

# Plasma 25-hydroxyvitamin D level and the risk of frailty among Chinese community-based oldest-old: evidence from the CLHLS study

**Qi Xiao**

Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology

**Meiliyang Wu**

Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology

**Jinrui Cui**

Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology

**Mengmei Yuan**

Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology

**Ye Chen**

Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology

**Tieying Zeng** (✉ [984451641@qq.com](mailto:984451641@qq.com))

<https://orcid.org/0000-0002-0093-7907>

---

## Research article

**Keywords:** China; oldest-old; frailty; 25(OH)D level; biomarkers

**Posted Date:** February 28th, 2020

**DOI:** <https://doi.org/10.21203/rs.2.15995/v3>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

---

**Version of Record:** A version of this preprint was published at BMC Geriatrics on April 6th, 2020. See the published version at <https://doi.org/10.1186/s12877-020-01523-w>.

# Abstract

**Background:** Vitamin D deficiency has been linked to the risk of frailty. However, there are limited methods for evaluations of the potential association of vitamin D with frailty in a longevous (80+) population. The aim of this study was to examine the association between plasma 25-hydroxyvitamin D [25(OH)D] levels and the risk of frailty among the Chinese community based oldest-old. **Methods:** Secondary analysis of data compiled in the 2011 wave of the Chinese Longitudinal Healthy Longevity Survey (n=1324) was performed. Frailty was assessed by the Study of Osteoporotic Fractures (SOF) index. Multivariate logistic regression and spline smoothing with threshold effect analysis were performed to investigate the association between 25(OH)D level and the risk of frailty after adjusting for socio-demographic variables, health characteristics and confounding biomarkers. **Results:** The mean age was  $92.89 \pm 7.92$  years, and 844 (63.7%) participants were women. In all, data from 426 (33.2%, 95% confidence interval, CI: 29.66-34.69) frail participants were recorded. After adjustment for confounding covariates, the level of 25(OH)D was significantly related to frailty. By spline smoothing with threshold effect analysis, a monotonically negative association between 25(OH)D and frailty was identified. Subgroup analyses revealed that the association did not differ by sex or age. **Conclusions:** The 25(OH)D level was inversely associated with the risk of frailty among the Chinese community-based oldest-old.

## Background

Frailty, as a geriatric syndrome, represents a reduced ability to rebuild homeostasis in response to external stressors during daily life(1). Frailty in the elderly is well established to be related to long-term adverse health outcomes (such as falls, depression, disability, dependency, and mortality) that cannot be completely explained by ageing, functional decline, or comorbidities(2-5).

Of the numerous existing frailty measures, many often rely on measuring physical function, with some being less likely to be readily available in clinical settings and, therefore, having limited use(6-8). Common approaches such as the Frailty Index(9, 10) and the Frailty Phenotype(11) are no exceptions. In contrast, the Study of Osteoporotic Fractures (SOF) frailty index employs only 3 simple self-reported frailty components, muscle strength, low energy, and unintentional weight loss(7). Frailty identified through this measure has been associated with falls, disability, fractures, and death(6, 12), and the SOF index is regarded as a useful tool for assessments of the physical aspects of frailty at the population level(7, 8, 13).

Vitamin D, which is primarily synthesized in the skin upon exposure to sunlight, is necessary for human musculoskeletal health maintenance(14); its deficiency is proven to be the cause of muscle weakness(15), sarcopenia(16), falls(17), and fracture(18). A growing body of evidence has suggested that a low level of its active form, namely, 25-hydroxyvitamin D [25(OH)D], is related to the risk of frailty(19-33). The underlying pathogenic mechanisms of this relationship could be explained through 3 pathways: the first is the invalidation of regulatory effects of vitamin D on calcium flux, mineral homeostasis and protein anabolism in muscle tissue(23, 24); the second is bone metabolic disturbance by secondary hyperparathyroidism(25); and the last is the possible anti-inflammatory property of vitamin D(26).

However, since the cutaneous synthesis of vitamin D shows great variability across populations(34), studies exploring its association in elderly Asian populations are limited. Moreover, as this cutaneous synthesis process decreases with age(35), and limited outdoor activities may also accelerate vitamin D deficiency(14), the relationship between 25(OH)D and frailty in the oldest-old people (aged  $\geq 80$  years) remains unclear. Since the oldest-old will be the fastest-growing group between now and 2050(11), the association between 25(OH)D level and the risk of frailty in this age group may have important public health implications for health-care planning and practice.

Therefore, this study aimed to examine the association between 25(OH)D level and the risk of frailty among 1324 oldest-old adults of the eight “longevity areas” in the Chinese Longitudinal Healthy Longevity Survey (CLHLS)(36, 37). Given the evidence in previous studies, we hypothesized that a lower level of 25(OH)D would be associated with the risk of frailty in Chinese community-based oldest-old people.

## Methods

### *Study design and participants*

Participants in the biomarker substudy from the 6<sup>th</sup> (2011) wave of the CLHLS were recruited in this secondary analysis. The CLHLS is the first and largest nationwide, community-based, longitudinal prospective cohort survey concerning older adults in China(38). It provides information on the health status, socio-economic characteristics, and lifestyles of elderly individuals, including a large percentage of the oldest population(37). The in-depth study was launched in eight “longevity areas” of China (Laizhou of Shandong Province, Xiayi of Henan Province, Zhongxiang of Hubei Province, Mayang of Hunan Province, Sanshui of Guangdong Province, Yongfu of Guangxi Autonomous Region, Chengmai of Hainan Province, Rudong of Jiangsu Province), where the density of centenarians was exceptionally high and the environmental quality was very good, as evaluated and officially designated by the expert committee of the Chinese Gerontology Association(36).

During the in-depth study, the Chinese Center for Disease Control and Prevention (CDC) local network medical doctors conducted physical examinations of the participants and collected biomarker datasets containing approximately 30 indicators in routine blood tests, blood biochemical tests, and urine tests(36). More detailed descriptions have been previously published elsewhere(39-41).

Initially, a total of 2439 elderly participants were included in the study. We excluded those of younger age (less than 80, n=834, 34.2%) and those with missing data on SOF index components (n=281, 11.5%). Finally, we retained 1324 older adults in this study.

### *Outcome*

Consistent with previous studies of secondary analyses involving CLHLS data(42), frailty was defined by the SOF index in the current study. Three components were included in the index: underweight (defined as body mass index <18.5), low energy level (indicated by a positive response to the question “Over the last 6 months, have you been limited in activities because of a health problem?”), and muscle strength (inability to stand up from a chair without the assistance of arms). As suggested, participants with two or more of the three components were defined as frail.

### *Exposure*

Fasting venous blood was collected after an overnight fast from all willing participants. Procedures for the collection and shipment of blood samples were described in detail elsewhere(14). 25(OH)D was assayed by an enzyme-linked immunoassay using Immunodiagnostic Systems Limited (IDS Ltd, Boldon, UK). The 25(OH)D level was expressed as nmol/L.

### *Covariates*

We adjusted for socio-demographic variables, health characteristics and confounding biomarkers in the models. Socio-demographic variables included age, sex (female/male), marital status (married/other), residence (rural/other), education level (no schooling/≥1 year of schooling), and co-residence [with family member(s)/other].

Health characteristics included lifestyles and chronic diseases. Lifestyles consisted of smoking (yes/no), drinking (yes/no), and regular exercise (yes/no) at present. Chronic diseases included hypertension (yes/no), diabetes mellitus (yes/no), heart diseases (yes/no), cerebrovascular diseases (yes/no), and respiratory diseases (yes/no). Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg(43). Diabetes mellitus was diagnosed by fasting plasma glucose  $\geq 7.0$  mmol/L(14, 44). Other diseases were identified by self-report.

Confounding biomarkers were 11 indicators on routine blood tests and blood biochemistry tests (36). According to previous relevant studies(19), these 11 indicators, which were largely investigated in relation to frailty, were analysed in this study: 1) inflammatory marker: C reactive protein (CRP); 2) immune marker: counts of leukocytes (WBC); 3) clinical markers: plasma albumin (ALB), total cholesterol (CHO), serum creatinine (CREA), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglyceride (TG), and haemoglobin (HGB); and 4) oxidative stress markers: malondialdehyde (MDA) and superoxide dismutase (SOD). All standard laboratory techniques were performed by the central clinical laboratory at Capital Medical University in Beijing.

Overall, few data points for most confounding variables were missing (1.05%). For the missing values, we performed multiple imputations by chained equations to increase the predictive power(45). The distributions of the observed data and imputed data are described in **Supplementary Table S1 (see Additional file 1)**. For all the covariates, the distributions of observed and imputed values were similar.

### *Statistical analysis*

Categorical variables were expressed as numbers and percentages, and continuous data were described as the mean (standard deviation, SD) or median (interquartile range, IQR). Characteristics among groups were compared by ANOVA, Kruskal–Wallis test or  $\chi^2$  test. The IQR of the 25(OH)D level was used to divide the data into four categories. The cutoff points were 26.13, 35.89, and 50.00 nmol/L.

We used multilayer logistic regression models based on the likelihood ratio test (LRT) to determine the association between 25(OH)D level and the risk of frailty. The Box-Tidwell method was used to test the linearity between logit P and all continuous variables(46). Therefore, we used continuous terms for all the confounding biomarkers and categorized age as subgroups with 80-89, 90-99, and  $\geq 100$  years. Data are reported as odds ratios (ORs) and 95% confidence intervals (CIs) in both unadjusted and adjusted logistic regression models. A *p*-value of the Hosmer-Lemeshow test  $>0.05$  indicated reasonable goodness of fit(47).

Different from previous studies, to examine the linear trend across levels of 25(OH)D, we further performed spline smoothing analysis and threshold effect analysis in the current study, which were relatively novel in studies examining the respondents' dose-response relationship between 25(OH)D and frailty. Instead of a priori assumptions, spline smoothing analysis is a form of mixed modelling based on the generalized additive model (GAM)(48), whereby a set of associated items, for example, 25(OH)D and frailty, can visually demonstrate the linear or curvilinear relationship by figures. The threshold effect analysis, which is based on the piece-wise regression model(49), can further examine whether this relationship is segmental.

Subgroup analyses and their interactions were tested to explore whether sex and age subgroups would confound the association between 25(OH)D level and frailty. Sensitivity analysis was performed in participants with complete variables and multiple imputations separately.

A two-tailed *p*-value  $<0.05$  was considered statistically significant in all analyses. Statistical analyses were conducted by IBM SPSS Statistics Version 22.0, except that the spline smoothing analysis, threshold effect analysis, and multiple

imputations were performed by R software Version 3.4.3 (<http://www.R-project.org>) and Empower® ([www.empowerstats.com](http://www.empowerstats.com)).

**Table 1.** Participant characteristics.

Variables	All participants (n=1324)	Categories (nmol/L)				Statistics <sup>a</sup>
		Q <sub>1</sub> (≤26.13)	Q <sub>2</sub> (26.13–35.89)	Q <sub>3</sub> (35.89–50.00)	Q <sub>4</sub> (>50.00)	
<b>Socio-demographics, n (%)</b>						
Age (80-112), M (SD)	92.89 (7.92)	95.63 (7.49)	93.37 (7.72)	91.85 (7.85)	90.70 (7.78)	25.207***
Female	844 (63.7)	251 (75.8)	236 (71.3)	200 (60.2)	157 (47.6)	68.190***
Married	294 (22.3)	44 (13.3)	60 (18.2)	83 (25.1)	107 (32.7)	40.503***
Rural	1124 (84.9)	282 (85.2)	282 (85.2)	265 (79.8)	295 (89.4)	11.925**
No schooling	998 (76.4)	279 (85.8)	257 (78.4)	242 (74.2)	220 (67.1)	33.410***
With household member(s)	950 (73.2)	263 (82.2)	236 (72.2)	225 (69.7)	226 (69.1)	25.873***
<b>Health characteristics, n (%)</b>						
Smoking	148 (11.3)	28 (8.5)	39 (11.8)	37 (11.2)	44 (13.5)	4.337
Drinking	167 (12.7)	32 (9.7)	41 (12.5)	45 (13.6)	49 (14.9)	0.218
Regular exercise	178 (13.9)	27 (8.4)	38 (11.9)	54 (16.7)	59 (18.6)	17.317***
Hypertension	785 (62.2)	197 (61.9)	195 (62.1)	192 (61.5)	201 (63.0)	0.155
Diabetes mellitus	98 (7.4)	28 (8.5)	25 (7.6)	24 (7.3)	21 (6.4)	1.057
Heart diseases	91 (7.0)	24 (7.4)	24 (7.4)	27 (8.4)	16 (4.9)	3.398
Cerebrovascular diseases	102 (7.8)	34 (10.4)	31 (9.5)	18 (5.5)	19 (5.8)	8.630*
Respiratory diseases	116 (8.9)	29 (9.0)	32 (9.8)	23 (7.0)	32 (9.8)	2.080
<b>Biomarkers, M (IQR)</b>						
CRP (mg/L)	1.01 (0.41,2.93)	1.12 (0.38,3.35)	0.93 (0.43,3.05)	0.96 (0.41,2.54)	1.09 (0.39,2.75)	1.491

ALB (g/L)	39.10 (35.90,42.40)	37.90 (35.30,41.40)	38.60 (35.48,42.12)	39.70 (36.70,42.93)	39.90 (37.20,42.80)	29.923***
CHO (mmol/L)	4.16 (3.52,4.79)	4.03 (3.49,4.72)	4.21 (3.51,4.79)	4.21 (3.47,4.97)	4.20 (3.70,4.78)	4.186
CREA (mmol/L)	78 (65,96)	69 (60,85)	77 (63,93)	82 (69,98)	87 (71,102)	76.765***
HDLC (mmol/L)	1.23 (1.03,1.49)	1.20 (1.01,1.45)	1.25 (1.04,1.51)	1.27 (1.03,1.55)	1.23 (1.04,1.46)	5.065
LDLC (mmol/L)	2.45 (1.94,3.02)	2.40 (1.92,2.97)	2.42 (1.89,3.05)	2.41 (1.86,3.08)	2.54 (2.04,3.00)	5.147
TG (mmol/L)	0.79 (0.59,1.10)	0.78 (0.59,1.07)	0.79 (0.58,1.09)	0.82 (0.61,1.16)	0.77 (0.57,1.07)	6.429
SOD (IU/mL)	58.53 (53.43,63.24)	56.75 (51.75,62.97)	58.18 (53.49,63.20)	58.75 (53.33,63.06)	59.39 (55.39,64.24)	18.975***
MDA (µmol/L)	4.71 (3.73,5.79)	4.81 (3.93,5.89)	4.87 (3.88,5.91)	4.84 (3.82,5.83)	4.33 (3.25,5.55)	27.303***
WBC (10 <sup>9</sup> /L)	5.30 (4.30,6.40)	4.80 (4.00,6.00)	5.10 (4.10,6.10)	5.60 (4.57,6.60)	5.60 (5.60,6.80)	34.983***
HGB (g/L)	118 (106,131)	121 (110,133)	120 (107,132)	116 (105,129)	117 (105,131)	11.618***
Frailty, n (%)	426 (33.2)	162 (48.9)	112 (33.8)	93 (28.0)	59 (17.9)	76.606***

M (SD), mean (standard deviation); M (IQR), median (interquartile range).

<sup>a</sup> Coefficient of ANOVA, Kruskal-Wallis test or  $\chi^2$  test among categories of plasma 25(OH)D level.

\* <0.05, \*\* <0.01, \*\*\* <0.001.

Abbreviations: CRP, C reactive protein; ALB, plasma albumin; CHO, total cholesterol; CREA, plasma creatine; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; SOD, superoxide dismutase; TG, triglyceride; SOD, superoxide dismutase; MDA, malondialdehyde; WBC, white blood cell count; HGB, haemoglobin.

## Results

### Sample characteristics

The characteristics of the participants were compared according to the 25(OH)D level categories. The full detailed characteristics of all participants are shown in **Table 1**. The mean  $\pm$  SD age of the study population was 92.89  $\pm$  7.92 years, and 63.7% were women (n=844). The number of participants with frailty was 426 (33.2%, 95% CI: 29.66-34.69). The median 25(OH)D concentration was 35.89 nmol/L, and participants with higher 25(OH)D levels (35.89–50.00,

>50.00 nmol/L) were significantly younger than those with lower levels ( $\leq 26.13$ , 26.13–35.89 nmol/L) and were more likely to be male, married, have  $\geq 1$  year of schooling and perform regular exercise.

#### *Association between the level of 25(OH)D and the risk of frailty*

As shown in **Table 1**, 48.9%, 33.8%, 28.0% and 17.9% of participants in the lowest to highest 25(OH)D categories reported frailty. There was a significant inverse association between categorical 25(OH)D level and the risk of frailty in the multivariate logistic regression models. The ORs and 95% CIs for the association between categories of 25(OH)D level and frailty are presented in **Table 2**. After eliminating the interferences of all confounding factors, the ORs of frailty were 3.239 (95% CI: 2.113–4.967,  $p < 0.001$ ) for the lowest category ( $\leq 26.13$  nmol/L) of 25(OH)D level, 2.341 (95% CI: 1.519–3.609,  $p < 0.001$ ) for the second-lowest category (26.13–35.89 nmol/L), and 1.703 (95% CI: 1.088–2.664,  $p = 0.20$ ) for the third-lowest category (30.33–44.46 nmol/L) compared to the highest level subgroup ( $> 50.00$  nmol/L).

**Table 2.** The associations between serum level of 25(OH)D (nmol/L) and the risk of frailty.

Variables	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>	Model 4 <sup>d,e</sup>
Categories				
$\leq 26.13$	4.964 (3.332,7.396) ***	3.472 (2.273,5.303) ***	3.437 (2.248,5.255) ***	3.239 (2.113,4.967) ***
26.13–35.89	2.822 (1.881,4.234) ***	2.414 (1.571,3.710) ***	2.420 (1.573,3.723) ***	2.341 (1.519,3.609) ***
35.89–50.00	1.835 (1.204,2.797) **	1.526 (1.102, 2.683) *	1.722 (1.102,2.692) *	1.703 (1.088,2.664) *
$> 50.00$	reference	reference	reference	reference

<sup>a</sup> Unadjusted model, OR (95% CI).

<sup>b</sup> Adjusted for **socio-demographics** (age, sex, marital status, residence, education level, and co-residence), OR (95% CI).

<sup>c</sup> Adjusted for **socio-demographics** (age, sex, marital status, residence, education level, and co-residence) and **health characteristics** (smoking, drinking, regular exercise, hypertension, diabetes mellitus, heart diseases, cerebrovascular diseases, and respiratory diseases), OR (95% CI).

<sup>d</sup> Adjusted for **socio-demographics** (age, sex, marital status, residence, education level, and co-residence), **health characteristics** (smoking, drinking, regular exercise, hypertension, diabetes mellitus, heart diseases, cerebrovascular diseases, and respiratory diseases) and **confounding biomarkers** (CRP, ALB, CHO, CREA, HDLC, LDLC, TG, SOD, MDA, WBC, and HGB), OR (95% CI).

<sup>e</sup>  $p$ -value for the Hosmer-Lemeshow test was 0.653; prediction in accuracy was 74.3% in model 4.

\*  $< 0.05$ , \*\*  $< 0.01$ , \*\*\*  $< 0.001$ .

#### *The dose-response relationship between the level of 25(OH)D and the risk of frailty*

Consistent with the results displayed in **Table 2**, a continuous negative curve was observed between 25(OH)D and the risk of frailty in the analysis using spline smoothing ( $p$  for trend  $< 0.001$ , **Figure 1**). **Table 3** shows that the  $p$ -value of the log-likelihood ratio test in the threshold effect analysis was 0.317 in the adjusted model, which showed that the tendency of the association between 25(OH)D and frailty was monotonical with no inflection.

#### *Subgroup analyses*

Subgroup analyses showed that the  $p$ -value for interaction was 0.9753 for sex and 0.1077 for age, which revealed that the association of 25(OH)D level with frailty did not significantly differ by sex or age after adjusting for a series of covariates (**Figure 2**).

**Table 3.** Threshold effect analysis of 25(OH)D (nmol/L) using the piece-wise regression model

Variables	Crude <sup>a</sup> OR (95% CI)	Adjusted <sup>b</sup> OR (95% CI)
Continuous	0.967 (0.960, 0.975) ***	0.975 (0.965, 0.984) ***
Cutoff		
≤33.96	0.948 (0.929, 0.967) ***	0.963 (0.939, 0.988) ***
>33.96	0.978 (0.966, 0.989) ***	0.981 (0.966, 0.996) *
<i>p</i> -value of log-likelihood ratio test	0.032	0.317

<sup>a</sup> Crude: no adjustment.

<sup>b</sup> Adjusted for **socio-demographics** (age, sex, marital status, residence, education level, and co-residence), **health characteristics** (smoking, drinking, and regular exercise, hypertension, diabetes mellitus, heart diseases, cerebrovascular diseases, and respiratory diseases) and **confounding biomarkers** (CRP, ALB, CHO, CREA, HDLC, LDLC, TG, SOD, MDA, WBC, and HGB).

\* <0.05, \*\* <0.01, \*\*\* <0.001.

### *Sensitivity analysis*

We performed the multivariate analysis in those participants with complete variables and multiple imputations separately. As displayed in **Supplementary Table S2 (see Additional file 1)**, the present findings showed similar results.

## Discussion

In this community-based study, after adjustment for a variety of potential confounding factors, we observed a robust and monotonically negative association of 25(OH)D with frailty among a group of oldest-old individuals in China. In addition, by examining the relationship between different subgroups of participants, we also indicated that this association was consistent across sex and age groups.

### *Comparison with other studies*

The relationship between 25(OH)D level and frailty has rarely been investigated among the oldest-old individuals. As hypothesized, the present findings suggested that the 25(OH)D level was related to frailty after adjustment for numerous confounders. The findings from our study were relatively consistent with those of previous studies involving older adults in the Netherlands(25, 32), Mexico(23), northern Taiwan(33) and Germany (31).

Limited studies have demonstrated the shape of the association between 25(OH)D level and frailty. In a study of 1606 old men aged  $73.8 \pm 5.9$  years in the USA, a segmented negative curvilinear association between 25(OH)D level and odds of frailty was identified(21). However, this association was not observed among 6307 old women in America(20) and was replaced by a U-shaped curvilinear association. For the present study, we identified a robust and monotonically negative association between 25(OH)D and frailty in older Chinese adults.

Chronic diseases, lifestyles, and some biomarkers have been studied as potential risk factors of frailty in the existing literature (11, 19, 24). However, the association between 25(OH)D and frailty was not substantially confounded after adding these covariates in the models of our study. This suggested that 25(OH)D was independently associated with the risk of frailty. However, it remains inconclusive whether other possible factors not included in this study might contribute to the relationship between 25(OH)D and frailty.

Due to differences in latitudes, seasons, measurements of frailty, the adequacy of adjustment for potential confounders, and clinical heterogeneity between races and ethnicities(34), some variations from previous studies were also found in this study. First, our study reported that the median 25(OH)D level of elderly individuals was 35.89 nmol/L, which was lower than the median levels of those participants in Taiwan(33), the Netherlands(25), and Germany (27). In addition, the prevalence of frailty was 33.2%, which was much higher than the 13% reported in Japanese elderly(8) and the 17% reported in US older women(6). Since the 25(OH)D level and frailty status are closely related to ageing(19), these differences could also be partly explained by the oversampling of oldest-old people in this study.

Second, the association between 25(OH)D level and frailty has been reported to be different across sex(20, 21, 27, 28, 30). A study of participants in Italy identified that vitamin D insufficiency was associated with frailty only in men (30). However, conflicting results were reported in studies involving older women in the USA(24), Spain(29), and Portugal(28). In this regard, our study detected that 25(OH)D level was associated with frailty regardless of sex, which was similar to the findings of the study of individuals in Germany(27). In addition, our study also indicated that this association did not differ among octogenarian, nonagenarian, and centenarian subgroups.

### *Strength and limitations*

The strength of the current study was the large number of Chinese community-based participants with the collection of plasma blood samples during the survey. This allowed us to investigate the shape of the association between 25(OH)D level and frailty and to adjust for important potential confounding variables. To our knowledge, this was the first study that investigated the relationship between 25(OH)D level and frailty in a nationwide study of Chinese oldest-old people. The present study included a large population of older Chinese adults aged 80 years and over, which allowed robust conclusions to be drawn with respect to these participants.

This study also has certain limitations. First, a dichotomous outcome measure for frailty was used in this study; hence, the pre-frail status was not taken into account. Second, some of the clinical diseases were self-reported. For this condition, we adjusted hypertension and diabetes status by clinical data in place of self-reporting to eliminate information bias. Third, this was a descriptive cross-sectional design that did not allow us to evaluate whether a change in 25(OH)D level was a cause or a consequence of frailty.

## **Conclusion**

With a population-based design, this study indicates that the 25(OH)D level is monotonically and negatively associated with frailty in the Chinese community-dwelling population. The results of the present study, along with those of other existing epidemiological studies, reinforce the importance of the investigation of the full explanation of the association between 25(OH)D and frailty. Further longitudinal studies are needed to verify our initial cross-sectional findings so that we may identify an effective intervention to stem the rapidly increasing prevalence of frailty associated with an ageing population.

## **List Of Abbreviations**

CLHLS, Chinese Longitudinal Healthy Longevity Survey; 25-hydroxyvitamin D, 25(OH)D; SOF, Study of Osteoporotic Fractures; FI, Frailty Index; CGA, comprehensive geriatric assessment; CHS, Cardiovascular Health Study; CDC, Center for Disease Control and Prevention; SD, standard variance; IQR, interquartile range; LRT, Likelihood Ratio Test; OR, odds ratio; CI, confidence interval; GAM, generalized additive model; CRP, C reactive protein; ALB, plasma albumin; CHO, total cholesterol; CREA, plasma creatine; SOD, superoxide dismutase; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TG, triglyceride; SOD, superoxide dismutase; MDA, malondialdehyde; WBC, white blood cell count; HGB, hemoglobin.

# Declarations

## Ethics approval and consent to participate

The CLHLS study was approved by the Research Ethics Committee of Peking University (IRB00001052-13074), and all participants or their proxy respondents provided written informed consent.

## Consent for publication

Not applicable.

## Availability of data and material

The CLHLS questionnaires are available at <https://sites.duke.edu/centerforaging/programs/chinese-longitudinal-healthy-longevity-survey-clhls/survey-documentation/questionnaires/>. The full datasets used in this analysis are available from the corresponding author upon reasonable request.

## Competing interests

The authors declare that they have no competing interests.

## Funding

Data of this study is from the National Basic Research Program of China (2013CB530700), National Natural Science Foundation of China (71233001), United States Department of Health and Human Services. National Institutes of Health. National Institute on Aging (R01 AG023627). This study was also supported by the National Natural Science Foundation of China (71573097).

## Authors' contributions

Xiao Qi and Zeng Tieying conceived the study; Xiao Qi and Wu Meiliyang analyze the data; Cui Jinrui, Yuan Mengmei, and Chen Ye helped interpret the data; Xiao Qi wrote the manuscript. All authors contributed to the manuscript revision and approved the final manuscript.

## Acknowledgments

We thank Akshya Vasudev and Kenneth Micheal Madden for their helpful comments.

# References

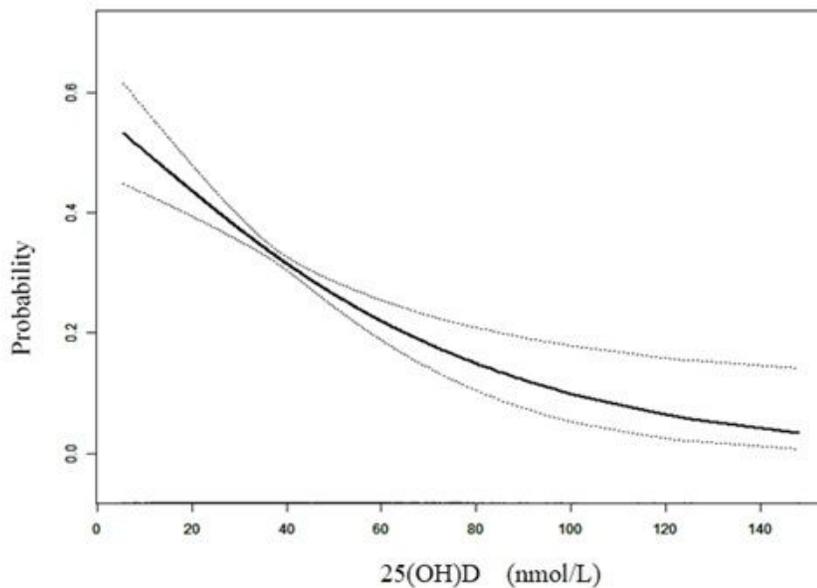
1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *The Lancet*. 2013;381(9868):752-62.
2. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review. *Journal of the American Geriatrics Society*. 2012;60(8):1487-92.
3. Kojima G. Frailty as a Predictor of Future Falls Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc*. 2015;16(12):1027-33.
4. Kojima G. Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis. *Disabil Rehabil*. 2017;39(19):1897-908.
5. At J, Bryce R, Prina M, Acosta D, Ferri CP, Guerra M, et al. Frailty and the prediction of dependence and mortality in low- and middle-income countries: a 10/66 population-based cohort study. *BMC Med*. 2015;13(1):138.

6. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Cawthon PM, Stone KL, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Archives Of Internal Medicine*. 2008;168(4):382-9.
7. Erusalimsky JD, Grillari J, Grune T, Jansen-Duerr P, Lippi G, Sinclair AJ, et al. In Search of 'Omics'-Based Biomarkers to Predict Risk of Frailty and Its Consequences in Older Individuals: The FRAILOMIC Initiative. *Gerontology*. 2016;62(2):182-90.
8. Cable N, Hiyoshi A, Kondo N, Aida J, Sjoqvist H, Kondo K. Identifying Frail-Related Biomarkers among Community-Dwelling Older Adults in Japan: A Research Example from the Japanese Gerontological Evaluation Study. *Biomed Res Int*. 2018:8.
9. Rockwood K, Mitnitski A. Frailty in Relation to the Accumulation of Deficits. *The Journals of Gerontology: Series A*. 2007;62(7):722-7.
10. Rockwood K, Mitnitski A. Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty. *Clinics in geriatric medicine*. 2011;27(1):17-26.
11. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2001;56(3):M146-56.
12. Bradlee ML, Mustafa J, Singer MR, Moore LL. High-Protein Foods and Physical Activity Protect Against Age-Related Muscle Loss and Functional Decline. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2017;73(1):88-94.
13. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue Q-L, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev*. 2016;26:53-61.
14. Matchar DB, Chei CL, Yin ZX, Koh V, Chakraborty B, Shi XM, et al. Vitamin D Levels and the Risk of Cognitive Decline in Chinese Elderly People: the Chinese Longitudinal Healthy Longevity Survey. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2016;71(10):1363-8.
15. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. *The American journal of clinical nutrition*. 2004;80(3):752-8.
16. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. *The Journal of clinical endocrinology and metabolism*. 2003;88(12):5766-72.
17. Murad MH, Elamin KB, Abu Elnour NO, Elamin MB, Alkatib AA, Fatourechi MM, et al. Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. *The Journal of clinical endocrinology and metabolism*. 2011;96(10):2997-3006.
18. Hill TR, Aspray TJ. The role of vitamin D in maintaining bone health in older people. *Therapeutic advances in musculoskeletal disease*. 2017;9(4):89-95.
19. Kane AE, Sinclair DA. Frailty biomarkers in humans and rodents: Current approaches and future advances. *Mechanisms of Ageing and Development*. 2019;180:117-28.
20. Ensrud KE, Ewing SK, Fredman L, Hochberg MC, Cauley JA, Hillier TA, et al. Circulating 25-hydroxyvitamin D levels and frailty status in older women. *The Journal of clinical endocrinology and metabolism*. 2010;95(12):5266-73.
21. Ensrud KE, Blackwell TL, Cauley JA, Cummings SR, Barrett-Connor E, Dam TT, et al. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. *Journal of the American Geriatrics Society*. 2011;59(1):101-6.
22. Wong YY, McCaul KA, Yeap BB, Hankey GJ, Flicker L. Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the Health in Men Study. *The Journal of clinical endocrinology and metabolism*. 2013;98(9):3821-8.

23. Gutierrez-Robledo LM, Avila-Funes JA, Amieva H, Meillon C, Acosta JL, Navarrete-Reyes AP, et al. Association of low serum 25-hydroxyvitamin D levels with the frailty syndrome in Mexican community-dwelling elderly. *The aging male : the official journal of the International Society for the Study of the Aging Male*. 2016;19(1):58-63.
24. Buta B, Choudhury PP, Xue QL, Chaves P, Bandeen-Roche K, Shardell M, et al. The Association of Vitamin D Deficiency and Incident Frailty in Older Women: The Role of Cardiometabolic Diseases. *Journal of the American Geriatrics Society*. 2017;65(3):619-24.
25. Vaes AMM, Brouwer-Brolsma EM, Toussaint N, de Regt M, Tieland M, van Loon LJC, et al. The association between 25-hydroxyvitamin D concentration, physical performance and frailty status in older adults. *European journal of nutrition*. 2019;58(3):1173-81.
26. van den Berg KS, Arts MHL, Collard RM. Vitamin D deficiency and course of frailty in a depressed older population. 2018:1-7.
27. Spira D, Buchmann N, Konig M, Rosada A, Steinhagen-Thiessen E, Demuth I, et al. Sex-specific differences in the association of vitamin D with low lean mass and frailty: Results from the Berlin Aging Study II. *Nutrition (Burbank, Los Angeles County, Calif)*. 2019;62:1-6.
28. Sousa-Santos AR, Afonso C, Santos A. The association between 25(OH)D levels, frailty status and obesity indices in older adults. 2018;13(8):e0198650.
29. Alvarez-Ríos AI, Guerrero JM, García-García FJ, Rodríguez-Mañas L, Medrano-Campillo P, de la Torre Lanza MA, et al. Associations between frailty and serum N-terminal propeptide of type I procollagen and 25-hydroxyvitamin D in older Spanish women: The Toledo Study for Healthy Aging. *Experimental gerontology*. 2015;69:79-84.
30. Shardell M, Hicks GE, Miller RR, Kritchevsky S, Andersen D, Bandinelli S, et al. Association of Low Vitamin D Levels With the Frailty Syndrome in Men and Women. *The Journals of Gerontology: Series A*. 2009;64A(1):69-75.
31. Pabst G, Zimmermann AK, Huth C, Koenig W, Ludwig T, Zierer A, et al. Association of low 25-hydroxyvitamin D levels with the frailty syndrome in an aged population: results from the KORA-age Augsburg study. *The journal of nutrition, health & aging*. 2015;19(3):258-64.
32. Puts MTE, Visser M, Twisk JWR, Deeg DJH, Lips P. Endocrine and inflammatory markers as predictors of frailty. *Clinical Endocrinology*. 2005;63(4):403-11.
33. Chang C-I, Chan D-C, Kuo K-N, Hsiung CA, Chen C-Y. Vitamin D insufficiency and frailty syndrome in older adults living in a Northern Taiwan community. *Arch Gerontol Geriatr*. 2010;50:S17-S21.
34. Bahrami A, Sadeghnia HR, Tabatabaeizadeh SA, Bahrami-Taghanaki H, Behboodi N, Esmaeili H, et al. Genetic and epigenetic factors influencing vitamin D status. 2018;233(5):4033-43.
35. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D<sub>3</sub>. *The Journal of clinical investigation*. 1985;76(4):1536-8.
36. Zeng Y, Vaupel JW. Chinese Longitudinal Healthy Longevity Survey (CLHLS), Biomarkers Datasets, 2009, 2012, 2014. Inter-university Consortium for Political and Social Research [distributor]; 2019.
37. Zeng Y, Vaupel J, Xiao Z, Liu Y, Zhang C. Chinese Longitudinal Healthy Longevity Survey (CLHLS), 1998-2014. Inter-university Consortium for Political and Social Research [distributor]; 2017.
38. Xiao Q, Wu M, Zeng T. Social support networks in Chinese older adults: health outcomes and health related behaviors: a path analysis. *Aging & mental health*. 2019:1-9.
39. Zeng Y, Feng Q, Hesketh T, Christensen K, Vaupel JW. Survival, disabilities in activities of daily living, and physical and cognitive functioning among the oldest-old in China: a cohort study. *Lancet*. 2017;389(10079):1619-29.
40. Lv X, Li W, Ma Y, Chen H, Zeng Y, Yu X, et al. Cognitive decline and mortality among community-dwelling Chinese older people. 2019;17(1):63.

41. Liu Z, Han L, Feng Q, Dupre ME, Gu D, Allore HG, et al. Are China's oldest-old living longer with less disability? A longitudinal modeling analysis of birth cohorts born 10 years apart. *BMC Med.* 2019;17(1):23.
42. Lv YB, Gao X, Yin ZX, Chen HS, Luo JS, Brasher MS, et al. Revisiting the association of blood pressure with mortality in oldest old people in China: community based, longitudinal prospective study. *Bmj.* 2018;361:k2158.
43. Sun D, Sun X, Xu Y, Wu T, Tao L. Superoxide dismutase activity and risk of cognitive decline in older adults: Findings from the Chinese Longitudinal Healthy Longevity Survey. *Experimental gerontology.* 2019;118:72-7.
44. Yin ZX, Shi XM, Kraus VB, Fitzgerald SM, Qian HZ, Xu JW, et al. High normal plasma triglycerides are associated with preserved cognitive function in Chinese oldest-old. *Age Ageing.* 2012;41(5):600-6.
45. Dupre ME, Gu D, Warner DF, Yi Z. Frailty and type of death among older adults in China: prospective cohort study. *Bmj.* 2009;338:b1175.
46. Gaudry M, J. Wills M. Estimating the functional form of travel demand models. *Transportation Research.* 1978;12:257-89.
47. Cole T. Applied logistic regression. D. W. Hosmer and S. Lemeshow, Wiley, New York, 1989. No. of pages: xiii + 307. Price: £36.00. *Statistics in Medicine - STAT MED.* 1991;10:1162-3.
48. Turlach B. Spline Smoothing. 2016. p. 1-8.
49. B. Onukogu I. When is Piece-Wise Regression Really Necessary? *Biometrical Journal - BIOM J.* 1984;26:559-66

## Figures

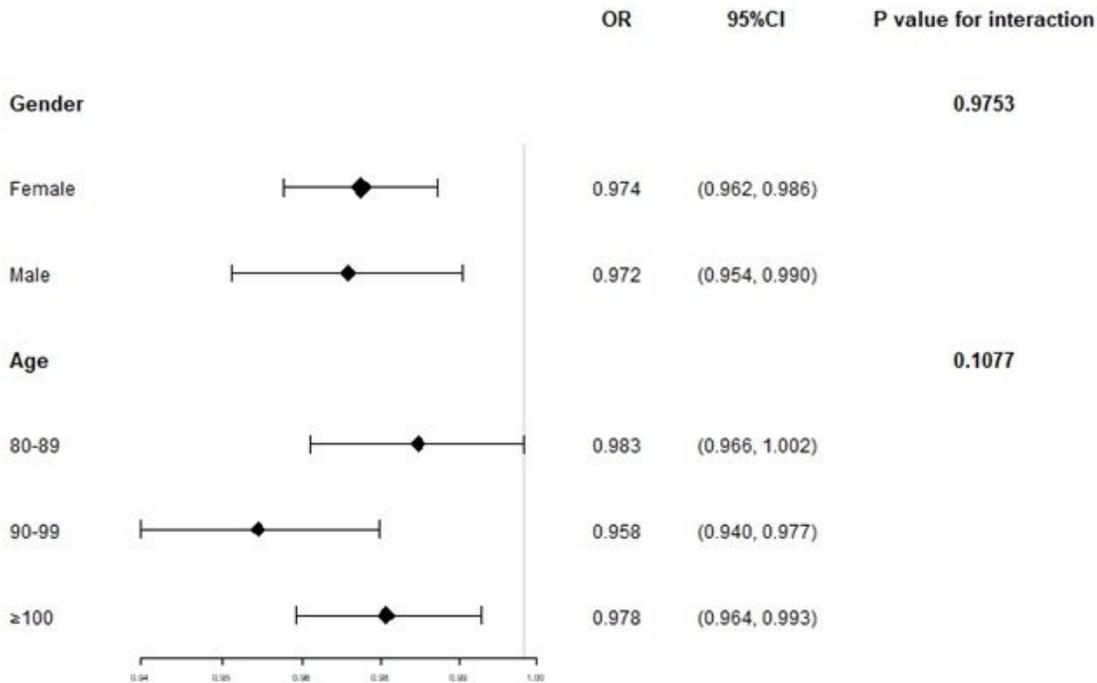


**Figure 1.** The dose-response relationship of 25(OH)D level and risk of frailty in the full adjusted model. Lines=estimated probability of frailty with 25(OH)D, dotted lines=95% confidence intervals.

### Figure 1

The dose-response relationship of 25(OH)D level and risk of frailty adjusted for socio-demographics (age, gender, marital status, residence, education level, and co-residence), health characteristics (smoking, drinking, regular exercise, hypertension, diabetes mellitus, heart diseases, cerebrovascular diseases, and respiratory diseases) and confounding

biomarkers (CRP, ALB, CHO, CREA, HDLC, LDLC, TG, SOD, MDA, WBC, and HGB). Lines=estimated probability of frailty with 25(OH)D, dotted lines=95% confidence intervals.



**Figure 1.** Subgroup analyses for the association between 25(OH)D and frailty in the fully adjusted model.

## Figure 2

Subgroup analyses for the association between 25(OH)D and frailty adjusted for marital status, residence, education level, and co-residence, smoking, drinking, and regular exercise, hypertension, diabetes mellitus, heart diseases, cerebrovascular diseases, respiratory diseases, CRP, ALB, CHO, CREA, HDLC, LDLC, TG, SOD, MDA, WBC, and HGB.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1SupplementaryTablesrevision.docx](#)
- [Additionalfile2STROBEchecklistrevision.docx](#)