Associations of Dental Health With the Progression of Hippocampal Atrophy in
Community-Dwelling Individuals: The Ohasama Study

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Although tooth loss and periodontitis have been considered risk factors for Alzheimer's
disease, recent longitudinal researches have not found a significant association with hippocampal atrophy. Therefore, this study aimed to clarify a longitudinal association between the number of teeth present (NTP) and hippocampal atrophy dependent on the severity of periodontitis in a late middle-aged and older adult population.

**Methods**

This study included community-dwelling individuals aged ≥55 years who had no cognitive decline and had undergone brain magnetic resonance imaging (MRI) and oral and systemic data collection twice at 4-year intervals. Hippocampal volumes were obtained from MRIs by automated region-of-interest analysis. The mean periodontal probing depth (mean PD) was used as a measure of periodontitis. Multiple regression analysis was performed with the annual symmetric percentage change (SPC) of the hippocampal volume as the dependent variable and including an interaction term between NTP and mean PD as the independent variable. The interaction details were examined using the Johnson–Neyman technique and simple slope analysis. The three-way interaction of NTP, mean PD, and time on hippocampal volume was analyzed using a linear mixed-effects model, and the interaction of NTP and time was examined in subgroups divided by the median mean PD. In all models, dropout bias was adjusted by inverse probability weighting.

**Results**

The data of 172 participants were analyzed. The qualitative interaction between NTP and
mean PD was significant for the annual SPC in the left hippocampus. The regression coefficient of the NTP on annual SPC in the left hippocampus was significantly positive (B=0.038, \( P=.026 \)) at the low-level mean PD (mean-1SD) and significantly negative (B=-0.054, \( P=.001 \)) at the high-level mean PD (mean+1SD). Similar results were obtained in the linear mixed-effects model; the interaction of NTP and time was significant in the higher mean PD group.

**Discussion**

In a late middle-aged and older cohort, fewer teeth were associated with a faster rate of left hippocampal atrophy in patients with mild periodontitis, whereas having more teeth was associated with a faster rate of atrophy in those with severe periodontitis. The importance of keeping teeth healthy is suggested.
**Abbreviations:** AD, Alzheimer's disease; AIC, Akaike's Information Criterion; CAL, clinical attachment loss; GM, gray matter; GMV, gray matter volume; hsCRP, high-sensitivity C-reactive protein; log_hsCRP, log-transformed high-sensitivity C-reactive protein; MMSE, Mini-Mental State Examination; MR, magnetic resonance; MTL, medial temporal lobe; NTP, number of teeth present; PD, periodontal probing depth; ROI, region of interest; SD, standard deviation; SE, standard error; SPC, symmetric percent change; TIV, total intracranial volume; VBM, voxel-based morphometry.

**Introduction**

The risk factors for dementia include diabetes mellitus and depression, but not all factors have been determined; only 40% of all dementia cases are attributable to known modifiable risk factors. Tooth loss and periodontitis, caused by oral bacterial infection, have been recently suggested as risk factors for Alzheimer's disease (AD) and related dementia, respectively. Tooth loss and periodontitis are highly prevalent worldwide, and if associated with the onset and progression of dementia, evaluation of their impact is important.

The clinical manifestations of AD are attributable to the progressive loss of neurons and synapses, with significant atrophy of memory-related structures in the medial temporal lobe.
(MTL) at an early stage, especially in the hippocampus and entorhinal cortex. Atrophy in the MTL, particularly in the hippocampus, has been identified as a potential biomarker for AD. Longitudinal studies have reported that many risk factors for AD are significantly associated with hippocampal atrophy. Regarding oral risk factors, animal studies have confirmed that a reduced number of teeth and the associated reduced masticatory activity cause hippocampal degeneration, and that the chronic oral administration of periodontal bacteria induces neurodegeneration in the hippocampus of wild-type mice. Previous studies in humans have reported the relationship between 1) the number of teeth, whole-brain volume, and gray matter volume (GMV); 2) the number of teeth and left hippocampal volume in older adults with cognitive impairment; and 3) people with edentulism and right hippocampus atrophy. However, these were cross-sectional studies. Although a longitudinal analysis recently reported that treatment of periodontitis improved AD-related brain atrophy, a previous study stated that the severity of periodontitis and tooth loss are not associated with morphological changes in the brain.

In laboratory animals, tooth loss and periodontitis models are created as independent, and their interaction is not considered. However, in humans, tooth loss and periodontitis occur simultaneously in the oral cavity. In patients with mild periodontitis in each tooth, the increase in inflammation per increase in the number of teeth may be sufficiently small. Therefore, the decrease in masticatory function due to a smaller number of teeth is likely to cause brain
atrophy. However, in those with severe periodontitis in each tooth, the increase in inflammation per tooth is non-negligible, and a large number of teeth may conversely cause brain atrophy owing to the increase in inflammation in the oral cavity. If this hypothesis is correct, then, the association between the number of teeth and changes in brain morphology depends on the degree of periodontitis. Therefore, a more detailed understanding of the relationship between the number of teeth and GMV changes in the human brain requires the use of statistical models that consider the interaction between the number of teeth and the degree of periodontitis.

This study aimed to evaluate the association between volume change rate in the hippocampus and the interaction of baseline number of teeth with the baseline periodontitis status (as a moderator variable) in a late middle-aged and older adult population living in the community, using longitudinal automated region-of-interest (ROI) and voxel-based morphometry (VBM) analysis.

Methods

Study design

This study was conducted as part of the Ohasama Study, a prospective cohort study on hypertension and cardiovascular disease that began in 1986 in the general population of
Ohasama, Iwate Prefecture, located in northern Japan. Further information on the Ohasama study is described in the eMethods. The inclusion criteria for the present analyses were men and women aged ≥55 years who had at least two brain magnetic resonance (MR) images taken 4 years apart and had undergone an oral examination by dentists. The exclusion criteria were the presence of edentulism and suspected cognitive decline at baseline.

**Participants**

Figure 1 presents a flow diagram of the study participant selection procedure. We contacted all 3,147 Ohasama residents aged at least 55 years between 2009 and 2017. Overall, 1,156 residents wished to participate in the home blood pressure measurements, among whom 714 also wished to participate in additional MRI and dental examinations between April 2009 and 2017 (brain MRIs have been included in the database from April 2009). Among those residents, 296 had undergone at least two head MR scans at 4-year intervals on record. We excluded 40 participants with missing dental data, two with missing medical data, and 34 with edentulism. Nineteen with baseline Mini-Mental State Examination (MMSE) scores ≤24 (maximum score: 30) points were excluded due to cognitive impairment. Eight participants
with no MRI data (six file open errors and two who did not provide consent for the use of MRI data) were excluded, and another 21 were excluded because preprocessing of their MRI findings was not completed successfully due to segmentation failure from bad tissue contrast. Finally, 172 participants (the follow-up group) were included in the analyses. The mean ± standard deviation (SD) follow-up period was 4.0 ± 0.1 years. Conversely, of the 418 who did not undergo more than one MRI scan, 215 were considered as the non-follow-up group, after excluding 125 with missing data, 38 individuals with edentulism, and 40 with MMSE scores ≤24 points.

**Data collection**

At the baseline, anthropometric measurements and blood samples were collected and questionnaires on medical history, medication status, and smoking and drinking status were administered. Hypertension was defined as self-measured blood pressure (home blood pressure) of ≥135/85 mmHg, antihypertensive drug use, or a history of hypertension. Diabetes was defined as a non-fasting blood glucose of ≥200 mg/dL, a glycated hemoglobin concentration of ≥6.5%, the use of diabetic medications, or a history of diabetes. Hypercholesterolemia was defined as a total cholesterol level of ≥220 mg/dL, antihypercholesterolemic drug use, or history of hypercholesterolemia. History of cerebrovascular/cardiovascular disease was defined as brain stroke or ischemic heart
disease and was confirmed by an interview, head MRI, or electrocardiogram. Drinking and smoking history was categorized as “never,” “former,” or “current.” The duration of education was classified as <10 years or ≥10 years. The body mass index was calculated by dividing the weight in kilograms by the height in meters squared. As the distribution of high-sensitivity C-reactive protein (hsCRP) measured by blood tests significantly deviated from the normal distribution, logarithmic transformation of hsCRP was used for the statistical analyses (log_hsCRP). Depressive symptoms were assessed using the Zung Self-Rating Depression Scale in an interview. Cognitive functioning was assessed using the MMSE in an interview at the baseline and follow-up surveys.

**Oral examination**

Specially trained dentists counted the number of teeth present (NTP) and the periodontal probing depth (PD). The NTP was counted by excluding the remaining roots. Then, PD was measured at four points, three buccal and one palatal, on all teeth. The mean of all PD was used as the “mean PD.” The mean PD is an index of PD gain per tooth, and when multiplied by the NTP, it is considered to reflect the degree of periodontitis in the entire oral cavity. As the mean PD itself was considered inappropriate as an indicator of the severity of periodontitis in the entire oral cavity, it was used only as a moderator variable for the NTP,
and the main effect of the mean PD was excluded from the interpretation of the analysis results. Clinical attachment loss (CAL), often used in epidemiological studies, reflects the cumulative history of past inflammation. Using CAL as the moderator of the NTP was inappropriate because only the cumulative history of inflammation around the present teeth was evaluated, ignoring the cumulative history of inflammation around the missing teeth before they were extracted.

**MRI acquisition and preprocessing**

All MR images were captured using the EXCELART Vantage (1.5T) (Toshiba Medical Systems, Tochigi, Japan) installed at the General Hanamaki Hospital (Iwate, Japan). The parameters of the axial FE3D sequence were as follows: repetition time, 14 ms; echo time, 5.5 ms; flip angle, 20°; 110 slices, (slice thickness, 1.5 mm); matrix, 256 × 256; field of view, 220 mm; pixel size, 0.8594 × 0.8594 mm; and scan time, 4 min 59 s.

The MR images were preprocessed using Statistical Parametric Mapping (SPM12, RRID: SCR_007037) and Computational Anatomy Toolbox for SPM (CAT12, RRID: SCR_019184) in MATLAB R2019b (MATHWORKS Corp., Natick, MA, USA). Preprocessing details are described in eMethods.

**ROI-based volume**
To validate the volumetric changes in the left and right hippocampus, the "estimate mean values inside ROI" of CAT12 were used to calculate the GMV of the hippocampus of both baseline and follow-up scans. The percentage of volume change between the baseline and follow-up scans was calculated as the symmetric percentage change using the following equation: SPC: 200 × (follow-up GMV – baseline GMV)/(baseline GMV + follow-up GMV).30

Statistical analyses

The Mann–Whitney U test and Fisher’s exact test were used to compare basic characteristics between the follow-up and no follow-up groups and between subgroups.

To adjust for any potential bias due to non-random dropout, we generated inverse probability weights (IPW) that accounted for the probability of undergoing a second MRI scan.32 A binary indicator of the follow-up or no follow-up group was predicted by a logistic model with baseline variables. Weights were calculated as the inverse of the predicted probability of being in the follow-up group. Participants with characteristics with a higher probability of no follow-up had a greater weight in all the following statistical analyses.

In univariate analysis, a single regression analysis was performed using the annual SPC, which was calculated by dividing the SPC of the left and right hippocampus by the
observation period (years) as the dependent variable. Age, sex, hypertension, diabetes, dyslipidemia, cerebral cardiovascular disease, smoking, alcohol consumption, education, body mass index, log hsCRP, Zung Self-Rating Depression Scale, and baseline MMSE scores, NTP, mean PD were each used as independent variables.

To analyze the association between hippocampal volume change and the interaction of NTP with mean PD, multiple regression analysis was performed using the annual SPC of the left and right hippocampus as the dependent variable. We fed both the NTP and mean PD as continuous variables into the statistical models: Model 1, in which only age, sex, NTP, and mean PD were independent variables; Model 2, in which the interaction term between NTP and mean PD was added to Model 1; and Model 3, in which all other variables were added to Model 2. The interaction details were examined using the Johnson–Neyman technique and simple slope analysis.

Next, we performed two sensitivity analyses. First, to determine whether the interaction between the NTP and mean PD is also associated with changes in cognitive function, we conducted an analysis using the MMSE model, in which the dependent variable in Model 3 was replaced by the annual change in the MMSE from baseline to follow-up ((follow-up MMSE – baseline MMSE)/observation period (years)). Adjusting for baseline cognitive status in regression analyses for cognitive change can introduce significant bias in the direction of the cross-sectional association between the baseline cognitive status and the baseline
independent variable.\textsuperscript{34} Therefore, in the MMSE model, the baseline MMSE score was excluded from the independent variables for the analysis. Second, a linear mixed-effects model was used to analyze the three-way interaction of time, NTP, and mean PD with the hippocampal volume as the dependent variable. Time was represented as years from baseline for each participant. This model was adjusted for the total intracranial volume (TIV) in addition to the same independent variables as in Model 3, as well as each variable interacted with time. The continuous variables "age, time, BMI, MMSE, SDS, log hsCRP, TIV, NTP, and mean PD" were mean-centered. As there were only two time points per participant, only random intercepts were included for each participant. We performed subgroup analysis to interpret the three-way interaction, dividing the two groups by the median mean PD, and examined the interaction between the NTP and time.

Statistical analyses were performed using R4.2.1 (R Software for Statistical Computing, Vienna, Austria),\textsuperscript{35} and the "interactions" and "sjplot" packages were used to analyze and plot the interactions. The "lme4" and "LmerTest" packages were used for the linear mixed effects model analysis. In all analyses, the significance level was set at 5%.

\textit{Longitudinal VBM}
Longitudinal VBM was conducted within the hippocampal ROI to search for clusters with significant interaction between the NTP and mean PD associated with the 4-year GMV change rate. Methods for longitudinal VBM are described in the eMethods.

**Standard protocol approvals, registrations, and patient consents**

This study was approved by the Institutional Review Board of the Teikyo University School of Medicine (approval number: 16-075-8) and the Tohoku University Tohoku Medical Megabank Organization (approval number: 2021-4-004) and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

**Data availability**

Due to the sensitive nature of the data and ethical concerns, the data from this cohort cannot be made available to other researchers.

**Results**

**Study Sample**
A comparison of the basic characteristics of the follow-up and no follow-up groups is shown in Table 1. Compared to the no follow-up group, the follow-up group had significantly higher SDS score and lower mean PD. In all subsequent statistical analyses, this bias was adjusted using IPW. The absolute standardized mean differences between the follow-up and no follow-up groups were <0.1, indicating a good covariate balance between the groups (eFigure 1).  

The hippocampal volume

The ROI-based hippocampal volumes were left (2564 [SD=284] mm$^3$) and right (2897 [SD=314] mm$^3$) at baseline and left (2462 [SD=292] mm$^3$) and right (2783 [SD=319] mm$^3$) at follow-up (eFigure 2).

Univariate analysis

Age and duration of education were significantly associated with annual SPC in the left hippocampus, while age, cerebrovascular/cardiovascular disease, and duration of education were significantly associated with the annual SPC in the right hippocampus. The NTP and mean PD showed no association with the annual SPC in either hippocampus (eTable 1).
Multiple regression analysis with continuous variables

When multiple regression analysis was performed with annual SPC of the left hippocampus as the dependent variable (Table 2), in Model 1, only age was significant ($R^2=0.17$, adjusted $R^2=0.15$); in Model 2, NTP, mean PD, and interaction of NTP and mean PD became significant, in addition to age ($R^2=0.26$, adjusted $R^2=0.24$). These variables were also significant in model 3 ($R^2=0.30$, adjusted $R^2=0.23$), in which various correction items were applied. When the annual SPC of the right hippocampus was used as the dependent variable (Table 3), age, mean PD, and interaction of NTP and mean PD were significant in Model 2, and only age was significant in Models 1 and 3.

The plots of the interactions of the NTP and mean PD in Model 3 with the annual SPCs of the left hippocampus as dependent variables are shown in Figure 2A, B. In the Johnson–Neyman plot that shows the size and significance of the regression coefficient throughout all observed levels of moderator variable, the regression coefficient of the NTP on the annual SPC in the left hippocampus had a significant positive coefficient when the mean PD was <2.17 and a significant negative coefficient when the mean PD was >3.18 (Figure 2A). When the mean PD was at three levels (mean, +1SD and -1SD), the regression coefficient of NTP on annual SPC in the left hippocampus was significantly positive (B=0.038, 95% confidence
interval [CI]: 0.004 to 0.071, \( P = .026 \)) at the low level (-1SD) and significantly negative (\( B = -0.054, 95\% \text{ CI}: -0.087 \text{ to } -0.021, \ P = .001 \)) at the high level (+1SD) (Figure 2B).

**Sensitivity analysis**

As multiple regression analysis with continuous variables detected a significant interaction between the NTP and mean PD only in the left hippocampus, sensitivity analysis was performed for the left hippocampus only.

The results of the analysis of MMSE model are presented in eTable 2. The interaction between the NTP and mean PD was significant (\( P = .044 \)), and the NTP (\( B = 0.042, 95\% \text{ CI}: 0.007 \text{ to } 0.077, \ P = .018 \)) and mean PD were significantly associated with annual change in the MMSE score, in addition to age, \( \log \) hsCRP, and Zung Self-Rating Depression Scale. In the Johnson–Neyman plot, the regression coefficient of the NTP on the annual change in MMSE had a significant positive coefficient when the mean PD was <2.69 mm (eFigure 3A). The regression coefficient of NTP on MMSE annual change significantly decreased as the mean PD increased, as did the regression coefficient of NTP on annual SPC in the left hippocampus. When the mean PD was at three levels (mean, +1SD and -1SD), the regression coefficient of the NTP on annual change in MMSE was significantly positive (\( B = 0.018, 95\% \text{ CI}: 0.004 \text{ to } 0.032, \ P = .012 \)) only at the low level (-1SD) (eFigure 3B).
The results of the linear mixed-effects model analysis are shown in eTable 3. Age, time, SDS, TIV, age × time, BMI × time, and three-way interaction among NTP, mean PD, and time (B=-1.41, 95% CI: -2.01 to -0.81, \( P<.001 \)) were significantly associated with the left hippocampal volume. The basic characteristics of the two subgroups, divided by the median mean PD (2.60 mm), are shown in Table 4. The lower mean PD group had significantly higher NTP, and a significantly higher percentage of drinkers and participants with more than 10 years of education compared to another group. The results of the subgroup analysis are presented in eTables 4 and 5 and Figure 3. In the lower mean PD group, the interaction between the NTP and time was not significant (B=0.61, 95% CI: -0.34 to 1.56, \( P=.211 \)); however, the regression coefficient of time on left hippocampal volume tended to decrease as NTP decreased (Figure 3A, B). In the higher mean PD group, the interaction between the NTP and time was significant (B=-0.86, 95% CI: -1.62 to -0.09, \( P=.031 \)), with the regression coefficient of time on the left hippocampal volume significantly decreasing as NTP increased (Figure 3C, D).

**Longitudinal VBM**
The results for the hippocampal ROI-based VBM are shown in eTable 6. Central portion of the left hippocampus was detected as a region where the negative interaction between the NTP and mean PD was significantly associated with the rate of GMV change (pFWE=0.035 cluster level). In a small region of the right hippocampus, a trend for a negative interaction between the NTP and mean PD, associated with the GMV change rate, was detected (P<.001 uncorrected voxel level, cluster size=18 voxels).

Discussion

This study demonstrated that the interaction between the NTP and the severity of periodontitis is associated with morphological changes in the left hippocampus. In patients with mild periodontitis, the left hippocampus atrophied as the NTP decreased, while in patients with severe periodontitis, atrophy of the left hippocampus progressed as the NTP increased.

There was no previous analysis of the interaction between the NTP and mean PD, making it difficult to estimate its effect size. Therefore, no prior power analysis was performed, and all available samples were used as most observational studies do. The effect size of the interaction in this study (increase in R² from Model 1 to Model 2: ΔR²=0.09) was large enough.
The follow-up group in this study had a significantly smaller mean PD value than that of the no follow-up group. As the mean PD was one of the exposure factors in this study, it would have been appropriate to correct for dropout bias using IPW.

The hippocampal volumes calculated by manual tracing (left: 3,210 [SD=397] mm³, right: 3,293 [SD=424] mm³ and left: 2165.71 [SE=49.13] mm³, right: 2141.06 [SE=52.87] mm³) have been reported. The ROI-based hippocampal volume obtained in this study was reasonable compared to these previous reports.

In this study, the NTP had no association with the annual SPC of the left and right hippocampus in Model 1, which did not include an interaction term. However, in Model 2, which included an interaction term, the NTP (left hippocampus only), mean PD, and their interaction were statistically significant. In the left hippocampus only, this significance remained in Model 3, which included many correction terms. This interaction was qualitative in that the direction of the association between the independent variable (NTP) and the dependent variable (annual SPC of the left hippocampus) was reversed depending on the value of the moderator variable (mean PD). These results support our hypothesis that when the degree of periodontitis of each tooth is mild, the association between the number of teeth and brain morphology is directly expressed; however, in cases of severe periodontitis of each tooth, the increase in inflammation per tooth may be not negligible. This interaction of the
NTP and mean PD may explain why previous studies have been unable to show an association between periodontitis, number of teeth, and brain morphological changes.\textsuperscript{21}

Given the partial regression coefficient of age ($B=-0.043$) in Model 3 for the left hippocampus (Table 2), the increase in the rate of atrophy of the left hippocampus due to one less tooth at the low-level mean PD (-1 SD: 2.05 mm) was equivalent to approximately 0.9 years of age ($0.038/0.043=0.884$); conversely, the increase in the rate of atrophy of the left hippocampus due to one more tooth at a high-level mean PD (+1 SD: 3.71 mm) was equivalent to approximately 1.3 years of age ($0.054/0.043=1.256$).

The results of the MMSE model suggested that cognitive decline was greater with fewer teeth in participants with mean PD <2.69 mm. However, there was no significant association between the NTP and annual change in MMSE when the mean PD was $\geq$2.69 mm. As the number of teeth is generally negatively correlated with age (i.e., having more teeth corresponds with younger age), cognitive decline due to a large number of teeth may be less detectable than that associated with hippocampal atrophy, which precedes cognitive decline.\textsuperscript{39}

In the linear mixed effects model, the three-way interaction between the NTP, mean PD, and time was significantly associated with the left hippocampal volume. In the higher mean PD group, there was a significant negative interaction of the NTP and time on left
hippocampal volume, confirming that the higher the number of teeth, the more progressive
the left hippocampal atrophy over time. In contrast, in the lower mean PD group, the
interaction between the NTP and time was not significant. However, there was a trend toward
more progressive atrophy of the left hippocampus over time with a smaller number of teeth.
The results of the linear mixed effects model support the results of Model 3.

The results of longitudinal VBM for the hippocampus support the influence of the interaction
between the NTP and mean PD on the rate of volume change in the left hippocampus, even
from a voxel-wise analysis, and suggest that a similar interaction may exist in a portion of the
right hippocampus. Left hippocampal atrophy is purportedly greater than right hippocampal
atrophy in patients with AD, and our VBM results support the possibility that the interaction
between NTP and mean PD is associated with AD.

In this study, log hsCRP showed no significant association with the annual SPC of the left
hippocampus. In a previous study showing a cross-sectional association between chronic
systemic inflammation and hippocampal volume, CRP ≥3 mg/L at ≥2 time points was defined
as chronic low-grade inflammation. Periodontitis is a chronic inflammation and increases
CRP in severe cases; however, in this study, only 11 participants had CRP levels ≥3 mg/L.

Porphyromonas gingivalis, a major pathogen of periodontitis, might cause temporary
bacteremia even with daily activities, such as toothbrushing and chewing. Moreover,

Porphyromonas gingivalis has been reported to invade the human brain and produce toxic
proteases that increase amyloid-β production. Even periodontitis without elevated CRP might affect AD risk and hippocampal morphology.

The strength of the present study is that it demonstrates that having more teeth may be a risk factor for dementia in patients with severe periodontitis. Considering that younger participants generally have more teeth even in the older adult group, our finding that the atrophy rate of the left hippocampus is greater with more teeth in the mean PD >3.18 mm is extremely important as it indicates that periodontitis may have a greater association with left hippocampal atrophy than the association exhibited by age.

As previous studies have suggested, it is important to preserve masticatory function and related neurological activity by retaining teeth to maintain brain health. However, the results of this study suggest that retaining more teeth with severe periodontitis may promote hippocampal atrophy. Controlling periodontal disease progression through regular dental visits is crucial, whereas teeth with severe periodontitis may need to be extracted and replaced with appropriate prostheses.

This study had some limitations. First, the data used were extracted from a voluntary epidemiological survey conducted in only one region of Japan. The dropout bias for the second MRI scan could be adjusted using IPW. However, the volunteer bias for the first MRI scan could not be corrected due to the lack of blood samples and dental data in those who
did not participate in the first MRI scan. The small number of participants in this study (n=172) may include a large proportion of health-conscious individuals and may not accurately reflect the characteristics of the general population of the region as a whole. As the comparison of the basic characteristics of the follow-up and no follow-up groups indicate, the prevalence of severe periodontitis in particularly may be low and, therefore, larger studies are needed to increase generalizability. Second, we did not consider the changes in the number of teeth or periodontitis since the baseline survey was conducted. Third, all possible confounding factors could not be adjusted. Diet,\textsuperscript{45} lifestyle,\textsuperscript{46} statin,\textsuperscript{47} and \textit{ApoE4} genes \textsuperscript{48} have been suggested to be associated with cognitive and brain structure change. However, the presence or absence of the \textit{ApoE4} gene was not investigated because the data used in this study were obtained from a cohort primarily targeting cardiovascular disease. We did not have data on diet, precise antihypercholesterolemic drug type, or lifestyle other than drinking and smoking history. Although diet and lifestyle are also associated with periodontitis \textsuperscript{49,50} and the \textit{ApoE4} gene has been suggested to influence inflammation-induced hippocampal atrophy,\textsuperscript{41} we cannot rule out the possibility that significant confounding by these factors has not been corrected in this study. In addition, smoking history was analyzed using three category variables, and if a quantitative variable such as pack-years had been used, the results might be different. Future studies should verify our results using data from other cohorts, and analyses should be conducted that consider the effects of other factors.
In conclusion, this study revealed that having fewer teeth is associated with a faster rate of left hippocampal atrophy in patients with mild periodontitis, whereas having more teeth is associated with a faster rate of atrophy in those with severe periodontitis. This finding indicates that periodontitis may have a greater association with left hippocampal atrophy than the association exhibited by age. Furthermore, in cases of mild periodontitis, fewer teeth may be associated with a subsequent decline in cognitive function. These results highlight the importance of preserving the health of the teeth and not just retaining the teeth. Future studies should validate our findings using data from other cohorts.
References


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longitudinal changes in hippocampal volume among Japanese community dwellers.

*Eur J Clin Nutr.* 2021;75(6):946-953; doi: 10.1038/s41430-020-00734-z


Figure legends

Figure 1. Flow diagram of the study participant selection procedure

- Residents aged ≥55 years invited to participate in Ohasama study between 2009 and 2017 (N = 3,147)
- Residents participated in home blood pressure measurements (n = 1,156)
- Residents underwent head MRI and dental examinations between 2009 April and 2017 (n = 714)
- Residents who underwent at least 2 head MRI scans at 4-year intervals (n = 296)
  - Excluded (n = 126):
    - Missing dental data (40)
    - Missing medical data (2)
    - People with edentulism (34)
    - MMSE scores ≤ 24 (19)
    - No MRI data (8)
    - MRI segmentation failure from bad tissue contrast (21)
- Residents who did not undergo more than 1 MRI scan (n = 418)
  - Excluded (n = 203):
    - Missing dental data (104)
    - Missing medical data (21)
    - People with edentulism (38)
    - MMSE scores ≤ 24 (40)
- Follow-up group (n = 172)
- No follow-up group (n = 215)

Figure 2. Interaction between the number of teeth present and the mean PD for annual symmetric percentage change of the left hippocampus in Model 3

A, The Johnson–Neyman plot indicates the size and significance of the slope of number of teeth present on annual symmetric percentage change of the left hippocampus throughout all observed levels of the mean PD. The shaded regions indicate 95% confidence intervals. B, Simple slope plot of the interaction between the number of teeth present and the mean PD on annual symmetric percentage change of the left hippocampus for four levels (-1 SD, mean, +1 SD, and 4.5 mm) of mean PD is shown. *Significant partial regression coefficient (P < .05).
Abbreviations: NTP, number of teeth present; PD, periodontal probing depth; SPC, symmetric percentage change.

**Figure 3. Interaction between time and number of teeth present for the left hippocampal volume in lower and higher mean PD groups**

**A and C**, The Johnson–Neyman plot indicates the size and significance of the slope of time on left hippocampal volume throughout all observed levels of the number of teeth present.

The shaded regions indicate 95% confidence intervals. **B and D**, Simple slope plot of the interaction between time and number of teeth present on left hippocampal volume for three levels (-1 SD, mean, +1 SD) of the number of teeth present is shown. *Significant partial regression coefficient (P<.05). Abbreviations: NTP, number of teeth present; PD, periodontal probing depth; SPC, symmetric percentage change.
probing depth.
Table 1. Baseline characteristics of the participants in follow-up and no follow-up group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Follow-up group (n=172)</th>
<th>No follow-up group (n=215)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>66.9 ± 6.9</td>
<td>67.4 ± 7.7</td>
<td>.735</td>
</tr>
<tr>
<td>Female, n (%</td>
<td>120 (69.8)</td>
<td>138 (64.2)</td>
<td>.278</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>106 (61.6)</td>
<td>144 (67.0)</td>
<td>.286</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>17 (9.9)</td>
<td>27 (12.6)</td>
<td>.426</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>93 (54.1)</td>
<td>105 (48.8)</td>
<td>.357</td>
</tr>
<tr>
<td>Cerebrovascular/cardiovascular disease, n (%)</td>
<td>11 (6.4)</td>
<td>19 (8.8)</td>
<td>.446</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td>.481</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>16 (9.3)</td>
<td>22 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>21 (12.2)</td>
<td>35 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Never smoker, n (%)</td>
<td>135 (78.5)</td>
<td>158 (73.5)</td>
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<tr>
<td>Drinking history</td>
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<td>.390</td>
</tr>
<tr>
<td>Current drinker, n (%)</td>
<td>73 (42.4)</td>
<td>87 (40.5)</td>
<td></td>
</tr>
<tr>
<td>Former drinker, n (%)</td>
<td>7 (4.1)</td>
<td>16 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Never drinker, n (%)</td>
<td>92 (53.5)</td>
<td>112 (52.1)</td>
<td></td>
</tr>
<tr>
<td>≥10 years of education, n (%)</td>
<td>86 (50.0)</td>
<td>117 (54.4)</td>
<td>.413</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>23.6 ± 2.9</td>
<td>24.0 ± 3.3</td>
<td>.135</td>
</tr>
<tr>
<td>log_hsCRP, mean ± SD</td>
<td>5.9 ± 1.3</td>
<td>6.1 ± 1.2</td>
<td>.109</td>
</tr>
<tr>
<td>SDS score, mean ± SD</td>
<td>30.9 ± 6.1</td>
<td>29.7 ± 6.0</td>
<td>.035</td>
</tr>
<tr>
<td>MMSE score, mean ± SD</td>
<td>28.5 ± 1.6</td>
<td>28.5 ± 1.6</td>
<td>.910</td>
</tr>
<tr>
<td>NTP, mean ± SD</td>
<td>18.0 ± 8.0</td>
<td>19.1 ± 7.7</td>
<td>.158</td>
</tr>
<tr>
<td>Mean PD, mean ± SD</td>
<td>2.7 ± 0.7</td>
<td>3.0 ± 0.8</td>
<td>.009</td>
</tr>
</tbody>
</table>

Abbreviations: NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; BMI, body mass index; log_hsCRP, log-transformed high-sensitivity C-reactive protein; SD, standard deviation.

*P-values were determined using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.
Table 2. Results of the regression analysis with the annual SPC of the left hippocampus as dependent variable (Models 1–3)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>P</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.052 (-0.077 to -0.026)</td>
<td>&lt;.001</td>
<td>-0.048 (-0.072 to -0.023)</td>
</tr>
<tr>
<td>Female sex</td>
<td>-0.138 (-0.501 to 0.225)</td>
<td>.454</td>
<td>-0.032 (-0.355 to 0.291)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Diabetes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cerebrovascular/cardiovascular disease</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Smoking history</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Drinking history</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration of education</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Body mass index</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>log_hsCRP</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>SDS score</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Baseline MMSE score</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>NTP</td>
<td>-0.004 (-0.030 to 0.022)</td>
<td>.782</td>
<td>0.145 (0.061 to 0.229)</td>
</tr>
<tr>
<td>Mean PD</td>
<td>0.292 (-0.053 to 0.636)</td>
<td>.097</td>
<td>1.030 (0.516 to 1.544)</td>
</tr>
<tr>
<td>NTP × mean PD</td>
<td>N/A</td>
<td>N/A</td>
<td>-0.051 (-0.080 to -0.023)</td>
</tr>
</tbody>
</table>

B, partial regression coefficient; CI, confidence interval

*The dependent variable was the annual SPC of the left hippocampus. Model 1: age, sex, NTP, and mean PD were independent variables. Model 2: the interaction term between NTP and mean PD was added to model 1. Model 3: the confounding factors were added to Model 2.

Abbreviations: SPC, symmetric percent change; NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; log_hsCRP, log-transformed high-sensitivity C-reactive protein.
Table 3. Results of the regression analysis with the annual SPC of the right hippocampus as dependent variable (Models 1–3)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>P</th>
<th>Model 2</th>
<th>P</th>
<th>Model 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>-0.058 (-0.081 to -0.036)</td>
<td>&lt;.001</td>
<td>-0.055 (-0.077 to -0.034)</td>
<td>&lt;.001</td>
<td>-0.048 (-0.071 to -0.026)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>0.162 (-0.224 to 0.548)</td>
<td>.409</td>
<td>0.236 (-0.129 to 0.601)</td>
<td>.203</td>
<td>0.276 (-0.190 to 0.741)</td>
<td>.244</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Cerebrovascular/cardiovascular disease</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Drinking history</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Duration of education</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>log_hsCRP</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.017 (-0.133 to 0.167)</td>
<td>.824</td>
</tr>
<tr>
<td><strong>SDS score</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Baseline MMSE score</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>NTP</strong></td>
<td>-0.008 (-0.036 to 0.019)</td>
<td>.555</td>
<td>0.097 (-0.002 to 0.196)</td>
<td>.056</td>
<td>0.071 (-0.027 to 0.170)</td>
<td>.153</td>
</tr>
<tr>
<td><strong>Mean PD</strong></td>
<td>0.219 (-0.124 to 0.561)</td>
<td>.209</td>
<td>0.738 (0.105 to 1.372)</td>
<td>.023</td>
<td>0.580 (-0.046 to 1.207)</td>
<td>.069</td>
</tr>
<tr>
<td><strong>NTP × mean PD</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>-0.036 (-0.072 to -0.000)</td>
<td>.048</td>
<td>-0.030 (-0.066 to 0.004)</td>
<td>.082</td>
</tr>
</tbody>
</table>

B, partial regression coefficient; CI, confidence interval

*The dependent variable was the annual SPC of the left hippocampus. Model 1: age, sex, NTP, and mean PD were independent variables. Model 2: the interaction term between NTP and mean PD was added to Model 1. Model 3: the confounding factors were added to Model 2.

Abbreviations: SPC, symmetric percent change; NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; log_hsCRP, log-transformed high-sensitivity C-reactive protein.
Table 4. Baseline characteristics of the participants in the subgroups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lower mean PD (≤2.60 mm)</th>
<th>Higher mean PD (&gt;2.60 mm)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>66.1 ± 6.8</td>
<td>67.8 ± 6.9</td>
<td>.111</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>60 (70.6)</td>
<td>60 (70.6)</td>
<td>&gt;.999</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>51 (59.3)</td>
<td>55 (64.0)</td>
<td>.638</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>7 (8.1)</td>
<td>10 (11.6)</td>
<td>.611</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>43 (50.0)</td>
<td>50 (58.1)</td>
<td>.359</td>
</tr>
<tr>
<td>Cerebrovascular/cardiovascular disease, n (%)</td>
<td>4 (4.7)</td>
<td>7 (8.1)</td>
<td>.535</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td>.465</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>9 (10.5)</td>
<td>7 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>8 (9.3)</td>
<td>13 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Never smoker, n (%)</td>
<td>69 (80.2)</td>
<td>66 (76.7)</td>
<td></td>
</tr>
<tr>
<td>Drinking history</td>
<td></td>
<td></td>
<td>.036</td>
</tr>
<tr>
<td>Current drinker, n (%)</td>
<td>41 (47.7)</td>
<td>32 (37.2)</td>
<td></td>
</tr>
<tr>
<td>Former drinker, n (%)</td>
<td>6 (7.0)</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Never drinker, n (%)</td>
<td>39 (45.3)</td>
<td>53 (61.6)</td>
<td></td>
</tr>
<tr>
<td>≥10 years of education, n (%)</td>
<td>50 (58.1)</td>
<td>36 (41.9)</td>
<td>.047</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>23.2 ± 2.9</td>
<td>24.0 ± 2.9</td>
<td>.061</td>
</tr>
<tr>
<td>log_hsCRP, mean ± SD</td>
<td>5.8 ± 1.3</td>
<td>6.1 ± 1.3</td>
<td>.143</td>
</tr>
<tr>
<td>SDS score, mean ± SD</td>
<td>31.6 ± 6.4</td>
<td>30.3 ± 5.6</td>
<td>.190</td>
</tr>
<tr>
<td>MMSE score, mean ± SD</td>
<td>28.7 ± 1.5</td>
<td>28.3 ± 1.7</td>
<td>.167</td>
</tr>
<tr>
<td>NTP, mean ± SD</td>
<td>19.8 ± 7.6</td>
<td>16.2 ± 8.1</td>
<td>.002</td>
</tr>
<tr>
<td>Mean PD, mean ± SD</td>
<td>2.2 ± 0.2</td>
<td>3.2 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TIV, mean ± SD</td>
<td>1427.9 ±127.8</td>
<td>1418.1 ± 124.5</td>
<td>.960</td>
</tr>
<tr>
<td>Left hippocampal volume, mean ± SD</td>
<td>2605.72 ± 247.61</td>
<td>2522.60 ± 312.10</td>
<td>.063</td>
</tr>
<tr>
<td>Right hippocampal volume, mean ± SD</td>
<td>2942.94 ± 284.64</td>
<td>2850.25 ± 336.84</td>
<td>.086</td>
</tr>
<tr>
<td>Annual SPC of the left hippocampus, mean ± SD</td>
<td>-1.06 ± 1.02</td>
<td>-0.99 ± 1.05</td>
<td>.727</td>
</tr>
<tr>
<td>Annual SPC of the right hippocampus, mean ± SD</td>
<td>-1.14 ± 1.05</td>
<td>-0.86 ± 1.19</td>
<td>.358</td>
</tr>
</tbody>
</table>

Abbreviations: SPC, symmetric percent change; NTP, number of teeth present; PD, periodontal probing depth; MMSE, Mini-Mental State Examination; SDS, Zung Self-Rating Depression Scale; BMI, body mass index; log_hsCRP, log-transformed high-sensitivity
C-reactive protein; TIV, total intracranial volume; SD, standard deviation. *P-values were determined using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.
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Satoshi Yamaguchi, Takahisa Murakami, Michihiro Satoh, et al.
Neurology® published online July 5, 2023
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