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Original Article

ORIGINAL ARTICLE

Association of urinary albumin:creatinine ratio with incident frailty in older populations

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ABSTRACT

Background. The longitudinal relationship of albuminuria with incident frailty remains unknown. Therefore we aimed to evaluate the relation of albuminuria with the risk of incident frailty in older adults.
Methods. A total of 1115 participants ≥65 years of age (average age 80.3 years) who were free of frailty in the Chinese Longitudinal Healthy Longevity Survey were included. The outcome was incident frailty, defined as a frailty index ≥0.25 during follow-up. Cox proportional hazards models were used to assess the association of the urinary albumin:creatinine ratio (UACR) with frailty.
Results. During a median follow-up duration of 5.3 years, 295 (26.5%) participants developed incident frailty. Overall, the UACR was significantly positively associated with the risk of incident frailty (P for trend = 0.005), with a significantly higher risk of incident frailty in participants in the quartile 4 of UACR {≥13.43 mg/g; hazard ratio [HR] 1.64 [95% confidence interval (CI) 1.13–2.37]} compared with those in quartile 1 (<0.73 mg/g). Consistently, when UACRs were assessed as clinical categories, compared with participants with UACR <10 mg/g, those with UACR ≥30 mg/g had a higher HR of incident frailty [HR 1.61 (95% CI 1.17–2.20)]. Accounting for the competing risk of death also did not substantially change the results. In addition, a stronger positive association between UACR and incident frailty was found in those with a higher high-sensitivity C-reactive protein level (hs-CRP) (P for interaction = 0.045).
Conclusion. Albuminuria was positively associated with the risk of incident frailty, particularly in those with higher hs-CRP, emphasizing the importance of managing both albuminuria and inflammation for primary prevention of frailty.

Keywords: albuminuria, elderly, frailty, high-sensitivity C-reactive protein

INTRODUCTION

Frailty is a clinical syndrome characterized by an age-related decline in multiple physiological functions, leading to a greater vulnerability to even minimal stressors [1, 2], which increases susceptibility to adverse outcomes, including falls, mobility decline, hospitalization, institutionalization and mortality [3–7]. The prevalence of frailty is expected to increase alongside rapid growth in the ageing population [1] and therefore frailty has become one of the most urgent contemporary public health challenges due to global trends of population ageing. As such, it is important to identify more modifiable risk factors to prevent or

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delay the onset of frailty and thereby decrease the subsequent public health burden in the older population.

The mechanism underlying frailty remain unclear. However, the cellular and molecular mechanisms involved, including insulin resistance, oxidative stress and chronic inflammation [8, 9], are commonly associated with albuminuria [10, 11], a surrogate measure of endothelial dysfunction [12]. Moreover, albuminuria has been linked to the initiation and progression of atherosclerosis and is an early indicator for chronic kidney disease progression and cardiometabolic diseases [13]. Although subclinical and clinical cardiovascular diseases have been documented as crucial factors of frailty among older adults [14], to date, only a few cross-sectional studies have examined the relationship between albuminuria and frailty [15–17] and the prospective association between albuminuria and frailty remains unknown.

To address this aforementioned gap in knowledge, the present study aimed to evaluate the prospective relationship of albuminuria with the risk of incident frailty in older adults, using data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS).

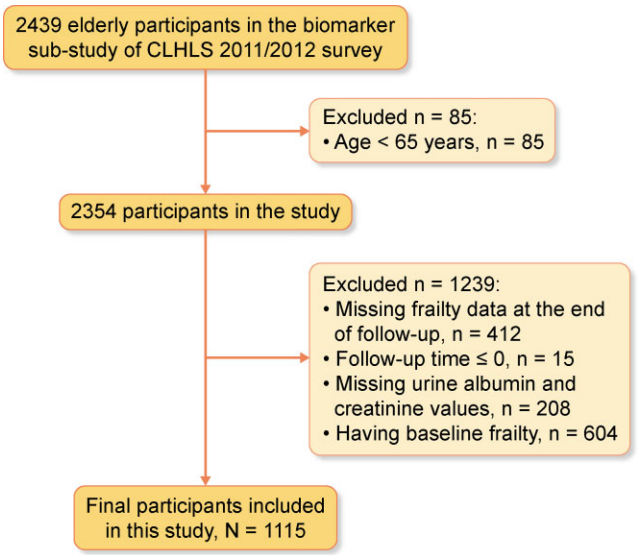

FIGURE 1: Flow chart of the participants in the current analysis.

MATERIALS AND METHODS

Study design and population

This study utilized data from the CLHLS, an ongoing prospective cohort study established in 1998 to investigate the determinants of health and longevity in older adults. The subsequent follow-up and recruitment of new participants were conducted in 2000, 2002, 2005, 2008, 2011, 2014 and 2018, with an estimated 90% response rate during each wave. The CLHLS used a multistage cluster sampling approach and covered 23 of 31 provinces in China, accounting for 85% of the total population in China. A more detailed description of the CLHLS is available elsewhere [18]. The CLHLS was conducted by the Center for Healthy Aging and Development Studies, National School of Development of Peking University and was approved by the ethics committee of Peking University. Written informed consent was obtained from every participant or proxy (next of kin or guardian).

Since albuminuria was first and mainly measured in the biomarker substudy of CLHLS 2011–2012 survey, we used the 2011–2012 wave as the baseline survey and the current study included three rounds of CLHLS data from 2011 to 2018. Among the 2439 elderly individuals, we excluded participants who were <65 years of age ($n = 85$), had missing data on frailty during follow-up ($n = 412$), had an incorrect follow-up date ($n = 15$), had missing data on urine albumin and creatinine values ($n = 208$) and had frailty at baseline ($n = 604$). A total of 1115 participants were included in the final analysis (Figure 1).

Exposure variables and covariates

Fasting venous blood samples and urine samples were collected from participants by trained medical personnel and all laboratory analyses were conducted by the central clinical laboratory at Capital Medical University in Beijing. Serum creatinine was determined with the picric acid method and albuminuria was measured by dry chemistry reagent test strips (Siemens Diagnostics, TArrytown, NY, USA). Fasting plasma glucose, high-sensitivity C-reactive protein (hs-CRP), triglycerides (TG) and total cholesterol (TC) were measured by an automatic biochemistry analyser (Hitachi 7180; Hitachi, Tokyo, Japan) using commercially available diagnostic kits (Roche Diagnostic, Mannheim, Germany) [19]. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation for the Chinese population [20]. Urinary albumin:creatinine ratio (UACR) was calculated and reported in milligrams per gram.

Sociodemographic characteristics and lifestyle information was obtained through a standardized and structured questionnaire in the baseline survey, including age, sex (male or female), education years, residence (rural or urban), marital status (married or other), smoking status (current smoker, former smoker or non-smoker), alcohol consumption (current drinker, former drinker or non-drinker) and economic independence status (yes or no).

Blood pressure and anthropometric measurements, including height and weight, were taken using the standard operating procedures. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Hypertension was defined as mean systolic blood pressure (SBP) ≥140 mmHg and/or mean diastolic blood pressure (DBP) ≥90 mmHg or diagnosed by a physician at baseline. Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L or diagnosed by a physician at baseline.

Outcome

To capture an individual's cumulative number of health deficiencies, frailty status was ascertained by the frailty index (FI), which includes health deficits such as symptoms, signs and disabilities. In the current study, 34 items were used to calculate the FI [21] and each deficit variable was dichotomized or polychotomized and mapped to the interval 0–1 to represent the severity of the deficit. Then the FI score was calculated by summing all deficits and dividing by the total number of deficits ($n = 34$), with a range from 0 to 1. Frailty was defined as FI ≥0.25 [21, 22].

Statistical analysis

Baseline characteristics of the study population are presented as mean ± standard deviation (SD) for continuous variables and proportions for categorical variables. Comparisons of baseline

Table 1. Population characteristics by quartiles of ACR

Characteristics	Quartiles of ACR (mg/g)				P-value
	Q1 (<0.73)	Q2 (0.73–<3.77)	Q3 (3.77–<13.43)	Q4 (≥13.43)	
Subjects, *n*	278	279	279	279	
Male, *n* (%)	186 (66.9)	175 (62.7)	137 (49.1)	124 (44.4)	< 0.001
Age (years), mean ± SD	77.2 ± 10.1	79.0 ± 9.2	81.4 ± 10.2	83.7 ± 10.4	< 0.001
BMI (kg/m^2), mean ± SD	22.3 ± 8.8	24.0 ± 27.7	22.5 ± 11.2	22.0 ± 6.1	0.426
Economic independence, *n* (%)	117 (43.0)	109 (39.5)	89 (32.5)	76 (27.9)	< 0.001
Urban residence, *n* (%)	10 (3.6)	16 (5.7)	17 (6.1)	9 (3.2)	0.260
Married, *n* (%)	174 (63.7)	172 (62.8)	133 (48.5)	119 (43.9)	< 0.001
Smoking status, *n* (%)					0.095
Never	176 (65.4)	176 (64.0)	196 (71.5)	198 (73.9)	
Former	27 (10.0)	33 (12.0)	18 (6.6)	21 (7.8)	
Current	66 (24.5)	66 (24.0)	60 (21.9)	49 (18.3)	
Drinking status, *n* (%)					0.066
Never	190 (69.9)	187 (69.0)	205 (75.1)	215 (79.3)	
Former	19 (7.0)	19 (7.0)	14 (5.1)	18 (6.6)	
Current	63 (23.2)	65 (24.0)	54 (19.8)	38 (14.0)	
Education years, *n* (%)					< 0.001
0	116 (41.9)	125 (45.0)	150 (54.0)	177 (64.1)	
≥1	161 (58.1)	153 (55.0)	128 (46.0)	99 (35.9)	
History of diseases					
Hypertension, *n* (%)	143 (51.8)	155 (56.6)	178 (64.0)	199 (71.6)	< 0.001
Diabetes, *n* (%)	15 (5.5)	23 (8.4)	20 (7.2)	25 (9.2)	0.386
Laboratory results, mean ± SD					
TG (mmol/L)	1.0 ± 0.7	1.0 ± 0.7	1.1 ± 0.7	1.0 ± 0.6	0.459
TC (mmol/L)	4.3 ± 1.0	4.4 ± 1.0	4.4 ± 0.9	4.3 ± 1.0	0.401
hs-CRP (mg/L)	2.0 ± 5.3	2.4 ± 5.4	2.6 ± 6.1	3.8 ± 9.7	0.013
eGFR (mL/min/1.73 m^2)	106.5 ± 29.5	102.5 ± 27.7	95 ± 26.1	93.1 ± 32.5	< 0.001

characteristics according to UACR quartiles were performed by the chi-squared test for categorical variables or analysis of variance (ANOVA) for continuous variables.

The follow-up person-time for each participant was calculated from baseline until a first frailty diagnosis, the date of death, the last wave before the participant's departure from the survey or the end of the study (2018), whichever came first. Cox proportional hazards models were used to assess the association of UACR with frailty, adjusting for age, sex, BMI, smoking status, drinking status, residence, educational background, marital status, economic independence status, diabetes, hypertension, eGFR, hs-CRP, TG and TC at baseline. The proportional hazards assumption was tested by the Schoenfeld residuals test and no significant deviation from proportionality in hazards over time was detected. Considering the comparatively high mortality rates in older age, the Fine–Gray competing risk model was also used to examine the association while accounting for death as a competing risk to test the robustness of the results.

To evaluate the potential effect modification, stratified analyses were further assessed according to age (<80 or ≥80 years), sex (female or male), BMI (<24 or ≥24 kg/m^2), smoking status (never or ever), drinking status (never or ever), education years (0 or ≥1 year), hypertension (yes or no), diabetes (yes or no), eGFR (<90 or ≥90 mL/min/1.73 m^2), hs-CRP (median <0.82 or ≥0.82 mg/L), TG (<1.7 or ≥1.7 mmol/L) and TC (<5.2 or ≥5.2 mmol/L), which were selected *a priori* based on prior empirical evidence.

A two-tailed P-value <0.05 was considered to be statistically significant in all analyses. Analyses were performed using R software (http://www.R-project.org/).

RESULTS

Characteristics of study participants

As illustrated in the flow chart (Figure 1), a total of 1115 participants were included in the current study. The average age of the study population was 80.3 years (SD 10.3). The median UACR was 3.77 mg/g (interquartile range 0.73–13.43).

Baseline characteristics of the study participants by UACR quartiles are shown in Table 1. Participants with a higher UACR were older, had higher BMI and hs-CRP levels, lower education and eGFR higher prevalence of hypertension and diabetes and were less likely to be male, economically independent or married.

Relationship of UACR with incident frailty

During a median follow-up duration of 5.3 years (4395 person-years), a total of 295 (26.5%) participants developed frailty. Overall, UACR was significantly positively associated with the risk of incident frailty (P for trend = 0.005) (Table 2). When UACRs were assessed as quartiles, compared with participants in quartile 1 (<0.73 mg/g), a significantly higher risk of incident frailty was found in participants in quartile 4 [≥13.43 mg/g;

Table 2. Association of ACR with incident frailty

ACR	Events, *n*/*N*	Incidence rate per 1000 person-years	Crude models		Adjusted model 1[a]		Adjusted model 2[b]	
			HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Quartiles (mg/g)								
Q1 (<0.73)	55/278	45.3	Ref		Ref		Ref	
Q2 (0.73–<3.77)	59/279	51.9	1.12 (0.77, 1.62)	0.548	1.11 (0.76, 1.65)	0.585	1.12 (0.77, 1.63)	0.560
Q3 (3.77–<13.43)	80/279	75.3	1.79 (1.27, 2.52)	< 0.001	1.28 (0.88, 1.86)	0.203	1.33 (0.92, 1.92)	0.130
Q4 (≥13.43)	101/279	102.9	2.57 (1.85, 3.57)	< 0.001	1.64 (1.13, 2.37)	0.009	1.48 (1.03, 2.12)	0.033
P for trend			< 0.001		0.005		0.021	
Categories								
<10	172/769	54.1	Ref		Ref			
10–<20	37/115	89.2	1.66 (1.16, 2.39)	0.006	1.07 (0.72, 1.61)	0.729	1.12 (0.76, 1.67)	0.570
20–<30	22/62	105.9	2.35 (1.50, 3.67)	< 0.001	1.37 (0.83, 2.25)	0.214	1.20 (0.70, 2.05)	0.500
≥30	64/169	108.3	2.24 (1.68, 2.99)	< 0.001	1.61 (1.17, 2.20)	0.003	1.44 (1.06, 1.96)	0.021

[a]Model 1: adjusted for baseline age, sex, BMI, smoking status, drinking status, residence, educational background, marital status, economic independence status, diabetes, hypertension, estimated glomerular filtration rate, hs-CRP, TG and TC.
[b]Model 2: using the Fine–Gray competing risk model based on Model 1.

HR 1.64 (95% CI 1.13–2.37)]. Consistently, when UACRs were assessed as clinical categories, compared with participants with a UACR <10 mg/g, those with a UACR ≥30 mg/g had a higher hazard of incident frailty [HR 1.61 (95% CI 1.17–2.20)]. In addition, 243 (21.8%) participants died during the follow-up period; accounting for the competing risk of death did not substantially change the results (Table 2).

Stratified analyses by potential effect modifiers

Stratified analyses were performed to further assess the relation of UACR (per quartile increment; Figure 2) with the risk of incident frailty in various subgroups. A stronger positive association between UACR and incident frailty was found in those with a higher hs-CRP level (P for interaction = 0.045). None of the other variables, including age, sex, BMI, smoking status, drinking status, education years, hypertension, diabetes, eGFR, TG and TC, significantly modified the association between UACR and incident frailty.

DISCUSSION

In this community-based prospective study, we first demonstrated that increased UACR was significantly associated with a higher risk of incident frailty among the elderly population >65 years of age. In addition, the albuminuria–frailty relation was particularly evident in those with higher hs-CRP levels.

Our study supports and extends previous studies examining the association between albuminuria and frailty. Ballew *et al.* [16], using data from the Atherosclerosis Risk in Communities (ARIC) Study, reported that albuminuria had independent associations with frailty prevalence among community-dwelling older men and women. Yang *et al.* [15] also found that albuminuria was independently associated with the prevalence of pre-frailty/frailty among elderly inpatients. Moreover, another analysis using the I-Lan Longitudinal Aging Study showed that the prevalence of pre-frailty/frailty increased across the UACR quartiles [17]. Of note, those prior studies were all cross-sectional in design and causality cannot be determined due to the ambiguous temporal ordering of the exposure and outcome.

The current study is a prospective analysis among Chinese older adults and provides some new insights into this field. First, albuminuria was positively associated with the risk of incident frailty. The potential mechanisms linking albuminuria and incident frailty are still not fully understood, but it is biologically plausible. Albuminuria, as an important marker for endothelial dysfunction and atherosclerosis, was related to cerebral atherosclerosis and peripheral vascular disease. On the one hand, peripheral vascular disease has been shown to be independently associated with multiple domains of functional dependence [23]. On the other hand, cerebral atherosclerosis precedes both cerebral microangiopathy and macroangiopathy and then interrupts the integrity of frontal-subcortical circuits that are associated with the magnitude of ageing phenotypes, including cognitive impairment, functional decline and slow walking speed [24], all of which are documented risk factors for frailty.

Second, we observed that hs-CRP may modify the relation between albuminuria and incident frailty, with a stronger positive association in those with higher hs-CRP levels. Consistently, previous studies have found that microalbuminuria accompanied by evidence of subclinical inflammation is significantly correlated with blood pressure regulation [25], atherosclerotic process [26] and metabolic abnormalities, including full-blown metabolic syndrome, obesity and concentric left ventricle hypertrophy [27, 28]. It was hypothesized that isolated microalbuminuria may represent a more benign profile, whereas 'inflammatory microalbuminuria' may precede and predispose to the development of cardiovascular abnormalities [25]. Chronic inflammation, negatively impacting on endothelial integrity and blood flow control in the microcirculation, could decrease the blood flow to the skeletal muscle [29], leading to greater loss of muscle mass and strength [30], which has been considered a precursor syndrome or the physical manifestation of frailty [31]. On the other hand, endothelial dysfunction could potentially lead to peripheral vascular disease, which is an essential risk factor of slow gait speed, decreased muscle strength and physical disability [23]. Moreover, microalbuminuria is associated with increased insulin resistance [11] and insulin resistance has been explained partly by inflammatory processes [32]. Thus it is physiologically plausible that albuminuria and hs-CRP may jointly increase the risk of frailty and our results emphasize the importance of managing both albuminuria and elevated hs-CRP for primary prevention of frailty.

This study had several strengths, including its relatively large sample size of older Chinese adults (particularly the oldest old), prospective design and comprehensive subjective and

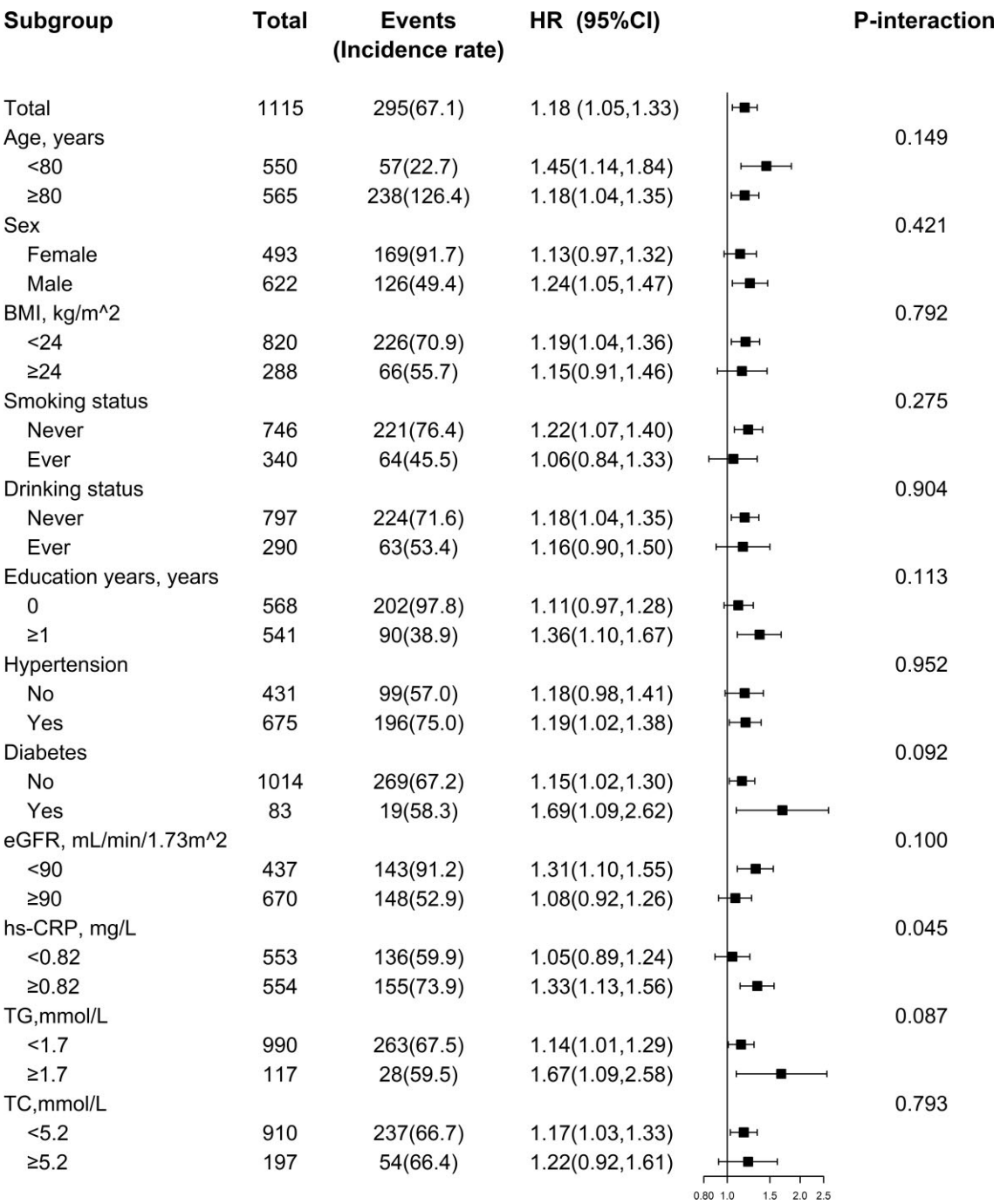

FIGURE 2: Stratified analysis of the impact of UACR (per quartile increment) on incident frailty by potential effect modifiers. Adjusted for baseline age, sex, BMI, smoking status, drinking status, residence educational background, marital status, economic independence status, diabetes, hypertension, eGFR, hs-CRP, TG and TC, if not be stratified.

objective measures of frailty. Nevertheless, there are several limitations of our study. First, although we have carefully controlled for several identified and potential confounders, such as sociodemographic information and lifestyle factors, unmeasured or unknown residual confounding remains possible. Second, the albuminuria level was based on a one-time assessment. Further studies are warranted to assess the changing trends of albuminuria status over time and its association with frailty. Third, serum creatinine was determined by the picric acid method and eGFR was calculated using the MDRD equation for the Chinese population. Since the MDRD equation is not reliable when eGFR is >60 mL/min/1.73 m^2, we compared the prevalence of CKD using several equations, including the Berlin Initiative Study 1 (BIS1) equation [33], Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [33] and Asian-modified CKD-EPI equation [34], and found that the MDRD equation may overestimate eGFR levels (Supplementary data, Table S1). However, the adjustments for eGFR levels, calculated with

different equations, did not substantially change the positive association of UACR with incident frailty (Supplementary data, Table S2). Moreover, none of the eGFR levels significantly modified the association between UACR and incident frailty (Supplementary data, Table S3). Fourth, the CLHLS oversampled the oldest old, therefore our findings have limited generalizability to relatively younger populations. Owing to these limitations, further confirmation of the reported findings in future studies is necessary.

CONCLUSION

This study first analysed the prospective association between albuminuria and frailty among older adults and found that albuminuria was positively associated with the risk of incident frailty, particularly in those with higher hs-CRP. If further confirmed, our data suggest that measurement of UACR might possibly improve early detection and primary prevention of frailty and emphasized the importance of managing both albuminuria and inflammation for primary prevention of frailty.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

M.L. and X.Q. designed and conducted the research and wrote the manuscript. M.L., P.H. and C.L. performed the data management and statistical analyses. All authors reviewed/edited the manuscript for important intellectual content and read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

No disclosures were reported.

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