Oral Status and Dementia Onset: Mediation of Nutritional and Social Factors

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Abstract

Some modifiable risk factors for dementia are closely related to oral health. Although eating and speaking abilities are fundamental oral functions, limited studies have focused on the effect of malnutrition and lack of social interaction between oral health and dementia. We investigated the mediating effects of nutritional and social factors on the association between the number of teeth and the incidence of dementia. This 6-y cohort study used data from the Japan Gerontological Evaluation Study targeting older adults aged 65 y and above. The number of teeth (exposure) and covariates in 2010 (baseline survey), mediators (weight loss, vegetable and fruit intake, homeboundness, social network) in 2013, and the onset of dementia (outcome) between 2013 and 2016 were obtained. The Karlson–Holm–Breen mediation method was applied. A total of 35,744 participants were included (54.0% women). The mean age at baseline was 73.1 ± 5.5 y for men and 73.2 ± 5.5 y for women. A total of 1,776 participants (5.0%) had dementia during the follow-up period. There was a significant total effect of the number of teeth on the onset of dementia (hazard ratio, 1.14; 95% CI, 1.01–1.28). Controlling for nutritional and social mediators, the effect of the number of teeth was reduced to 1.10 (95% CI, 0.98–1.25), leaving an indirect effect of 1.03 (95% CI, 1.02–1.04). In the sex-stratified analysis, the proportion mediated by weight loss was 6.35% for men and 4.07% for women. The proportions mediated by vegetable and fruit intake and homeboundness were 4.44% and 4.83% for men and 8.45% and 0.93% for women, respectively. Furthermore, the proportion mediated by social networks was 13.79% for men and 4.00% for women. Tooth loss was associated with the onset of dementia. Nutritional and social factors partially mediated this association.

Keywords: dental public health, epidemiology, cohort studies, gerontology, psychosocial factors, nutrition/nutritional sciences

Introduction

Dementia is a serious public health concern in rapidly aging societies. It is a syndrome that causes a decline in memory, the ability to think, appropriate behavior, and the performance of daily life activities. Dementia is a leading cause of disability among older populations worldwide (World Health Organization [WHO] 2020). The current number of people living with dementia is estimated to be over 50 million. This number is projected to increase to 152 million by 2050 (Alzheimer's Disease International 2018). The cost of dementia in the United States was estimated to be $818 billion in 2015 and is projected to increase up to $2 trillion by 2030 (Wimo et al. 2017). Dementia exerts a significant burden on families and caregivers (WHO 2020). Hence, prevention of the onset of dementia and its progression in patients with dementia should be considered a global health priority.

Livingston et al. (2020) suggested 12 modifiable risk factors for dementia: hearing loss, lower education, smoking, depression, infrequent social contact, traumatic brain injury, hypertension, physical inactivity, air pollution, excessive alcohol consumption, obesity, and diabetes. Oral health has been reported to be associated with some of these modifiable factors, such as metabolic syndromes (Nibali et al. 2013), depression (Cademartori et al. 2018), physical activity (De Oliveira

Ferreira et al. 2019), and infrequent social contact (Igarashi et al. 2021). Consequently, oral health may affect the risk of dementia through these modifiable risk factors. However, most of the previous studies examining the association between oral health and dementia have mainly focused on biological

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A supplemental appendix to this article is available online.

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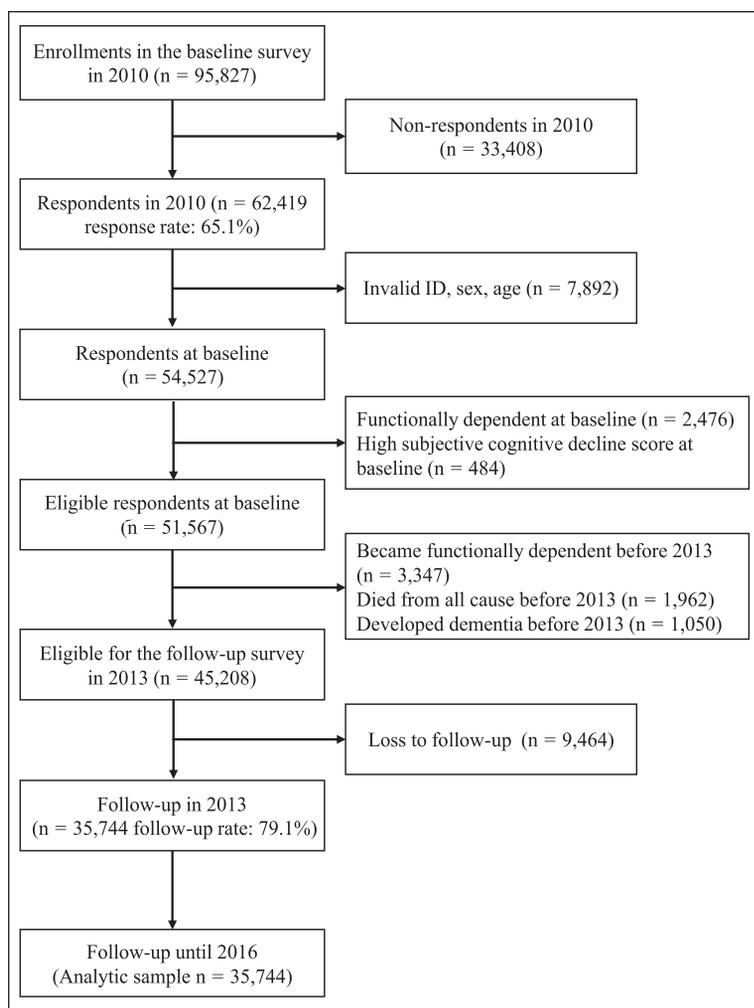Email: aida.ohp@tmd.ac.jp

Figure 1. The flowchart of the participants for the analysis.

mechanisms, such as periodontal inflammation and the central nervous system pathways, and there are critiques of the causality of these biological mechanisms on the association between oral health and dementia (Thomson and Barak 2021). As mentioned earlier, infrequent social contact, obesity, and diabetes are modifiable risk factors of dementia (Livingston et al. 2020), and speaking and eating abilities are fundamental oral functions related to these modifiable risks. However, few studies have examined the effects of a lack of social interaction and nutrition intake to explain the mechanisms between oral health and dementia.

Mediation analysis is a practical method to determine the contribution of oral health to dementia through modifiable risk factors. The mediation analysis method suggested by Karlson, Holms, and Breen (KHB) can be used to examine multiple pathways between the exposure and the outcome (Kohler et al. 2011). Using the KHB method, a previous study investigated the mediation effects of communication and eating difficulty on the association between tooth loss and future functional disability (Yin et al. 2020). Functional disabilities among older adults could be one of the consequences of dementia. Hence,

these factors may also mediate the association between tooth loss and dementia. However, the mediation effect of nutritional and social factors on the association between tooth loss and the incidence of dementia has not been studied. Thus, we aimed to investigate the mediating effect of nutritional and social factors on the association between tooth loss and the onset of dementia among older Japanese adults, considering the potentially modifiable risk factors. We hypothesized that tooth loss increases the risk of dementia onset, and nutritional and social factors mediate their relation.

Materials and Methods

Study Design and Population

In this prospective cohort study, we used data from the Japan Gerontological Evaluation Study (JAGES) from years 2010 (baseline), 2013, and 2016. The JAGES is an ongoing cohort study for functionally independent older adults aged 65 y or above (Kondo et al. 2018). In 2010, postal survey questionnaires were distributed across 13 municipalities. In 6 of these municipalities, all eligible individuals were sent questionnaires. In the remaining municipalities, questionnaires were randomly sent to eligible participants. We excluded the functionally dependent participants at baseline and the 2013 follow-up. Furthermore, participants who experienced the onset of dementia or became ineligible for the survey or died or were lost to follow-up before 2013 were also excluded, because we wanted to examine the effect of the mediators in 2013. In addition, participants who answered negatively to all 3 questions on "the Kihon Checklist–Cognitive Function," which indicated subjective cognitive decline, were excluded (Tomata et al. 2017). The participant selection process is shown in Figure 1.

Exposure Variable

The number of teeth at baseline was used as the exposure variable as an indicator of tooth loss. The response to the question "How many natural teeth do you have?" was used to assess the number of teeth in 4 categories ($\geq$20/10–19/1–9/0 teeth). We dichotomized this variable as $\geq$20 teeth (0) and <20 teeth (1), assuming that more than 20 teeth represent a minimum functional dentition based on WHO recommendations (WHO 2013).

Outcome

The onset of dementia from 2013 to 2016 was used as the outcome. We linked the JAGES data to the public long-term insurance system maintained by each municipality (Yamamoto et al. 2012; Tani et al. 2019). In-home assessments were performed by trained investigators dispatched by municipalities (Hisano

2009; Minister Health Labour Welfare [MHLW] 2018; Tani et al. 2019). Details of in-home assessment are provided in Appendix Description 1.

Mediators

The mediators were determined from the 2013 survey. We used weight loss and vegetable and fruit intake as the nutritional factors. The answers to "Have you lost more than 3 kg over the past 6 mo?" (yes/no) (Nakamura et al. 2016) and "How often did you eat fruits and vegetables over the past month?" (≥twice a day/once a day/4–6 times a week/2–3 times a week/once a week/<once a week/never) were used to assess weight loss and fruit/vegetable intake, respectively. We dichotomized the fruit and vegetable intake variables into "once a day or more" and "less than once a day" (Nakamura et al. 2016). We used homeboundness and social network as social factors. Reponses to "How often do you go out?" provided in 6 categories (almost every day/2 or 3 times a week/once a week/once or twice a month/several times a year/rarely) were used to derive a binary homeboundness variable (once a week or more/less than once a week) (Koyama et al. 2016). Furthermore, responses to "How many friends/acquaintances have you seen over the past month?" in 5 categories (none/1–2/3–5/6–9/10 or more) were used to measure the social network. In this analysis, the social network variable was dichotomized as "≥10" and "0–9" (Aida et al. 2016). Weight loss, vegetable and fruit intake, homeboundness, and social network measured in 2010 were used as covariates to represent the baseline mediators.

Covariates

Covariates were selected based on a systematic review (Wu et al. 2016). We selected sex (men/women), age (65–69/70–74/75–79/80–84/≥85), and marital status (no partner/having partner) as demographic characteristics; denture use (yes/no) as the oral health–related covariate; education level (<9 y/10–12 y/≥13 y) and annual equivalent household income (Japanese million yen; <1/1–1.99/2–2.99/3–3.99/≥4) as socioeconomic covariates; having treatments for diabetes (yes/no) and hypertension (yes/no) as health status–related covariates; and smoking status (current/past/never), drinking status (current/past/never), and walking time (<30 min/30–59 min/60–89 min/≥90 min) as lifestyle covariates.

Statistical Analysis

A mediation analysis was conducted to understand the effect of mediators using the KHB method (Kohler et al. 2011). A directed acyclic graph is shown in Figure 2. The KHB method allowed covariate-adjusted estimation of the mediated proportion with multiple mediators. It was implemented using the khb stata package (Kohler et al. 2011). A complementary log-log regression analysis with the discrete-time hazard model was used within the KHB method to estimate hazard ratios (HRs)
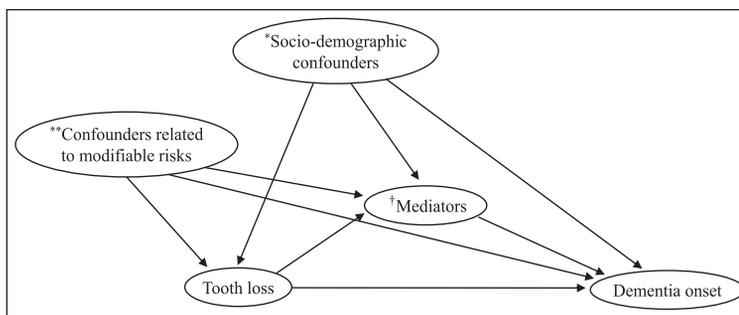

Figure 2. Directed acyclic graph for the mediation analysis. *Sociodemographic confounders (2010): sex, age, marital status, denture use, and income. **Confounders related to modifiable risks (2010): education level, hypertension, diabetes, drinking history, and smoking history. †Mediators (2013): weight loss, vegetable and fruit intake, homeboundness, and social network.

and 95% confidence intervals (CIs), as the KHB method cannot be used with the continuous-time survival model (Seblova et al. 2018). The complementary log-log regression model was suitable for rare outcomes (cumulative incidence of dementia was 5.0%). The discrete model was fitted for the annual records of the onset of dementia or other causes of censoring: death, loss to follow-up, or the end of follow-up. We calculated total, direct, and indirect effects for all mediators simultaneously, allowing calculation of the mediated proportion for each mediator (proportion mediated = indirect effect / total effects * 100). In addition to the analysis including both sexes, a sex-stratified analyses was conducted because sex differences have been reported in the onset of dementia (Li and Singh 2014), and the function of mediators might differ between them.

Model 1 included mediators (weight loss, vegetable and fruit intake, homeboundness, and social network) from 2013, with baseline sex, age, and baseline mediators as covariates. Model 2 was additionally adjusted for baseline marital status, denture use, educational level, household income, presence of diabetes and hypertension, smoking status, drinking status, and walking time.

We conducted several sensitivity analyses to 1) assess the robustness of mediators, 2) validate our imputation procedure, and 3) compare our results with causal mediation analysis (Discacciati et al. 2019). Further details of sensitivity analyses are provided in Appendix Description 2.

Missing information related to mediators and covariates was iteratively imputed using random forest multivariate imputation (Stekhoven and Bühlmann 2012). Imputation was implemented using the *missforest* python package. All other analyses were conducted using Stata MP 16.0 (Stata Corporation LP). The significance level was set at *P* < 0.05. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Ethical Approval

The Ethics Committee of the National Center for Geriatrics and Gerontology (approval number: 992), Chiba University (approval number: 2493), and Tohoku University Graduate

School of Medicine (21–40) provided ethical approval for the JAGES.

Results

A total of 35,744 participants were included in the analysis. Table 1 shows the descriptive characteristics (54.0% women). The mean age at baseline was 73.1 ± 5.5 y for men and 73.2 ± 5.5 y for women. At baseline, 13,580 participants (38.0%) had ≥20 teeth, and 1,776 participants (5.0%) had dementia onset between 2013 and 2016 (54.9% women). The mean time of dementia onset was 2,074 d (range = 1,096–2,328 d). Additional descriptive characteristics are presented in Appendix Tables 1 to 4.

Table 2 shows the results of the mediation analysis decomposed to total, direct, and indirect effects of the number of teeth on the onset of dementia using the KHB method. After adjusting for covariates, there was a significant total effect of the number of teeth on the onset of dementia (HR, 1.14; 95% CI, 1.01–1.28). Controlling for nutritional and social mediators, the effect of the number of teeth was reduced to 1.10 (95% CI, 0.98–1.25), leaving an indirect effect of 1.03 (95% CI, 1.02–1.04).

Table 3 presents the results of the proportion mediated between the number of teeth and the onset of dementia. In the sex-stratified analysis, the mediators we used explained the association between the number of teeth and the onset of dementia by 29.41% for men and 17.45% for women after adjusting for covariates. The mediated proportion of weight loss was 6.35% for men and 4.07% for women, while it was 4.44% in men and 8.45% in women for vegetable and fruit intake. Homeboundness and social network mediated proportions were 4.83% for men and 0.93% for women and 13.79% for men and 4.00% for women, respectively. Appendix Table 5 shows the variable specific results of the analysis with fully adjusted. Weight loss, low consumption of vegetable and fruit intake, homeboundness, and low social network were associated with the onset of dementia. Diabetes was associated with the onset of dementia; on the other hand, the direction of the association of hypertension was opposite.

Results of our sensitivity analyses were consistent with the trend of our main results (Appendix Tables 6–14). However, in the complete case analysis (Appendix Tables 10 and 11), the proportion of social network was largest among women.

Discussion

To the best of our knowledge, this is the first study to evaluate the mediation effects of multiple factors on oral health and dementia. Tooth loss was associated with the onset of dementia. In addition, there were significant mediating effects between tooth loss and the onset of dementia; multiple mediators explained one-third to one-fifth of the relationship. The direct effect was not significant after adjusting for the mediators and covariates. Therefore, most of the pathways may be explained by the mediators we used in this study. For men,

social factors, such as social network and homeboundness, were the main mediators. For women, nutritional factors, such as vegetable and fruit intake and weight loss, were the major mediators. These results suggest the importance of oral health in dementia, particularly social factors in men and nutritional factors in women.

Our finding of the mediating effects of social factors is consistent with previous evidence. Social isolation and physical inactivity are modifiable risk factors for the onset of dementia (Livingston et al. 2020). Oral functions, such as speaking, smiling, and eating, considerably affect social interactions. Hence, an association between tooth loss and fewer social interactions has been observed (Igarashi et al. 2021). Furthermore, having fewer teeth predicted homeboundness (Koyama et al. 2016). Homeboundness can increase the risk of social isolation and physical inactivity (Nicholson 2012). Therefore, a decrease in social interaction due to poor oral health could be associated with the onset of dementia. Social factors played a more important role among men than among women in this study. The prevalence of social isolation could explain this result as older men in Japan tend to be more isolated after retirement and have lower social participation compared to women (Ejiri et al. 2019).

The mediation effects of vegetable and fruit intake can also be explained by several studies. A systematic review reported that tooth loss was associated with nutritional status (Toniazzo et al. 2018). Studies have suggested that vegetables and fruits have protective effects against the onset of dementia through the action of vitamin E, carotenoids, and polyphenols (Hughes et al. 2010). Consumption of potassium-rich vegetables can help lower blood pressure (McDonough et al. 2017). However, in relation to hypertension, our analysis showed a negative association with dementia. As our variable on hypertension asked about its treatment history, participants with the hypertension treatment possibly had good blood pressure control. The actual blood pressure measurements should be used in a future study because hypertension is an established risk factor for dementia (Livingston et al. 2020). Accordingly, it is reasonable to argue that vegetable intake could mediate the association between tooth loss and dementia. Moreover, the decline in food intake due to poor oral status can also cause weight loss (Nakamura et al. 2016), which also showed a significant mediation effect in our study.

Our findings are consistent with the study that reported the protective roles of vegetables on the onset of dementia, especially in women (Hughes et al. 2010). Regarding sex differences, Hughes et al. (2010) suggested the role of antioxidant metabolism in Alzheimer disease, the difference in pathophysiology between men and women, and the difference in the amount of vegetable consumption between both sexes (Hughes et al. 2010).

Our findings also highlight the importance of social aspects in oral health. Previous studies, including systematic reviews on the relationship between tooth loss and dementia, showed inconsistent findings (Yamamoto et al. 2012; Cerutti-Kopplin et al. 2016; Wu et al. 2016). Thomson and Barak 2021

Table 1. Demographic Characteristics Divided by the Onset of Dementia in 2013 to 2016 after Multivariate Imputation ($n = 35,744$).

Characteristic		Onset of Dementia: Men				Onset of Dementia: Women			
		Total ($n = 16,451$), n (%[a])	No ($n = 15,650$), %[b]	Yes ($n = 801$), %[b]	P Value[c]	Total ($n = 19,293$), n (%[a])	No ($n = 18,318$), %[b]	Yes ($n = 975$), %[b]	P Value[c]
Exposure variable (2010)									
Number of teeth	≥20	6,375 (38.8)	96.7	3.3	<0.001	7,205 (37.3)	96.8	3.2	<0.001
	0–19	10,076 (61.2)	94.1	5.9		12,088 (62.7)	93.9	6.1	
Mediator variable (2013)									
Weight loss	No	13,973 (84.9)	95.6	4.4	<0.001	16,591 (86.0)	95.5	4.5	<0.001
	Yes	2,478 (15.1)	92.4	7.6		2,702 (14.0)	91.4	8.6	
Vegetable and fruit intake (≥once a day)	No	4,032 (24.5)	94.5	5.5	0.025	2,775 (14.4)	92.5	7.5	<0.001
	Yes	12,419 (75.5)	95.3	4.7		16,518 (85.6)	95.4	4.6	
Homeboundness (≤once a week)	No	15,854 (96.4)	95.5	4.5	<0.001	18,566 (96.2)	95.3	4.7	<0.001
	Yes	597 (3.6)	85.3	14.7		727 (3.8)	86.2	13.8	
Social network (≥10)	No	10,703 (65.1)	94.0	6.0	<0.001	11,353 (58.8)	93.8	6.2	<0.001
	Yes	5,748 (34.9)	97.3	2.7		7,940 (41.2)	96.6	3.4	
Covariates (2010)									
Age	65–69	5,162 (31.4)	98.4	1.6	<0.001	5,882 (30.5)	99.0	1.0	<0.001
	70–74	5,295 (32.2)	96.8	3.2		6,318 (32.7)	97.4	2.6	
	75–79	3,611 (22.0)	94.1	5.9		4,342 (22.5)	93.4	6.6	
	80–84	1,818 (11.1)	87.5	12.5		2,028 (10.5)	85.6	14.4	
	≥85	565 (3.4)	80.4	19.6		723 (3.7)	75.7	24.3	
Marital status	No partner	1,926 (11.7)	93.5	6.5	<0.001	7,286 (37.8)	92.4	7.6	<0.001
	Having partner	14,525 (88.3)	95.4	4.6		12,007 (62.2)	96.5	3.5	
Denture use	No	7,853 (47.7)	95.6	4.4	0.005	9,704 (50.3)	95.6	4.4	<0.001
	Yes	8,598 (52.3)	94.7	5.3		9,589 (49.7)	94.3	5.7	
Educational level (y)	<9	7,048 (42.8)	93.7	6.3	<0.001	9,809 (50.8)	94.1	5.9	<0.001
	10–12	5,496 (33.4)	96.3	3.7		6,980 (36.2)	95.6	4.4	
	≥13	3,907 (23.7)	96.1	3.9		2,504 (13.0)	96.5	3.5	
Annual equivalent household income (1 million yen)	<1	1,528 (9.3)	92.0	8.0	<0.001	3,036 (15.7)	94.1	5.9	0.072
	1–1.99	6,036 (36.7)	94.9	5.1		6,972 (36.1)	94.8	5.2	
	2–2.99	4,345 (26.4)	95.6	4.4		4,883 (25.3)	95.1	4.9	
	3–3.99	2,656 (16.1)	95.8	4.2		2,544 (13.2)	95.8	4.2	
	≥4	1,886 (11.5)	96.5	3.5		1,858 (9.6)	95.2	4.8	
Hypertension	No	8,941 (54.3)	94.7	5.3	0.005	10,072 (52.2)	95.0	5.0	0.645
	Yes	7,510 (45.7)	95.6	4.4		9,221 (47.8)	94.9	5.1	
Diabetes mellitus	No	14,024 (85.2)	95.4	4.6	0.001	17,393 (90.2)	95.1	4.9	0.021
	Yes	2,427 (14.8)	93.8	6.2		1,900 (9.8)	93.8	6.2	
Drinking history	Current	9,715 (59.1)	95.9	4.1	<0.001	2,853 (14.8)	97.4	2.6	<0.001
	Past	861 (5.2)	92.5	7.5		178 (0.9)	93.3	6.7	
	Never	5,875 (35.7)	94.2	5.8		16,262 (84.3)	94.5	5.5	
Smoking history	Current	2,922 (17.8)	94.6	5.4	0.111	502 (2.6)	93.6	6.4	0.316
	Past	8,917 (54.2)	95.0	5.0		855 (4.4)	94.5	5.5	
	Never	4,612 (28.0)	95.6	4.4		17,936 (93.0)	95.0	5.0	
Walking time	<30 min	4,754 (28.9)	93.5	6.5	<0.001	6,286 (32.6)	93.6	6.4	<0.001
	30–59 min	5,997 (36.5)	95.2	4.8		7,171 (37.2)	95.1	4.9	
	60–89 min	2,764 (16.8)	95.9	4.1		2,820 (14.6)	95.9	4.1	
	≥90 min	2,936 (17.8)	96.9	3.1		3,016 (15.6)	96.5	3.5	
	Total	16,451 (100.0)	95.1	4.9		19,293 (100.0)	94.9	5.1	

[a]Column percentage.
[b]Row percentage.
[c]Pearson's χ^2 test.

critically look at the causal relationship between teeth and dementia; they based their critique on the concept that tooth loss was the result of cognitive decline in childhood. Although their critiques focused on biological mechanisms between oral health and dementia, they did not mention social functions of oral health and their consequences, such as social isolation, which is an established risk factor for dementia (Livingston et al. 2020). Speaking and smiling are basic social functions of

Table 2. Direct and Indirect Effect of the Number of Teeth on the Onset of Dementia Using the Karlson–Holm–Breen (KHB) Methods (*n* = 35,744).

Characteristic	Model 1				Model 2			
	β	HR	95% CI	*P* Value	β	HR	95% CI	*P* Value
Total[a] (*n* = 35,744)								
Total effect	0.19	1.20	(1.08–1.35)	0.001	0.13	1.14	(1.01–1.28)	0.041
Direct effect	0.15	1.16	(1.04–1.30)	0.008	0.10	1.10	(0.98–1.25)	0.113
Indirect effect	0.04	1.04	(1.03–1.04)	<0.001	0.03	1.03	(1.02–1.04)	<0.001
Men (*n* = 16,451)								
Total effect	0.23	1.25	(1.07–1.47)	0.006	0.12	1.13	(0.95–1.35)	0.176
Direct effect	0.18	1.19	(1.01–1.40)	0.033	0.09	1.09	(0.91–1.30)	0.340
Indirect effect	0.05	1.05	(1.04–1.06)	<0.001	0.04	1.04	(1.03–1.05)	<0.001
Women (*n* = 19,293)								
Total effect	0.15	1.16	(1.00–1.35)	0.048	0.14	1.15	(0.97–1.36)	0.102
Direct effect	0.12	1.13	(0.97–1.32)	0.111	0.12	1.12	(0.95–1.33)	0.177
Indirect effect	0.03	1.03	(1.02–1.04)	<0.001	0.02	1.02	(1.02–1.03)	<0.001

Model 1: The number of teeth as exposure, weight loss, vegetable and fruit intake, homeboundness, social network as mediators, age and baseline mediators as covariates included in the models. Model 2: model 1 + marital status, denture use, income, education level, hypertension, diabetes mellitus, drinking history, smoking history, and walking time included in the models as covariates.
β, β-coefficient; CI, confidence interval; HR, hazard ratio.
[a]Sex was adjusted in all models.

Table 3. Proportion Mediated between the Number of Teeth and the Onset of Dementia by Using Karlson–Holm–Breen (KHB) Methods (*n* = 35,744).

Mediator Category	Mediator	Proportion Mediated, %	
		Model 1	Model 2
Total[a] (*n* = 35,744)			
Nutritional mediators	Weight loss	5.13	5.48
	Vegetable and fruit intake	5.88	6.95
Social mediators	Homeboundness	2.35	2.35
	Social network	6.31	7.65
Total		19.67	22.43
Men (*n* = 16,451)			
Nutritional mediators	Weight loss	4.67	6.35
	Vegetable and fruit intake	3.70	4.44
Social mediators	Homeboundness	3.90	4.83
	Social network	9.55	13.79
Total		21.82	29.41
Women (*n* = 19,293)			
Nutritional mediators	Weight loss	5.42	4.07
	Vegetable and fruit intake	8.38	8.45
Social mediators	Homeboundness	1.22	0.93
	Social network	4.11	4.00
Total		19.13	17.45

Model 1: The number of teeth as exposure, weight loss, vegetable and fruit intake, homeboundness, social network as mediators, age and baseline mediators as covariates included in the models. Model 2: model 1 + marital status, denture use, income, education level, hypertension, diabetes mellitus, drinking history, smoking history, and walking time included in the models as covariates.
[a]Sex was adjusted in all models.

oral health. Therefore, deterioration of oral health can increase the risk of less social interaction and loneliness (Rouxel et al. 2017; Igarashi et al. 2021). Our study examined these points and showed a higher proportion of social factors related to oral health and dementia. Further studies are needed to confirm the causal effects of the social aspects of oral health on dementia.

This study has useful implications for public health. Social isolation is a risk factor for dementia (Livingston et al. 2020), and prevention of social isolation is important in the political agenda for aging societies (Donovan and Blazer 2020). Policies

supporting oral health care, such as subsidies to preventive care (Aida et al. 2021), can help maintain social relationships with family and friends through the positive effects of better oral health on social life and eventually contribute to a reduced risk of dementia. In addition, adequate vegetable and fruit intake, besides maintaining good oral health, could reduce the risk of dementia.

This study had several strengths. First, we used data from 3 time points in a relatively large cohort. Our results reflected the longitudinal effects of tooth loss on dementia onset compared

with a cross-sectional study or mediation analysis with baseline mediators. For this purpose, we considered a discrete model that includes the time trend. Second, we considered multiple nutritional and social mediators using the KHB method. Therefore, the mediated proportions were estimated by considering multiple mediators in the same model.

This study had some limitations. First, we used a self-reported questionnaire for the number of teeth as the exposure variable, mediators, and all covariates but not clinical examinations. However, the validity of the self-reported number of teeth has been reported (Sekundo et al. 2019). The self-reported questionnaire is considered to cause nondifferential misclassification; thus, the observed associations were considered robust. Second, the 4 mediators we used had only 3 y of follow-up, which did not necessarily indicate a causal effect. Weight loss, vegetable and fruit intake, homeboundness, and social network are likely to have been ingrained from a younger age, and we cannot deny the possibility of reverse causality. To reduce the possibility of this reverse causation, we excluded participants with dementia at 3 y from the baseline. Third, the KHB method was not based on a counterfactual framework, as suggested by VanderWeele (2016). Therefore, as a sensitivity analysis, we applied mediation analysis with the counterfactual framework, and the results were consistent with the main analysis. However, there may be unmeasured interactions between the variables. Fourth, because our target was the older population, the follow-up rate of the cohort was relatively low. Those who were lost to the follow-up had higher morbidity, including dementia (Appendix Table 4). The follow-up of healthier participants may underestimate the association between tooth loss and dementia. Fifth, we dichotomized the mediators. If there was misclassification, it might lead to biased results for direct and indirect effects (Richiardi et al. 2013). Sixth, we could not determine the reason for the tooth loss. There was a possibility that cognitive decline occurring before the baseline caused tooth loss. However, the results of the previous studies related to the association between cognitive decline and tooth loss were not consistent (Wu et al. 2016). To reduce the effect of this bias, we excluded participants who had high subjective cognitive decline.

Conclusion

Nutritional and social factors partially mediated the association between tooth loss and the onset of dementia.

Author Contributions

S. Kiuchi, J. Aida, contributed to conception, design, data acquisition, analysis, and interpretation, drafted the manuscript; U. Cooray, T. Kusama, contributed to design, data analysis, and interpretation, critically revised the manuscript; T. Yamamoto, H. Abbas, N. Nakazawa, contributed to data interpretation, critically revised the manuscript; K. Kondo, K. Osaka, contributed to data acquisition and 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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