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Serum 25-hydroxyvitamin D, frailty, and mortality among the Chinese oldest old: Results from the CLHLS study

Lin Liu [a,1], Chaolei Chen [a,1], Kenneth Lo [a,b,c], Jiayi Huang [a], Yuling Yu [a], Yuqing Huang [a,**], Yingqing Feng [a,*]

[a] Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
[b] Centre for Global Cardiometabolic Health, Department of Epidemiology, Brown University, Providence, USA
[c] Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China

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Abstract *Background and aims:* In this study, the aim is to explore whether frailty status modified the associations of serum 25(OH)D levels with all-cause and cause-specific mortality in the oldest old Chinese population.
Methods and results: A total of 1411 participants aged at least 80 years were enrolled in the Chinese Longitudinal Healthy Longevity Survey (CLHLS). Information on serum 25(OH)D level, frailty status, and covariates were examined at baseline. All-cause and cause-specific mortality status were ascertained during the follow-up survey conducted in 2017–2018 by using the ICD-10 codes. Cox proportional hazard models with stratified analyses were performed to evaluate potential associations. Over a median follow-up of 3.2 years, 722 (51.2%) participants were deceased, including 202 deaths due to circulatory diseases, and 520 deaths due to noncirculatory causes. After multivariable adjustment, the lowest quartile of serum 25(OH)D levels (Hazard Ratios (95% Confidence Intervals), 1.85 (1.45–2.36), 1.85 (1.45–2.36), 1.73 (1.31–2.29), respectively) and frailty (Odd Ratios (95% Confidence Intervals), 1.91 (1.60–2.29), 2.67 (1.90–3.74), 1.64 (1.31–2.05)) were associated with significantly higher risk of all-cause mortality, circulatory mortality, and noncirculatory mortality, respectively. In addition, we observed significant interactions among 25(OH)D and frailty on the risk of all-cause and cause-specific mortality (all *P*-interaction < 0.001). Similar results were found in sensitivity analyses by excluding participants who died in the first year of follow-up and using clinical cutoffs of serum 25(OH)D levels.
Conclusion: Low serum 25(OH)D levels were associated with higher risk of all-cause and cause-specific mortality among the oldest old of the Chinese population, and the associations were significantly stronger in individuals with frailty.

Introduction

Vitamin D, also known as "sunshine vitamin" and "anti-rachitic vitamin," is a group of fat-soluble steroids, which is the essential for life [1]. Vitamin D has a significant role in calcium homeostasis and metabolism as well as

* Corresponding author. Fax: +86-20-83827812.
** Corresponding author.
E-mail addresses: hyq513@126.com (Y. Huang), fyq1819@163.com (Y. Feng).
[1] Lin Liu and Chaolei Chen contributed equally to this paper.

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cardiovascular system and malignancy [2–4]. Vitamin D deficiency was associated with adverse outcomes, including coronary artery disease [5], hypertension [6], insulin resistance [7], cognitive impairment [8], and all-cause mortality [9].

Previous epidemiological research found that vitamin D deficiency was prevalent among older adults in China. Lu et al. found that among the old adults aged 50–70 years in Shanghai and Beijing, the rates of vitamin D deficiency and insufficiency were 24.4% and 69.2%, respectively [10]. Other studies found that vitamin D deficiency rates were over 80% in the elderly [11], indicating that increasing age might be associated with vitamin D deficiency.

With increasing life expectancy, frailty has become a common health problem, which may lead to adverse health outcomes such as falls, disabilities, depression, and the worse quality of life [12]. Previous meta-analyses have suggested an inverse association between serum vitamin D level and frailty, the pooled odd ratio of frailty for the lowest versus the highest level of vitamin D was 1.27 (95% confidence interval (CI) = 1.17–1.38)), and frailty will further increase the risk of all-cause mortality. The pooled hazard ratio (HR) = 1.35 (95% CI 1.05–1.74) [13,14].

As suggested by previous studies, vitamin D deficiency significantly affects the health of older adults and further increases the risk of mortality, and the association may be more profound for people with frailty. However, few studies have evaluated the interaction between vitamin D status and frailty, particularly among the oldest old of the Chinese population, who are susceptible to the adverse effect of vitamin D deficiency. Therefore, the purpose of this study was to determine the relationship between vitamin D status and all-cause and cause-specific mortality, and whether this relationship interacted with frailty status using data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS).

Method

Study design and population

CLHLS is an ongoing prospective community-based study with a multistage cluster sampling approach. More details of this study have been published elsewhere [15]. A total of 2546 participating older adults have provided blood sample tests in the 7th wave (2014) of CLHLS. We excluded 925 participants who were younger than 80 years (n = 818), then we excluded people with missing serum 25(OH)D values (n = 33), missing data for defining frailty (n = 68), or had incorrect death date record (n = 6). For the remaining 1621 oldest old participants, follow-up status was obtained from 1411 of them (Fig. 1). We compared the baseline characteristics of the participants who stayed or were lost from the cohort, and there has been no significant difference in baseline variables (Table S1). All participants or their legal representatives signed written consent forms to participate in the baseline and follow-up survey. CLHLS was approved by the institutional review board of Duke University health system institutional review board.

Measurement of serum 25(OH)D

Fasting venous blood was collected from participants after an overnight fast. Procedures for the collection and shipment of blood samples were described in detail elsewhere [16]. Serum 25(OH)D was assayed by an enzyme-linked immunoassay using Immunodiagnostic Systems Limited (Bolton, UK). The 25(OH)D level was expressed as nmol/L and further divided into 4 groups by sex-specific quartiles. To be specific, the cutoff of Serum 25(OH)D in nmol/L were 30.45, 42.45, and 55.95 in male and 21.70, 30.70, and 42.40 in female subjects.

Definition of frailty

Frailty was defined by the osteoporotic fractures index, which had good biological age ability among Chinese elderly [17]. 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). Participants were classified as having frailty with two or more of the three components [18].

Assessment of covariates

We further collected sociodemographic variables, health characteristics, and the levels of biomarkers in the study. Sociodemographic variables included age, sex (male/female), economic income (high/medium/low), residence (rural/other), marital status (in marriage/other), education level (more than 1 year of schooling/other), frailty (yes/no), co-residence (live alone/other), and vitamin supplements (almost every day/occasionally/rarely or never). Health characteristics included current smoking practice (yes/no), alcohol consumption habits (yes/no), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body mass index (kg/m^2) and self-reported hypertension, diabetes mellitus, stroke and other cerebrovascular diseases, cardiovascular disease, respiratory disease, and cancer. Levels of biomarkers included total cholesterol (TC, mmol/L), creatinine (mmol/L), and albumin (g/L). Economic income was classified as "high," "medium," and "low" by the question "Compared with other locals, how do you think about your economic position?" Participants who indicated "yes" to the questions "Do you currently smoke?" "Do you currently drink alcohol?" and "Do you exercise regularly?" were defined as current smokers and alcohol drinkers as well as doing regular exercise, respectively.

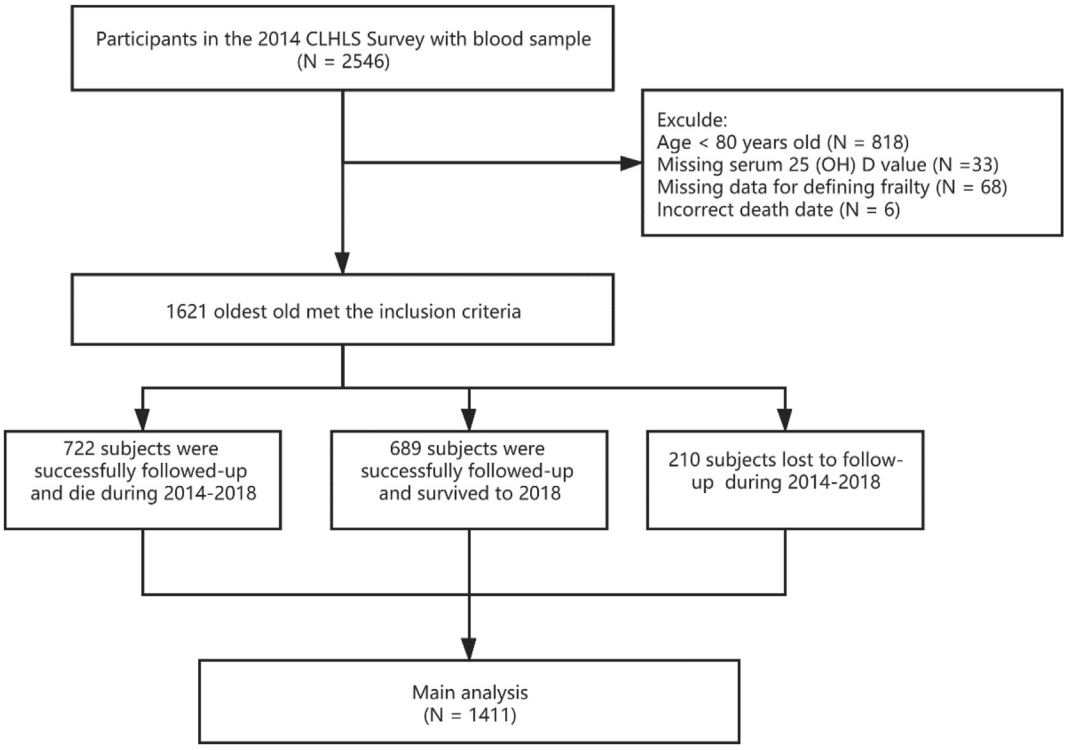

Figure 1 Flow chart of study participants.

Outcomes

Participants' survival status (all-cause mortality, circulatory mortality, and noncirculatory mortality) was ascertained during the follow-up survey in 2017–2018. Circulatory mortality was ascertained by ICD-10 (international classification of diseases, 10th revision) codes of I00–I99.

Statistical analysis

Baseline characteristics were presented as mean (continuous variables) or frequency distribution (categorical variables). One-way ANOVA or chi-square tests were applied to compare the differences among serum 25(OH)D quartiles for continuous and categorical variables, respectively. We used the Cox proportional hazard model to investigate the relationship between serum 25(OH) D and all-cause and cause-specific mortality. Serum 25(OH) D was treated as categorical (highest quartile as reference) or as continuous exposure (per 1 standard error reduction) in the model. Kaplan–Meier curves and log-rank tests were performed to compare the differences of mortality among quartiles of serum 25(OH)D. Three regression models were fitted, model 1 was adjusted for no confounders, model 2 was adjusted for age and gender, model 3 was adjusted for all confounders. We further evaluated the relationship between serum 25(OH)D and frailty and the relationship between frailty and all-cause and cause-specific mortality using logistic regression and Cox regression, respectively.

To assess the joint associations between serum 25(OH) D, frailty and mortality, we calculated the fully adjusted hazard ratios (HRs) and 95% confidence intervals (95% CI) of lower quartiles when compared with the highest quintiles of serum 25(OH) D, stratified by frailty status, and *P*-interaction were calculated. We also classified participants according to quartiles for serum 25(OH) D and frailty status for Cox regression analysis, using nonfrail participants with the highest quartile of serum 25(OH) D as reference.

We further performed the following sensitivity analyses to evaluate the robustness of our results: (1) excluding participants who died in the first year; (2) including the participants who lost to follow-up (n = 210); and (3) using the clinically defined cutoffs of serum 25(OH) D (25, 50, and 75 nmol/L) instead of quartiles. All analyses mentioned above were performed using R 4.0.0 (R Foundation for Statistical Computing). A two-tailed p-value < 0.05 was considered statistically significant in all analyses.

Results

Baseline characteristics

We included 1411 oldest old participants in the analysis. Table 1 presented the baseline characteristics as categorized by quartiles of serum 25(OH)D. In brief, the mean age of study participants was 92.26 years and 62.4% participants were female. The average 25(OH)D concentration of

Table 1 Baseline characteristics of study participants by quartiles of sex-specific serum 25(OH)D concentrations.

	Overall	Q1	Q2	Q3	Q4	*P*-value
N	1411	353	350	354	354	
Age, years	92.26 ± 7.77	94.31 ± 7.56	92.46 ± 7.48	91.53 ± 7.76	90.76 ± 7.85	<0.001
Female	881 (62.4)	220 (62.3)	218 (62.3)	222 (62.7)	221 (62.4)	0.999
Current smoking practice	140 (10.0)	40 (11.4)	33 (9.5)	28 (8.0)	39 (11.1)	0.407
Alcohol consumption habits	155 (11.1)	49 (14.0)	37 (10.6)	39 (11.1)	30 (8.6)	0.164
Economic income						0.165
High	179 (12.8)	51 (14.5)	54 (15.6)	41 (11.6)	33 (9.4)	
Medium	1080 (77.0)	264 (75.2)	255 (73.5)	274 (77.6)	287 (81.8)	
Low	143 (10.2)	36 (10.3)	38 (11.0)	38 (10.8)	31 (8.8)	
Rural residents	1116 (79.1)	264 (74.8)	252 (72.0)	279 (78.8)	321 (90.7)	<0.001
In marriage	333 (23.9)	80 (23.1)	79 (22.7)	90 (25.6)	84 (24.3)	0.801
Regular exercise	161 (11.7)	32 (9.3)	46 (13.5)	37 (10.7)	46 (13.3)	0.250
Education, >1 year	299 (21.7)	78 (22.4)	72 (21.4)	78 (22.5)	71 (20.6)	0.913
Frailty (%)	470 (33.3)	183 (51.8)	115 (32.9)	94 (26.6)	78 (22.0)	<0.001
Live alone (%)	354 (25.4)	58 (16.6)	71 (20.5)	90 (25.9)	135 (38.7)	<0.001
Vitamin supplements						0.010
Almost everyday	36 (2.6)	5 (1.4)	6 (1.7)	10 (2.8)	15 (4.2)	
Occasionally	181 (12.9)	30 (8.5)	51 (14.7)	45 (12.7)	55 (15.5)	
Rarely or never	1190 (84.6)	317 (90.1)	291 (83.6)	298 (84.4)	284 (80.2)	
Systolic blood pressure, mmHg	144.24 ± 25.78	142.38 ± 30.61	145.71 ± 25.37	144.91 ± 23.07	143.97 ± 23.36	0.356
Diastolic blood pressure, mmHg	79.77 ± 14.66	79.51 ± 14.68	78.35 ± 12.43	79.82 ± 13.54	81.39 ± 17.39	0.052
Body mass index, kg/m^2	19.82 ± 5.72	18.76 ± 6.24	20.27 ± 5.26	20.08 ± 5.56	20.18 ± 5.66	<0.001
Serum 25(OH)D, nmol/L	38.29 ± 20.23	18.03 ± 6.46	29.89 ± 5.74	40.86 ± 7.27	64.24 ± 18.57	<0.001
Total cholesterol, mmol/L	4.71 ± 1.03	4.76 ± 1.12	4.70 ± 1.08	4.65 ± 1.03	4.71 ± 0.90	0.571
Creatinine, mmol/L	84.80 ± 31.76	85.82 ± 40.05	87.86 ± 35.02	83.98 ± 26.91	81.59 ± 21.70	0.058
Albumin, g/L	41.60 ± 4.61	40.16 ± 4.23	41.48 ± 6.55	42.36 ± 3.27	42.39 ± 3.23	<0.001
Hypertension	386 (27.5)	89 (25.2)	86 (24.7)	96 (27.4)	115 (32.8)	0.067
Diabetes mellitus	29 (2.1)	8 (2.3)	8 (2.3)	8 (2.3)	5 (1.4)	0.811
Cardiovascular disease	127 (9.0)	33 (9.3)	34 (9.7)	27 (7.6)	33 (9.4)	0.770
Stroke and cerebrovascular disease	83 (5.9)	26 (7.4)	18 (5.2)	14 (4.0)	25 (7.1)	0.173
Respiratory disease	111 (7.9)	27 (7.6)	31 (8.9)	29 (8.2)	24 (6.8)	0.769
Cancer	6 (0.4)	0 (0.0)	0 (0.0)	4 (1.1)	2 (0.6)	0.062

Data are represented as mean (standard deviation) for continuous variables and n (%) for categorical variables. Q, quartiles.

participants was 38.29 nmol/L and 33.3% (n = 470) of them were classified as having frailty. Participants with a lower level of serum 25(OH)D tended to be older, lived in urban areas, and lived alone, being classified as having frailty, less prevalent in taking vitamin supplements, had lower BMI, and albumin level. The distributions of baseline serum 25(OH)D in male and female subjects were depicted in Fig. S1. Additionally, we provided the cut-off value of sex-specific quartiles of serum 25(OH)D, as shown in Table S2. The fourth quartile of 25(OH)D (Q4) was 55.95 nmol/L in men and 42.40 nmol/L in women, while the first quartiles were 30.45 and 21.70 nmol/L in men and women, respectively.

Serum 25(OH)D and frailty

In the cross-sectional analysis, we found a significant and inverse association between serum 25(OH)D level and the odds of frailty. Individuals in the first (Q1) and second (Q2) quartiles had higher odds of frailty when compared with the highest level (Q4). These associations remained significant after the adjustment of multiple potential confounders, the Model 3 HRs were 2.91 (95% CI, 1.95−4.36) for Q1 and 1.56 (1.04−2.35) for Q2 in the final model (Table S3).

Serum 25(OH)D and mortality

Over a median follow-up period of 3.2 years (IQR, 1.7−3.5 years), 722 (51.2%) participants died, including 202 deaths due to circulatory diseases, and 520 deaths due to non-circulatory causes.

Table 2 presented the association between serum 25(OH)D and mortality. In the fully adjusted model, each SD reduction in 25(OH)D was associated with 29% (95% CI, 17%−43%) increment of the risk of all-cause mortality, 53% (24%−88%) increment of the risk of circulatory mortality, and 23% (10%−39%) increased risk of non-circulatory mortality. Compared with the highest quartile (Q4) of serum 25(OH)D, the multivariable-adjusted HRs (Model 3) for all-cause mortality were 1.51 (95% CI, 1.18−1.94) for Q2 and 1.85 (1.45−2.36) for Q1. Similarly, the HRs for circulatory mortality for Q2 and Q1 were 1.64 (1.01−2.67) and 2.31 (1.44−3.71), respectively, while HRs for noncirculatory mortality for Q2 and Q1 were 1.50 (1.13−2.00) and 1.73 (1.31−2.29), respectively. The relationships between serum 25(OH)D levels and all-cause and cause-specific mortality remained consistent in a sensitivity analysis after excluding participants who died in the first years of follow-up (Table S4). Similarly, after including the participants who lost to follow-up and using the clinically defined cutoffs of serum 25(OH)D did

Table 2 Cox-proportional hazard models for the association of serum 25(OH)D levels with all-cause and cause-specific mortality.

	Case/ total	Model 1	Model 2	Model 3
All-cause mortality				
Per SD decrease		1.5 (1.41, 1.69)	1.47 (1.34, 1.62)	1.29 (1.17, 1.43)
Quartiles				
Q4	252/ 353	Ref	ref	ref
Q3	193/ 350	1.23 (0.97, 1.56)	1.16 (0.92, 1.48)	1.08 (0.83, 1.39)
Q2	152/ 354	1.83 (1.46, 2.30)	1.73 (1.38, 2.17)	1.51 (1.18, 1.94)
Q1	125/ 354	2.77 (2.23, 3.44)	2.37 (1.90, 2.94)	1.85 (1.45, 2.36)
P-trend		<0.001	<0.001	<0.001
Circulatory mortality				
Per SD decrease		1.76 (1.47, 2.11)	1.81 (1.5, 2.19)	1.53 (1.24, 1.88)
Quartiles				
Q4	79/353	ref	ref	ref
Q3	53/350	1.43 (0.88, 2.30)	1.37 (0.85, 2.21)	1.28 (0.77, 2.11)
Q2	41/354	2.15 (1.36, 3.38)	2.05 (1.30, 3.28)	1.64 (1.01, 2.67)
Q1	29/354	3.66 (2.39, 5.61)	3.26 (2.12, 5.01)	2.31 (1.44, 3.71)
P-trend		<0.001	<0.001	<0.001
Noncirculatory mortality				
Per SD decrease		1.48 (1.33, 1.64)	1.37 (1.23, 1.53)	1.23 (1.10, 1.39)
Quartiles				
Q4	173/ 353	ref	ref	ref
Q3	140/ 350	1.17 (0.89, 1.54)	1.11 (0.84, 1.45)	1.02 (0.76, 1.38)
Q2	111/ 354	1.74 (1.34, 2.26)	1.64 (1.27, 2.13)	1.50 (1.13, 2.00)
Q1	96/354	2.50 (1.95, 3.21)	2.10 (1.63, 2.70)	1.73 (1.31, 2.29)
P-trend		<0.001	<0.001	<0.001

Data presented hazard ratio (95% confidence interval). SD, standard deviation and Q, quartiles.
Model 1, adjust for none.
Model 2, adjust for age and gender.
Model 3, adjust for age, gender, smoke, alcohol, economic income, rural residents, in marriage, regular exercise, education, live alone, systolic blood pressure, diastolic blood pressure, body mass index, hypertension, diabetes mellitus, cardiovascular disease, stroke and cerebrovascular disease, respiratory disease, cancer, vitamin supplements, total cholesterol, creatinine, albumin, and frailty.

not have substantial influence on these findings (Tables S5 and S6).

Association between serum 25(OH)D and mortality stratified by frailty status

Table 3 showed the association between serum 25(OH)D and mortality as stratified by frailty status. Participants in the highest quartile of 25(OH)D were the reference group. There was a significant interaction between serum 25(OH)D and frailty with all-cause, circulatory and noncirculatory mortality (all $P < 0.001$). The lowest quartile of 25(OH)D significantly associated with a higher risk of all-cause mortality in both frail (HR: 2.01, 95% CI: 1.34, 3.01) and nonfrail (HR: 1.86, 95% CI: 1.35, 2.57) participants, but the associations were more pronounced in participants with frailty (all *P*-interaction < 0.001). Similar findings were observed when using circulatory or noncirculatory mortality as outcomes.

Fig. 2 displayed these data with nonfrail individuals in the highest quartile of 25(OH)D as the reference group. Participants in the lowest quartile of 25(OH)D and with frailty had significantly higher risk of all-cause mortality (A) (HR: 3.36, 95% CI: 2.49–4.52), circulatory mortality (B) (HR: 5.41, 95% CI: 3.01–9.79), and noncirculatory mortality (C) (HR: 2.67, 95% CI: 1.88–3.80) as compared to the reference group.

Discussion

In the present prospective community-based study among the oldest old in China, the association of serum 25(OH)D with mortality (all-cause and cause-specific) was significantly affected by frailty. The inverse relationship between serum vitamin D and mortality was stronger in frail participants as compared to those without frailty, and the results remained similar in the sensitivity analysis. Given the complex interplay between vitamin D deficiency and frailty, further longitudinal studies should verify the causal relationship and the associated pathways.

Consistent with previous studies [19–22], we found an inverse relationship between serum 25(OH)D levels, all-cause mortality, and circulatory mortality. Similar relationships were reported in different populations such as the Chinese elderly [19], the US residents [21,22], and the Israelis [20], which supported the conclusion of a recent meta-analysis that included more than 25,000 participants. The meta-analysis has indicated inverse relationships between serum 25(OH)D levels and all-cause mortality and cause-specific mortality for both men and women, and the associations were consistent across various countries [23]. However, different relationships, such as reverse J-shaped and U-shaped associations between serum 25(OH)D and all-cause mortality, were demonstrated in other studies [24–26]. A systematic review that included 26 cross-sectional or longitudinal studies has suggested an inverse association between serum 25(OH)D concentration and frailty severity among participants over 60 years old [27]. A Mendelian Randomization analysis revealed a reverse association between serum 25(OH)D with all-cause mortality, cancer mortality, and other mortality but not with increased cardiovascular mortality [28], indicating that these relationships may vary by age, race, and physical conditions. Furthermore, well-designed longitudinal studies were needed to clarify the relationship and the feasible mechanism between serum 25(OH)D with mortality.

Few studies have demonstrated the interaction between serum 25(OH)D and frailty in their associations with all-cause and cause-specific mortality. In the KORA study (Cooperative Health Research in the Region of

Table 3 Cox-proportional hazard models for the associations of serum 25(OH)D levels with all-cause and cause-specific mortality by frailty status.

	Case/total	Quartiles of serum 25(OH)D concentrations				Per SD decrease	*P*-trend	*P*-interaction
		Q4 (highest)	Q3	Q2	Q1 (lowest)			
All-cause mortality								
Frailty	350/470	ref	1.43 (0.92, 2.21)	1.62 (1.05, 2.49)	2.01 (1.34, 3.01)	1.32 (1.12, 1.55)	<0.001	<0.001
Nonfrailty	372/941	ref	0.85 (0.61, 1.10)	1.38 (1.01, 1.89)	1.86 (1.35, 2.57)	1.28 (1.11, 1.47)	<0.001	
Circulatory mortality								
Frailty	106/470	ref	2.06 (0.84, 5.05)	2.10 (0.87, 5.05)	2.83 (1.22, 6.56)	1.64 (1.18, 2.28)	<0.001	<0.001
Nonfrailty	96/941	ref	0.90 (0.47, 1.71)	1.32 (0.70, 2.49)	2.58 (1.41, 4.75)	1.55 (1.16, 2.05)	<0.001	
Noncirculatory mortality								
Frailty	244/470	ref	1.28 (0.77, 2.13)	1.58 (0.96, 2.60)	1.89 (1.19, 3.00)	1.25 (1.03, 1.52)	<0.001	<0.001
Nonfrailty	276/941	ref	0.85 (0.59, 1.24)	1.43 (0.99, 2.06)	1.68 (1.15, 2.45)	1.22 (1.04, 1.42)	<0.001	

Data are presented as hazard ratio (95% confidence interval). Q, quartiles and SD, standard deviation.
Analyses were adjusted for age, gender, smoke, alcohol, economic income, rural residents, in marriage, regular exercise, education, live alone, systolic blood pressure, diastolic blood pressure, body mass index, hypertension, diabetes mellitus, cardiovascular disease, stroke and cerebrovascular disease, cancer, vitamin supplements, total cholesterol, creatinine, and albumin.

Augsburg-Age Study), which includes 727 participants aged at least 65 years, lower 25(OH)D levels were significantly associated with increased all-cause mortality (OR = 3.39 and 95% CI: 1.08−10.65), and the association was partly mediated by frailty status [29]. Similarly, among 4731 adult participants from the Third National Health and Nutrition Examination Survey, those who were frail and had low serum 25(OH)D levels had a higher risk (OR = 1.67, 95% CI: 1.00−2.82) of all-cause mortality than those who had high serum 25(OH)D levels [30]. Flicker. et al. [31] found an inverse association between vitamin D and all-cause mortality (HR = 1.20, 95% CI, 1.02−1.42) independent of frailty among 4203 men aged 70−88 years from Western Australia. In the present study, participants were older (mean age: 92.26 years) and were from Chinese communities, which might suggest the differential effect of frailty on the association between serum 25(OH)D with all-cause mortality in previous studies. In addition, the present study has added evidence that frailty significantly affected the association of serum 25(OH)D levels and cause-specific mortality.

Higher mortality risk was observed in individuals with frailty combined with low serum 25(OH)D levels, and multiple mechanisms might help to explain this relationship. First, vitamin D plays a crucial role in skeletal muscle function. Deficiency of vitamin D may decrease the gene transcription of mRNA, subsequent protein synthesis, and further influence the differentiation of skeletal muscles [32]. In addition, vitamin D deficiency may lead to the decreased concentration of vitamin D receptor, which results in type II muscle fiber atrophy [33]. Older adults are more likely to suffer from frailty, which will increase their risk of falling down and exacerbate their frailty status when they have to stay in bed and be less capable to go outside for sunlight exposure, then further decrease the vitamin D synthesis [34,35]. Secondly, vitamin D deficiency may confer increased cardiovascular risk, include the development of electrolyte imbalances, pancreatic β cells dysfunction, and renin-angiotensin system activation [36]. Moreover, disrupted adaptive immune responses with severe vitamin D deficiency can result in an inflammatory milieu that promotes vascular dysfunction and insulin resistance [37]. Both disrupted adaptive immune responses and vitamin D deficiency can lead to negative cardiovascular effects while the frailty status was more likely to increase the risk of noncardiovascular death.

Several limitations should be noted when interpreting these findings. First, vitamin D and frailty were both examined at baseline, the possibility of reverse causation cannot be fully excluded in our study. Second, some factors (e.g., calcium and parathyroid hormone) that might influence vitamin D metabolism were not collected in the CLHLS. Furthermore, data on several vitamin D-related covariates, including sunlight exposure, intensity of physical activity, and the types of vitamin D supplementation of participants were not available in the study. However, the rate of habitual intake of vitamin D supplements was very low in the Chinese older adults, therefore it might have little influence on the estimation of vitamin D levels in the present study [38]. Third, the follow-up time was relatively short (3.2 years). However, our study included the oldest old population, which had a median age of 92.26 years with a high mortality rate (51.2%). Therefore, the study had sufficient statistical power to examine the relationship between vitamin D levels and mortality risk, and to determine the interaction effect of frailty status. Fourth, status of serum vitamin D and frailty was obtained only once at baseline; therefore, the changes across the cohort were not clear. However, we argue if that is a major flaw of this study, given the short follow-up time. Finally, although participants of the CLHLS were the national representative of Chinese populations, extrapolating the findings of our study to geographically or ethnically different populations should be cautious.

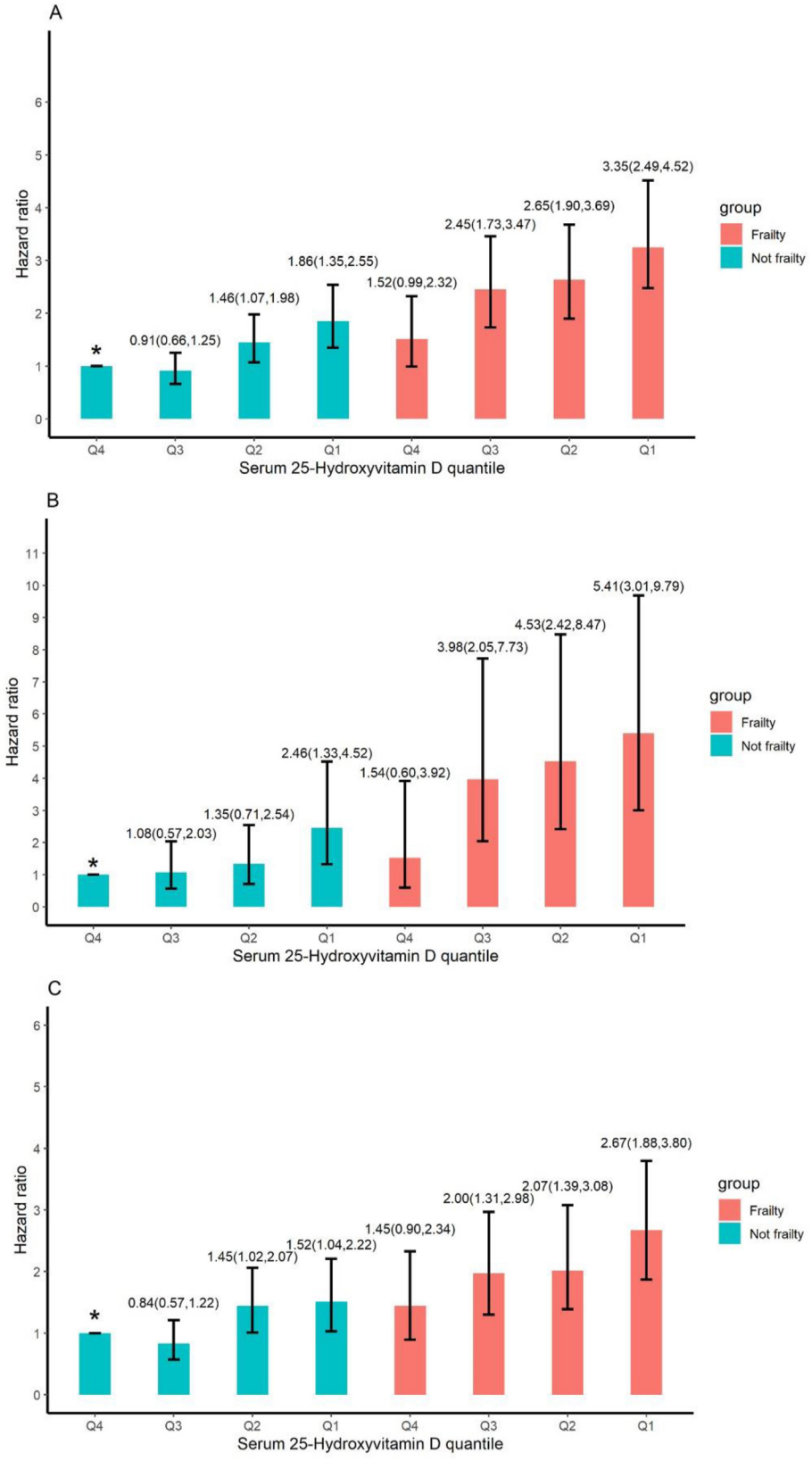

Figure 2 Association of serum 25(OH)D with all-cause mortality (A), circulatory mortality (B), and noncirculatory mortality (C) within frailty strata. Data are presented as hazard with 95% confidence interval, adjusting for age, gender, smoke, alcohol, economic income, rural residents, in marriage, regular exercise, education, live alone, systolic blood pressure, diastolic blood pressure, body mass index, hypertension, diabetes mellitus, cardiovascular disease, stroke and cerebrovascular disease, cancer, vitamin supplements, total cholesterol, creatinine, and albumin. Q4 represents individuals with the highest serum 25(OH)D level and Q1 represents individuals with the lowest. Individuals in the highest quartile of serum 25(OH)D and without frailty were used as the reference group (*).

Conclusion

In conclusion, our study suggested that the associations between low serum vitamin 25(OH)D and mortality were more pronounced in frail participants among a community of the oldest old in China. Our study highlighted the importance of frailty screening among the oldest old of the Chinese population, as it might improve the ability to identify individuals who could benefit most from improved vitamin D status.

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Author contributions

Y.F., Y.H., L.L., C.C., and J.H. designed the research study. L.L. and C.C. analyzed the data and performed statistical analysis. L.L., C.C., J.H., K.L., and Y.Y. wrote the paper. Y.F. and Y.H. had primary responsibility for the final content. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declared no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.05.033.

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