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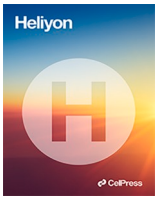

Research article

Associations of serum albumin and dietary protein intake with all-cause mortality in community-dwelling older adults at risk of sarcopenia

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ABSTRACT

Objective: The Asian Working Group for Sarcopenia 2019 consensus emphasized nutritional assessment and intervention for community-dwelling older people with sarcopenia status. This study aimed to examine the association of serum albumin and dietary protein intake (DPI) with all-cause mortality among older adults at risk of sarcopenia.

Methods: We enrolled 1763 older adults at risk of sarcopenia in the Chinese Longitudinal Healthy Longevity Survey (2012–2018) using calf circumference and handgrip strength. Serum albumin concentrations were measured using bromocresol green methods, and DPI frequency was evaluated using a semi-quantitative questionnaire at baseline. Cox proportional hazards models were used to explore the association of serum albumin and DPI with all-cause mortality.

Results: During 5606.3 person-years of follow-up (median: 3.28 years), 802 older people died. After adjusting for socio-demographics, health behaviors, and clinical characteristics, we observed an inverse linear association between serum albumin and all-cause mortality ($P_{\text{non-linear}} = 0.429$). Participants with low albumin levels (<40.0 g/L) had a 43 % higher risk of mortality than their counterparts (hazard ratio (HR) = 1.43, 95 % confidence interval (CI) = 1.22–1.66). There was no significant association between DPI and mortality ($P_s > 0.05$). Moreover, the association between low albumin and all-cause mortality remained significant in the lower DPI subgroup (HR = 1.47, 95 % CI = 1.18–1.85), but was not significant in the high DPI subgroup (HR = 1.15, 95 % CI = 0.92–1.39).

Conclusions: Serum albumin levels are inversely associated with all-cause mortality in community-based older adults at risk of sarcopenia. Sufficient dietary protein consumption may attenuate the effect of low serum albumin on increased mortality and potential mechanisms for the interaction warrant further exploration.

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1. Introduction

Sarcopenia, defined as age-related loss of skeletal muscle mass plus loss of muscle strength and/or reduced physical function, is associated with multiple adverse health outcomes and increased mortality [1–4]. The Asian Working Group for Sarcopenia (AWGS) 2019 consensus emphasized nutritional assessment and adequate dietary protein intake (DPI) for community-dwelling older individuals with sarcopenia risk, yet related epidemiological evidence is limited. As the aging process accelerates, China is expected to have the largest number of older people in the world, leading to a substantial late-life disease burden [5,6]. A recent modelling study predicted that the mean life expectancy of the mainland Chinese population would reach 81.3 years by 2035 [7]. To prevent premature death from sarcopenia, it is necessary to explore the role of protein-related nutritional factors among sarcopenic older adults from low- and middle-income countries.

Albumin is the most abundant plasma protein in the circulation and is commonly used as an indicator of malnutrition [8,9]. In community settings, hypoproteinemia results from the combination of inadequate calorie and protein intake and chronic inflammation [10]. Several longitudinal studies have provided evidence that low albumin was associated with increased mortality in both community settings and patients with various diseases [9,11,12]; however, little is known about the relationship between albumin and mortality in community-dwelling older people at risk of sarcopenia. Pathological mechanisms of hypoalbuminemia include insufficient raw materials, decreased synthetic function, and increased protein loss [13]. Intake reduction is a major cause of chronic malnutrition in older people [14]. The AWGS 2019 consensus suggested that older people considered at risk of sarcopenia should consume adequate dietary protein to maintain nutritional status. Over the past three decades, the proportion of older Chinese people with insufficient protein intake has increased significantly [15]. Recent reviews have suggested inconsistent causality between DPI and mortality in previous observational studies [16,17]. Langsetmo et al. enrolled 5790 community-dwelling older men in America and found that low protein intake was associated with an 11 % increased risk of death [18]; however, another prospective cohort study showed that high protein intake was not associated with mortality among older individuals in Australia [19]. In addition, several studies have shown that a high-protein diet was positively associated with muscle strength and physical activities in patients with sarcopenia [20–22]. With the aging process, older adults with sarcopenia-related symptoms are often accompanied by reduced digestive and metabolic functions [23]. Both albumin and dietary protein are valuable nutritional indicators that may be associated with survival in sarcopenic older adults. As an important health behavior factor, whether DPI affects albumin levels and its relationship with mortality requires further investigation in sarcopenic populations.

Based on relevant physiological mechanisms and previous findings, we hypothesize that albumin levels and DPI are negatively correlated with the risk of mortality; and the relationship between albumin and mortality may be influenced by DPI. To address these knowledge gaps, this prospective study aimed to investigate the independent and interactive associations of serum albumin and DPI with all-cause mortality in community-dwelling older adults at risk of sarcopenia.

2. Methods

2.1. Sarcopenia risk

Sarcopenia risk was determined using the Ishii screening test, based on three indicators: age, calf circumference, and handgrip strength [24]. The Ishii screening test was originally developed by Japanese researchers, and its accuracy for sarcopenia screening has been confirmed among community-dwelling older adults in Asia, including China [25,26]. Calf circumference in the largest gastrocnemius muscle was measured using a standard scale, with participants barefoot and dressed in light clothing. Trained investigators measured handgrip strength twice with each hand using a hand dynamometer (WL-1000, Nan Tong, China) and the maximum value was recorded. Ishii test score was calculated as follows: (1) $0.62 \times (\text{age} - 64) - 3.09 \times (\text{handgrip strength} - 50) - 4.64 \times (\text{calf circumference} - 42)$ for males; (2) $0.8 \times (\text{age} - 64) - 5.09 \times (\text{handgrip strength} - 34) - 3.28 \times (\text{calf circumference} - 42)$ for females. According to recommended threshold values, men with Ishii scores $\geq$105 or women with Ishii scores $\geq$120 were defined as being at risk of sarcopenia [24].

2.2. Study population

This study utilized data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS), which is an ongoing longitudinal study of Chinese older adults that was established in 1998 with follow-up surveys every 2–3 years. The CLHLS cohort is a project focused on longevity, its sampling strategy is to first include all centenarians who agree to participate in the survey. Then, investigators match nonagenarians (aged 90–99), octogenarians (aged 80–89), and septuagenarians (aged 70–79) at a 1:1 ratio, and those aged 60–69 at a 2:1 ratio. Details of the study design and sampling methods have been reported previously [27]. Since 2008, the CLHLS has added in-depth surveys in eight longevity regions (Rudong County in Jiangsu Province, Xiayi County in Henan Province, Zhongxiang City in Hubei Province, Mayang County in Hunan Province, Yongfu County in Guangxi Province, Laizhou City in Shandong Province, Chengmai County in Hainan Province, and Sanshui District in Guangdong Province), and collected more comprehensive data from physical examinations and blood samples. In the current study, 3523 participants were initially recruited from the 2012 and 2014 waves and followed up until 2018. Participants aged <60 years (n = 37) and those with missing data on calf circumference (n = 42), handgrip strength (n = 432), serum albumin (n = 81), or DPI (n = 86) were excluded. Thus, 2832 participants were screened using the Ishii test, of whom 2106 were identified as at risk of sarcopenia and included in this study; while 726 individuals without sarcopenia

risk were excluded. Participants who were lost to follow-up for the first interview (n = 327) or had invalid death time (n = 16) were also excluded, owing to inconclusive survival time. Finally, a total of 1763 older people at risk of sarcopenia (88.31 ± 10.49 years; 60.81 % female) were included in the final analysis. The participant recruitment flowchart was shown in Supplementary Fig. 1. The CLHLS was approved by the Ethics Committee of Peking University (No. IRB00001052-13074). Signed written informed consents were obtained from all participants or their legal representatives.

2.3. Survival data

Participants' survival status was ascertained during follow-up surveys in 2014 and 2018. When available, information on the vital status and date of death were collected from officially issued death certificates. Otherwise, death information was collected from the next-of-kin or local residential committees who were familiar with the decedents. Survival duration (in months) was calculated based on the time interval between the first interview and the date of death or their latest valid follow-up survey.

2.4. Albumin measurement

Trained nurses collected 5 mL fasting (overnight) venous blood samples from all participants at baseline. Samples were centrifuged at 2500 rpm for 10 min, then transported in a −20 °C cold chain and stored at −80 °C for analysis. Levels of albumin, total cholesterol, triglycerides, fasting blood glucose, and high sensitivity C-reactive protein (hs-CRP) were measured using a sequential automatic analyzer (Hitachi 7108, Tokyo, Japan) with a commercial diagnostic kit (Roche Diagnostic). All laboratory analyses were conducted by the central clinical laboratory at Capital Medical University in Beijing; details have been published elsewhere [28]. The definition of low albumin used in previous studies has been inconsistent [9]. Although albumin levels <35 g/L have traditionally been considered to indicate hypoalbuminemia, only 9.5 % of participants in this study had hypoalbuminemia. A recent large-scale Chinese cohort study proposed that a cut-off value of 40.0 g/L could be a more appropriate indicator to monitor hypoalbuminemia in community-dwelling older adults [12]. Thus, considering the statistical power in multiple adjusted models, a threshold of <40.0 g/L for low albumin was used, in accordance with previous recommendations [12,29]. We also divided albumin into sex-specific tertiles to explore the trend relationship between albumin levels and mortality.

2.5. DPI assessment

The frequency of DPI was evaluated using a semi-quantified questionnaire during face-to-face interviews. Six high quality protein-rich food sources were investigated, four of which were from animal sources, including meats, fish, eggs, and dairy products, and two were from plant sources, including nuts and bean products. Meats comprised lean meat (beef, lamb, veal, pork, etc.) and poultry (chicken, duck, goose, etc.). Fish and seafood included river or marine fish, prawns, crabs, lobsters, mussels, oysters, clams, etc. Dairy products included milk, yoghurt, and cheese. Nuts included almonds, walnuts, pine nuts, hazelnuts, cashews, pumpkin seeds, and sesame seeds, etc. Bean products included all beans, lentils, chickpeas, split peas, and tofu. Participants were asked to report their consumption of each protein-rich food, and the responses categorized into five groups: "eat almost every day = 5 point"; "not every day, but at least once a week = 4 points"; "not weekly, but at least once a month = 3 points"; "not monthly, but sometimes eat = 2 points"; and "eat little or never = 1 point". Total DPI score (possible range: 6–30 points) was calculated by summing the points for each protein-rich food. DPI diversity was categorized as high (≥14 points) or low (<14 points) according to the media. In addition, DPI scores were categorized into tertiles (Q1: 6–11 points; Q2: 12–15 points; and Q3: 16–30 points), to explore whether there was a dose-response effect on mortality. Similarly, animal protein intake (possible range: 4–20 points) and plant protein intake (possible range: 2–10 points) were calculated and categorized separately. The above dietary frequency assessment methods, based on CLHLS data, showed good validity, and were associated with multiple adverse health outcomes in previous studies [30,31]. Details of the DPI questionnaire were described in Supplementary Table 1.

2.6. Covariates

The following covariates were collected at baseline and considered as potential confounders based on published literature reports [12,17,32,33]: age, sex, ethnicity (Han vs others), education (illiterate or literate), marital status (have no spouse, including widowed or divorced vs married), living status (living alone vs with others), residence (urban vs rural), current smoking (yes vs no), current alcohol consumption (yes vs no), regular exercise (yes vs no), type of staple food (rice, wheat, and others), and daily amount of staple food intake (g/day). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Activities of daily living (ADL) were evaluated using the six-item Katz scale, and participants with total scores <6 points were defined as having ADL impairment [34]. Cognitive function was assessed using the Chinese version of the Mini-Mental State Examination (MMSE). Illiterate subjects with an MMSE score <18 or literate subjects with an MMSE score <24 were defined as having cognitive impairment [35]. Participants who had systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or who were diagnosed by a doctor were defined as having hypertension. Chronic disease-related biomarkers included total cholesterol, triglycerides, blood glucose, and hs-CRP. History of cerebrovascular disease, respiratory disease, and cancer diagnosed by a doctor were collected through a structured self-reported questionnaire. Medical treatment was defined as receiving inpatient or outpatient medical services during the last year (yes vs no).

2.7. Statistical analysis

Continuous variables were described using the mean ± standard deviation or median (interquartile range). Categorical variables were described as numbers and percentages. Cox proportional hazards models with restricted cubic splines (RCS) were used to explore the dose-response relationship between serum albumin, DPI, and all-cause mortality. Three knots (set at the 10th, 50th, and 90th percentiles) were selected based on the lowest value for the Akaike information criterion. Unadjusted and adjusted models satisfied the proportional hazards assumption after applying the Schoenfeld residuals test. Model 1 was adjusted for age. Model 2 was additionally adjusted for sex, ethnicity, education, marital status, living status, residence, smoking, drinking, regular exercise, amount of staple food, and BMI. Model 3 was further adjusted for ADL, cognitive function, hypertension, cholesterol, triglycerides, glucose, hs-CRP, cerebrovascular disease, respiratory disease, cancer, and medical treatment. Hazard ratio (HR) and 95 % confidence interval (CI) were calculated. We added cross-product terms to test the multiplicative interaction between albumin and DPI, and HRs for low albumin on all-cause mortality in different DPI subgroups (stratified by median) were calculated separately.

The following sensitivity analyses were conducted to check the robustness of the main results. (1) In independent analyses of the associations of serum albumin and DPI with all-cause mortality, serum albumin and DPI were additionally adjusted for each other. (2) A subgroup analysis stratified by underweight (BMI <18.5) was conducted in assessing the association between albumin and mortality. (3) Deaths within the first year of follow-up (n = 139) were excluded to minimize the impact of reverse causality bias on the associations. Additionally, we utilized the mice (multiple imputation by chained equations) package in R software [36] to impute missing data for exposure factors (serum albumin and DPI) and screening indicators (CC and HS). Subsequently, the median values from the 10 imputed datasets were used for the pooled sensitivity analyses. (4) After using multiple imputation methods to fill in 187 participants with missing albumin or DPI data, we included 1821 valid participants and repeated the independent and interaction analyses. (5) We also performed multiple imputation for 487 participants with missing HS or CC data, and re-included 2016 valid samples to test the stability of the interaction. All analyses were performed using R 4.2.0 (R Foundation for Statistical Computing). A two-tailed *P*-value <0.05 was considered statistically significant in all analyses.

Table 1
Characteristics of 1763 older adults at risk of sarcopenia stratified by albumin level.

Characteristic	Overall (n = 1763)	Albumin ≥40.0 g/L (n = 981)	Albumin <40.0 g/L (n = 782)	*P*-value
Socio-demographic				
Age, years	88.31 ± 10.49	86.76 ± 10.42	90.23 ± 10.28	<0.001
Female, n (%)	1072 (60.81)	602 (61.37)	470 (60.10)	0.589
Han ethnic, n (%)	1628 (92.34)	913 (93.07)	715 (91.43)	0.201
Rural, n (%)	1433 (81.28)	780 (79.51)	653 (83.50)	0.032
Live alone, n (%)	440 (24.96)	239 (24.36)	201 (25.70)	0.518
Illiterate, n (%)	1309 (74.25)	731 (74.52)	578 (73.91)	0.774
Have no spouse, n (%)	1217 (69.03)	641 (65.34)	576 (73.66)	<0.001
Health status/behaviors				
Type of staple food, n (%)				<0.001
Rice	841 (47.70)	521 (53.11)	320 (40.92)	
Wheat	427 (24.20)	234 (23.85)	193 (24.68)	
Others	495 (28.08)	226 (23.04)	269 (34.40)	
Amount of staple food, g/day	250 (200, 300)	250 (200, 350)	250 (200, 300)	0.824
Animal protein intake score	9.81 ± 3.46	10.02 ± 3.52	9.62 ± 3.41	0.021
Plant protein intake score	3.24 ± 1.76	3.39 ± 1.87	3.13 ± 1.66	0.003
Total dietary protein intake score	13.05 ± 4.36	13.41 ± 4.43	12.76 ± 4.28	0.002
BMI, kg/m^2	20.50 ± 3.48	20.75 ± 3.41	20.18 ± 3.54	0.001
Smoking, n (%)	215 (12.19)	118 (12.03)	97 (12.40)	0.811
Drinking, n (%)	213 (12.08)	141 (14.37)	72 (9.21)	<0.001
Regular exercise, n (%)	189 (10.72)	119 (12.31)	70 (8.95)	0.031
ADL impairment, n (%)	453 (25.69)	189 (19.27)	264 (33.76)	<0.001
Cognitive impairment, n (%)	849 (48.16)	435 (44.34)	414 (52.94)	<0.001
Hypertension, n (%)	734 (41.63)	449 (45.77)	285 (36.45)	<0.001
Cerebrovascular disease, n (%)	125 (7.09)	61 (6.22)	64 (8.18)	0.031
Respiratory disease, n (%)	170 (9.64)	84 (8.56)	86 (10.10)	0.028
Cancer, n (%)	69 (3.91)	44 (4.48)	25 (3.20)	0.252
Medical treatment, n (%)	727 (41.24)	443 (45.16)	284 (36.32)	<0.001
Biological markers				
Fasting blood glucose, mmol/L	4.67 (3.93, 5.46)	4.79 (4.04, 5.55)	4.49 (3.85, 5.31)	<0.001
Total cholesterol, mmol/L	4.46 ± 1.02	4.82 ± 0.95	4.01 ± 0.93	<0.001
Triglycerides, mmol/L	0.91 (0.67, 1.25)	1.03 (0.76, 1.38)	0.79 (0.59, 1.06)	<0.001
hs-CRP, mg/L	1.12 (0.46, 2.93)	0.98 (0.42, 2.23)	1.42 (0.51, 4.63)	<0.001

Notes: BMI, body mass index; ADL, activities of daily living; hs-CRP, high sensitivity C-reactive protein.
P values were generated by Student's t-test, Kruskal-Wallis, or Chi-square test.

3. Results

3.1. Demographic characteristics

The mean age of the 1763 older adults with sarcopenia risk included in this study was 88.31 ± 10.49 years, and 60.81 % were female. A total of 782 (44.36 %) participants were classified as having a low albumin level (<40.0 g/L). Participants who had low albumin levels were more likely to be older, have low BMI, physical disability, cognition impairment, cerebrovascular disease, respiratory disease, low blood glucose, low cholesterol, low triglycerides, and high hs-CRP. As shown in Supplementary Fig. 2, there were significant positive associations between DPI and serum albumin levels in men ($\beta = 0.18$, $P < 0.001$) and women ($\beta = 0.17$, $P < 0.001$). The baseline characteristics of all participants were shown in Table 1.

3.2. Associations of serum albumin levels with all-cause mortality

After 5606.3 person-years of follow-up (median: 3.28 years), 802 older people died. As shown in Fig. 1, an inverse linear association between albumin levels and all-cause mortality was observed after adjusting for all covariates ($P_{\text{non-linear}} = 0.429$). HRs of all-cause mortality for serum albumin levels stratified by sex were shown in Table 2. When included as a continuous variable, the HR of mortality was 1.18 (95%CI: 1.08–1.21) for per 5 g/L decrease in serum albumin. Participants with low albumin (<40.0 g/L) had a 43 % higher mortality risk than those with high albumin (HR = 1.43, 95 % CI = 1.22–1.66). When albumin levels were included as tertiles, there was a graded negative relationship between albumin level and mortality risk in all participants ($P_{\text{trend}} < 0.001$). Compared with participants in the highest tertile, those in the lowest tertile had a 66 % higher risk of all-cause mortality (HR: 1.66, 95 % CI: 1.38–2.10). In sex-specific analyses, the association between serum albumin and all-cause mortality was stable in both men and women.

3.3. Associations of DPI with all-cause mortality

As shown in Fig. 1, DPI score was not associated with all-cause mortality risk ($P_{\text{overall}} = 0.369$). Table 3 presented the HRs for all-cause mortality by DPI tertiles. The multivariate HR of the highest DPI group (≥16) for all-cause mortality compared with the lowest DPI group (<12) was 0.88 (95 % CI: 0.70–1.12, $P = 0.308$). No significant graded associations were found between DPI score and mortality risk in men ($P_{\text{trend}} = 0.315$) and women ($P_{\text{trend}} = 0.697$). Besides, neither animal protein intake nor plant protein intake was significantly associated with the risk of all-cause mortality in the total sample (Supplementary Table 2).

3.4. Interaction between serum albumin and DPI on all-cause mortality

As Supplementary Table 3 showed, the cross-product terms of albumin (as a continuous variable) and DPI (as a dichotomous variable) was statistically significant after adjusting for all covariates in model 3. Associations between serum albumin and mortality stratified by DPI score were presented in Table 4. In the low DPI group (<14), low albumin was associated with a 47 % (HR = 1.47, 95 % CI = 1.18–1.85) higher risk of mortality; however, in the high DPI subgroup (≥14), the association between low albumin and mortality was not significant in the fully adjusted model (HR = 1.15, 95 % CI = 0.92–1.38). Similarly, in both men and women, HRs for mortality in the low DPI group were more pronounced than in the high DPI group. We observed significant interactions between albumin and DPI in the total sample ($P_{\text{interaction}} = 0.034$) and women ($P_{\text{interaction}} = 0.012$) from the fully adjusted model.

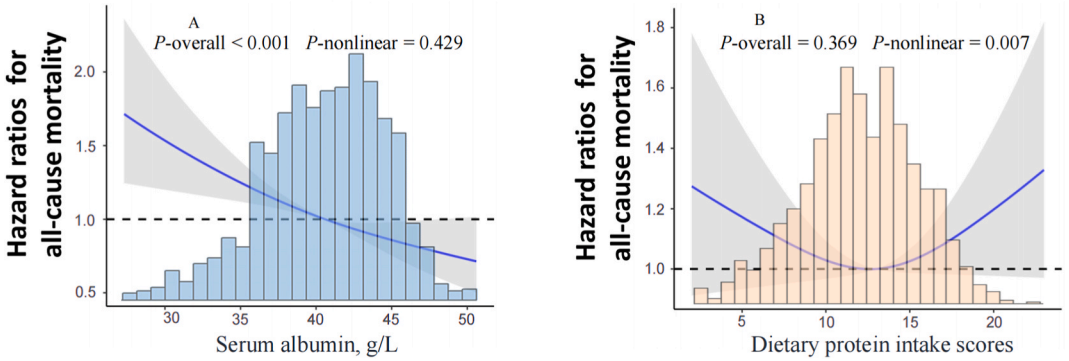

Fig. 1. Restricted cubic splines analysis of the associations of serum albumin and dietary protein intake with all-cause mortality among older adults at risk of sarcopenia. Adjusted for age, sex, ethnicity, education, marital status, living status, residence, smoking, drinking, type and daily amount of staple food, BMI, ADL, cognitive function, hypertension, blood glucose, cholesterol, triglycerides, hs-CRP, cerebrovascular disease, respiratory disease, cancer, and medical treatment.

Table 2
Cox regression analyses of the association between serum albumin levels and all-cause mortality.

Group	Participants	Deaths, n%	Model 1		Model 2		Model 3	
			HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value
As continuous variable								
Total sample								
Per 5 g/L decrease	1763	940 (53.32)	1.26 (1.18–1.35)	<0.001	1.21 (1.10–1.31)	<0.001	1.18 (1.08–1.21)	<0.001
Men								
Per 5 g/L decrease	691	338 (48.91)	1.30 (1.15–1.47)	<0.001	1.26 (1.13–1.37)	<0.001	1.21 (1.10–1.50)	0.016
Women								
Per 5 g/L decrease	1072	602 (56.16)	1.24 (1.13–1.36)	<0.001	1.18 (1.09–1.31)	0.001	1.16 (1.04–1.31)	<0.001
Cut-off at 40.0 g/L								
Total sample								
Albumin ≥40.0 g/L	981	417 (42.51)	Ref.	–	Ref.	–	Ref.	–
Albumin <40.0 g/L	782	523(66.88)	1.56 (1.36–1.79)	<0.001	1.53 (1.31–1.78)	<0.001	1.43 (1.22–1.66)	<0.001
Men								
Albumin ≥40.0 g/L	379	144 (37.99)	Ref.	–	Ref.	–	Ref.	–
Albumin <40.0 g/L	312	194 (62.18)	1.69 (1.33–2.14)	<0.001	1.58 (1.21–2.05)	<0.001	1.45 (1.10–1.92)	0.009
Women								
Albumin ≥40.0 g/L	602	273 (45.35)	Ref.	–	Ref.	–	Ref.	–
Albumin <40.0 g/L	470	329 (70.00)	1.51 (1.28–1.81)	<0.001	1.48 (1.23–1.79)	<0.001	1.45 (1.18–1.78)	<0.001
Cut-off by tertiles								
Total sample								
Q3 (≥42.5 g/L)	596	233 (39.09)	Ref.	–	Ref.	–	Ref.	–
Q2 (≥38.5 and < 42.5 g/L)	585	313 (53.50)	1.51 (1.26–2.26)	<0.001	1.43 (1.19–1.71)	<0.001	1.30 (1.07–1.54)	0.006
Q1 (<38.5 g/L)	582	394 (67.70)	1.90 (1.60–1.81)	<0.001	1.76 (1.48–2.10)	<0.001	1.66 (1.38–2.10)	<0.001
P-trend				<0.001		<0.001		<0.001
Men								
Q3 (≥42.6 g/L)	228	77 (33.77)	Ref.	–	Ref.	–	Ref.	–
Q2 (≥38.7 and < 42.6 g/L)	240	120 (50.00)	1.66 (1.22–2.25)	<0.001	1.62 (1.34–2.44)	<0.001	1.56 (1.14–2.14)	0.005
Q1 (<38.7 g/L)	223	141 (63.23)	1.91 (1.42–2.58)	<0.001	1.81 (1.45–2.62)	0.002	1.71 (1.22–2.41)	<0.001
P-trend				<0.001		<0.001		<0.001
Women								
Q3 (≥42.4 g/L)	368	156 (42.39)	Ref.	–	Ref.	–	Ref.	–
Q2 (≥38.4 and < 42.4 g/L)	345	193 (55.94)	1.43 (1.15–1.79)	0.001	1.35 (1.08–1.68)	0.008	1.28 (1.02–1.64)	0.026
Q1 (<38.4 g/L)	359	263 (70.47)	1.88 (1.52–2.34)	<0.001	1.73 (1.39–2.14)	<0.001	1.65 (1.30–2.06)	<0.001
P-trend				<0.001		<0.001		<0.001

Model 1: adjusted for age. Model 2: additionally adjusted for sex, ethnicity, education, marital status, living status, residence, regular exercise, smoking, drinking, type and daily amount of staple food, and BMI. Model 3: additionally adjusted for ADL, cognitive function, hypertension, blood glucose, cholesterol, triglycerides, hs-CRP, cerebrovascular disease, respiratory disease, cancer, and medical treatment.

Table 3
Cox regression analyses of the association between dietary protein intake and all-cause mortality stratified by sex.

Group	Participants	Deaths, n%	Model 1		Model 2		Model 3	
			HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value
Total sample								
Q1 (<12)	521	288 (55.28)	Ref.	–	Ref.	–	Ref.	–
Q2 (≥12 and < 16)	632	331 (52.37)	1.01 (0.84–1.18)	0.862	1.02 (0.86–1.21)	0.835	1.03 (0.82–1.27)	0.697
Q3 (≥16)	610	321 (52.62)	0.95 (0.81–1.14)	0.617	0.96 (0.81–1.14)	0.672	0.88 (0.70–1.12)	0.308
P-trend				0.851		0.788		0.634
Men								
Q1 (<12)	211	113 (53.55)	Ref.	–	Ref.	–	Ref.	–
Q2 (≥12 and < 16)	251	113 (45.02)	0.89 (0.66–1.19)	0.433	0.89 (0.66–1.18)	0.421	0.85 (0.65–1.17)	0.346
Q3 (≥16)	229	112 (48.91)	0.84 (0.63–1.12)	0.244	0.84 (0.62–1.11)	0.236	0.81 (0.61–1.09)	0.193
P-trend				0.501		0.487		0.315
Women								
Q1 (<12)	310	175 (56.45)	Ref.	–	Ref.	–	Ref.	–
Q2 (≥12 and < 16)	381	218 (57.22)	1.09 (0.88–1.35)	0.411	1.13 (0.91–1.39)	0.832	1.02 (0.80–1.29)	0.368
Q3 (≥16)	381	209 (54.86)	0.99 (0.81–1.23)	0.868	1.00 (0.82–1.25)	0.932	1.13 (0.88–1.40)	0.861
P-trend				0.599		0.429		0.697

Model 1: adjusted for age. Model 2: additionally adjusted for sex, ethnicity, education, marital status, living status, residence, regular exercise, smoking, drinking, type and daily amount of staple food, and BMI. Model 3: additionally adjusted for ADL, cognitive function, hypertension, blood glucose, cholesterol, triglycerides, hs-CRP, cerebrovascular disease, respiratory disease, cancer, and medical treatment.

Table 4
Cox regression analyses of the association between low albumin and all-cause mortality stratified by dietary protein intake.

Group	Participants	Deaths, n (%)	Model 1		Model 2		Model 3		*P* for interaction
			HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value	
Total sample									0.034
High DPI									
Albumin ≥40.0 g/L	427	195 (45.67)	Ref.	–	Ref.	–	Ref.	–	
Albumin <40.0 g/L	387	253 (65.37)	1.32 (1.10–1.64)	0.004	1.23 (1.02–1.57)	0.036	1.15 (0.92–1.38)	0.197	
Low DPI									
Albumin ≥40.0 g/L	554	222 (40.07)	Ref.	–	Ref.	–	Ref.	–	
Albumin <40.0 g/L	395	270 (68.35)	1.78 (1.47–2.16)	<0.001	1.63 (1.32–2.03)	<0.001	1.47 (1.18–1.85)	<0.001	
Men									0.306
High DPI									
Albumin ≥40.0 g/L	183	80 (43.72)	Ref.	–	Ref.	–	Ref.	–	
Albumin <40.0 g/L	149	91 (61.07)	1.55 (1.08–2.58)	0.031	1.52 (1.05–2.21)	0.024	1.37 (1.02–1.96)	0.042	
Low DPI									
Albumin ≥40.0 g/L	196	64 (32.65)	Ref.	–	Ref.	–	Ref.	–	
Albumin <40.0 g/L	126	103 (63.19)	2.10 (1.49–2.97)	<0.001	1.96 (1.31–2.95)	0.001	1.78 (1.18–2.43)	0.027	
Women									0.012
High DPI									
Albumin ≥40.0 g/L	244	115 (47.13)	Ref.	–	Ref.	–	Ref.	–	
Albumin <40.0 g/L	238	162 (68.07)	1.34 (1.04–1.73)	0.022	1.17 (0.88–1.54)	0.267	1.11 (0.82–1.43)	0.537	
Low DPI									
Albumin ≥40.0 g/L	358	158 (44.13)	Ref.	–	Ref.	–	Ref.	–	
Albumin <40.0 g/L	232	167 (71.98)	1.64 (1.31–2.08)	<0.001	1.51 (1.17–1.95)	0.002	1.49 (1.10–1.90)	0.009	

Adjusted for age, sex, ethnicity, education, marital status, living status, residence, regular exercise, smoking; drinking, type and daily amount of staple food, BMI, ADL, cognitive function, hypertension, blood glucose, cholesterol, triglycerides, hs-CRP, cerebrovascular disease, respiratory disease, cancer, and medical treatment.
$P_{interaction}$ was generated from Model 3.

3.5. Sensitivity analyses

After additional adjustment for DPI, we observed similar HRs for the associations between low serum albumin and mortality (Supplementary Table 4). Likewise, the association between DPI and mortality was materially unchanged in the fully adjusted model when albumin was added as a covariate (Supplementary Table 5). In addition, after excluding participants who died in the first year of follow-up, the significant association of serum albumin with all-cause mortality was consistent with the result of our main analyses (Supplementary Table 6), and the interactions between serum albumin and DPI on mortality remained stable in the fully adjusted model (Supplementary Table 7). Significant positive associations of low albumin (per 5 g/L decrease) with higher all-cause mortality were observed in both the underweight (BMI <18.5) and non-underweight subgroups (BMI ≥18.5) (Supplementary Table 8). Additionally, we also used multiple imputed datasets to check the stability of the main results. Specifically, the baseline characteristics of the samples did not change significantly when we filled in missing data for albumin and DPI using multiple imputation methods, and the independent and interaction associations of low albumin and DPI with all-cause mortality were almost unchanged (Supplementary Tables 9–12). The interaction between albumin and DPI on mortality also remained significant after imputing missing HS and CC data (Supplementary Table 13).

4. Discussion

In this prospective cohort study of a nationally representative sample of Chinese older adults, we found that low serum albumin was associated with a higher risk of all-cause mortality among community-dwelling older adults at risk of sarcopenia, and DPI modified the relationship between albumin and mortality.

Consistent with our results, most previous studies have demonstrated a negative association between serum albumin levels and mortality in community and clinical settings. Albumin was proven to be an effective predictor of death in patients with various diseases, including chronic kidney disease [37], hip fractures [38], and cancer [39]. Besides, large-scale cohort studies in the United

States [40] and China [12] have confirmed that low serum albumin was associated with higher mortality risk among community-dwelling adults. Notably, Sahyoun et al. found that albumin was associated with short-term mortality, but not with long-term mortality, among older adults living in care homes [41]. Previous community-based studies have focused primarily on the general older population and did not specifically consider sarcopenic status. Although our findings on the association between albumin and mortality risk are not novel, this is the first study to focus on community-dwelling older people at risk of sarcopenia.

Decreased serum albumin is common in individuals with malnutrition, inflammation, and hypermetabolic states, mainly due to decreased albumin synthesis or increased leakage [42]. Various mechanisms may explain the relationship between low albumin and higher mortality. First, despite difficulties in diagnosing malnutrition, albumin is reported to be a good marker of nutritional status in older individuals [9,43]. A lack of serum albumin needed for muscle synthesis in older people may be partly responsible for decline in physical function, which can lead to premature death. A recent CLHLS-based cross-sectional study showed that serum albumin was significantly associated with subjective and objective physical performance [44]. Second, hypoalbuminemia may increase blood viscosity and the risk of thrombosis, while high serum albumin can elevate circulating blood volume, thereby decreasing the risk of cardiovascular events [45]. Third, low serum albumin often indicates impaired liver function, and the lack of protein can also lead to multiple organ failure and chronic diseases [46,47]. Previous studies also demonstrated that serum albumin was inversely associated with diabetes [48], metabolic syndrome [49], and inflammation state [50].

In this study, we found a positive association between DPI and serum albumin levels, but DPI was not significantly associated with mortality risk in either sex. Findings regarding the association between DPI and mortality risk in previous observational studies are inconsistent. Similar to our results, an Italian prospective cohort study found no significant association between protein intake and mortality among older adults in the community [51]. In addition, another study of 70,696 community middle-aged Japanese adults showed that animal protein intake was not associated with all-cause mortality risk [52]. By contrast, Lv et al. observed that consumption of protein-rich food was associated with lower mortality risk in Chinese community-dwelling older adults aged 80 years or older [53]. We considered that the significant association between DPI and mortality detected in the study reported by Lv et al. study might be due to the general health of the sample, while results may be heterogeneous among the sarcopenic older people in our study. A recent meta-analysis of prospective cohort studies suggested that total protein intake and animal protein intake were positively associated with all-cause mortality, while plant protein intake was inversely associated with all-cause mortality [17]. There is no standardized measure for dietary protein diversity, and the relationship of DPI with health outcomes may differ due to inconsistencies in the types and numbers of food groups included [53]. Older adults at risk of sarcopenia may have more severe reductions in digestive and metabolic functions than those without sarcopenia [54]; thus, dietary proteins may not be used effectively for muscle cell synthesis. Future studies should be conducted to clarify the relationship between quantitative dietary protein consumption and mortality risk in sarcopenic older adults.

Another innovative finding of this study was the moderating role of DPI in the relationship between low albumin and mortality risk. We observed a significant interaction ($P_{\text{interaction}} = 0.034$) between albumin and DPI on the mortality for the first time. The association between low albumin and all-cause mortality remained significant in the lower DPI subgroup (HR = 1.47, 95 % CI = 1.18–1.85), but was not significant in the high DPI subgroup (HR = 1.15, 95 % CI = 0.92–1.39). These findings indicated that the effect of low albumin on all-cause mortality was attenuated by high DPI, and this characteristic was consistent in both males and females. Although the mechanism underlying the interaction between DPI and albumin on mortality is unclear, there are several possible explanations. Protein intake is positively associated with serum pre-albumin, which can promote the synthesis of albumin and delay the decrease in albumin in hypoproteinemic conditions [55]; however, in a state of low dietary intake and hypoproteinemia combined, the body lacks sufficient raw materials to supply the liver for albumin synthesis [56]. In such a situation, muscle loss in older people with hypoproteinemia is further exacerbated to meet the physiological demand for protein, leading to an increased risk of death. In addition, protein-rich foods, such as lean meat, poultry, fish, legumes, nuts, milk, and dairy products, are also rich in nutrients, such as calcium, iron, vitamin D, and polyunsaturated fatty acids, which play a protective role in decreasing mortality associated with hypoalbuminemia [57–59]. Finally, a high-protein diet is associated with higher dietary quality and anti-inflammatory properties, which can improve the excessive albumin depletion caused by inflammation [60]. This, in turn, mitigates the negative impact of low serum albumin levels on all-cause mortality. This longitudinal study had clinical implications for the long-term survival of older adults with sarcopenic status. We suggested that serum albumin level could be a useful biomarker of mortality risk among community-dwelling older adults at risk of sarcopenia. Moreover, the interaction between DPI and albumin indicated that maintaining sufficient dietary protein intake might be of potential value in attenuating the adverse effects of hypoproteinemia. This longitudinal study contributes to understanding the value of maintaining nutritional status in sarcopenic older individuals with low albumin levels. Future interventional studies are needed to explore the effectiveness of increasing dietary protein intake.

5. Limitations

We acknowledged some limitations regarding the design and measurement in the current study. First, appendicular skeletal muscle mass and standardized physical performance indicators (gait speed/5-time chair stand test) were not available in baseline data from the CLHLS. Thus, we used the Ishii test to screen for sarcopenia, which has proven to be an accurate and operable tool for Asian populations. In the future, multiple sarcopenia screening and diagnostic tools should be applied to validate our results. Second, although the CLHLS dietary frequency questionnaire was confirmed as a valid assessment tool in previous epidemiological studies, we were unable to quantify DPI due to the absence of detailed quantitative dietary assessments. Besides, since we could not adjust for energy intake in the analysis, the type and amount of staple food were included as alternative covariates. Third, since blood sample and comprehensive physical examination data were only available from participants in eight longevity areas in the CLHLS, we could not

obtain a large sample size at baseline. Besides, due to the sampling method of CLHLS, 79.92 % of the participants in this study were oldest-old adults (≥80 years), which might lead to limitations in the generalizability of the results. Future studies across a wider range of age groups are needed to verify the age and sex differences in the interaction between albumin and DPI. Fourth, information on disease history obtained through self-reported questionnaires might lead to recall bias. Furthermore, future research will need to consider various chronic conditions, including liver disease and connective tissue disease. Fifth, we only evaluated exposure factors at a single time point. To mitigate the impact of changes in these factors over time, longitudinal measures of albumin levels and DPI should be included in future studies. One of the future research directions is to further explore the potential mediating role of serum albumin between DPI and mortality using repeated measurements of albumin data. Finally, the effect of protein supplements was not considered in this study because information about nutrient supplements was first collected in 2018; however, only 0.81 % of participants from the eight longevity areas self-reported taking protein supplements in the 2018 wave. We considered that this small percentage of participants taking protein supplements was unlikely to have significantly biased our main results.

6. Conclusions

Serum albumin levels are associated with all-cause mortality in community-based older adults at risk of sarcopenia. Sufficient dietary protein consumption may attenuate the effect of low albumin on increased mortality and potential mechanisms for the interaction between these factors warrants further exploration.

Ethics statement

The study design was approved by the Ethics Committee of Beijing Hospital. The CLHLS was approved by the Ethics Committee of Peking University (No. IRB00001052-13074). All subjects (or guardians) provided written informed consent before participating in the survey.

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Data availability statement

The raw data used in the current study can be found on the platform of Peking university open research data: https://opendata.pku.edu.cn/dataverse/CHADS.

CRediT authorship contribution statement

Chi Zhang: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Conceptualization. **Luyao Zhang:** Methodology, Formal analysis. **Lvtao Zeng:** Software, Methodology. **Yongjun Wang:** Writing – review & editing, Formal analysis. **Liru Chen:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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