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Association of 3-year change in frailty index with risk of all-cause mortality among older Chinese population: a national cohort study

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Abstract

Background Evidence on the association of dynamic change in frailty index (FI) with risk of all-cause mortality in the older Chinese population is limited. This study aimed to explore the association of 3-year change in FI with risk of all-cause mortality in an older Chinese population.

Methods We analyzed the data of 4969 participants from the Chinese Longitudinal Healthy Longevity Survey. The primary outcome was all-cause mortality, which was a binary variable and defined as completed data and censored data. Cox proportional-hazard models were used to assess the association of 3-year change in FI with risk of all-cause mortality by using hazard ratios (HRs) and 95% confidence intervals (CIs). Subgroup analyses were conducted to explore the association of 3-year change in FI with risk of all-cause mortality. Additionally, a restricted cubic spline analysis was also conducted to describe the dose-response association.

Results During a median of 4.08 years of follow-up, deaths were observed in 1388 participants. We observed a 1.27-fold higher risk of all-cause mortality with increase in FI ≥ 0.045 versus change in FI < 0.015 (HR = 2.27, 95% CI: 1.89–2.73). Similar significant associations were observed in the subgroup analyses by age, sex, and residence at baseline. Additionally, a nonlinear dose-response association of 3-year change in FI with risk of all-cause mortality was observed (*P* overall < 0.001 and *P* nonlinear < 0.001).

Conclusions Excessive increase in FI was positively associated with an increased risk for all-cause mortality. Approaches to reducing FI may be of great significance in improving the health of older Chinese individuals.

Keywords Dynamic change in frailty index, All-cause mortality, Older Chinese population, Prospective cohort study, Dose-response association

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Introduction

According to the World Population Aging 2020 [1], 727 million persons globally were ≥65 years old, and the number is expected to reach over 1.5 billion by 2050 (from 9.3 to 16.0%). With the global increase in the older population, the resulting health and economic system burden is also increasing; thus, the prevention or reduction of age-related complications has received increased attention [1, 2].

Frailty is a clinically identifiable state of diminished physiological reserve and increased vulnerability to a broad range of adverse health outcomes [3, 4]. The frailty index (FI) is commonly used to estimate the degree of frailty based on accumulated deficits in multiple health domains [5, 6], and the prevalence of frailty (FI≥0.25) was 44.20% among older Chinese population [7]. Notably, frailty can be reversible or ameliorated by adequate nutritional supplementation and appropriate physical exercise [8, 9]; that is, early identification and amelioration of frailty are of great significance to the health of the older population. Previous studies have demonstrated that FI was associated with several adverse outcomes, such as falls [10], disability [11], and dementia [12]. Although the association between FI and risk of all-cause mortality has been explored, most previous studies were often based on FI at a certain time point [7, 13, 14]. Considering that FI is modifiable, the association of its dynamic change with all-cause mortality is of great public health significance. Previous studies have also found that frailty fluctuations in older adults are not negligible, meanwhile, frailty fluctuations represent a relevant yet hitherto untapped facet of frailty, which could contribute to a better understanding of frailty development as well as could help to better understand frailty development in older adults and its association to other adverse outcomes [15]. Although several studies have explored the association of dynamic change in FI with all-cause mortality [16, 17], the relevant studies are still few, particularly among older Chinese populations.

Therefore, to fill the gap, we aimed to explore the association of 3-year change in FI with risk of all-cause mortality among an older Chinese population and further assess whether the association differed by age, sex, and residence. In addition, we also aimed to explore the dose-response association of 3-year change in FI with risk of all-cause mortality.

Methods

Study participants and design

Data for this study were obtained from the Chinese Longitudinal Healthy Longevity Survey (CLHLS). We selected the 2011–2012, 2014 and 2017–2018 surveys as baseline, first follow-up and second follow-up examination, which randomly recruited 9765 older participants in half of the counties or cities in 22 provinces of China [18]. We excluded participants aged<65 years (n=86), those who were lost to follow-up or died at the first follow-up examination (n=3670), those with missing information of death time from the first follow-up to the second follow-up examination (n=8), those with missing FI information or <30 FI items at baseline examination (n=387), and those with missing FI information or FI items<30 at the first follow-up examination (n=645). Finally, 4969 participants were enrolled (median age: 81 years). All study participants provided signed informed consent, and the study was approved by the Biomedical Ethics Committee of Peking University.

Data collection

Baseline data were collected by trained research staff who administered a standard questionnaire to collect information on demographic characteristics, lifestyle risk factors, Mini-mental State Examination (MMSE) scores, and disease history. The Chinese version of the MMSE was used to assess the cognitive function, which was adapted from the international MMSE, and the MMSE score ranges from 0 to 30, with higher scores indicating better cognitive function [19–21]. The FI was assessed using a 38-item FI questionnaire. We constructed the FI questionnaire following a standard procedure [22]. The FI was based on health deficits, defined as symptoms, signs, disabilities, and diseases [22]. Criteria for health deficits to be included in the FI were [23]: association with the health status; had a prevalence>1%; generally increased with age; no early-age onset; and affecting several physiological systems. Each health deficit was scored from 0 to 1, or missing. For each participant, the FI score was calculated as the sum of deficit scores divided by the number of deficits included and ranged from 0 to 1. We constructed a 38-item FI following an established study using data from the CLHLS [23]. After the FI was calculated, all participants were categorized as robust (FI≤0.12), pre-frail (0.12<FI≤0.25), or frail (FI>0.25) [24]. The variables used to construct the FI and coding are defined in Supplementary Table S1. Other covariates, including educational status, household income in the previous year, marital status, living pattern, current smoking, current alcohol drinking and current physical activity, were defined according to a previous study based on the CLHLS [25]. Educational status was classified as "never educated" and "ever educated". Household income in the previous year was classified as <15,000 Chinese Yuan (CNY) and ≥15,000 CNY. Marital status was classified as "married and living with a spouse" and "married but not living with a spouse, divorced, widowed, and never married". Living pattern was divided into "living alone" and "living with others". Current smoking, alcohol drinking, and physical activity were classified as

"current smoking" and "current non-smoking", "current alcohol drinking" and "current non-alcohol drinking", and "current physical activity" and "non-current activity", respectively.

Participants were asked to wear light clothes and be barefoot when measuring anthropometric indices (height and weight) by trained staff following a standard protocol. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a mercury sphygmomanometer (upper arm type; Yuyue, Jiangsu, China) on the unclothed right upper arm after at least a 5-min rest, with participants in a seated position [26]. The measurements were repeated twice at 1-min intervals, and the average was used for further analysis.

The same questionnaire and measurement methods used at the baseline examination were used during the follow-up examinations in the 2014 and 2017–2018 surveys. Incident deaths were mainly based on death certificates provided by local authorities or relatives of the deceased if death information was not available.

Statistical analysis

The 3-year change in FI was calculated as the FI at the end of the first follow-up minus that at baseline. Continuous variables were described as medians (interquartile ranges) due to the skewed distribution and categorical variables as number (percentage). Wilcoxon rank sum and χ^2 tests were used to test differences in baseline variables between sex. The 3-year change in FI was classified into five groups as follows: <-0.045, -0.045 to <-0.015, -0.015 to <0.015, 0.015 to <0.045 and ≥0.045, with stable FI (-0.015 to <0.015) as the reference group [17]; meanwhile, both "<-0.045" and "-0.045 to <-0.015" groups were defined as FI loss, and both "0.015 to <0.045" and "≥0.045" were defined as FI gain. Kaplan-Meier survival curves for cumulative survival rate and cumulative hazard of the five groups were drawn. The log-rank tests were performed to determine the difference across these groups. The proportional-hazard assumption was tested by using Schoenfeld residuals analysis [27], with Kaplan-Meier survival curves were also considered to test the proportional-hazard assumption, and 3-year change in FI and living pattern were not fit for proportional-hazard assumption (Supplementary Table S2 and Supplementary Figure S1). The association of 3-year change in FI with risk of all-cause mortality were investigated by Cox proportional-hazard regression models, estimating hazard ratios (HRs) and 95% confidence intervals (CIs). The Cox proportional-hazard regression models began with model 1 (unadjusted). Model 2 adjusted for age and sex at baseline. Model 3 adjusted for variables in model 2 plus residence, household income in the previous year, educational status, marital status, living pattern, current smoking status, current alcohol drinking status, and current physical activity status at baseline. Model 4 adjusted for variables in model 3 plus MMSE score, BMI, SBP, DBP, resting heart rate (RHR) and FI at baseline. Sensitivity analyses were used to test the robustness of the results by excluding 481 participants with MMSE<18 at baseline in model 5, and by additional including 910 participants with <30 FI items at baseline or first follow-up examination in model 6. In addition, because not all variables were fit for the proportion-hazard assumption, we another adjusted for the interaction item (3-year change in FI × the natural logarithm of survival time) in all the 6 models and the interaction item (living pattern × the natural logarithm of survival time) in model 3 to model 6 [28]. Linear trends across 3-year change in FI groups were evaluated by considering a median value within each group as continuous variables. Cox proportional-hazard regression models were further used to explore the association of 3-year change in FI status with risk of all-cause mortality, with adjusting the same covariates in model 4 (except FI at baseline).

Moreover, we evaluated the interaction between the 3-year change in FI with age, sex, and residence and their effects on the risk of all-cause mortality using Cox proportional-hazard regression models adjusted for the same covariates in model 4. In addition, Cox proportional-hazard regression models stratified by age (65 to <80 years and ≥80 years), sex (men and women), and residence (city/town and village) at baseline were used to explore the association of 3-year change in FI with risk of all-cause mortality in different subgroup.

To describe the dose-response association of 3-year change in FI with risk of all-cause mortality, we used restricted cubic splines (RCS) incorporated in the Cox proportional-hazard regression models. We considered 3-year change in FI=0 as the reference. The covariates were the same as those in model 4.

Data were analyzed using SAS v9.4 (SAS Institute, Cary, NC, USA) and R v4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as two-sided $\alpha=0.05$.

Results

Baseline characteristics of the study participants according to sex

Table 1 shows the baseline characteristics of the study participants according to sex. Data for household income in the previous year≥15,000 CNY, ever received education, married and living with spouse, current smoking, current alcohol drinking, current physical activity, MMSE score, height, weight, and BMI at baseline were higher for men than for women, whereas data for age,

Table 1 Baseline characteristics of study participants based according to sex

Characteristics	Total ($n=4969$)	Men ($n=2394$)	Women ($n=2575$)	*P* value
Age (years)	81.00 (73.00–89.00)	79.00 (73.00–86.00)	82.00 (74.00–91.00)	< 0.001
City or town dweller (%)	2326 (46.81)	1144 (47.79)	1182 (45.90)	0.184
Household income in the previous year ≥ 15,000 CNY (%)	2381 (47.92)	1190 (49.71)	1191 (46.25)	0.015
Ever received education (%)	2346 (47.36)	1686 (70.57)	660 (25.73)	< 0.001
Married and living with spouse (%)	2269 (45.84)	1486 (62.38)	783 (30.49)	< 0.001
Living alone (%)	915 (18.57)	362 (15.25)	553 (21.65)	< 0.001
Current smoking (%)	1018 (20.57)	874 (36.63)	144 (5.62)	< 0.001
Current alcohol drinking (%)	951 (19.31)	752 (31.77)	199 (7.78)	< 0.001
Current physical activity (%)	1939 (39.47)	1020 (42.98)	919 (36.18)	< 0.001
MMSE score	27.00 (24.00–28.00)	28.00 (26.00–29.00)	26.00 (22.00–28.00)	< 0.001
Height (cm)	157.00 (150.00–165.00)	164.00 (159.00–169.00)	150.00 (146.00–156.00)	< 0.001
Weight (kg)	52.00 (45.00–61.00)	57.00 (50.00–65.00)	48.00 (41.00–55.00)	< 0.001
BMI (kg/m^2)	21.34 (19.02–23.88)	21.48 (19.23–23.81)	21.11 (18.67–24.03)	0.007
SBP (mmHg)	135.00 (122.50–150.00)	132.50 (122.00–147.00)	137.50 (124.50–150.00)	< 0.001
DBP (mmHg)*	80.00 (72.50–87.50)	80.00 (72.50–88.00)	80.00 (72.50–87.50)	0.567
RHR (beat/min)	74.00 (68.00–80.00)	72.00 (68.00–80.00)	75.00 (70.00–80.00)	< 0.001
Frailty index	0.11 (0.08–0.16)	0.11 (0.07–0.15)	0.13 (0.09–0.18)	< 0.001
3-year change in frailty index	0.01 (-0.03–0.06)	0.01 (-0.03–0.06)	0.01 (-0.03–0.06)	0.627

Data are median (interquartile range) or number (percentage)

CNY, Chinese yuan; MMSE, Mini-mental State Examination; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; RHR, resting heart rate

*: Mean ± standard deviation of DBP by sex were 80.76 ± 11.38 mmHg and 80.60 ± 11.71 mmHg

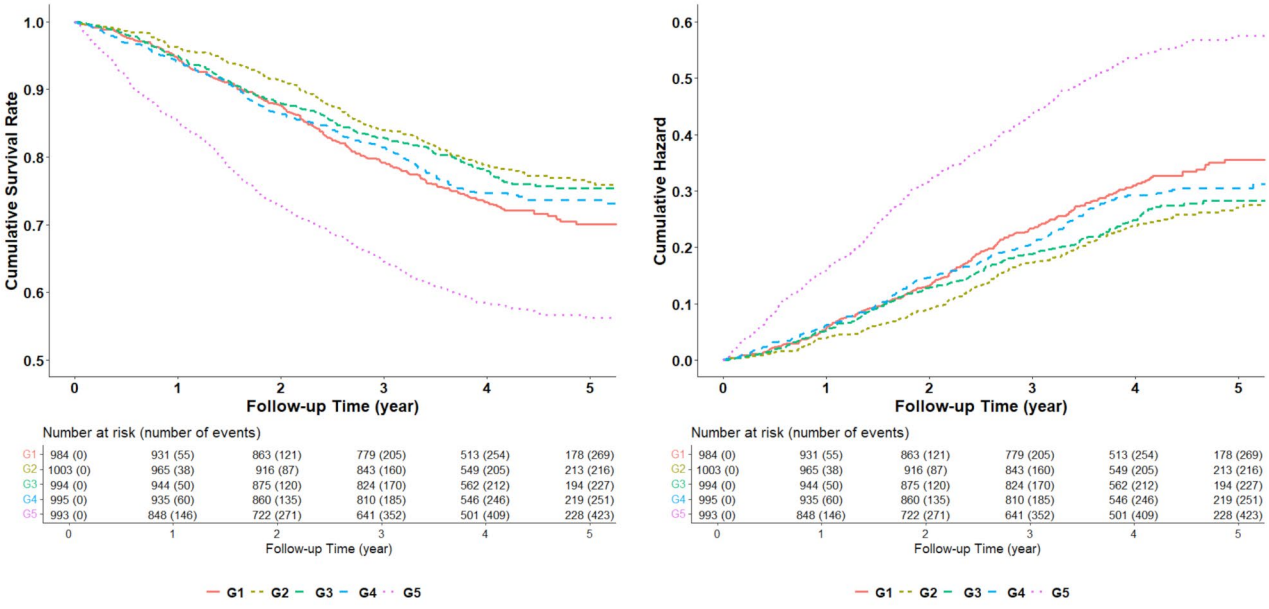

Fig. 1 Kaplan-Meier curves for cumulative mortality rate according to five groups of 3-year change in frailty index. G1, <-0.045; G2, -0.045 to <-0.015; G3, -0.015 to < 0.015; G4, 0.015 to < 0.045; G5, ≥ 0.045

living alone, SBP, RHR and FI at baseline were lower for men than for women (all $P<0.05$).

Risk of all-cause mortality by groups of 3-year change in FI

During a median follow-up duration of 4.08 years, 1388 patients died, with the mortality were 75.58/1000 person-years (death developed 683 in men, with the mortality were 78.05/1000 person-years and death developed 705 in women, with the mortality were 73.32/1000 person-years). Figure 1 shows the Kaplan-Meier curves for the cumulative survival rate and cumulative hazard of all-cause mortality with five groups of 3-year change in FI (both $P<0.001$ for log rank tests). Table 2 shows the risk of all-cause mortality by groups of 3-year change in FI. After adjusting for potential confounders, the risk of all-cause mortality was increased with FI gain ≥ 0.045

Table 2 Risk of all-cause mortality by groups of 3-year change in frailty index in an older Chinese population

Characteristics	3-year change in frailty index					*P* for trend
	<-0.045	-0.045 to <-0.015	-0.015 to < 0.015	0.015 to < 0.045	≥ 0.045	
No. of participants (*n*)	923	720	931	782	1613	
No. Death (*n*)	254	167	192	181	594	
Mortality rate*	74.34	60.67	53.18	60.79	105.91	
Model 1[a]	**0.55 (0.45–0.68)**	0.88 (0.72–1.09)	1.00	**1.47 (1.20–1.80)**	**4.15 (3.50–4.91)**	< 0.001
Model 2[b]	**0.49 (0.40–0.60)**	**0.79 (0.65–0.98)**	1.00	**1.36 (1.11–1.67)**	**3.24 (2.73–3.84)**	< 0.001
Model 3[c]	**0.69 (0.56–0.86)**	0.84 (0.68–1.04)	1.00	1.20 (0.97–1.48)	**2.39 (2.00–2.86)**	< 0.001
Model 4[d]	**0.54 (0.42–0.68)**	**0.80 (0.64–1.00)**#	1.00	1.22 (0.98–1.51)	**2.27 (1.89–2.73)**	< 0.001
Sensitivity analysis						
Model 5[e]	**0.43 (0.33–0.56)**	**0.76 (0.60–0.96)**	1.00	**1.27 (1.01–1.60)**	**2.78 (2.28–3.39)**	< 0.001
Model 6[f]	**0.44 (0.36–0.55)**	**0.76 (0.62–0.93)**	1.00	1.19 (0.98–1.45)	**2.41 (2.04–2.84)**	< 0.001

Data are hazard ratios (HRs) and 95% confidence intervals (CIs). The interaction item (3-year change in FI × the natural logarithm of survival time) was adjusted in all the 6 models, and the interaction item (living pattern × the natural logarithm of survival time) was adjusted in model 3 to model 6. Likelihood tests were used in the 6 models and all *P*-value < 0.001

Bold values showed statistical significance ($P < 0.05$)

*: 1000 person-years

#: HR (95% CI) with three decimals was 0.801 (0.644–0.997), and the *P*-value was 0.047

[a]: Unadjusted

[b]: Adjusted for age and sex at baseline

[c]: Adjusted for variables in model 2 plus residence, household income in the previous year, educational status, marital status, living pattern, current smoking status, current alcohol drinking status, and current physical activity status at baseline

[d]: Adjusted for variables in model 3 plus Mini-Mental State Examination score, body mass index, systolic blood pressure, diastolic blood pressure, resting heart rate and frailty index at baseline

[e]: Adjusted for variables in model 4 excluding participants with Mini-Mental State Examination score < 18 at baseline

[f]: Adjusted for variables in model 4 additional including 910 participants with < 30 FI items at baseline or first follow-up examination

versus stable FI (-0.015 to <0.015) of 3-year change in FI (HR = 2.27, 95% CI: 1.89–2.73), and decreased with FI loss > 0.045 versus stable FI (-0.015 to <0.015) of 3-year change in FI (HR = 0.54, 95% CI: 0.42–0.68). In addition, the results of the sensitivity analysis in models 5 and 6 revealed a similar association of the 3-year change in FI with risk of all-cause mortality.

Figure 2 illustrates the association of 3-year change in FI with risk of all-cause mortality according to age, sex, and residence at baseline. We first observed that age modified the association between 3-year change in FI and risk of all-cause mortality (age×FI change interaction, *P* for interaction = 0.016), and no statistically significant interaction between 3-year change in FI and sex / residence at baseline on all-cause mortality risk was observed (*P* for interaction = 0.386 and *P* for interaction = 0.803). The subgroup analysis of association between 3-year change in FI and risk of all-cause mortality on age, sex, and residence at baseline was also consistent with the results in Table 2.

Dose-response association of 3-year change in FI with risk of all-cause mortality

The adjusted dose-response association of 3-year change in FI with risk of all-cause mortality in the RCS analysis is presented in Fig. 3. The RCS results illustrate that as compared with 3-year change in FI = 0, risk of all-cause mortality increased with an increase in FI gain, and a nonlinear dose-response association of 3-year change in FI with risk of all-cause mortality was observed (*P* overall < 0.001 and *P* nonlinear < 0.001). Sensitivity analyses excluding participants with MMSE scores < 18 and additional including 910 participants with < 30 FI items at baseline or first follow-up examination demonstrate similar results with the study participants.

Risk of all-cause mortality by 3-year change in FI status

Figure 4 illustrates the association of 3-year change in FI status with risk of all-cause mortality. After adjusting for potential confounding factors, compared with remain pre-frail status both in baseline and first follow-up examination, with 3-year change from pre-frail to robust and persistent robust had lower 41% and 50% risks of all-cause mortality (HR = 0.59, 95% CI: 0.49–0.70 and HR = 0.50, 95% CI: 0.40–0.63); whereas, the 3-year change in FI from robust to frail, pre-frail to frail, and persistent frail to frail were associated with higher (1.68-fold, 1.89-fold, and 1.13-fold, respectively) risks of all-cause mortality (HR = 2.68, 95% CI: 1.97–3.65, HR = 2.89, 95% CI: 2.34–3.57 and HR = 2.13, 95% CI: 1.67–2.71). In addition, the results of sensitivity analyses revealed similar results.

Discussion

Our study indicated that the 3-year change in FI was positively associated with the risk of all-cause mortality in an older Chinese population, with a nonlinear

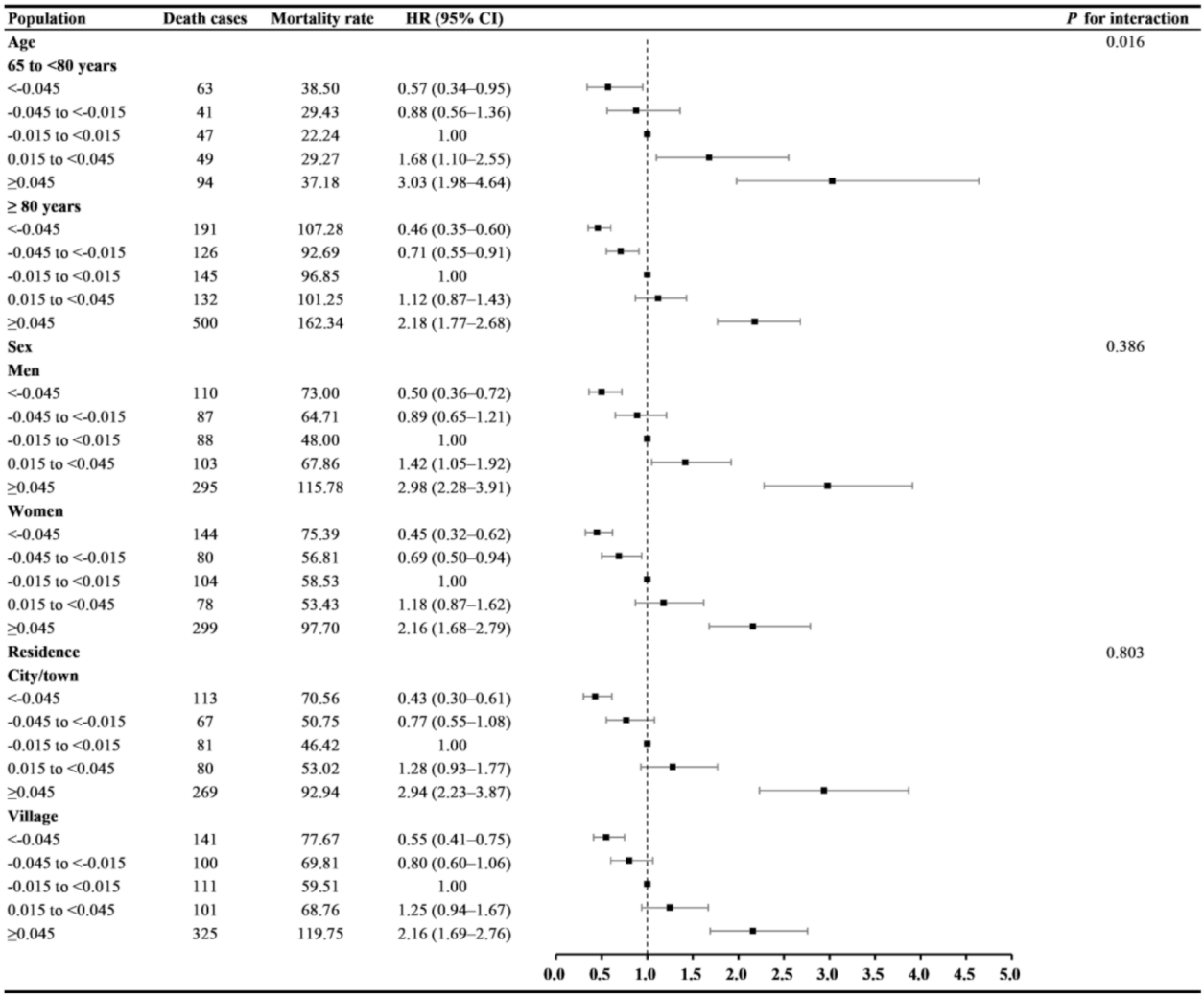

Fig. 2 Association of 3-year change in frailty index with risk of all-cause mortality by age, sex, and residence. The mortality rate was demonstrated by 1000 person-years. Adjusting for two interaction items (3-year change in FI × the natural logarithm of survival time and living pattern × the natural logarithm of survival time), age, sex, residence, household income in the previous year, educational status, marital status, living pattern, current smoking status, current alcohol drinking status, current physical activity status, Mini-Mental State Examination score, body mass index, systolic blood pressure, diastolic blood pressure, resting heart rate, and frailty index at baseline; residence-stratified analyses were not adjusted for residence

dose-response association of 3-year change in FI with risk of all-cause mortality was observed.

In the current study, the increase in FI could increase the risk of all-cause mortality; meanwhile, persistent frail status may also increase the risk of all-cause mortality. However, previous studies of the association between dynamic change in FI and risk of all-cause mortality have been inconsistent [29, 30]. Several previous studies demonstrated similar results with our study. One cohort study conducted in Korea enrolled 953 participants (aged≥65 years, with a mean follow-up 56.9 months) and demonstrated that a 1.37-fold higher risk of composite outcome of mortality and institutionalization with worse group (increase in FI≥0.03) versus stable group (change in FI<0.03) [29]. Another study which including 4 cohorts: HRS cohort (enrolled 6963 participants aged 65 to 105 years, a median follow-up 10.6 years), SHARE cohort (enrolled 2849 participants aged 65 to 101 years, a median follow-up 7.3 years), ELSA cohort (enrolled 1650 participants aged 65 to 87 years, a median follow-up 10.0 years), and LASA cohort (enrolled 1287 participants aged 65 to 89 years, a median follow-up 10.9 years), and demonstrated that with each 0.01 increase in FI gain, 56%, 24%, 40% and 71% higher risks of all-cause mortality, respectively [30]. In addition, another two cohort studies conducted in America focusing on Medicare beneficiaries also demonstrated similar results [17, 31]. One cohort study enrolled 995,664 Medicare beneficiaries (mean age 77 years, over 1-year follow-up) and demonstrated 1.30-fold, 68%, and 39% higher risks of

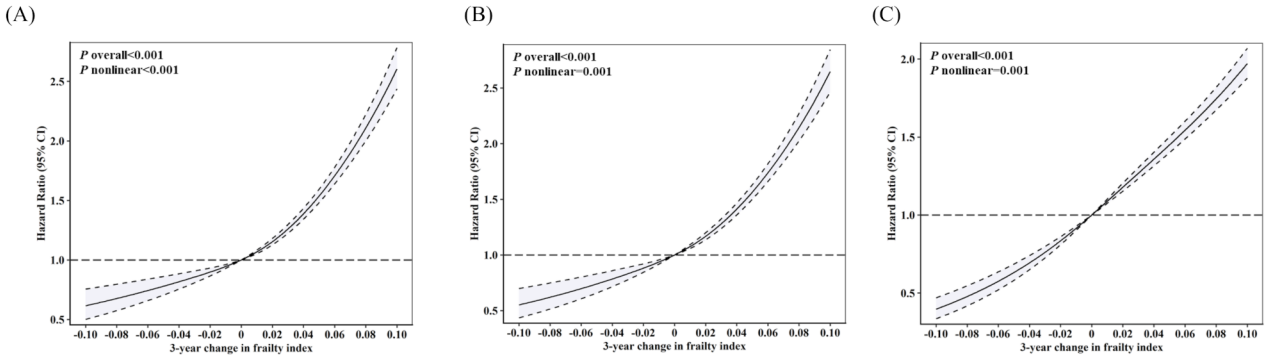

Fig. 3 Association of 3-year change in frailty index on a continuous scale with risk of all-cause mortality in total participants **(A)**, exclude participants with MMSE score < 18 **(B)**, and additional include 910 participants with < 30 FI items at baseline or first follow-up examination **(C)**. Hazard ratios and 95% confidence intervals (CIs) are from a Cox proportional-hazard regression model with restricted cubic splines, with 3-year change in frailty index = 0 as references and adjusting for two interaction items (3-year change in FI × the natural logarithm of survival time and living pattern × the natural logarithm of survival time), age, sex, residence, household income in the previous year, educational status, marital status, living pattern, current smoking status, current alcohol drinking status, current physical activity status, Mini-Mental State Examination score, body mass index, systolic blood pressure, diastolic blood pressure, resting heart rate, and frailty index at baseline

FI status in 2011/2012	FI status in 2014	Death cases	Mortality rate	HR (95% CI)
Study participants				
Robust	Robust	253	39.11	0.59 (0.49–0.70)
Robust	Pre-frail	230	68.20	1.20 (1.00–1.44)
Robust	Frail	72	161.31	2.68 (1.97–3.65)
Pre-frail	Robust	127	55.46	0.50 (0.40–0.63)
Pre-frail	Pre-frail	350	89.66	1.00
Pre-frail	Frail	181	215.48	2.89 (2.34–3.57)
Frail	Robust	14	105.11	0.40 (0.22–0.73)
Frail	Pre-frail	47	110.08	0.51 (0.35–0.73)
Frail	Frail	114	234.90	2.13 (1.67–2.71)
Exclude participants with MMSE score <18				
Robust	Robust	241	37.99	0.57 (0.48–0.69)
Robust	Pre-frail	211	65.51	1.28 (1.05–1.56)
Robust	Frail	63	154.91	3.38 (2.42–4.71)
Pre-frail	Robust	102	48.63	0.42 (0.33–0.54)
Pre-frail	Pre-frail	278	80.06	1.00
Pre-frail	Frail	130	198.63	3.50 (2.76–4.44)
Frail	Robust	10	108.03	0.39 (0.20–0.75)
Frail	Pre-frail	24	86.15	0.51 (0.32–0.81)
Frail	Frail	64	200.91	1.87 (1.37–2.54)
Additional include 910 participants with < 30 FI items at baseline or first follow-up examination				
Robust	Robust	275	40.00	0.58 (0.49–0.68)
Robust	Pre-frail	289	74.51	1.33 (1.13–1.58)
Robust	Frail	109	150.83	2.85 (2.20–3.70)
Pre-frail	Robust	152	58.59	0.47 (0.38–0.57)
Pre-frail	Pre-frail	412	91.79	1.00
Pre-frail	Frail	266	207.48	3.20 (2.67–3.85)
Frail	Robust	19	112.94	0.32 (0.19–0.56)
Frail	Pre-frail	70	118.33	0.41 (0.30–0.57)
Frail	Frail	203	258.45	2.00 (1.63–2.45)

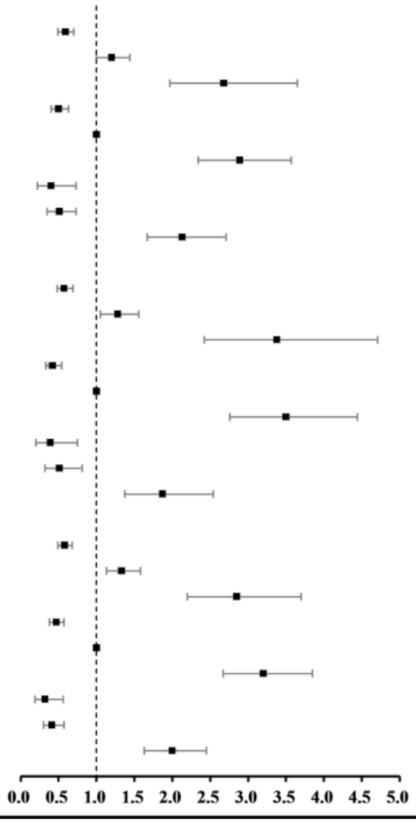

Fig. 4 Association of 3-year change in FI status with risk of all-cause mortality. The mortality rate was demonstrated by 1000 person-years. Adjusting for two interaction items (3-year change in FI × the natural logarithm of survival time and living pattern × the natural logarithm of survival time), age, sex, residence, household income in the previous year, educational status, marital status, living pattern, current smoking status, current alcohol drinking status, current physical activity status, Mini-Mental State Examination score, body mass index, systolic blood pressure, diastolic blood pressure, and resting heart rate at baseline

all-cause mortality with each 0.10 increase in FI among participants that were not frail, those with mild frailty, and those with moderate-to-severe frailty, respectively [31]. Another cohort study on 5672 Medicare beneficiaries (aged≥65 years, 4-year follow-up) and demonstrated 1.35-fold, 96%, and 99% higher risks of all-cause mortality with a large increase group (1-year change in FI>0.045) versus stable FI (1-year change in FI<0.015) among participants in the pre-frail, mildly frail and moderate-to-severely frail groups, respectively [31]. However, other studies reported inconsistent results [16, 32]. A cohort study conducted in Canada enrolled 3585 participants who attended cardiac rehabilitation (mean age 61.9 years, 5-year follow-up) and demonstrated no significant association of FI change with all-cause mortality [32]; whereas another study based on three longitudinal Swedish Twin Registry cohorts enrolled 3689 participants (mean age 74 years, a max follow-up 31.6 years) and also demonstrated no significant association [16]. The inconsistency among previous studies may be owing to differences in participant demography, FI assessment methods, confounding factors adjusted in the models, and sample sizes, all of which may have affected the results. In addition, an interaction between statistical significance interaction between 3-year change in FI and age at baseline on all-cause mortality risk was observed in the current study, which indicated that there was effect modification between 3-year change in FI and age in relation to risk of all-cause mortality.

The mechanism underlying the association between dynamic change in FI and risk of all-cause mortality remains unclear. Several biological mechanisms can be used to explain this association. First, several biomarkers may play a role in the mechanism underlying frailty [33–35], such as C-reactive protein, elevated glucose, and decreased haemoglobin levels, which could further lead to increased incident of death [36–38]. Second, potential causes of frailty, such as aging or poor nutritional status, are positively associated with mortality [39]. Third, a previous study indicated that frailty was significantly associated with decreased physical and mental function, both of which could contribute to a poor prognosis [40].

To our knowledge, this is the first study exploring the association of dynamic change in FI with risk of all-cause mortality in an older Chinese population from 22 provinces in China, which indicated that the results could be extended to the general older Chinese population. In addition, the study also considered the association between repeated measures of FI and risk of all-cause mortality. However, several limitations should be noted. First, information on whether the change in FI was owing to a modified lifestyle or other reasons is lacking, which may have biased the results. Second, information on FI was based on self-reported information, which may have led to misclassification. However, a previous study demonstrated that characteristics in an FI constructed exclusively from test-based measures yielded were similar with those in a self-report-based FI [41]. Third, although several potential confounding factors were adjusted, we could not properly adjust for nutrient consumption or genetic variables because of incomplete data. Fourth, the classification was based on one older population in the USA rather than older Chinese population, which may also have effect on the results; meanwhile, because our results were obtained from an older Chinese population, there are limitations in extrapolating the results to populations living in other regions. Finally, because the current study was based on only three examination information, it was not possible to explore the association between FI trajectory of FI and risk of all-cause mortality.

In conclusion, we observed that a great increase in FI was positively associated with an increased risk of all-cause mortality and that differences in age may influence the effect of the change in FI on all-cause mortality, which illustrated that improving frailty-related factors may reduce the risk of among older Chinese population; meanwhile, persistent frail status was also positively associated with risk of all-cause mortality. Therefore, the older Chinese population should pay more attention to preventing an increase in FI or persistent frailty status. Further multicenter, large-sample studies should be conducted to provide more evidence for improving the health status of older populations, especially older Chinese population.

Abbreviations

FI	Frailty index
MMSE	Mini-mental State Examination
CNY	Chinese Yuan
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HR	Hazard ratio
CI	Confidence interval
RHR	Resting heart rate
RCS	Restricted cubic spline

Supplementary Information

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Supplementary Material 1

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Author contributions

Dechen Liu participated in the design, data analysis, and writing of this study. Guoli Yan and Jinjin Wang provided supervision and guidance at all stages including the analyses. Qianqian Ma, Mingyu Zuo and Yuqi Niu assisted with drafting the article. Guoli Yan prepared for the manuscript for publication.

All authors reviewed and commented on drafts of the manuscript, and contributed to the article and approved the submitted version.

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Data availability
The datasets supporting this article are publicly available from the project of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). The datasets analyzed during the current study are available at: https://opendata.pku.edu.cn/dataverse/CHADS.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki, and approved by the Research Ethics Committee of Peking University. All study participants or their legal proxy respondents must obtain and sign written informed consent before completing each study questionnaire.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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