

Revised: 7 April 2021 Accepted: 8 April 2021

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ORIGINAL ARTICLE

Journal of General and Family Medicine

WILEY

Oral health-related quality of life is associated with physical frailty: A cross-sectional study of Japanese community-dwelling older adults

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Funding information

Japan Society for the Promotion of Science, Grant/Award Number: 17H03740, 25291107 and 19K07915

Abstract

Background: Physical frailty is related to adverse outcomes, and poor oral health has been linked to malnourishment. Subjective measures of oral health-related quality of life (OHRQoL) have been used as indicators of the oral health problems of older adults, and they have been associated with malnourishment. This study aimed to assess OHRQoL's association with physical frailty.

Methods: Cross-sectional study was conducted using data from the Nagasaki Islands Study that enrolled participants aged ≥60 years at Japanese national medical checkups from 2014 to 2019. Physical frailty phenotype criteria were determined using the modified Fried frailty phenotype model. OHRQoL was assessed using the Geriatric Oral Health Assessment Index (GOHAI). Dentists conducted clinical dental examinations. Simple correlation and linear regression analyses were performed to investigate the associations of number of physical frailty phenotype criteria with GOHAI and other oral health indicators.

Results: Among 1341 participants with a mean age of 72 years, GOHAI score was significantly associated with number of physical frailty phenotype criteria (B = -0.01, 95% confidence interval: -0.02 to -0.01, p < 0.001). The association remained significant after adjustment for age, sex, body mass index, history of hypertension, history of diabetes mellitus, smoking status, Kessler-6 score, and number of remaining teeth. **Conclusions:** Oral health-related quality of life was associated with physical frailty in Japanese community-dwelling older adults.

KEYWORDS

epidemiology, functional tooth unit, frailty, oral health-related quality of life

Yuya Motoishi and Hirotomo Yamanashi contributed equally to this work.

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1 | INTRODUCTION

Frailty is a decline in functioning across multiple physiological systems accompanied by an increased vulnerability to adverse health outcomes and elevated healthcare costs. Frailty is gaining international attention as the older adult population rises globally.¹ One of the two major frailty assessment instruments is the frailty phenotype described by Fried et al,² which consists of five criteria: weakness, slow gait speed, low physical activity, exhaustion, and unintentional weight loss. Risk factors for onset or progression of frailty span a wide range of aspects and conditions, covering sociodemographic (e.g., advanced age, low education, loneliness, living alone), clinical (e.g., obesity, malnutrition, polypharmacy), lifestyle-related (e.g., physical inactivity, low protein intake, smoking), and biological domains (e.g., inflammation, micronutrient deficits).¹ Malnutrition and low protein intake are two of the various risk factors that contribute to the onset or progression of frailty.¹ Poor oral health has been linked to a higher frequency of habitual inadequate food intake, leading to malnourishment.³

Previous studies have shown subjective oral health to be associated with physical frailty.^{4,5} However, no previous studies have investigated the association between oral health-related quality of life (OHRQoL) and physical frailty. The Geriatric Oral Health Assessment Index (GOHAI), an indicator of OHRQoL, was designed to assess the oral health problems of older adults.^{6,7} The GOHAI covers three domains: the functional domain; the psychosocial domain; and the pain or discomfort domain. A crosssectional study of Lebanese older adults found that participants suffering from malnutrition, as defined by the Mini-Nutritional Assessment Index, had more biting and chewing problems than did those without malnutrition and that GOHAI scores were inversely associated with malnourishment.⁸

We hypothesized that frailty is associated with subjective measures of OHRQoL because frail older adults might suffer from several oral symptoms contributing to malnourishment. This study aimed to assess whether OHRQoL is associated with physical frailty among community-dwelling older adults living on remote islands in Japan and to explore the associations between specific domains of OHRQoL and physical frailty.

2 | METHODS

2.1 | Study settings and participants

Cross-sectional study using data from the Nagasaki Islands Study, a prospective cohort study performed in Goto City in the western islands of Japan, was conducted.⁹ Details of the selection process and procedures of examination used in this study have been published elsewhere.⁹ The participants were recruited at medical check-ups, and members of the general population aged ≥40 years living in Goto City were targeted for enrollment. The Ethical Committee of Nagasaki University approved this study (Project Registration Number: 14051404, 20141002-5; Nagasaki, Japan), which was conducted according to the ethical standards defined in the 1964 Declaration of Helsinki and in its subsequent amendments. Written informed consent was obtained from all participants. Of 4958 participants enrolled from 2014 to 2019, 1341 were included after excluding participants who declined to undergo an oral health check-up (n = 3041), were aged <60 years (n = 456), had history of stroke (n = 75), or had missing data on GOHAI score (n = 30), handgrip strength (n = 2), medical history (n = 5), smoking status (n = 4), or depression scale score (n = 4). All eligible participants provided written informed consent at each study site.

2.2 | Data collection and laboratory measurements

Body weight and height were measured with participants wearing light-weight clothing and without shoes, and body mass index (BMI) was then calculated. Handgrip strength was recorded with the participant in a standing posture with an arm extended in a natural position. The handgrip dynamometer (Matsumiya Ika Seiki Seisakujo Smedley Dynamometer 0-1019-01) was adjusted for each participant so that their second proximal phalanxes were positioned around the handle. Handgrip strength was measured twice for each hand, and the maximum score of all recorded values for both sides was used in the analysis.

The researchers and trained nurses obtained information on medical history of stroke, hypertension, and diabetes mellitus; smoking status; and drinking status and administered the Kessler-6 scale.¹⁰ Smoking and drinking status were categorized as current, former, or never.

2.3 | Clinical dental examination and functional tooth units

Clinical dental examinations to assess tooth status were performed by trained and calibrated dentists. The participants were asked to lie on a bed in the supine position, and the examinations were carried out under illumination using a dental mirror and a periodontal probe.

The dentists examined carious status and noted types of prosthetic restoration. The remaining teeth were counted. Functional tooth units (FTUs) were defined as pairs of opposing natural teeth (i.e., sound, filled, and decayed teeth) and artificial teeth on implant-supported, fixed (bridge pontics), or removable prostheses.¹¹ Untreated carious teeth with extensive coronal destruction and missing teeth were regarded as nonfunctional. For the determination of FTUs, only posterior teeth were counted. Two opposing premolars were defined as one FTU, and two opposing molars were defined as two FTUs. Thus, a person with complete dentition had 12 FTUs (excluding third molars/wisdom teeth). The number of FTUs was further divided by tooth composition into natural teeth FTUs (n-FTUs) and the total number of FTUs (t-FTUs).

2.4 | General Oral Health Assessment Index

The GOHAI, which was developed to assess OHRQoL,^{6,7} comprises 12 items grouped into three domains: (a) the functional domain (eating, speaking, swallowing); (b) the psychosocial domain (concerns, relational discomfort, appearance); and (c) the pain or discomfort domain (drugs, gingival sensitivity, discomfort when chewing certain foods). The score of each item ranged from 1 to 5, and the cumulative score on the 12 questions is the overall GOHAI score (range: 12-60).

2.5 | Physical frailty phenotype

We defined frailty using the modified Fried physical frailty phenotype model.² Table 1 shows the five frailty phenotype criteria: weakness, slow gait speed, low physical activity, exhaustion, and unintentional weight loss.⁹

2.6 | Statistical analysis

We treated age, height, weight, BMI, handgrip strength, number of teeth, n-FTUs, t-FTUs, GOHAI score, Kessler-6 score, and number of physical frailty phenotype criteria as continuous variables. Sex, smoking status, drinking status, hypertension, and diabetes mellitus were treated as categorical variables. We performed a simple correlation analysis of the associations of handgrip strength and frailty score with the other variables. Multivariable linear regression analysis was used to examine the associations of handgrip strength and the number of physical frailty phenotype criteria with GOHAI score. Potential confounders for handgrip strength and physical frailty were age, sex, medical history of hypertension (yes, no), depressive mood as assessed by the Kessler-6 score, and smoking (current, former, never).^{1,5} The number of remaining teeth was also treated as a confounding factor because previous studies showed that the

TABLE 1 Physical frailty phenotype

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number of remaining teeth was associated with GOHAI score and physical frailty.^{13,14} We also used multivariable linear regression analysis to examine the associations of handgrip strength and the number of physical frailty phenotype criteria with the numbers of remaining teeth and FTUs. To assess the associations for each domain of OHRQoL, we used multivariable linear regression analyses to examine the associations of handgrip strength and the number of physical frailty phenotype criteria with each GOHAI domain score.

We additionally analyzed the receiver operating characteristic (ROC) curve, sensitivity, specificity, positive likelihood ratio (LR), and negative LR. In the ROC curve analysis including relevant values to predict frailty (excluding pre-frail subjects) using GOHAI score, nonfrail subjects were treated as the reference group. All *p* Values for statistical tests were two-tailed, and *p* < 0.05 was considered significant. All statistical analyses were performed using Stata 14 (StataCorp).

3 | RESULTS

3.1 | General characteristics of the study population

Table 2 shows the participants' characteristics. There were 1341 participants, with a mean age of 72 years (standard deviation [SD] \pm 7.2). A total of 876 (65.3%) participants were classified as nonfrail, 442 (33.0%) were classified as pre-frail, and 23 (1.7%) were classified as frail. We found 287 (21.4%) participants to have low handgrip strength. The examinations found means (SD) of 18.5 (9.2) remaining teeth, 4.6 (4.3) n-FTUs, and 9.5 (3.4) t-FTUs. The mean (SD) GOHAI score was 55.3 (5.6).

Table 3 shows the results of the simple correlation analysis of the associations of handgrip strength and the number of physical frailty phenotype criteria with the other variables.

Male sex, height, body weight, BMI, number of remaining teeth, n-FTUs, and GOHAI score were positively correlated with handgrip

| TABLE I Thysical naity pictotype | | | | |
|----------------------------------|--|--|--|--|
| (1) Weakness | Defined as the maximum handgrip strength in a total of four trials for both hands of <28 kg in men and <18 kg in women, based on an Asian population reference. ¹² | | | |
| (2) Slow gait speed | Determined using a questionnaire with the following items: "Can you walk as fast as others of the same age?" and "Can you walk continuously for 1 km or more?" Answers were scored as 1 = yes or 2 = no. Participants who answered no to both questions were categorized as frail using the slow gait speed criterion. | | | |
| (3) Low physical activity | Determined using the following question: "How often do you go out for daily activities, such as walking, shopping, and working?" Answers were scored as 1 = more than 2 days a week or 2 = less than once a week. Participants who answered 2 to this question were categorized as frail using the low physical activity criterion. | | | |
| (4) Exhaustion | Determined using the Kessler-6 screening scale instead of the original version of the Center for Epidemiologic Studies Depression Scale. The following two statements were read as follows: "During the past 30 days, how often did you feel so depressed that nothing could cheer you up?" and "During the past 30 days, how often did you feel that everything was an effort?" Answers were scored as 1 = <i>all of the time</i> , 2 = <i>most of the time</i> , 3 = <i>some of the time</i> , 4 = <i>a little of the</i> <i>time</i> , or 5 = <i>none of the time</i> . Participants who answered <i>all of the time</i> or <i>most of the time</i> to either of these questions were categorized as frail using the exhaustion criterion. | | | |
| (5) Unintentional weight loss | Defined as unwanted weight loss of \ge 3 kg within 6 months, based on an interview. | | | |

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strength. Age, Kessler-6 score, smoking status, and drinking status were inversely correlated with handgrip strength. For the number of physical frailty phenotype criteria, positive correlations were observed with age, Kessler-6 score, history of hypertension, history of diabetes mellitus, smoking status, and drinking status, and inverse correlations were observed with male sex, height, body weight, number of remaining teeth, n-FTUs, and GOHAI score.

3.2 | Physical frailty and GOHAI

In the simple linear regression analysis, GOHAI score was significantly associated with handgrip strength and the number of physical frailty phenotype criteria, with *B* coefficients of 0.22 (95% confidence interval [CI]: 0.13 to 0.30, p < 0.001) and -0.02 (95% CI: -0.03 to -0.02, p < 0.001), respectively (Table 4). The association between GOHAI score and the number of physical frailty phenotype criteria

| TABLE 2 C | linical characteristics o | of the study population |
|-----------|---------------------------|-------------------------|
|-----------|---------------------------|-------------------------|

| Variable | |
|---|---------------|
| Number of participants | 1341 |
| Age, years | 71.7 ± 7.2 |
| Male sex | 524 (39.1) |
| Height, cm | 155.3 ± 8.5 |
| Body weight, kg | 55.8 ± 10.6 |
| Body mass index, kg/m ² | 23.0 ± 3.3 |
| Handgrip strength, kg | 26.5 ± 9.1 |
| Number of remaining teeth | 18.5 ± 9.2 |
| Natural functional tooth units | 4.6 ± 4.3 |
| Total functional tooth units | 9.5 ± 3.4 |
| GOHAI score | 55.3 ± 5.6 |
| Kessler-6 score | 1.49 ± 2.64 |
| Hypertension | 604 (45.0) |
| Diabetes mellitus | 111 (8.3) |
| Smoking status | |
| Current | 88 (6.6) |
| Former | 305 (22.7) |
| Never | 948 (70.7) |
| Drinking status | |
| Current | 464 (34.6) |
| Former | 89 (6.6) |
| Never | 788 (58.8) |
| Number of physical frailty phenotype criteria | 0.5 ± 0.7 |
| Weakness | 287 (21.4) |
| Slow gait speed | 192 (14.3) |
| Low physical activity | 27 (2.0) |
| Exhaustion | 21 (1.6) |
| Unintentional weight loss | 95 (7.1) |

Note: Data are presented as mean ± standard deviation or n (%). Abbreviation: GOHAI, Geriatric Oral Health Assessment Index. TABLE 3 Simple correlation analysis of handgrip strength and the number of physical frailty phenotype criteria with other variables

| | Handgrip | o strength | Number of physical frailty phenotype criteria | | |
|---------------------------------------|----------|------------|---|------------|--|
| | r | p Value | r | p Value | |
| Age, years | -0.36 | <0.001 | 0.39 | <0.001 | |
| Male sex | 0.74 | <0.001 | -0.07 | 0.013 | |
| Height, cm | 0.74 | <0.001 | -0.25 | <0.001 | |
| Body weight, kg | 0.56 | <0.001 | -0.15 | <0.001 | |
| Body mass index, kg/m ² | 0.18 | <0.001 | -0.01 | 0.577 | |
| Number of remaining teeth | 0.22 | <0.001 | -0.23 | <0.001 | |
| Natural functional tooth units | 0.19 | <0.001 | -0.18 | <0.001 | |
| Total functional tooth units | -0.03 | 0.234 | -0.01 | 0.787 | |
| GOHAI score | 0.13 | <0.001 | -0.17 | <0.001 | |
| Kessler-6 score | -0.12 | <0.001 | 0.23 | <0.001 | |
| Hypertension | -0.03 | 0.228 | 0.15 | <0.001 | |
| Diabetes mellitus | -0.01 | 0.760 | 0.08 | 0.002 | |
| Smoking status | -0.49 | <0.001 | 0.06 | 0.020 | |
| Drinking status | -0.46 | <0.001 | 0.12 | <0.001 | |

Abbreviation: GOHAI, Geriatric Oral Health Assessment Index.

remained significant after adjustment for age, sex, BMI, history of hypertension, history of diabetes mellitus, smoking status, Kessler-6 score, and number of remaining teeth (B = -0.01, 95% CI: -0.02 to -0.01, p < 0.001) although the association between GOHAI score and handgrip strength was not significant after adjustment.

The linear regression analysis of the association between physical frailty and GOHAI score was further assessed for each GOHAI domain (Table S1). Handgrip strength was positively associated with the functional domain of the GOHAI after adjustment for confounding factors, but this variable was not associated with the psychosocial or pain/discomfort domains of the GOHAI. The number of physical frailty phenotype criteria was inversely associated with the functional and psychosocial domains of the GOHAI after adjustment for confounding factors, but this variable was not associated with the pain/discomfort domain of the GOHAI.

3.3 Physical frailty and functional tooth units

Table 5 shows the linear regression analyses of the associations of handgrip strength and the number of physical frailty phenotype criteria with the number of remaining teeth, n-FTUs, and t-FTUs. The *B* coefficient of handgrip strength was positively significant for the number of remaining teeth (B = 0.22, 95% CI: 0.17 to 0.27,

p < 0.001) and n-FTUs (B = 0.41, 95% CI: 0.30 to 0.53, p < 0.001). Both of these coefficients remained significant after adjustment for age, sex, BMI, history of hypertension, history of diabetes mellitus, smoking status, and Kessler-6 score. The *B* coefficient of the number of physical frailty phenotype criteria was inversely significant for the number of remaining teeth (B = -0.02, 95% CI: -0.02 to -0.01, p < 0.001) and n-FTUs (B = -0.03, 95% CI: -0.04to -0.02, p < 0.001). After adjustment for confounding factors, the coefficient of the number of physical frailty phenotype criteria remained significant for the number of remaining teeth but not for n-FTUs. No significant associations were found between t-FTUs and handgrip strength or the number of physical frailty phenotype criteria.

TABLE 4Multivariable linear regression analysis of theassociations of handgrip strength and the number of physical frailtyphenotype criteria with GOHAI score

| | GOHAI score | | | | | |
|---|---------------|----------------------------|------------|--|--|--|
| | B coefficient | 95% confidence interval | p Value | | | |
| Handgrip strength | | | | | | |
| Crude | 0.22 | (0.13, 0.30) | <0.001 | | | |
| Model 1 | 0.07 | (0.02, 0.12) | 0.005 | | | |
| Model 2 | 0.04 | (-0.01, 0.09) | 0.115 | | | |
| Number of physical frailty phenotype criteria | | | | | | |
| Crude | -0.02 | (-0.03, -0.02) | <0.001 | | | |
| Model 1 | -0.02 | (-0.03, -0.01) | <0.001 | | | |
| Model 2 | -0.01 | (-0.02, -0.01) | <0.001 | | | |

Note: Model 1 adjusted for age, sex, and body mass index. Model 2 adjusted for the variables in model 1 and history of hypertension, history of diabetes mellitus, smoking status, Kessler-6 score, and number of remaining teeth.

Abbreviation: GOHAI, Geriatric Oral Health Assessment Index.

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3.4 | Receiver operating characteristic curve

We tested whether we could predict frailty using a simple GOHAI cutoff score (Table S2). For predicting frailty, the GOHAI score cutoff point of \leq 52 had a sensitivity of 65.2%, a specificity of 81.7%, a positive LR of 3.6, and a negative LR of 0.4. The area under the ROC curve for predicting frailty using GOHAI score was as high as 0.734 (95% CI: 0.617 to 0.851) (Figure S1).

4 | DISCUSSION

We found handgrip strength and physical frailty to be associated with OHRQoL, as defined by the subjective items of the GOHAI. In the additional analyses of the GOHAI domains, only the functional domain of the GOHAI was associated with both handgrip strength and physical frailty. To the best of our knowledge, this is the first study to report the association between subjective OHRQoL and physical frailty. We also found that handgrip strength was associated with the numbers of remaining teeth and n-FTUs but not with the number of t-FTUs. Physical frailty was also associated with the number of remaining teeth, but physical frailty was not statistically significantly associated with the number of n-FTUs. Because the functional domain of the GOHAI includes the functions of eating, speaking, and swallowing, oral functional decline caused by reduced masticatory ability may be a background mechanism of the association between subjective OHRQoL and physical frailty.

Although previous studies have reported associations between simple subjective oral health questions and physical frailty, our study demonstrated more precisely how OHRQoL items were associated with physical frailty. In a previous prospective cohort study of 1622 older British men, physical frailty was associated with "self-rated oral health" (good or excellent vs. fair or poor), with an adjusted odds ratio (OR) of 1.56 (95% Cl: 1.18 to 2.07) after adjustment for age, social

| | Number of remaining teeth | | | Natural functional tooth units | | | Total functional tooth units | | |
|---|---------------------------|-------------------------------|---------|--------------------------------|-------------------------------|---------|------------------------------|-------------------------------|------------|
| | B coefficient | 95% confidence interval | p Value | B coefficient | 95% confidence interval | p Value | B coefficient | 95% confidence interval | p Value |
| Handgrip stre | Handgrip strength | | | | | | | | |
| Crude | 0.22 | (0.17, 0.27) | <0.001 | 0.41 | (0.30, 0.53) | <0.001 | -0.09 | (-0.23, 0.06) | 0.234 |
| Model 1 | 0.05 | (0.02, 0.09) | 0.002 | 0.09 | (0.02, 0.16) | 0.008 | 0.09 | (0.00, 0.17) | 0.039 |
| Model 2 | 0.05 | (0.02, 0.08) | 0.003 | 0.09 | (0.02, 0.16) | 0.014 | 0.08 | (-0.01, 0.16) | 0.074 |
| Number of physical frailty phenotype criteria | | | | | | | | | |
| Crude | -0.02 | (-0.02, -0.01) | <0.001 | -0.03 | (-0.04, -0.02) | <0.001 | 0.00 | (-0.01, 0.01) | 0.787 |
| Model 1 | -0.01 | (-0.01, -0.00) | 0.005 | -0.01 | (-0.02, 0.00) | 0.074 | -0.01 | (-0.02, 0.00) | 0.147 |
| Model 2 | -0.01 | (-0.01, -0.00) | 0.003 | -0.01 | (-0.02, 0.00) | 0.094 | -0.01 | (-0.02, 0.00) | 0.299 |

TABLE 5 Multivariable linear regression analysis of the associations of handgrip strength and the number of physical frailty phenotype criteria with functional tooth units

Note: Model 1 adjusted for age, sex, and body mass index. Model 2 adjusted for the variables in model 1 and history of hypertension, history of diabetes mellitus, smoking status, and Kessler-6 score.

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class, smoking status, history of diabetes or cardiovascular disease, and use of medication for dry mouth at baseline.⁴ The association was marginally significant at 3-year follow-up, when the adjusted OR was 1.55 (95% CI: 0.99 to 2.41).⁴ A prospective cohort study of 1151 older Japanese adults over 2 years found that, of three subjective measures of oral health, "difficulties eating tough foods" (yes, no) and "experience having a dry mouth" (yes, no) were associated with new-onset physical frailty after adjustment for age, sex, BMI, chronic conditions, depressive symptoms, cognitive function, living arrangements, annual income, and smoking status. "Difficulties in swallowing tea or soup" (yes, no) was not associated with new-onset physical frailty.⁵ The results of our study were compatible with these findings.

A possible explanation for the association between frailty and OHRQoL should be considered. Fried presented a "vicious cycle" of physical frailty: Decreases in strength, power, resting metabolic rate, and VO₂ max because of aging lead to low activity and low energy expenditure. These changes, in turn, contribute to the development of chronic undernutrition and more severe physical frailty.² In this model, chronic malnutrition has a major effect on the development of frailty. In a previous prospective Japanese cohort study (n = 3134), low masticatory ability, as measured by maximum occlusal force, was correlated with low serum albumin level.¹⁵ Furthermore, a study of 2108 Japanese communitydwelling older women found that poor dietary protein intake was associated with frailty.¹⁶ This evidence from previous work suggests that impaired oral function contributes to decreased eating and swallowing function, which leads to malnourishment and physical frailty. In our study, n-FTUs and the number of remaining teeth, indicators of oral function, were associated with the number of physical frailty phenotype criteria. Impaired oral function has previously been reported to be associated with a lower level of OHRQoL.¹⁷ Therefore, impaired oral function also negatively affects self-rated oral health. Consequently, impaired oral function may be a common pathway to frailty and low OHRQoL.

Another explanation is that low psychosocial domain of OHRQoL may lead to a poor social contact, which are the risks for the physical frailty. We found the psychosocial domain of the GOHAI score was associated with the number of physical frailty phenotype criteria after adjustment for confounding factors including the remaining teeth, which is an indicator of masticatory ability. The psychosocial domain of the GOHAI includes the limitation of contacts with people or eating in front of people. Those with low score of these questions may have a poor social contact and have high risk for physical frailty.¹⁸

We found that the area under the ROC curve for predicting frailty using GOHAI score was as high as 0.734. This finding suggests that subjective screening tests using the GOHAI can be used as a rational pre-screening tool for frailty because the GOHAI is noninvasive and easily assessed in clinical and community settings. Thus, early intervention by physiotherapists, speech therapists, and dentists may be beneficial to prevent physical frailty among high-risk older adults.

4.1 | Limitations of the study

Some limitations of the present study should be mentioned. First, the definition of physical frailty of current study was not the same as the original Fried frailty phenotype model or the revised Japanese version of the Cardiovascular Health Study criteria.^{2,12} Second, because this was a cross-sectional study, we were not able to establish cause–effect relationships. Third, although healthy community dwellers were recruited as study participants, it is possible that some participants had unknown organic diseases, which may have biased the results. However, we excluded participants with stroke because this is a potential confounding factor.

5 | CONCLUSION

Oral health-related quality of life was found to be associated with physical frailty in Japanese community-dwelling older adults. Subjective OHRQoL might be helpful as a simple pre-screening tool to identify frailty in this population. Further research using longitudinal data should be carried out to explore the causal inference of the association between OHRQoL and frailty, potentially contributing to a preventive strategy for frailty.

ACKNOWLEDGMENTS

The authors would like to thank the members of the Department of Health and Social Welfare National Health Insurance Health Policy Planning and Evaluation Division in Goto City who helped with the community health check-up examinations, as well as those who participated in this study. We are also grateful to all members of the Nagasaki Islands Study team for conducting this study. We also thank Jennifer Barrett, PhD, from Edanz Group (https://en-author-servi ces.edanzgroup.com/ac) for editing a draft of this manuscript. This work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (Grant Numbers: 17H03740, 25291107, and 19K07915).

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Motoishi Y, Yamanashi H, Kitamura M, et al. Oral health-related quality of life is associated with physical frailty: A cross-sectional study of Japanese community-dwelling older adults. *J Gen Fam Med*. 2021;00:1–7. https://doi.org/10.1002/jgf2.450