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Title page

Association between number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

Running Title: number of teeth and frailty among older Chinese

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Abstract

Objectives To explore the association between number of teeth and frailty among Chinese older adults using a nationally representative sample.

Design Cross-sectional analysis was carried out using the 2014 wave data from Chinese Longitudinal Health Longevity Survey which employed a targeted random-sampling design.

Setting Communities from nearly half of the counties and cities in 22 out of 31 provinces throughout China.

Participants Of the 6934 interviewees aged > 65 years in 2014 wave data, the finally analysis include 3829 older adults who have complete data on the variables included in the study.

Primary and secondary outcome measures Outcome variables included frailty measured by Frailty Index and number of teeth. Covariates included demographic characteristics (i.e. age, gender, co-residence, marital status, years of education, financial support, and income of household) and health behaviors (i.e. smoking, drinking, and exercise). Univariate analyses were employed to test the relationship between frailty and oral health conditions and other covariates. A multiple linear regression model was used, employing frailty score as the dependent variable and number of teeth together with significant covariates as independent variables.

Results The mean age of the participant was 83.76 (SD = 9.80). Their mean frailty score was 8.33 (SD = 5.69), mean number of teeth at present was 9.58 (SD = 10.10). Older adults' age, gender, tooth number, co-residence, marital status, financial support, smoking, alcohol consumption, and exercise significantly predicted frailty score (R^2= 0.29, p=0.00). After adjusting for the sociodemographic factor and health behaviors, more teeth were significantly associated with lower frailty score (B=-0.05, p=0.00).

Conclusions The number of teeth is significantly associated with frailty score among Chinese older adults. Older adults with more teeth showed a lower frailty score. Future studies may be needed to elucidate the specific mechanisms underlying which oral health is related to frailty.

Key words Frailty; older adults; number of teeth; China; oral health

Article summary:

- This is the first study on frailty and oral health conducted in China.
- This study used a large nationally representative sample.
- This study measured frailty using the Frailty Index which included chronic conditions, daily activities, and cognitive function, etc.
- The covariates of this study included the measurement of sociodemographic factors and health behaviors, which enabled the assessment of several confounding factors.
- This is a cross-sectional study which cannot indicate casual relationships between frailty and oral health

Association between number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

Introduction

Because of the decline in fertility and the increase in longevity, the number of people aged 60 years or older is growing faster than all the younger age groups, and this number is expected to double by 2050. [1] Diseases within the elderly population are estimated to become the next global public health challenge, having profound effects on health systems, workforce, and budgets. [2]

Frailty is one of the most problematic expressions of population aging, [3] with a prevalence of 10%-27% for those older than 65 years and 45% for those older than 85 years. [4] Frailty is a clinical condition defined as a reduced ability to cope with acute or external stressors in everyday life due to aging-associated decline in reserve and function. [5] It is associated with a higher risk of falls, hospitalization, nursing home residence, disability, and death [6], putting a significant burden on the person, the family, and public health systems.

Frailty is believed to develop due to the reduced physiological reserve caused by the cumulative molecular and cellular damage during aging, and become evident when physiological decline reaches an aggregate crucial level. [3] Although the pathophysiological changes underlying and preceding frailty are incompletely understood, multiple causes, inter-relationships, and complex pathways have been proposed according to current research findings. [7] There is evidence that frailty may be modifiable and it is considered to have greater reversibility than disability. [8]

Therefore, it is important to develop interventions targeting risk factors to maintain older adults' quality of life and delay or prevent the development of frailty and its subsequent need for long-term care. [9] So far, the proposed risk factors of frailty include physiological changes with aging, inflammation, sarcopenia, polypharmacy, social isolation, and malnutrition. [10] Notably, emerging research showed that frailty was significantly associated with oral health and functions, including tooth number, [11,12,13] functional dentition, [14] chewing ability, [15,16] periodontitis, [13] utilization of dental services

[12,17,18,] and self-perception of oral health. [15,17] More teeth were significantly associated with lower risk of developing frailty [12,13,14,18] because tooth loss might be caused by severe periodontal disease which can trigger higher levels of inflammatory markers and contribute to the development of frailty. [15] In addition, another line of evidence proposed that tooth loss can change one's food selection and nutrients intake, resulting in malnutrition and contributing to the development of frailty.

However, the current evidence is controversial and some studies did not find a significant association between number of teeth and frailty. [9, 11, 16, 17] The conflicting results might be caused by the involved confounders of the subjects and the population from which they are drawn. At present, the association between tooth number and frailty is poorly understood in developing countries, especially in China which has the largest population and the most rapid aging speed in the world. This study is the first study that verifies the relationships between tooth number and frailty among the Chinese population using a large nationally representative sample.

Methods

Study design and population

We used data from the Chinese Longitudinal Health Longevity Survey (CLHLS), the first national longitudinal project to investigate the determinants of health and longevity of older adults in China from a multidisciplinary perspective. [19] The survey has been conducted every three years in seven waves, from 1998 to 2014, in a randomly selected older adults from nearly half of the counties and cities in 22 out of 31 provinces throughout China. These data represent about 85% of Chinese total population. A targeted random-sampling design was employed to ensure representativeness. Internationally compatible questionnaires were used to collect a comprehensive set of information, including demographic characteristics, family and household characteristics, lifestyle and diet, economic resources, social support, myriad physical, psychological and cognitive health conditions, etc. All information was obtained during in-home face-to-face interviews. The data from the CLHLS are of high quality according to its representativeness and randomness of attrition. [20] The details of the sampling

design, response rates, and systematic assessments of data quality across numerous measures were described elsewhere. [21] The present study utilized cross-sectional data from the 2014 wave of the CLHLS.

Patient involvement

Participants or public were not involved in the development of the study design or outcome measures. Participation was voluntary and could be terminated at any time. Results will not be distributed to the participants themselves. All data were used strictly confidentially and anonymously.

Outcome variables

Various measurements exist for assessing frailty, with Frailty Index (FI) and frailty phenotype being the most common applications. [22] The FI was defined as the proportion of accumulated deficits, [23] and calculated by the proportion of the number of health deficits presented to the total number of possible health deficits for a given person. [19] For samples of CLHLS, FI has been found to be a valid and reliable frailty measure and an independent and robust predictor of adverse outcomes among the Chinese elderly. [24, 25]

Following the established research, [17,19,24, 25] we used 38 indicators of health deficits encompassing nine major sets of components: cognitive functioning (a score of 23 or lower in the Chinese version of the Mini-Mental State Examination was considered cognitively impaired), chronic disease conditions (self-reports from a list of 11 diseases, e.g., diabetes, heart disease, stroke, arthritis), Activity of Daily Living disability (needing help in performing the six basic daily activities, e.g., eating, bathing), Instrumental Activity of Daily Living disability (needing help in performing the eight independent living activities, e.g., cooking, shopping), functional limitations (five objective examinations of physical function, e.g., hand behind lower back, standing from sitting a chair), self-rated health (self-assessed current global health and health status compared with one year ago), hearing and vision impairment, psychological distress (often/always felt fearful/anxious, lonely/isolated, or useless), and others (abnormal heart rhythm, interviewer-rated health, number of serious illnesses in the past two years).

Each item was dichotomized and coded 1 in the presence of a deficit (otherwise 0). A score of 2 was assigned for individuals with more than one serious illness in the past two years that led to admission to hospital or a period of confinement in bed. Thus, the total score of these 38 items were 39. [24] The FI was calculated as the total score of an individual divided by the maximum total score of 39. However, we used the number of deficits instead of FI to measure the level of the frailty of a given respondent in regression models for the purpose to be consistent with its components. [19]

Independent variable

Self-reported number of teeth was recorded using the following question: "How many natural teeth do you still have?" In addition, chewing pain was recorded by the question: "During the past 6 months, did you have a toothache more than once, when biting or chewing?".

Covariates

The main covariates were demographic characteristics and health behaviors. Demographic variables include age, gender, co-residence condition (with household members, alone, or in an institution), marital status (currently married and living with spouse or married but not living with spouse vs others), years of education, financial support (sufficient, insufficient), and total income of household for the last year. Health behaviors included smoking (never smoker, former smoker, current smoker), alcohol consumption (never drink, former drinker, current drinker), do exercise regularly, and do physical labor regularly.

Statistical analysis

Baseline characteristics of subjects were reported as mean and standard deviation (SD) for continuous variables and numbers and proportion for categorical variables. Univariate analyses testing oral health conditions and covariates with frailty status were carried out using t-test or analysis of variance. All statistical analyses were performed using SPSS software for Windows (SPSS Inc., Chicago, IL, version 22).

A multiple linear regression model was used, employing frailty score as the dependent variable and the dental variables (number of teeth and chewing pain) as independent variables. Demographic and behavioral covariates identified as statistically significant in the univariate analysis were also included.

Results

Of the 7019 interviewees in 2014 CHLHS, we included 6934 participants aged > 65 years initially. The final analysis include 3829 older adults who have complete data on frailty and other explanatory factors used in the analysis. The main characteristics of 3829 participants and the frail score are described in Table 1. The mean scores of frailty were 8.33 (SD = 5.69; range = 1-29). The mean number of teeth at present was 9.58 (SD = 10.10; range = 0-36). The mean age of the participant was 83.76 (SD = 9.80; range = 65-113); 51.6% were women and 45% were married. Among all subjects, 33% reported former or current smoking, 27.4% reported former or current alcohol consumption.

No significant differences were found in frailty scores based on chewing pain (p=0.21), total income of household (p=0.51), or doing physical labor regularly (p=0.09) (Table 1). The analysis also showed that the frailty scores were higher among those who were older, women, single, and living in an institution. Moreover, smoking, alcohol consumption and exercise were significantly associated with the level of frailty. Participants with higher frailty scores had fewer years of education, insufficient financial support and lower number of teeth.

Multiple linear regression model

The multiple linear regression models included gender, age, number of teeth, co-residence condition, marital status, years of education, financial support, smoking and drinking condition, exercise and physical labor.

Results from Model I showed that frailty increased with age (B = 0.25, p=0.00) (Table 2), which meant that when age increased about one year, the frailty score increased by 0.25 points. In addition, frailty score was higher among female (B= 1.54, p=0.00), which meant that female older adults had 1.54 points more frailty score than male older adults. But, regardless of age and gender, more teeth

were associated with lower frailty score (B=-0.04, p=0.00), which meant that for participants who had one more tooth than the other participants, their frailty scores decreased by 0.04 points. Model II showed that after adding sociodemographic variables, age, gender, and tooth number were still significantly associated with frailty scores. Additionally, subjects who were living in an institution (B=-2.34, p=0.00), had insufficient financial support (B=1.44, p=0.00) were more likely to have higher frailty score. Model III showed results controlling for health behaviors. Participants who were a former smoker (B=0.92, p=0.00), former drinker (B=1.37, p=0.00), and did not exercise at present (B=2.00, p=0.00) were more likely to have higher frailty scores. Participants who were a current drinker (B=-1.00, p=0.00) have significantly lower frailty score. Current smoking and years of education were not significantly associated with frailty scores. The final model explains 29% (adjusted R2= 0.29, p=0.00) of the variability in frailty scores.

Discussion

Drawing from the world's largest aging population, we use data from a nationwide longitudinal survey in China to examine the association between frailty and tooth number. The main findings suggested that tooth number was significantly related to frailty, after adjusting for age, gender, and smoking, etc. According to our results, more teeth are associated with a lower prevalence of frailty. To the best of our knowledge, this is the first study exploring the association between frailty and oral health among Chinese older adults.

When exploring the association between frailty and tooth number, previous studies measured frailty using the frailty phenotype. The frailty phenotype is based on a pre-defined set of five criteria exploring the presence/absence of signs or symptoms (i.e. involuntary weight loss, exhaustion, slow gait speed, poor handgrip strength, and sedentary behavior). [26] It is widely used in geriatric community to identify frailty older adults. However, there is a growing tendency to view frailty from a multidimensional perspective consisting of physical, psychological, social, and recently also environmental frailty. [27] Although the frailty phenotype is convenient to be applied at the first contact

with the subject, specific conditions (such as disability or cognitive impairment) may affect the reliability or clinical utility of the frailty phenotype results. Studies using frailty phenotype cannot rule out confounding factors caused by cognitive impairment, which is not only an important domain of frailty [28] but also significantly related to tooth number among older adults. [29] In particular, disabling conditions may affect the predictive value of the phenotype for negative health-related events due to a sort of 'ceiling effect'. [26] In our study, FI which describes a more global concept of frailty was used to measure frailty. FI is more acceptable due to its broader approach to the diagnosis of frailty and the inclusion of cognitive and psychosocial markers rather than solely relying on physical markers. [7] In our study, the important aspects of frailty such as cognitive impairment, physical limitations, chronic diseases, and comorbidity were well included in FI. In the previous studies, the influence of chronic diseases or comorbidity on mediating the association between frailty and oral health remains controversial. [9, 11] Therefore, in our study, by calculating frailty scores, frailty was understood in a global view and the results contribute to a broader and supplementary explanation on current understanding of the relationship between frailty and tooth number.

Our finding is in accordance with two previous cross-sectional studies performed in Brazil [12] and US [18] which showed that fewer teeth were significantly related to frailty. Also, our finding is consistent with two cohort studies performed in Japan [14] and Mexico [13] which showed that more natural teeth were significantly associated with lower risk of developing frailty. Interestingly, two cross-sectional studies performed in Japan [9] and Mexico [17] found no significant association between frailty and tooth number. In addition, a Danish cohort study [11] and a Thai cross-sectional study [16] did not find a significant association between tooth number and frailty when adjusted for all the confounders. In conclusion, current evidence supports that the relationship between frailty and tooth number exists in the older population in Brazil, US, Japan, Mexico, and China, but does not exist in Danish and Thai older population. Besides country, the current conflicting evidence might be caused by several other factors including the study design, the age of the participants, covariates, the ways of defining tooth number, and the cultural context from which the participants came from.

In China, oral diseases are very common, particularly among older adults. Participants in our study had an average tooth number of 9.58 which was much lower compared with 19.8 teeth among their counterpart in the US. [30] However, about 30% of older adults had never visited a dentist during their lifetime, and only about 7% of older adults received preventive oral services during the past year. [29] Several reasons might contribute to the high percentage of oral health problems that are untreated in older Chinese. Firstly, older adults in our study, with a mean age of 83.76 years, have witnessed huge turmoil and social transition in China (e.g., the three years' great famine, the cultural revolution). Due to the hunger, poverty, and low education level, these older adults received poor healthcare services accumulated through the majority of their lifetime, resulting in their inadequate knowledge of oral health, poor oral care behaviors and oral health status. Additionally, the Chinese public healthcare policy does not value oral health as a priority. Over 85% of the total expenses for oral health care is covered by patients' out-of-pocket payments. About 83% of older people must pay for the whole cost of dental care by themselves, and 26.3% of older people are not able to afford dental treatment. [29] Therefore, oral health services are not being utilized efficiently, although the numbers of dentists and oral health institutions have increased in recent years. Altogether, these factors contribute to the poor oral health conditions which are reflected mainly in the tooth number, likely strengthening the association of tooth loss with frailty. To explore the association between tooth number and frailty among Chinese older population is of great importance due to its large population, fast aging speed, and inadequate healthcare resources. Understanding the effect of oral health on frailty could give an accurate insight into design of interventions to prevent or delay frailty among Chinese older adults.

Before designing an effective intervention to prevent or delay frailty by maintaining oral health, a few core questions should be fully understood. First, there is a lack of an optimal set of indicators for global oral health in older adults. Tooth loss can only represent a part of the overall oral condition because there are other determinants of oral function for individuals with tooth loss. Denture use which can restore some oral function was taken into consideration in some of the current studies, while was not in the others. Moreover, some studies used tooth number as a continuous variable while others ranked it

into several degrees. Current studies used various indicators, which might attenuate the comparability. Future study should establish a valid and reliable measurement of global oral health to classify those who are properly rehabilitated (using functional denture), those have no periodontal problems, and those with complex oral conditions which could increase the risk of developing other chronic conditions and favoring energy imbalance. [16] On the other hand, the established indicators of global oral health should be sensitive to the changes in oral condition to verify the effectiveness of relevant interventions. Secondly, the underlying mechanisms of the association between tooth number and frailty remain unknown. It was proposed that tooth loss could contribute to frailty through malnutrition, inflammation, and psychosocial mechanisms. [13] Current findings support that severe periodontitis is associated with the incidence of frailty. Tooth loss as a final consequence of periodontitis could contribute to frailty through inflammation. Inflammatory factors derived from the body's response to periodontal infection, may disseminate to other organs and alter their metabolism. [17, 29] However, the evidence regarding inflammation and frailty in human beings is still conflicting. [31] On the other hand, some studies proposed that tooth loss could lead to frailty through malnutrition. Tooth loss could reduce one's chewing ability and alter food selection, thus consuming inadequate nutrients for life and physiological function, and finally contributing to the development of frailty. [32] However, this hypothesis is opposite to the findings in animal models where dietary restriction could significantly extend lifespan. [33] Moreover, recently there is another line of evidence suggesting that diet could contribute to frailty through inflammation because diet itself is a key source of inflammation. [31] Therefore, to design specific strategies to prevent frailty, future study should elaborate on exploring the exact mechanisms of how tooth number is related to frailty. For instance, by including inflammatory biomarkers and behavioral variables, such as daily choice of food or diet, future studies could depict a brighter picture of the mechanism underlying oral health and frailty with the goal of identifying etiologic factors that are subject to public health interventions.

Strengths and limitations

This study has some strengths. Firstly, this analysis was performed based on a large nationally representative sample of older Chinese, enhancing the generalizability of the results. Secondly, the multidisciplinary approach of the CHLHS and the large range of data collected allowed us to calculate frailty scores and adjust the analyses for demographics and health behaviors to be related to the outcome. Finally, the present study measured frailty by calculating the frailty score which assesses comprehensive health conditions and is reliable in large sample study. However, our data must be interpreted with caution. The self-reported tooth number might be subjective, although it has been widely used as a measure of oral health in epidemiological surveys. [18-14] Another weakness is the cross-sectional nature of this study. Future studies, preferably longitudinal studies, are needed to confirm the results and understand the causal relationship between oral health and frailty. [15]

In conclusion, the results of our study confirmed an association between frailty and tooth number among older Chinese, independent of socioeconomic and health behaviors, highlighting the importance of tooth maintenance among older adults. [12] The finding of the present study along with that reported in earlier research suggests that improving oral health could potentially have a preventive impact on frailty.

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Disclosure statement

The authors declare no conflict of interest.

Author contributions

Yaohua Gu and Wenwen Wu are the co-first authors of this manuscript, they conceived the study, drafted the manuscript, and devoted equally to the study; Zhijie Zou performed the data analysis; Xiaoli Chen, Qing Zhang, Xianwu Luo, and Xianbo Pei revised the manuscript.

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Tables

Table 1 Characteristics and frailty score of older Chinese (N=3829)

Variable		Frailty score	*P*
Age			0.00
Mean (SD)	83.76 ± 9.80	8.33 ± 5.69	
Gender			0.00
Male	1855 (48.4%)	7.08 ± 5.21	
Female	1974 (51.6%)	9.50 ± 5.88	
Number of teeth			0.00
Mean (SD)	9.58 ± 10.10	8.33 ± 5.69	
Chewing pain			0.21
Yes	542 (14.2%)	8.07 ± 5.02	
No	3287 (85.8%)	8.37 ± 5.80	
Co-residence			0.00
With household members	3041 (79.4%)	8.38 ± 5.86	
Alone	722 (18.9%)	7.84 ± 4.87	
In an institution	66 (1.7%)	11.39 ± 5.45	
Marital status			0.00
Married	1724 (45%)	6.55 ± 4.90	
Single	2105 (55%)	9.79 ± 5.88	
Education years	2.55 ± 3.54	8.33 ± 5.69	0.00
Financial support			0.00
Sufficient	3205(83.7%)	8.08 ± 5.61	
Insufficient	624 (16.3%)	9.59 ± 5.95	
Total income of your household last year	31873.11 ± 30371.25	8.33 ± 5.69	0.51
Smoking			0.00
No smoker=0	2565 (67%)	8.77 ± 5.81	
Former smoker=1	539 (14.1%)	8.58 ± 5.83	
Current smoker=2	725 (18.9%)	6.57 ± 4.78	
Alcohol consumption			0.00
Never drink	2781 (72.6%)	8.70 ± 5.77	
Former drinker	395 (10.3%)	9.29 ± 5.86	
Current drinker	653 (17.1%)	6.20 ± 4.66	
Exercise or not at present			0.00
Yes	1221 (31.9%)	6.19 ± 4.04	
No	2608 (68.1%)	9.33 ± 6.07	
Do physical labor regularly			0.09
Yes	3157 (82.4%)	8.26 ± 5.65	
No	672 (17.6%)	8.67 ± 5.86	

Table 2 Multivariate linear regression analysis for factors associated with frailty among older Chinese

		Model 1			Model 2			Model 3		
Variable		B	SE	ß	B	SE	ß	B	SE	ß
Constant		-13.26	0.79		-11.75	0.85		-12.54	0.85	
Age		0.25	0.01	0.44***	0.23	0.01	0.40***	0.22	0.01	0.39***
Gender (reference: male)		1.54	0.16	0.14***	1.27	0.18	0.11***	1.29	0.20	0.11***
Tooth number		-0.04	0.01	-0.07***	-0.04	0.01	-0.07***	-0.03	0.01	-0.05***
Co-residence (reference: with household members)	Living alone				-1.30	0.22	-0.09***	-1.15	0.21	-0.08***
	In an institution				2.34	0.61	0.05***	2.20	0.59	0.05***
Marital status (reference: married)					0.70	0.20	0.06**	0.66	0.20	-0.06**
Years of education					-0.06	0.03	-0.04*	-0.01	0.03	-0.01
Financial support (reference: sufficient)					1.44	0.21	0.09***	1.17	0.21	0.08***
Smoking (reference: never smoker)	Former smoker							0.92	0.25	0.06***
	Current smoker							-0.27	0.23	-0.02
Alcohol consumption (reference: never drink)	Former drinker							1.37	0.28	0.07***
	Current drinker							-1.00	0.22	-0.07***
Exercise regularly (reference: yes)								2.00	0.17	0.16***

$P < 0.05$*; $P < 0.01$**; $P < 0.001$***.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,16
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8,17

		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11,12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

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Title page

Association between number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

Running Title: number of teeth and frailty among older Chinese

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Abstract

Objectives To explore the association between number of teeth and frailty among Chinese older adults using a nationally representative sample.

Design Cross-sectional analysis was carried out using the 2014 wave data from Chinese Longitudinal Health Longevity Survey which employed a targeted random-sampling design.

Setting Communities from nearly half of the counties and cities in 22 out of 31 provinces throughout China.

Participants Of the 6934 interviewees aged ≥ 65 years in 2014 wave data, the finally analysis include 3635 older adults who have complete data on the variables included in the study.

Primary and secondary outcome measures Outcome variables included frailty measured by Frailty Index and number of teeth. Covariates included demographic characteristics (i.e. age, gender, co-residence, marital status, years of education, financial support), body mass index (BMI), and health behaviors (i.e. smoking, drinking, and exercise). Univariate logistic regression was employed to test the factors associated with frailty. Multiple logistic regression model was used, employing frailty score as the dependent variable and number of teeth together with significant covariates as independent variables.

Results The prevalence of frailty is 27.68% according to the Frailty Index. The mean number of teeth present was 9.23 (SD=10.03). Multiple logistic regression showed that older adults' demographic variables, health behaviors, BMI, tooth number, and chewing pain were significantly associated with frailty. After adjusting for the covariates, older adults with fewer tooth were at significantly higher odds of frailty than those with 20 teeth or more (no teeth: odds ratio [OR]=2.07, 95%CI=1.53-2.80; 1-10 teeth: OR=1.77, 95%CI=1.31-2.38), except for older adults with 11-20 teeth (OR=1.30, 95%CI=0.93-1.82).

Conclusions The fewer number of teeth is significantly associated with frailty status among Chinese older adults. Future studies are needed to elucidate the specific mechanisms underlying how oral health status is associated with frailty.

Key words Frailty; older adults; number of teeth; China; oral health

Article summary:

- This is the first study on frailty and oral health conducted in China.
- This study used a large nationally representative sample.
- This study measured frailty using the Frailty Index which included chronic conditions, daily activities, and cognitive function and so forth.
- The covariates of this study included the measurement of sociodemographic factors, nutritional status and health behaviors, which enabled the assessment of several confounding factors.
- This is a cross-sectional study which cannot indicate casual relationships between frailty and oral health.

Association between number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

Introduction

Populations around the world are rapidly aging. As an inevitable demographic transition, aging population is poised to become the next global public health challenge.[1] Frailty is one of the most problematic expressions of population aging.[2] Prevalence of frailty in community-dwelling older adults is 10%-27% for those older than 65 years and 45% for those older than 85 years.[3] Frailty is a clinical condition which is defined as a reduced ability to cope with acute or external stressors in daily life due to aging-associated decline in reserve and function.[4] It is associated with a higher risk of falls, hospitalization, nursing home residence, disability, and death,[5] which putting a significant burden on the person, the family, and public health systems.

Frailty is believed to develop due to the reduced physiological reserve caused by the cumulative molecular and cellular damage during aging, and become evident when physiological decline reaches an aggregate crucial level.[2] Although the pathophysiological changes underlying and preceding frailty are incompletely understood, multiple causes, inter-relationships, and complex pathways have been proposed according to current research findings.[6] Evidence shows that frailty may be modifiable and it is considered to have greater reversibility than disability.[7]

It is important to develop interventions targeting risk factors to maintain older adults' quality of life and delay or prevent the development of frailty and its subsequent need for long-term care.[8] Until now, the proposed risk factors of frailty include physiological changes with aging, inflammation, sarcopenia, polypharmacy, social isolation, and malnutrition.[9] Notably, emerging research showed that frailty was significantly associated with oral health and functions, including tooth number,[10-12] functional dentition,[13] chewing ability,[14,15] periodontitis,[12] utilization of dental services,[11,16,17] and self-perception of oral health.[14,16] More teeth were significantly associated with lower risk of developing frailty[11,12,13,17] because tooth loss might be caused by severe periodontal disease which can trigger higher levels of

inflammatory markers and contribute to the development of frailty.[14] Another line of evidence proposed that tooth loss can change one's food selection and nutrients intake, resulting in malnutrition and contributing to the development of frailty.[12]

The current evidence on the relationship between the number of teeth and frailty is controversial.[8,10,15,16] The conflicting results might be caused by the involved confounders of the subjects and the population from which they were recruited. On the other hand, previous studies measured frailty using the frailty phenotype, which is based on a pre-defined set of five criteria exploring the presence/absence of signs or symptoms (i.e. involuntary weight loss, exhaustion, slowness, poor handgrip strength, and sedentary behavior).[18] There is a growing tendency to view frailty from a multidimensional perspective consisting of physical, psychological, social, and recently environmental frailty.[19] Although the frailty phenotype is convenient to be applied, specific conditions (such as disability or cognitive impairment) can affect the reliability or clinical utility of the frailty phenotype results. Studies using frailty phenotype cannot rule out confounding factors caused by cognitive impairment, which is not only an important domain of frailty[20] but also significantly related to tooth number among older adults.[21] In particular, disabling conditions may affect the predictive value of the phenotype for negative health-related events due to a sort of 'ceiling effect'.[18]

Therefore, the Frailty Index (FI) which assesses a broader spectrum of disorders than the frailty phenotype might provide more information on exploring the association between tooth loss and frailty. Moreover, the association between tooth number and frailty is poorly understood in developing countries, especially in China which has the largest population and the most rapid aging speed in the world. Therefore, the present study is not only the first study that measures FI when exploring the association between tooth loss and frailty, but also the first study that investigated this relationship among the Chinese older adults using a large nationally representative sample.

Methods

Study design and population

We used data from the Chinese Longitudinal Health Longevity Survey (CLHLS), the first national longitudinal project to investigate the determinants of health and longevity of older adults in China from a multidisciplinary perspective.[22] The survey has been conducted every three years in seven waves, from 1998 to 2014, in randomly selected older adults from nearly half of the counties and cities in 22 out of 31 provinces in China. These data represent about 85% of the Chinese population. A targeted random-sampling design was employed to ensure representativeness. Internationally compatible questionnaires were used to collect a comprehensive set of information, including demographic characteristics, family and household characteristics, lifestyle and diet, economic resources, social support, myriad physical, psychological and cognitive health conditions, etc. All the information was obtained through face-to-face interviews as well as some basic physical examinations at the interviewee's home. Interviews were based on voluntary participation and written informed consent was obtained from the participants prior to the recruitment.

The data from the CLHLS are of high quality according to its representativeness and randomness of attrition.[23] The response rate of the oldest-old (older than 80 years) in CLHLS was very high (98%) because the Chinese oldest-old in general may be proud of being a member of long-lived group and be willing to talk to outside people. However, the response rate decreased among younger older adults aged 65-79 (94.9%).[24] The average proportion of incompleteness of an item rated for each respondent in the CLHLS is less than 10 percent.[25] The details of the sampling design, response rates, and systematic assessments of data quality across numerous measures were described elsewhere.[26] The present study utilized cross-sectional data from the 2014 wave of the CLHLS. This study was approved by the Ethical Committee of the Medical College of Wuhan University.

Patient and public involvement

Participants or public were not involved in the development of the study design or outcome measures. Participation was voluntary and could be terminated at any time. Results will not be distributed to the participants themselves. All data were used strictly confidentially and anonymously.

Outcome variables

Various measurements exist for assessing frailty, with Frailty Index (FI) and frailty phenotype being the most common applications.[27] The FI was defined as the proportion of accumulated deficits,[28] and calculated by the proportion of the number of health deficits presented to the total number of possible health deficits for a given individual.[22] For samples of CLHLS, the FI has been found to be a valid and reliable frailty measure and an independent and robust predictor of adverse outcomes among the Chinese elderly.[29, 30]

As presented in Table 1, we used 38 indicators of health deficits encompassing nine major sets of components following the established research[17,22,29,30]: cognitive functioning, chronic disease conditions (self-reports from a list of 11 diseases), Activity of Daily Living disability (ADL, needing help in performing the six basic daily activities), Instrumental Activity of Daily Living disability (IADL, needing help in performing the eight independent living activities), functional limitations (five objective examinations of physical function), self-rated health, hearing and vision impairment, psychological distress, and others (abnormal heart rhythm, interviewer-rated health, number of serious illnesses in the past two years).

Table 1 Health deficits included in calculating the Frailty Index

Components	Measurement	Deficit	Score
Cognitive impairment	The Chinese version of the Mini-Mental State Examination	≤ 23	1
Chronic disease conditions	Hypertension, diabetes, tuberculosis, heart disease, stroke/cerebrovascular disease, bronchitis/asthma, cancer, arthritis, bedsores, gastric/duodenal ulcer, Parkinson's disease	Yes	11
Activity of Daily Living disability	Eating, bathing, dressing, toileting, transferring, continence	Not able to do independently	6
Instrumental Activity of Daily Living disability	Visiting neighbors, cooking meals, shopping, washing clothing, walking continuously for 1 kilometer, lifting a weight of 5 kilograms, continuously crouching and standing up three times, using public transportation	Not able to do independently	8
Functional limitations	Putting hand behind neck, putting hand behind lower back, raising arm upright, standing up from sitting a chair, picking up a book from the floor	Not able to do	5
Self-rated health	Self-assessed current global health	Bad	1
Hearing and vision impairment	Hearing and vision loss	Yes	2
Psychological distress	Felt fearful/anxious, lonely/isolated, or useless	Often/always	1
Others	Heart rhythm	Abnormal	1
	Interviewer-rated health	Bad	1
	Number of serious illnesses in the past two years	One/two or more	1/2
Total			39

Both face-to-face interviews and basic physical examinations were adopted to obtain the above information of each participant. Cognitive functioning, functional limitations, rhythm of heart, interviewer-rated health were assessed by the interviewers who were intensively trained according to a nationally standardized procedure before the survey.[25] The other information, such as chronic disease conditions and psychological distress, were recorded according to the response of the participants or the proxy of the participants who were unable to give accurate answers due to impaired hearing, vision or recall problems.[25]

Each item was dichotomized and coded 1 in the presence of a deficit (otherwise 0). A score of 2 was assigned for individuals with more than one serious illness in the past two years that led to admission to hospital or a period of confinement in bed. The total score of these 38 items was 39.[29] The FI of each participant was calculated as total score of an individual divided by the maximum total score

of 39. The FI score rang from 0-1 (no deficit present, to all deficits present). In the present study, the FI is categorized as non-frailty (0-0.21) and frailty (>0.21).[31,32]

Independent variable

Self-reported number of teeth was recorded using the following question: "How many natural teeth do you still have?" In addition, chewing pain was recorded by the question: "During the past 6 months, did you have a toothache more than once, when biting or chewing?". For those older adults who were not able to answer these questions due to cognitive, hearing or linguistic impairments, their closest relative or caregiver will be asked to answer them.[25] The number of teeth left of the older adults in this survey is similar to that in the Second National Epidemiological Survey on Oral Health, which confirms that the results of this survey represent the general patterns of tooth loss among the elderly in China.[33] In the present study, to be accordance with practical and clinical importance, number of teeth was categorized into four categories: 0 tooth, 1-10 teeth, 11-20 teeth, > 20 teeth.[11]

Covariates

Based on the well-established literature on the factors influencing frailty, we included covariates for basic demographic characteristics, body mass index (BMI) and health behaviors. Demographic variables include age (65-79 years, 80-89 years, 90-99 years, ≥ 100 years), gender, co-residence condition (with household members vs alone or in an institution), marital status (currently married and living with spouse or married but not living with spouse vs others), years of education (received no education vs received more than one year of education), financial support (sufficient vs insufficient). BMI was calculated and included as an indicator of nutritional status. BMI (kg/m^2) was defined as the ratio between weight and the square of height. In the present study, BMI was grouped into four categories: <18.5, 18.5-23.9, 24-27.9, ≥28. Health behaviors included smoking (yes vs no), alcohol consumption (yes vs no), do exercise regularly (yes vs no), and do physical labor regularly (yes vs no).

Statistical analysis

Baseline characteristics of subjects were reported as frequency and percentages for categorical variables. We examined the association between frailty and the potential covariates using the Chi-squared

test. Univariate logistic regression was carried out to calculate the crude odds ratios (OR) of the independent variables in the association with frailty status. Multiple logistic regression model was used, employing frailty status as the dependent variable and the dental variables (number of teeth and chewing pain) and covariates as independent variables. Demographic, nutritional and behavioral covariates identified as statistically significant in the univariate analysis were included in the multiple logistic regression to adjust for the relationship between frailty and the tooth number. P values of less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the participants

Of the 7019 interviewees in 2014 CHLHS, we included 6934 participants aged ≥ 65 years initially. The final analysis included 3635 older adults who has complete data on frailty and other explanatory factors used in the analysis. The main characteristics of 3635 participants and the frailty status are described in Table 2. The average age of the participants was 84.27 years (SD= 9.92) and 38.3% (n=1393) of them were aged between 65 years to 79 years. More than half of the participants were female (n=1884, 51.8%), single (n=2051, 56.4%) and living with household members (n=2918, 80.3%). Furthermore, 52.9% of the older adults hadn't received any education (n=1924), while 83.5% (n=3034) had sufficient financial support. For health behaviors, 66.3% (n=2411) never smoke, 72% (n=2618) never drink alcohol, 82.3% (n=2992) do physical labor regularly, while 68.2% (n=2478) did not do exercise. More than half of the subjects (n=2012, 55.4%) had normal BMI.

Tooth loss and frailty status of the participants

Among all subjects, the average number of teeth was 9.23 (SD= 10.03), 32.4% (n=1179) of the participants had 1 to 10 teeth, and the majority of them reported no chewing pain (n=3066, 84.3%). The average score of the FI was 0.16 (SD= 0.14) and the prevalence of frailty is 27.68%.

Table 2 Participant characteristics by frailty

Variable	Total (n=3635)	Non-frailty (n=2629)	Frailty (n=1006)	χ^2	p-value
Age categories (years), n(%)				628.52	0.000
65-79	1393 (38.3%)	1248 (47.5%)	145 (14.4%)		
80-89	1201 (33.0%)	906 (34.5%)	295 (29.3%)		
90-99	761 (20.9%)	390 (14.8%)	371 (36.9%)		
≥100+	280 (7.7%)	85 (3.2%)	195 (19.4%)		
Gender, n(%)				95.33	0.000
Male	1751 (48.2%)	1398 (53.2%)	353 (35.1%)		
Female	1884 (51.8%)	1231 (46.8%)	653 (64.9%)		
Co-residence, n(%)				7.02	0.008
With household members	2918 (80.3%)	2080 (79.2%)	836 (83.1%)		
Alone or In an institution	717 (19.7%)	547 (20.8%)	170 (16.9%)		
Marital status, n(%)				187.98	0.000
Married	1584 (43.6%)	1329 (50.6%)	255 (25.3%)		
Single	2051 (56.4%)	1300 (49.4%)	751 (74.7%)		
Years of schooling, n(%)				149.47	0.000
>0	1711 (47.1%)	1399 (53.2%)	312 (31.0%)		
0	1924 (52.9%)	1230 (46.8%)	694 (69.0%)		
Sufficient financial support, n(%)				16.47	0.000
Yes	3034 (83.5%)	2235 (85.0%)	799 (79.4%)		
No	601 (16.5%)	394 (15.0%)	207 (20.6%)		
Smoking, n(%)				50.78	0.000
No	2411 (66.3%)	1676 (63.8%)	735 (73.1%)		
Yes	1224 (33.7%)	953 (36.2%)	271 (26.9%)		
Drinking, n(%)				61.60	0.000
No	2618 (72.0%)	1834 (69.8%)	784 (77.9%)		
Yes	1017 (28.0%)	795 (30.2%)	222 (22.1%)		
Do physical labor regularly, n(%)				6.40	0.011
Yes	2992 (82.3%)	2190 (83.3%)	802 (79.7%)		
No	643 (17.7%)	439 (16.7%)	204 (20.3%)		
Do exercise, n(%)				166.65	0.000
Yes	1157 (31.8%)	999 (38.0%)	158 (15.7%)		
No	2478 (68.2%)	1630 (62.0%)	848 (84.3%)		
Teeth number, n(%)				182.13	0.000
>20	672 (18.5%)	594 (22.6%)	78 (7.8%)		
11-20	643 (17.7%)	519 (19.7%)	124 (12.3%)		
1-10	1179 (32.4%)	814 (31.0%)	365 (36.3%)		
0	1141 (31.4%)	702 (26.7%)	439 (43.6%)		
Chewing pain, n(%)				0.75	0.387
No	3066 (84.3%)	2209 (84.0%)	857 (85.2%)		
Yes	569 (15.7%)	420 (16.0%)	149 (14.8%)		
BMI*, kg/m^2, n(%)				86.32	0.000
<18.5	633 (17.4%)	364 (13.8%)	269 (26.7%)		
18.5-23.9	2012 (55.4%)	1529 (58.2%)	483 (48.0%)		
24-27.9	748 (20.6%)	563 (21.4%)	185 (18.4%)		
≥28	242 (6.7%)	173 (6.6%)	69 (6.9%)		

*BMI refers to Body Mass Index.

Tooth number and other influencing factors of frailty

According to the Chi-square tests, the frailty status is associated with demographic variables (i.e., age category, gender, co-residence condition, marital status, years of schooling, financial support), health behaviors (i.e., smoking, drinking, doing physical labor, doing exercise), BMI and tooth number ($p<0.05$). No significant differences were found in frailty status based on chewing pain ($p=0.387$) (Table 2).

Univariate and multiple logistic regressions were carried out to report both of the crude ORs and adjusted ORs of the independent variables as presented in Table 3. In the final multiple logistic regression model, number of teeth is a significant factor in determining frailty after adjusting for covariates including age category, gender, co-residence, marital status, years of schooling, financial support, smoking, drinking, doing exercise, doing physical labor, and BMI.

Participants of older age were at a significantly higher risk of frailty than those participants aged 65 to 79 years (80-89 years old: OR=2.29, 95%CI=1.81-2.91; 90-99 years old: OR=5.76, 95%CI=4.41-7.51; 100 years and older: OR=11.82, 95%CI=8.31-16.80). Female participants, had a significantly higher risk of being frail (OR=1.40, 95%CI=1.12-1.74). For participants who lived alone or in an institution, the risk of frailty was significantly lower (OR=0.58, 95%CI=0.46-0.72). Single older adults had a significantly higher risk of frailty than married older adults (OR=1.42, 95%CI=1.15-1.76). Participants who were illiterate had a significantly higher risk of frailty than those who received education (OR=1.18, 95%CI=0.96-1.44). Participants with insufficient financial support had a significantly higher risk of frailty than those who had sufficient financial support (OR=1.52, 95%CI=1.22-1.88).

Smoking and drinking were significantly associated with frailty in unadjusted analysis, but the association attenuated to non-significance in the adjusted analysis. Participants who did not do physical labor regularly or exercise had a significantly higher risk of frailty than those who did physical labor (OR=1.65, 95%CI=1.32-2.06) or exercise regularly (OR=2.65, 95%CI=2.15-3.27) also had a significantly greater risk of frailty than those who did not. Participants with abnormal BMI were at a significantly higher risk of frailty than those within normal BMI range ($<18.5 kg/m^2$: OR=1.55, 95%CI=1.25-1.93; $24-27.9 kg/m^2$: OR=1.46, 95%CI=1.17-1.82; $\geq 28 kg/m^2$: OR=2.06, 95%CI=1.46-2.90).

Participants with fewer teeth were at a significantly higher risk of frailty than those with more than 20 teeth (no tooth: OR=2.07, 95%CI=1.53-2.80; 1-10 teeth: OR=1.77, 95%CI=1.31-2.38), except for participants

with 11-20 teeth (OR=1.30, 95%CI=0.93-1.82). Participants who had chewing pain had a significantly higher risk of frailty than those with no chewing pain (OR=1.64, 95%CI=1.28-2.08).

Table 3 Multiple logistic regression of factors associated with frailty

Independent variables	Unadjusted ORs* (95%CI)	p	Adjusted ORs (95%CI)	p
Age category, years (65-79 as reference)				
80-89	2.80 (2.26-3.48)	0.000	2.29 (1.81-2.91)	0.000
90-99	8.19 (6.55-10.23)	0.000	5.76 (4.41-7.51)	0.000
≥100+	19.75 (14.52-26.85)	0.000	11.82 (8.31-16.80)	0.000
Gender (male as reference)				
Female	2.10 (1.81-2.44)	0.000	1.40 (1.12-1.74)	0.003
Co-residence (with household members as reference)	0.77 (0.64-0.94)	0.008	0.58 (0.46-0.72)	0.000
Alone or In an institution				
Marital status (married as reference)				
Single	3.01 (2.56-3.54)	0.000	1.42 (1.15-1.76)	0.001
Years of schooling (>0 as reference)				
0	2.53 (2.17-2.95）	0.000	1.18 (0.96-1.44)	0.110
Sufficient financial support (yes as reference)				
No	1.47 (1.22-1.77)	0.000	1.52 (1.22-1.89)	0.000
Smoking (no as reference)				
Yes	0.65 (0.55-0.76)	0.000	1.16 (0.93-1.45)	0.187
Drinking (no as reference)				
Yes	0.65 (0.55-0.78)	0.000	0.95 (0.76-1.19)	0.660
Do physical labor regularly (yes as reference)				
No	1.27 (1.06-1.53)	0.012	1.65 (1.32-2.06)	0.000
Do exercise (yes as reference)				
No	3.29 (2.73-3.97)	0.000	2.65 (2.15-3.27)	0.000
Teeth number (>20 as reference)				
0	4.76 (3.66-6.20)	0.000	2.07 (1.53-2.80)	0.000
1-10	3.42 (2.62-4.46)	0.000	1.77 (1.31-2.38)	0.000
11-20	1.82 (1.34-2.47)	0.000	1.30 (0.93-1.82)	0.122
Chewing pain (no as reference)				
Yes	0.91 (0.75-1.12)	0.387	1.64 (1.28-2.08)	0.000
BMI*, kg/m^2 (18.5-23.9 as reference)				
<18.5	2.34 (1.94-2.82)	0.000	1.55 (1.25-1.923)	0.000
24-27.9	1.04 (0.86-1.26)	0.692	1.46 (1.17-1.82)	0.001
≥28	1.26 (0.94-1.70)	0.124	2.06 (1.46-2.90)	0.000

*BMI refers to Body Mass Index; ORs refers to odds ratios; CI refers to confidence interval.

Discussion

We use data from a nationwide longitudinal survey in China to examine the association between frailty and tooth number. Both of the univariate and multiple logistic regressions were performed to explore the association between the tooth number and frailty. Considering the relationship between tooth number and frailty might not be pure linear, we transferred the continuous variable FI into dichotomous variable as non-

frail and frail to obtain more practical information of clinical benefit. In addition, age and tooth number were categorized into four groups according to clinical importance to improve the effectiveness of the multiple logistic regression model. The main findings suggested that, after adjusting for sociodemographic, health behavioral and nutritional variables, older adults with fewer teeth had significantly high odds of frailty than those with more than 20 teeth, except for participants with 11-20 teeth. To the best of our knowledge, this is the first study exploring the association between frailty and oral health among Chinese older adults.

According to our results, the prevalence of frailty was 27.68%, which is consistent with previous reported prevalence of frailty among community-dwelling older adults in the Asia-Pacific region.[9] Older adults with less than 11 teeth were at higher odds of being frail while no significant difference in frailty risk was found between older adults with 11-20 teeth and those with more than 20 teeth, suggesting a non-linear relationship between tooth number and frailty. Two cross-sectional studies from Brazil and the United States indicated that older adults with more than 20 teeth had a lower chance of being frail than edentulous individuals.[11,17] One cohort study in Japan suggested that older adults having 20 teeth or more with nine or more occluding pairs of teeth had a significantly lower risk of frailty.[8] By using linear analysis, a cohort study in Mexico suggested that each additional tooth was associated with a lower probability of developing frailty.[12] However, two cross-sectional studies performed in Mexico[16] and Thailand[15] and one cohort study in Denmark[10] did not find significant association between number of teeth and frailty. Taken together, current evidence supports that the relationship between frailty and tooth number exists in the older population in Brazil, US, Japan, Mexico, and China, but does not exist in Danish and Thai older adults. These conflicting findings might be explained by several other factors, including the study design, demographic covariates such as age, gender and education level, the ways of defining tooth number, and the cultural context from which the participants came from. Our findings confirmed the association among Chinese older adults that fewer teeth are related to being frailer. However, our study observes an absence of significant difference between older adults with 11-20 teeth and those with more than 20 teeth after adjusting a variety of confounders. This finding might imply that older adults with 11-20 teeth might have comparable oral condition with older adults with 20 teeth or more in chances of being frail. However, previous studies reported 20 teeth as the dividing point of being frail. The inconsistence might be explained by several reasons.

First, the dividing point of teeth number for being frail among older adults might lie within the range from 11 to 20 teeth, but current studies fail to recognize it. Future studies could explore the specific turning points of the relationship between frailty and tooth number as well as explaining underlying mechanisms. In addition, the distribution of tooth number among the participants in the present study might be different from these of the previous studies. Chinese older adults have worse oral health compared with their counterparts in developed countries.[34] Therefore, the characteristics of tooth number among older Chinese might lead to a different form of its association with frailty. Moreover, the important covariates included in the previous studies varied from the present study, such as the number of occluding pairs of teeth, functional teeth and chewing pain. In addition, our study used FI rather than frailty phenotype to identify the frail status of the participants. Instead of solely relying on physical markers,[6] FI included a broader combination of health status, such as cognitive impairment, psychosocial status, physical limitations, and chronic diseases. Some of these health status variables were viewed as covariates in the analysis of previous studies. However, these hypotheses, as well as issue of causal order, should be further evaluated in longitudinal studies.

Demographic factors are significantly associated with frailty in our study. Congruent with the previous findings, participants who were older, female, single, illiterate, and suffering from insufficient financial support had a significantly higher risk of being frail. We also find that the association between age and frailty is the strongest association among associations between the other variables and frailty. However, it is unexpected that those who living alone or in an institution (OR=0.58) had a lower risk of being frail. It is possible that this association identified by our study might be caused by selection bias. That is, older adults living alone or living in an institution could be recruited to the survey only if their health condition was good enough to complete the interview all by themselves because they had no proxy around to offer help during the interview. Therefore, healthier older adults in an institution were selected in the survey. Health behaviors including doing physical labor regularly and doing exercise are significantly associated with a lower risk of being frail. In previous studies, physical activities were not considered as a covariate. However, emerging evidence suggests that physical activities could act as a remedy against frailty[35] Longitudinal survey is needed to confirm the causal relationship. Our findings also suggest that smoking and drinking are not significantly associated with frailty after adjusting the confounders. This result is in line with previous studies.[12,17]

BMI is a basic indicator of the nutritional status. Underweight, overweight and obese older adults were at a significantly higher risk of frailty than those with normal BMI according to our findings as well as previous study.[17] The association between frailty and BMI highlights the importance of nutrition in understanding frailty. Current evidence suggests that both of the nutrition quantity (i.e. energy intake) and nutrients quality are related to frailty,[36] but the causal relationship needs to be confirmed by further studies. Identifying the relationship between nutrition and frailty is helpful in understanding the association between frailty and tooth number, because some studies proposed that tooth loss could lead to frailty through malnutrition. Tooth loss could reduce one's chewing ability and alter food selection, thus consuming inadequate nutrients for life and physiological function, and finally contributing to the development of frailty.[37] However, this hypothesis is not verified in population study and is opposite with the findings in animal models where dietary restriction could significantly extend lifespan.[38] The role of nutrition on mediating the relationship between frailty and tooth number is still unclear. On the other hand, current findings support that severe periodontitis is associated with the incidence of frailty. Tooth loss as a final consequence of periodontitis could contribute to frailty through inflammation. Inflammatory factors derived from the body's response to periodontal infection, may disseminate to other organs and alter their metabolism.[16,21] However, the evidence regarding inflammation and frailty in human beings is still conflicting.[39] There is a lack of study on understanding of the interrelationships among tooth number, inflammation, nutrition and frailty. By including global oral health indicators, inflammatory biomarkers, nutritional biomarkers and behavioral variables, such as daily choice of food or diet, future studies could depict a brighter picture of the mechanism underlying tooth number and frailty with the goal of identifying etiologic factors that are subject to public health interventions.

Strengths and limitations

This study has some strengths. First, this analysis was performed based on a large nationally representative sample of older Chinese and the response rate of the participants in CLHLS was high (from 94.9% to 98%), enhancing the generalizability of the results. Second, the multidisciplinary approach of the CHLHS and the large range of data collected allowed us to calculate FI and adjust the

analyses for demographics, nutrition status and health behaviors to be related to the outcome. Third, the present study measured frailty by calculating the FI which assesses comprehensive health conditions and is reliable in large sample study, contributing to a broader and supplementary explanation on previous findings. However, our data must be interpreted with caution. The self-reported tooth number might be subjective, although it has been widely used as a measure of oral health in epidemiological surveys.[13,17] More information on oral health is limited because the CLHLS was not specifically designed for dentate studies. Tooth loss might be inadequate in representing oral functions when understanding the deeper connections between oral health and frailty. Another weakness is the cross-sectional nature of this study. As the time of tooth loss and being frail was not determined, causal relationship could not be established. Previous studies hypothesized that tooth loss could contribute to malnutrition or inflammation, resulting in developing frailty. However, tooth loss could present as one of the consequences or manifestations during the frailty process instead of being the initiator of frailty. For instance, frailty could contribute to losing functional teeth and reducing masseter muscle thickness.[8] Therefore, longitudinal studies are needed in understanding the relationship between frailty and tooth number.

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Disclosure statement

The authors declare no conflict of interest.

Author contributions

Yaohua Gu and Xiaodong Tan contributed to conception and design of the study and drafting the manuscript. Jinbing Bai, Xuyu Chen, Wenwen Wu contributed to acquisition, analysis, and interpretation of the data and revising the manuscript. All of the authors approved the version to be published.

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Data availability statement

Data are available in the public open access repository of Peking University.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12

		(*b*) Report category boundaries when continuous variables were categorized	6-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between the number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

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Title page

Association between the number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

Running Title: the number of teeth and frailty among older Chinese

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Word count: 4211 words

Abstract

Objectives To explore the association between the number of teeth and frailty among older Chinese adults using a nationally representative sample.

Design Cross-sectional analysis was carried out using the 2014 wave data from the Chinese Longitudinal Health Longevity Survey, which used a targeted random-sampling design.

Setting This research was conducted in communities from nearly half of the counties and cities in 22 out of 31 provinces throughout China.

Participants Of the 6934 interviewees aged ≥ 65 years, the final analysis included 3635 older adults who had completed the 2014 wave survey on the variables included in the study.

Primary and secondary outcome measures Outcome variables included frailty, measured by the Frailty Index, and number of teeth. Covariates included demographic characteristics (i.e., age, sex, co-residence, marital status, years of education and financial support), body mass index (BMI), and health behaviours (i.e., smoking, drinking and exercise). Univariate logistic regressions were used to test the factors associated with frailty. A multiple logistic regression model was used, employing the frailty score as the dependent variable and the number of teeth together with significant covariates as the independent variables.

Results The prevalence of frailty was 27.68%. The mean number of teeth present was 9.23 (SD=10.03). The multiple logistic regression showed that older adults' demographic variables, health behaviours, BMI, tooth number, and chewing pain were significantly associated with frailty. After adjusting for the covariates, older adults with fewer teeth had significantly higher odds of frailty than those with 20 or more teeth (no teeth: odds ratio [OR]=2.07, 95%CI=1.53-2.80; 1-10 teeth: OR=1.77, 95%CI=1.31-2.38), except for older adults with 11-20 teeth (OR=1.30, 95%CI=0.93-1.82).

Conclusions The presence of fewer teeth is significantly associated with frailty status among older Chinese adults. Future studies are needed to explain the specific mechanisms underlying how oral health status is associated with frailty.

Key words Frailty; older adults; number of teeth; China; oral health

Article summary:

- This is the first study on frailty and oral health conducted in China.
- This study used a large nationally representative sample.
- This study measured frailty using the Frailty Index, which included chronic conditions, daily activities, cognitive function and so forth.
- The covariates of this study included the measurement of sociodemographic factors, nutritional status and health behaviours, which enabled the assessment of several confounding factors.
- This is a cross-sectional study that cannot indicate causal relationships between frailty and oral health.

Association between the number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

Introduction

Populations around the world are rapidly ageing. As an inevitable demographic transition, the ageing population is poised to become the next global public health challenge.[1] Frailty is one of the most problematic expressions of population ageing.[2] The prevalence of frailty in community-dwelling older adults is 10%-27% for those older than 65 years and 45% for those older than 85 years.[3] Frailty is a clinical condition that is defined as a reduced ability to cope with acute or external stressors in daily life due to ageing-associated decline in reserve and function.[4] It is associated with a higher risk of falls, hospitalization, nursing home residence, disability, and death,[5] which places a significant burden on the person, the family, and public health systems.

Frailty is believed to develop due to a reduced physiological reserve caused by cumulative molecular and cellular damage during ageing and become evident when physiological decline reaches an aggregate crucial level.[2] Although the pathophysiological changes underlying and preceding frailty are incompletely understood, multiple causes, inter-relationships, and complex pathways have been proposed according to current research findings.[6] Evidence shows that frailty may be modifiable and is considered to have greater reversibility than disability.[7]

It is important to develop interventions targeting risk factors to maintain older adults' quality of life and delay or prevent the development of frailty and its subsequent need for long-term care.[8] Until now, the proposed risk factors for frailty include physiological changes with ageing, inflammation, sarcopenia, polypharmacy, social isolation, and malnutrition.[9] Notably, emerging research has shown that frailty is significantly associated with oral health and functions, including tooth number,[10-12] functional dentition,[13] chewing ability,[14,15] periodontitis,[12] utilization of dental services,[11,16,17] and self-perception of oral health.[14,16] More teeth were significantly associated with a lower risk of developing frailty[11,12,13,17] because tooth loss might be caused by severe periodontal diseases, which can trigger

higher levels of inflammatory markers and contribute to the development of frailty.[14] Another line of evidence has proposed that tooth loss can change one's food selection and nutrient intake, resulting in malnutrition and contributing to the development of frailty.[12]

The current evidence on the relationship between the number of teeth and frailty is controversial.[8,10,15,16] The conflicting results might be caused by the confounders of the subjects and the population from which they were recruited. Previous studies have measured frailty using the frailty phenotype, which is based on a pre-defined set of five criteria exploring the presence/absence of signs or symptoms (i.e., involuntary weight loss, exhaustion, slowness, poor handgrip strength and sedentary behaviour).[18] There is a growing tendency to view frailty from a multidimensional perspective consisting of physical, psychological, social, and most recently environmental frailty.[19] Although the frailty phenotype is conveniently applied, specific conditions (such as disability or cognitive impairment) can affect the reliability or clinical utility of the frailty phenotype results. Studies using frailty phenotypes cannot rule out confounding factors caused by cognitive impairment, which not only is an important domain of frailty[20] but also is significantly related to tooth number among older adults.[21] In particular, disabling conditions may affect the predictive value of the phenotype for negative health-related events due to a sort of 'ceiling effect'.[18]

The Frailty Index (FI), which assesses a broader spectrum of disorders than the frailty phenotype, might provide more information on exploring the association between tooth loss and frailty. Moreover, the association between tooth number and frailty is poorly understood in developing countries, especially in China, which has the largest population and the most rapidly ageing population in the world. Therefore, the present study is the first study that not only measures FI when exploring the association between tooth loss and frailty but also investigates this relationship among older Chinese adults using a large nationally representative sample.

Methods

Study design and population

We used data from the Chinese Longitudinal Health Longevity Survey (CLHLS), which is the first national longitudinal project to investigate the determinants of health and longevity of older adults in China from a multidisciplinary perspective.[22] The survey was conducted every three years in seven waves, from 1998 to 2014, in randomly selected older adults from nearly half of the counties and cities in 22 out of 31 provinces in China. These data represent approximately 85% of the Chinese population. A targeted random-sampling design was employed to ensure representativeness. Internationally compatible questionnaires were used to collect a comprehensive set of information, including demographic characteristics, family and household characteristics, lifestyle and diet, economic resources, social support, myriad physical, psychological and cognitive health conditions, etc. All the information was obtained through face-to-face interviews as well as some basic physical examinations at the interviewee's home. Interviews were based on voluntary participation and written informed consent was obtained from the participants prior to recruitment.

The data from the CLHLS are of high quality according to its representativeness and randomness of attrition.[23] The response rate of the oldest-old (older than 80 years) participants in the CLHLS was very high (98%) because the Chinese oldest-old adults, in general, may be proud to be a member of such a long-lived group are willing to talk to outside people. However, the response rate decreased among younger older adults aged 65-79 (94.9%).[24] The average proportion of incompleteness of an item rated for each respondent in the CLHLS is less than 10%.[25] The details of the sampling design, response rates, and systematic assessments of data quality across numerous measures have been described elsewhere.[26] The present study utilized cross-sectional data from the 2014 wave of the CLHLS. This study was approved by the Ethical Committee of the Medical College of Wuhan University.

Patient and public involvement

Participants and the public were not involved in the development of the study design or outcome measures. Participation was voluntary and could be terminated at any time. The results will not be distributed to the participants themselves. All data were used strictly confidentially and anonymously.

Outcome variables

Various measurements exist for assessing frailty, with the Frailty Index (FI) and frailty phenotype being the most common applications.[27] The FI is defined as the proportion of accumulated deficits,[28] and calculated by the proportion of the number of health deficits presented to the total number of possible health deficits for a given individual.[22] For samples of the CLHLS, the FI has been found to be a valid and reliable frailty measure, and an independent and robust predictor of adverse outcomes among the Chinese elderly population.[29, 30]

As presented in Table 1, we used 38 indicators of health deficits encompassing nine major sets of components following the established research[17,22,29,30]: cognitive functioning, chronic disease conditions (self-reports from a list of 11 diseases), Activity of Daily Living disability (ADL, needing help in performing the six basic daily activities), Instrumental Activity of Daily Living disability (IADL, needing help in performing the eight independent living activities), functional limitations (five objective examinations of physical function), self-rated health, hearing and vision impairment, psychological distress, and others (e.g., abnormal heart rhythm, interviewer-rated health, number of serious illnesses in the past two years).

Table 1 Health deficits included in calculating the Frailty Index

Components	Measurement	Deficit	Score
Cognitive impairment	The Chinese version of the Mini-Mental State Examination	≤ 23	1
Chronic disease conditions	Hypertension, diabetes, tuberculosis, heart disease, stroke/cerebrovascular disease, bronchitis/asthma, cancer, arthritis, bedsores, gastric/duodenal ulcer, Parkinson's disease	Yes	11
Activity of Daily Living disability	Eating, bathing, dressing, toileting, transferring, continence	Not able to do independently	6
Instrumental Activity of Daily Living disability	Visiting neighbors, cooking meals, shopping, washing clothing, walking continuously for 1 kilometer, lifting a weight of 5 kilograms, continuously crouching and standing up three times, using public transportation	Not able to do independently	8
Functional limitations	Putting hand behind neck, putting hand behind lower back, raising arm upright, standing up from sitting a chair, picking up a book from the floor	Not able to do	5
Self-rated health	Self-assessed current global health	Bad	1
Hearing and vision impairment	Hearing and vision loss	Yes	2
Psychological distress	Felt fearful/anxious, lonely/isolated, or useless	Often/always	1
Others	Heart rhythm	Abnormal	1
	Interviewer-rated health	Bad	1
	Number of serious illnesses in the past two years	One/two or more	1/2
Total			39

Both face-to-face interviews and basic physical examinations were conducted to obtain the above information of each participant. Cognitive functioning, functional limitations, rhythm of the heart, and interviewer-rated health were assessed by the interviewers who were intensively trained according to a nationally standardized procedure before the survey.[25] Other information, such as chronic disease conditions and psychological distress, was recorded according to the response of the participants or the proxy of the participants who were unable to give accurate answers due to impaired hearing, vision or recall problems.[25]

Each item was dichotomized and coded as 1 if a deficit was presence (otherwise 0). A score of 2 was assigned for individuals with more than one serious illness in the past two years that led to hospital admission or a period of bed confinement. The total score of these 38 items was 39.[29] The FI of each participant was calculated as the total score of an individual divided by the maximum total score of 39.

The FI scores ranged from 0-1. Cut-off points of FI are needed to identify frail older adults and to estimate the prevalence of frailty at the population level.[31] At present, the universally accepted category of FI scores are as follows: non-frail (0-0.10), vulnerable (0.10-0.21), frail (0.22-0.44), and frailest (≥ 0.45).[31] In the present study, the FI is categorized as non-frailty (0-0.21) and frailty (>0.21).[32]

Independent variable

The self-reported number of teeth was recorded using the following question: "How many natural teeth do you still have?" In addition, chewing pain was recorded by the question: "During the past 6 months, did you have a toothache more than once, when biting or chewing?" For older adults who were not able to answer these questions due to cognitive, hearing or linguistic impairments, their closest relative or caregiver was asked to answer for them.[25] The number of teeth of the older adults in this survey is similar to that in the Second National Epidemiological Survey on Oral Health, which confirms that the results of this survey represent the general patterns of tooth loss among elderly adults in China.[33] In accordance with practical and clinical importance, the present study grouped the number of teeth into four categories: 0 tooth, 1-10 teeth, 11-20 teeth, and > 20 teeth.[11]

Covariates

Based on well-established literature on the factors influencing frailty, we included covariates for basic demographic characteristics, body mass index (BMI) and health behaviours. Demographic variables include age (65-79 years, 80-89 years, 90-99 years, ≥ 100 years), sex, co-residence condition (with household members, alone, in an institution), marital status (currently married and living with spouse, married but not living with spouse, others), years of education (received no education, received more than one year of education), financial support (sufficient, insufficient). BMI (kg/m^2) was defined as the ratio between the weight and the square of the height. In the present study, BMI was grouped into four categories: <18.5, 18.5-23.9, 24-27.9, and ≥28. Health behaviours included smoking (yes vs. no), alcohol consumption (yes vs. no), regular exercise (yes vs. no), and regular physical labour (yes vs. no).

Statistical analysis

Baseline characteristics of the subjects were reported as frequency and percentages for categorical variables. We examined the association between frailty and the potential covariates using the Chi-squared test. Univariate logistic regressions were carried out to calculate the crude odds ratios (OR) of the independent variables in association with frailty status. A multiple logistic regression model was used, employing frailty status as the dependent variable, and the dental variables (number of teeth and chewing pain) and covariates as the independent variables. Demographic, nutritional and behavioural covariates identified as statistically significant in the univariate analyses were included in the multiple logistic regression to adjust for the relationship between frailty and the tooth number. P values of less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the participants

Of the 7019 interviewees who participated in the 2014 CHLHS, we initially included 6934 participants aged ≥ 65 years. The final analysis included 3635 older adults who had complete data on frailty and other explanatory factors used in the analyses. The main characteristics of 3635 participants and the frailty status are described in Table 2. The average age of the participants was 84.27 years (SD= 9.92) and 38.3% (n=1393) of them were aged between 65 years and 79 years. More than half of the participants were female (n=1884, 51.8%), single (n=2051, 56.4%), and living with household members (n=2918, 80.3%). Furthermore, 52.9% of the older adults had not received any education (n=1924), while 83.5% (n=3034) had sufficient financial support. For health behaviours, 66.3% (n=2411) never smoked, 72% (n=2618) never drank alcohol, 82.3% (n=2992) did physical labour regularly, while 68.2% (n=2478) did not exercise. More than half of the subjects (n=2012, 55.4%) had a normal BMI.

Tooth loss and frailty status of the participants

Among all the subjects, the average number of teeth was 9.23 (SD= 10.03), 32.4% (n=1179) of the participants had 1 to 10 teeth, and the majority of them reported no chewing pain (n=3066, 84.3%). The average FI score was 0.16 (SD= 0.14), and the prevalence of frailty was 27.68%.

Table 2 Participant characteristics by frailty

Variable	Total (n=3635)	Non-frailty (n=2629)	Frailty (n=1006)	χ^2	p-value
Age categories (years), n(%)				628.52	<0.001
65-79	1393 (38.3%)	1248 (47.5%)	145 (14.4%)		
80-89	1201 (33.0%)	906 (34.5%)	295 (29.3%)		
90-99	761 (20.9%)	390 (14.8%)	371 (36.9%)		
≥100+	280 (7.7%)	85 (3.2%)	195 (19.4%)		
Sex, n(%)				95.33	<0.001
Male	1751 (48.2%)	1398 (53.2%)	353 (35.1%)		
Female	1884 (51.8%)	1231 (46.8%)	653 (64.9%)		
Co-residence, n(%)				7.02	0.008
With household members	2918 (80.3%)	2080 (79.2%)	836 (83.1%)		
Alone or In an institution	717 (19.7%)	547 (20.8%)	170 (16.9%)		
Marital status, n(%)				187.98	<0.001
Married	1584 (43.6%)	1329 (50.6%)	255 (25.3%)		
Single	2051 (56.4%)	1300 (49.4%)	751 (74.7%)		
Years of schooling, n(%)				149.47	<0.001
>0	1711 (47.1%)	1399 (53.2%)	312 (31.0%)		
0	1924 (52.9%)	1230 (46.8%)	694 (69.0%)		
Sufficient financial support, n(%)				16.47	<0.001
Yes	3034 (83.5%)	2235 (85.0%)	799 (79.4%)		
No	601 (16.5%)	394 (15.0%)	207 (20.6%)		
Smoking, n(%)				50.78	<0.001
No	2411 (66.3%)	1676 (63.8%)	735 (73.1%)		
Yes	1224 (33.7%)	953 (36.2%)	271 (26.9%)		
Drinking, n(%)				61.60	<0.001
No	2618 (72.0%)	1834 (69.8%)	784 (77.9%)		
Yes	1017 (28.0%)	795 (30.2%)	222 (22.1%)		
Do physical labor regularly, n(%)				6.40	0.011
Yes	2992 (82.3%)	2190 (83.3%)	802 (79.7%)		
No	643 (17.7%)	439 (16.7%)	204 (20.3%)		
Do exercise, n(%)				166.65	<0.001
Yes	1157 (31.8%)	999 (38.0%)	158 (15.7%)		
No	2478 (68.2%)	1630 (62.0%)	848 (84.3%)		
Teeth number, n(%)				182.13	<0.001
>20	672 (18.5%)	594 (22.6%)	78 (7.8%)		
11-20	643 (17.7%)	519 (19.7%)	124 (12.3%)		
1-10	1179 (32.4%)	814 (31.0%)	365 (36.3%)		
0	1141 (31.4%)	702 (26.7%)	439 (43.6%)		
Chewing pain, n(%)				0.75	0.387
No	3066 (84.3%)	2209 (84.0%)	857 (85.2%)		
Yes	569 (15.7%)	420 (16.0%)	149 (14.8%)		
BMI*, kg/m^2, n(%)				86.32	<0.001
<18.5	633 (17.4%)	364 (13.8%)	269 (26.7%)		
18.5-23.9	2012 (55.4%)	1529 (58.2%)	483 (48.0%)		
24-27.9	748 (20.6%)	563 (21.4%)	185 (18.4%)		
≥28	242 (6.7%)	173 (6.6%)	69 (6.9%)		

*BMI refers to Body Mass Index.

Tooth number and other influencing factors of frailty

According to the Chi-square tests, frailty status is associated with demographic variables (i.e., age category, sex, co-residence condition, marital status, years of schooling and financial support), health behaviours (i.e., smoking, drinking, doing physical labour and exercise), BMI, and tooth number ($p<0.05$). No significant differences were found in frailty status based on chewing pain ($p=0.387$) (Table 2).

Univariate and multiple logistic regressions were carried out to report both the crude ORs and adjusted ORs of the independent variables as presented in Table 3. In the final multiple logistic regression model, the number of teeth is a significant factor in determining frailty after adjusting for covariates, including age category, sex, co-residence, marital status, years of schooling, financial support, smoking, drinking, doing exercise, doing physical labour, and BMI.

Participants of older age were at a significantly higher risk of frailty than those participants aged 65 years to 79 years (80-89 years old: OR=2.29, 95%CI=1.81-2.91; 90-99 years old: OR=5.76, 95%CI=4.41-7.51; 100 years and older: OR=11.82, 95%CI=8.31-16.80). Female participants had a significantly higher risk of being frail (OR=1.40, 95%CI=1.12-1.74). For participants who lived alone or in an institution, the risk of frailty was significantly lower (OR=0.58, 95%CI=0.46-0.72). Single older adults had a significantly higher risk of frailty than married older adults (OR=1.42, 95%CI=1.15-1.76). Participants with insufficient financial support had a significantly higher risk of frailty than those who had sufficient financial support (OR=1.52, 95%CI=1.22-1.88).

Smoking and drinking were significantly associated with frailty in the unadjusted analyses, but the association decreased to non-significance in the adjusted analyses. Participants who did not perform physical labour regularly or exercise had a significantly higher risk of frailty than those who did physical labour regularly (OR=1.65, 95%CI=1.32-2.06) or exercise (OR=2.65, 95%CI=2.15-3.27). Participants with abnormal BMI were at a significantly higher risk of frailty than those within the normal BMI range (<18.5 kg/m^2: OR=1.55, 95%CI=1.25-1.93; 24-27.9 kg/m^2: OR=1.46, 95%CI=1.17-1.82; ≥ 28 kg/m^2: OR=2.06, 95%CI=1.46-2.90).

Participants with fewer teeth were at a significantly higher risk of frailty than those with more than 20 teeth (no teeth: OR=2.07, 95%CI=1.53-2.80; 1-10 teeth: OR=1.77, 95%CI=1.31-2.38), except for participants with 11-20 teeth (OR=1.30, 95%CI=0.93-1.82). Participants who had chewing pain had a significantly higher risk of frailty than those with no chewing pain (OR=1.64, 95%CI=1.28-2.08).

Table 3 Multiple logistic regression of factors associated with frailty

Independent variables	Unadjusted ORs* (95%CI)	p	Adjusted ORs (95%CI)	p
Age category, years (65-79 as reference)				
80-89	2.80 (2.26-3.48)	<0.001	2.29 (1.81-2.91)	<0.001
90-99	8.19 (6.55-10.23)	<0.001	5.76 (4.41-7.51)	<0.001
≥100+	19.75 (14.52-26.85)	<0.001	11.82 (8.31-16.80)	<0.001
Sex (male as reference)				
Female	2.10 (1.81-2.44)	<0.001	1.40 (1.12-1.74)	0.003
Co-residence (with household members as reference)	0.77 (0.64-0.94)	0.008	0.58 (0.46-0.72)	<0.001
Alone or In an institution				
Marital status (married as reference)				
Single	3.01 (2.56-3.54)	<0.001	1.42 (1.15-1.76)	0.001
Years of schooling (>0 as reference)				
0	2.53 (2.17-2.95)	<0.001	1.18 (0.96-1.44)	0.110
Sufficient financial support (yes as reference)				
No	1.47 (1.22-1.77)	<0.001	1.52 (1.22-1.89)	<0.001
Smoking (no as reference)				
Yes	0.65 (0.55-0.76)	<0.001	1.16 (0.93-1.45)	0.187
Drinking (no as reference)				
Yes	0.65 (0.55-0.78)	<0.001	0.95 (0.76-1.19)	0.660
Do physical labor regularly (yes as reference)				
No	1.27 (1.06-1.53)	0.012	1.65 (1.32-2.06)	<0.001
Do exercise (yes as reference)				
No	3.29 (2.73-3.97)	<0.001	2.65 (2.15-3.27)	<0.001
Teeth number (>20 as reference)				
0	4.76 (3.66-6.20)	<0.001	2.07 (1.53-2.80)	<0.001
1-10	3.42 (2.62-4.46)	<0.001	1.77 (1.31-2.38)	<0.001
11-20	1.82 (1.34-2.47)	<0.001	1.30 (0.93-1.82)	0.122
Chewing pain (no as reference)				
Yes	0.91 (0.75-1.12)	0.387	1.64 (1.28-2.08)	<0.001
BMI*, kg/m^2 (18.5-23.9 as reference)				
<18.5	2.34 (1.94-2.82)	<0.001	1.55 (1.25-1.923)	<0.001
24-27.9	1.04 (0.86-1.26)	0.692	1.46 (1.17-1.82)	0.001
≥28	1.26 (0.94-1.70)	0.124	2.06 (1.46-2.90)	<0.001

*BMI refers to Body Mass Index; ORs refers to odds ratios; CI refers to confidence interval.

Discussion

We used data from a nationwide longitudinal survey in China to examine the association between frailty and tooth number. Both univariate and multiple logistic regressions were performed to explore the association between tooth number and frailty. Considering that the relationship between tooth number and frailty might not be purely linear, we transformed the continuous variable FI into a dichotomous variable as non-frail and frail to obtain more practical information about clinical benefit. In addition, age and tooth number were categorized into four groups according to clinical importance to improve the effectiveness of the multiple logistic regression model. The main findings suggested that, after adjusting for sociodemographic, health behavioural and nutritional variables, older adults with fewer teeth had significantly higher odds of frailty than those with more than 20 teeth, except for participants with 11-20 teeth. To the best of our knowledge, this is the first study exploring the association between frailty and oral health among older Chinese adults.

According to our results, the prevalence of frailty was 27.68%, which is consistent with the previously reported prevalence of frailty among community-dwelling older adults in the Asia-Pacific region.[9] Older adults with fewer than 11 teeth were at higher odds of being frail, while no significant difference in frailty risk was found between older adults with 11-20 teeth and those with more than 20 teeth, suggesting a non-linear relationship between tooth number and frailty. Two cross-sectional studies from Brazil and the United States indicated that older adults with more than 20 teeth had a lower chance of being frail than edentulous individuals.[11,17] One cohort study in Japan suggested that older adults who have 20 or more teeth with nine or more occluding pairs of teeth had a significantly lower risk of frailty.[8] By using linear analysis, a cohort study in Mexico suggested that each additional tooth was associated with a lower probability of developing frailty.[12] However, two cross-sectional studies performed in Mexico[16] and Thailand[15] and one cohort study in Denmark[10] did not find a significant association between the number of teeth and frailty. Collectively, current evidence supports that the relationship between frailty and tooth number exists in the older population in Brazil, the US, Japan, Mexico, and China, but does not exist in Danish and Thai older adults. These conflicting findings might be explained by several factors, including the study design, demographic covariates such as age, sex and education

level, the ways of defining tooth number, and the cultural context from which the participants came from. Our findings confirmed the association among older Chinese adults that fewer teeth are related to being frailer. However, our study observed an absence of a significant difference between older adults with 11-20 teeth and those with more than 20 teeth after adjusting for a variety of confounders. This finding might imply that older adults with 11-20 teeth might have comparable chances of being frail with older adults having 20 or more teeth. However, previous studies reported 20 teeth as the cut-off point of being frail. The inconsistency might be explained by several reasons. First, the cut-off point of teeth number for being frail among older adults might lie within the range from 11 to 20 teeth, but current studies fail to recognize it. Future studies could explore the specific turning points of the relationship between frailty and tooth number and explain the underlying mechanisms. Second, the distribution of tooth number among the participants in the present study might be different from those of previous studies. Chinese older adults have worse oral health compared with their counterparts in developed countries.[34] Therefore, the characteristics of tooth number among older Chinese adults might lead to a different form of its association with frailty. Third, the important covariates included in the previous studies varied from the present study, such as the number of occluding pairs of teeth, functional teeth and chewing pain. Moreover, our study used FI rather than frailty phenotype to identify the frailty status of the participants. Instead of solely relying on physical markers,[6] FI included a broader combination of health status, such as cognitive impairment, psychosocial status, physical limitations, and chronic diseases. Some of these health status variables were viewed as covariates in the analyses of previous studies. However, these hypotheses, as well as the issue of causal order, should be further evaluated in longitudinal studies.

To fully control the potential confounders impacting the association between frailty and tooth number, our study included variables of demographic factors and health behaviours. Congruent with the previous findings, participants who were older, female, single, and suffering from insufficient financial support had a significantly higher risk of being frail. Health behaviours, including regular physical labour and exercise, are significantly associated with a lower risk of being frail. In previous studies,

physical activities were not considered as a covariate. However, emerging evidence suggests that physical activities could act as a remedy against frailty.[35] A longitudinal survey is needed to confirm the causal relationship. In line with previous studies, our findings also suggest that smoking and drinking are not significantly associated with frailty.[12,17]

BMI was included in our study as a basic indicator of nutritional status. Underweight, overweight and obese older adults were at a significantly higher risk of frailty than those with normal BMI according to our findings as well as a previous study.[17] Identifying the relationship between nutrition and frailty is helpful in understanding the association between frailty and tooth number because some studies proposed that tooth loss could lead to frailty through malnutrition. Tooth loss could reduce one's chewing ability and alter food selection, thus consuming inadequate nutrients for life and physiological function, and finally contributing to the development of frailty.[36] However, this hypothesis has not been verified in a population study and is opposite to the findings in animal models where dietary restriction could significantly extend lifespan.[37] The role of nutrition in mediating the relationship between frailty and tooth number is still unclear. On the other hand, current findings support that severe periodontitis is associated with the incidence of frailty. Tooth loss as a final consequence of periodontitis could contribute to frailty through inflammation. Inflammatory factors derived from the body's response to periodontal infection may disseminate to other organs and alter their metabolism.[16,21] However, the evidence regarding inflammation and frailty in human beings is still conflicting.[38] There is a lack of studies on understanding the interrelationships among tooth number, inflammation, nutrition and frailty. By including global oral health indicators, inflammatory biomarkers, nutritional biomarkers and behavioural variables, such as daily choice of food or diet, future studies could portray a clearer picture of the mechanisms underlying tooth number and frailty with the goal of identifying aetiologic factors that are subject to public health interventions.

Strengths and limitations

This study has some strengths. First, this analysis was performed based on a large nationally representative sample of older Chinese adults, and the response rate of the participants in the CLHLS

was high (from 94.9% to 98%), enhancing the generalizability of the results. Second, the multidisciplinary approach of the CHLHS and the large range of data collected allow us to calculate FI and adjust the analyses for demographics, nutrition status and health behaviours to be related to the outcome. Third, the present study measured frailty by calculating the FI, which assesses comprehensive health conditions and is reliable in large sample studies, contributing to a broader and supplementary explanation of previous findings. However, our data must be interpreted with caution. The self-reported tooth number might be subjective, although it has been widely used as a measure of oral health in epidemiological surveys.[13,17] Information on oral health is limited because the CLHLS was not specifically designed for dentate studies. Tooth loss might be inadequate in representing oral functions when understanding the deeper connections between oral health and frailty. Another weakness is the cross-sectional nature of this study. As the time of tooth loss and development of frailty were not determined, a causal relationship could not be established. Previous studies hypothesized that tooth loss could contribute to malnutrition or inflammation, resulting in developing frailty. However, tooth loss could present as one of the consequences or manifestations during the frailty process instead of being the initiator of frailty. For instance, frailty could contribute to losing functional teeth and reducing masseter muscle thickness.[8] Therefore, longitudinal studies are needed to understand the relationship between frailty and tooth number.

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Disclosure statement

The authors declare no conflict of interest.

Author contributions

Yaohua Gu, Wenwen Wu and Xiaodong Tan contributed to conception and design of the study and drafting the manuscript. Jinbing Bai, Xuyu Chen, Zhijie Zou and Liping Yu contributed to acquisition, analysis, and interpretation of the data. Xiaoli Chen, Qing Zhang, Xianbo Pei, Xianwu Luo and Xin Liu revised the manuscript. All of the authors approved the version to be published.

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Data availability statement

Data are available in the public open access repository of Peking University.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12

		(*b*) Report category boundaries when continuous variables were categorized	6-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between the number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

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Keywords:	frailty, older adults, China, number of teeth, oral health

Title page

Association between the number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

Running Title: the number of teeth and frailty among older Chinese

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Abstract

Objectives To explore the association between the number of teeth and frailty among older Chinese adults using a nationally representative sample.

Design Cross-sectional analysis was carried out using the 2014 wave data from the Chinese Longitudinal Health Longevity Survey, which used a targeted random-sampling design.

Setting This research was conducted in communities from nearly half of the counties and cities in 22 out of 31 provinces throughout China.

Participants Of the 6934 interviewees aged ≥ 65 years, the final analysis included 3635 older adults who had completed the 2014 wave survey on the variables included in the study.

Primary and secondary outcome measures Outcome variables included frailty, measured by the Frailty Index, and number of teeth. Covariates included demographic characteristics (i.e., age, sex, co-residence, marital status, years of education and financial support), body mass index (BMI), and health behaviours (i.e., smoking, drinking and exercise). A univariate logistic regression was used to test the factors associated with frailty. A multiple logistic regression model was used, using the frailty score as the dependent variable and the number of teeth together with significant covariates as the independent variables.

Results The prevalence of frailty was 27.68%. The mean number of teeth present was 9.23 (SD=10.03). The multiple logistic regression showed that older adults' demographic variables, health behaviours, BMI, tooth number, and chewing pain were significantly associated with frailty. After adjusting for the covariates, older adults with fewer teeth had significantly higher odds of frailty than those with 20 or more teeth (no teeth: odds ratio [OR]=2.07, 95%CI=1.53-2.80; 1-10 teeth: OR=1.77, 95%CI=1.31-2.38), except for older adults with 11-20 teeth (OR=1.30, 95%CI=0.93-1.82).

Conclusions The presence of fewer teeth is significantly associated with frailty status among older Chinese adults. Future studies are needed to explain the specific mechanisms underlying how oral health status is associated with frailty.

Key words Frailty; older adults; number of teeth; China; oral health

Article summary:

- This is the first study on frailty and oral health conducted in China.
- This study used a large nationally representative sample.
- This study measured frailty using the Frailty Index, which included chronic conditions, daily activities, cognitive function and so forth.
- The covariates of this study included the measurement of sociodemographic factors, nutritional status and health behaviours, which enabled the assessment of several confounding factors.
- This is a cross-sectional study that cannot indicate causal relationships between frailty and oral health.

Association between the number of teeth and frailty among Chinese older adults: A nationwide cross-sectional study

Introduction

Populations around the world are rapidly ageing. As an inevitable demographic transition, the ageing population is estimated to become the next global public health challenge.[1] Frailty is one of the most problematic expressions of population ageing.[2] The prevalence of frailty in community-dwelling older adults is 10%-27% for those older than 65 years and 45% for those older than 85 years.[3] Frailty is a clinical condition that is defined as a reduced ability to cope with acute or external stressors in daily life due to ageing-associated decline in reserve and function.[4] It is associated with a higher risk of falls, hospitalization, nursing home residence, disability, and death,[5] which places a significant burden on the individual, the family, and public health systems.

Frailty is believed to develop due to a reduced physiological reserve caused by cumulative molecular and cellular damage during ageing and become evident when physiological decline reaches an aggregate crucial level.[2] Although the pathophysiological changes underlying and preceding frailty are incompletely understood, multiple causes, inter-relationships, and complex pathways have been proposed according to current research findings.[6] Evidence shows that frailty may be modifiable and is considered to have greater reversibility than disability.[7]

It is important to develop interventions targeting risk factors to maintain older adults' quality of life and delay or prevent the development of frailty and its subsequent need for long-term care.[8] Until now, the proposed risk factors for frailty include physiological changes with ageing, inflammation, sarcopenia, polypharmacy, social isolation, and malnutrition.[9] Notably, emerging research has shown that frailty is significantly associated with oral health and functions, including tooth number,[10-12] functional dentition,[13] chewing ability,[14,15] periodontitis,[12] utilization of dental services,[11,16,17] and self-perception of oral health.[14,16] More teeth were significantly associated with a lower risk of developing frailty[11,12,13,17] because tooth loss might be caused by severe periodontal diseases, which can trigger

higher levels of inflammatory markers and contribute to the development of frailty.[14] Another line of evidence has proposed that tooth loss can change one's food selection and nutrient intake, resulting in malnutrition and contributing to the development of frailty.[12]

The current evidence on the relationship between the number of teeth and frailty is controversial.[8,10,15,16] The conflicting results might be caused by the confounders of the subjects and the population from which they were recruited. Previous studies have measured frailty using the Frailty Phenotype, which is based on a pre-defined set of five criteria exploring the presence/absence of signs or symptoms (i.e., involuntary weight loss, exhaustion, slowness, poor handgrip strength and sedentary behaviour).[18] There is a growing tendency to view frailty from a multidimensional perspective consisting of physical, psychological, social, and most recently environmental frailty.[19] Although the Frailty Phenotype is conveniently applied, specific conditions (such as disability or cognitive impairment) can affect the reliability or clinical utility of the Frailty Phenotype results. Studies using Frailty Phenotypes cannot rule out confounding factors caused by cognitive impairment, which not only is an important domain of frailty[20] but also is significantly related to tooth number among older adults.[21] In particular, disabling conditions may affect the predictive value of the phenotype for negative health-related events due to a sort of 'ceiling effect'.[18]

The Frailty Index (FI), which assesses a broader spectrum of disorders than the Frailty Phenotype, might provide more information on exploring the association between tooth loss and frailty. Moreover, the association between tooth number and frailty is poorly understood in developing countries, especially in China, which has the largest population and the most rapidly ageing population in the world. Therefore, the present study is the first study that not only measures FI when exploring the association between tooth loss and frailty but also investigates this relationship among older Chinese adults using a large nationally representative sample.

Methods

Study design and population

We used data from the Chinese Longitudinal Health Longevity Survey (CLHLS), which is the first national longitudinal project to investigate the determinants of health and longevity of older adults in China from a multidisciplinary perspective.[22] The survey was conducted every three years in seven waves, from 1998 to 2014, in randomly selected older adults from nearly half of the counties and cities in 22 out of 31 provinces in China. These data represent approximately 85% of the Chinese population. A targeted random-sampling design was employed to ensure representativeness. Internationally compatible questionnaires were used to collect a comprehensive set of information, including demographic characteristics, family and household characteristics, lifestyle and diet, economic resources, social support, myriad physical, psychological and cognitive health conditions, etc. All the information was obtained through face-to-face interviews as well as some basic physical examinations at the interviewee's home. Interviews were based on voluntary participation and written informed consent was obtained from the participants prior to recruitment.

The data from the CLHLS are of high quality according to its representativeness and randomness of attrition.[23] The response rate of the oldest-old (older than 80 years) participants in the CLHLS was very high (98%) because the Chinese oldest-old adults, in general, may be proud to be a member of such a long-lived group are willing to talk to outside people. However, the response rate decreased among younger older adults aged 65-79 (94.9%).[24] The average proportion of incompleteness of an item rated for each respondent in the CLHLS is less than 10%.[25] The details of the sampling design, response rates, and systematic assessments of data quality across numerous measures have been described elsewhere.[26] The present study utilized cross-sectional data from the 2014 wave of the CLHLS. This study was approved by the Ethical Committee of the Medical College of Wuhan University.

Patient and public involvement

Participants and the public were not involved in the development of the study design or outcome measures. Participation was voluntary and could be terminated at any time. The results will not be distributed to the participants themselves. All data were used strictly confidentially and anonymously.

Outcome variables

Various measurements exist for assessing frailty, with the Frailty Index (FI) and Frailty Phenotype being the most common applications.[27] The FI is defined as the proportion of accumulated deficits,[28] and calculated by the proportion of the number of health deficits presented to the total number of possible health deficits for a given individual.[22] For samples of the CLHLS, the FI has been found to be a valid and reliable frailty measure, and an independent and robust predictor of adverse outcomes among the Chinese elderly population.[29, 30]

As presented in Table 1, we used 38 indicators of health deficits encompassing nine major sets of components following the established research[17,22,29,30]: cognitive functioning, chronic disease conditions (self-reports from a list of 11 diseases), Activity of Daily Living disability (ADL, needing help in performing the six basic daily activities), Instrumental Activity of Daily Living disability (IADL, needing help in performing the eight independent living activities), functional limitations (five objective examinations of physical function), self-rated health, hearing and vision impairment, psychological distress, and others (e.g., abnormal heart rhythm, interviewer-rated health, number of serious illnesses in the past two years).

Table 1 Health deficits included in calculating the Frailty Index

Components	Measurement	Deficit	Score
Cognitive impairment	The Chinese version of the Mini-Mental State Examination	≤ 23	1
Chronic disease conditions	Hypertension, diabetes, tuberculosis, heart disease, stroke/cerebrovascular disease, bronchitis/asthma, cancer, arthritis, bedsores, gastric/duodenal ulcer, Parkinson's disease	Yes	11
Activity of Daily Living disability	Eating, bathing, dressing, toileting, transferring, continence	Not able to do independently	6
Instrumental Activity of Daily Living disability	Visiting neighbors, cooking meals, shopping, washing clothing, walking continuously for 1 kilometer, lifting a weight of 5 kilograms, continuously crouching and standing up three times, using public transportation	Not able to do independently	8
Functional limitations	Putting hand behind neck, putting hand behind lower back, raising arm upright, standing up from sitting a chair, picking up a book from the floor	Not able to do	5
Self-rated health	Self-assessed current global health	Bad	1
Hearing and vision impairment	Hearing and vision loss	Yes	2
Psychological distress	Felt fearful/anxious, lonely/isolated, or useless	Often/always	1
Others	Heart rhythm	Abnormal	1
	Interviewer-rated health	Bad	1
	Number of serious illnesses in the past two years	One/two or more	1/2
Total			39

Both face-to-face interviews and basic physical examinations were conducted to obtain the above information of each participant. Cognitive functioning, functional limitations, rhythm of the heart, and interviewer-rated health were assessed by the interviewers who were intensively trained according to a nationally standardized procedure before the survey.[25] Other information, such as chronic disease conditions and psychological distress, was recorded according to the response of the participants or the proxy of the participants who were unable to give accurate answers due to impaired hearing, vision or recall problems.[25]

Each item was dichotomized and coded as 1 if a deficit was present (otherwise 0). A score of 2 was assigned for individuals with more than one serious illness in the past two years that led to hospital admission or a period of bed confinement. The total score of these 38 items was 39.[29] The FI of each participant was calculated as the total score of an individual divided by the maximum total score of 39.

The FI scores ranged from 0-1. Cut-off points of FI are needed to identify frail older adults and to estimate the prevalence of frailty at the population level.[31] At present, the universally accepted category of FI scores are as follows: non-frail (0-0.10), vulnerable (0.10-0.21), frail (0.22-0.44), and frailest (≥ 0.45).[31] In the present study, the FI is categorized as non-frailty (0-0.21) and frailty (>0.21).[32]

Independent variable

The self-reported number of teeth was recorded using the following question: "How many natural teeth do you still have?" In addition, chewing pain was recorded by the question: "During the past 6 months, did you have a toothache more than once, when biting or chewing?" For older adults who were not able to answer these questions due to cognitive, hearing or linguistic impairments, their closest relative or caregiver was asked to answer for them.[25] The number of teeth of the older adults in this survey is similar to that in the Second National Epidemiological Survey on Oral Health, which confirms that the results of this survey represent the general patterns of tooth loss among elderly adults in China.[33] In accordance with practical and clinical importance, the present study grouped the number of teeth into four categories: 0 tooth, 1-10 teeth, 11-20 teeth, and > 20 teeth.[11]

Covariates

Based on well-established literature on the factors influencing frailty, we included covariates for basic demographic characteristics, body mass index (BMI) and health behaviours. Demographic variables include age (65-79 years, 80-89 years, 90-99 years, ≥ 100 years), sex, co-residence condition (with household members, alone, in an institution), marital status (currently married and living with spouse, married but not living with spouse, others), years of education (received no education, received more than one year of education), financial support (sufficient, insufficient). BMI (kg/m^2) was defined as the ratio between the weight and the square of the height. In the present study, BMI was grouped into four categories: <18.5, 18.5-23.9, 24-27.9, and ≥28. Health behaviours included smoking (yes vs. no), alcohol consumption (yes vs. no), regular exercise (yes vs. no), and regular physical labour (yes vs. no).

Statistical analysis

Baseline characteristics of the subjects were reported as frequency and percentages for categorical variables. We examined the association between frailty and the potential covariates using the Chi-squared test. A univariate logistic regression was carried out to calculate the crude odds ratios (OR) of the independent variables in association with frailty status. A multiple logistic regression model was used, employing frailty status as the dependent variable, and the dental variables (number of teeth and chewing pain) and covariates as the independent variables. Demographic, nutritional and behavioural covariates identified as statistically significant in the univariate analysis were included in the multiple logistic regression to adjust for the relationship between frailty and the tooth number. P values of less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the participants

Of the 7019 interviewees who participated in the 2014 CHLHS, we initially included 6934 participants aged ≥ 65 years. The final analysis included 3635 older adults who had complete data on frailty and other explanatory factors used in the analyses. The main characteristics of 3635 participants and the frailty status are described in Table 2. The average age of the participants was 84.27 years (SD= 9.92) and 38.3% (n=1393) of them were aged between 65 years and 79 years. More than half of the participants were female (n=1884, 51.8%), single (n=2051, 56.4%), and living with household members (n=2918, 80.3%). Furthermore, 52.9% of the older adults had not received any education (n=1924), while 83.5% (n=3034) had sufficient financial support. For health behaviours, 66.3% (n=2411) never smoked, 72% (n=2618) never drank alcohol, 82.3% (n=2992) did physical labour regularly, while 68.2% (n=2478) did not exercise. More than half of the subjects (n=2012, 55.4%) had a normal BMI.

Tooth loss and frailty status of the participants

Among all the subjects, the average number of teeth was 9.23 (SD= 10.03), 32.4% (n=1179) of the participants had 1 to 10 teeth, and the majority of them reported no chewing pain (n=3066, 84.3%). The average FI score was 0.16 (SD= 0.14), and the prevalence of frailty was 27.68%.

Table 2 Participant characteristics by frailty

Variable	Total (n=3635)	Non-frailty (n=2629)	Frailty (n=1006)	χ^2	p-value
Age categories (years), n(%)				628.52	<0.001
65-79	1393 (38.3%)	1248 (47.5%)	145 (14.4%)		
80-89	1201 (33.0%)	906 (34.5%)	295 (29.3%)		
90-99	761 (20.9%)	390 (14.8%)	371 (36.9%)		
≥100+	280 (7.7%)	85 (3.2%)	195 (19.4%)		
Sex, n(%)				95.33	<0.001
Male	1751 (48.2%)	1398 (53.2%)	353 (35.1%)		
Female	1884 (51.8%)	1231 (46.8%)	653 (64.9%)		
Co-residence, n(%)				7.02	0.008
With household members	2918 (80.3%)	2080 (79.2%)	836 (83.1%)		
Alone or In an institution	717 (19.7%)	547 (20.8%)	170 (16.9%)		
Marital status, n(%)				187.98	<0.001
Married	1584 (43.6%)	1329 (50.6%)	255 (25.3%)		
Single	2051 (56.4%)	1300 (49.4%)	751 (74.7%)		
Years of schooling, n(%)				149.47	<0.001
>0	1711 (47.1%)	1399 (53.2%)	312 (31.0%)		
0	1924 (52.9%)	1230 (46.8%)	694 (69.0%)		
Sufficient financial support, n(%)				16.47	<0.001
Yes	3034 (83.5%)	2235 (85.0%)	799 (79.4%)		
No	601 (16.5%)	394 (15.0%)	207 (20.6%)		
Smoking, n(%)				50.78	<0.001
No	2411 (66.3%)	1676 (63.8%)	735 (73.1%)		
Yes	1224 (33.7%)	953 (36.2%)	271 (26.9%)		
Drinking, n(%)				61.60	<0.001
No	2618 (72.0%)	1834 (69.8%)	784 (77.9%)		
Yes	1017 (28.0%)	795 (30.2%)	222 (22.1%)		
Do physical labor regularly, n(%)				6.40	0.011
Yes	2992 (82.3%)	2190 (83.3%)	802 (79.7%)		
No	643 (17.7%)	439 (16.7%)	204 (20.3%)		
Do exercise, n(%)				166.65	<0.001
Yes	1157 (31.8%)	999 (38.0%)	158 (15.7%)		
No	2478 (68.2%)	1630 (62.0%)	848 (84.3%)		
Teeth number, n(%)				182.13	<0.001
>20	672 (18.5%)	594 (22.6%)	78 (7.8%)		
11-20	643 (17.7%)	519 (19.7%)	124 (12.3%)		
1-10	1179 (32.4%)	814 (31.0%)	365 (36.3%)		
0	1141 (31.4%)	702 (26.7%)	439 (43.6%)		
Chewing pain, n(%)				0.75	0.387
No	3066 (84.3%)	2209 (84.0%)	857 (85.2%)		
Yes	569 (15.7%)	420 (16.0%)	149 (14.8%)		
BMI*, kg/m^2, n(%)				86.32	<0.001
<18.5	633 (17.4%)	364 (13.8%)	269 (26.7%)		
18.5-23.9	2012 (55.4%)	1529 (58.2%)	483 (48.0%)		
24-27.9	748 (20.6%)	563 (21.4%)	185 (18.4%)		
≥28	242 (6.7%)	173 (6.6%)	69 (6.9%)		

*BMI refers to Body Mass Index.

Tooth number and other influencing factors of frailty

According to the Chi-square tests, frailty status is associated with demographic variables (i.e., age category, sex, co-residence condition, marital status, years of schooling and financial support), health behaviours (i.e., smoking, drinking, doing physical labour and exercise), BMI, and tooth number ($p<0.05$). No significant differences were found in frailty status based on chewing pain ($p=0.387$) (Table 2).

Univariate and multiple logistic regressions were carried out to report both the crude ORs and adjusted ORs of the independent variables as presented in Table 3. In the final multiple logistic regression model, the number of teeth is a significant factor in determining frailty after adjusting for covariates, including age category, sex, co-residence, marital status, years of schooling, financial support, smoking, drinking, doing exercise, doing physical labour, and BMI.

Participants of older age were at a significantly higher risk of frailty than those participants aged 65 years to 79 years (80-89 years old: OR=2.29, 95%CI=1.81-2.91; 90-99 years old: OR=5.76, 95%CI=4.41-7.51; 100 years and older: OR=11.82, 95%CI=8.31-16.80). Female participants had a significantly higher risk of being frail (OR=1.40, 95%CI=1.12-1.74). For participants who lived alone or in an institution, the risk of frailty was significantly lower (OR=0.58, 95%CI=0.46-0.72). Single older adults had a significantly higher risk of frailty than married older adults (OR=1.42, 95%CI=1.15-1.76). Participants with insufficient financial support had a significantly higher risk of frailty than those who had sufficient financial support (OR=1.52, 95%CI=1.22-1.88).

Smoking and drinking were significantly associated with frailty in the unadjusted analyses, but the association decreased to non-significance in the adjusted analyses. Participants who did not perform physical labour regularly or exercise had a significantly higher risk of frailty than those who did physical labour regularly (OR=1.65, 95%CI=1.32-2.06) or exercise (OR=2.65, 95%CI=2.15-3.27). Participants with abnormal BMI were at a significantly higher risk of frailty than those within the normal BMI range (<18.5 kg/m^2: OR=1.55, 95%CI=1.25-1.93; 24-27.9 kg/m^2: OR=1.46, 95%CI=1.17-1.82; ≥ 28 kg/m^2: OR=2.06, 95%CI=1.46-2.90).

Participants with fewer teeth were at a significantly higher risk of frailty than those with more than 20 teeth (no teeth: OR=2.07, 95%CI=1.53-2.80; 1-10 teeth: OR=1.77, 95%CI=1.31-2.38), except for participants with 11-20 teeth (OR=1.30, 95%CI=0.93-1.82). Participants who had chewing pain had a significantly higher risk of frailty than those with no chewing pain (OR=1.64, 95%CI=1.28-2.08).

Table 3 Multiple logistic regression of factors associated with frailty

Independent variables	Unadjusted ORs* (95%CI)	p	Adjusted ORs (95%CI)	p
Age category, years (65-79 as reference)				
80-89	2.80 (2.26-3.48)	<0.001	2.29 (1.81-2.91)	<0.001
90-99	8.19 (6.55-10.23)	<0.001	5.76 (4.41-7.51)	<0.001
≥100+	19.75 (14.52-26.85)	<0.001	11.82 (8.31-16.80)	<0.001
Sex (male as reference)				
Female	2.10 (1.81-2.44)	<0.001	1.40 (1.12-1.74)	0.003
Co-residence (with household members as reference)	0.77 (0.64-0.94)	0.008	0.58 (0.46-0.72)	<0.001
Alone or In an institution				
Marital status (married as reference)				
Single	3.01 (2.56-3.54)	<0.001	1.42 (1.15-1.76)	0.001
Years of schooling (>0 as reference)				
0	2.53 (2.17-2.95)	<0.001	1.18 (0.96-1.44)	0.110
Sufficient financial support (yes as reference)				
No	1.47 (1.22-1.77)	<0.001	1.52 (1.22-1.89)	<0.001
Smoking (no as reference)				
Yes	0.65 (0.55-0.76)	<0.001	1.16 (0.93-1.45)	0.187
Drinking (no as reference)				
Yes	0.65 (0.55-0.78)	<0.001	0.95 (0.76-1.19)	0.660
Do physical labor regularly (yes as reference)				
No	1.27 (1.06-1.53)	0.012	1.65 (1.32-2.06)	<0.001
Do exercise (yes as reference)				
No	3.29 (2.73-3.97)	<0.001	2.65 (2.15-3.27)	<0.001
Teeth number (>20 as reference)				
0	4.76 (3.66-6.20)	<0.001	2.07 (1.53-2.80)	<0.001
1-10	3.42 (2.62-4.46)	<0.001	1.77 (1.31-2.38)	<0.001
11-20	1.82 (1.34-2.47)	<0.001	1.30 (0.93-1.82)	0.122
Chewing pain (no as reference)				
Yes	0.91 (0.75-1.12)	0.387	1.64 (1.28-2.08)	<0.001
BMI*, kg/m^2 (18.5-23.9 as reference)				
<18.5	2.34 (1.94-2.82)	<0.001	1.55 (1.25-1.923)	<0.001
24-27.9	1.04 (0.86-1.26)	0.692	1.46 (1.17-1.82)	0.001
≥28	1.26 (0.94-1.70)	0.124	2.06 (1.46-2.90)	<0.001

*BMI refers to Body Mass Index; ORs refers to odds ratios; CI refers to confidence interval.

Discussion

We used data from a nationwide longitudinal survey in China to examine the association between frailty and tooth number. To the best of our knowledge, this is the first study exploring the association between frailty and oral health among older Chinese adults. Both univariate and multiple logistic regressions were performed to explore the association between tooth number and frailty. Considering that the relationship between tooth number and frailty might not be purely linear, we transformed the continuous variable FI into a dichotomous variable as non-frail and frail to obtain more practical information about clinical benefit. In addition, age and tooth number were categorized into four groups according to clinical importance to improve the effectiveness of the multiple logistic regression model. The main findings suggested that, after adjusting for sociodemographic, health behavioural and nutritional variables, older adults with fewer teeth had significantly higher odds of frailty than those with more than 20 teeth, except for participants with 11-20 teeth.

According to our results, the prevalence of frailty was 27.68%, which is consistent with the previously reported prevalence of frailty among community-dwelling older adults in the Asia-Pacific region.[9] Older adults with fewer than 11 teeth were at higher odds of being frail, while no significant difference in frailty risk was found between older adults with 11-20 teeth and those with more than 20 teeth, suggesting a non-linear relationship between tooth number and frailty. Two cross-sectional studies from Brazil and the United States indicated that older adults with more than 20 teeth had a lower chance of being frail than edentulous individuals.[11,17] One cohort study in Japan suggested that older adults who have 20 or more teeth with nine or more occluding pairs of teeth had a significantly lower risk of frailty.[8] By using linear analysis, a cohort study in Mexico suggested that each additional tooth was associated with a lower probability of developing frailty.[12] However, two cross-sectional studies performed in Mexico[16] and Thailand[15] and one cohort study in Denmark[10] did not find a significant association between the number of teeth and frailty. Collectively, current evidence supports that the relationship between frailty and tooth number exists in the older population in Brazil, the US, Japan, Mexico, and China, but does not exist in Danish and Thai older adults. These conflicting findings might be explained by several factors, including the study design, demographic covariates such as age, sex and education

level, the ways of defining tooth number, and the cultural context from which the participants came from. Our findings confirmed the association among older Chinese adults that fewer teeth are related to being frailer. However, our study observed an absence of a significant difference between older adults with 11-20 teeth and those with more than 20 teeth after adjusting for a variety of confounders. This finding might imply that older adults with 11-20 teeth might have comparable chances of being frail with older adults having 20 or more teeth. However, previous studies reported 20 teeth as the cut-off point of being frail. The inconsistency might be explained by several reasons. First, the cut-off point of teeth number for being frail among older adults might lie within the range from 11 to 20 teeth, but current studies fail to recognize it. Future studies could explore the specific turning points of the relationship between frailty and tooth number and explain the underlying mechanisms. Second, the distribution of tooth number among the participants in the present study might be different from those of previous studies. Chinese older adults have worse oral health compared with their counterparts in developed countries.[34] Therefore, the characteristics of tooth number among older Chinese adults might lead to a different form of its association with frailty. Third, the important covariates included in the previous studies varied from the present study, such as the number of occluding pairs of teeth, functional teeth and chewing pain. Moreover, our study used FI rather than Frailty Phenotype to identify the frailty status of the participants. Instead of solely relying on physical markers,[6] FI included a broader combination of health status, such as cognitive impairment, psychosocial status, physical limitations, and chronic diseases. Some of these health status variables were viewed as covariates in the analyses of previous studies. However, these hypotheses, as well as the issue of causal order, should be further evaluated in longitudinal studies.

To fully control the potential confounders impacting the association between frailty and tooth number, our study included variables of demographic factors and health behaviours. Congruent with the previous findings, participants who were older, female, single, and suffering from insufficient financial support had a significantly higher risk of being frail. Health behaviours, including regular physical labour and exercise, are significantly associated with a lower risk of being frail. In previous studies,

physical activities were not considered as a covariate. However, emerging evidence suggests that physical activities could act as a remedy against frailty.[35] A longitudinal survey is needed to confirm the causal relationship. In line with previous studies, our findings also suggest that smoking and drinking are not significantly associated with frailty.[12,17]

BMI was included in our study as a basic indicator of nutritional status. Underweight, overweight and obese older adults were at a significantly higher risk of frailty than those with normal BMI according to our findings as well as a previous study.[17] Identifying the relationship between nutrition and frailty is helpful in understanding the association between frailty and tooth number because some studies proposed that tooth loss could lead to frailty through malnutrition. Tooth loss could reduce one's chewing ability and alter food selection, thus consuming inadequate nutrients for life and physiological function, and finally contributing to the development of frailty.[36] However, this hypothesis has not been verified in a population study and is opposite to the findings in animal models where dietary restriction could significantly extend lifespan.[37] The role of nutrition in mediating the relationship between frailty and tooth number is still unclear. On the other hand, current findings support that severe periodontitis is associated with the incidence of frailty. Tooth loss as a final consequence of periodontitis could contribute to frailty through inflammation. Inflammatory factors derived from the body's response to periodontal infection may disseminate to other organs and alter their metabolism.[16,21] However, the evidence regarding inflammation and frailty in human beings is still conflicting.[38] There is a lack of studies on understanding the interrelationships among tooth number, inflammation, nutrition and frailty. By including global oral health indicators, inflammatory biomarkers, nutritional biomarkers and behavioural variables, such as daily choice of food or diet, future studies could portray a clearer picture of the mechanisms underlying tooth number and frailty with the goal of identifying aetiologic factors that are subject to public health interventions.

Strengths and limitations

This study has some strengths. First, this analysis was performed based on a large nationally representative sample of older Chinese adults, and the response rate of the participants in the CLHLS

was high (from 94.9% to 98%), enhancing the generalizability of the results. Second, the multidisciplinary approach of the CHLHS and the large range of data collected allow us to calculate FI and adjust the analyses for demographics, nutrition status and health behaviours to be related to the outcome. Third, the present study measured frailty by calculating the FI, which assesses comprehensive health conditions and is reliable in large sample studies, contributing to a broader and supplementary explanation of previous findings. However, our data must be interpreted with caution. The self-reported tooth number might be subjective, although it has been widely used as a measure of oral health in epidemiological surveys.[13,17] Information on oral health is limited because the CLHLS was not specifically designed for dentate studies. Tooth loss might be inadequate in representing oral functions when understanding the deeper connections between oral health and frailty. Another weakness is the cross-sectional nature of this study. As the time of tooth loss and development of frailty were not determined, a causal relationship could not be established. Previous studies hypothesized that tooth loss could contribute to malnutrition or inflammation, resulting in developing frailty. However, tooth loss could present as one of the consequences or manifestations during the frailty process instead of being the initiator of frailty. For instance, frailty could contribute to losing functional teeth and reducing masseter muscle thickness.[8] Therefore, longitudinal studies are needed to understand the relationship between frailty and tooth number.

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Disclosure statement

The authors declare no conflict of interest.

Author contributions

Yaohua Gu, Wenwen Wu and Xiaodong Tan contributed to conception and design of the study and drafting the manuscript. Jinbing Bai, Xuyu Chen, Zhijie Zou and Liping Yu contributed to acquisition, analysis, and interpretation of the data. Xiaoli Chen, Qing Zhang, Xianbo Pei, Xianwu Luo and Xin Liu revised the manuscript. All of the authors approved the version to be published.

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Data availability statement

Data are available in the public open access repository of Peking University.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12

		(*b*) Report category boundaries when continuous variables were categorized	6-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.