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CLINICAL STUDY

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Frailty transitions and risk of chronic kidney disease: insights from the China Health and Retirement Longitudinal Study

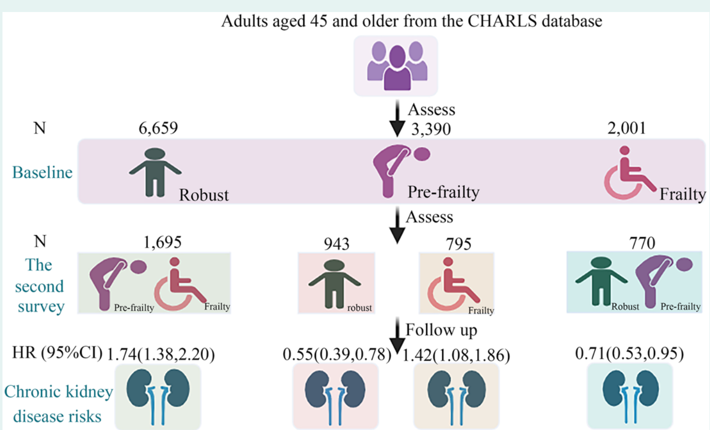
Xiaotong Sun[a], Che Wang[b], Rujie Zheng[a], Zhihao Liu[b], Wenjuan Song[a], Xiaoyu Du[a], Chunlei Liu[b] and Chengzhi Lu[c]

[a]The First Central Clinical School, Tianjin Medical University, Tianjin, China; [b]School of Medicine, Nankai University, Tianjin, China; [c]Department of Cardiology, Tianjin First Central Hospital, Tianjin, China

ABSTRACT

Background: Frailty is increasingly recognized as a critical factor in the risk of chronic kidney disease (CKD), and it is also a condition that can undergo transitions. However, the relationship between frailty transitions and CKD risk in aging populations remains underexplored. This study aims to investigate the association between frailty transitions and CKD risk in middle-aged and older adults using data from the China Health and Retirement Longitudinal Study.
Methods: Frailty was assessed using a 40-item Frailty Index (FI), with participants categorized into three groups: robust (FI ≤ 0.10), pre-frail (0.10 < FI ≤ 0.21), and frail (FI > 0.21). Frailty transitions were tracked between the first and second waves of the study. Data on CKD incidence were obtained from self-reported physician-diagnosed kidney disease. Cox proportional hazards models were employed to evaluate the risk of CKD, with adjustments made for potential confounders.
Results: Among 12,050 participants (52.60% female, mean age 58.37), those who progressed to frailty or pre-frailty had an increased risk of CKD compared with stable participants (HR 1.74, $p < 0.001$). In contrast, individuals who recovered from frailty to robust or pre-frail status had a reduced CKD risk (HR 0.71, $p = 0.023$). The results of the sensitivity analysis, which showed consistent findings, support the reliability of the results.
Conclusion: Frailty transitions are significantly associated with the risk of CKD. Worsening frailty is linked to an increased risk of CKD, while improvement in frailty is associated with a lower risk of CKD.

GRAPHICAL ABSTRACT



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CONTACT Chengzhi Lu 5020200072@nankai.edu.cn Department of Cardiology, Tianjin First Center Hospital, 24 Fukang Road, Nankai District, Tianjin 300192, P.R. China.

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1. Instruction

As the global population continues to age, frailty has emerged as a prevalent geriatric syndrome and a growing health challenge [1]. A meta-analysis conducted across 62 countries worldwide revealed that the prevalence of frailty, as measured by the frailty index, is as high as 24%, with pre-frailty affecting 49% of middle-aged and older adults [2]. Increased vulnerability resulting from cumulative physiological decline characterizes frailty, leading to disproportionate health deterioration from minor stressors. Adverse health outcomes in older adults, such as falls, disability, hospitalization, and mortality, are strongly associated with frailty [1,3–5]. Frailty is not only a clinical syndrome but also a significant public health concern that worsens with age, affecting both quality of life and the healthcare system.

Over the past few decades, chronic kidney disease (CKD) has developed into a significant global public health concern. Between 1990 and 2017, the global prevalence of CKD increased by 29.3%, while its all-age mortality rate rose by 41.5% [6]. By 2040, CKD is projected to be the fifth leading cause of death globally [7]. Elucidating the relationship between frailty and CKD will yield important insights for preventing and managing CKD in the aging population. Frailty and CKD share common pathophysiological mechanisms, particularly those involving systemic inflammation and oxidative stress [8]. Earlier studies have shown that frailty may accelerate the progression of CKD. In the Seattle Kidney Study (SKS), which focused on non-dialysis-dependent CKD patients, a robust association with the decline in kidney function was identified for frailty. These findings suggest that increased frailty may accelerate CKD progression and further impair estimated glomerular filtration rate (eGFR) [9].

Despite these insights, notable gaps persist in the existing literature concerning the relationship between frailty and CKD. Many studies are cross-sectional and lack investigations into the future risk of CKD, while others focus solely on baseline frailty status without considering changes in frailty over time. Notably, increasing evidence suggests that frailty can improve with appropriate intervention [10]. More importantly, studying changes in frailty, rather than just a single frailty status, provides a more comprehensive understanding of how shifts in various physiological functions relate to disease development, such as the relationship between frailty changes and the onset of CKD. Addressing these research gaps is essential for clarifying the relationship between frailty and CKD and for developing more targeted and effective interventions to mitigate the burden of both conditions. However, the notion that improving frailty could potentially reduce the prevalence of chronic CKD remains somewhat speculative among clinicians, as there is currently limited concrete evidence linking frailty interventions to kidney outcomes. Our study addresses this critical gap by providing valuable data on how transitions in frailty status are correlated with CKD risk, offering nephrologists a new perspective on managing frailty in the context of kidney health. Specifically, this research investigates frailty as a dynamic process rather than a static baseline characteristic, thereby emphasizing the importance of frailty transitions whether progression or recovery in the development of kidney health. This approach is particularly important as it recognizes the reversible nature of frailty.

This study leverages the CHARLS database to examine the association between frailty index (FI) transitions and CKD risk among older Chinese adults. A major strength of this study is its focus on the dynamic transitions of frailty over time, which enables a more nuanced understanding of how changes in frailty status, whether deterioration or recovery, are correlated with the risk of CKD. This dynamic approach offers several advantages over previous studies that solely examined baseline frailty, as it more accurately captures the opportunity for intervention and the possibility of improvement, especially in elderly populations. We hypothesize that progression of frailty will be correlated with an increased risk of CKD, while improvement in frailty will be linked to a lower risk of CKD.

2. Methods

2.1. Study design and population

The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative cohort investigating individuals across 28 provinces in China, all aged 45 and above [11]. It gathers comprehensive data on demographics, health, family dynamics, and economic status [11]. Baseline data were collected in 2011, with follow-up assessments conducted in 2013, 2015, and 2018. Approved by the Peking University Biomedical Ethics Committee, CHARLS offers valuable insights into aging in China, with informed consent obtained from all participants.

This study utilized data from the 2011 baseline survey (17,705 participants), along with the 2013 (second wave), 2015 (third wave), and 2018 (fourth wave) CHARLS surveys. The inclusion criteria were as follows: (1) age ≥ 45 years; (2) participation in the baseline survey and at least one follow-up wave after the second wave; (3) availability of valid data on frailty and CKD, with no prior diagnosis of kidney disease (including eGFR < 60 mL/min/1.73 $m^2$and a self-reported physician diagnosis of kidney disease) in the first two waves. Following the exclusion of participants with incomplete CKD follow-up data, 12,050 participants were included in the primary analysis (Figure 1).

2.2. Assessment of frailty

Frailty was assessed using the FI, which quantifies the accumulation of health deficits associated with aging. The index can be adapted but should consist of a minimum of 30 health deficit items for a reliable evaluation [12]. This study involved the development of a frailty index (FI) using established criteria, which included 40 indicators. These included

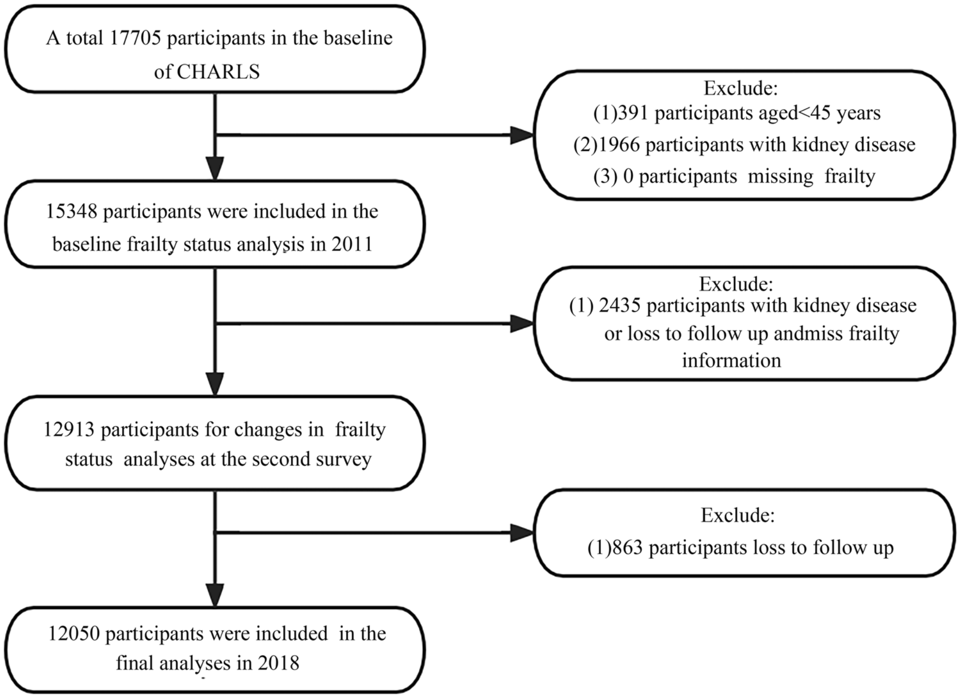

Figure 1. Selection process of the study population.

11 items assessing limitations in activities of daily living, 6 items related to disability, 13 chronic conditions (excluding kidney disease), 9 mobility-related items and cognitive status adjustments using telephone interviews (Table S1). The 40 indicators were scored as a continuous variable between 0 and 1 (0 = no health deficit, 1 = health deficit), and lower scores indicated better cognitive function. FI was calculated by dividing the total health deficit score by the number of items completed, where higher scores reflected greater frailty. This comprehensive FI assessment provided a robust measure of frailty in the study population. FI was categorized into three groups: robust (FI ≤ 0.10), pre-frail (0.10 < FI ≤ 0.21), and frail (FI > 0.21) [5,13,14]. Frailty levels have been commonly assessed using this method in previous CHARLS studies [15].

The total frailty index (Total FI) was derived by summing the baseline FI and the FI measured during the second survey. The frailty index change was calculated by subtracting the baseline FI from the FI at the second survey.

2.3. Covariates

The study collected demographic data (age, sex, marital status, education, and geographic location), health-related behaviors (smoking, alcohol consumption, and sleep quality), medical history and medication use (hypertension, diabetes, and hyperlipidemia), and blood test indicators (serum creatinine, cystatin C, and uric acid). Anthropometric measurements, were taken following standard protocols, including weight and height, with BMI calculated as weight/height [2] (kg/m^2) [16]. The eGFR was computed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which combines creatinine and cystatin C levels [17], as follows:

$$\begin{aligned}\text{eGFR}\left(\text{mL/min/1.73m2}\right) &= 135 \times \min\left(\text{Cr}/\text{k},1\right)\alpha \times \max\left(\text{Cr}/\text{k},1\right) - 0.601 \\ &\times \min\left(\text{CysC}/0.8,1\right) - 0.375 \times \max\left(\text{CysC}/0.8,1\right) \\ &- 0.711 \times 0.995\ \text{age} \times 0.969\left[\text{if female}\right].\end{aligned}$$

In this formula, Cr represents serum creatinine (mg/dL) and CysC represents serum cystatin C (mg/L). The constant K is 0.7 for females and 0.9 for males, while the α value is −0.248 for females and −0.207 for males. Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, or a history of hypertension or use of antihypertensive medication [18]. Diabetes is defined by a self-reported diagnosis of diabetes, use of hypoglycemic medications, fasting glucose levels ≥ 7 mmol/L, or a glycosylated hemoglobin (HbA1c) ≥ 6.5%. Hyperlipidemia is characterized by a self-reported diagnosis of hyperlipidemia, use of lipid-lowering drugs, or any of the following blood lipid thresholds: TC ≥ 240 mg/dL, LDL ≥ 160 mg/dL, TG ≥ 200 mg/dL, or HDL < 40 mg/dL [19].

2.4. Outcome measures

The primary outcome of this study was the risk of CKD, defined as a self-reported physician diagnosis of kidney disease, as indicated by t the reply to the question: "Have you been diagnosed with kidney disease (except for tumor and cancer) by a doctor?" [20,21]. If the respondent answered 'yes' the subsequent question asked for the time of diagnosis, providing a variable for the event's occurrence time.

The survival status variable was derived from the 'Whether Individual Died' data in waves 3 and 4. Unfortunately, the exact time of death for deceased individuals in these two waves was not recorded. Therefore, for deceased individuals, death time was calculated by subtracting the baseline follow-up time from the follow-up time of death.

2.5. Statistical analyses

All continuous variables were presented as mean ± standard deviation (SD) for normally distributed data, and median with interquartile range (IQR) for skewed data. Categorical variables were expressed as frequencies and percentages. Group comparisons were conducted using the Kruskal-Wallis H test for continuous variables and the chi-square test for categorical variables. For continuous variables with missing values, multiple imputation methods were used for data completion. For categorical variables, probabilistic imputation methods were applied to handle the missing data effectively.

To investigate the relationship between changes in frailty and the risk of CKD, Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI). The Schoenfeld residuals test is used to assess the proportional hazards assumption in Cox regression analysis, verifying the validity of the Cox proportional hazards model (Table S2). All included variables were initially analyzed using univariate regression, and those with a p-value < 0.05 were selected (Table S3). After considering the impact of each variable on both the outcome and exposure, a total of 15 selected variables were included as covariates in the multivariate regression analysis. Total FI and FI difference were categorized into quartiles, with the lowest quartile serving as the reference. Additionally, trend tests were performed by treating the quartile values as continuous variables in the regression models [22].

Subgroup analyses were conducted, stratified by demographic characteristics and health behaviors, to explore potential effect modifications and interactions between subgroup variables, frailty transitions, and CKD risk. Finally, sensitivity analyses were conducted to address potential biases: (1) frailty status was reassessed at the third wave to confirm the stability of frailty transitions. (2) Considering the significant impact of frailty on mortality among older adults, the Fine-Gray test using the Cumulative Incidence Function (CIF) can be employed to assess the competing risks between CKD and death.

All statistical analyses were conducted using R software (version 4.4.0) and DecisionLinnc-V1.1.1.0 [23]. P-values were two-sided, and statistical significance was set at $p < 0.05$.

3. Results

3.1. Baseline characteristics

Based on the inclusion and exclusion criteria, a total of 12,050 participants (52.60% female, mean age: 58.37 years) from the CHARLS database were included in the final outcome analysis, which had a median follow-up duration of 5 years. Table 1 presents a summary of the baseline characteristics of the participants. Compared to robust individuals, those categorized as frail demonstrated several significant demographic and clinical differences. Frail participants were notably older (mean age: 63.22 years), had a greater proportion of females (66.32%) and a lower likelihood of being married, with 22.79% of participants being unmarried. Additionally, frail individuals exhibited significantly lower educational attainment, with only 0.80% having completed college, and had a higher tendency to reside in rural areas (94.40%). Furthermore, frail individuals reported poorer sleep quality, with 58.82% experiencing poor sleep, compared to 37.89% in the robust group. Moreover, individuals with frailty demonstrated a greater prevalence of comorbid conditions. The rates of hypertension, diabetes and hyperlipidemia were markedly elevated in this group.

The baseline characteristics of the excluded population are presented in Table S4, which shows that these characteristics were nearly identical to those of the included population across all groups.

3.2. Association of changes in frailty status with incident chronic kidney disease

The analysis revealed a distinct association between transitions in frailty status and the risk of CKD. A total of 1,695 participants (25.45%) initially classified as robust transitioned to a pre-frail or frail state, while 770 participants (38.48%) who were frail at baseline recovered to a pre-frail or robust state. The percentage and number of CKD patients in 2018, categorized by initial frailty status and frailty transition individuals, were shown in Table 2. Among individuals who were robust at baseline, the prevalence of CKD patients in 2018 was 4.91%. The proportion of CKD patients who transitioned from robust to frail or pre-frail status increased to 6.90%. Conversely, among those who were frail at baseline, the prevalence of CKD patients in 2018 was 11.14%. The proportion of CKD patients among individuals who transitioned from frail to robust or pre-frail status decreased to 8.83%.

Table 3 presented the relationship between transitions in frailty status and the risk of CKD. To control for the effects of covariates, three different models were applied in the analysis, with all three yielding consistent results. In the third model, participants who progressed to a pre-frail or frail state exhibited a notably higher risk of CKD compared to those who remained robust (HR 1.74, 95% CI 1.38-2.20, $p < 0.001$). Conversely, frail participants who recovered to a pre-frail or robust state demonstrated a significantly reduced risk of CKD compared to those who remained frail (HR 0.71, 95% CI 0.53-0.95, $p = 0.023$). Among individuals identified as pre-frail at baseline, those who improved to a robust state had a lower risk of CKD compared to those who remained pre-frail (HR 0.55, 95% CI 0.39-0.78, $p = 0.001$). In contrast, individuals who progressed to a frail state exhibited an

Table 1. Baseline characteristics of participants included in the 2011 baseline frailty status analyses.

Characteristics	Overall	Robust	Pre-frail	Frail	P value
N	12,050	6,659	3,390	2,001	
Age, mean (SD), years	58.37 (8.98)	56.30 (8.12)	59.57 (8.84)	63.22 (9.68)	<0.001
Sex, n (%)					
Female	6,338 (52.60%)	3,063 (46.00%)	1,948 (57.46%)	1,327 (66.32%)	<0.001
Male	5,712 (47.40%)	3,596 (54.00%)	1,442 (42.54%)	674 (33.68%)	
Education, n (%)					
College+	231 (1.91%)	169 (2.54%)	46 (1.36%)	16 (0.80%)	<0.001
High school	1,195 (9.92%)	866 (13.00%)	250 (7.37%)	79 (3.95%)	
Primary-	10,624 (88.17%)	5,624 (84.46%)	3,094 (91.27%)	1,906 (95.25%)	
Marital, n (%)					
Married	9,969 (82.73%)	5,687 (85.40%)	2,737 (80.74%)	1,545 (77.21%)	<0.001
Unmarried	2,081 (17.27%)	972 (14.60%)	653 (19.26%)	456 (22.79%)	
Location, n (%)					
City	1,050 (8.71%)	676 (10.15%)	262 (7.73%)	112 (5.60%)	<0.001
Village	11,000 (91.29%)	5,983 (89.85%)	3,128 (92.27%)	1,889 (94.40%)	
Smoking, n (%)					
Ever	938 (7.78%)	459 (6.89%)	282 (8.32%)	197 (9.85%)	<0.001
Never	7,573 (62.85%)	3,992 (59.95%)	2,201 (64.92%)	1,380 (68.96%)	
Now	3,539 (29.37%)	2,208 (33.16%)	907 (26.76%)	424 (21.19%)	
Drinking, n (%)					
No	7,956 (66.02%)	4,042 (60.70%)	2,340 (69.03%)	1,574 (78.66%)	<0.001
Yes	4,094 (33.98%)	2,617 (39.30%)	1,050 (30.97%)	427 (21.34%)	
BMI, mean (SD), kg/m^2	23.62 (3.96)	23.49 (3.76)	23.81 (4.22)	23.75 (4.12)	<0.001
Sleep quality, n (%)					
Good	7,484 (62.11%)	4,707 (70.69%)	1,953 (57.61%)	824 (41.18%)	<0.001
Bad	4,566 (37.89%)	1,952 (29.31%)	1,437 (42.39%)	1,177 (58.82%)	
Hypertension, n (%)					
No	6,985 (57.97%)	4,366 (65.57%)	1,760 (51.92%)	859 (42.93%)	<0.001
Yes	5,065 (42.03%)	2,293 (34.43%)	1,630 (48.08%)	1,142 (57.07%)	
Hyperlipidemia, n (%)					
No	8,151 (67.64%)	4,769 (71.62%)	2,176 (64.19%)	1,206 (60.27%)	<0.001
Yes	3,899 (32.36%)	1,890 (28.38%)	1,214 (35.81%)	795 (39.73%)	
Diabetes, n (%)					
No	10,489 (87.05%)	6,037 (90.66%)	2,854 (84.19%)	1,598 (79.86%)	<0.001
Yes	1,561 (12.95%)	622 (9.34%)	536 (15.81%)	403 (20.14%)	
Hypertension drug, n (%)					
No	9,115 (75.64%)	5,496 (82.53%)	2,399 (70.77%)	1,220 (60.97%)	<0.001
Yes	2,935 (24.36%)	1,163 (17.47%)	991 (29.23%)	781 (39.03%)	
Hyperlipidemia drug, n (%)					
No	11,279 (93.60%)	6,436 (96.65%)	3,105 (91.59%)	1,738 (86.86%)	<0.001
Yes	771 (6.40%)	223 (3.35%)	285 (8.41%)	263 (13.14%)	
Diabetes drug, n (%)					
No	11,586 (96.15%)	6,557 (98.47%)	3,210 (94.69%)	1,819 (90.90%)	<0.001
Yes	464 (3.85%)	102 (1.53%)	180 (5.31%)	182 (9.10%)	
Uric acid, mean (SD), mg/dL	4.39 (1.19)	4.42 (1.19)	4.39 (1.20)	4.28 (1.18)	<0.001
Serum creatinine, mean (SD), mg/dL	0.76 (0.16)	0.77 (0.16)	0.75 (0.16)	0.74 (0.16)	<0.001
Cystatin C, mean (SD), mg/dL	0.96 (0.17)	0.95 (0.16)	0.97 (0.17)	0.98 (0.17)	<0.001
eGFR, mean (SD), mL/min/1.73 m^2	88.40 (13.77)	89.97 (13.64)	87.18 (13.75)	85.26 (13.50)	<0.001

P values were calculated by the Kruskal-Wallis H test for continuous variables and Chi-square tests for categorical variables. TC, Total cholesterol; TG, Triglyceride; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol, eGFR, estimated Glomerular Filtration Rate.

Table 2. Percentage and number of CKD patients in 2018 with initial frailty status and frailty transition individuals.

Baseline	CKD patients; N(Percentage)	Changes in frailty status	CKD patients; N(Percentage)
robust	327 (4.91%)	stable robust	210 (4.23%)
		robust to frail/pre-frail	117 (6.90%)
pre-frail	268 (7.91%)	stable pre-frail	137 (8.29%)
		pre-frail to robust	45 (4.77%)
		pre-frail to frail	86 (10.82%)
frail	223 (11.14%)	stable frail	155 (12.59%)
		frail to robust/pre-frail	68 (8.83%)

Abbreviations: N = Number of individuals diagnosed with CKD in 2018.

increased risk (HR 1.42, 95% CI 1.08-1.86, $p = 0.013$). Overall, progression to a frail state was associated with a higher risk of CKD events, whereas recovery from frailty was linked to a reduced CKD risk.

3.3. Associations of total frailty index and difference in frailty index with the incident of CKD

The total frailty index and changes in frailty index were both significantly associated with the incidence of CKD. The analysis highlighted the impact of changes in frailty scores over two cycles on CKD risk during the follow-up period. Table 4 presented the association between total FI and the risk of incident CKD. After adjusting for confounding factors, participants in the highest quartile of total FI exhibited a significantly higher risk of incident CKD compared to those in the lowest quartile (HR 3.56, 95% CI 2.82-4.50, $p < 0.001$). Similarly, elevated risks were observed in the third and second quartiles. Trend analysis revealed a positive association between increasing total FI and the risk of CKD events (all P for trend < 0.001). These findings underscored a strong

Table 3. Association of changes in frailty status with risks of CKD.

	Events/Number	Model 1 HR (95%CI)	P	Model 2 HR (95%CI)	P	Model 3 HR (95%CI)	P
Stable robust	210/4964	1 (reference)		1 (reference)		1 (reference)	
Robust to pre-frail/ frail	117/1695	1.65 (1.32, 2.07)	<0.001	1.76 (1.39, 2.21)	<0.001	1.74 (1.38, 2.20)	<0.001
Stable pre-frail	137/1652	1 (reference)		1 (reference)		1 (reference)	
Pre-frail to robust	45/943	0.56 (0.40, 0.79)	0.001	0.56 (0.40, 0.78)	0.001	0.55 (0.39, 0.78)	0.001
Pre-frail to frail	86/795	1.32 (1.01, 1.73)	0.043	1.41 (1.08, 1.86)	0.013	1.42 (1.08, 1.86)	0.013
Stable frail	155/1231	1 (reference)		1 (reference)		1 (reference)	
Frail to robust/ pre-frail	68/770	0.69 (0.52, 0.92)	0.011	0.67 (0.50, 0.89)	0.006	0.71 (0.53.0.95)	0.023

Model 1 were unadjusted.
Model 2 was adjusted for age, sex, education, geographic location, smoking status.
Model 3 further adjusted for hypertension status, diabetes status, hyperlipidemia status, hypertension drug, hyperlipidemia drug, diabetes drug, uric acid, serum creatinine, cystatin C, and eGFR.

Table 4. Association of total frailty index with risks of CKD.

	Events/Number	Model 1 HR (95%CI)	P	Model 2 HR (95%CI)	P	Model 3 HR (95%CI)	P
Total FI*		1.02 (1.01, 1.02)	<0.001	1.02 (1.02, 1.02)	<0.001	1.02 (1.02, 1.02)	<0.001
T1 of total FI	115/3035	1 (reference)		1 (reference)		1 (reference)	
T2 of total FI	159/2992	1.42 (1.11, 1.80)	0.004	1.51 (1.19, 1.92)	0.001	1.50 (1.18, 1.97)	0.001
T3 of total FI	210/3029	1.86 (1.48, 2.34)	<0.001	2.10 (1.67, 2.65)	<0.001	2.04 (1.62, 2.86)	<0.001
T4 of total FI	334/2994	3.07 (2.48, 3.79)	<0.001	3.71 (2.96, 4.65)	<0.001	3.56 (2.82, 4.50)	<0.001
P for trend			<0.001		<0.001		<0.001

The total frailty index (total FI) was calculated by summing the baseline FI and the FI measured during the second survey. Total FI* = total FI *100, Participants were categorized into tertiles: T1 (lowest quartile), T2 (second quartile), T3 (third quartile), and T4 (highest quartile) based on their total FI scores.
Model 1 were unadjusted.
Model 2 was adjusted for age, sex, education, geographic location, smoking status.
Model 3 further adjusted for hypertension status, diabetes status, hyperlipidemia status, hypertension drug, hyperlipidemia drug, diabetes drug, uric acid, serum creatinine, cystatin C, and eGFR.

Table 5. Association of the frailty index difference with risks of CKD.

	Events/Number	Model 1 HR (95%CI)	P	Model 2 HR (95%CI)	P	Model 3 HR (95%CI)	P
△FI *		1.02 (1.01, 1.03)	<0.001	1.02 (1.01, 1.03)	<0.001	1.02 (1.01, 1.03)	<0.001
T1 of △FI	211/3264	1 (reference)		1 (reference)		1 (reference)	
T2 of △FI	187/3048	0.91 (0.74, 1.11)	0.348	0.89 (0.72, 1.09)	0.248	0.90 (0.73, 1.11)	0.335
T3 of △FI	200/3094	0.99 (0.81, 1.21)	0.950	0.97 (0.79, 1.19)	0.759	0.97 (0.80, 1.19)	0.792
T4 of △FI	362/3087	1.40 (1.16, 1.68)	<0.001	1.39 (1.16, 1.68)	<0.001	1.39 (1.16, 1.68)	<0.001
P for trend			<0.001		<0.001		<0.001

△FI was calculated by the FI at the second survey minus the FI at baseline. △FI*=△FI*100. Participants were categorized into tertiles: T1 (lowest quartile), T2 (second quartile), T3 (third quartile), and T4 (highest quartile) based on their FI difference scores.
Model 1 were unadjusted.
Model 2 was adjusted for age, sex, education, geographic location, smoking status.
Model 3 further adjusted for hypertension status, diabetes status, hyperlipidemia status, hypertension drug, hyperlipidemia drug, diabetes drug, uric acid, serum creatinine, cystatin C, and eGFR.

correlation between higher frailty burden and an increased risk of CKD.

Table 5 showed the association between change in FI and risks of incident CKD. Participants in the highest quartile of difference in FI had significantly higher risks of incident CKD compared to those in the lowest quartile (HR 1.39, 95% CI 1.16-1.68, $p < 0.001$). However, no significant risks were observed in the third and second quartiles. It was noteworthy that the trend tests indicated increasing trends in the risk of incident CVD with the increasing difference in Frailty Index (all P for trend < 0.001). The distributions of total FI and difference in FI were described in Figures S1 and S2.

3.4. Subgroup analysis

Subgroup analyses were conducted in adjusted Model 3 to assess potential effect modification of the association between frailty transitions and CKD. Although the interaction analysis did not reach statistical significance, suggesting no significant effect modification between subgroups, the independent effects still revealed notable associations The subgroup analysis revealed a statistically significant increase in the risk of incident CKD associated with transitioning from a healthy to frail state among subgroups with a BMI > 18.5 kg/m^2, as well as regardless of current smoking status, alcohol consumption, sleep quality, hypertension status, hyperlipidemia status, and diabetes status (Tables S5–S13).

Table 6. Association of changes in frailty status with risks of CKD in different subgroup.

	Female	Men		45y ≤ Age < 65y	Age ≥ 65y	
	HR (95%CI)	HR (95%CI)	P for interaction	HR (95%CI)	HR (95%CI)	P for interaction
Stable robust	1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Robust to pre-frail/ frail	1.77 (1.23, 2.56)	1.69 (1.24, 2.29)	0.693	1.55 (1.18, 2.02)	2.65 (1.57, 4.48)	0.090
Stable pre-frail	1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Pre-frail to robust	0.59 (0.35, 0.97)	0.50 (0.32, 0.80)	0.466	0.52 (0.35, 0.77)	0.73 (0.36, 1.49)	0.687
Pre-frail to frail	1.32 (0.89, 1.96)	1.38 (0.94, 2.04)		1.40 (1.02, 1.93)	1.46 (0.86, 2.49)	
Stable frail	1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Frail to robust/ pre-frail	0.62 (0.42, 0.90)	0.94 (0.58, 1.52)	0.267	0.81 (0.57, 1.15)	0.51 (0.29, 0.89)	0.141

Model was adjusted for age, sex, education, geographic location, smoking status, hypertension status, diabetes status, hyperlipidemia status, hypertension drug, hyperlipidemia drug, diabetes drug, uric acid, serum creatinine, cystatin C, and eGFR.

Table 7. Association of changes in frailty status between the third survey and baseline with the risk of CKD.

		Model 1		Model 2		Model 3	
	Events/Number	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Stable robust	137/3830	1 (reference)		1 (reference)		1 (reference)	
Robust to pre-frail/ frail	108/1782	1.71 (1.33, 2.21)	<0.001	1.82 (1.41, 2.37)	<0.001	1.84 (1.41, 2.39)	<0.001
Stable pre-frail	86/1314	1 (reference)		1 (reference)		1 (reference)	
Pre-frail to robust	26/715	0.55 (0.36, 0.85)	0.008	0.53 (0.34, 0.83)	0.005	0.54 (0.35, 0.84)	0.006
Pre-frail to frail	69/779	1.37 (1.00, 1.88)	0.051	1.50 (1.09, 2.07)	0.013	1.50 (1.09, 2.07)	0.014
Stable frail	113/1030	1 (reference)		1 (reference)		1 (reference)	
Frail to robust/ pre-frail	28/518	0.48 (0.32, 0.73)	0.001	0.45 (0.29, 0.68)	<0.001	0.45 (0.30, 0.69)	<0.001

Model 1 were unadjusted.
Model 2 was adjusted for age, sex, education, geographic location, smoking status.
Model 3 further adjusted for hypertension status, diabetes status, hyperlipidemia status, hypertension drug, hyperlipidemia drug, diabetes drug, uric acid, serum creatinine, cystatin C, and eGFR.

This association was also observed across different genders (Female: HR = 1.77, 95% CI: 1.23-2.56, $p = 0.002$; Male: HR = 1.69, 95% CI: 1.24-2.29, $p = 0.001$) and age groups (45 ≤ Age < 65 years: HR = 1.55, 95% CI: 1.18-2.02, $p = 0.001$; Age ≥ 65 years: HR = 2.65, 95% CI: 1.57-4.48, $p < 0.001$), see in Table 6. Additionally, the association was significant among married individuals and those living in city areas. From the above results, it could be observed that this trend was evident in the majority of subgroups. Interestingly, although the subgroup distribution of increased CKD risk in the population transitioning from pre-frailty to frailty was similar to that in the robust to pre-frail/frail groups, the number of subgroups with statistical significance was fewer. Overall, these findings highlighted a strong association between worsening frailty status and an increased risk of CKD across most of the different subgroups.

In contrast, improvement in frailty status was associated with a significant reduction in CKD risk in certain subgroups. Transitioning from pre-frailty to a robust state was associated with a statistically significant reduction in CKD risk among subgroups with a BMI between 18.5 and 25 kg/m^2, as well as among those regardless of hyperlipidemia status, hypertension status, alcohol consumption, sleep quality, and gender (Female: HR = 0.59, 95% CI: 0.35-0.97, $p = 0.039$; Male: HR = 0.50, 95% CI: 0.32-0.80, $p = 0.004$). In addition, this association was observed in subgroups without diabetes, those aged 45-65 years, married individuals, those living in rural areas, and nonsmokers. However, among individuals transitioning from frailty to robust or pre-frailty, fewer subgroups demonstrated a significant association with improved CKD risk compared to those in the pre-frail group at baseline who experienced an improvement in their frailty status.

3.5. Sensitivity analyses

The sensitivity analysis, conducted by reassessing frailty status based on data from the third survey, produced findings that were largely in line with the primary results of the study. Notably, frailty progression remained significantly associated with an increased risk of CKD. Table 7 showed that, after adjusting for multiple confounders, individuals transitioning from a robust state to a pre-frail or frail state exhibited a significantly higher risk of CKD (HR 1.84, 95% CI 1.41-2.39, $p < 0.001$). This consistency with the main analysis further strengthened the association between deteriorating frailty status and an increased risk of CKD. Additionally, the protective effect of frailty recovery was confirmed. Individuals who recovered from a frail state to a more robust or pre-frail condition demonstrated a significantly reduced risk of CKD (HR 0.45, 95% CI 0.30-0.69, $p < 0.001$). This finding emphasized the potential of improving frailty status to mitigate the risk of CKD.

Additionally, considering the competing risk of death and CKD incidence, the results of a competing risk model was used to reassess the association between frailty transitions and the risk of CKD were presented in Table 8. Individuals transitioning from a robust state to a pre-frail or frail state exhibited a significantly higher risk of CKD (HR 1.75, 95% CI

Table 8. Association of changes in frailty status with the risk of CKD: a cox competing risks regression model.

		Model 1		Model 2		Model 3	
	Events/Number	HR (95%CI)	adj. P	HR (95%CI)	adj. P	HR (95%CI)	adj. P
Stable robust	222/5156	1 (reference)		1 (reference)		1 (reference)	
Robust to pre-frail/ frail	123/1183	1.65 (1.32, 2.06)	<0.001	1.76 (1.41, 2.21)	<0.001	1.75 (1.39, 2.19)	<0.001
Stable pre-frail	142/1763	1 (reference)		1 (reference)		1 (reference)	
Pre-frail to robust	51/1000	0.57 (0.41, 0.79)	<0.001	0.56 (0.4, 0.78)	<0.001	0.56 (0.40, 0.78)	<0.001
Pre-frail to frail	96/905	1.15 (1.00, 1.31)	0.043	1.19 (1.04, 1.36)	0.011	1.19 (1.04, 1.36)	0.012
Stable frail	191/1528	1 (reference)		1 (reference)		1 (reference)	
Frail to robust/ pre-frail	75/835	0.70 (0.52, 0.92)	0.011	0.68 (0.51, 0.90)	0.006	0.72 (0.54, 0.97)	0.028

Model 1 were unadjusted.
Model 2 was adjusted for age, sex, education, geographic location, smoking status.
Model 3 further adjusted for hypertension status, diabetes status, hyperlipidemia status, hypertension drug, hyperlipidemia drug, diabetes drug, uric acid, serum creatinine, cystatin C, and eGFR.

1.39-2.19, $p < 0.001$), whereas those who recovered from a pre-frail state showed a significantly reduced risk of CKD (HR 0.56, 95% CI 0.40-0.78, $p < 0.001$). Compared to individuals who remained in a stable frail state, those who transitioned from frail to robust or pre-frail exhibited a significantly reduced risk of CKD (HR: 0.72, 95% CI: 0.54-0.97, $p = 0.028$).

4. Discussion

To determine the impact of changes in frailty status on the incidence of CKD, this study employed longitudinal analysis using nationally representative sample data from the Chinese middle-aged and elderly population. Robust participants who developed frailty or pre-frail demonstrated a higher risk of CKD incidence compared to stable robust participants. In contrast, frail participants who recovered to a robust/pre-frail status, as well as pre-frail participants who returned to a robust status, showed a reduced risk of CKD incidence compared to those with stable health. In addition, higher total FI and an increase in FI were associated with elevated risks of incident CKD. Similarly, populations evaluated for changes in frailty across different survey periods exhibited comparable risks for CKD. The competing risks model, which adjusted for mortality risk alongside CKD outcomes, corroborated these findings, thereby enhancing the confidence in the conclusions drawn from the study.

Prior research has identified frailty as a crucial factor influencing outcomes in CKD patients, with several studies examining the complex relationship between frailty and CKD, providing valuable insights. For instance, the SPRINT trial highlighted a significant association between urinary biomarkers of tubular injury, fibrosis, and proximal tubular reabsorption capacity with the frailty index [24]; Additionally, a medical study from Western Ireland demonstrated that even mild CKD was correlated with functional impairment and frailty [25]. Our study further explored the relationship between changes in frailty status and the occurrence of CKD events, an aspect not previously addressed in the literature. A recent meta-analysis of community-dwelling older adults reported that, over a mean follow-up of 3.9 years, the pooled transition rates among those who were frail at baseline were 3.3% to robust, 40.3%to pre-frail, and 54.5% remaining frail [26,27]. It was noteworthy that in a follow-up study from the Longitudinal Aging Study Amsterdam, a 0.01 increase in the FI was associated with a 3% increase in the risk of mortality [28]. Our study corroborated these findings, highlighting the dynamic nature of frailty status, and extended the analysis to explore the previously unexamined relationship between frailty status transitions and the risk of CKD, using comprehensive assessments of frailty. More importantly, we discovered that participants who transitioned from frailty to robust/ prefrail states had a reduced risk of CKD compared to those who remained persistently frail. The group with a worsening transition from prefrail status also showed similar results. We also assessed the dynamic nature of frailty status through the total FI and changes in FI. A more pronounced change in frailty status, along with a higher cumulative FI, was strongly associated with an increased risk of CKD events, further corroborating our previous findings. This finding highlighted that the progression of frailty increases the risk of CKD. In contrast, frail participants who recovered to robust/prefrail states and prefrail participants who recovered to robust states showed a reduced risk of CKD events compared to stable participants, indicating that reversing frailty has significant benefits for CKD events. In our sensitivity analysis, we reassessed the distribution of the population across different frailty assessment periods and conducted a competing risk model analysis that accounted for mortality. The results were largely consistent. Previous studies have only established the association between the static state of frailty and the occurrence and prognosis of kidney disease. For example, frailty is an important predictor of adverse outcomes in patients with CKD, and in elderly patients with advanced CKD, frailty is closely associated with the malnutrition-inflammation syndrome [8,27]. The prevalence of frailty among patients undergoing hemodialysis might be as high as 73% [29]. However, these conclusions did not offer a clear understanding of the relationship between frailty transitions and CKD, and our study addressed this gap. The mechanisms underlying the association between frailty transitions and incident CKD in healthy individuals are not yet fully understood. The transition in frail patients reflects the presence of multiple interconnected issues, including comorbidities, polypharmacy, diminished physiological reserve across multiple organ systems, and cognitive decline [30,31]. These factors may all contribute to the rapid decline in kidney function [32].

Several studies have highlighted the roles of inflammation, oxidative stress, and glomerular dysfunction as key contributors to both frailty and CKD [8,9,33]. One plausible explanation is that changes in frailty status affected glomerular function and disrupted homeostasis, thereby facilitating the strong association with the incidence of CKD. Furthermore, elderly individuals with a higher frailty index often exhibit disturbances in electrolyte balance, including disruptions in calcium and phosphate metabolism [34], which are also considered potential contributors to CKD development [35,36]. Moreover, the increased comorbid burden in patients experiencing frailty transitions further elevates the risk of CKD, with poor glycemic control and fluctuating blood pressure contributing to microvascular damage within the kidneys, ultimately leading to renal failure [36–39].

Since the frailty score in our study was based on 40 indicators related to activities of daily living, different populations may exhibit distinct distributions and transitions in frailty scores. To explore the relationship between frailty transitions and the risk of CKD in different subgroups in more detail, we conducted further subgroup analyses. Although the interaction analysis did not yield statistically significant results, this suggested that these subgroup variables did not significantly modulate the relationship between frailty transitions and CKD risk, and that this association was independent and robust. The transition from pre-frail to frail and from robust to frail could be collectively categorized as worsening physical frailty, while the transition from frail to robust or pre-frail was categorized as improvement in frailty status. When worsening physical frailty occurred, the risk of CKD increased, whereas improvement in frailty status was associated with a decreased risk of CKD. This finding was observed across various subgroups, including different genders, age groups, sleep statuses, hypertension and hyperlipidemia conditions, alcohol consumption habits, and individuals with a BMI between 18.5 and 25 kg/m^2. It was also specifically observed in nonsmokers, married individuals, and those without diabetes, thereby encompassing nearly all subgroups. However, no association between frailty recovery and a reduced risk of CKD incidence was observed in populations with low or high BMI, individuals with diabetes, smokers, unmarried individuals, and those living in urban areas. This may be attributed to the unique underlying disease characteristics and conditions specific to these groups, as well as differences in sample characteristics, which could confound the observed association. These comorbidities may obscure the relationship between frailty transitions and CKD risk, thereby attenuating the apparent impact of frailty changes on CKD. For example, the unmarried population may not only have a higher risk of hypertension and diabetes but also face other factors that influence CKD development, such as a higher dietary inflammatory index [40–42]. These additional health risks and lifestyle factors could confound the relationship between frailty transitions and CKD, masking the potential association in this subgroup. In addition, low BMI is associated with factors like malnutrition and muscle loss, which can negatively affect kidney function [43,44]. A study in the US Medicare population showed that people living in counties with higher levels of air pollution have an increased risk of CKD [45]. Obesity and diabetes are both pro-inflammatory conditions that lead to the significant activation of inflammatory mediators such as IL-6, TNF-α, and C-reactive protein (CRP), all of which contribute to the impairment of glomerular and tubular functions in the kidneys [46–49]. All of the above could potentially serve as residual confounding factors, affecting the main conclusions of the study. Additionally, for the population who were still smoking, no decrease in the risk of CKD occurrence was observed in those who experienced improvement in frailty. Smoking itself is a risk factor for chronic diseases, particularly cardiovascular, respiratory, and kidney diseases [50–52]. Even if frailty improves, the negative effects of smoking may still be significant enough to maintain a high risk for CKD. In summary, most of the different subgroups in our study yielded similar conclusions, indicating that our findings were broadly applicable and have significant clinical value. This consistency across various groups strengthens the generalizability of our research, highlighting its potential to inform clinical practices and health interventions for a wide range of populations.

Our study carries significant clinical and public health implications. Firstly, individuals who are frail or pre-frail should be identified as the primary target population for CKD prevention strategies. Frailty is a reversible condition, and the present study demonstrates that individuals who successfully reverse their frailty status exhibit a significantly reduced risk of CKD. This finding further underscores the feasibility and importance of frailty interventions in preventing CKD. Moreover, this finding provides crucial evidence underscoring the importance of frailty management for general practitioners and nephrologists, offering a strong foundation for developing clinical strategies focused on addressing frailty as a means to reduce CKD risk and promote overall health. Additionally, these findings provide valuable insights for future research and hypothesis generation, as the observed trends may help guide further investigations to validate the heightened CKD risk or sensitivity to frailty transitions noted in clinical practice. Therefore, this underscores the importance of frailty assessment in the primary prevention of CKD, particularly in its earlier stages before the onset of other comorbid conditions. In conclusion, prioritizing early intervention and prevention of frailty, especially in vulnerable populations, is essential for preventing irreversible kidney damage and preserving renal health.

Our study has several limitations. First, the assessment of disease outcomes, such as CKD, partly depended on self-reported data regarding whether participants had been diagnosed by a physician. A prominent study using CHARLS data found that self-reported hypertension and diabetes often underestimated true prevalence, with sensitivities of 73.24% for hypertension and 49.21% for diabetes [11,53]. This highlights the potential discrepancy between patient self-awareness and actual diagnosed conditions. Secondly, our study did not perform a component analysis of the FI to identify which specific components of FI might contribute most to recovery. Thirdly, our study is limited by its focus on a Chinese elderly cohort. Expanding the research to include elderly populations from multiple countries would provide a more comprehensive understanding of how FI transitions influence CKD outcomes across diverse populations. Cross-country comparisons could identify universal and region-specific factors influencing FI recovery and CKD risk, enhancing the generalizability of findings and supporting tailored interventions for global frailty management in CKD prevention. Fourthly, the data collected in the database does not encompass all potential variables, and the covariates included in our study are limited. However, the clinical significance of frailty as an independent contributor to CKD risk is complex and multifaceted. Consequently, we were unable to fully account for residual confounders that may influence the outcomes. This limitation highlights the potential impact of unmeasured confounding factors on the results. Additionally, a limitation of this database is the lack of detailed ICD codes for diseases and the absence of continuous or uninterrupted eGFR measurements for staging and grading CKD. This prevents us from further subclassifying the disease. Due to these limitations, we are unable to explore in greater detail the transitions of frailty in patients at different stages of CKD or identify which individuals are more likely to progress to CKD. Finally, one inherent limitation of large-scale studies in the general population is the relatively low prevalence of CKD and the absence of detailed statistics on specific pathological changes. However, individuals undergoing kidney aging with advancing age, even in the absence of primary glomerular or tubular diseases, may still face an increased risk of developing CKD. Incorporating kidney pathology data would be invaluable for exploring the relationship between frailty transitions and kidney pathology, thereby enhancing our understanding of these risks and mechanisms.

5. Conclusion

In conclusion, the different transitions in frailty status are significantly associated with the risk of CKD. When an individual's physical health declines into a frail state, the risk of CKD increases. Conversely, when an individual transitions from frailty to a healthier state, the risk of CKD decreases. This suggests that improving frailty status may be an effective strategy in reducing CKD risk, highlighting the importance of early intervention and monitoring in frail populations.

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Author contributions

CRediT: **Xiaotong Sun**: Conceptualization, Formal Analysis, Writing – Original Draft; **Che Wang**: Conceptualization, Writing – Review & Editing; **Rujie Zheng & Zhihao Liu**: Data Curation; **Wenjuan Song, Xiaoyu Du, & Chunlei Liu**: Writing – Review & Editing; **Chengzhi Lu**: Supervision, Funding Acquisition.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Declarations

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Data availability statement

The data used in this study are openly available and can be accessed through the CHARLS website at http://charls.pku.edu.cn.

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