CLINICAL INVESTIGATION

# Tooth Loss and Risk of Dementia in the Community: the Hisayama Study

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**OBJECTIVES:** To clarify the effect of tooth loss on development of all-cause dementia and its subtypes in an elderly Japanese population.

**DESIGN:** Prospective cohort study.

**SETTING:** The Hisayama Study, Japan.

**PARTICIPANTS:** Community-dwelling Japanese adults without dementia aged 60 and older (N = 1,566) were followed for 5 years (2007–2012).

**MEASUREMENTS:** Participants were classified into four categories according to baseline number of remaining teeth (≥20, 10–19, 1–9, 0). The risk estimates of the effect of tooth loss on the development of all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VaD) were computed using a Cox proportional hazards model.

**RESULTS:** During follow-up, 180 (11.5%) subjects developed all-cause dementia; 127 (8.1%) had AD, and 42 (2.7%) had VaD. After adjusting for potential confounders, there was a tendency for the multivariable-adjusted hazard ratio of all-cause dementia to increase with decrease in number of remaining teeth (*P* for trend = .04). The risk of all-cause dementia was 1.62 times as great in subjects with 10 to 19 teeth, 1.81 times as great in those with one to nine teeth, and 1.63 times as great in those with no teeth as in those with 20 teeth or more. An inverse association was observed between number of remaining teeth and risk of AD (*P* for trend = .08), but no such association was observed with risk of VaD (*P* for trend = .20).

**CONCLUSION:** Tooth loss is associated with an increased risk of all-cause dementia and AD in the Japanese population. **J Am Geriatr Soc 65:e95–e100, 2017.**

**Key words: Alzheimer's disease; epidemiology; oral health; prospective cohort study; vascular dementia**

The increase in the incidence of dementia is a substantial public health concern in aging societies. Approximately 46.8 million people worldwide have dementia, and the incidence is 9.9 million per year.[1] The number of people living with dementia will nearly double every 20 years, but the causes of dementia, especially Alzheimer's disease (AD), are unclear, and there is a lack of treatments and health service settings for this disorder.[2,3] Therefore, intensified research studies are needed to identify factors that have the potential to decrease the risk of dementia and thereby decrease the burden of this disease on health systems.

A growing number of research studies have focused on the link between oral health and cognitive status. In particular, many research studies have assessed the association between number of teeth and cognitive function,[4–15] but the results of observational longitudinal studies on the effect of tooth loss on cognitive function are inconsistent. A recent systematic review of the literature suggested that tooth loss was associated with greater risk of cognitive impairment and dementia,[16] whereas another reported that tooth loss was not consistently associated with those outcomes.[17] The inconsistency might be due to methodological deficiencies in this field, such as the lack of representativeness of the population, definitive assessment of cognitive function, and professional clinical oral examination. Thus, the existing evidence of a causal relationship between tooth loss and development of dementia is insufficient.

The purpose of the current study was to elucidate the effect of tooth loss on the development of dementia and its subtypes by targeting a general population of elderly adults

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in Japan using neuropathological and neuroimaging data for definitive diagnosis of dementia types and data from clinical oral examinations by dentists for evaluation of tooth loss.

## METHODS

### Study Population

This study was based on data from the Hisayama Study, a population-based prospective cohort study of cardiovascular disease and its risk factors established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area in southern Japan.[18] According to national census data, the age, occupational distributions, and nutrient intake of the population of Hisayama have been similar to those of Japan as a whole during the past 50 years.[19] Full community surveys of health status and neurological conditions of residents aged 40 and older have been conducted every 1 to 2 years since 1961. In addition, comprehensive surveys of dementia in elderly adults have been undertaken since 1985.[20]

In 2007 and 2008, 1,996 residents aged 60 and older (86.3% of the total population this age) participated in a screening examination. After excluding 167 subjects with dementia at the baseline examination in 2007 and 2008, 202 subjects with missing oral examination, and 61 subjects with missing responses to survey questions on other covariates used in the analysis, the remaining 1,566 subjects (691 men, 875 women) were enrolled in the present study. Written informed consent was obtained from all subjects. The Kyushu University Institutional Review Board for Clinical Research approved this study.

### Follow-Up Survey

Subjects were followed prospectively for 5 years (June 2007 to November 2012). Detailed information about the follow-up survey on dementia has been provided elsewhere.[18] In brief, a daily monitoring system was established in the study team and local physicians or members of the town's Health and Welfare Office to obtain information on new events, including stroke, cognitive impairment, and dementia.

When a participant was suspected of experiencing new neurological symptoms, including dementia, the study team evaluated him or her for the presence of dementia. This team, which consisted of stroke physicians and psychiatrists, conducted physical and neurological examinations, neuropsychological tests, interviews of the family and attending physician, and a review of the clinical records. Letters or telephone calls were also used to collect health information of subjects who did not undergo examinations or had moved away. In addition, comprehensive surveys of cognitive function, including neuropsychological tests (Hasegawa Dementia Scale—Revised[21] and Mini-Mental State Examination[22]), were conducted in 2012. When a subject died, all the available clinical information was reviewed, the attending physician and the family of the deceased were interviewed, and permission for autopsy was obtained from the family. During follow-up, 108 subjects died, of whom 63 underwent brain examination at autopsy. No subjects were lost to follow-up.

### Diagnosis of Dementia

Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised, Third Edition*, criteria.[23] Subjects with AD were identified according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.[24] Vascular dementia (VaD) was defined according to the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria.[25] Clinical information, including neuroimaging, was used to diagnose possible or probable dementia subtypes. Expert stroke physicians and psychiatrists adjudicated each case of dementia. The accuracy of clinical diagnosis of AD and VaD were estimated using neuropathological data, with AD diagnosed pathologically according to the National Institute on Aging—Reagan Institute criteria,[26] and VaD was confirmed according to the absence of neuropathological evidence of other forms of dementia. Of 347 individuals with dementia (including subjects with dementia at baseline) during follow-up, 53 underwent autopsy. Agreement rates between clinical diagnosis and pathological diagnosis were 0.80 for AD and 0.68 for VaD.

### Evaluation of Tooth Loss

At the baseline examination in 2007 and 2008, calibrated dentists performed a clinical oral examination, following the method of the Third National Health and Nutrition Examination Survey.[27] The dentists were trained, and consensus discussions were held before initiation of the examination. Expert dentists evaluated and verified the reliability of the oral examination by examining volunteers with characteristics similar to those of the study population. The number of remaining teeth was recorded for each subject to evaluate tooth loss. Remaining teeth were defined as healthy, carious, or treated (including crowned, inlay, and abutment teeth for prostheses), inclusive of completely erupted third molars. Unerupted or congenitally missing teeth, root tips, and extremely mobile teeth that were indicated for extraction were not included as remaining teeth. According to the established data of the extent of tooth loss, the number of remaining teeth was grouped into four categories (≥20, 10–19, 1–9, 0).[28–34] The dentists also evaluated denture use for each subject during the clinical oral examination.

### Measurements of Other Risk Factors

A wide range of covariates was included in the analyses as potential confounding risk factors based on prior literature. At the baseline examination, trained interviewers reviewed a self-administered questionnaire that covered demographic characteristics, current occupation, medical history and treatment, physical activity, smoking habits, alcohol intake, tooth brushing frequency, and regular dental visits. Sex and age (60–74 or ≥75) were used as

demographic characteristics. Occupation was used to stratify subjects into socioeconomic strata (white-collar workers, blue-collar workers, unemployed, homemakers, part-time workers). White-collar workers included managers, professionals, office workers, and service and sales workers; blue-collar workers included skilled and elementary workers and agricultural, forestry, and fishery workers. A low level of education was defined as less than 10 years of formal education. Blood pressure was measured three times using a standard mercury sphygmomanometer in the sitting position after at least 5 minutes rest. The mean of three measurements was used for the analysis. Hypertension was defined as blood pressure of 140/90 mmHg or greater or current use of antihypertensive agents. A blood sample was collected from the antecubital vein in the morning after overnight fasting, and fasting levels of plasma glucose were determined using the hexokinase method. Glycosylated hemoglobin (HbA1c) levels were measured using latex aggregation immunoassay (Determiner HbA1C, Kyowa Medex, Tokyo, Japan) and were estimated as a National Glycohemoglobin Standardization Program equivalent value. Diabetes mellitus was diagnosed as a fasting plasma glucose level of 126 mg/dL (7.0 mmol/L), 2-hour postload or postprandial plasma glucose level of 200 mg/dL (11.1 mmol/L), or current treatment with insulin or oral hypoglycemic medication. History of stroke was defined on the basis of all the clinical data available in the Hisayama Study. Body height and weight were measured in light clothing without shoes, and body mass index was calculated and dichotomized as less than 25.0 kg/m$^2$or 25 kg/m$^2$ or greater. Physical activity was defined as engaging in exercise one or more times per week during leisure time, and subjects were divided into two groups: an active group and an inactive group.[35] Smoking habits and alcohol intake were categorized as ever or current versus never. Tooth brushing frequency was categorized as once per day of less versus more than one time per day. With regard to regular dental visits, subjects were categorized as visiting the dentist for oral care at least once every 6 months or not.

### Statistical Analyses

Descriptive statistics were used to characterize the subjects. Linear trends in frequencies of risk factors across number of remaining teeth categories (≥20, 10–19, 1–9, 0) were tested using logistic regression analysis. Subjects were censored at date of death or end of follow-up for survival analyses. Incidence rates of dementia were calculated using the person-year method. Crude and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model. The assumption of the proportional hazards was checked graphically using log cumulative hazard plots for outcomes. In multivariable adjustment, the covariates were selected using a backward selection method. Heterogeneity in the association between subgroups was tested by adding multiplicative interaction terms to the relevant Cox model. All analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY). Two-sided $P < .05$ was considered statistically significant in all the cases. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines for the analysis of observational data were followed.[36]

## RESULTS

Baseline characteristics of the study population according to number of remaining teeth are shown in Table 1. The likelihood of being aged 75 and older, a smoker, a nondrinker; having hypertension, low education, nonregular visits to the dentist; brushing teeth less than twice a day; and using denture increased gradually with decrease in number of remaining teeth. Frequency of occupation type was significantly different across number of remaining teeth categories.

**Table 1. Baseline Characteristics of Study Population According to Number of Remaining Teeth**

| Characteristic | ≥20, n = 893 | 10–19, n = 348 | 1–9, n = 204 | 0, n = 121 | *P* for Trend |
|---|---|---|---|---|---|
| Women, % | 54.8 | 58.0 | 55.9 | 57.9 | .44 |
| Aged ≥75, % | 18.0 | 36.5 | 52.0 | 71.1 | <.001 |
| Occupation, % | | | | | |
| White-collar | 15.5 | 12.9 | 7.4 | 6.6 | .001[a] |
| Blue-collar | 15.2 | 15.5 | 22.5 | 24.8 | |
| Unemployed, homemakers, part-time workers | 69.3 | 71.6 | 70.1 | 68.6 | |
| Education <10 years, % | 36.5 | 44.8 | 54.5 | 61.7 | <.001 |
| Hypertension, % | 57.1 | 65.8 | 57.4 | 71.9 | .007 |
| Diabetes mellitus, % | 19.6 | 26.7 | 21.6 | 24.0 | .12 |
| History of stroke, % | 3.7 | 7.8 | 4.4 | 4.1 | .38 |
| Body mass index ≥25 kg/m$^2$, % | 25.6 | 30.7 | 24.5 | 25.6 | .90 |
| Physical inactivity, % | 44.7 | 48.3 | 49.0 | 50.4 | .11 |
| Ever or current smoker, % | 38.3 | 42.0 | 43.6 | 45.5 | .046 |
| Never drinker, % | 43.0 | 44.3 | 47.5 | 57.9 | .004 |
| Tooth brushing frequency ≤1 times per day, % | 31.9 | 35.9 | 37.7 | 48.8 | <.001 |
| Dental care less than once every 6 months, % | 79.3 | 77.0 | 83.8 | 93.4 | .001 |
| Denture use, % | 14.1 | 66.4 | 69.1 | 76.9 | <.001 |

[a]Tested using Pearson chi-square test.

**Table 2. Likelihood of Development of Dementia and Its Subtypes According to Number of Remaining Teeth**

| | ≥20, n = 893 | 10–19, n = 348 | 1–9, n = 204 | 0, n = 121 | *P* for Trend |
|---|---|---|---|---|---|
| Person-years at risk | 4,554 | 1,678 | 951 | 545 | |
| All-cause dementia, n | 66 | 50 | 35 | 29 | |
| Crude incidence rate[a] | 14.5 | 29.8 | 36.8 | 53.2 | |
| Crude HR (95% CI) | Reference | 2.09 (1.45–3.03) | 2.60 (1.73–3.92) | 3.83 (2.47–5.93) | <.001 |
| Adjusted HR (95% CI)[b] | Reference | 1.62 (1.06–2.46) | 1.81 (1.11–2.94) | 1.63 (0.95–2.80) | .04 |
| Alzheimer's disease, n | 46 | 33 | 25 | 23 | |
| Crude incidence rate[a] | 10.1 | 19.7 | 26.3 | 42.2 | |
| Crude HR (95% CI) | Reference | 1.97 (1.26–3.09) | 2.66 (1.63–4.32) | 4.34 (2.63–7.16) | <.001 |
| Adjusted HR (95% CI)[b] | Reference | 1.39 (0.83–2.32) | 1.73 (0.97–3.07) | 1.62 (0.87–3.04) | .08 |
| Vascular dementia, n | 13 | 16 | 8 | 5 | |
| Crude incidence rate[a] | 2.9 | 9.5 | 8.4 | 9.2 | |
| Crude HR (95% CI) | Reference | 3.40 (1.64–7.08) | 3.03 (1.26–7.31) | 3.38 (1.20–9.48) | .002 |
| Adjusted HR (95% CI)[b] | Reference | 3.19 (1.38–7.36) | 2.49 (0.87–7.13) | 1.94 (0.55–6.80) | .20 |

[a]Per 1,000 person-years.
[b]Adjusted for sex, age, occupation, education, hypertension, diabetes mellitus, history of stroke, alcohol intake, tooth brushing frequency, regular visits to the dentist, and denture use.
HR = hazard ratio; CI = confidence interval.

During the median follow-up of 5.3 years (range 0.1–5.4 years), 180 subjects (64 men, 116 women) developed dementia (127 AD, 42 VaD); nine with AD and eight with VaD had other coexisting subtypes of dementia, of which eight were a mixed type of AD and VaD. These cases were counted as events in the analysis for each subtype.

Table 2 shows the crude incidence rates and estimated HRs and 95% CIs of dementia and its subtypes according to number of remaining teeth. Having fewer remaining teeth was significantly associated with greater risk of development of all-cause dementia (*P* for trend < .001). This inverse association remained significant after adjustment for all covariates (sex, age, occupation, education, hypertension, diabetes mellitus, history of stroke, alcohol intake, tooth brushing frequency, regular visits to the dentist, and denture use; (*P* for trend = .04). The multivariable-adjusted hazard of all-cause dementia was higher in subjects with 10 to 19 teeth (HR = 1.62, 95% CI = 1.06–2.46), one to nine teeth (HR = 1.81, 95% CI = 1.11–2.94), and no teeth (HR = 1.63, 95% CI = 0.95–2.80) than in those with 20 teeth or more.

With regard to dementia subtypes, the crude incidence of AD increased significantly with fewer remaining teeth (*P* for trend < .001), but this tendency did not reach statistical significance in the multivariable-adjusted analysis (*P* for trend = .08). Although the multivariable-adjusted hazard of VaD was significantly higher in subjects with 10 to 19 teeth (HR = 3.19, 95% CI = 1.38–7.36) than in those with 20 teeth or more, a significant inverse association between number of remaining teeth and multivariable-adjusted hazard of VaD was not observed (*P* for trend = .20). In addition, no evidence was found of heterogeneity in the associations between number of remaining teeth and risk of dementia and its subtypes between sexes (all *P* for heterogeneity > .10).

## DISCUSSION

This prospective cohort study of an elderly Japanese population demonstrated an inverse association between number of remaining teeth and risk of development of all-cause dementia and AD, indicating that subjects with greater tooth loss were at greater risk of onset of dementia. Tooth loss was estimated using data from clinical oral examinations performed by dentists, and dementia subtypes were determined on the basis of brain morphological data (neuroimaging and neuropathology), unlike previous studies.[4–15] The present prospective cohort study investigated the association between tooth loss evaluated through a professional oral examination and risk of dementia and its subtypes in an elderly general population. These findings highlighted the clinical value of maintaining healthy dentition throughout life to reduce the risk of dementia in the general population.

Several prospective studies have examined the association between tooth loss and risk of all-cause dementia.[6–9,12] A prospective cohort study of elderly Japanese adults demonstrated that subjects with few remaining teeth without dentures had a significantly higher incidence of all-cause dementia than those with 20 teeth.[6] Similarly, in an elderly cohort with type 2 diabetes mellitus, tooth loss appeared to be significantly related to greater risk of incident all-cause dementia.[8] These findings are in agreement with those of the current study, although other cohort studies failed to reveal a significant association.[7,9,12] These discrepancies may have arisen from differences in evaluation of tooth loss (clinical oral examination vs self-report) and control for the confounding effects of oral health behavior (adjusted vs unadjusted).

With respect to subtypes of dementia, the present study revealed that tooth loss is associated with the development of AD, but not VaD. To the knowledge of the authors, no prospective study has demonstrated a significant association between tooth loss and risk of development of AD,[4,9,12] although these studies have some limitations, including small sample size and imprecise (self-reported) assessment of number of remaining teeth. Meanwhile, few studies have investigated the association between tooth loss and VaD. A cross-sectional study reported that multiple tooth loss was independently associated with vascular cognitive impairment in individuals with acute ischemic stroke,[15] whereas a prospective cohort study of Swedish women revealed that

tooth loss did not increase the risk of incident VaD.[12] Although the present study failed to reveal a significant association, the number of VaD events were limited. Thus, further large-scale studies are warranted to elucidate the association between number of teeth and development of each dementia subtype.

Several plausible pathways may account for the relationship between tooth loss and development of dementia in an elderly Japanese population. First, it has been suggested that masticatory stimulation with normal occlusion increases cerebral blood flow, activation of the cortical area, and blood oxygen levels.[37–39] Thus, poorer masticatory performance resulting from tooth loss might negatively affect brain function, which may result in development of dementia. Second, dietary changes resulting from tooth loss have been known to play a role in dementia risk. It was hypothesized that the decrease in masticatory performance due to tooth loss could lead to poor nutritional status, which might in turn affect dementia risk.[28,40] Third, the influence of chronic inflammation on development of dementia, especially in AD, is one possible pathway. Chronic systemic inflammation linked to periodontal disease, which is a major cause of tooth loss in adults, could contribute to the pathogenesis of AD.[41,42] Finally, there is a possibility that poor oral health is a marker of overall health status, including potential risk factors for dementia, because common oral conditions such as tooth loss reflect history of diseases, health behavior, and health care throughout the life course of an individual.[43]

The strengths of the present study are the population-based prospective design, the perfect follow-up of the subjects except for those who died, and the availability of morphological examination for accurate diagnosis of dementia subtypes, although some potential limitations of the study should be noted. One weakness is that information was not available regarding confounding factors during follow-up. Lack of this information may have reduced the accuracy of the findings to some extent. In addition, although some potential confounding variables were adjusted for in the multivariable-adjusted analyses, there may have been residual confounding at baseline because of unmeasured factors such as depression.

In conclusion, the present study demonstrated that tooth loss is a risk factor for development of all-cause dementia and AD in an elderly Japanese population. The findings emphasize the clinical importance of promoting and supporting opportunities for dental care and treatment, especially in terms of maintenance of teeth from an early age for reducing the risk of dementia in later life.

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**Author Contributions:** Takeuchi: study concept and design, statistical analysis, interpretation of data, writing manuscript as principal author. Ohara: study concept and design, data collection, endpoint adjudication, statistical analysis, interpretation of data, writing and critical review of the manuscript. Furuta: data collection, statistical analysis, interpretation of data, critical review of manuscript. Takeshita, Shibata, Yoshida: data collection, interpretation of data, critical review of manuscript. Hata: data collection, endpoint adjudication, statistical analysis, interpretation of data, critical review of manuscript. Yamashita: study concept and design, interpretation of data, writing and critical review of the manuscript. Ninomiya: study coordination, study concept and design, data collection, endpoint adjudication, statistical analysis interpretation of data, writing and critical review of manuscript. All authors read and approved the final version of the manuscript.

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