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Exploring the relationship between oral health and multiple health conditions: An outcome-wide approach

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Abstract

Purpose: A growing body of evidence suggests that oral health is associated with a wide range of health outcomes; however, opinions tend to vary because of inconsistent findings. This study aimed to simultaneously examine the association between oral health status and multiple health and well-being indicators using outcome-wide epidemiology.

Methods: Data were obtained from the Japan Gerontological Evaluation Study. Oral health status was categorized as: ≥20 teeth, 10-19 teeth with dental prosthesis, 0-9 teeth with prosthesis, 10-19 teeth without prosthesis, and 0-9 teeth without prosthesis. We examined the associations between oral health status in 2013 and 35 health and well-being outcomes in 2019, including physical/cognitive health, psychological distress, subjective health, social well-being, prosocial/altruistic behaviors, and health behaviors, using two databases (n=32,827 and 15,905).

Results: Compared to individuals with ≥20 teeth, those with <20 teeth had a 10-33% higher risk of mortality and a 7-10% higher risk of functional disability six years later. Additionally, individuals with fewer than 20 teeth tended to go out less frequently and eat fewer vegetables and fruits. Furthermore, individuals with 0-9 teeth without a prosthesis were more likely to have severe functional disability (risk ratio (RR):1.17, 95% confidence interval (CI):1.05-1.31), engage in fewer intellectual activities (standardized difference: 0.17, 95% CI: 0.10-0.24), and feel more hopeless (RR: 1.21, 95% CI: 1.04-1.41).

Conclusions: The prevention of tooth loss and prosthodontic treatment may be associated with reduced mortality and functional disability, as well as maintenance of intellectual ability, frequency of going out, and improvements in dietary lifestyle.

Keywords: Outcome studies, Cohort studies, Systemic health/disease, Prosthesis, Oral health

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1. Introduction

In the past two decades, several studies have shown an association between oral health and a wide range of health and well-being outcomes, including mortality, chronic diseases, cardiovascular diseases, functional capacity, general well-being, comfort, and fundamental dignity[1–4]. Due to the cumulative effects of oral health through the life course of individuals, oral disorders have become the tenth leading cause of "total years lived with disability" among individuals aged ≥70 years[5]. However, most previous studies examined the relationship between a single oral health exposure and a single general health outcome, which has created multiple testing problems[6]. Furthermore, the lack of comparability between these studies on oral and general health outcomes has made it difficult to identify which health outcomes, affected by oral health, contribute more significantly to healthy longevity.

To address these issues, outcome-wide epidemiology, introduced by VanderWeele[7], simultaneously assesses the association between single exposures and multiple outcomes. This approach can aid in prioritizing public health recommendations by determining which health outcomes are most strongly affected by oral health exposure. Moreover, outcome-wide modeling provides additional methodological benefits, as it is less prone to selective reporting and "*P*-hacking," which is the practice of either intentionally or unintentionally using varying analytical approaches to achieve results with $P < 0.05$[8].

Given the importance of considering aging populations, it is crucial to examine the effects of oral health on multiple outcome domains, including health conditions and well-being, from a policy perspective. Therefore, this longitudinal study aimed to simultane-

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ously examine the association between oral health status and multiple health and well-being indicators among older adults during a six-year follow-up period.

2. Method of research

2.1. Study population

Data for this study were obtained from the Japan Gerontological Evaluation Study (JAGES), a nationwide longitudinal study investigating the social determinants of healthy aging among people aged ≥65 years in Japan[9,10]. In 2010, self-reported questionnaires were mailed to 147,101 independent individuals from 26 municipalities (response rate: 65.5%; valid responses in 2010: 88,177; valid response rate: 91.5%). A follow-up survey was conducted in 2013, with a total of 58,137 participants and a follow-up rate of 65.9%. We created two analytical samples by linking these 58,137 individuals to either the 2019 follow-up survey (n=15,905) or the national long-term care insurance database, which included information on all-cause mortality, dementia, and functional disability until 2019 (n=32,827). A flowchart of the study is presented in **Figure 1**.

The JAGES was approved by the Ethics Committees on Human Subjects at the National Center for Geriatrics and Gerontology (No. 992), Faculty of Medicine at Chiba University (No. 2493), Graduate School of Medical and Dental Sciences at Tokyo Medical and Dental University (No. D2021-016), and the Graduate School and Faculty of Medicine at Kyoto University (No. R3153). Written informed consent was assumed based on the voluntary return of the questionnaire, which was approved by the Ethics Committee. This study adhered to STROBE guidelines.

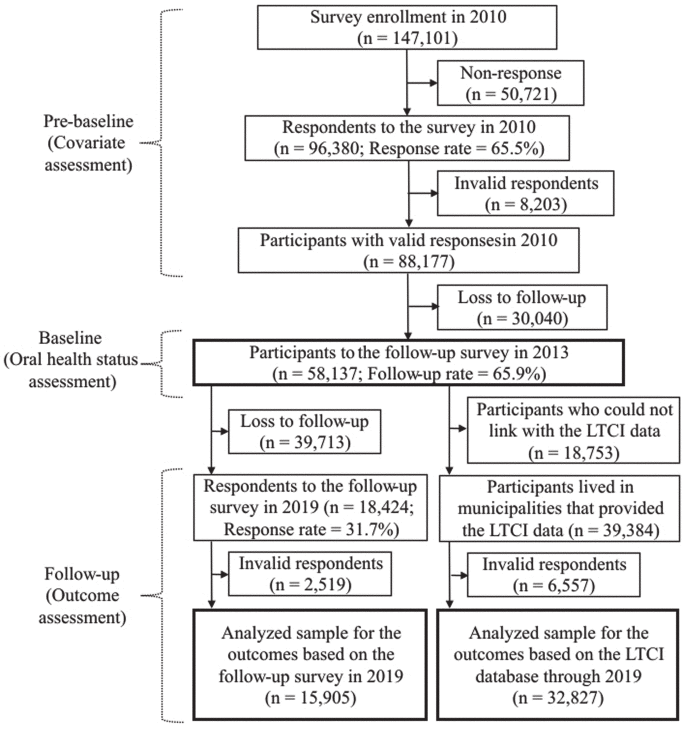

Fig. 1. Flowchart of sample selection (n=15,905 for the outcomes based on the follow-up survey in 2019 and n=32,827 for the outcomes based on the long-term care insurance database)

2.2. Measures

2.2.1. Oral health status

To determine oral health exposure, we used two combined indicators: the number of teeth and the use of dental prostheses. Many previous studies on oral health have used these indicators because they can enable researchers to easily determine dental health status through self-report questionnaires and compare the findings with other studies[11,12].

The self-reported number of teeth was categorized into three groups: ≥20, 10-19, and 0-9 teeth. While the World Health Organization's established questionnaire for assessing the current oral health status of a population groups the number of teeth into four categories (≥20, 10–19, 1–9, 0)[13], we merged 0 and 1-9 teeth to avoid creating a category with a small number of participants. Regarding the use of dental prostheses (e.g., implants, bridges, or removable dentures), five oral health status categories were used: ≥20 teeth, 10-19 teeth with prosthesis, 0-9 teeth with prosthesis, 10-19 teeth without prosthesis, and 0-9 teeth without prosthesis, which was adopted from a previous study[14].

2.2.2. Outcomes

Based on VanderWeele's framework of human flourishing[15], we selected 35 health and well-being outcomes in 2019 from the following domains: physical/cognitive health (death, dementia, and functional disability assessed through both computer-based and home-visit interviews by trained health professionals)[16], self-rated health, body mass index (BMI), instrumental independence, intellectual activity, social participation, self-reported hypertension, diabetes, dyslipidemia, heart disease, stroke, and respiratory disease; psychological distress (depressive symptoms and hopelessness); subjective well-being (happiness and life satisfaction); social well-being (participation in hobby, sports, learning, or cultural groups or in senior citizens clubs), number of friends seen within a month, frequency of meeting friends, going out, receiving emotional social support, and receiving instrumental social support; pro-social/altruistic behaviors (volunteering and sharing skills and experiences); and health behaviors (eating meat and fish, eating vegetables and fruits, walking, sedentary lifestyle, and health screening). All continuous outcomes were standardized (mean = 0; standard deviation = 1). The definitions of all outcomes are presented in Table S1.

2.2.3. Covariates

All pre-baseline covariates were obtained from a 2010 survey conducted three years before the oral health status assessment. We selected pre-baseline covariates to control for all observed potential confounders while avoiding adjustment for factors on the causal pathway, which could lead to an underestimation of the effect[17]. The selected covariates were considered because they were likely caused by either or both oral health status and outcomes, thereby serving as potential confounders. The following demographic factors were included as covariates: age, sex, marital status, whether living alone, educational level, employment status, and equivalent household income. In addition, we adjusted for smoking and drinking habits reported in the pre-baseline survey. Furthermore, we controlled for the pre-baseline values of all outcomes in the 2010 survey. Data on participation in learning or cultural groups, sharing of skills and experiences, and a sedentary lifestyle were not included

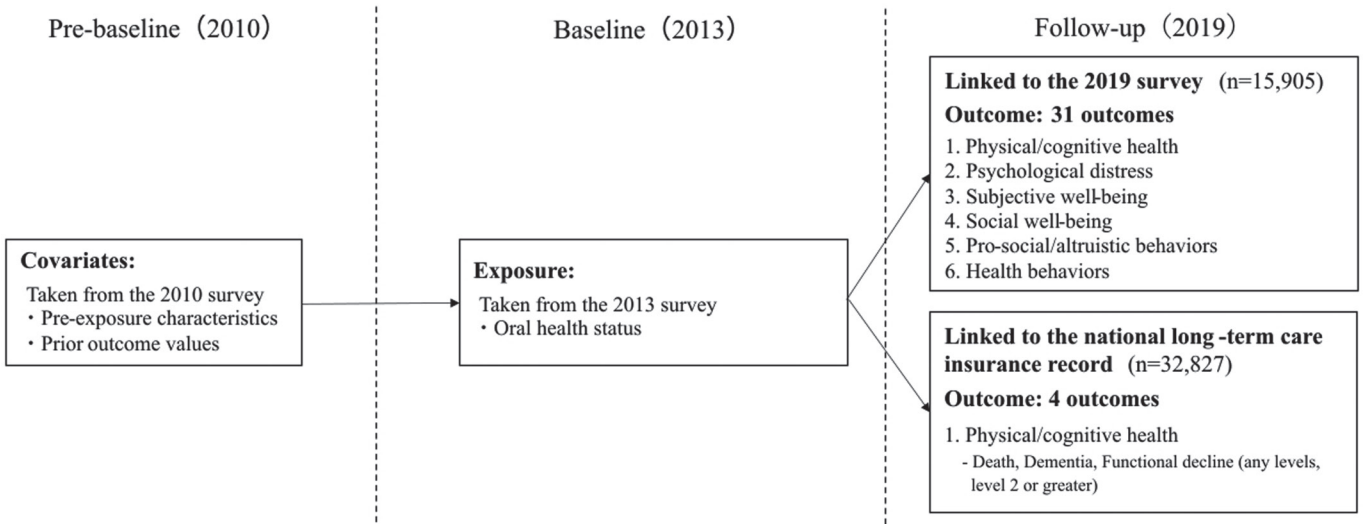

Fig. 2. Temporal order of data linkage and variables included in the analysis

due to insufficient data. Adjusting for pre-baseline outcome values helps address potential reverse causation[17].

2.3. Statistical analysis

We employed a longitudinal outcome-wide analytical method for this study. While other analytical approaches, such as multilevel modeling for longitudinal data and structural equation modeling, could be useful when assessing the impact of higher-level variables (e.g., neighborhood-level characteristics) or longitudinal trajectories of outcomes (i.e., analysis of repeated observations), or when investigating the structural relationships between variables, they are beyond the scope of this study and generally require additional data and stronger assumptions. Therefore, we employed an outcome-wide approach, which is the simplest option requiring minimal assumptions to answer our research question. A diagram illustrating the temporal order of data linkage and the variables included in the analysis is shown in **Figure 2**, and a directed acyclic graph is provided in **Figure S1**.

We employed an independent linear regression model for each continuous outcome, adjusted for baseline covariates and outcomes. For examining the association between oral health and each binary outcome in 2019, we estimated risk ratios (RRs) and their 95% confidence intervals (CI) using a modified Poisson regression with robust standard errors and adjustments for all other covariates[18]. To account for multiple testing, Bonferroni correction was employed.

Subsequently, we calculated E-values for the association between oral health and each outcome to assess the robustness of our effect estimates to unmeasured confounding[19]. E-values measure the minimum strength of association on the RR scale that an unmeasured confounder would need to have with both exposure and outcome to explain the observed association above and beyond the identified covariates.

Furthermore, we conducted a sensitivity analysis adjusting for outcome values at baseline (2013) to avoid residual confounding if the confounder values changed between the pre-baseline and baseline waves. In addition, we conducted a sensitivity analysis to examine the relationship between oral health status and health outcomes using the national long-term care insurance database, adjusting for covariates (e.g., sex, age, income, education, employment status, marital status, whether living alone, smoking, and drinking behaviors), and excluding potential mediators.

We imputed all missing data using multiple imputations through chained equations, created 20 imputed datasets, and combined the estimates based on Rubin's rule[20]. We then merged the findings from the aforementioned analyses. All statistical analyses were conducted using STATA 17.0 Standard Edition (StataCorp LLC, College Station, TX, StataCorp LLC).

3. Results

The pre-baseline demographic characteristics recorded in 2010 were stratified according to oral health status in the analytical sample obtained by linking the 2010 and 2013 surveys with the 2019 survey (**Table 1**; n=32,827). It was observed that better oral health status was more prevalent among married individuals, those with better health conditions, and those with better subjective health, whereas worse oral health status was found among individuals who lived alone, had lower education levels, lower equivalent household income, and greater psychological distress. The pre-baseline characteristics of the analytical sample obtained by linking the 2010 and 2013 survey data with the national long-term care insurance data are presented in **Table S2** (n=15,905). The observed trends are similar to those presented in **Table 1**.

Table 2 presents the RRs for binary outcomes and the standardized differences for continuous outcomes with 95% CIs after adjusting for all covariates. Compared to individuals with ≥20 teeth, those with fewer teeth in 2013 were more likely to die, have a functional disability, go out less frequently, and eat fewer vegetables and fruits in 2019. Additionally, individuals with 0-9 teeth without prosthesis in 2013 were more likely to die (RR: 1.33, 95% CI: 1.19-1.48), have severe functional disability (any level, RR: 1.10, 95% CI: 1.02-1.19; level 2 or higher functional disability, RR: 1.17, 95% CI: 1.05-1.31), be involved

Table 1. Pre-baseline demographic characteristics in 2010 stratified by oral health status among the analytic sample linking the 2010 and 2013 surveys to the 2019 survey (n = 15,905)

	Overall (n =15,905)	Oral health status				
		20 or more teeth (n=9,186)	10-19 teeth with prosthesis (n=2,467)	0-9 teeth with prosthesis (n=2,775)	10-19 teeth without prosthesis (n=791)	0-9 teeth without prosthesis (n=686)
Sociodemographic Factors						
Age, mean (SD)	71.0 (4.3)	70.5 (3.9)	71.1 (4.3)	72.5 (4.9)	71.1 (4.2)	72.7 (4.7)
Sex, n (%)						
Female	8135 (51.1)	4802 (52.3)	1295 (52.5)	1352 (48.7)	371 (46.9)	315 (45.9)
Marital status, n (%)						
Married	12660 (79.6)	7509 (81.7)	1966 (79.7)	2068 (74.5)	607 (76.8)	509 (74.3)
Living alone, n (%)						
Yes	1780 (11.2)	992 (10.8)	297 (12.0)	309 (11.1)	92 (11.6)	89 (13.0)
Educational attainment, n (%)						
<9 years	5764 (36.2)	2894 (31.5)	893 (36.2)	1193 (43)	380 (48.0)	405 (59.0)
Employment, n (%)						
Current worker	4359 (27.4)	2510 (27.3)	660 (26.8)	735 (26.5)	260 (32.8)	194 (28.2)
Equivalent income, n (%)						
<2 million yen	6743 (42.4)	3511 (38.2)	1068 (43.3)	1353 (48.8)	400 (50.7)	410 (59.8)
2–4 million yen	7125 (44.8)	4351 (47.4)	1117 (45.3)	1116 (40.2)	325 (41.1)	216 (31.5)
Physical/Cognitive Health						
Bad self-rated health, n (%)	1654 (10.4)	828 (9)	282 (11.4)	350 (12.6)	87 (11.0)	105 (15.3)
Body mass index, mean (SD)	22.9 (2.9)	22.8 (2.8)	22.9 (2.8)	23.0 (3.0)	23.3 (3.1)	23.6 (3.2)
Instrumental independence, mean (SD)	0.2 (0.5)	0.1 (0.4)	0.1 (0.5)	0.2 (0.6)	0.2 (0.6)	0.3 (0.7)
Intellectual activity, mean (SD)	0.3 (0.6)	0.2 (0.5)	0.3 (0.6)	0.3 (0.6)	0.4 (0.7)	0.4 (0.7)
Social role, mean (SD)	0.6 (0.9)	0.6 (0.9)	0.6 (0.9)	0.6 (0.9)	0.6 (0.9)	0.7 (1.0)
Self-reported hypertension, n (%)	7583 (47.7)	4267 (46.5)	1174 (47.6)	1380 (49.7)	396 (50.1)	366 (53.4)
Self-reported diabetes, n (%)	2095 (13.2)	1116 (12.1)	319 (12.9)	443 (15.9)	118 (14.9)	100 (14.5)
Self-reported dyslipidemia, n (%)	2526 (15.9)	1632 (17.8)	395 (16.0)	353 (12.7)	94 (11.8)	53 (7.7)
Self-reported heart disease, n (%)	1870 (11.8)	1002 (10.9)	323 (13.0)	368 (13.3)	88 (11.1)	89 (13.0)
Self-reported stroke, n (%)	142 (0.9)	66 (0.7)	24.1 (1.0)	33 (1.2)	12.1 (1.5)	7 (1.0)
Self-reported respiratory disease, n (%)	455 (2.9)	256 (2.8)	72 (2.9)	72 (2.6)	28 (3.5)	27 (3.9)
Psychological Distress						
Depressive symptoms, mean (SD)	2.7 (2.8)	2.5 (2.7)	2.9 (2.8)	3.0 (3.0)	3.1 (3.1)	3.5 (3.3)
Hopeless, n (%)	2195 (13.8)	1077 (11.7)	357 (14.5)	477 (17.2)	146 (18.5)	139 (20.2)
Subjective Health						
Unhappiness, mean (SD)	3.8 (1.8)	3.6 (1.7)	3.8 (1.8)	4.0 (1.8)	4.0 (1.8)	4.2 (1.9)
Life satisfaction, n (%)	2417 (15.2)	1269 (13.8)	410 (16.6)	458 (16.5)	147 (18.6)	134 (19.5)
Social Well-beings						
Participation in hobby group, mean (SD)	4.5 (1.6)	4.4 (1.6)	4.5 (1.6)	4.7 (1.5)	4.8 (1.5)	4.9 (1.5)
Participation in sports group, mean (SD)	4.9 (1.6)	4.8 (1.7)	4.9 (1.6)	5.0 (1.6)	5.1 (1.5)	5.3 (1.4)
Participation in senior citizens club, mean (SD)	5.6 (1.0)	5.6 (0.9)	5.6 (1.0)	5.5 (1.1)	5.5 (1.0)	5.5 (1.0)
Frequency of meeting friends, mean (SD)	3.2 (1.5)	3.1 (1.5)	3.2 (1.5)	3.2 (1.5)	3.3 (1.5)	3.3 (1.5)
Number of friends seen within a month, mean (SD)	1.2 (1.3)	1.1 (1.2)	1.2 (1.3)	1.3 (1.3)	1.3 (1.3)	1.4 (1.3)
Frequency of going out, mean (SD)	1.5 (0.8)	1.4 (0.7)	1.5 (0.8)	1.6 (0.8)	1.5 (0.8)	1.7 (0.9)
Receiving emotional social support, n (%)	648 (4.1)	329 (3.6)	85 (3.4)	133 (4.8)	48 (6.0)	53 (7.7)
Receiving instrumental social support, n (%)	602 (3.8)	342 (3.7)	78 (3.2)	104 (3.7)	43 (5.5)	35 (5.0)
Pro-social/Altruistic Behaviors						
Volunteering, mean (SD)	5.5 (1.1)	5.5 (1.1)	5.5 (1.0)	5.5 (1.1)	5.5 (1.0)	5.7 (0.8)
Health Behaviors						
Smoking, n (%)	1488 (9.4)	646 (7.0)	255 (10.3)	380 (13.7)	103 (13.0)	105 (15.2)
Drinking, n (%)	6886 (43.3)	4126 (44.9)	1079 (43.7)	1104 (39.8)	320 (40.4)	258 (37.5)
Eating meat and fish, mean (SD)	2.8 (1.1)	2.7 (1.1)	2.9 (1.1)	2.9 (1.1)	3.1 (1.2)	3.1 (1.2)
Eating vegetables and fruits, mean (SD)	1.7 (0.9)	1.7 (0.9)	1.8 (0.9)	1.9 (1.0)	1.9 (1.0)	2.1 (1.1)
Walking, mean (SD)	2.7 (1.0)	2.7 (1.0)	2.7 (1.0)	2.7 (1.1)	2.8 (1.1)	2.8 (1.1)
Health screening, n (%)	4769 (30.0)	2471 (26.9)	757 (30.7)	948 (34.2)	309 (39.1)	284 (41.3)

Abbreviation: SD, Standard deviation

Table 2. Associations between oral health status and subsequent health and well-being (n = 32,827 or 15,905)

	10-19 teeth with prosthesis	0-9 teeth with prosthesis	10-19 teeth without prosthesis	0-9 teeth without prosthesis
	RR/β† (95%CI)	RR/β† (95%CI)	RR/β† (95%CI)	RR/β† (95%CI)
Physical/Cognitive Health				
Death§	1.10 * (1.01, 1.21)	1.26 *** (1.17, 1.35)	1.16 * (1.03, 1.32)	1.33 *** (1.19, 1.48)
Dementia§	1.02 (0.93, 1.12)	1.02 (0.94, 1.10)	1.14 * (1.01, 1.30)	1.05 (0.93, 1.18)
Functional disability (Any levels)§	1.06 * (1.01, 1.13)	1.07 * (1.02, 1.13)	1.14 ** (1.05, 1.24)	1.10 * (1.02, 1.19)
Functional disability (≥ Level 2)§	1.03 (0.95, 1.13)	1.04 (0.97, 1.13)	1.10 (0.97, 1.25)	1.17 ** (1.05, 1.31)
Self-rated health	1.10 (0.99, 1.2)	1.02 (0.93, 1.12)	1.11 (0.96, 1.29)	1.01 (0.86, 1.18)
Body mass index	-0.01† (-0.03, 0.02)	0.01† (-0.03, 0.03)	0.01† (-0.04, 0.05)	-0.01† (-0.06, 0.03)
Instrumental independence	0.01† (-0.03, 0.05)	0.07 *** (0.03, 0.11)	0.03† (-0.04, 0.10)	0.04† (-0.04, 0.12)
Intellectual activity	0.01† (-0.03, 0.05)	0.07† *** (0.04, 0.11)	0.05† (-0.01, 0.11)	0.17† *** (0.10, 0.24)
Social role	0.01† (-0.04, 0.04)	0.02† (-0.02, 0.06)	0.05† (-0.01, 0.11)	-0.07† (-0.14, 0.01)
Self-reported hypertension	1.03 (0.99, 1.08)	1.02 (0.99, 1.06)	1.09 ** (1.03, 1.16)	1.06 (0.99, 1.13)
Self-reported diabetes	1.05 (0.96, 1.14)	1.09 * (1.01, 1.17)	1.10 (0.95, 1.26)	1.06 (0.92, 1.21)
Self-reported dyslipidemia	0.96 (0.87, 1.06)	0.89 (0.79, 1.01)	0.90 (0.74, 1.10)	0.78 (0.59, 1.02)
Self-reported heart disease	0.99 (0.90, 1.09)	0.93 (0.84, 1.04)	1.02 (0.86, 1.21)	0.90 (0.75, 1.08)
Self-reported stroke	1.04 (0.81, 1.33)	1.15 (0.90, 1.45)	1.26 (0.90, 1.76)	1.34 (0.93, 1.93)
Self-reported respiratory disease	0.98 (0.82, 1.16)	1.06 (0.90, 1.25)	0.78 (0.58, 1.06)	1.06 (0.82, 1.39)
Psychological Distress				
Depressive symptoms	0.04† * (0.01, 0.08)	0.02† (-0.03, 0.06)	0.01† (-0.06, 0.07)	0.03† (-0.04, 0.10)
Hopeless	1.12* (1.01, 1.24)	1.04 (0.94, 1.16)	1.11 (0.95, 1.30)	1.21 * (1.04, 1.41)
Subjective Health				
Happiness	0.05† * (0.01, 0.10)	0.02† (-0.02, 0.07)	0.04† (-0.03, 0.11)	0.05† (-0.03, 0.14)
Life satisfaction	1.05 (0.95, 1.17)	1.03 (0.93, 1.14)	0.92 (0.78, 1.10)	1.08 (0.92, 1.27)
Social Well-beings				
Participation in hobby group	0.01† (-0.03, 0.05)	0.01† (-0.03, 0.05)	-0.01† (-0.09, 0.06)	0.02† (-0.05, 0.09)
Participation in sports group	0.02† (-0.02, 0.06)	0.04† * (0.01, 0.08)	0.03† (-0.03, 0.10)	0.05† (-0.03, 0.12)
Participation in senior citizens club	-0.01† (-0.05, 0.04)	-0.05† * (-0.09, -0.01)	-0.03† (-0.10, 0.04)	-0.02† (-0.10, 0.05)
Participation in learning or cultural groups ¶	0.02† (-0.02, 0.07)	0.01† (-0.04, 0.05)	0.05† (-0.03, 0.12)	0.05† (-0.04, 0.14)
Frequency of meeting friends	0.02† (-0.02, 0.05)	0.01† (-0.03, 0.04)	0.02† (-0.04, 0.09)	-0.08† * (-0.15, -0.01)
Number of friends seen within a month	0.05† * (0.01, 0.08)	0.03† (-0.01, 0.07)	0.06† (-0.01, 0.12)	0.03† (-0.04, 0.10)
Frequency of going out	0.02† (-0.02, 0.06)	0.09† *** (0.05, 0.13)	0.07† * (0.01, 0.13)	0.11† ** (0.03, 0.18)
Receiving emotional social support	1.24 * (1.02, 1.52)	1.08 (0.88, 1.31)	1.23 (0.91, 1.64)	0.95 (0.69, 1.31)
Receiving instrumental social support	1.09 (0.89, 1.34)	1.14 (0.94, 1.38)	1.01 (0.74, 1.36)	0.98 (0.71, 1.37)
Pro-social/Altruistic Behaviors				
Volunteering	0.01† (-0.03, 0.06)	-0.04† (-0.12, 0.03)	-0.04† (-0.12, 0.03)	-0.07† (-0.15, 0.01)
Sharing skills and experiences ¶	0.03† (-0.01, 0.08)	-0.01† (-0.08, 0.08)	-0.01† (-0.08, 0.08)	-0.05† (-0.13, 0.03)
Health Behaviors				
Eating meat and fish	0.01† (-0.04, 0.04)	0.02† (-0.02, 0.06)	0.11† ** (0.05, 0.17)	0.01† (-0.06, 0.08)
Eating vegetables and fruits	0.05† * (0.01, 0.09)	0.09† *** (0.05, 0.13)	0.17† *** (0.11, 0.24)	0.14† *** (0.07, 0.21)
Walking	-0.02† (-0.06, 0.02)	-0.01† (-0.04, 0.04)	0.06† (-0.01, 0.13)	-0.07† (-0.14, 0.01)
Sedentary lifestyle ¶	1.01 (0.83, 1.23)	1.01 (0.84, 1.22)	0.93 (0.67, 1.28)	0.82 (0.58, 1.17)
Health screening	0.98 (0.93, 1.04)	0.96 (0.91, 1.01)	1.05 (0.97, 1.14)	1.10 * (1.02, 1.20)

The participants with 20 or more teeth were regarded as a reference category. Abbreviation: RR, risk ratio; β, standardized difference; CI, confidence interval. A higher score in RR and β indicates an estimate of worse health and well-being outcomes. We estimated standardized differences for the continuous outcomes using multiple linear regression and risk ratios for the binary outcomes using modified Poisson regression. We adjusted for pre-baseline covariates (age, sex, marital status, living alone, educational attainment, employment, equivalent income) as well as pre-baseline levels of outcomes wherever data were available.

†All continuous variables (body mass index, instrumental independence, intellectual activity, social role, depressive symptoms, happiness, participation in hobby group, participation in sports group, participation in senior citizens club, participation in learning or cultural groups, frequency of meeting friends, number of friends seen within a month, frequency of going out, volunteering, sharing skills and experiences, eating meat and fish, eating vegetables and fruits, walking, and age) were standardized (mean = 0, standard deviation = 1), and β could be interpreted as a standard deviation change.

‡*$P < 0.05$ before Bonferroni correction; ** $P < 0.01$ before Bonferroni correction; *** $P < 0.05$ after Bonferroni correction (the P -value cutoff for Bonferroni correction is $P < 0.05/35 = 0.0014$).

§Regression was performed by using the study sample linking the 2010 and 2013 surveys to the national long-term care insurance data (n = 43,783) for the outcomes of death, dementia, and functional disability and by using the study sample linking the 2010 and 2013 surveys to the 2019 survey (n = 32,395) for other outcomes.

¶Pre-baseline levels of outcomes were not available.

in fewer intellectual activities (coefficient: 0.17, 95% CI: 0.10-0.24), feel more hopeless (RR: 1.21, 95% CI: 1.04-1.41), undergo fewer health screenings (RR: 1.10, 95% CI: 1.02-1.20), and meet friends less frequently (coefficient: 0.11, 95% CI: 0.03-0.18) in 2019. Even after accounting for multiple testing through Bonferroni correction, the associations between oral health and mortality, intellectual ability, and consumption of vegetables and fruits remained below the threshold of $P < 0.05$. However, there was no strong evidence of an association with any other health or well-being outcome.

The estimated E-values are listed in **Table 3**. The observed associations between oral health status and subsequent health and well-being outcomes were moderately robust against unmeasured confounders. For instance, an unmeasured confounder associated with both 0-9 teeth without a dental prosthesis and the risk of mortality with an RR of 1.99—above and beyond the adjusted covariates—could suffice to explain the association; however, weaker joint unmeasured confounding associations could not. Unmeasured confounding associations of 1.67-fold were required for each covariate to shift the CI to a null value. However, none of the estimated associations between the observed covariates and mortality was stronger than RR > 1.67. One exception could be oral malignancy, which could be associated with both the number of teeth and health conditions. Nonetheless, the incidence rate of oral cancer is 0.0002 in Japan[21], indicating that the possibility of confounding by oral malignancy is very low.

The results of the sensitivity analyses adjusted for baseline outcome values are presented in **Table S3**. The results showed a similar tendency to that of the main analysis, although some relationships were attenuated. In addition, the results of another sensitivity analysis that examined the relationship between oral health status and health outcomes in the national long-term care insurance database, adjusting for covariates and excluding potential mediators, are presented in **Table S4**. The results showed the same tendency with stronger associations than those in the main analyses.

4. Discussion

This study aimed to examine the association between oral health status and multiple health and well-being indicators using outcome-wide epidemiology. The findings indicate that having fewer than 20 teeth was associated with poor physical and cognitive health outcomes (all-cause mortality, functional disability, and reduced intellectual activity), poorer social well-being outcomes (meeting friends and going out less frequently), and eating fewer vegetables and fruits. By examining multiple outcomes simultaneously, this study found that mortality was strongly associated with oral health status. However, we did not observe significant associations between oral health and other health outcomes.

4.1. Physical/cognitive health

Our findings regarding the relationship between poor oral health status and mortality are consistent with previous meta-analyses and systematic reviews[22,23]. Furthermore, another systematic review reported that oral function (functional dentition with occluding pairs and maximum bite force) and the number of teeth were associated with frailty[24], which is in line with our findings. Regarding cognitive function, we observed a positive relationship between poor oral health and intellectual disability, in line with previous studies, including a systematic review and meta-analysis that examined the association between cognitive complaints/deficits and masticatory dysfunction, as well as the number of teeth[25,26]. However, the relationship between oral health and dementia was not significant in this study, which differs from a previous study using the same cohort[27]. This discrepancy may be attributed to the use of different analytical approaches. For instance, our model was adjusted for variables that were highly related to mediating factors, for instance, social participation in 2010 was highly correlated with social participation in 2013 and later years. As such, even pre-baseline exposure might be highly correlated with the mediating factors influencing the association between oral health and dementia at later time points. Therefore, we conducted a sensitivity analysis that excluded these mediating factors from the model and adjusted for the same confounding variables as those used in previous studies, which yielded similar results. Moreover, it is important to consider that Kiuchi *et al.* focused only on the number of teeth as an exposure, while our study used a combination of tooth number and dental prosthesis use. Despite this difference, our sensitivity analyses, which included the same covariates as those in the previous study, did not demonstrate any contradictory findings (**Table S4**).

We did not observe a distinct relationship between oral health and self-reported diagnosed diseases, contrary to the findings of a systematic umbrella review[1]. Our survey inquired about diseases under treatment but not disease incidence. Therefore, this study may have captured relatively mild disease conditions compared with previous studies, which might explain the null findings.

The robust association of oral health with the final outcome (mortality) was identified in this study, whereas that with other physical and cognitive health indicators was not. This may be because one of the characteristics of oral health is weakly associated with several factors. Therefore, the underestimation resulting from overadjustment might have affected the identification of associations with other physical and cognitive health indicators. Although there was a possibility of underestimation, the significant association of mortality indicates a strong association between oral health status and mortality.

4.2. Psychological distress and subjective health

Previous empirical studies have reported the causal effect of tooth loss on depression[28], the association between better oral health status and happiness[11], and the relationship between occlusal force and psychological frailty[29]. Another study reported null associations between oral health status and life satisfaction[12]. However, it is important to note that this study included individuals with full dentition (28 teeth), which is a stricter definition than that used in our study. In our study, we observed a similar tendency in the domains of depressive symptoms, hopelessness, happiness, and life satisfaction. Deteriorated oral health status was associated with greater psychological distress and poorer subjective health, while only hopelessness appeared to be significantly related to oral health.

4.3. Social well-being and pro-social/altruistic behavior

Previous studies, including a systematic review, reported that tooth loss and not using dental prostheses were the main predictors of social isolation and fewer social interactions[30–32]. In this study, however, we could not identify a clear relationship between oral health status and any social well-being indicator or pro-social/altruistic behavior, except for the frequency of going out. This may be

Table 3. Robustness to unmeasured confounding (E-values) of associations between oral health status and subsequent health and well-being

	10-19 teeth with prosthesis		0-9 teeth with prosthesis		10-19 teeth without prosthesis		0-9 teeth without prosthesis	
	E-value for point estimate*	E-value for confidence limit†	E-value for point estimate*	E-value for confidence limit†	E-value for point estimate*	E-value for confidence limit†	E-value for point estimate*	E-value for confidence limit†
Physical/Cognitive Health								
Death‡	1.44	1.11	1.84	1.63	1.61	1.20	1.99	1.67
Dementia‡	1.17	1.00	1.16	1.00	1.55	1.11	1.27	1.00
Functional disability (Any levels)‡	1.33	1.08	1.35	1.17	1.54	1.28	1.44	1.17
Functional disability (≥ Level 2)‡	1.44	1.00	1.27	1.00	1.44	1.00	1.62	1.28
Self-rated health	1.41	1.00	1.19	1.00	1.48	1.00	1.11	1.00
Body mass index	1.05	1.00	1.03	1.00	1.10	1.00	1.12	1.00
Instrumental independence	1.12	1.00	1.34	1.20	1.20	1.00	1.18	1.00
Intellectual activity	1.12	1.00	1.35	1.22	1.28	1.00	1.62	1.43
Social role	1.06	1.00	1.15	1.00	1.28	1.00	1.33	1.00
Self-reported hypertension	1.23	1.00	1.18	1.00	1.39	1.18	1.31	1.00
Self-reported diabetes	1.29	1.00	1.39	1.08	1.45	1.00	1.34	1.00
Self-reported dyslipidemia	1.29	1.00	1.51	1.10	1.45	1.00	1.88	1.00
Self-reported heart disease	1.11	1.00	1.33	1.00	1.11	1.00	1.46	1.00
Self-reported stroke	1.23	1.00	1.55	1.00	1.83	1.00	2.00	1.00
Self-reported respiratory disease	1.19	1.00	1.28	1.00	1.92	1.00	1.34	1.00
Psychological Distress								
Depressive symptoms	1.24	1.06	1.14	1.00	1.09	1.00	1.20	1.00
Hopeless	1.50	1.12	1.26	1.00	1.48	1.00	1.73	1.25
Subjective Health								
Happiness	1.28	1.07	1.18	1.00	1.19	1.00	1.28	1.00
Life satisfaction	1.30	1.00	1.21	1.00	1.43	1.00	1.36	1.00
Social Well-beings								
Participation in hobby group	1.10	1.00	1.10	1.00	1.10	1.00	1.11	1.00
Participation in sports group	1.17	1.00	1.22	1.00	1.20	1.00	1.25	1.00
Participation in senior citizens club	1.07	1.00	1.26	1.06	1.20	1.00	1.20	1.00
Frequency of meeting friends	1.14	1.00	1.08	1.00	1.18	1.00	1.35	1.11
Number of friends seen within a month	1.26	1.10	1.21	1.00	1.33	1.09	1.21	1.00
Frequency of going out	1.17	1.00	1.40	1.28	1.32	1.00	1.44	1.21
Receiving emotional social support	1.80	1.17	1.38	1.00	1.76	1.00	1.29	1.00
Receiving instrumental social support	1.43	1.00	1.57	1.00	1.22	1.00	1.08	1.00
Pro-social/Altruistic Behaviors								
Volunteering	1.12	1.00	1.23	1.00	1.25	1.00	1.35	1.00
Health Behaviors								
Eating meat and fish	1.04	1.00	1.14	1.00	1.44	1.24	1.08	1.00
Eating vegetables and fruits	1.26	1.09	1.39	1.27	1.60	1.43	1.53	1.32
Walking	1.14	1.00	1.03	1.00	1.30	1.00	1.34	1.00
Sedentary lifestyle	1.16	1.00	1.17	1.00	1.29	1.00	1.67	1.00
Health screening	1.14	1.00	1.26	1.00	1.28	1.00	1.44	1.16

*E-values for effect estimates are the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome, above and beyond the measured covariates, to fully explain away the observed associations between oral health status and the outcomes.

†E-values for the 95% confident interval limit closest to the null denote the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome, above and beyond the measured covariates, to shift the 95% confident interval to include the null value.

‡The analytic sample size was n = 39,384 for the outcomes of death, dementia, and functional disability and that for other outcomes was n = 18,424.

because the effects were dispersed, as manifested in the association between oral health status and the frequency of going out, which serves as a collective indicator of these domains.

4.4. Health behaviors

Some systematic reviews and meta-analyses have reported an association between tooth loss and a greater risk of malnutrition[33],

and the relationship between dental status, number of teeth, bite force, and chewing problems with food and nutrient intake[34]. These findings are supported by our finding that deteriorated oral health is associated with eating fewer vegetables and fruits. Another systematic review reported that poor oral health negatively affects physical fitness and performance[35]. However, we did not find evidence of a relationship between oral health and other health behaviors. This could be due to the bidirectional association between oral health status and health behaviors, where the effects might have been canceled out, although we considered the possibility of reverse causation to be equally feasible.

4.5. Implications

The outcome-wide approach used in this study enabled a comprehensive understanding of the degree of association between oral health and various health outcomes[7]. The findings indicated that mortality was most strongly associated with oral health, suggesting that poor oral health increases the risk of mortality, which is critical for formulating effective public health recommendations.

Unlike previous studies on oral health that focused on single indicators, this study examined the effects of both the number of teeth and prosthetic use. We found that prosthetic use may be related to life expectancy after tooth loss, particularly in individuals with fewer than ten teeth. This finding has pertinent implications when developing policies and/or strategies for promoting public dental health, as it indicates that even if people experience tooth loss, the use of dental prostheses could protect them from various health risks. Nonetheless, maintaining >20 teeth is associated with health later in life, highlighting the need for prioritizing oral disease prevention.

The relationship between oral and systemic health can be attributed to factors such as malnutrition, inflammation, and social participation. These factors are crucial mortality risks that are significantly associated with oral health. First, lower weight and BMI have been associated with mortality[36,37]. Additionally, deteriorated oral health can cause malnutrition, leading to deteriorated general health, which is supported by a study reporting the mediating effect of weight loss[33,38]. Second, oral health problems can exacerbate inflammation and systemic health problems, including mortality[39]. Third, meta-analytic reviews have reported that social isolation and loneliness are risk factors for mortality[40,41]. Furthermore, poor dental status is associated with eating alone[14], which increases the risk of weight loss[42]. Thus, a lack of social participation stemming from deteriorated oral health can lead to adverse health outcomes. In addition, evidence indicates that the relationship between tooth loss and depressive symptoms is mediated by oral function and orofacial appearance[43].

4.6. Strengths and limitations

This study has several strengths. First, to the best of our knowledge, this is the first study to employ an outcome-wide approach to examine oral health status. Second, this approach allowed us to clarify the priorities while formulating public health recommendations based on the most critical associations. Third, this study utilized data from a large nationwide sample, enabling us to conduct an outcome-wide analysis. Fourth, the longitudinal cohort design ensured temporal ordering of associations of oral health status with various covariates and outcomes and enabled extensive adjustments for potential confounders, including outcomes recorded at an earlier time, thus addressing reverse causation. Finally, this study used objectively measured values of mortality, dementia, and functional disability from the long-term care insurance database, which included reliable official records of municipalities.

Although the present study reveals important findings, it has some limitations. First, because the JAGES involved a self-reported survey, the possibility of self-reporting bias needs to be considered. Although the validity of the number of teeth in the self-report was confirmed[44,45], we acknowledge that misclassification of tooth counts and dental prosthetic status may still exist. However, misclassification stemming from this bias can lead to overestimation when healthy individuals provide a higher number of teeth and unhealthy individuals provide a lower number, which may not occur frequently. In addition, if misclassification occurred randomly, the bias would be null, suggesting that the present results are robust. Second, confounding effects may have been caused by an unmeasured third variable. However, a wide range of controlled covariates and E-value analyses were employed to alleviate this concern. Third, there is a possibility of selection bias due to sampling, loss to follow-up, missing data, and the analytical sample being conditional on survival up to 65 years (i.e., those who were ≥65 at enrollment), leading to a lack of representativeness. If a larger number of unhealthy individuals had participated, the association between oral health and health outcomes might have been stronger. Fourth, there is a possibility of selection bias due to deaths during the follow-up period, which may have resulted in the potential underestimation of exposure-outcome associations[46]. Fifth, a six-year follow-up period may not be sufficient to detect the effects of oral health conditions on health, leading to the possibility that outcomes that did not occur within a short period of time were underestimated. Sixth, our analysis may capture the cumulative effect of chronic oral health conditions, and the pre-baseline covariate may be on the intermediate pathways. However, because we adjusted for the pre-baseline outcome, for the effect estimate to correspond to the cumulative effect, the past oral condition prior to the pre-baseline needs to affect the outcomes in the follow-up wave independent of the pre-baseline outcome, which is less likely to occur[47]. Seventh, we adjusted for pre-baseline outcome values; however, this adjustment may be imperfect, and residual confounding is possible when these values vary substantially between the pre-baseline and baseline waves. Therefore, we conducted a sensitivity analysis adjusted for the outcome values at baseline and confirmed trends similar to those in the main analysis. Eighth, this study did not consider the number of occlusal supports, chewing ability, or occlusal force as exposures. Therefore, a future study using these variables as exposures is warranted. Ninth, the question regarding the use of prostheses in the survey was not sufficiently specific to distinguish the types of prostheses, which may have had different effects on health outcomes. Further studies are needed to determine the differences in the impact of different types of dental prosthetics on health outcomes. Tenth, we used the categories of ≥20, 10-19, and 0-9 teeth for the number of teeth to ease interpretation and allow a non-linear relationship with the outcomes. While we acknowledge that categorization might lead to the loss of important information and cause underestimation of the extent of variation between groups[48], the effect of chance variations would have been reduced by avoiding the categories comprising only a few participants. Finally, our findings in the Japanese population may not apply to other populations; however, they may have valuable implications for countries with aging populations.

5. Conclusions

In conclusion, the findings of this study suggest that prevention of tooth loss and dental prosthesis treatment are associated with a reduced risk of mortality and functional disability, as well as the maintenance of intellectual ability, frequency of going out, and improved dietary lifestyle, thereby promoting a healthier later life.

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Author contributions

SK contributed to the conception and design of the study, performed all statistical analyses, interpreted the results, and drafted the manuscript. YT, KT, AN, KS, TK, and TY contributed to the conception, design, and data interpretation and critically commented on the manuscript. JA contributed to the conception, design, and data interpretation and critically revised the manuscript. All authors provided their final approval and agreed to be accountable for all aspects of this study.

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Conflict of interest statement

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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