Regular Research Article

Differences in Brain Volume by Tooth Loss and Cognitive Function in Older Japanese Adults

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ABSTRACT

Background: We investigated the association between tooth loss and structural brain volume and its mediating effect on the association between tooth loss and cognitive function in older Japanese. Methods: A cross-sectional study was conducted by using the data of 494 randomly sampled community-dwelling individuals aged 65–84 years living in Tokamachi City, Japan. Total brain volume (TBV), gray matter volume (GMV), white matter volume (WMV), and hippocampal volume (HV) were measured with magnetic resonance imaging. The association of self-reported number of teeth (≥20, 1–19, and 0) with cognitive function assessed with the Japanese version of the Quick Mild Cognitive Impairment screen and structural brain volume was examined. Causal mediation analysis was performed to evaluate the mediating effect of structural brain volume. Age, sex, socioeconomic status, health behavior, comorbid conditions, and total intracranial volume were adjusted. Results: Respondents with no teeth showed lower cognitive function (coefficient = −4.01; 95% confidence interval [CI]: −7.19, −0.82), lower TBV (coefficient = −10.34; 95% CI: −22.84, 2.17), and lower GMV (coefficient = −6.92; 95% CI: −14.84, 0.99) than those with ≥20 teeth (P for trends were 0.003, 0.035, and 0.047, respectively). The number of teeth was not significantly associated with WMV or HV. GMV showed a significant mediating effect on the association between the number of teeth and cognitive function (coefficient = −0.38; 95% CI: −1.14, −0.002, corresponding to 9.0% of the total effect), whereas TBV did not. Conclusions: GMV was suggested to mediate the relationship between tooth loss and lower cognitive function. (Am J Geriatr Psychiatry 2022; 30:1271–1279)
INTRODUCTION

The global number of people living with dementia has been rising by population aging. In the last 25 years, the number of people with dementia doubled, and 50 million people live with dementia.1 By 2050, it is estimated that the number of dementia will increase by three times and reach 150 million.2 Modifiable risk factors, including education, lifestyles, and social networks, reportedly contribute to 40% of dementia onset.3 It is anticipated to prevent or delay the onset of dementia by addressing the modifiable risk factors.

Although it is largely preventable, more than 3.5 billion people in the world are affected by oral diseases.4 Tooth loss is the final outcome of oral diseases that impairs masticatory function, limits dietary choices, and decreases nutritional status.5 Many studies have reported the association between tooth loss and cognitive decline and dementia.6−8 For example, a meta-analysis of 8 cohort studies reported that having <20 teeth is associated with a 20% increased risk of dementia onset.9 A study of older people in Japan reported a significant association of tooth loss with subjective cognitive complaints after considering time-invariant confounders.10 Furthermore, a natural experiment study in the United Kingdom reported that limitation in the instrumental activity of daily living, risk of future dementia onset,9 increased by tooth loss.10

While these findings support that tooth loss is a risk factor of cognitive decline and dementia, the biological mechanisms underlying this relationship are still unclear.11,12 A study reported that social and nutritional factors mediated the association between tooth loss and dementia onset in Japanese older adults by 10% and 12%, respectively.13 Meanwhile, animal studies have suggested the role of the central nervous system related to a reduction in sensory stimulation by tooth loss.11,14 For example, many animal models with masticatory dysfunction have reported a reduction in hippocampal volume (HV).14 Also, after molar teeth extraction, changes in brain volumes, including a reduction in gray matter volume (GMV), were observed in mice.15 However, a few studies have investigated the difference in structural brain volume by tooth loss in humans.16−19 The only population-based study was conducted in Sweden,17 reporting that total brain volume (TBV) and GMV were significantly lower among older adults who lost teeth, whereas there was no significant difference in HV or white matter volume (WMV).17 Their study also confirmed that those with tooth loss had a lower cognitive function.17 However, it was not evaluated whether the difference in structural brain volume explains the association between tooth loss and cognitive function.

The present study aimed to 1) investigate the association between tooth loss and structural brain volume and 2) estimate its mediating effect on the association between tooth loss and cognitive function in older adults in Japan.

METHODS

Study Participants

A cross-sectional study was conducted using data from the baseline survey of the Neuron to Environmental Impact across Generations (NEIGE)
study conducted in Tokamachi City, Niigata, Japan, in September and October 2017. Community-dwelling older people aged 65–84 years living in two areas (downtown and mountain area) of the city, without receiving a long-term care certification (i.e., independent in daily life), were randomly selected. Of the 1,346 recruited people, 527 participated in the survey (participation rate = 39.2%). The detail of the sampling strategy and survey procedure is reported in the cohort profile paper. In the present study, participants with missing information on variables were excluded: 32 respondents lacked the data from magnetic resonance imaging (MRI) and 1 respondent lacked information on childhood subjective socioeconomic status, arriving at the data of 494 individuals for analysis (mean age [standard deviation {SD}] = 73.2 [5.5] years; 47.4% were male). All participants gave written consent to participate in the survey.

**Tooth Loss**

As an indicator of tooth loss, the number of teeth was assessed by a self-reported questionnaire: “How many natural teeth do you have?” with response options of ≥20, 10–19, 5–9, 1–4, and no teeth. We grouped the response as ≥20, 1–19, and no teeth. The variable was used as a categorical variable in linear regression analysis, whereas it was used as a continuous variable in the mediation analysis to consider the dose-response relationship. The validity of self-reported number of teeth among older people has been reported. The questionnaire also asked if the respondents used dentures. However, the variable on denture utilization was not used in the analysis because all respondents with no teeth used dentures.

**Cognitive Function**

The respondents’ cognitive function was assessed with the Japanese version of the Quick Mild Cognitive Impairment (QMI-) screen. It comprises six domains: orientation, word registration, clock drawing, delayed recall, verbal fluency, and logical memory; and the total score ranges between 0 (indicating marked impairment) and 100 (suggesting no impairment). The QMCI-J has been previously validated in this study participants with the Japanese version of the standard Mini-Mental State Examination (MMSE-J). A recent systematic review supports QMCI as a more accurate screening test for cognitive impairment than MMSE.

**Structural Brain Volume**

The data on brain images were acquired by structural MRI, using a 1.5 Tesla scanner (MAGNETOM Avanto fit, Siemens, Germany) with the following parameters: repetition time = 1700 ms, echo time = 4.31 ms, flip angle = 15°, field of view = 230 × 230 mm, acquisition matrix size = 256 × 256 mm, slice thickness = 1.25 mm, and number of slices = 144. Automatic segmentation following the Desikan-Killiany Atlas was performed using FreeSurfer Version 6.0 (http://surfer.nmr.mgh.harvard.edu). A manual quality check of the data was conducted. Following to a previous study, TBV, GMV, WMV, and HV were calculated.

**Covariates**

Self-reported questionnaires were utilized to assess the following variables based on previous review paper on determinants of remaining teeth and dementia: age (years old), sex (male or female), years of education (<10 years or ≥10 years), smoking status (never smoker or current/past smoker), alcohol drinking (not current drinker or current drinker), childhood subjective socioeconomic status (high/middle-high/middle or middle-low/low), equivalent income (<2.0 million JPY, ≥2.0 million JPY, or do not know), having hypertension (no, yes), and having diabetes (no, yes). In addition, average walking time (<60 minutes or ≥60 minutes per day) was adjusted in the causal mediation analysis because physical activity is associated with brain volume and cognitive function. Total intracranial volume (TIV) assessed by MRI was also included as a covariate in the analysis for structural brain volume.

**Statistical Analysis**

First, the association between tooth loss and cognitive function was examined by multivariable linear regression analysis. Three models were constructed: a model adjusted for age and sex (model 1); a model further adjusted for childhood socioeconomic status, years of education, and equivalent income (model 2);
and a model further adjusted for alcohol drinking, smoking status, hypertension, and diabetes (model 3). P for trend was calculated to assess the dose-response relationship.

Second, the association between tooth loss and structural brain volume was examined by multivariable linear regression analysis. Three models were constructed by adjusting for TIV and the same covariates as in the models of cognitive function. P for trend was calculated to assess the dose-response relationship.

Third, causal mediation analysis was performed to examine whether structural brain volume mediates the association between tooth loss and cognitive function. The causal mediation analysis decomposes the total effect (TE) of tooth loss on cognitive function into the path through brain volume (i.e., natural indirect effect, NIE) and the path not through brain volume (i.e., natural direct effect, NDE) under the assumptions of no unmeasured exposure-outcome confounding, no unmeasured exposure-mediator confounding, no unmeasured mediator-outcome confounding, and no mediator affected by the exposure. The variable of the number of teeth was coded as ≥20 (coded 1), 1–19 (coded 2), and no teeth (coded 3) and used as a continuous variable to consider the dose-response relationship. TE, NIE, NDE were estimated as a difference in cognitive function between having ≥20 and no teeth. Each mediator (i.e., TBV, GMV, WMV, and HV) was separately included in the mediation model. All covariates, including TIV and walking time, were adjusted. The 95% confidence interval (CI) for TE, NIE, and NDE were estimated by bootstrap with 2,000 repetitions. The CI for proportion mediated was not estimated because it is highly variable, and NIE is recommended to assess the significance of mediating effect.

We used Stata MP version 17.0. (StataCorp) for all analysis. The Stata package paramed was used for the causal mediation analysis. This study followed Strengthening the Reporting Observational Studies in Epidemiology (STROBE) guidelines.

RESULTS

Table 1 describes the demographic characteristics of the study participants. Among them, 297 (60.1%) had ≥20 teeth, 152 (30.8%) had 1–19 teeth, and 45 (9.1%) had no teeth. Cognitive function was significantly lower in those with fewer teeth: the mean (SD) of QMCI-J score for those with ≥20 teeth, 1–19 teeth, and no teeth were 63.2 (9.4), 59.0 (11.6), and 55.4 (10.7), respectively. Structural brain volume (ml) was lower for people with fewer teeth: the mean (SD) of TBV for those with ≥20 teeth, 1–19 teeth, and no teeth were 1059.3 (94.2), 1032.5 (101.8), and 1034.8 (79.7); that of GMV were 575.5 (46.5), 561.5 (46.3), and 558.7 (42.1); that of WMV were 443.6 (49.6), 428.1 (52.1), and 429.0 (42.6); and that of HV were 7.3 (0.8), 7.1 (0.7), and 6.9 (0.8), respectively. As for the distribution of covariates, those with fewer teeth were more likely to be older, male, have fewer years of education, have lower equivalent income, be current/past smokers, not current drinkers, have hypertension, and have diabetes, some of which were not statistically significant. TIV, walking time per day, and childhood subjective socioeconomic status were not associated with the number of teeth.

Figure 1 illustrates the association between tooth loss and cognitive function. Compared to people with ≥20 teeth, those with 1–19 teeth and no teeth had −3.01 (95% CI: −4.99, −1.03) and −5.24 (95% CI: −8.44, −2.04) lower scores of QMCI-J after adjusting for age and sex (model 1). The association partly explained and remained significant after adjusting for socioeconomic status (model 2: coefficients [95% CI] for 1–19 teeth and no teeth were −2.45 [−4.40, −0.49] and −4.40 [−7.56, −1.25], respectively). After adjusting for health behavior and comorbid conditions, the association remained significant (model 3: coefficients [95% CI] for 1–19 teeth and no teeth were −2.25 [−4.22, −0.29] and −4.01 [−7.19, −0.82], respectively). There was a significant dose-response relationship in the association (P for trend in model 3 = 0.003).

Table 2 reports the association between tooth loss and structural brain volume. After adjusting for age, sex, and TIV, those with fewer teeth had lower TBV and GMV (model 1). The results did not change after adjusting for socioeconomic status (model 2). In model 3, after adjusting for health behavior and comorbid condition, those with fewer teeth had lower TBV (coefficient [95% CI] for 1–19 teeth and no teeth were −7.05 [−14.77, 0.67] and −10.34 [−22.84, 2.17], respectively; P for trend = 0.035). They also had lower GMV [coefficient [95% CI] for 1–19 teeth and no teeth were −3.52 [−8.41, 1.36] and −6.92 [−14.84, 0.99],
respectively; P for trend = 0.047). As for WMV and HV, the models did not show significant differences or dose-response relationships by the number of teeth, although the point estimates consistently indicated that those with less than 20 teeth had lower WMV and those with no teeth had lower HV.

Table 3 reports the results from the causal mediation analysis. Significant NIE was observed for GMV (coefficient = −0.38; 95% CI: -1.14, -0.002), which corresponded to 9.0% of the TE. The NIEs for TBV, WMV, and HV were not significant (coefficient [95% CI] was −0.00 [-0.46, 0.45], 0.15 [-0.12, 0.92], and −0.21 [-0.98, 0.10], respectively).

**DISCUSSION**

This study found that fewer teeth were associated with lower TBV and GMV among older adults. In addition, this study is the first to report the mediating effect of structural brain volume on the association between tooth loss and cognitive function. That is, GMV mediated the association between tooth loss and cognitive function by 9.0%, suggesting that tooth loss may influence cognitive function through the deterioration of GMV. These results should be interpreted with caution because of a cross-sectional design.
### TABLE 2. Association Between the Number of Remaining Teeth and Brain Volume

<table>
<thead>
<tr>
<th>Outcome: TBV (ml)</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coef. (95% CI)</td>
<td>p Value</td>
<td>Coef. (95% CI)</td>
</tr>
<tr>
<td>Remaining teeth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>1–19</td>
<td>−7.45 (−15.11, 0.21)</td>
<td>0.057</td>
<td>−7.96 (−15.70, −0.22)</td>
</tr>
<tr>
<td>0</td>
<td>−11.67 (−24.05, 0.70)</td>
<td>0.064</td>
<td>−11.95 (−24.43, 0.54)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.018</td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>Outcome: GMV (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remaining teeth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>1–19</td>
<td>−4.16 (−8.98, 0.66)</td>
<td>0.091</td>
<td>−4.17 (−9.04, 0.71)</td>
</tr>
<tr>
<td>0</td>
<td>−8.22 (−16.01, −0.43)</td>
<td>0.039</td>
<td>−8.05 (−15.92, −0.19)</td>
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<tr>
<td>P for trend</td>
<td>0.016</td>
<td></td>
<td>0.019</td>
</tr>
<tr>
<td>Outcome: WMV (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remaining teeth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>1–19</td>
<td>−4.92 (−10.43, 0.58)</td>
<td>0.080</td>
<td>−5.17 (−10.73, 0.40)</td>
</tr>
<tr>
<td>0</td>
<td>−5.09 (−13.98, 3.80)</td>
<td>0.261</td>
<td>−5.01 (−13.99, 3.97)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.081</td>
<td></td>
<td>0.081</td>
</tr>
<tr>
<td>Outcome: HV (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remaining teeth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>1–19</td>
<td>−0.04 (−0.16, 0.08)</td>
<td>0.521</td>
<td>−0.03 (−0.16, 0.09)</td>
</tr>
<tr>
<td>0</td>
<td>−0.17 (−0.36, 0.03)</td>
<td>0.102</td>
<td>−0.14 (−0.34, 0.06)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.123</td>
<td></td>
<td>0.206</td>
</tr>
</tbody>
</table>

**Notes:**
- Coef.: coefficient; CI: confidence interval; TBV: total brain volume; GMV: gray matter volume; WMV: white matter volume; HV: hippocampal volume.
- Model 1: adjusted for age, sex, and total intracranial volume.
- Model 2: model 1 + childhood socioeconomic status, years of education, and equivalent income.
- Model 3: model 2 + alcohol drinking, smoking status, hypertension, and diabetes.
Mediator

<table>
<thead>
<tr>
<th>Mediator</th>
<th>TE Coef. (95% CI)</th>
<th>NDE Coef. (95% CI)</th>
<th>NIE Coef. (95% CI)</th>
<th>PM %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBV</td>
<td>−4.18 (−6.93, −1.54)</td>
<td>−4.17 (−6.91, −1.55)</td>
<td>0.00 (−0.46, 0.45)</td>
<td>0.1</td>
</tr>
<tr>
<td>GMV</td>
<td>−4.20 (−6.93, −1.55)</td>
<td>−5.82 (−6.50, −1.25)</td>
<td>−0.38 (−1.14, 0.002)</td>
<td>9.0</td>
</tr>
<tr>
<td>WMV</td>
<td>−6.21 (−6.92, −1.62)</td>
<td>−6.36 (−7.20, −1.83)</td>
<td>−0.15 (−0.12, 0.92)</td>
<td>NA</td>
</tr>
<tr>
<td>HV</td>
<td>−4.19 (−6.95, −1.54)</td>
<td>−5.98 (−6.77, −1.23)</td>
<td>−0.21 (−0.98, 0.10)</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Notes: Coef.: coefficient; CI: confidence interval; TBV: total brain volume; GMV: gray matter volume; WMV: white matter volume; HV: hippocampal volume; TE: total effect; NDE: natural direct effect; NIE: natural indirect effect; PM: proportion mediated.

Models were adjusted for age, sex, total intracranial volume, childhood socioeconomic status, years of education, equivalent income, alcohol drinking, smoking status, walking time, hypertension, and diabetes.

Confidence intervals were estimated by bootstrap with 2000 repetitions.

To the best of our knowledge, four previous studies have investigated the difference in structural brain volume by tooth loss in humans.16–19 A population-based cross-sectional study in Swedish older people (mean age = 73.2 years) found that those with complete tooth loss had significantly lower TBV and GMV than those with complete dentition by 52.7 ml and 37 ml, respectively, whereas WMV and HV were not significantly different.17 The results of the present study are consistent with their findings. The magnitude of the association was smaller in the present study than theirs, which could be because of a different reference category of tooth loss. Interestingly, our results on HV were also consistent with theirs in that those with complete tooth loss, but not those with parietal tooth loss, had lower HV. The other studies were conducted with small sample sizes (ranges from 15 to 70) and found that tooth loss is associated with lower HV18 and GMV,16,19 and volumes in regions including the caudate nucleus and temporal pole.16 However, these studies did not adjust for important confounders such as socioeconomic status.

The biological mechanisms of the relationship between tooth loss, smaller brain volume, and cognitive decline remain unclear; however, several hypotheses are suggested.11,17,29 The first explanation is that tooth loss leads to a reduction in sensory stimulation during chewing. Chewing increases cerebral blood flow in the sensorimotor cortex.29,30 Second, poor nutrition has been reported as a pathway of tooth loss and low cognitive function,13 and poor diet quality is associated with low brain volume.31 Thus, poor nutrition due to tooth loss5 may induce brain atrophy and cognitive decline. Third, chewing can attenuate stress-related responses.32 Chronic stress is associated with the HV of older people.33 Thus, chronic stress increased by masticatory dysfunction may lead to cognitive decline through brain atrophy. Fourth, chronic inflammation due to periodontal diseases is suggested as one of the mechanisms of poor oral condition and cognitive decline.34 However, a study reported that periodontal condition was not associated with total brain volume after 14 years of follow-up.35 It has been reported that patients with Alzheimer’s disease have less cortical gray matter than healthy older adults, with the amount of reduction varying in 10–30% by cortical region and disease severity.36 Therefore, low sensory stimulation, poor diet, and chronic stress due to tooth loss may reduce GMV, which in turn lead to cognitive function decline. Importantly, these hypothetical mechanisms are mainly supported by animal or human studies in laboratory settings.11,17,29 Population-based longitudinal studies are needed for further investigation.

This study has several limitations. First, no causal conclusion can be made because this is a cross-sectional study. Bidirectional associations between tooth loss and the central nervous system have been suggested. In other words, reduced sensory feedback during mastication may decrease stimulation to the brain, or masticatory dysfunction may reflect decreased motor control ability in the brain.11 Also, tooth loss may indicate past cognitive decline or other confounders.12 Second, the number of teeth was assessed with a single self-reported question. However, self-report information on the number of teeth has previously been validated with clinical examination.21
Selection bias may influence the result because it is expected that those who participated in the survey were healthy and cognitively independent despite employing a random sampling procedure. Further, the participants were limited to those aged <85 years. The association between tooth loss, structural brain volume, and cognitive function might be greater if we could include people aged ≥85 years. Fourth, the results might not be generalized to urban areas in Japan because the survey was conducted in a rural city. Tooth loss and cognitive impairment are less prevalent in areas with high socioeconomic status in Japan. Thus, the association may be smaller in urban cities.

In conclusion, this study found that Japanese older adults with tooth loss had lower TBV and GMV, and the difference in GMV mediated the association of tooth loss with low cognitive function by 9.0%. The findings and the mechanisms should be evaluated in future longitudinal studies.

**ETHICS APPROVAL**

This study was approved by the ethics committee of Niigata University (approval number: 2666).

**DATA AVAILABILITY STATEMENT**

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

**DATA STATEMENT**

The data have not been previously presented orally or by poster at scientific meetings.

**DISCLOSURES**

The authors have no disclosures to report.

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**AUTHOR CONTRIBUTIONS**

Y. Matsuyama, contributed to conception, design, data analysis and interpretation, drafted the manuscript; T. Fujiwara, H. Murayama, M. Machida, S. Inoue, and Y. Shobugawa contributed to conception, design, data interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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