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

Do-Hyung Kim, Seong-Nyum Jeong, Jae-Hong Lee

Department of Periodontology, Daejeon Dental Hospital, Institute of Wonkwang Dental Research, Wonkwang University College of Dentistry, Daejeon, Korea

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, anthropomorphic measurements, lifestyle factors, and comorbidities.

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
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
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).
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%)
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/m²), 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) | \(P\)       |
|-------------------------------|-------------------------------------------------|---------------------------------------------|-------------|
| Total No.                     | 10,115                           | 10,115                                        |             |
| Total %                       | 100                              | 100                                          |             |
| Sex                           |                                  |                                              | 0.997       |
| Male                          | 7,237                            | 7,237                                         |             |
| Female                        | 2,878                            | 2,878                                         |             |
| Age group (yr)                |                                  |                                              | 1.000       |
| 40–49                         | 4,694                            | 4,694                                         |             |
| 50–59                         | 3,301                            | 3,301                                         |             |
| 60–69                         | 1,690                            | 1,690                                         |             |
| 70–79                         | 430                              | 430                                           |             |
| Household income*             |                                  |                                              | <0.001      |
| First quintile                | 3,495                            | 3,535                                         |             |
| Second quintile               | 1,350                            | 1,305                                         |             |
| Third quintile                | 1,563                            | 1,457                                         |             |
| Fourth quintile               | 2,179                            | 2,063                                         |             |
| Fifth quintile                | 1,528                            | 1,755                                         |             |
| Insurance status              |                                  |                                              | <0.001      |
| MAP                           | 2                                | 10                                            |             |
| NHIS (self-employed)          | 2,733                            | 2,994                                         | 0.1         |
| NHIS (employee)               | 7,380                            | 7,111                                         | 0.303       |
| Body mass index (kg/m²)       |                                  |                                              | 0.363       |
| <18.5 (underweight)           | 205                              | 213                                           |             |
| 18.5–23 (normal)              | 3,359                            | 3,459                                         |             |
| 23–25 (overweight)            | 2,801                            | 2,802                                         |             |
| ≥25 (obese)                   | 3,750                            | 3,641                                         |             |
| Total cholesterol (mg/dL)     |                                  |                                              | 0.375       |
| ≤240 (normal)                 | 8,572                            | 8,618                                         |             |
| >240 (abnormal)               | 1,543                            | 1,497                                         |             |
| Smoking status                |                                  |                                              | <0.001      |
| Non-smoker                    | 5,254                            | 6,342                                         |             |
| Former smoker                 | 1,206                            | 1,082                                         |             |
| Current smoker                | 3,655                            | 2,691                                         |             |
| Drinking status               |                                  |                                              | <0.001      |
| Non                           | 1,751                            | 5,118                                         |             |
| 1–3 times/week                | 4,438                            | 4,373                                         |             |
| 4–7 times/week                | 3,926                            | 3,753                                         |             |
| Physical activity             |                                  |                                              | <0.001      |
| None                          | 4,831                            | 5,144                                         |             |
| 1–3 times/week                | 4,173                            | 4,345                                         |             |
| 4–7 times/week                | 1,111                            | 1,021                                         |             |
| Remaining teeth               |                                  |                                              | <0.001      |
| 1–9                           | 4,592                            | 5,215                                         |             |
| 10–19                         | 3,232                            | 2,678                                         |             |
| 20–28                         | 2,291                            | 2,222                                         |             |
| Comorbid disease              |                                  |                                              | <0.001      |
| Hypertension (yes)            | 5,245                            | 4,966                                         |             |
| Diabetes mellitus (yes)       | 2,938                            | 2,660                                         |             |

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

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) |        | 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) |        | 1.24 (1.16–1.32) | **<0.001** | 1.08 (1.01–1.16) | **0.016** | 1.04 (0.90–1.27) | 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) |        | 1.16 (1.09–1.24) | **<0.001** | 1.00 (0.95–1.06) | 0.140 | 1.05 (0.90–1.27) | 0.514 |

Boldface denotes statistically significant values (*P*<0.05).

HR: hazard ratio, CI: confidence interval.

*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).
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
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.

ACKNOWLEDGEMENTS

The NHIS-HEALS data used (NHIS-2018-2-080) were supplied by the NHIS. The authors declare that they have no potential conflicts of interest with the NHIS or financial disclosures to report.

REFERENCES

1. Sposato LA, Kapral MK, Fang J, Gill SS, Hackam DG, Cipriano LE, et al. Declining incidence of stroke and dementia: coincidence or prevention opportunity? JAMA Neurol 2015;72:1529-31. [PUBMED] [CROSSREF]

2. Sorbi S, Hort J, Erkinjuntti T, Fladby T, Gainotti G, Gurvit H, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. Eur J Neurol 2012;19:1159-79. [PUBMED] [CROSSREF]

3. Alzheimer’s Association. Alzheimer’s Association Report: 2017 Alzheimer’s disease facts and figures. Alzheimers Dement 2017;13:325-73. [CROSSREF]

4. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology 2013;80:1778-83. [PUBMED] [CROSSREF]

5. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol 2013;9:106-18. [PUBMED] [CROSSREF]

6. Abbayya K, Puthanakar NY, Naduwimani S, Chidambar YS. Association between periodontitis and Alzheimer’s disease. N Am J Med Sci 2015;7:241-6. [PUBMED] [CROSSREF]

7. O’Brien JT, Thomas A. Vascular dementia. Lancet 2015;386:1698-706. [PUBMED] [CROSSREF]

8. Iadecola C. The pathobiology of vascular dementia. Neuron 2013;80:844-66. [PUBMED] [CROSSREF]

9. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197-204. [PUBMED] [CROSSREF]

10. Lee JH, Jeong SN, Choi SH. Predictive data mining for diagnosing periodontal disease: the Korea National Health and Nutrition Examination Surveys (KNHANES V and VI) from 2010 to 2015. J Public Health Dent 2019;79:44-52. [PUBMED] [CROSSREF]
11. Lee JH, Oh JY, Youk TM, Jeong SN, Kim YT, Choi SH. Association between periodontal disease and non-communicable diseases: a 12-year longitudinal health-examinee cohort study in South Korea. Medicine (Baltimore) 2017;96:e7398.

12. Lee JH, Lee JS, Park JY, Choi JK, Kim DW, Kim YT, et al. Association of lifestyle-related comorbidities with periodontitis: a nationwide cohort study in Korea. Medicine (Baltimore) 2015;94:e1567.

13. Choi JK, Kim YT, Kweon HJ, Park EC, Choi SH, Lee JH. Effect of periodontitis on the development of osteoporosis: results from a nationwide population-based cohort study (2003–2013). BMC Womens Health 2017;17:77.

14. Lee JH, Kweon HH, Choi JK, Kim YT, Choi SH. Association between periodontal disease and prostate cancer: results of a 12-year longitudinal cohort study in South Korea. J Cancer 2017;8:2959-65.

15. Philip P, Rogers C, Kruger E, Tennant M. Oral hygiene care status of elderly with dementia and in residential aged care facilities. Gerodontology 2012;29:e306-11.

16. Ghezzi EM, Ship JA. Dementia and oral health. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;89:2-5.

17. Maurer K, Rahming S, Prvulovic D. Dental health in advanced age and Alzheimer’s disease: a possible link with bacterial toxins entering the brain? Psychiatry Res Neuroimaging 2018;282:132-3.

18. 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;17:113-8.

19. Lafon A, Pereira B, Dufour T, Rigouby V, Giroud M, Béjot Y, et al. Periodontal disease and stroke: a meta-analysis of cohort studies. Eur J Neurol 2014;21:1155-61.

20. Lee JH, Lee JS, Choi JK, Kweon HJ, Kim YT, Choi SH. National dental policies and socio-demographic factors affecting changes in the incidence of periodontal treatments in Korean: A nationwide population-based retrospective cohort study from 2002-2013. BMC Oral Health 2016;16:118.

21. Choi S, Kim K, Chang J, Kim SM, Kim SJ, Cho HJ, et al. Association of chronic periodontitis on Alzheimer’s disease or vascular dementia. J Am Geriatr Soc 2019;67:1234-9.

22. Yoo JJ, Yoon JH, Kang MJ, Kim M, Oh N. The effect of missing teeth on dementia in older people: a nationwide population-based cohort study in South Korea. BMC Oral Health 2019;19:61.

23. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734–46.

24. Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. JAMA 2004;292:2901-8.

25. Takeuchi K, Ohara T, Furuta M, Takeshita T, Shibata Y, Hata J, et al. Tooth loss and risk of dementia in the community: the Hisayama study. J Am Geriatr Soc 2017;65:e95-100.

26. Zhu J, Li X, Zhu F, Chen L, Zhang C, McGrath C, et al. Multiple tooth loss is associated with vascular cognitive impairment in subjects with acute ischemic stroke. J Periodontal Res 2015;50:683-8.

27. Okamoto N, Morikawa M, Okamoto K, Habu N, Iwamoto J, Tomioka K, et al. Relationship of tooth loss to mild memory impairment and cognitive impairment: findings from the Fujiwara-kyo study. Behav Brain Funct 2010;6:77.

28. Okamoto N, Morikawa M, Okamoto K, Habu N, Hazaki K, Harano A, et al. Tooth loss is associated with mild memory impairment in the elderly: the Fujiwara-kyo study. Brain Res 2010;1349:68-75.
29. Lee JH, Choi JK, Kim SH, Cho KH, Kim YT, Choi SH, et al. Association between periodontal flap surgery for periodontitis and vasculogenic erectile dysfunction in Koreans. J Periodontal Implant Sci 2017;47:96-105.
PUBMED | CROSSREF

30. Lee JH, Choi JK, Jeong SN, Choi SH. Charlson comorbidity index as a predictor of periodontal disease in elderly participants. J Periodontal Implant Sci 2018;48:92-102.
PUBMED | CROSSREF

31. Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenber A, van Swieten J, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. Arch Neurol 2004;61:668-72.
PUBMED | CROSSREF

32. Sparks Stein P, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E, et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer’s disease. Alzheimers Dement 2012;8:196-203.
PUBMED | CROSSREF

33. Foschi F, Izard J, Sasaki H, Sambri V, Prati C, Müller R, et al. Treponema denticola in disseminating endodontic infections. J Dent Res 2006;85:761-5.
PUBMED | CROSSREF

34. Miklossy J, Kis A, Radenovic A, Miller L, Forro L, Martins R, et al. Beta-amyloid deposition and Alzheimer’s type changes induced by Borrelia spirochetes. Neurobiol Aging 2006;27:228-36.
PUBMED | CROSSREF

35. D’Aiuto F, Parkar M, Andreou G, Suvan J, Brett PM, Ready D, et al. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. J Dent Res 2004;83:156-60.
PUBMED | CROSSREF

36. Fernando MS, Ince PG; MRC Cognitive Function and Ageing Neuropathology Study Group. Vascular pathologies and cognition in a population-based cohort of elderly people. J Neurol Sci 2004;226:13-7.
PUBMED | CROSSREF

37. Straka M, Trapezanlidis M. Periodontitis and stroke. Neuroendocrinol Lett 2013;34:200-6.
PUBMED

38. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer’s disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 2008;7:812-26.
PUBMED | CROSSREF

39. Lee JH, Oh JY, Choi JK, Kim YT, Park YS, Jeong SN, et al. Trends in the incidence of tooth extraction due to periodontal disease: results of a 12-year longitudinal cohort study in South Korea. J Periodontal Implant Sci 2017;47:264-72.
PUBMED | CROSSREF

40. Kim YT, Choi JK, Kim DH, Jeong SN, Lee JH. Association between health status and tooth loss in Korean adults: longitudinal results from the National Health Insurance Service-Health Examinee Cohort, 2002-2015. J Periodontal Implant Sci 2019;49:158-70.
PUBMED | CROSSREF