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# Longitudinal relationship of severe periodontitis with cognitive decline in older Japanese

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*Background and Objective:* Epidemiologic data examining the longitudinal relationship between periodontitis and cognitive status are very limited, especially in Asian populations. The present study examined the longitudinal relationship of periodontitis with cognitive decline in 85 Japanese community-dwelling individuals (average age: 79.3 years) for whom data were available from comprehensive health examinations conducted in 2010 and 2013.

*Material and Methods:* Based on a baseline full-mouth periodontal examination, severe periodontitis was defined using a Centers for Disease Control and Prevention/American Academy of Periodontology definition. Cognitive decline during the 3-year study period was defined using the results of the Mini-Mental State Examination (MMSE). Information on age, gender, education, depression, body mass index, smoking status, alcohol use, exercise, hypertension, diabetes, history of cardiovascular disease and stroke, and baseline MMSE scores were obtained and tested as potential confounders in the statistical models.

*Results:* Among 85 study participants, 21 (24.7%) were defined as having severe periodontitis. Multivariable Poisson regression analyses revealed that severe periodontitis was significantly associated with an increased risk of cognitive decline [adjusted relative risk = 2.2; 95% confidence interval (95% CI): 1.1–4.5]. Furthermore, multivariable linear regression analyses revealed that participants with severe periodontitis had a 1.8-point greater decrease (95% CI: −3.3 to −0.2) in MMSE score than those without severe periodontitis.

*Conclusion:* Within the limitations related to its small sample size, the findings of the present study suggest that severe periodontitis is significantly associated with future decline in cognitive function among community-dwelling older Japanese subjects.

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Dementia is characterized by progressive and irreversible cognitive decline. It is associated with a significant social and financial burden (1,2); therefore, it is recognized as an important age-related public health problem. Japan has become a super-aged society, with the highest proportion of older people in the world. In 2014, there were 33 million people (25.9% of the total population) over the age of 65 (3). A recent study reported that the prevalence of dementia in Japan among those ≥ 65 years of age is > 10%, which corresponds to > 3 million older individuals. This number is expected to increase to 3.25 million by 2020 (4). In 2012, the Ministry of Health, Labor and Welfare of Japan formulated a 5-year plan for the early detection of dementia and to improve care for people with dementia ("Orange Plan") (5).

According to previous reports, there are several risk factors for cognitive decline: age, family history, genetics, smoking, alcohol consumption, physical activity, drug use and symptoms of depression (6,7). Several vascular risk factors (e.g. hypertension and dyslipidemia), cardiovascular disease (CVD), stroke and diabetes are also suggested to increase the risk of cognitive decline (8,9). In addition, potentially a significant association between cognitive impairment and periodontitis has been reported in previous epidemiological studies (10–14). Kamer *et al.* reported that older adults with periodontal inflammation (probing depth ≥ 4 mm in ≥ 10% of teeth) demonstrated impaired cognitive function (11). Stewart *et al.* investigated this relationship among adults participating in the third National Health and Nutrition Examination Survey (NHANES III). They demonstrated that the proportion of sites with clinical attachment loss ≥ 3 mm was significantly associated with poor cognitive performance (13). Another study of NHANES III participants demonstrated that elevated serum antibody levels against periodontal bacteria were associated with lower cognitive test scores (14). However, most of the studies (11,13,14) conducted to date had a cross-sectional design. An assertion of reverse causality (i.e. cognitive status affects periodontal health status) can be made for the results from cross-sectional studies. In fact, some studies reported that patients with cognitive impairment have a higher risk of periodontitis owing to impaired ability to perform proper oral hygiene measures or to attend a dentist regularly for check-ups and treatment (15,16). Further studies are needed to establish an unambiguous cause-and-effect relationship.

Investigating the relationship between periodontitis and cognitive impairment in longitudinal, instead of cross-sectional, studies is important to gain insight into periodontitis as a potential risk factor for cognitive decline. Such insights in turn may lead to the development of new strategies to prevent the development of dementia because periodontitis is largely modifiable. With this background, the present longitudinal study investigated whether periodontitis in elderly Japanese people could be a risk factor for cognitive decline.

## Material and methods

### Study design and population

The present study is based on two separate-year data collections from a geriatric health examination conducted in the town of Tosa, Kochi Prefecture, Japan. Based on a long-term-care insurance program launched in 2004, the health-care center of Tosa town promotes comprehensive health examinations for residents > 75 years of age. The health-care center in Tosa recruited participants using leaflets for a geriatric health examination, which were distributed to every household with individuals > 75 years of age in Tosa town. Information was collected on a wide range of health-related aspects. A neuropsychological assessment, blood pressure recording, anthropometric examination and a questionnaire-based examination were conducted. Neuropsychological assessment was carried out by trained psychologists. The Mini-Mental State Examination (MMSE), which is one of the most commonly used cognitive functioning tests, was used during cognitive assessment. MMSE scores range from 0 to 30, and a higher score indicates better performance (17). The presence of depressive symptoms was assessed using the Japanese version of the 15-item Geriatric Depression Scale (which yields scores ranging from 0 to 15), with higher scores indicating depression of greater severity (18). Blood pressure recordings were obtained from the right arm of the participants in a sitting position after 5 min of rest. Anthropometric evaluations included measurements of height and weight that were used to calculate body mass index (BMI). A self-administered questionnaire was used to collect data on age, education, smoking status, drinking frequency, exercise habits, medical diagnosis of hypertension and diabetes, usage of prescription medications (antidepressants and antidiabetic agents, including insulin) and history of CVD and stroke.

The comprehensive health examination described was conducted in 2010 (Examination 1) and in 2013 (Examination 2). In addition, a dental examination was conducted in 2010 (Examination 1). Two qualified dentists, using sufficient artificial illumination and a constant-pressure probe (Vivacare TPS probe; Vivadent Co., Schaan, Liechtenstein) assessed clinical attachment loss and probing depth at six sites around each tooth (excluding third molars). Before the examination, calibrations were performed on volunteer patients at the Niigata University Medical & Dental Hospital. The interexaminer agreement (± 1 mm) was 83.3% for clinical attachment loss and 87.5% for probing depth.

Three-hundred and thirty-two individuals, of 960 residents of Tosa who were > 75 years of age in 2010, excluding individuals in hospitals or nursing homes, participated in Examination 1. Two-hundred and eighty-four individuals, of 942 residents of Tosa > 75 years of age in 2013, excluding individuals in hospitals or nursing homes, participated in Examination 2. Overall, 182 individuals completed both Examinations 1 and 2, with 150 individuals participating in only Examination 1 and 102 individuals participating in only Examination 2. Individuals who completed both Examinations 1 and 2 were considered as the source population. Written informed consent was obtained from all 182 individuals.

Among the source population ($n$ = 182), 64 individuals with a baseline number of < 2 teeth, 21 individuals with a baseline MMSE score of < 24 and 12 individuals with incomplete data were excluded. Ultimately, 85 participants were selected and included in the analyses. Figure 1 shows the selection of study participants.

We used the Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) definition (19), where ≥ 2 teeth was necessary to categorize each participant with regard to the presence or absence of severe periodontitis. To obtain reliable information based on the self-administered questionnaire, and to estimate the risks of developing dementia, a cut-off MMSE score of 24 was used. This cut-off point was reported to have a sensitivity of 83% and a specificity of 93% in the diagnosis of dementia among Japanese subjects (20).

This study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by The Ethical Committee of Faculty of Medicine, Kyoto University, Kyoto, Japan. We also followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines in reporting this study.

### Predictor

The principal predictor variable was periodontal health status based on a clinical periodontal examination conducted in 2010. Using the CDC/AAP definition (19), severe periodontitis was defined as ≥ 2 interproximal sites with clinical attachment loss of ≥ 6 mm (not on the same tooth) and ≥ 1 interproximal sites with probing depth ≥ 5 mm. After the periodontal examination, the CDC/AAP definition was updated and published in 2012 (21), in which a definition for mild periodontitis was newly proposed, but the definition for severe periodontitis remained unchanged.

### Outcome

The outcome of interest was cognitive function decline, which was estimated using the difference between the MMSE score at Examination 2 (2013) and at Examination 1 (2010). Negative values indicated a decrease in MMSE score. Change in MMSE score was analyzed in two ways. First, as a binary variable: the incidence of a decrease of ≥ 3 points in the MMSE score. This cut-off point was used in previous study investigating the association between oral health and risk of cognitive decline (22). Second, as a quantitative variable.

### Covariates

All covariates were defined using the baseline data obtained for the study participants (Examination 1). Age, BMI and baseline MMSE score were considered as continuous variables. Lower education was defined as school attendance for less than 7 years. Depression was defined by a score of 6 or greater on the 15-item Geriatric Depression Scale. Hypertension was defined by self-reported medical diagnosis and/or the current use of antihypertensive medications and/or systolic/diastolic blood pressure ≥ 140/90 mm/Hg. Diabetes was defined by self-reported medical diagnosis and/or the current use of antidiabetic medications. History of CVD and stroke was based on a history of a physician informing the subject of these conditions and was recorded as 'yes' or 'no'. Smoking status was specified as two categories: never smoker or former/current smoker. Alcohol drinking was specified as either 'yes' or 'no'. Regular exercise habits was defined as currently exercising ≥ 30 min per session and ≥ 2 times per wk.

### Statistical analyses

Selected baseline characteristics were compared between the groups with and without severe periodontitis. The student's *t*-test for continuous variables and the chi-square test for categorical variables were used to test differences in the means and the percentages of the baseline characteristics between the two groups.

The association of baseline periodontal health status (with/without severe periodontitis) with a decrease of > 3 points in MMSE score over the study period (as a binary variable) was examined using Poisson regression with robust error variance. The association of baseline periodontal health status with MMSE score change (as a continuous variable) was examined using linear regression analysis with robust standard errors. For each outcome, age, gender, education, depression, BMI, smoking status, alcohol use, exercise, hypertension, diabetes, and history of CVD and stroke were tested as potential confounders in the multivariable models based on previous studies (6–9). Three regression models were developed: Model 1 (age-adjusted model); Model

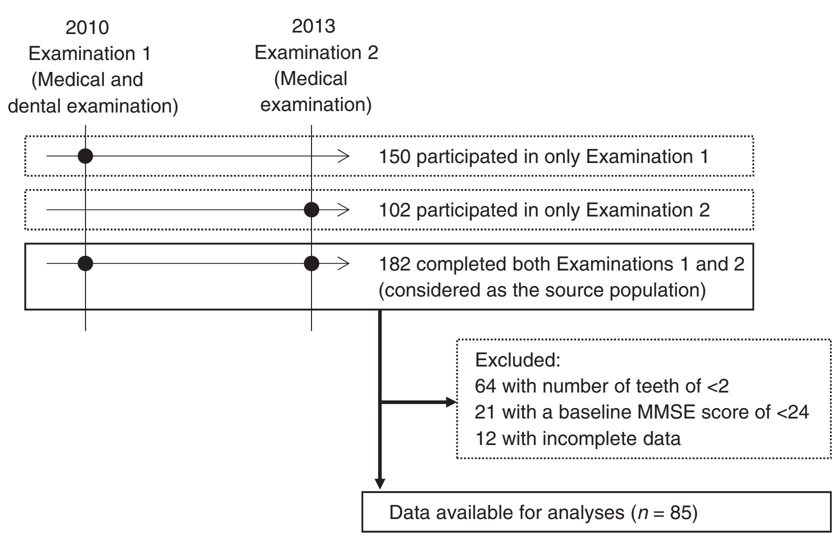


*Fig. 1.* Selection of study participants. MMSE, Mini-Mental State Examination.

2 (full model); and Model 3 (parsimonious model). The full model included all covariate parameters. The parsimonious model was selected after backward-elimination modeling assessment with a significance level for retention of $p < 0.2$. Furthermore, effect modification with age, gender and education was evaluated by adding interaction terms between the main exposure and each of the third variables in the regression models. Interaction terms found to be statistically nonsignificant were not included in the model.

The level of significance was set at $\alpha = 0.05$. All calculations and statistical analyses were performed using the statistical software package STATA (version 14; Stata Corp., College Station, TX, USA).

## Results

Among 85 study participants, 21 (24.7%) were defined as having severe periodontitis. The mean baseline MMSE score was 27.6 (SD = 1.9). Over the study period of 3 years, 21 (24.7%) participants demonstrated a decrease in MMSE score of ≥ 3 points. The mean change in MMSE score was −0.8 (SD = 2.8). The frequencies of participants stratified according to MMSE score are presented in Fig. 2.

Table 1 shows study participants' baseline characteristics according to periodontal health status. The groups with and without severe periodontitis were similar with regard to baseline demographic, socio-economic and health status, and health behavior. Although the prevalence of diabetes tended to be higher in individuals with severe periodontitis than in those without, the difference did not reach statistical significance ($p = 0.06$).

Table 2 shows the results from the Poisson regression analyses of the incidence of a decrease of ≥ 3 points in MMSE score. In Model 1, severe periodontitis was associated with a significantly increased risk of MMSE decline. The age-adjusted relative risk (RR) for participants with severe periodontitis was 2.8 [95% confidence interval (CI): 1.4–5.6] compared with those without severe periodontitis. For Models 2 and 3, severe periodontitis remained statistically significant after controlling for potential confounders and baseline MMSE score. In Model 2, the adjusted RR for participants with severe periodontitis was 2.2 (95% CI: 1.1–4.5).

Table 3 shows the results from linear regression analyses of the relationship between periodontal health status and MMSE score change. In Models 1, 2 and 3, a significant decrease in MMSE score was consistently observed among those with severe periodontitis compared with those without severe periodontitis. Participants with severe periodontitis had a 1.8-point greater decrease in MMSE score than did those without severe periodontitis (coefficient = −1.8; 95% CI: −3.3 to −0.2) in Model 2.

There were no statistically significant interactions of periodontitis with age, gender or education. Stratification according to these variables did not yield appreciable differences in the relationship between periodontitis and cognitive decline.

## Discussion

To the best of our knowledge, this is the first study performed in Japan demonstrating a longitudinal association between periodontitis and cognitive impairment among older adults. In this small study, community-dwelling

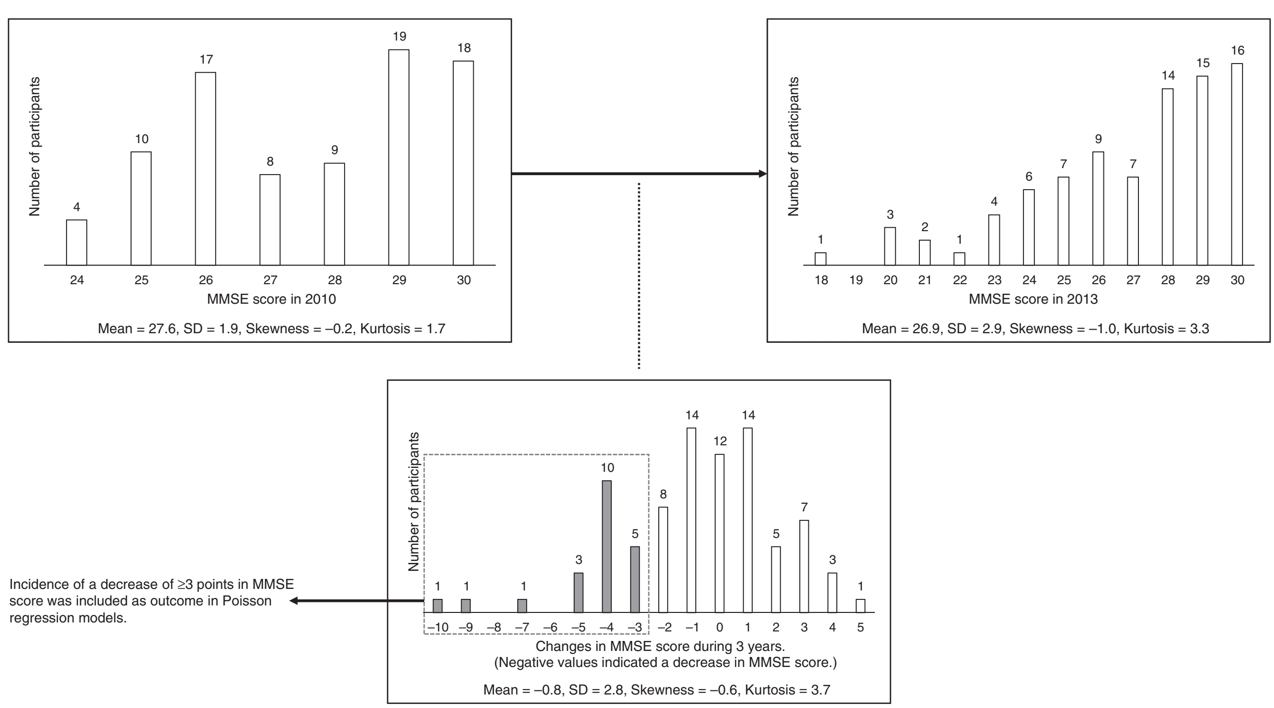


*Fig. 2.* Frequency table of participants stratified according to Mini-Mental State Examination (MMSE) score.

*Table 1.* Selected baseline characteristics of the study participants according to periodontal disease status

| | | Oral health status | | |
|---|---|---|---|---|
| | All participants ($n$ = 85) | No severe periodontal disease ($n$ = 64) | Severe periodontal disease ($n$ = 21) | $p$* |
| Demographic and socio-economic status | | | | |
| Age, mean (SD) | 79.3 (3.7) | 79.3 (3.7) | 79.5 (3.7) | 0.83 |
| Gender, $n$ (%) | | | | |
| Men | 30 (35.3) | 21 (32.8) | 9 (42.9) | 0.40 |
| Women | 55 (64.7) | 43 (67.2) | 12 (57.1) | |
| Education less than high school, $n$ (%) | 57 (67.1) | 41 (64.1) | 16 (76.2) | 0.31 |
| Health status and health behavior | | | | |
| Number of teeth, mean (SD) | 16.4 (7.6) | 16.7 (7.9) | 15.4 (7.0) | 0.50 |
| MMSE score, mean (SD) | 27.6 (1.9) | 27.6 (1.9) | 27.6 (2.1) | 0.98 |
| BMI, mean (SD), kg/m$^2$ | 23.4 (2.8) | 23.4 (2.7) | 23.3 (3.2) | 0.86 |
| Depression, $n$ (%) | 17 (20.0) | 14 (21.9) | 3 (14.3) | 0.45 |
| Hypertension, $n$ (%) | 65 (76.5) | 51 (79.7) | 14 (66.7) | 0.22 |
| Diabetes, $n$ (%) | 5 (5.9) | 2 (3.1) | 3 (14.3) | 0.06 |
| History of CVD, $n$ (%) | 9 (10.6) | 7 (10.9) | 2 (9.5) | 0.86 |
| History of stroke, $n$ (%) | 8 (9.4) | 6 (9.4) | 2 (9.5) | 0.98 |
| Previous/current smoker, $n$ (%) | 23 (27.1) | 16 (25.0) | 7 (33.3) | 0.46 |
| Current drinker, $n$ (%) | 14 (16.5) | 11 (17.2) | 3 (14.3) | 0.76 |
| Exercise regularly, $n$ (%) | 25 (29.4) | 20 (31.3) | 5 (23.8) | 0.52 |

BMI, body mass index; CVD, cardiovascular disease; MMSE, Mini-Mental State Examination.
*$p$ value for the comparison of selected characteristics between groups.

*Table 2.* Incidence rate ratio of Mini-Mental State Examination (MMSE) score decline during the study period according to periodontitis status

| | Severe periodontitis (vs. no severe periodontitis) | |
|---|---|---|
| Model | RR (95% CI) | $p$ |
| Model 1 (age adjusted) | 2.8 (1.4–5.6) | 0.01 |
| Model 2 (all covariates included) | 2.2 (1.1–4.5) | 0.03 |
| Model 3 (parsimonious model[a]) | 2.1 (1.03–4.5) | 0.04 |

95% CI, 95% confidence interval; RR, relative risk.
[a]Selected after backward-elimination modeling assessment (adjusted for gender, education, depression and diabetes).

*Table 3.* Mini-Mental State Examination (MMSE) score change during the study period according to periodontitis status

| | Severe periodontitis (vs. no severe periodontitis) | |
|---|---|---|
| Model | Coefficient (95% CI) | $p$ |
| Model 1 (age adjusted) | −2.1 (−3.8 to −0.4) | 0.01 |
| Model 2 (all covariates included) | −1.8 (−3.3 to −0.2) | 0.03 |
| Model 3 (parsimonious model[a]) | −1.8 (−3.3 to −0.3) | 0.02 |

95% CI, 95% confidence interval.
[a]Selected after backward-elimination modeling assessment (adjusted for gender, education, hypertension and diabetes).

older Japanese with severe periodontitis had more than a two-fold higher risk of cognitive decline, as determined using the MMSE score, than did individuals without severe periodontitis after controlling for other important baseline health characteristics in multivariable Poisson regression analyses. This observation suggests a causal relationship between severe periodontitis and cognitive function. The prevalence of dementia appears to be increasing, largely as a result of the aging population and lifestyle changes all over the world, including Japan (4). In light of this trend, our finding of an increased risk of cognitive decline associated with periodontitis has important clinical, public health and societal ramifications.

In this study, changes in MMSE score were included as both categorical and continuous variables in the analyses. Severe periodontitis was associated with both types of outcome. When we chose a $\geq 4$ point decline in MMSE score as an outcome (16 participants experienced this), the association remained significant (adjusted RR = 3.2, 95% CI: 1.3–8.2, in the fully adjusted Poisson model).

The finding of the current study concurs with previous epidemiologic studies, although these involved few Asian participants. Kaye *et al.* (23) demonstrated that, in older men, rates of progression of periodontitis were associated with increased risk of poor cognitive performance. Stewart *et al.* reported that gingival inflammation, as assessed using the gingival index, was significantly associated with cognitive decline (24). Noble *et al.* reported that high serum antibody levels to *Actinomyces naeslundii* genospecies-2 were associated with a risk of developing incident Alzheimer's disease (25). Sparks Stein *et al.* observed elevated antibody levels to *Fusobacterium nucleatum* and *Prevotella intermedia* in individuals before the development of cognitive impairment (26).

In the current study, MMSE score was used as a cognitive functioning test. It is easily administered and takes less than 10 min to complete in most cases. Therefore, it is suitable for epidemiological research. Since its creation in 1970s (17), the MMSE has been validated (20) and widely used. However, the MMSE has several weaknesses. The instrument relies heavily on verbal responses and reading and writing. Therefore, individuals who are visually or hearing impaired, have low language literacy or have other communication disorders may perform poorly, even when cognitively intact. The MMSE has low sensitivity for identification of frontal lobe dysfunction or mild cognitive impairment (27). In addition, repetitive testing with the same instrument may produce practice effects (28). Because our study investigated the association of periodontitis using only the MMSE, future studies using another cognitive functioning test or physician diagnosis of dementia as an outcome are necessary.

Increasing evidence suggests that periodontitis poses a chronic systemic inflammatory burden through the presence of elevated inflammatory mediators (29). Several inflammatory mediators (e.g. interleukin-1, interleukin-6 and tumor necrosis factor-$\alpha$) have been suggested to increase the risk of dementia (30). Moreover, during the periodontal inflammatory response, excessive production of reactive oxygen species occurs, which causes oxidative stress (31). Systemic inflammation and oxidative stress can contribute to vascular dysfunction and vascular disease, for example, atherosclerosis (32). Vascular dysfunction has important roles in the pathogenesis of dementia (33,34). In addition, periodontitis is suggested to be a risk factor for diabetes, stroke and CVD (35); therefore, periodontitis may also have an effect on dementia indirectly through these adverse clinical conditions.

A recent study (36) also suggested that a periodontal pathogen and its components could reach the brain and accelerate neuroinflammation. Poole *et al.* identified the presence of lipopolysaccharide from *Porphyromonas gingivalis* in the brain tissues of patients with Alzheimer's disease from 12-h postmortem samples.

Although the present study provides a novel finding with a longitudinal association between periodontal status and cognitive function in an Asian (Japanese) older population, several limitations merit consideration. First, the source population of our study consisted of individuals who participated in comprehensive health examinations conducted in a local town in Japan. No statistically significant differences were observed in the selected characteristics (e.g. MMSE score, periodontal health status) in 2010 between individuals who completed Examinations 1 and 2 ($n$ = 182), and individuals who participated only in Examination 1 ($n$ = 150) (Table 4). However, we could not obtain data on the reasons why individuals chose not to participate in the geriatric health examination. Because there was no information on the cognitive function and periodontal health of the older general population in the town of Tosa, we could not compare the characteristics between the population of the present study and the general population. A nationwide survey in Japan reported that the prevalence of severe periodontitis (community periodontal index = 4) in dentate individuals ≥ 75 years of age was 26.6% (37). Although no great gap was observed in periodontal health, it can be assumed that those who declined to participate in the examination might be more likely to be less concerned about their overall health (38). Furthermore, individuals who were hospitalized or were living in nursing homes could not be included. In this context, the present sample may be healthier than the general population; therefore, further studies are needed to reach a consensus on the association between periodontitis and dementia. Second, information related to periodontal status at the follow-up examination and periodontal therapy during the study was not obtained. This could have been a missed opportunity to perform preliminary analyses on the effect of change in periodontal status and periodontal therapy on cognitive status. Future studies should investigate whether a worsening of periodontitis severity is associated with worsening cognitive deterioration and evaluate the contribution of periodontal therapy to reducing the risk of the development or progression of cognitive impairment. Third, because other information previously recognized as relevant to cognitive function, such as socio-economic status (including financial stability and occupation), apolipoprotein E genotype, family history of dementia and serum inflammatory mediator levels (30,39,40), was not collected, a number of other potentially important confounders could not be included in the analyses. Residual confounding

*Table 4*. Comparison of selected characteristics between individuals participating in both Examinations 1 and 2 (source population) and Examination 1 only

| | Examinations 1 and 2 $n$ = 182 | Examination 1 $n$ = 150 | $p^{\dagger}$ |
|---|---|---|---|
| Demographic and socio-economic status | | | |
| Age, mean (SD) | 80.6 (4.3) | 81.5 (5.0) | 0.08 |
| Gender, % | | | |
| Men | 31.9 | 36.7 | 0.36 |
| Women | 68.1 | 63.3 | |
| Education less than high school, % | 71.4 | 73.6 | 0.69 |
| Health status and health behavior | | | |
| Number of teeth, mean (SD) | 9.8 (9.9) | 9.3 (9.6) | 0.67 |
| Edentulous, % | 33.9 | 34.5 | 0.91 |
| Severe periodontitis, % | 22.1 | 31.4 | 0.15 |
| Baseline MMSE score, mean (SD) | 26.2 (2.8) | 26.0 (3.6) | 0.10 |
| BMI (kg/m$^2$), mean (SD) | 23.0 (3.0) | 22.4 (3.4) | 0.14 |
| Depression, % | 27.6 | 34.8 | 0.20 |
| Hypertension, % | 73.6 | 70.7 | 0.55 |
| Diabetes, % | 6.6 | 6.7 | 0.98 |
| History of CVD, % | 9.9 | 13.3 | 0.33 |
| History of stroke, % | 9.9 | 10.7 | 0.82 |
| Previous/current smoker, % | 26.9 | 26.7 | 0.96 |
| Current drinker, % | 13.7 | 8.7 | 0.15 |
| Exercise regularly, % | 26.9 | 30.0 | 0.54 |

BMI, body mass index; CVD, cardiovascular disease; MMSE, Mini-Mental State Examination.

$^{\dagger}p$ value for the comparison of selected characteristics between groups.

remains a risk. Finally, extension of the current findings to the general population is limited because the study population included only small numbers of dentate Japanese. The data were obtained from health examinations conducted by the local government in Tosa as a public health service. Power analysis was not performed before the study. The size of the study population was not based on a power analysis. However, our model, including periodontitis, could predict MMSE decline in older Japanese to some degree (Pearson goodness of fit = 53.8, $p = 0.936$ for the fully adjusted Poisson regression model; $F = 2.04$, $p < 0.05$, $R$-squared = 0.286, for the fully adjusted linear regression model). Our study provides novel information on the prevalence of severe periodontitis and the RR of cognitive decline among older Japanese. Future studies with larger, more diverse populations and more complete information will be necessary to substantiate the findings.

## Conclusion

In summary, within the limitations of the study in relation to its small sample size, our findings suggested that severe periodontitis is significantly associated with future decline in cognitive function among community-dwelling older Japanese subjects.

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## Location of funding agencies

Tokyo, Japan.

## Conflicts of interest

The authors have no conflicts of interest to report.

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