Received: 30 March 2023 | Revised: 18 January 2024 | Accepted: 19 January 2024

DOI: 10.1111/jcpe.13959

ORIGINAL ARTICLE

Journal of Clinical Periodontology WILEY

Tooth loss mediates the association between smoking and an increased risk of dementia among older adults: The JAGES prospective cohort study

Taro Kusama[1,2] | Kenji Takeuchi[1,2,3] | Sakura Kiuchi[2,4] | Yudai Tamada[2,3] | Takahiro Tabuchi[5] | Ken Osaka[2]

[1]Division of Statistics and Data Science, Liaison Center for Innovative Dentistry, Tohoku University Graduate School of Dentistry, Sendai, Japan

[2]Department of International and Community Oral Health, Tohoku University Graduate School of Dentistry, Sendai, Japan

[3]Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

[4]Frontier Research Institute for Interdisciplinary Sciences, Tohoku University, Sendai, Japan

[5]Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan

Correspondence
Kenji Takeuchi, Department of International and Community Oral Health, Tohoku University Graduate School of Dentistry, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan.
Email: kenji.takeuchi.c4@tohoku.ac.jp

Funding information
Japan Society for the Promotion of Science (JSPS) KAKENHI, Grant/Award Numbers: 22H03299, 21H03153, 22K17265, 21K19635, 20H00557, 19K20909, 19K24060, 19K19455, 19K19818, 19K11657, 19K10641, 19K04785, 19H03860, 19H03915, 19H03901; Ministry of Health, Labour and Welfare, Grant/Award Numbers: 23FA1022, 22FA1010, 22FA2001, 21FA1012, 19FA2001, 19FA1012; Japan Agency for Medical Research and Development (AMED), Grant/Award Numbers: JP22lk0310087, JP21dk0110037, JP21lk0310073, JP20dk0110034; Japan Science and Technology Agency, Grant/Award Number: JPMJOP1831; Innovative Research Program on Suicide Countermeasures; Sasakawa Sports Foundation; Japan Health Promotion & Fitness Foundation; Chiba Foundation for Health Promotion & Disease Prevention; the 8020 Promotion Foundation, Grant/Award Number: 19-2-06; Niimi University, Grant/Award Number: 1915010; Meiji Yasuda Life Foundation of Health and Welfare and the Research Funding for Longevity Sciences from the National Center for Geriatrics and Gerontology, Grant/Award Numbers: 21-20, 20-19

Abstract

Aim: Tooth loss has various causes; however, its cause-specific effects on health outcomes remain unclear. This study evaluated whether the association between past/current smoking and risk of dementia was mediated by tooth loss.

Materials and Methods: This 9-year-follow-up prospective cohort study targeted adults aged ≥65 years. Dementia incidence during 2013–2019, smoking status (never, past/current) in 2010 and the number of remaining teeth (≤19, ≥20) in 2013 were the outcome, exposure and mediator, respectively. We used causal mediation analysis to fit the Cox proportional hazards model and estimated the hazard ratio (HR) and 95% confidence interval (CI) of the natural indirect effect (NIE) of smoking on dementia incidence through tooth loss and their mediated proportions.

Results: Among 32,986 participants (mean age 72.6 years [1 SD = 5.4]; men 48.4%), the dementia incidence during follow-up was 2.11/100 person-years. Tooth loss significantly mediated the association between past/current smoking and dementia incidence; the NIE of fewer remaining teeth for past/current smokers compared to never smokers was HR = 1.03 (95% CI: 1.02–1.05), and the mediated proportion was 18.0%.

Conclusions: Tooth loss significantly mediates the association between past/current smoking and an increased risk of dementia among older adults.

KEYWORDS
Alzheimer's disease, memory disorders, oral health, periodontal diseases, tobacco use

Clinical relevance

Scientific rationale for study: Tooth loss is reportedly related to an increased risk of dementia. However, there are various ways to prevent tooth loss, including smoking cessation, but the effectiveness of specific interventions at reducing the risk of dementia remains unknown.

Principal findings: Our results suggest that tooth loss mediates the association between smoking and an increased risk of dementia among older adults.

Practical implications: Tobacco cessation is an effective clinical option for preventing tooth loss and subsequent dementia. Additionally, continuous oral care to prevent tooth loss in past smokers is important in preventing subsequent health problems.

1 | INTRODUCTION

As a result of ageing, globally, dementia has become one of the most prevalent and critical health issues among older adults (Livingston et al., 2020). Although the prevalence of dementia increases with age, a substantial proportion of dementia cases can be prevented or delayed by eliminating its risk factors (Livingston et al., 2020). Several studies have suggested that poor oral health, including periodontal diseases and tooth loss, is associated with an increased risk of dementia among older adults (Asher et al., 2022; Kiuchi et al., 2021; Lee et al., 2020; Takeuchi et al., 2017). Tooth loss is a highly prevalent health condition among the older adults (Kassebaum et al., 2014); therefore, it is possible that maintaining a satisfactory oral health throughout one's life can prevent dementia.

For appropriate causal inference, consistency of exposure is one of the requirements, and multiple versions of exposure are situations that violate consistency (Hernán, 2016; VanderWeele & Hernán, 2013). Alternatively, if there are multiple ways to be exposed, making causal inferences of the effect of exposure on the outcome becomes complicated. Regarding the association between tooth loss and the incidence of dementia, tooth loss is a consequence and not directly manipulated. Tooth loss is caused by several factors, including high sugar consumption, low fluoride application and tobacco smoking. These are major risk factors for dental caries or periodontal diseases, which subsequently lead to tooth loss (Kusama et al., 2022; Leite et al., 2018; Souto et al., 2019; Walsh et al., 2019). The influence of tooth loss on dementia risk may differ according to the cause of tooth loss. One possible approach to assess whether tooth loss mediates the effects of a specific risk factor on dementia is causal mediation analysis (CMA), which can estimate the effect of the mediator induced by exposure on the outcome based on the potential outcome framework (VanderWeele, 2015). Therefore, if tooth loss is treated as a mediator, its effect associated with a specific risk factor can be estimated.

In this study, we evaluated the association between smoking-associated tooth loss and the risk of dementia. Smoking is a major modifiable risk factor of tooth loss (Souto et al., 2019). Additionally, a previous review reported that smoking history is a major modifiable risk factor for dementia (Livingston et al., 2020). Therefore, we hypothesized that smoking would lead to tooth loss and thus increase an individual's risk of dementia. This study aimed to evaluate the association between smoking-associated tooth loss and the risk of dementia, using CMA.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This 9-year-follow-up cohort study was based on self-reported questionnaires and administrative databases. We used data from the Japan Gerontological Evaluation Study (JAGES), a large cohort study targeting adults aged ≥65 years in Japan (Kondo, 2016). The baseline survey was conducted in 2010 and included participants who had not received long-term care insurance (LTCI), while the follow-up questionnaire survey was conducted in 2013. We followed up the dementia incidence of the participants until 2019 based on the administrative databases. We initially excluded those whose ID/sex/age information was missing or invalid and those who had already received long-term care from follow-up participation. The surveys were conducted in 16 municipalities. In the baseline survey, questionnaires were mailed to the participants, after which they were retrieved if they consented to participate. We excluded those whose activities of daily living were not independent at baseline, and those who had already been diagnosed with dementia in 2013. We also excluded those whose information on smoking history in 2010 and number of remaining teeth in 2013 was missing.

2.2 | Outcome variable

We used the incidence of dementia during the 6-year follow-up period from 2013 as the outcome variable. Data on the incidence of dementia were obtained from the LTCI government database. Trained investigators performed in-home assessments of cognitive function using the LTCI scheme (Tamiya et al., 2011). In this assessment, cognitive disability grade was used to categorize the cognitive function of the applicants into eight levels. This grading is strongly correlated with Mini-Mental State Examination scores (Tago et al., 2022). A grade of level II or higher was defined as the onset of dementia (Noda et al., 2018).

2.3 | Exposure variable and mediator

A history of smoking in 2010 was used as the exposure variable. We asked the participants, 'Do you smoke?' and they answered one of the following: 'Yes', 'Quit (within the last 4 years)', 'Quit (5 or more years

ago)' and 'Never'. Based on their responses, we defined the participants as 'current smokers', 'past smokers' and 'never smokers', respectively.

We also used the number of remaining teeth in 2013 as a mediator. We asked the participants, 'How many natural teeth do you presently have?' and they answered as follows: '0', '1–4', '5–9', '10–19' or '20 or more'. We recategorized each answer into '≤19' and '≥20' based on the clinical importance (Watanabe et al., 2020). A previous study had evaluated the validity of the self-reported number of remaining teeth and reported sufficient accuracy in reflecting the clinically measured number of remaining teeth (Sekundo et al., 2019). For the sensitivity analysis, we also conducted a CMA using the number of remaining teeth, which was converted to class values as a continuous tooth count.

2.4 | Covariates

We included possible confounders as covariates in 2010 based on previous studies and clinical knowledge (Asher et al., 2022; Dietrich et al., 2015; Kiuchi et al., 2021; Lee et al., 2020; Takeuchi et al., 2017; Zhong et al., 2015). These included sex, age, equivalent income, education level, marital status, alcohol consumption, daily walking time, comorbidities (hypertension and diabetes) and obesity.

2.5 | Statistical analysis

Figure 1 shows the hypothesized causal diagram investigated in this study. We conducted a CMA to evaluate the association between smoking-associated tooth loss and the risk of dementia. In CMA, the effect of exposure on the outcome through the mediator is called the natural indirect effect (NIE), which is defined based on potential outcome frameworks as follows: 'How much the outcome would change on average if the exposure were fixed at level $a = 1$ but the mediator were changed from the level it would take if $a = 0$ to the level it would take if $a = 1$' (VanderWeele, 2015). When the NIE is non-zero, we can presume that exposure changes the mediator, and the mediator changes the outcome, which means that mediation exists.

In this study, we attempted to estimate the effect of smoking-associated tooth loss, particularly on the risk of dementia, using a CMA. In the regression model, we fitted the Cox proportional hazard model to the outcome regression model and the logistic regression model to the mediator regression model and calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for NIE, natural direct effect (NDE) and total effect. NDE is the effect of exposure on the outcome, not through the mediator, while the sum of the NIE and NDE is equal to the total effect. Additionally, we calculated the proportion mediated (PM), that is, the extent to which the NIE explained the proportion of the total effect. For the model employing the continuous tooth count as a mediator, we fitted the linear regression model to the mediator regression model. We used the Stata command *med4way* to obtain each estimate (Discacciati et al., 2018). Based on the cause-specific hazard model, we treated competing risks due to death as censored in the survival time analysis (Lau et al., 2009).

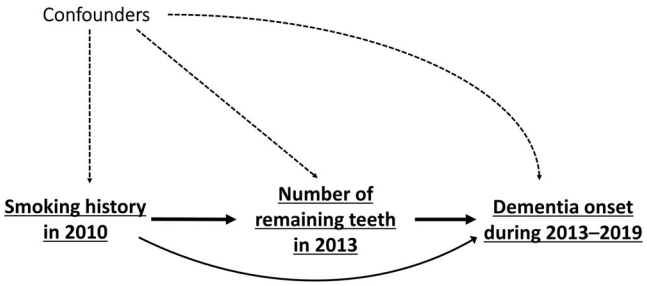

FIGURE 1 Directed acyclic graph for the causal diagram of the present study. Based on potential outcome frameworks, we hypothesized that smoking history leads to tooth loss and subsequently affects the risk of dementia in an individual. Potential confounders of the relationship between exposure, outcome and mediators were also considered.

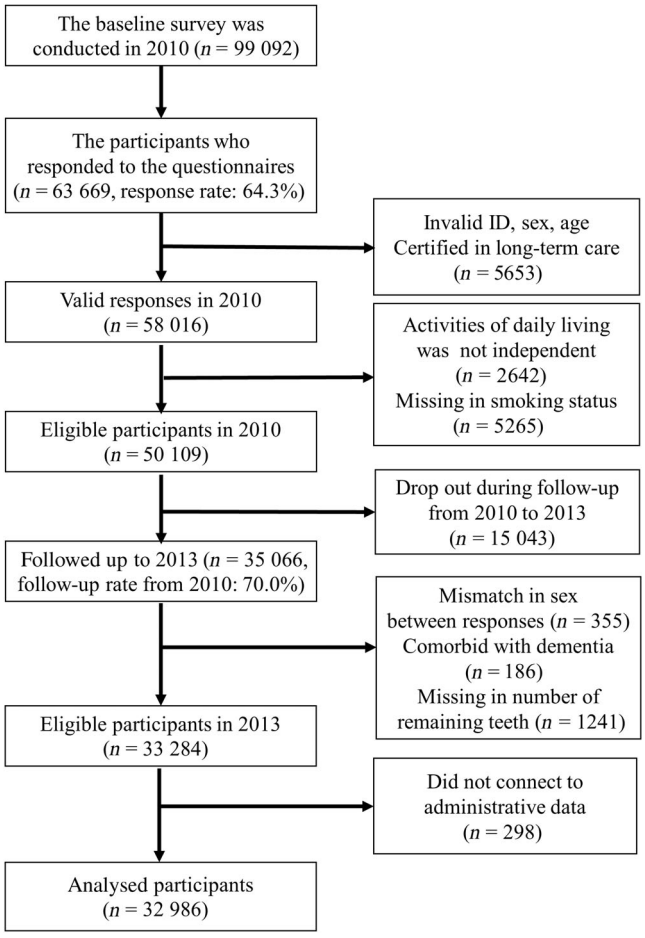

FIGURE 2 Flowchart of the participants' inclusion.

To reduce selection bias, we created 10 imputed datasets using multivariate imputation by chained equations, including all variables used in the analysis, and combined each estimate from the imputed datasets based on Rubin's rule. To identify the strength of the unmeasured covariates affecting the estimates, we calculated the mediational E-values of NIE and NDE. The mediational E-values of the NIE

TABLE 1 Characteristics of the participants at baseline.

Characteristics in 2010	All participants		Number of remaining teeth in 2013			
			≥20		≤19	
	n	%	*n*	%	*n*	%
Total	32,986	100.0	16,514	100.0	16,472	100.0
Smoking status						
Never	19,683	59.7	10,451	63.3	9232	56.0
Past	9803	29.7	4769	28.9	5034	30.6
Current	3500	10.6	1294	7.8	2206	13.4
Sex						
Male	15,960	48.4	7814	47.3	8146	49.4
Female	17,026	51.6	8700	52.7	8326	50.6
Age (years)						
65–69	11,505	34.9	7016	42.5	4489	27.2
70–74	10,679	32.4	5554	33.6	5125	31.1
75–79	6706	20.3	2807	17.0	3899	23.7
80–84	3117	9.4	943	5.7	2174	13.2
≥85	979	3.0	194	1.2	785	4.8
Equivalent income (JPY)						
<2.00 million	13,242	40.1	6053	36.6	7189	43.6
2.00–3.99 million	12,095	36.7	6715	40.7	5380	32.7
≥4.00 million	3377	10.2	1961	11.9	1416	8.6
Missing	4272	13.0	1785	10.8	2487	15.1
Education (years)						
≤9	13,660	41.4	5852	35.5	7808	47.4
10–12	12,432	37.7	6689	40.5	5743	34.9
≥13	6408	19.4	3755	22.7	2653	16.1
Missing	486	1.5	218	1.3	268	1.6
Marital status						
With a spouse	24,644	74.7	13,017	78.8	11,627	70.6
Without a spouse	7897	23.9	3336	20.2	4561	27.7
Missing	445	1.4	161	1.0	284	1.7
Alcohol consumption						
Never	18,529	56.2	8907	53.9	9622	58.4
Past	1027	3.1	454	2.8	573	3.5
Current	13,118	39.8	7025	42.5	6093	37.0
Missing	312	0.9	128	0.8	184	1.1
Walking time (min/day)						
≥60	10,651	32.3	5613	34.0	5038	30.6
30–59	11,528	35.0	6017	36.4	5511	33.5
<30	9344	28.3	4199	25.4	5145	31.2
Missing	1463	4.4	685	4.2	778	4.7
Comorbidity						
Hypertension	13,138	39.8	6373	38.6	6765	41.1
Diabetes	4086	12.4	1831	11.1	2255	13.7
Missing	8126	24.6	4293	26.0	3833	23.3

TABLE 1 (Continued)

Characteristics in 2010	All participants		Number of remaining teeth in 2013			
			≥20		≤19	
	n	%	*n*	%	*n*	%
Obesity (body mass index: kg/m^2)						
<30	31,575	95.7	15,966	96.7	15,609	94.8
≥30	626	1.9	287	1.7	339	2.0
Missing	785	2.4	261	1.6	524	3.2

represent the minimum strength of the association that the unmeasured confounder would require for both the mediator and the outcome, conditional on the measured covariates, to explain the mediating effect (Smith & VanderWeele, 2019). A complete case analysis was also conducted for the sensitivity analysis. We have also presented the sex-stratified results of our main analysis. To eliminate the possibility of reverse causation between exposure or mediator and outcome, we also conducted a sensitivity analysis among those who could be followed up for more than 3 years (>1095 days). Statistical significance was set at $\alpha = .05$. We used Stata/MP (version 17.0; Stata Corp.) to perform the statistical analyses.

3 | RESULTS

A flowchart of the participant inclusion process is shown in Figure 2. In the 32,986 analysed participants, the mean age was 72.6 (1 SD = 5.4) years at baseline, and 48.4% of them were men. The characteristics of the participants before and after multiple imputations are presented in Tables 1 and S1. During the follow-up period from 2013, 12.1% ($n = 3975$) of the participants developed dementia. The median observation period from 2013 was 2298 days (interquartile range [IQR] = 2137–2627 days), and the incidence rate of dementia was 2.11 per 100 person-years. Those who had ≤19 remaining teeth and ≥20 remaining teeth were 49.9% ($n = 16{,}472$) and 50.1% ($n = 16{,}514$), respectively. The proportion of those whose smoking status at baseline was 'never,' 'past' and 'current' was 59.7% ($n = 19{,}683$), 29.7% ($n = 9803$) and 10.6% ($n = 3500$), respectively. Sex- and age-adjusted Kaplan–Meier curves indicated a higher cumulative incidence of dementia among current and past smokers than among never smokers (Figure 3). In addition, those with ≤19 remaining teeth presented a higher cumulative incidence of dementia than those with ≥20 remaining teeth (Figure S1).

The results of the association between the number of remaining teeth and the risk of dementia are shown in Table 2. After adjusting for all covariates and smoking status, having ≤19 remaining teeth was significantly associated with an increased risk of dementia (HR = 1.10; 95% CI: 1.03–1.18). We observed a positive association between smoking history and the number of remaining teeth (Table S2).

Table 3 presents the results of CMA. Smoking history including past and current smoking was associated with an increased risk of dementia, and fewer remaining teeth significantly mediated the association (NIE: HR = 1.03; 95% CI: 1.02–1.05; PM = 18.0%). In addition, this analysis revealed that although the total effect of past smoking on dementia risk was not significant, the NIE of past smoking through fewer remaining teeth was significantly associated with an increased risk of dementia compared with never smoking (HR = 1.02; 95% CI: 1.01–1.03; PM = 19.1%). Similarly, we observed a positive

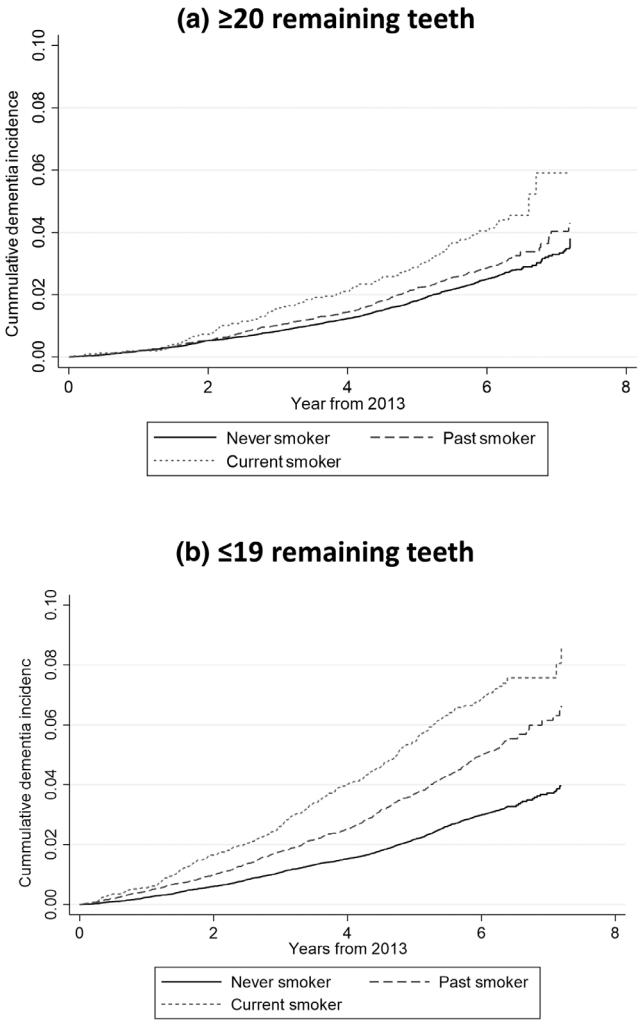

FIGURE 3 Kaplan–Meier curves of cumulative dementia incidence proportion by smoking status adjusted for sex and age among (a) those with ≥20 remaining teeth and (b) ≤19 remaining teeth ($n = 32{,}986$).

TABLE 2 Association between the number of remaining teeth and dementia incidence ($n = 32,986$).

	Model 1[a]	Model 2[b]
	HR (95% CI)	HR (95% CI)
Number of remaining teeth (binary)		
≥20	1.00 (Ref.)	1.00 (Ref.)
≤19	1.16 (1.09, 1.24)***	1.10 (1.03, 1.18)**
Number of remaining teeth (continuous)		
Per one remaining tooth decrease	1.000 (Ref.) 1.009 (1.006, 1.012)***	1.000 (Ref.) 1.006 (1.003, 1.009)***

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; Ref., reference.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, smoking status, alcohol consumption, marital status, income, education level, walking time, hypertension, diabetes and obesity.
**$p < .01$; ***$p < .001$.

TABLE 3 Mediation effect of tooth loss (≤19/≥20) on the association between smoking status and the risk of dementia ($n = 32,986$).

	Model 1[a]	Model 2[b]
	HR (95% CI)	HR (95% CI)
Exposure: Past smoker (ref. never smoker)		
TE	1.11 (1.003–1.22)*	1.10 (0.996–1.21)
NIE	1.02 (1.01–1.04)**	1.02 (1.01–1.03)**
NDE	1.09 (0.98–1.19)	1.08 (0.98–1.19)
PM	20.0%	19.1%
Exposure: Current smoker (ref. never smoker)		
TE	1.59 (1.40–1.78)***	1.54 (1.36–1.73)***
NIE	1.07 (0.996–1.15)	1.06 (0.98–1.13)
NDE	1.52 (1.32–1.71)***	1.49 (1.29–1.68)***
PM	12.0%	10.2%
Exposure: Past/current smoker (ref. never smoker)		
TE	1.20 (1.10–1.31)***	1.18 (1.08–1.29)**
NIE	1.04 (1.02–1.06)***	1.03 (1.02–1.05)***
NDE	1.16 (1.06–1.27)**	1.15 (1.05–1.26)**
PM	19.0%	18.0%

Note: Mediator was binary variable of remaining teeth (≤19/≥20).
Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; NDE, natural direct effect; NIE, natural indirect effect; PM, proportion mediated; TE, total effect.
[a]Adjusted for sex and age.
[b]Adjusted for sex, age, equivalent income, education level, marital status, alcohol consumption, walking time, hypertension, diabetes and obesity.
*$p < .05$; **$p < .01$; ***$p < .001$.

NIE through fewer remaining teeth in the association between current smoking and an increased risk of dementia compared with never smoking (HR = 1.06; 95% CI: 0.98–1.13; 10.2%). In the sensitivity analysis employing continuous tooth count as mediator, we also confirmed a significant NIE of smoking history with fewer remaining teeth on an increased risk of dementia as follows: for past/current smokers, HR = 1.04 (95% CI: 1.02–1.05; PM = 20.3%); past smokers, HR = 1.02 (95% CI: 1.01–1.03; PM = 20.4%); current smokers, HR = 1.07 (95% CI: 1.01–1.14; PM = 13.7%) (Table 4).

TABLE 4 Mediation effect of tooth loss (continuous tooth count) on the association between smoking status and the risk of dementia ($n = 32,986$).

	Model 1[a]	Model 2[b]
	HR (95% CI)	HR (95% CI)
Exposure: Past smoker (ref. never smoker)		
TE	1.11 (0.999–1.21)	1.10 (0.99–1.21)
NIE	1.02 (1.01–1.04)***	1.02 (1.01–1.03)**
NDE	1.08 (0.98–1.19)	1.08 (0.97–1.19)
PM	21.9%	20.4%
Exposure: Current smoker (ref. never smoker)		
TE	1.58 (1.39–1.77)***	1.53 (1.35–1.72)***
NIE	1.09 (1.02–1.16)*	1.07 (1.01–1.14)*
NDE	1.49 (1.29–1.68)***	1.46 (1.27–1.65)***
PM	15.6%	13.7%
Exposure: Past/current smoker (ref. never smoker)		
TE	1.20 (1.09–1.30)***	1.18 (1.07–1.28)**
NIE	1.04 (1.03–1.06)***	1.04 (1.02–1.05)***
NDE	1.15 (1.05–1.26)**	1.14 (1.04–1.25)**
PM	21.6%	20.3%

Note: Mediator was continuous count of remaining teeth.
Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; NDE, natural direct effect; NIE, natural indirect effect; PM, proportion mediated; TE, total effect.
[a]Adjusted for sex and age.
[b]Adjusted for sex, age, equivalent income, education level, marital status, alcohol consumption, walking time, hypertension, diabetes and obesity.
*$p < .05$; **$p < .01$; ***$p < .001$.

In the complete-case analysis, estimates were similar to those obtained from the imputed datasets (Table S3). In the sex-stratified analysis, the magnitude of each NIE was similar to that obtained from all male participants. In contrast, the point estimates of NIE were higher among female current smokers than among male current smokers (Tables S4 and S5). Among all participants in the present study, 30,074 (91.2%) were followed up for more than 3 years, and their results were similar to those of all other participants (Table S6). The mediational E-values for NIE and NDE are presented in Table S7.

4 | DISCUSSION

4.1 | Summary of main findings

The present study evaluated the association between smoking-associated tooth loss and dementia risk among independent older

adults, using CMA. Our findings revealed that fewer remaining teeth were significantly associated with an increased risk of dementia. In addition, both past and current smoking histories were strongly associated with fewer remaining teeth, and having fewer remaining teeth significantly mediated the association between both past and current smoking and an increased risk of dementia. Fewer remaining teeth significantly mediated the association between smoking and an increased dementia risk by approximately 20%.

4.2 | Comparison with previous findings and possible explanations

These results are consistent with those of previous studies. Previous systematic reviews have reported evidence of the relationship between smoking and tooth loss and between tooth loss and dementia onset (Leite et al., 2018; Souto et al., 2019). However, the pathway through which smoking leads to tooth loss and subsequently increases the risk of dementia has not yet been elucidated from the perspective of a potential outcome framework. In the present study, we employed CMA to confirm the significant mediating effect of smoking on the increased risk of dementia through tooth loss. In addition to confirming previous findings, our results provide evidence that tooth loss due to smoking significantly increases the risk of dementia among older adults; thus, tobacco control measures could be an effective option to prevent tooth loss and subsequent dementia onset.

In the present study, tooth loss due to smoking was significantly associated with an increased risk of dementia. However, a previous meta-analysis reported that although current smoking was associated with dementia risk, past smoking was not (Zhong et al., 2015). This discrepancy between the present result and previous findings can be explained as follows: The influence of smoking on health outcomes is reduced to some extent over time after smoking cessation (Yang et al., 2022). However, tooth loss is an irreversible disorder, and teeth lost due to smoking cannot be recovered. Therefore, tooth loss is considered a risk factor for dementia, even after smoking cessation, and a significant path-specific effect of past smoking on dementia through tooth loss could have been observed. In addition, the statistical power of NIE is higher than that of other estimators (VanderWeele, 2015), and this feature also contributes to the present results.

4.3 | Implication from clinical and public health perspectives

From a clinical perspective, tobacco cessation is essential to preventing periodontal diseases and tooth loss and maintaining systemic health later in life; therefore, instructions on tobacco cessation in dental settings would be an effective intervention for maintaining the health conditions of patients with smoking habits (Carr & Ebbert, 2012). In addition, the present results suggest that past smoking could affect the risk of dementia through tooth loss. Therefore, it is essential for those who quit smoking to receive continuous oral care to maintain favourable oral health and reduce the risk of dementia due to tooth loss (Ramseier et al., 2020). From a public health perspective, strategies to reduce smoking and promote tobacco cessation in the population are critical to preventing poor oral health and subsequent health problems (Smith et al., 2020).

4.4 | Limitations and strengths of the study

The present study has several limitations. First, owing to selection bias, the survey was conducted in 16 municipalities; therefore, it is possible that the representativeness of the participants was influenced by the limited number of municipalities. However, the included municipalities are located throughout Japan, and their characteristics (e.g. size, density and population structure) vary. This ensured the representativeness of the results. In addition, although a proportion of participants was missed through the data linkage, the proportion was relatively small, and some of them were not eligible for the present study; therefore, selection bias was considered small (Lee et al., 2021). The survey employed total or random sampling methods with relatively high response and follow-up rates, which increased the representativeness of the analysed population. In addition, underestimation of the relationship between smoking status and dementia could have occurred as a result of attrition bias by death, especially among very old adults (Hernán et al., 2008). Although we observed a significant positive association between tooth loss due to smoking and dementia onset, further studies are required to confirm the robustness of our results. Second, we used self-reported number of remaining teeth and smoking status; therefore, information bias may have affected our results. Although the validity of the self-reported number of remaining teeth and smoking status has been confirmed elsewhere (Sekundo et al., 2019; Wong et al., 2012), the misclassification of these statuses affected the estimates. Misclassifications of variables in the present study were considered non-differential. Therefore, the estimates were biased towards the null association; that is, there is a possibility that the estimates were underestimated (VanderWeele, 2016; Whitcomb & Naimi, 2020). We observed a similar significant association even in the analysis with more accurate measurements. In addition, future studies assessing pack-years of tobacco smoking would contribute to confirming the dose–response relationship.

This study also has several strengths. First, we included a large analysed population, which contributed to increased statistical power and provided more accurate estimates. Second, we employed CMA, which enabled us to estimate the mediation effect based on potential outcome frameworks, thus allowing us to estimate the cause-specific effect of tooth loss on the risk of dementia. Third, exposure to smoking and tooth loss are unfeasible interventions in a randomized controlled trial, and we employed large observational datasets and emulated a target trial. This contributes to higher generalizability than clinical trials with limited participants and interventions (Hernán & Robins, 2016).

5 | CONCLUSIONS

The present 9-year-follow-up prospective cohort study suggested that tooth loss mediates the association between both past and current smoking and an increased risk of dementia among older adults. Preventing tooth loss through tobacco control measures is an effective public health and clinical approach to maintaining healthy conditions later in life.

AUTHOR CONTRIBUTIONS

T.K., K.T., S.K. and Y.T. contributed to the conception and design of the study. T.T. and K.O. contributed to conception and acquisition of data. All authors contributed to analysis and interpretation of data, drafting and critical revision of the manuscript and approval of the final manuscript.

FUNDING INFORMATION

This study used data from the Japan Gerontological Evaluation Study (JAGES). This study was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (grant numbers: 19H03901, 19H03915, 19H03860, 19K04785, 19K10641, 19K11657, 19K19818, 19K19455, 19K24060, 19K20909, 20H00557, 21K19635, 22K17265, 21H03153, 22H03299), Ministry of Health, Labour and Welfare (19FA1012, 19FA2001, 21FA1012, 22FA2001, 22FA1010, 23FA1022), Japan Agency for Medical Research and Development (AMED) (JP20dk0110034, JP21lk0310073, JP21dk0110037, JP22lk0310087), Japan Science and Technology Agency (OPERA, JPMJOP1831) from the Japan Science and Technology (JST), Innovative Research Program on Suicide Countermeasures (1–4), Sasakawa Sports Foundation, Japan Health Promotion & Fitness Foundation, Chiba Foundation for Health Promotion & Disease Prevention, the 8020 Promotion Foundation (adopted number: 19-2-06), Niimi University (1915010) and Meiji Yasuda Life Foundation of Health and Welfare and the Research Funding for Longevity Sciences from the National Center for Geriatrics and Gerontology (20-19, 21-20).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are from the JAGES study. All enquiries are to be addressed at the data management committee via e-mail: dataadmin.ml@jages.net. All JAGES datasets have ethical or legal restrictions for public deposition due to inclusion of sensitive information from the human participants.

ETHICS STATEMENT

The 2010 and 2013 JAGES and their follow-up survey followed the procedures approved by the Ethics Committee on Research of Human Subjects at Nihon Fukushi University (nos 10-05 and 13-14).

INFORMED CONSENT

Informed consent was obtained from all participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kusama, T., Takeuchi, K., Kiuchi, S., Tamada, Y., Tabuchi, T., & Osaka, K. (2024). Tooth loss mediates the association between smoking and an increased risk of dementia among older adults: The JAGES prospective cohort study. *Journal of Clinical Periodontology*, 1–9. https://doi.org/10.1111/jcpe.13959