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# Association of frailty and its trajectory with the risk of cancer: evidence from the China health and retirement longitudinal study (CHARLS)

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## Abstract

**Background** Frailty can be identified in both middle-aged and older adults. However, longitudinal studies that examine whether frailty is associated with incident cancer are currently lacking. This study aimed to comprehensively examine the impact of baseline frailty levels and their changing trajectories over time on the risk of cancer.

**Methods** We assessed frailty status using the frailty index based on data from the China Health and Retirement Longitudinal Study (CHARLS) from 2011 to 2020. First, the association between baseline frailty and cancer risk was analyzed using the Cox proportional hazards model. Second, based on the CHARLS data from 2011 to 2020, we used Group-based trajectory modeling (GBTM) to identify trajectories of frailty development during the four follow-up periods from 2011 to 2020. Cox proportional hazards model was used to analyze the association between frailty trajectories and the risk of cancer incidence during the follow-up period.

**Results** A total of 17,708 participants were involved at the baseline survey in CHARLS 2011. During a mean follow-up period of 8.05 years, 248 cancer events occurred. Compared with non-frailty individuals, participants in pre-frailty and frailty states had a 34% (hazard ratio [HR]: 1.34, 95% confidence interval [CI]: 1.03–1.75) and 66% (HR: 1.66, 95% CI: 1.07–2.56) increased risk of overall cancer incidence, respectively. Based on repeated measurements from 2011 to 2018, three trajectories of frailty were identified among 9,173 participants. Compared to the low-level stable group, the high-level increase group had the highest risk of cancer, with an associated HR (95% CI) of 5.43 (1.07–5.73). This was followed by the medium-level increase group, with an associated HR (95% CI 2.86 (1.27–6.43). When stratified by sex and age, participants aged ≥ 60 years and female participants in the high-level increase frailty group had a higher risk of developing cancer.

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**Conclusion** Frailty is associated with cancer risk. Medium and high levels of the frailty index are significantly associated with an increased risk of cancer incidence. In addition, more attention should be paid to the risk of cancer in people aged ≥ 60 years and in women with high levels of frailty.

**Keywords** Cancer incidence, CHARLS, Cohort study, Frailty trajectory

## Introduction

Research on the global burden of disease shows that cancer has become one of the main causes of death in most countries and is a major global public health problem. Millions of people die from cancer annually, which poses a serious threat to public health [1]. According to the World Health Organization (WHO) cancer data for 2022, there were approximately 20 million new cases of cancer worldwide in 2020, with a staggering 9.7 million deaths, resulting in significant population loss and a heavy economic burden [2]. Additionally, the situation regarding cancer prevention and treatment in China is not optimistic. In 2022, there were 4.8247 million new cases of cancer in China, accounting for more than one-fifth of the global total [3]. Moreover, the annual medical expenditure for the treatment of malignant tumors in China exceeded 200 billion RMB [4].

Because the incidence of most cancers increases with age and shows a rapid rise from middle age [5], cancer can be considered an age-related disease. Compared with chronological age, frailty, as an indicator of ageing and biological age, can more accurately predict the risk of adverse health outcomes in middle-aged and older adults [6]. Frailty is a clinical syndrome that can easily lead to a variety of adverse health outcomes, which is characterized by reduced physiological reserves, decreased ability to stabilize the internal environment, and increased susceptibility to stressful events [7]. With the accelerated ageing of the Chinese, frailty has become a major public health priority worldwide. A meta-analysis of 81,258 community residents aged ≥ 65 years from China found that the overall prevalence of frailty was 10% [8]. However, frailty is not limited to older adults, as a prospective cohort study of over 500,000 people with chronic diseases in China found that the frailty prevalence in adults aged 50–64 years was 3.4% [9].

As a comprehensive indicator of physiology, psychology, and function, frailty is associated with a range of health outcomes, including mortality, cardiovascular disease, diabetes, falls, fractures, and disability [10–15]. Stress and stimulation caused by cancer diagnosis and treatment deplete physiological reserves, which may further lead to frailty [16]. Frailty may also lead to chemotherapy intolerance, postoperative complications, disease progression and increased mortality risk in patients with cancer [17]. This association may be related to the multiple mechanisms by which frailty affects cancer progression, with chronic low-grade inflammation, muscle wasting, and metabolic disorders playing key roles. Individuals with frailty are typically in a state of chronic low-grade inflammation accompanied by elevated pro-inflammatory factors. Inflammation promotes cell proliferation, inhibits cell death, and assists in tumor angiogenesis and metastasis [18]. This weakness is also often accompanied by muscle wasting (muscle atrophy) and metabolic disorders. Changes in metabolism and protein degradation may promote cancer development by regulating cytokines [19]. Oxidative stress levels are typically higher in frail individuals than in healthy individuals. Increased oxidative stress not only accelerates ageing but may also promote mutations and proliferation of cancer cells by altering DNA repair mechanisms [20]. These biological mechanisms suggest a possible association between frailty and cancer, and this association has received increasing attention in recent years.

However, previous studies have mainly focused on the risks and consequences of frailty in patients with cancer. Few studies have investigated whether frailty in community residents increases the risk of cancer. In the existing literature, the use of the Fried phenotype or frailty index to assess frailty, has not reached a consistent conclusion regarding the association between frailty and cancer diagnosis or incidence. Moreover, few studies have focused on high-income countries [21–23], which may not accurately reflect the relationship between frailty and cancer under different socioeconomic backgrounds, health statuses, or lifestyles, leading to limited generalizability of the findings. In addition, most previous studies on the relationship between frailty and cancer did not consider frailty as a continuum [24]. These studies only considered frailty status at a single point in time as an exposure factor and rarely considered the change in frailty levels, ignoring its variability or reversibility [25, 26]. However, the process of frailty changes, especially its exacerbation or alleviation, may have different impacts on cancer incidence. However, current research rarely focuses on this aspect, thus failing to comprehensively evaluate the potential complex relationship between frailty and cancer. Therefore, a long-term assessment of changes in frailty levels is essential to reveal the association between changing frailty trajectories and cancer incidence. Based on this, we assessed the association between frailty, its trajectory, and subsequent cancer incidence risk in middle-aged and older adults from the China Health and Retirement Longitudinal Study (CHARLS) cohort using longitudinal analysis.

## Methods

### Study population

The data for this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS). This project is a longitudinal survey of Chinese individuals aged ≥ 45 years that includes information on demographic characteristics, lifestyle, and health status. A baseline survey for this study was conducted from June 2011 to March 2012. A multi-stage random sampling method was used to investigate middle-aged and older adults aged ≥ 45 years in 28 provinces of China. A total of 17,708 respondents were involved and the survey was conducted every two years. All the participants were interviewed face-to-face and underwent physical examinations conducted by trained investigators. In this study, health status was updated through multiple rounds of surveys (e.g. 2013, 2015, and 2018) during the follow-up period, and the most recent data are currently being followed up until 2020. The description of CHARLS and its survey questionnaire has been published elsewhere [27]. All participants in CHARLS provided written informed consent, and the CHARLS project was approved by the Biomedical Ethics Committee of Peking University (IRB00001052-11015).

In this study, we excluded individuals with baseline aged < 45 years, missing age information, loss to follow-up, missing items constituting > 10% of the frailty index, with a history of cancer before 2011. A total of 14,566 participants were included in this study to investigate the association between baseline frailty and cancer risk. We then included eligible participants with < 10% missing items constituting the frailty index during the first four survey periods (2011, 2013, 2015, and 2018) and excluded those diagnosed with cancer between 2011 and 2018. Finally, a total of 9173 participants were used for the analysis of the association between frailty trajectory and cancer risk. The details of the inclusion process are shown in Figs. 1.1and 1.2.

### Measurement of frailty index

Based on the variable selection criteria of the frailty index, this study referred to the variables included in previous studies and health measures available in CHARLS. We selected 45 health variables, including activities of daily living (6 items), instrumental activities of daily living (5 items), physical function limitations (9 items), sensory function (5 items), mental health indicators (5 items), chronic diseases (14 items), and subjective function (self-rated health, 1 item). Each health-related variable was coded on a 0.00 (no deficit) to 1.00 (present deficit) scale, as shown in Table S1. Because this study aimed to examine the association between frailty and cancer risk, the outcome variable "cancer" was not included in the frailty index. Finally, the frailty index included 44 health-related variables. Participants with 10% or less missing data for variables were retained. Because the proportion of missing data for all items was < 10%, the effectiveness and stability of median imputation were found to be not inferior to complex missing data imputation methods [28]. Therefore, the medians of the corresponding items were used to fill in the missing data to maximize the sample size in this study.

The scores of the 44 health variables were summed and divided by the theoretical maximum score of 44, resulting in a score representing the frailty index for each participant, ranging from 0 to1. Referring to previous studies, a frailty index of ≤ 0.10 was considered non-frailty, that of > 0.10 but < 0.25 was considered pre-frail, and that of ≥ 0.25 was considered frail [29].

### Determination of cancer

The participants were asked whether they had ever been told by a doctor that they had cancer or a malignant tumor (excluding non-melanoma skin cancer). Participants who answered 'yes' were considered cancer survivors. To further understand the type of cancer, the participants were asked which organ or part of the body they currently have or previously had cancer in. Both primary and metastatic tumors were included.

### Assessment of covariates

Information regarding sociodemographic characteristics, health-related behaviors, and history of chronic diseases was collected at baseline using a semi-structured questionnaire. Sociodemographic characteristics included age, sex, type of residence (urban, rural), educational level (illiterate, primary school or below, secondary to vocational school, university or above), and marital status (married, divorced, unmarried). Health-related behaviors included smoking status (yes, no), alcohol consumption, and sleep duration. In this study, smoking was defined as smoking > 100 cigarettes in one's lifetime. Participants who had smoked in the past but had quit were classified as former smokers, whereas those who reported current smoking were classified as current smokers. In our analysis, both former and current smokers were considered smokers. Drinking status included: (1) drinking, more than once a month; (2) drinking, but less than once a month; (3) drinking nothing at all. Chronic disease history included hypertension, dyslipidemia (elevated low-density lipoprotein, triglycerides or total cholesterol, or low high-density lipoprotein), diabetes or hyperglycemia, chronic lung disease (chronic bronchitis or emphysema), liver disease (except fatty liver and tumors), heart problems (heart attack, coronary heart disease, angina, and congestive heart failure), stroke, kidney disease (except tumors), stomach or other digestive system disease (except tumors), mental illness, memory disorders,

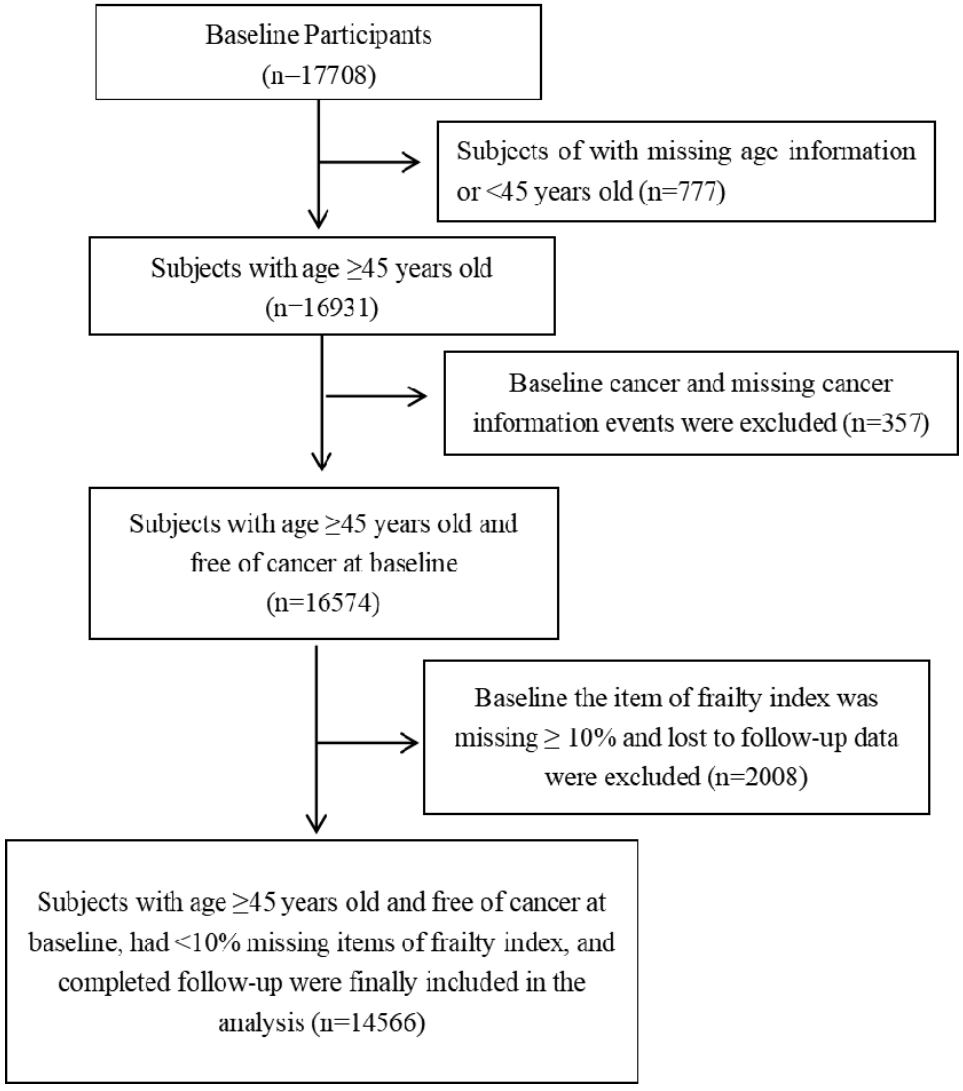


**Fig. 1.1** Flow chart of inclusion and exclusion of the cohort population for the association between baseline frailty and follow-up cancer

arthritis, and asthma.Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared, obtained from general health examinations. Based on their BMI, participants were categorized as underweight (< 18.5 kg/m$^2$), normal (18.5–23.9 kg/m$^2$), overweight (24–27.9 kg/m$^2$), and obese(≥ 28 kg/m$^2$) [30].

### Statistical analysis

Continuous variables with a normal distribution were expressed as mean ± standard deviation and compared between groups using a t-test or analysis of variance. Categorical variables were expressed as frequencies and proportions and compared between groups using the $\chi^2$ test. The Cox proportional hazards model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) to assess the association between each variable and cancer risk. Person-years were calculated from the baseline until the date of incident cancer, death, loss to follow-up, or last wave in 2020, whichever occurred first. Schoenfeld residuals were used to check the proportional hazards assumption, with all variables meeting the assumption. The Cox proportional hazards model was used to assess differences in the effects of different factors on cancer incidence and to perform subgroup analyses. Three models were fitted for all participants: Model 1 only considered the association between the frailty index and cancer risk; Model 2 was adjusted for age, sex, and type of residence; and Model 3 was further adjusted for all risk factors and analyzed the relationship between baseline frailty and cancer at follow-up. Additionally, Group-based trajectory modeling (GBTM) was used to determine the trajectory of frailty and map changes in frailty during the follow-up period. GBTM is a statistical method used to analyze individual changes over time in

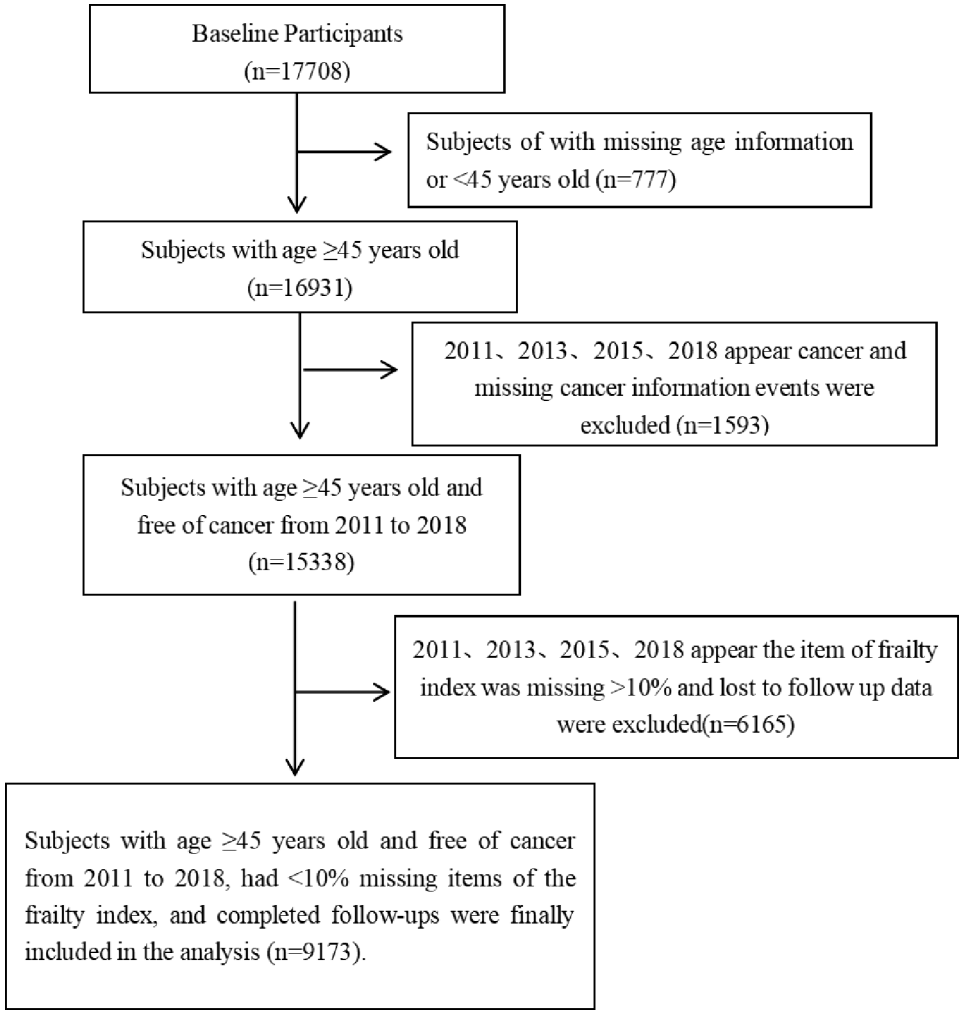


**Fig. 1.2** Flow chart of inclusion and exclusion of the cohort population for the association between frailty trajectory and follow-up cancer

longitudinal data. This method groups individuals based on their change trajectories and identifies groups with similar developmental trends within a specific period, thus revealing heterogeneity between different groups [31]. Using this methodology, a truncated normal distribution model was used to identify potential developmental trajectory patterns of frailty index scores during the first four waves of the survey (2011, 2013, 2015, and 2018). The frailty change trajectories of participants with at least four study visits were plotted based on their frailty index scores. To determine the optimal number of frailty change trajectories, several models were fitted, ranging from one to five trajectory groups. The model with the best fit was selected according to the following criteria: (1) the average posterior probability for each trajectory group was >0.70, (2) the sample size was >5.0%; (3) the 2-fold Bayesian Information Criterion (BIC) change was >6. Based on these criteria, three groups of trajectory models were selected to best fit the data. Based on the trajectory shapes and trends output by the GBTM, changes in the trajectories can be divided into three patterns: stable, increasing, and decreasing. However, according to the frailty index levels, changes in the trajectories can be divided into three levels: low, medium, and high. Using both methods, the frailty index trajectory groups in this study were named as the low-level stable group, medium-level increasing group, and the high-level increasing group. We calculated the HR and 95% CI based on three models: Model 1 considered only the association between frailty trajectory groups and cancer; Model 2 adjusted for age, sex, and type of residence; and Model 3 was further adjusted for other risk factors. All statistical analyses were performed using SPSS 28.0 and Stata 17.0 software. A $P$ value of $<0.05$ was considered statistically significant.

### Sensitivity analysis

Because being underweight may be a predictor of cancer [32] and to account for potential reverse causality, we re-examined the effect of frailty on the risk of cancer after

excluding underweight individuals and participants who developed cancer during the first year of follow-up.

## Results

### Characteristics of the study population

A flowchart of participant inclusion at baseline and follow-up is shown in Figs. 1.1 and 1.2. A total of 14,566 participants were included in this study. The mean age of the study population was 59.14 ± 9.52 years, and 6912 (47.45%) were male individuals. The sample characteristics classified according to frailty variable categories are shown in Table 1. Based on the grading criteria for frailty, 49.60%, 42.04%, and 8.36% of the participants were classified as non-frailty, pre-frailty, and frailty, respectively. Compared with pre-frail and frail participants, non-frail participants were more likely to live in rural areas, be married, be younger, have a lower cancer incidence, have higher education levels, have longer sleep duration, be non-smokers and non-drinkers, and be of normal weight.

### Associations between baseline frailty and incident cancer

During a mean follow-up of 8.05 years, 248 incident cancer events occurred, with an incidence rate of 0.21%. Using non-frailty as the reference, the associations of pre-frailty and frailty with cancer risk remained significant in the full model after adjustment for all covariates, with HR (95% CI) of 1.34 (1.03–1.75) and 1.66 (1.07–2.56), respectively. The association between the frailty index and cancer risk showed that for every 0.1 increase in the frailty index, the overall risk of cancer development was 1.22 (1.07–1.39).

Results stratified by age showed that the association between the frailty index and cancer was statistically significant only among participants aged < 60 years, with HR (95% CI) of 1.25 (1.01–1.55). However, among participants aged ≥ 60 years, the associations between pre-frailty, frailty, and frailty index, and risk of cancer incidence were not statistically significant, with HR (95% CI) of 1.09 (0.73–1.61), 1.25 (0.69–2.26), and 1.14 (0.95–1.37), respectively. Results stratified by sex showed that among women, the associations between pre-frailty, frailty index, and cancer were statistically significant, with HR (95% CI) of 1.51 (1.03–2.21) and 1.26 (1.05–1.50), respectively. In contrast, among men the associations between pre-frailty, frailty, and frailty index and risk of cancer incidence were not statistically significant, with HR (95% CI) of 1.04 (0.70–1.55), 1.33 (0.64–2.74), and 1.09 (0.87–1.37), respectively, as shown in Table 2.

**Table 1** Baseline characteristics of study participants

| Characteristic | Total (14,566) | Frailty stage | | | |
|---|---|---|---|---|---|
| | | Non-frailty (7225) | Pre-frailty (6144) | Frailty (1197) | *P* value |
| Age, years, mean (SD) | 59.14 (9.52) | 56.82 (8.64) | 60.59 (9.46) | 65.70 (10.28) | < 0.001 |
| Male, n (%) | 6912 (47.45) | 3887 (53.80) | 2587 (42.11) | 438 (36.59) | < 0.001 |
| Rural village, n (%) | 11,367 (78.04) | 5384 (74.52) | 4951 (80.58) | 1032 (86.22) | < 0.001 |
| Education level, n (%) | | | | | < 0.001 |
| Illiteracy | 3980 (27.32) | 1466 (20.29) | 1951 (31.75) | 563 (47.03) | |
| Elementary school or blow | 5795 (39.78) | 2695 (37.30) | 2644 (43.03) | 456 (38.10) | |
| Middle to vocational school | 4448 (30.54) | 2826 (39.11) | 1453 (23.65) | 169 (14.12) | |
| College or above | 343 (2.36) | 238 (3.29) | 96 (1.56) | 9 (0.75) | |
| Marital status, n (%) | | | | | < 0.001 |
| Married | 12,770 (87.67) | 6603 (91.40) | 5246 (85.38) | 921 (76.94) | |
| Divorced | 1670 (11.47) | 574 (7.94) | 835 (13.59) | 261 (21.80) | |
| Unmarried | 126 (0.86) | 48 (0.66) | 63 (1.03) | 15 (1.25) | |
| Smoking status, Yes, n (%) | 4452 (30.56) | 2499 (34.58) | 1695 (27.59) | 258 (21.55) | < 0.001 |
| Drinking status, n (%) | | | | | < 0.001 |
| Drinking, more than once a month | 3683 (25.28) | 2157 (29.86) | 1352 (22.00) | 174 (14.54) | |
| Drinking, but less than once a month | 1126 (7.74) | 626 (8.66) | 449 (7.31) | 51 (4.26) | |
| Drinking nothing | 9757 (66.98) | 4442 (61.48) | 4343 (70.69) | 972 (81.20) | |
| Sleep time, mean (SD) | 6.94 (2.19) | 7.31 (1.90) | 6.69 (2.28) | 6.09 (2.78) | < 0.001 |
| BMI Group, n (%) | | | | | |
| Underweight | 825 (5.66) | 311 (4.30) | 425 (6.92) | 89 (7.44) | < 0.001 |
| Normal | 8716 (59.84) | 4522 (62.59) | 3494 (57.03) | 700 (57.64) | |
| Overweight | 3600 (24.72) | 1802 (24.94) | 1522 (24.90) | 276 (22.40) | |
| Obesity | 1425 (9.78) | 590 (8.17) | 685 (11.15) | 153 (12.53) | |
| Cancer, n (%) | 248 (1.70) | 107 (1.48) | 116 (1.89) | 25 (2.09) | < 0.05 |

Abbreviations: BMI Body mass index

**Table 2** Association between baseline frailty and risk of cancer

| Group | Number of cases | Person-years | Model 1 h (95% CI) | Model 2 h (95% CI) | Model 3 h (95% CI) |
|---|---|---|---|---|---|
| Non-frailty | 107 | 477 | 1.00 | 1.00 | 1.00 |
| Pre-frailty | 116 | 482 | 1.31 (1.01,1.71) | 1.34 (1.03,1.75) | 1.34 (1.03,1.75) |
| Frailty | 25 | 100 | 1.59 (1.03,2.46) | 1.66 (1.07,2.56) | 1.66 (1.07,2.56) |
| Increase in frailty index per 0.1 | | | 1.21 (1.06,1.37) | 1.22 (1.07,1.39) | 1.22 (1.07,1.39) |
| **Grouped by age** | | | | | |
| **< 60 years old** | | | | | |
| Non-frailty | 62 | 174 | 1.00 | 1.00 | 1.00 |
| Pre-frailty | 57 | 262 | 1.48 (1.03,2.12) | 1.46 (1.01,2.10) | 1.42 (0.98,2.06) |
| Frailty | 9 | 68 | 2.01 (1.00,4.04) | 1.98 (0.98,4.01) | 1.92 (0.94,3.93) |
| Increase in frailty index per 0.1 | | | 1.28 (1.05,1.56) | 1.27 (1.03,1.55) | 1.25 (1.01,1.55) |
| **≥ 60 years old** | | | | | |
| Non-frailty | 45 | 304 | 1.00 | 1.00 | 1.00 |
| Pre-frailty | 59 | 220 | 1.05 (0.71,1.55) | 1.11 (0.75,1.65) | 1.09 (0.73,1.612) |
| Frailty | 16 | 32 | 1.18 (0.67,2.09) | 1.32 (0.74,2.35) | 1.25 (0.69,2.257) |
| Increase in frailty index per 0.1 | | | 1.11 (0.93,1.33) | 1.12 (0.97,1.39) | 1.14 (0.95,1.374) |
| **Grouped by sex** | | | | | |
| **Male** | | | | | |
| Non-frailty | 61 | 241 | 1.00 | 1.00 | 1.00 |
| Pre-frailty | 44 | 193 | 1.13 (0.76,1.66) | 1.06 (0.71,1.57) | 1.04 (0.70,1.55) |
| Frailty | 9 | 35 | 1.52 (0.76,3.07) | 1.36 (0.67,2.77) | 1.33 (0.64,2.74) |
| Increase in frailty index per 0.1 | | | 1.15 (0.93,1.42) | 1.10 (0.88,1.37) | 1.09 (0.87,1.37) |
| **Female** | | | | | |
| Non-frailty | 46 | 237 | 1.00 | 1.00 | 1.00 |
| Pre-frailty | 72 | 289 | 1.51 (1.04,2.19) | 1.56 (1.07,2.27) | 1.51 (1.03,2.21) |
| Frailty | 16 | 65 | 1.71 (0.97,3.025) | 1.83 (1.02,3.28) | 1.70 (0.93,3.10) |
| Increase in frailty index per 0.1 | | | 1.25 (1.06,1.47) | 1.28 (1.08,1.52) | 1.26 (1.05,1.50) |

Model 1 only considered the association between frailty index and cancer risk; Model 2 adjusted for age, sex, and type of residence; Model 3 further adjusted for all risk factors

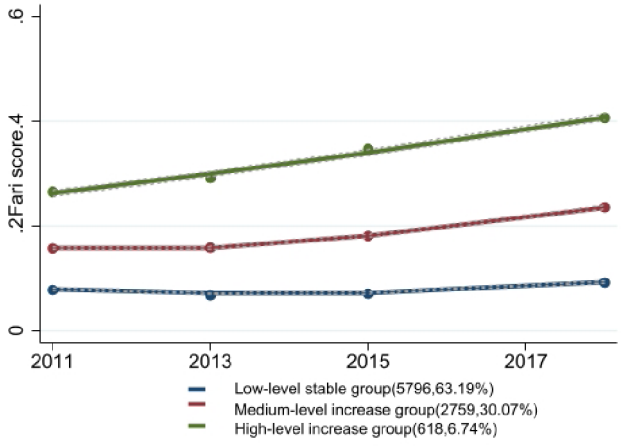


**Fig. 2** Grouping diagram of frailty development trajectory

### Associations between frailty trajectories and incident cancer

Based on repeated measures of frailty index data from 2011 to 2018, three frailty trajectories were identified among the 9173 participants, as shown in Fig. 2. Each trajectory was named the low-level stable group ($n = 5796$, 63.19%) according to level of frailty level and change pattern over time (stable or increased). It remained at approximately 0.075 throughout the follow-up period. The medium-level increase group ($n = 2759$, 30.07%) was characterized by a slow increase in frailty index from 0.16 at the beginning to 0.18 at the fourth year of follow-up and 0.24 at the seventh year of follow-up. The high-level increase group ($n = 618$, 6.74%) was characterized by a high frailty level at the beginning and gradually increased during the follow-up period, with a frailty index rising from 0.27 at the beginning to 0.35 at the fourth year and 0.41 at the seventh year of follow-up. Table 3 showed the GBTM model-fitting process.

During a median follow-up of 1.89 years, 31 cancer events were identified among the 9173 participants who attended all four follow-ups, with an incidence rate of 0.18%. The characteristics of the participants grouped according to the frailty trajectory are presented in Table S2. Using the low-level stable trajectory group as a reference, and after adjusting for all potential confounding factors, statistically significant associations were observed between different frailty trajectories and cancer incidence risk. The high-level increase trajectory group had the highest risk of cancer incidence, with HR (95% CI) of 5.43 (1.07–5.73), followed by the medium-level increase group, with an associated HR (95% CI) of 2.86

**Table 3** GBTM model-fitting process

| Group | Sub-group order | 2△BIC | Percentage of population by group | average posterior probability | Proportion of individuals with mean posterior probability > 0.7 |
|---|---|---|---|---|---|
| 1 | 3 | 6.92 | 100% | NA | NA |
| 2 | 2/2 | 11.10 | 76.80%/23.20% | 98.19%/94.84% | 97.89%/93.41% |
| 3 | 2/3/2 | 18.02 | 62.79%/30.36%/6.85% | 96.43%/92.33%/95.05% | 95.81%/90.11%/93.69% |
| 4 | 2/2/2/1 | 20.80 | 50.72%/30.83%/14.07%/3.37% | 94.44%/87.00%/91.29%/95.58% | 93.99%/84.62%/88.37%/95.16% |
| 5 | 1/2/1/2/1 | 23.58 | 15.07%/32.32%/47.83%/4.27%/0.52% | 89.69%/88.56%/93.45%/94.31%/97.60% | 86.41%/85.35%/92.66%/93.18 %/97.83% |

**Table 4** Association between the frailty developmental trajectory and the risk of cancer

| Variable | Number of cases | Person-years | Model 1 h (95% CI) | *P* value | Model 2 h (95% CI) | *P* value | Model 3 h (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|---|
| Low-level stable group | 12 | 11.50 | 1.00 | | 1.00 | | 1.00 | |
| Medium-level increase group | 14 | 21.0 | 2.49 (1.15,5.38) | 0.200 | 2.65 (1.20,5.87) | 0.016 | 2.86 (1.27,6.43) | 0.011 |
| High-level increase group | 5 | 6.50 | 4.11 (1.45,11.68) | 0.008 | 4.63 (1.56,13.74) | 0.060 | 5.43 (1.07,5.73) | 0.003 |
| **Grouped by age** | | | | | | | | |
| **< 60 years old** | | | | | | | | |
| Low-level stable group | 7 | 8.00 | 1.00 | | 1.00 | | 1.00 | |
| Medium-level increase group | 9 | 14.00 | 2.98 (1.11,8.01) | 0.030 | 3.09 (1.13,8.44) | 0.027 | 3.59 (1.29,10.03) | 0.015 |
| High-level increase group | 2 | 4.00 | 3.47 (0.72,16.79) | 0.120 | 3.89 (0.79,19.09) | 0.094 | 5.23 (1.02,26.73) | 0.047 |
| **≥ 60 years old** | | | | | | | | |
| Low-level stable group | 5 | 3.50 | 1.00 | | 1.00 | | 1.00 | |
| Medium-level increase group | 5 | 7.00 | 1.88 (0.54,6.49) | 0.319 | 2.02 (0.58,7.08) | 0.273 | 2.05 (0.57,7.36) | 0.271 |
| High-level increase group | 3 | 2.50 | 5.90 (1.41,24.70) | 0.015 | 6.64 (1.52,28.91) | 0.012 | 7.05 (1.57,31.66) | 0.011 |
| **Grouped by sex** | | | | | | | | |
| **Male** | | | | | | | | |
| Low-level stable group | 5 | 3.50 | 1.00 | | 1.00 | | 1.00 | |
| Medium-level increase group | 4 | 6.00 | 1.97 (0.53,7.34) | 0.312 | 2.05 (0.54,7.83) | 0.293 | 2.40 (0.62,9.36) | 0.207 |
| High-level increase group | 3 | 1.50 | 5.96 (1.42,24.96) | 0.015 | 5.88 (1.36,25.44) | 0.018 | 8.01 (1.80,35.65) | 0.006 |
| **Female** | | | | | | | | |
| Low-level stable group | 5 | 7.00 | 1.00 | | 1.00 | | 1.00 | |
| Medium-level increase group | 9 | 14.50 | 2.89 (0.97,8.62) | 0.057 | 3.30 (1.09,9.97) | 0.034 | 3.65 (1.18,11.28) | 0.025 |
| High-level increase group | 5 | 6.50 | 6.75 (1.95,23.30) | 0.003 | 8.64 (2.40,31.15) | 0.001 | 11.87 (3.11,45.33) | < 0.001 |

Model 1 only considered the association between frailty index and cancer risk; Model 2 adjusted for age, sex, and type of residence; Model 3 further adjusted for all risk factors

(1.27–6.43). However, when stratified by age and sex, the risk of cancer was found to be higher in participants with high levels of frailty in the ≥ 60 age group (HR: 7.05, 95% CI: 1.57–31.66 and in female participants (HR: 11.87, 95% CI: 3.11–45.33) (Table 4). Sensitivity analysis showed that the association between frailty trajectory and cancer remained consistent (Table S7).

## Discussion

This study explored the association between frailty level and cancer risk in middle-aged and older Chinese individuals from both static and dynamic perspectives. Results from the static single-node follow-up study showed that, compared with non-frail participants (frailty index ≤ 0.10), pre-frail (frailty index ≥ 0.1 and < 0.25) and frail (frailty index ≥ 0.25) participants at baseline were at a higher risk of developing cancer, which was independent of chronological age and common cancer risk factors. Many studies have shown that frailty is associated with cancer [33, 34]; however, previous studies have mainly focused on the impact of frailty on patients with cancer. Whether frailty can predict cancer risk in individuals without a history of cancer remains largely unexplored. Moreover, the studies that explore this topic are limited and have conflicting findings. A prospective study conducted in the United Kingdom that followed 340,000 participants without cancer at baseline found that frailty was associated with an increased risk of overall and site-specific cancer incidence [35]. Similarly, another large cohort study showed that frailty was significantly associated with an increased risk of cancer [36]. Conversely, a study by Klein involving 2515 participants aged 43–86 years in Beaver Dam, Wisconsin, found no clear association between frailty and self-reported cancer [37], which may be due to differences in the frailty classification criteria for different populations.

A study of older adults in the UK Biobank found no association between frailty and cancer incidence risk when stratified by age < 60 years and ≥ 60 years, which is similar to the findings of this study [23]. Subgroup analysis showed that the increased risk of cancer with every 0.1 increase in the frailty index was observed only in participants aged < 60 years and female participants. Similarly, a retrospective cohort study in Japan found that frailty often had a stronger predictive effect on adverse health outcomes in younger age groups and female individuals than in older age groups and male individuals [38]. Although no significant association was observed between frailty status and cancer incidence in the different subgroups in this study, some studies have suggested that frailty-related components in different subgroups may be associated with cancer risk. For example, a prospective cohort study using data from the UK Biobank found that lower grip strength was associated with an increased risk of cancer, and the observed association was consistent across sexes [39]. However, the exact mechanisms underlying the association between frailty and the risk of cancer remain poorly understood. Given that both frailty and cancer are closely related to ageing, several potential biological mechanisms may explain the bidirectional association between cancer and frailty, including chronic inflammation and immunosenescence [40, 41], increased inflammatory biomarkers, decreased mitochondrial function and shortened telomere length [42–44].

The occurrence and development of cancer are dynamic biological processes that are regulated by many factors. Therefore, a single baseline frailty measure may not accurately predict health outcomes. Thompson analyzed the relationship between frailty and mortality at baseline and follow-up and found that repeated measures of frailty at follow-up had better predictive power for 10-year mortality than baseline frailty, suggesting that regular assessment of frailty can improve predictive power [45]. Several studies have explored the association between frailty trajectory and conditions such as hypertension [46], diabetes [47], disability [48], cardiovascular events [49], and all-cause mortality [50], which further highlights the importance of considering frailty trajectory as a continuum over time. In this study, we found that compared with the group with consistently low-level frailty, the groups with medium- and high-level increase trajectories were associated with the risk of cancer. Additionally, the high-level increase group showed a faster increase in the frailty index than the medium-level increase group. This finding further highlights the importance of regularly assessing frailty and taking measures to delay frailty progression to reduce the risk of cancer and the burden of disease.

Frailty trajectory over time was found to be associated with cancer risk in all age groups over 45 years. Previous research has also suggested that the gradient of frailty trajectories varies among age groups [51]. This finding contributes to further discussion and analysis of integrating frailty into the management of cancer throughout the life stage, which may not only help to reduce the risk of cancer onset but also reduce the adverse events of cancer.

Interestingly, the higher risk was found among participants aged ≥ 60 years and female individuals. This observation is in line with the hypothesis of geriatrics that some interventions to slow down ageing can reduce the risk of various chronic diseases and extend healthy life expectancy [52]. Moreover, it is also consistent with the finding of the study by Stolz on the net effect of frailty trajectory in older adults on the European continent, which suggests that female individuals accumulate health deficits at a faster rate than male individuals [53].

It has been shown that frailty can reduce the tolerance of patients with cancer to treatment. Moreover, it can increase the risk of postoperative complications, disease progression and death [54], as well as readmission rates and healthcare costs, further increasing the economic burden caused by cancer [55]. Pre-frailty can be reversed to a healthy state if frailty is identified early and treated accordingly. Some frailty states can also be reversed to pre-frailty, leading to a reduction in the prevalence of disability, need for long-term care, and investment in healthcare resources [56]. Combined with the findings of this study, it is suggested that early screening and intervention measures for frailty should be developed specifically for individuals at high risk of developing cancer to prevent and control the occurrence and development of frailty.

The strengths of this study are as follows. First, it provides evidence from a representative Chinese population regarding the association between frailty and the risk of cancer development. Second, this study identified associations between frailty trajectory and cancer risk not only based on follow-up data but also after adjusting for potential confounders. Subgroup analyses were conducted to determine the effects of age and sex on the association between frailty and cancer risk. A series of sensitivity analyses were conducted to assess the robustness of the findings. However, this study has several limitations. First, the frailty index was based on self-reported results, which may introduce measurement errors. Similarly, the diagnosis of cancer was based on the self-report of a doctor's diagnosis, which can cause bias. However, the CHARLS data were collected by professionally trained investigators to reduce this bias. Second, although this study controlled for as many traditional cancer risk factors as possible, other potential confounders such as dietary habits and physical activity cannot

be completely excluded. Finally, during the COVID-19 pandemic, the study participants may have been lost to follow-up because of illness, isolation, or other reasons, which could impact the representativeness of the sample. Based on this, we used median imputation to fill in the missing data, assuming that the missing data followed a missing-at-random assumption. However, if the missing data are not random, this could potentially affect the conclusions of the study. Additionally, socioeconomic stress and mental health issues caused by the COVID-19 pandemic may have also influenced the relationship between frailty and cancer incidence. Therefore, future studies should further explore the long-term impact of the COVID-19 pandemic on frailty and cancer incidence risk.

## Conclusion

This study provides new evidence of the relationship between frailty and cancer incidence from both static and dynamic perspectives. Repeated measures indicated a strong association between high- and medium-level increases in the frailty index and the risk of developing cancer. Additionally, participants aged ≥ 60 years and women have a higher risk of developing cancer. Frailty status is a reversible risk factor; therefore, early screening and intervention measures for frailty in middle-aged and older adults will help reduce the burden of cancer, which has significant public health implications.

### Abbreviations

| | |
|---|---|
| BMI | Body Mass Index |
| CHARLS | China Health and Retirement Longitudinal Study |
| CI | Confidence Interval |
| GBTM | Group-Based Trajectory Modeling |
| HR | Hazard Ratio |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22959-y.

Supplementary Material 1

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### Author contributions

YL and JY conceived the study and designed the statistical analyses. QG and PL did the statistical analyses and prepared the draft of the manuscript. ZL, MM and NZ substantively revised the manuscript. YL and JY had primary responsibility for the final content.All authors contributed to the interpretation of data. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors read and approved the final manuscript.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

The methods used in this study involving human participants followed the ethical guidelines laid down in the 1964 Declaration of Helsinki and its subsequent revisions. Ethical approval for all waves of the CHARLS study was obtained from the Institutional Review Board (IRB) at Peking University. The IRB approval number is IRB00001052-11015. Written signed informed consent was obtained at recruitment from all participants, including legal representatives for illiterate participants

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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