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Plasma 25-Hydroxyvitamin D Concentrations Are Inversely Associated with All-Cause Mortality among a Prospective Cohort of Chinese Adults Aged ≥80 Years

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ABSTRACT

Background: High concentrations of plasma 25-hydroxyvitamin D [25(OH)D], a marker of circulating vitamin D, have been associated with a lower risk of mortality in epidemiologic studies of multiple populations, but the association for Chinese adults aged ≥80 y (oldest old) remains unclear.

Objective: We investigated the association between plasma [25(OH)D] concentration and all-cause mortality among Chinese adults aged ≥80 y.

Design: The present study is a prospective cohort study of 2185 Chinese older adults (median age: 93 y). Prospective all-cause mortality data were analyzed for survival in relation to plasma 25(OH)D using Cox proportional hazards regression models, with adjustments for potential sociodemographic and lifestyle confounders and biomarkers. The associations were measured with HR and 95% CIs.

Results: The median plasma 25(OH)D concentration was 34.4 nmol/L at baseline. Over the 5466 person-year follow-up period, 1100 deaths were identified. Men and women were analyzed together as no effect modification by sex was found. After adjusting for multiple potential confounders, the risk of all-cause mortality decreased as the plasma 25(OH)D concentration increased (P-trend <0.01). Compared with the lowest age-specific quartile of plasma 25(OH)D, the adjusted HRs for mortality for the second, third, and fourth age-specific quartiles were 0.72 (95% CI: 0.57, 0.90), 0.73 (95% CI: 0.58, 0.93), and 0.61 (95% CI: 0.47, 0.81), respectively. The observed associations were broadly consistent across age and other subgroups. Sensitivity analyses generated similar results after excluding participants who died within 2 y of follow-up or after further adjustment for ethnicity and chronic diseases.

Conclusions: A higher plasma 25-hydroxyvitamin D concentration was associated with a reduced risk of all-cause mortality among Chinese adults aged ≥80 y. This observed inverse association warrants further investigation in randomized controlled trials testing vitamin D supplementation in this age group. *J Nutr* 2019;0:1–9.

Keywords: 25-hydroxyvitamin D, mortality, survival, oldest old, Community-based

Introduction

Vitamin D is best known for its role in skeletal health and diseases (1); it also has been suggested to have beneficial effects on promoting overall health and reducing premature death (1–3). Many studies have reported that circulating 25-hydroxyvitamin D [25(OH)D], a major circulatory form of vitamin D, is inversely associated with mortality in multiple populations (4–8).

With aging, there is a concomitant decrease in the concentration of 25(OH)D in older adults as a result of reduced exposure to solar ultraviolet B radiation, impaired vitamin D synthesis in aging skin, and inefficient renal activation of 25(OH)D (9). Thus, hypovitaminosis D is prevalent among older adults and is recognized as an important public health concern (10). Many studies have tried to determine the associations between circulating 25(OH)D concentrations and mortality among older

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adults; generally, lower circulating 25(OH)D concentrations are associated with an elevated risk of mortality (7, 11–14). However, these findings are based on data that include only a modest number of oldest old and the majority of participants are octogenarians and nonagenarians, with centenarians being under-represented. It should also be noted that most cohort studies have been conducted in Western countries. Because ethnic differences may affect vitamin D metabolism and nutritional status (15–17), it is still unclear whether the findings of previous studies can be extrapolated directly to Asian populations. One cohort study of 1101 participants with a follow-up period of 24 y failed to find significant results ($P = 0.22$) in the rural population of Mainland China (18). This discordance may result partly from the extremely long follow-up time because a single serum 25(OH)D concentration at baseline would lose prognostic value over time (19, 20). More importantly, this study did not provide evidence on the oldest old as the participants had a mean age of 56 (±7.9) y. Hence, the association between plasma 25(OH)D concentration and mortality in the oldest old remains largely unexplored and calls for further investigation.

In this context, we conducted the present study to examine whether plasma 25(OH)D concentrations are associated with a risk of all-cause mortality among the oldest old based on data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) in longevity areas. This research, which used the largest sample of oldest old persons in a developing country, provides a unique opportunity to examine associations in a specific population among whom the prevalence of hypovitaminosis D is particularly high and the conventional risk markers for disease and mortality may differ from the risk factor profiles of younger age groups (21, 22).

Methods

Study population

The present study is a prospective, multicenter, community-based longitudinal cohort study. Participants in the CLHLS were living in 8 longevity areas spanning the northern, middle, and southern parts of China, representing three-quarters of the longevity areas selected by the Chinese Society of Gerontology. Compared with other areas, longevity areas have higher densities of centenarians and higher life expectancies. These areas include Chen Mai county (Hainan province), Yong Fu county (Guangxi province), Ma Yang county (Hunan province), Zhong Xiang city (Hubei province), Xia Yi county (He Nan province), San Shui city (Guangdong province), Lai Zhou city (Shandong province), and Ru Dong county (Jiangsu province). In total, 3233 participants were enrolled in the baseline survey in 2012 and 2014, and subsequent follow-up surveys were carried out in 2014 and 2017. We included 2185 participants aged ≥80 y (692 centenarians, 724 nonagenarians, 769 octogenarians) with available plasma 25(OH)D concentration data and no outliers (values that fall outside the limits of mean ±3 SD were defined as outliers), of which 294 were lost to follow-up (13.46%) (**Figure 1**). The study was approved by the biomedical ethics committee of Peking University and Duke University. Informed consent was obtained from all participants included in the study. The details of the CLHLS study have been reported elsewhere (23).

Assessment of plasma 25(OH)D and other biomarkers

Blood samples were collected from participants, by trained medical personnel, after an overnight fast. Five milliliters of venous blood were collected in heparin anticoagulant vacuum tubes, centrifuged at 1500 × *g* for 10 min, and plasma supernatants frozen at −20°C; samples were then shipped in batches on wet ice to the central laboratory where they were stored at −80°C until analysis. Plasma 25(OH)D was measured using an enzyme-linked immunoassay by Immunodiagnostic Systems Limited (24). The interassay and intra-assay coefficients of variation were <10% and <8%, respectively. Plasma creatinine was determined with the picric acid method. Lipid profile, fasting blood glucose, high sensitivity C-reactive protein, and albumin were assessed together by an Automatic Biochemistry Analyzer (Hitachi 7180), using commercially available diagnostic kits (Roche Diagnostic), as detailed elsewhere (25). All laboratory analyses were conducted by the central clinical laboratory at Capital Medical University in Beijing.

Assessment of deaths

We documented the date of death from family members of the deceased or local doctors. The survival time for participants was calculated from the date of blood draw to date of death. For patients who were alive, survival time was right censored as the date of the latest follow-up. Those who could not be found or contacted were defined as "lost to follow-up."

Covariates

Home interviews were carried out to collect information on participants' sociodemographics (age, education, and sex), lifestyle (alcohol consumption, physical exercise, smoking, and dietary habits), and prevalence of comorbidities by means of a structured questionnaire. Systolic and diastolic blood pressures were calculated as the average of 2 consecutive measurements. Anthropometric variables were measured by trained medical personnel, and biospecimens were collected. Fruit intake and vegetable intake were measured by asking the participants "Do you eat fresh fruit?" and "Do you eat fresh vegetables?" The answer choices included "almost every day," "almost every day except in winter," "occasionally," and "rarely or never." Responses of "almost every day" and "almost every day except in winter," were combined and labeled as "often," while "occasionally" and "rarely or never" were combined and defined as "not often." The question pertaining to meat intake read "How often do you eat meat?" The answer choices for meat intake included "almost every day," "occasionally," and "rarely or never." Those who answered "almost every day" were categorized into "often," while those who answered "occasionally" and "rarely or never" were grouped into "not often." Physical exercise was measured using the following question: "At present, do you regularly engage in exercise for fitness, such as walking, running, playing ball games, qi gong (a system of deep breathing exercise) or other exercise?" BMI was calculated as weight in kilograms divided by the height in meters squared (kg/m^2). Education was classified as "yes" if the subject reported at least 1 y of formal schooling, or "no" if <1 y. Cognitive function was assessed by the Mini-Mental State Examination (MMSE)

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Supplemental Tables 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
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Abbreviations used: AQ, age-specific quartile; CLHLS, Chinese Longitudinal Healthy Longevity Survey; IOF, International Osteoporosis Foundation; IOM, Institute of Medicine; MMSE, Mini-Mental State Examination; SQ, season-specific quartile; 25(OH)D, 25-hydroxyvitamin D.

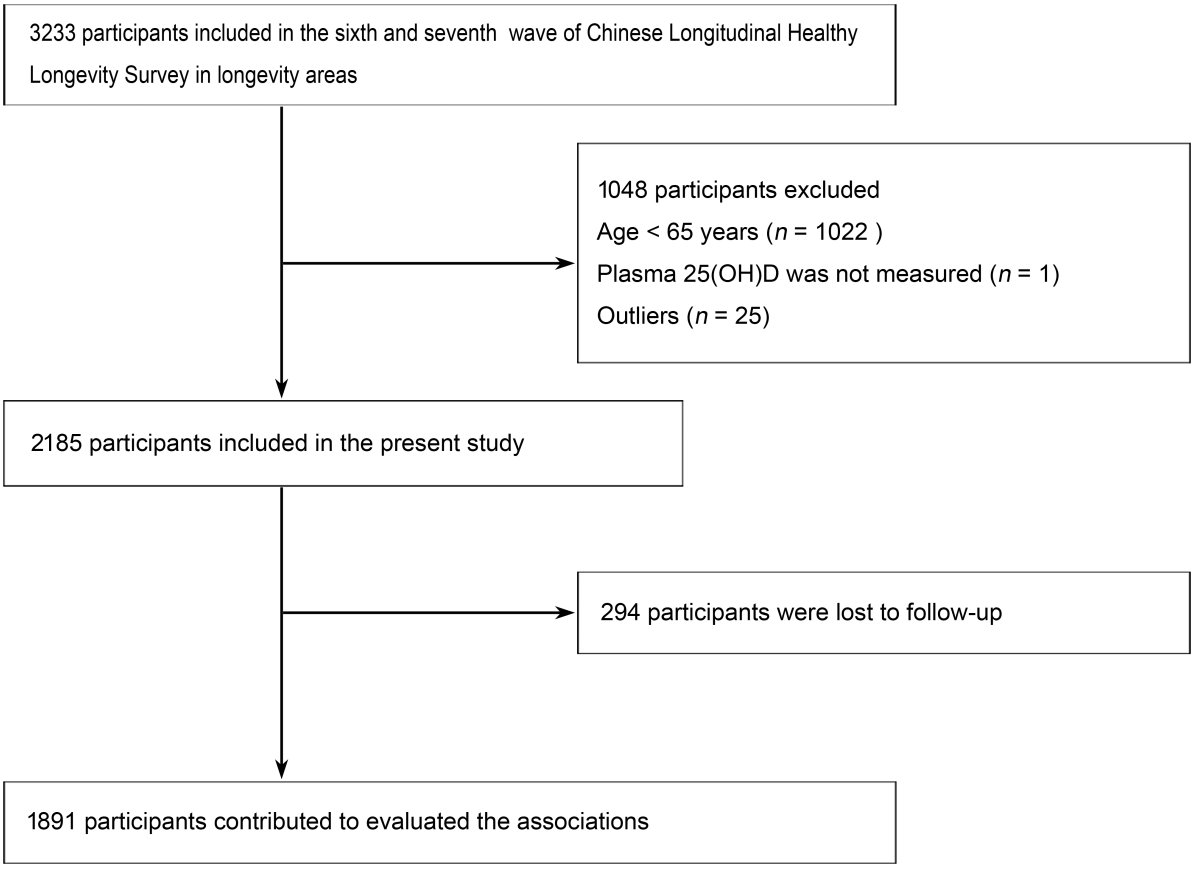

FIGURE 1 Flowchart of participant enrollment.

(26), which has been widely applied in epidemiologic studies. Frailty was defined according to the Study of Osteoporotic Fractures index (27) using 3 components: *1*) low body weight (BMI <18.5 kg/m^2); *2*) inability to rise from a chair without using one's arms; and *3*) reduced energy, as indicated by a response of "yes" to the following question: "For the last 6 mo, were you limited in activities because of a health problem?" Frailty status was defined as robust (0 components), prefrail (1 component), or frail (2 or 3 components); this has been shown to be a good measure of biological age in Chinese older adults (28). In the follow-up surveys, participants were asked to complete the same questionnaires to provide repeated measures on health, physical, social, and demographic information. Additional anthropometric variables, biospecimens, and mortality information were collected during follow-up.

Statistical analysis

Non-normally distributed data were described by medians and IQRs, normally distributed data were described by means and SDs, and categorical data were described by frequencies and percentages. In our study, all centenarians in the selected counties were invited to participate in an interview; subsequently, 1 octogenarian and 1 nonagenarian were randomly selected for interviews. Accordingly, plasma 25(OH)D concentrations were categorized into age-specific quartiles (AQ1–AQ4) as shown in **Supplemental Table 1**. Age-specific quartile ranges were derived from the combination of corresponding quartiles in each age group. Therefore, each age-specific quartile consists of the corresponding quartiles of all age groups. As a result, AQ1 ranged from 3.26 nmol/L [centenarian (≥100 y)] to 29.2 nmol/L [octogenarian (≥80–89 y)]; AQ2 ranged from 21.1 nmol/L [centenarian (≥100 y)] to 39.8 nmol/L [octogenarian (≥80–89 y)]; AQ3 ranged from 29.3 nmol/L [centenarian (≥100 y)] to 53.3 nmol/L [octogenarian (≥80–89 y)]; and AQ4 ranged from 41.5 nmol/L [centenarian (≥100 y)] to 90.7 nmol/L [octogenarian (≥80–89 y)]. Baseline characteristics across age-specific quartiles of plasma 25(OH)D concentrations were compared using analysis of variance for continuous variables with normal distribution, Kruskal-Wallis test for those with skewed distribution, and χ^2 test for categorical variables. Given that seasonal variation may affect concentrations of plasma 25(OH)D, we also categorized plasma 25(OH)D concentrations into season-specific quartiles (SQ1–SQ4) (Supplemental Table 1).

Kaplan-Meier curves were generated for age-specific quartiles of plasma 25(OH)D concentrations and log-rank tests were used to compare different groups. Cox proportional hazards regression models were used to estimate HR with 95% CI of all-cause mortality using the lowest age-specific quartile as reference group. Tests of linear trends were conducted by treating the median values for each age-specific quartile of plasma 25(OH)D as a continuous variable. The statistical significance of the interactions was assessed by adding a product term into the model. The Cox models were adjusted for potential confounders that may be associated with both plasma 25(OH)D concentration and mortality. Three models with different adjustments were used: the first model was adjusted for age, sex, city latitude, and season of blood draw; the second model was further adjusted for other baseline characteristics and lifestyle factors, including alcohol consumption (current/not current), BMI, education level, fruit intake (often/not often), frailty status [robust (reference)/prefrail/frail], meat intake (often/not often), MMSE score, physical exercise (yes/no), residence (rural/urban), systolic blood pressure, smoking (yes/no), and vegetable intake (often/not often); the third model was also adjusted for plasma albumin, creatinine, cholesterol, high sensitivity C-reactive protein, and triglycerides. Model 3 was considered to be the fully adjusted model. We conducted subgroup analyses of the associations of each 10-nmol/L increase in plasma 25(OH)D concentration with mortality

TABLE 1 Baseline characteristics of Chinese adults aged ≥80 y by age-specific quartile of plasma 25(OH)D concentration[1]

Characteristics	Plasma 25(OH)D concentrations				*P* value
	AQ 1[2] 3.26–29.2 nmol/L	AQ 2 21.1–39.8 nmol/L	AQ 3 29.3–53.3 nmol/L	AQ 4 41.5–90.7 nmol/L	
No. of participants	547	547	545	546	
Age, y	94 (86–100)	93 (87–100)	93 (86–100)	93 (86–100)	0.86
Female	412 (75.3)	385 (70.3)	338 (62.0)	278 (50.9)	<0.01
Season of blood draw	—	—	—	—	<0.01
March–May	277 (50.6)	193 (35.4)	153 (28.1)	125 (23.0)	
June–August	269 (49.2)	352 (64.5)	381 (69.9)	344 (63.2)	
September–November	1 (0.2)	1 (0.2)	11 (2.0)	75 (14.8)	
Residence in urban area	74 (13.7)	81 (14.9)	70 (13.0)	55 (10.2)	0.12
Education time ≥1, y	87 (16.1)	111 (20.4)	123 (22.9)	144 (26.6)	<0.01
Current smoker	41 (7.8)	53 (10.0)	47 (8.8)	72 (13.4)	0.04
Current drinker	49 (9.3)	56 (10.5)	72 (13.5)	72 (13.5)	0.07
Vegetable intake	—	—	—	—	<0.01
Often	291 (55.2)	339 (64.0)	335 (63.0)	259 (48.1)	
Not often	236 (44.8)	191 (36.0)	202 (37.6)	280 (52.0)	
Fruit intake	—	—	—	—	<0.01
Often	221 (41.9)	220 (41.2)	182 (33.8)	166 (30.6)	
Not often	306 (58.7)	314 (58.8)	357 (66.2)	376 (69.4)	
Meat intake	—	—	—	—	<0.01
Often	292 (57.3)	284 (54.3)	256 (48.6)	247 (46.5)	
Not often	218 (42.8)	239 (45.7)	271 (51.4)	284 (53.5)	
Currently engaged in physical exercise	50 (9.7)	54 (10.4)	72 (13.4)	82 (15.6)	0.01
Frailty[3]	—	—	—	—	<0.01
Robust	133 (27.5)	175 (35.1)	168 (33.5)	183 (36.9)	
Prefrail	134 (27.8)	158 (31.7)	181 (36.1)	200 (40.3)	
Frail	216 (44.7)	165 (33.1)	153 (30.5)	113 (22.8)	
Systolic blood pressure, mmHg	140 (125–160)	142 (125–160)	140 (128–160)	140 (128–160)	0.85
MMSE	20.0 (7.0–25.0)	22.0 (12.0–26.0)	24.0 (15.0–28.0)	25.0 (19.0–28.0)	<0.01
BMI, kg/m^2	20.0 (17.6–22.5)	20.0 (17.9–22.8)	20.0 (17.8–23.1)	20.1 (18.0–22.4)	0.79
Plasma glucose, mmol/L	4.70 (4.10–5.55)	4.69 (4.06–5.47)	4.70 (4.01–5.40)	4.65 (3.83–5.41)	0.38
Plasma total cholesterol, mmol/L	4.34 (3.64–5.09)	4.33 (3.63–5.05)	4.31 (3.61–5.02)	4.27 (3.77–4.90)	0.88
Plasma triglycerides, mmol/L	0.85 (0.64–1.18)	0.86 (0.63–1.20)	0.88 (0.65–1.30)	0.85 (0.64–1.14)	0.09
Plasma albumin, mmol/L	39.3 (36.0–42.5)	40.2 (37.0–43.7)	40.6 (37.3–43.6)	40.5 (37.6–43.1)	<0.01
Plasma high sensitivity C-reactive protein, mmol/L	1.24 (0.49–3.35)	1.00 (0.44–2.73)	1.03 (0.44–2.68)	1.23 (0.47–2.72)	0.07
Plasma creatinine, μmol/L	71.0 (61.1–87.0)	76.9 (64.0–93.2)	79.0 (67.0–93.4)	84.3 (68.0–101.8)	<0.01

[1]Continuous variables are expressed as medians and IQRs; categorical variables are expressed as frequencies (percentages). For details on the age ranges and plasma 25(OH)D concentration ranges, please refer to Supplemental Table 1. AQ, age-specific quartile; 25(OH)D, 25-hydroxyvitamin D.
[2]Age-specific quartile ranges were derived from the combination of corresponding quartiles in different age group (octogenarian, nonagenarian, and centenarian). Therefore, each quartile consists of the corresponding quartiles of all age groups. For details, please refer to specific ranges in Supplemental Table 1.
[3]Frailty was defined according to the Study of Osteoporotic Fractures index using 3 components: *1*) low body weight (BMI <18.5 kg/m^2); *2*) inability to rise from a chair without using one's arms; and *3*) reduced energy, as indicated by a response of "yes" to the following question: "For the last 6 mo, were you limited in activities because of a health problem?" Frailty status was defined as robust (0 components, reference), prefrail (1 component), or frail (2 or 3 components).

by groups based on age (centenarian/nonagenarian/octogenarian), BMI (kg/m^2) (<18.5, 18.5–24, >24), cognitive impairment [yes/no, defined as MMSE <24 (29)], frailty status (robust/prefrail/frail), sex (man/woman), physical exercise (yes/no), and season of blood draw (March–May, June–August, and September–November). We also explored possible interactions between plasma 25(OH)D and the aforementioned characteristics with respect to all-cause mortality.

We performed several sensitivity analyses to test robustness of the primary results including: additional adjustment for *1*) ethnicity (Han or minority) and 2) history of chronic diseases such as diabetes mellitus, heart disease, cerebrovascular disease, or respiratory diseases and; lag analysis to exclude *3*) participants who died within 2 y of the baseline interview and *4*) those who reported that they often took vitamin supplements. To compare the results obtained from primary analysis with those from clinically defined cutoffs, we also conducted sensitivity analyses based on the 25(OH)D thresholds recommended by the US Institute of Medicine (IOM), which resulted in 3 clinically defined groups: *1*) <30 nmol/L (deficient; reference group); *2*) ≥30 nmol/L but <50 nmol/L (insufficient); and *3*) ≥50 nmol/L (sufficient) (30, 31). We also applied cutoffs based on the recommendations of the International Osteoporosis Foundation (IOF) Working Group (32,): *1*) <25 nmol/L (severely deficient; reference group); *2*) ≥25 nmol/L but <50 nmol/L (deficient); *3*) ≥50 nmol/L but <75 nmol/L (insufficient); and *4*) ≥75 nmol/L (sufficient).

Analyses were conducted using STATA, version 13 (StataCorp). All *P*-values were 2-tailed, with statistical significance set at α of 0.05.

Results

Baseline characteristics

The baseline characteristics by age-specific quartile of plasma 25(OH)D concentration are shown in Table 1. The median

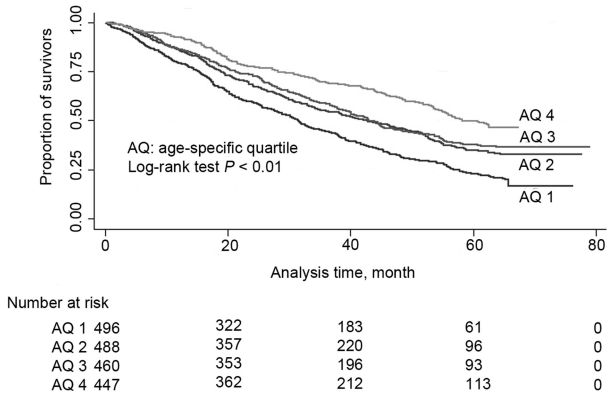

FIGURE 2 Kaplan-Meier plot showing risk of all-cause mortality by age-specific quartile of plasma 25(OH)D concentration among Chinese adults aged ≥80 y. For details on the age ranges and plasma 25(OH)D concentration ranges, please refer to Supplemental Table 1.

plasma 25(OH)D concentration was 34.4 nmol/L (IQR: 25.0–48.0 nmol/L), with an estimated 38.6% of participants manifesting vitamin D deficiency (<30 nmol/L) and 24.9% showing severe deficiency (<25 nmol/L). Compared with participants with higher plasma 25(OH)D concentrations, those with lower plasma 25(OH)D concentrations tended to be women, nonsmokers; they reported less vegetable intake, more fruit and meat intake, and a lack of physical exercise; they were frailer, had lower MMSE scores, and were more likely to have lower concentrations of plasma albumin and creatinine. Compared with participants re-interviewed in the follow-up waves in 2014 and 2017, individuals who were lost to follow-up were more likely to be frailer, live in urban areas, reported a lack of physical exercise, and have lower vegetable and fruit intake; they also tended to have higher concentrations of plasma 25(OH)D and creatinine but lower albumin and total cholesterol (**Supplemental Table 2**).

Age-specific quartiles and season-specific quartiles of plasma 25(OH)D and all-cause mortality

During a total of 5466 person-years of follow-up, 1100 deaths were identified. Figure 2 shows the Kaplan-Meier curves for all-cause mortality by different age-specific quartile of plasma 25(OH)D concentration. The risk of all-cause mortality decreased with increasing plasma 25(OH)D concentration (*P*-trend <0.01), with fully adjusted HRs for the second, third, and fourth age-specific quartiles of 0.72 (95% CI: 0.57, 0.90), 0.73 (95% CI: 0.58, 0.93), and 0.61 (95% CI: 0.47, 0.81), respectively, compared with the first age-specific quartile (Table 2). Evaluating the risk of mortality for each 10-nmol/L increase in plasma 25(OH)D concentration yielded an adjusted-HR of 0.89 (95% CI: 0.84, 0.95). Regarding season-specific quartiles, the HRs for all-cause mortality for the second, third, and fourth season-specific quartiles were 0.69 (95% CI: 0.56, 0.87), 0.74 (95% CI: 0.58, 0.94), and 0.58 (95% CI: 0.44, 0.76), respectively, relative to the lowest season-specific quartile in the fully adjusted model (*P*-trend <0.01).

Sensitivity analyses

The results of the sensitivity analyses (**Supplemental Table 3**) were materially unchanged from those of the primary results after also adjusting for ethnicity [HR = 0.61 (95% CI: 0.47, 0.81)] and history of chronic diseases [HR = 0.61 (95% CI: 0.46, 0.80)]; or after excluding those who died within 2 y of follow-up [HR = 0.54 (95% CI: 0.37, 0.78)] and those who reported taking vitamin supplements [HR = 0.60 (95% CI: 0.45, 0.82)]. Use of the IOM and IOF Working Group cutoffs in relation to all-cause mortality were generally consistent with the primary results (Table 3). Briefly, with the IOM recommendation, vitamin D sufficiency (≥50 nmol/L) was associated with better survival [HR = 0.67 (95% CI: 0.51, 0.88)] compared to vitamin D deficiency (>30 nmol/L). Similarly, with use of the recommended cutoffs from the IOF Working Group, vitamin D sufficiency (≥75 nmol/L) was associated with better survival [HR = 0.42 (95% CI: 0.19, 0.93)] compared to severe vitamin D deficiency (<25 nmol/L).

Subgroup analyses

Subgroup analyses stratified by various predefined factors are shown in **Supplemental Table 4**. Overall, we did not find evidence of statistically significant differences by age group, BMI, cognitive function, frailty status, sex, physical exercise, or season of blood draw (all *P*-interaction >0.1).

TABLE 2 Association between the plasma 25(OH)D concentration of Chinese adults aged ≥80 y and all-cause mortality by age-specific plasma 25(OH)D quartile[1]

	Risk by age-specific quartiles [HR (95% CI)] for all-cause mortality			
Model	AQ 1 [*n* = 547 (25.03%)]	AQ 2 [*n* = 547 (25.03%)]	AQ 3 [*n* = 545 (24.94%)]	AQ 4 [*n* = 546 (24.99%)]
Model 1[2]	1.00 (reference)	0.66 (0.55, 0.80)	0.65 (0.54, 0.80)	0.45 (0.36, 0.57)
Model 2[3]	1.00 (reference)	0.72 (0.58, 0.90)	0.71 (0.56, 0.89)	0.55 (0.42, 0.72)
Model 3[4]	1.00 (reference)	0.72 (0.57, 0.90)	0.73 (0.58, 0.93)	0.61 (0.47, 0.81)
	Risk by season-specific quartiles [HR (95% CI)] for all-cause mortality			
Model	SQ 1 [*n* = 550 (25.17%)]	SQ 2 [*n* = 548 (25.08%)]	SQ 3 [*n* = 542 (24.81%)]	SQ 4 [*n* = 545 (24.94%)]
Model 1	1.00 (reference)	0.66 (0.55, 0.79)	0.70 (0.58, 0.86)	0.42 (0.34, 0.53)
Model 2	1.00 (reference)	0.69 (0.56, 0.85)	0.74 (0.59, 0.93)	0.51 (0.39, 0.66)
Model 3	1.00 (reference)	0.69 (0.56, 0.87)	0.74 (0.58, 0.94)	0.58 (0.44, 0.76)

[1] For details on the age ranges and plasma 25(OH)D concentration ranges, please refer to Supplemental Table 1. AQ, age-specific quartile; SQ, season-specific quartile; 25(OH)D, 25-hydroxyvitamin D.

[2] Model 1: adjusted for age, season of blood draw, latitude, and sex.

[3] Model 2: further adjusted for alcohol consumption, BMI, education, fruit intake, meat intake, physical exercise, residence, systolic blood pressure, smoking, and vegetable intake.

[4] Model 3: further adjusted for albumin, cholesterol, creatinine, high sensitivity C-reactive protein, plasma glucose, and TG.

TABLE 3 Association between plasma 25(OH)D concentration of Chinese adults aged ≥80 y and all-cause mortality by different clinically defined cutoffs[1]

	Risk by the International Osteoporosis Foundation Working Group cutoff			
	<25 nmol/L (severely deficient)	25 to <50 nmol/L (deficient)	50 to <75 nmol/L (insufficient)	≥75 nmol/L (sufficient)
Model	*n* = 543 (24.85%)	*n* = 1154 (52.81%)	*n* = 431 (19.73%)	*n* = 57 (2.61%)
Model 1[2]	1.00 (reference)	0.67 (0.57, 0.78)	0.43 (0.34, 0.55)	0.23 (0.11, 0.51)
Model 2[3]	1.00 (reference)	0.74 (0.61, 0.89)	0.55 (0.42, 0.73)	0.32 (0.14, 0.69)
Model 3[4]	1.00 (reference)	0.73 (0.60, 0.89)	0.63 (0.47, 0.83)	0.42 (0.19, 0.93)
		Risk by the Institute of Medicine cutoff		
Model	<30 nmol/L (deficient)	0 to <50 nmol/L (insufficient)	≥50 nmol/L (sufficient)	—
	n = 843 (38.58%)	*n* = 854 (39.08%)	*n* = 488 (22.33%)	
Model 1	1.00 (reference)	0.71 (0.60, 0.84)	0.45 (0.36, 0.57)	—
Model 2	1.00 (reference)	0.79 (0.65, 0.95)	0.57 (0.44, 0.75)	—
Model 3	1.00 (reference)	0.79 (0.65, 0.97)	0.67 (0.51, 0.88)	—

[1]For details on the age ranges and plasma 25(OH)D concentration ranges, please refer to Supplemental Table 1. 25(OH)D, 25-hydroxyvitamin D.
[2]Model 1: adjusted for age, season of blood draw, latitude, and sex.
[3]Model 2: further adjusted for alcohol consumption, BMI, education, fruit intake, meat intake, physical exercise, residence, systolic blood pressure, smoking, and vegetable intake.
[4]Model 3: further adjusted for albumin, cholesterol, creatinine, high sensitivity C-reactive protein, plasma glucose, and TG.

Discussion

In the present community-based, prospective cohort study of Chinese adults aged ≥80 y, we found that a higher plasma 25(OH)D concentration, a marker of circulating vitamin D, was associated with a decreased risk of all-cause mortality after accounting for potential confounders. This observed association was broadly consistent across various other subgroups. Sensitivity analyses with additional adjustments for ethnicity or chronic diseases had no effect on the results. Excluding participants who died within 2 y of the baseline survey and participants who reported taking vitamin supplements did not materially change the results. We also found similar associations based on different clinically defined cutoffs.

In recent years, a growing body of evidence has proposed a broad range of potential extra-skeletal effects of vitamin D (33, 34). For example, a higher circulating 25(OH)D concentration may facilitate synthesis of cathelicidin, a peptide capable of destroying infectious agents. It also has been suggested that monocytes and/or macrophages are prevented from initiating an innate immune response when serum 25(OH)D concentrations are low (1). Further, a higher circulating serum 25(OH)D concentration may offer protection against the development of cancer (33). Taken together, these studies suggest that vitamin D may play a wide role in the pathogenesis of many disorders such as cardiovascular diseases, infectious diseases, autoimmune diseases, and cancer (1, 33, 35–38), all of which are important contributors to all-cause mortality.

Our findings are generally consistent with those of previous cohort studies, which have examined links between circulating 25(OH)D concentration and mortality among older adults (7, 12, 14, 39–41). In a meta-analysis of 8 cohort studies conducted in Europe and the United States by Schottker et al., compared with the top quintile of serum 25(OH)D concentration, the bottom quintile had HRs for all-cause mortality of 1.54 (95% CI: 1.27, 1.86) and 1.57 (95% CI: 1.26, 1.95) for those aged 60–69 y and 70–79 y, respectively (42). Although participants in our cohort were much older (median age of 93 y), our results were consistent with those of Schottker et al., with an HR of 1.84 (95% CI: 1.41, 2.41) for those with the lowest age-specific quartile of plasma 25(OH)D concentration, using the top age-specific quartile as reference. Other published studies of the association between circulating 25(OH)D and mortality among the oldest old are scarce and have yielded mixed results. Pilz et al. reported an adjusted-HR of 1.56 (95% CI: 1.01, 2.40) for the lowest compared with the highest quartile of serum 25(OH)D among 961 female nursing home residents (mean age 83.7 y and mean follow-up 2.25 y) (43). Granic et al. reported a U-shaped association in the Newcastle 85+ Study of 775 women (mean age 85 y with a follow-up of 6 y) (44). In contrast, Formiga et al. did not detect significant results ($P = 0.86$) in a cohort of 312 subjects (aged 85 y, with a follow-up of 2.8 y) (45). Variations in sample size, number of outcomes, sex, follow-up duration, and circulating 25(OH)D concentration may contribute to the lack of agreement across studies regarding the association between circulating 25(OH)D concentration and mortality among the oldest old. Our research extends the findings of the aforementioned studies to a substantially larger community-based cohort of the oldest old in Asia.

We cannot exclude reverse causality, as it is very likely that lower plasma 25(OH)D concentrations are a consequence of ill health rather than a cause. To examine whether pre-existing poor health might result in limited outdoor activity, which in turn might lead to vitamin D deficiency (from decreased sunlight exposure), we re-analyzed the data after excluding participants who died within 2 y of the baseline interview; the results were materially unchanged. The observed associations were also robust to adjustments for frailty status, physical exercise, and even a variety of chronic diseases, all of which may be proxies for impaired mobility, limited outdoor activity, and poor health. Subgroup analyses based on these factors also yielded generally consistent results. These results are consistent with the data from several cohort studies in which serum 25(OH)D concentration was inversely associated with all-cause mortality independent of frailty, physical activity, and chronic diseases (44, 46, 47). Nevertheless, we are still not able to determine whether vitamin D supplementation will decrease the risk of all-cause and cause-specific mortality in the oldest old. A randomized controlled trial testing vitamin D supplementation would be the best way to answer this question by balancing all confounders known and unknown between intervention group and control group and avoiding reverse causality. However, currently available RCTs on vitamin D supplementation and mortality have shown conflicting results and most of the enrolled subjects in these trials were older adults aged <80 y, with some studies yielding null effects (48, 49) and

others showing positive effects (50). Adequately designed RCTs focusing on vitamin D supplementation and mortality among the community-living oldest old are awaited.

The circulating 25(OH)D concentrations vary across different ethnic groups, age groups, seasons, and outcomes (51). Previous cohort studies of this issue among older adults have reported median/mean serum 25(OH)D concentrations ranging from 17.5 nmol/L to 66 nmol/L (39, 43). In a recent nationally representative sample of the Chinese population aged >60 y, Chen et al. reported median serum 25(OH)D concentrations of 61.0 nmol/L for men and 53.7 nmol/L for women (31). We observed lower median plasma concentrations of 25(OH)D in the present study (41.4 nmol/L for men and 32.0 nmol/L for women) than did Chen et al. These lower plasma concentrations may be a result of the much older age of our participants. Using the cutoffs recommended by the IOM, participants with insufficient concentrations (>30 to <50 nmol/L) and sufficient concentrations (≥50 nmol/L) both had lower risks of death compared to the deficient group (≤30 nmol/L). These findings were generally the same with use of the cutoffs proposed by the IOF Working Group. Overall, these results suggest that a threshold of plasma 25(OH)D concentration indicative of increased mortality risk among Chinese oldest old persons is more likely to be 25–30 nmol/L rather than 50 nmol/L.

Our work has several strengths. The present study was conducted in a real-life setting and represents the broad spectrum of community-dwelling Chinese adults aged ≥80 y. To the best of our knowledge, this is the first study to investigate the distribution and association of plasma 25(OH)D concentration with mortality among the oldest old in a developing country. Our data also provide novel insights into potential ethnic variation in plasma 25(OH)D concentration and effects. In addition, we obtained data via in-home examinations of community-living participants. Most oldest-old Chinese live out their lives in the family home following the unique social characteristics of the traditionally and culturally family-care dominated Chinese society. It has been reported that community-living older adults are more representative, and have better vitamin D status because of better physical health and functioning relative to their institutionalized counterparts (52, 53). Our study also adjusted for numerous health-related behaviors and existing health conditions, including conditions that commonly indicate impaired mobility and limited outdoor activity. Finally, we used age-specific plasma 25(OH)D cutoffs, which facilitates adjusting for age variability in plasma 25(OH)D status across centenarians, nonagenarians, and octogenarians.

Several limitations should be considered when interpreting the results of this study. First, in an observational study of an older population such as this, the observed relationship may be subject to reverse causation, in part because of the influence of underlying diseases in this population. This study does not prove causation of mortality by low plasma 25(OH)D, as the possibility of residual confounding because of unmeasured or imprecisely measured factors cannot be excluded. Second, we were not able to explore specific causes of death in relation to plasma 25(OH)D concentration as these data were not available. Third, because plasma calcium and parathyroid hormone concentrations were not measured, we could not determine whether the association between plasma 25(OH)D concentration and mortality was partly mediated or confounded by calcium or secondary hyperparathyroidism. Also, we were not able to ascertain supplemental vitamin D intake. However, our results were robust to the exclusion of those who reported taking vitamin supplements (86% of our subjects reported not taking any supplements); thus, supplemental vitamin D intake is not likely to explain our results. In addition, measures of fruit, vegetable, and meat intake were coarse, relying on a few questions regarding consumption frequency; we also did not obtain data on sun exposure or dietary intake of vitamin D. It is well accepted that vitamin D is primarily synthesized in the skin after sun exposure, although dietary contributions should not be underestimated (54, 55). Further, participants were from 8 longevity areas, which could be different from other areas; therefore, the results of this study may not be generalizable to other regions and age groups. Finally, the proportion of participants lost to follow-up was relatively large and baseline plasma 25(OH)D concentrations per se decrease with age; thus, our results may be subject to attrition bias and may not have been sufficiently powered to avoid reverse causality. Nevertheless, given the aging population, even small differences could provide prognostic information on impaired survival in the oldest old, which would have significant practical implications for modifying care efforts.

In conclusion, higher plasma 25(OH)D concentrations were associated with a reduced risk of all-cause mortality among Chinese adults aged ≥80 y. This inverse association warrants further investigation in randomized controlled trials testing vitamin D supplementation in this age group.

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