major causative bacteria of periodontitis, are potential risk factors for AD [32]. Foschi et al. [33] reported that the persistent deposition of bacterial dental plaque caused by poor oral hygiene directly increases the risk of systemic bacteremia. In particular, the anaerobic bacteria commonly observed in moderate-to-severe periodontitis can affect the development of AD by directly entering the central nervous system via systemic circulatory or peripheral neural pathways. *Treponema denticola*, another of the major periodontal pathogens, is often detected in the trigeminal ganglion and is known to increase the synthesis of the Aβ 42 and P-tau proteins by glial and neuronal cells after entering the central nervous system [34].

In patients with severe periodontitis, lipopolysaccharides released by *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* induce the activation of systemic inflammatory factors and aggravate intimal hyperplasia in the carotid arteries, ultimately increasing the risk of atherosclerosis and stroke [19]. Higher levels of antibodies targeting periodontal pathogenic bacteria are associated with the accelerated formation of atheroma in the aorta. The treatment of progressive periodontitis has been shown to lead to clear decreases in the circulating concentrations of inflammatory substances and considerable improvement in vascular endothelial function [35].

Although VaD and MD have lower prevalence and incidence rates than AD, approximately 50% of AD patients show concurrent pathological findings of stroke or cerebrovascular disease, indicating a higher likelihood of being diagnosed with VaD and MD [36,37]. Mortality from VaD is higher than that from AD, with an extremely short mean survival time of 3–5 years. This seems to be due to the effects of concurrent coronary artery disease, which has a relatively high mortality rate [38]. This short survival time is one of the major reasons that long-term and large cohort studies examining the association between periodontitis and VaD are highly limited and lacking.

This study had several limitations. First, calibrated public health dentists examined the number of remaining teeth during oral health examinations but did not ask the reason for tooth loss. Although severe periodontitis is considered the main cause of tooth loss in adults, several other causes exist, such as dental caries, trauma, orthodontic treatment, and

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iatrogenic factors. Therefore, the association between severe periodontitis and tooth loss in the current study may have been exaggerated [39,40]. Second, the severity of dementia was not evaluated because of insufficient diagnostic and treatment records. Third, although the most common causes of dementia are multifactorial and heterogeneous, the current study considered only limited factors and did not include various genetic and familial factors such as the apolipoprotein E ε4 allele and family history. Therefore, the association between severe periodontitis and dementia may also have been exaggerated or underestimated.

Although our study had some limitations, severe periodontitis with very few remaining teeth may be considered a potential risk indicator or modifiable risk factor for the development of AD, VaD, and MD in Korean adults. Further comparative randomized controlled clinical studies with longer follow-up periods are required to strengthen the evidence for this conclusion and to determine the underlying mechanism of linkage between periodontitis and dementia.

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