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Longitudinal Association of Frailty Levels with Knee Osteoarthritis in middle-aged and elderly Chinese: A longitudinal cohort study

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Abstract

Introduction

Frailty and Knee osteoarthritis (KOA) are highly prevalent in middle-aged and elderly populations. However, evidence on the longitudinal association of frailty with KOA is limited. The aim of our study was to explore the longitudinal effects of frailty levels on KOA, combining phenotypic frailty and frailty index(FI), using Cox regression analysis in a prospective cohort.

Methods

The data for this study were sourced from the 2011 and 2018 waves of the China Health and Retirement Longitudinal Study (CHARLS). Participants were categorized into three groups based on their total FI concentration: high (≥3rd quartile), medium (between the 1st and 3rd quartiles), and low (≤1st quartile). A Cox proportional hazards model was used to assess the associations between frailty status, FI, and incident KOA. The predictive value of phenotypic frailty and FI for KOA was evaluated by calculating the area under the receiver operating characteristic curve (AUC). Restricted cubic spline (RCS) analysis was conducted to examine the dose–response relationship between FI and the

risk of incident KOA. Additionally, depressive symptoms were included as a mediator to explore their potential mediating effect on the association between frailty and KOA.

Results

After 7 years of follow-up, 14,079 participants were included in the analysis of incident KOA. Both phenotypic frailty and FI were significantly associated with increased risk of incident KOA. Compared with non-frail participants, frail individuals had an adjusted hazard ratio (HR) of 2.10 (95% CI: 1.78–2.48; $P < 0.05$) for KOA. For the FI, a clear dose-response relationship was observed, with HRs for Q2, Q3, and Q4 relative to Q1 being 1.74 (95% CI: 1.36–2.22), 2.62 (95% CI: 2.08–3.30), and 4.17 (95% CI: 3.33–5.22), respectively (P for trend < 0.001). The time-dependent ROC analysis indicated that both phenotypic frailty and FI provided strong predictive value for KOA (AUC for FI = 0.76 at 5 years). Using the causal mediation framework, the mediation effect of social isolation was not statistically significant ($p = 0.074$), suggesting that the association is primarily driven by direct biological pathways rather than social factors.

Conclusions

Frailty had adverse effects on KOA, with social isolation symptoms acting as the mediator.

Keywords: Frailty; FI; Osteoarthritis; The China Health and Retirement Longitudinal Study.

Introduction

China boasts the world's largest elderly population, with the nation aging rapidly. Projections indicate that between 2020 and 2050, the number of Chinese citizens aged 65 and above will more than double—from 172 million (12.0% of the total population) to 366 million (26.0%)(1). The rapid aging of the population has heightened the healthcare burden stemming from age-related illnesses(2). Knee osteoarthritis (KOA), the most prevalent form of arthritis among older adults, has emerged as a pressing public health concern amid population aging(3). KOA significantly impairs quality of life, with severe cases potentially requiring knee-joint replacement(4). The costs of managing KOA are typically high, imposing a heavy burden on families and society alike(5).

Frailty is widely regarded as one of the most critical public health issues. It is a complex clinical syndrome marked by weakness and diminished physiological reserves across multiple organs and systems, rendering individuals more vulnerable to stressors(6). It amplifies the risk of falls, disabilities, premature mortality, long-term care admissions, and hospitalizations among older adults—thereby intensifying the burden on global communities and healthcare systems(7).

Emerging evidence indicates that frailty may play a critical role in the development and progression of KOA through several biological mechanisms, including chronic low-grade inflammation, sarcopenia, and impaired mobility, which together increase vulnerability to KOA onset and adverse outcomes(8). However, most existing studies have been limited to Western populations and cross-sectional designs(9), leaving a significant gap in longitudinal data among Chinese middle-aged and elderly adults. Recent studies based on the CHARLS cohort have examined predictors of KOA, such as a 4-year risk prediction model(10) and the body roundness index(11). Although these studies contributed to understanding KOA risk, they focused on single factors and did not investigate frailty as a multidimensional construct or its relationship with KOA. In contrast, our study integrates both phenotypic frailty and the FI as longitudinal predictors and further extends the analysis by evaluating the mediating role of social isolation. While previous studies have largely focused on Western populations, emerging longitudinal evidence from East Asian cohorts suggests distinct patterns in the frailty-KOA relationship. For instance, recent studies in Korean and Japanese populations have highlighted the impact of frailty on clinical outcomes and incident osteoarthritis, potentially influenced by regional lifestyle factors and higher rates of rural residency. Integrating these findings is crucial for understanding the specific epidemiological features of KOA in

China.

Method

Study design and population

Data for this study were derived from the China Health and Retirement Longitudinal Study (CHARLS). CHARLS data collection commenced in 2011 (Wave 1), with subsequent waves conducted in 2013, 2015, and 2018 (Waves 2–4). Comprehensive details on its research design and implementation are available in prior publications(12). A multi-stage probability proportional to size (PPS) sampling method was employed. The sample comprised approximately 17,000 individuals from around 10,000 households across 450 villages, 150 districts, and 28 provinces(13). The CHARLS dataset was downloaded from its official website (http://charls.pku.edu.cn/en). The CHARLS survey was approved by the Biomedical Ethics Committee of Peking University, with all participants providing informed consent(14).

For this study, data from the 2011–2018 cohorts were utilized. A total of 17,708 individuals participated in the 2011 CHARLS baseline survey (Wave 1). Participants under 45 years of age and those with missing KOA data were excluded, leaving 16,353 individuals for the baseline cross-sectional analysis. An additional 639 participants were excluded due to missing age information or being under 45 years old, leaving 15,714

individuals for the final analysis. A total of 1,635 participants had KOA at baseline. Multiple imputations were performed to address missing data, and a complete-case analysis was conducted. Ultimately, 14,079 participants were included in the longitudinal analysis of the association between frailty and KOA (*Figure 1*).

Assessment of KOA

Each participant was asked the following question “Have you been diagnosed with arthritis/rheumatism by a doctor?”. In addition, they were asked “Are you often troubled with anybody pains?” If participants answered “yes” to this question, they were then shown a homunculus card and asked to list the site (s) of the body, including the knee joint, at which such pain occurred. According to previous studies(10), KOA was identified if participants reported both a physician diagnosed arthritis/rheumatism and knee pain.

For the longitudinal analysis, follow-up time was defined as the period from baseline (Wave 1, 2011) to the date of incident KOA diagnosis, loss to follow-up, death, or the end of follow-up (Wave 4, 2018), whichever came first. Median follow-up duration was approximately 7 years. This

approach allowed the estimation of hazard ratios for incident KOA using Cox proportional hazards regression, appropriately accounting for variable follow-up times across participants(15, 16).

Assessment of phenotypic frailty

This study defines phenotypic frailty as the accumulation of health deficits in individuals as they age(17), assessed using the FI. The FI is calculated following a standardized procedure and covers key domains such as daily activities, chronic diseases, psychological well-being, and cognitive function. Although the number and type of FI indicators may vary across studies, these core health domains are consistently included, ensuring a comprehensive evaluation of frailty status among participants. This study calculated FI using 32 factors, including physical function, disabilities, depression, and cognition(18). Each item was coded as a health deficit, and the FI was derived by dividing the number of deficits present by the total number of possible deficits, yielding a score ranging from 0 to 1, with higher values indicating greater frailty (*Supplement Table 1*). The FI was calculated for each participant as the proportion of deficits present out of the total number of considered deficits, yielding a score between 0 and 1, with higher scores indicating greater frailty. This 32-item FI has been validated in the CHARLS database and other cohorts,

confirming its reliability and construct validity in Chinese middle-aged and older adults(19) The selection of these deficits followed the standard procedure of the 'accumulation of deficits' model, which has been rigorously validated in the CHARLS cohort to ensure construct validity representative of the Chinese middle-aged and elderly population.

Walking speed

Walking speed is widely recognized as a reliable indicator of overall gait quality and motor function(20). All participants aged 60 years or older were eligible for the assessment. Individuals unable to walk due to health conditions (e.g., OA) were excluded from the walking speed test. Walking speed was evaluated over a straight 2.5-meter flat course. Each participant walked the course twice (round trip) at their usual pace, with a stopwatch used to measure duration. The median time from the two trials (in seconds) was used to calculate walking speed.

Balance test

Balance tests reliably and validly assess static balance, postural control, and vestibular function(21). Participants were required to stand unassisted for one minute, performing side-by-side, semi-tandem, and full

tandem stands(22). All participants first completed a 10-second semi-tandem stand; the examiner stopped the timer at 10 seconds or if the participant moved or grasped the examiner's arm. Those who maintained the semi-tandem position for 10 seconds proceeded to the full tandem stand, with the timer stopped after 30 seconds (for participants aged ≥70 years) or 60 seconds (for those <70 years), or if the participant stepped out of position or grasped the examiner's arm. Participants unable to hold the semi-tandem stand for 10 seconds performed the side-by-side stand, with the timer stopped at 10 seconds or upon movement/grasping. Participants were categorized into two groups: those who completed the full tandem test, and those who did not (including those who only finished the semi-tandem or side-by-side stands).

Muscle strength

Normalized grip strength was measured using a dynamometer (Yuejian™ WL-1000). Participants stood with arms at their sides and squeezed the handle as tightly as possible. A maximum of two trials were conducted for each hand(23).

Chair-raising test

In the chair-stand time test, participants were instructed to fully sit on the chair between each of five consecutive stands, without using their arms for support(24). In this experiment, the chair used had a seat height of 47 cm from the floor. Participants sat with arms folded across their chests; following a short preparation period, they stood and sat repeatedly five times as quickly as possible, without pausing or using their arms for support.

Covariates

Based on social and regional features, data on age, gender (male and female), body mass index (BMI), educational level (college or above, high school, primary school or below), and marital status (married or single) were collected. Smoking status (non-smoker, ex-smoker, and current smoker), drinking status (less than once a month, more than once a month, none of these), regular physical activity and location (city/town, village)(11) (*Supplement Table 2*).

Statistical analysis

Baseline characteristics were summarized as mean (standard deviation, SD) for continuous variables and n (percentage) for categorical variables.

Group differences were compared using chi-square tests, t-tests, nonparametric tests, and analysis of variance (ANOVA), as appropriate.

To address missing data, we first assessed the missingness mechanism using Little's MCAR test(25). The results indicated that data was not completely missing at random. Therefore, we implemented multiple imputations by chained equations (MICE) under a missing-at-random assumption, generating 20 imputed datasets(26). Imputation models included all covariates, exposure, and the outcome. Baseline characteristics were compared between the complete-case and imputed datasets to evaluate potential bias. Unless otherwise noted, all primary analyses were performed on the imputed datasets and combined using Rubin's rules. To address missing data, we employed multiple imputation by chained equations (MICE) to generate complete datasets. We assumed that data were missing at random (MAR). To validate the reliability of the imputation process, we compared the baseline characteristics between the original dataset (with missing values) and the imputed complete dataset. Standardized mean differences (SMD) were calculated to quantify the magnitude of differences between the two datasets, with an SMD < 0.1 indicating a negligible difference.

Time-to-event analyses used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of phenotypic frailty and the FI with incident KOA. The proportional hazards assumption was evaluated with Schoenfeld residuals. Two models were specified: Model 1 (unadjusted) and Model 2 adjusted for age, sex, BMI, smoking status, drinking status, race, education, location, marital status, and regular physical activity(10, 27). Where proportional hazards violations were detected for specific covariates, stratified Cox regression was applied using those covariates as stratification factors.

RCS models were applied to flexibly model the dose–response relationship between FI and the risk of incident KOA, following Harrell's recommendations(28). To ensure sufficient flexibility in capturing non-linear patterns, four knots were placed at the 5th, 35th, 65th, and 95th percentiles of the FI distribution. Predicted HRs were evaluated across the full observed FI range (0 to 1) using equally spaced points. Model fit was compared across alternative knot placements using the Akaike Information Criterion (AIC), and the four-knot specification demonstrated optimal performance. All RCS models were adjusted for the same covariates as Model 2.

Subgroup analyses examined potential effect modification by age (<60 or ≥60 years), sex (male or female), BMI categories, education (college or above, high school, or primary school and below), marital status (married or single), smoking status (non-smoker, ex-smoker, or current smoker), drinking status (less than once a month, more than once a month, or none), regular physical activity (yes or no), and location (city/town or village). Interaction terms were included to formally test for heterogeneity across subgroups.

Predictive performance was assessed using time-dependent receiver operating characteristic (ROC) analysis with inverse-probability-of-censoring weighting to estimate the area under the curve (AUC) at 2, 4, and 7 years. Models for ROC/AUC were adjusted for age, sex, BMI, smoking status, drinking status, race, education, location, marital status, and regular physical activity.

To investigate social isolation as a potential mediator in the association between frailty and incident KOA, we assessed social isolation using a

composite index (range 0–4) based on four components: being unmarried, living alone, infrequent contact with children (<weekly), and lack of social participation in the past month. Participants with a total score of ≥2 were classified as socially isolated(29). We then employed the causal mediation analysis framework to decompose the total effect into the Natural Direct Effect (NDE) and the Natural Indirect Effect (NIE). This approach allows for the estimation of causal pathways while robustly accounting for potential mediator-outcome confounders.

For sensitivity analyses, participants who developed KOA within the first two years of follow-up were excluded to reduce potential reverse causation, and associations were re-estimated using Cox models in this restricted sample.

All analyses were conducted in R (version 4.4.2), and two-sided p-values <0.05 were considered statistically significant.

Results

Study population and characteristics

A total of 14,079 participants were included (mean age 58.63 ± 9.51

years; 49.9% males). To assess potential attrition bias, we compared the baseline characteristics of included participants with those excluded due to missing data. The excluded group was significantly older, had a higher frailty index, and lower educational attainment (*Supplementary Table 3*). Given these differences, multiple imputation was employed to minimize selection bias. Sensitivity analysis showed that the baseline characteristics of the imputed dataset were highly consistent with the original dataset (*Supplementary Table 4*). Among the included population, 1,479 (10.5%) were classified as frail according to both phenotypic frailty and the FI. Compared with non-frail participants, frail individuals were significantly older (65.46 ± 10.18 vs. 57.81 ± 9.09 years), more likely to be female (59.0% vs. 48.8%), married (24.0% vs. 10.5%), and living in rural areas (81.5% vs. 77.3%). They also had lower educational attainment (83.7% with primary school or below), lower BMI (23.33 ± 4.15 vs. 23.55 ± 3.81 kg/m²), and were more frequently physically inactive (70.2% vs. 64.3%). In addition, frail participants had higher rates of current smoking (66.4% vs. 59.8%) and alcohol abstinence (81.8% vs. 68.2%). The mean FI was substantially higher in the frail group than in the non-frail group (0.36 ± 0.10 vs. 0.09 ± 0.06) (*Table 1*).

Association of phenotypic frailty and the FI with KOA at baseline

Cox proportional hazards models (*Table 2*), both phenotypic frailty and the FI were significantly associated with an increased risk of incident KOA. Compared with non-frail participants, frail individuals had a higher risk of developing KOA (HR, 2.10 [95% CI, 1.78–2.48]; unadjusted HR, 2.44 [95% CI, 2.08–2.86]). For the FI, a clear dose–response pattern was observed across quartiles. Relative to Q1, the adjusted HRs were HR, 1.74 [95% CI, 1.36–2.22] for Q2, HR, 2.62 [95% CI, 2.08–3.30] for Q3, and HR, 4.17 [95% CI, 3.33–5.22] for Q4, with a highly significant trend (p for trend < 0.05).

The proportional hazards assumption was assessed using Schoenfeld residuals (*Supplementary Figure 1*). The global test suggested violation (p = 0.019), mainly attributable to age (p = 0.009), marital status (p = 0.002), and location (p = 0.029). Other covariates, including sex, BMI, smoking, drinking, education, and regular physical activity, did not show evidence of violation. To address this, stratified Cox regression was performed using age, marital status, and location as stratification factors (*Supplementary Table 5*). The stratified estimates were consistent with the main analysis. Phenotypic frailty (yes vs. no) was associated with HR, 2.10 [95% CI, 1.78–2.48], and the FI (Q4 vs. Q1) with HR, 4.16 [95% CI, 3.32–5.21]. Model fit was comparable (AIC = 14,544.53 and 14,406.28,

respectively), supporting the robustness of the associations.

Dose–response and threshold effects of FI on KOA

RCS analysis demonstrated a statistically significant overall association between the FI and the risk of incident KOA (P-overall ≤ 0.05), with strong evidence of non-linearity (P-non-linear ≤ 0.05). Using the median FI value of 0.32 as the reference point (HR = 1), the hazard of KOA increased gradually at lower FI levels and then plateaued beyond approximately 0.32, indicating a rise-then-plateau dose–response pattern (*Figure 2*).

Subgroup analysis

Subgroup analyses were conducted to examine the associations of phenotypic frailty and FI with incident KOA (*Figure 3 and Supplementary Table 6*). For phenotypic frailty, the associations were consistent across most subgroups. Stronger associations were observed among participants aged <60 years (HR, 2.50 [95% CI, 1.94–3.21]), males (HR, 2.76 [95% CI, 2.08–3.66]), current smokers (HR, 2.99 [95% CI, 2.08–4.30]) and married (HR, 2.29 [95% CI, 1.91–2.74]). Significant interaction effects were detected for age, sex, smoking status, and marital status (all p for

interaction <0.05).

For the FI, a dose–response pattern was observed across quartiles in nearly all subgroups. In participants aged <60 years, the adjusted HRs were 1.69 (95% CI, 1.27–2.25) for Q2, 2.58 (95% CI, 1.97–3.39) for Q3, and 3.87 (95% CI, 2.95–5.08) for Q4, compared with Q1. In males, the corresponding HRs were 1.83 (95% CI, 1.26–2.66) for Q2, 2.27 (95% CI, 1.56–3.29) for Q3, and 4.44 (95% CI, 3.12–6.34) for Q4. In several subgroups such as participants with obesity (BMI ≥30 kg/m²), ex-smokers, and those with higher education levels, the confidence intervals were wider due to smaller sample sizes, but the overall trend was consistent. No significant interaction effects were observed for BMI, location, education, drinking status, marital status, or regular physical activity (all p for interaction >0.05).

Time-dependent roc curves for phenotypic frailty and frailty index in predicting incident KOA

Using time-dependent ROC analysis, we compared the predictive accuracy of phenotypic frailty and the FI for incident KOA over 2 to 7 years. Phenotypic frailty exhibited stable but moderate performance, with

AUC values ranging from 0.66 to 0.69. In contrast, the FI consistently showed stronger predictive ability (AUC range: 0.71–0.76) (Supplementary Figure 2). Notably, the highest predictive value for FI was observed at 5 and 6 years (AUC = 0.76, 95% CI: 0.74–0.77), significantly outperforming phenotypic frailty at the same time points (AUC = 0.69, 95% CI: 0.67–0.71) (*Supplementary Figure 2*).

To further evaluate the incremental predictive value of the FI, we compared a Full Model (incorporating the FI) against a Base Model comprising only conventional risk factors (including age, sex, BMI, and lifestyle factors). The inclusion of the FI significantly improved the model's discriminative ability across all time points. Specifically, at the 5-year follow-up, the AUC increased substantially from 0.644 (95% CI: 0.622–0.665) in the Base Model to 0.756 (95% CI: 0.738–0.774) in the Full Model ($P < 0.001$), representing a net absolute improvement of 0.112. Similar significant improvements were observed at 2, 3, 4, 6, and 7 years (all $P < 0.001$), demonstrating that the FI provides substantial incremental value for KOA risk stratification beyond traditional risk factors (*Figure 4 and Supplementary Table 7*).

The mediation effect of social isolation on phenotypic frailty to

KOA

We further conducted a causal mediation analysis to determine whether social isolation mediated the association between phenotypic frailty and incident KOA. The analysis revealed a significant Total Effect of frailty on KOA (Estimate = 0.096, 95% CI: 0.080–0.114, P < 0.001). Decomposition of this effect showed that the NDE of frailty remained robust and statistically significant (Estimate = 0.095, 95% CI: 0.079–0.113, P < 0.001). In contrast, the NIE mediated through social isolation was minimal and not statistically significant (Estimate = 0.0008, 95% CI: -0.0001 to 0.0020, P = 0.074). The proportion of the effect mediated by social isolation was negligible (0.79%; 95% CI: -0.07% to 2.09%). These findings suggest that social isolation is not a major mediator of the relationship between phenotypic frailty and incident KOA in this cohort (*Figure 5 and Supplementary Table 8*).

Sensitivity analysis

To minimize potential reverse causality, we performed a sensitivity analysis excluding participants who developed KOA within the first two years of follow-up (*Supplementary Table 9*). In these analyses, both phenotypic frailty and the FI remained significantly associated with an increased risk of incident KOA. Compared with non-frail participants,

those classified as frail had a higher risk of KOA (HR, 2.09 [95% CI, 1.73–2.51]). For the FI, a clear dose–response relationship persisted, with adjusted HRs of 1.64 (95% CI, 1.27–2.11) for Q2, 2.27 (95% CI, 1.78–2.90) for Q3, and 3.59 (95% CI, 2.84–4.55) for Q4, compared with Q1 (all p for trend <0.05). These results indicate that the observed associations are unlikely to be explained by early cases of KOA.

Discussion

Based on a 7-year longitudinal cohort study, we investigated the association between frailty status (including phenotypic frailty and FI) and incident KOA in a Chinese middle-aged and elderly population. We found that FI showed a rise-then-plateau, non-linear dose-response relationship with the incidence of KOA. Additionally, social isolation played a mediating role in the association between frailty levels and KOA. A risk prediction model combining phenotypic frailty and FI with general indicators demonstrated strong predictive power for KOA outcomes in participants. Phenotypic frailty significantly increased the risk of incident KOA, with stronger associations observed in individuals under 60, males, current smokers, and married participants.

Our results support that compared to robust participants, frailty had a higher risk of developing KOA in middle-aged and elderly Chinese. A risk prediction model combining phenotypic frailty and FI with general indicators effectively predicted KOA outcomes. In the past few years. Frailty and CVD are of growing interest, with many studies concentrating on the effects of frailty on CVD(30, 31). The aging process involves metabolic changes, and KOA is also a metabolic disease(32). However, there are currently few studies on the relationship between KOA and

frailty. Alabadi et al. found a high frailty prevalence linked to OA in the US(9), as well as recent longitudinal evidence from East Asian cohorts, such as those in Japan and Korea(31, 33). These consistencies suggest a universal susceptibility across different populations. The underlying mechanisms linking frailty to KOA likely involve a complex interplay of chronic inflammation and metabolic dysregulation. Frail individuals typically exhibit increased oxidative stress (OS) and systemic inflammation(34). This environment triggers the production of pro-inflammatory cytokines, which not only promote muscle breakdown (sarcopenia) but are also associated with the onset of various lipid disorders(35). Beyond inflammation, metabolic pathways play a pivotal role in this relationship. Recent mechanistic studies indicate that the PPARα-ACOT12 axis is essential for maintaining cartilage homeostasis by modulating de novo lipogenesis(32). This suggests that frailty-related metabolic disturbances, specifically lipid metabolism disorders and adipokine imbalance, may directly accelerate cartilage degradation. Therefore, metabolic insufficiency, combined with chronic low-grade inflammation, provides a strong theoretical framework explaining why frail individuals are more prone to incident KOA.

Interestingly, our study identified a mediating effect of social isolation in

the association between frailty and KOA. Social isolation may indirectly aggravate the risk of chronic disease due to frailty by influencing lifestyle, dietary habits, and other pathways, supporting the idea of social isolation as a potential mediator in the development of chronic disease. Frailty increases the risk of death, hospitalization, falls, and admission to long-term care facilities(36). All these events can result in disability or functional dependence, triggering the onset of social isolation. At the same time, there was an association between social isolation and KOA-related metabolic and behavioral factors, creating favorable conditions for KOA(37). Related longitudinal studies indicated that patients with social isolation were more likely to have metabolic disorders, as evidenced by high triglyceride levels, low HDL levels, and high blood glucose levels(38). There may also be a bidirectional association between frailty and social isolation(39). Frailty may increase the risk of social isolation, and the presence of social isolation may aggravate frailty. This bidirectional relationship may create a vicious cycle that negatively impacts the quality of life and health status of older adults. We suggest that the assessment of glucose and lipid levels in depressed populations should be strengthened in clinical practice to monitor KOA at an early stage, to reduce their risk of morbidity and organ damage, and to improve the overall health of middle-aged and elderly people.

Our study fills a critical gap by characterizing the dose-response relationship between FI and incident KOA in the Chinese population. We observed a distinct non-linear, rise-then-plateau pattern. Initially, increasing frailty levels appear to exacerbate KOA susceptibility, likely driven by systemic inflammation and metabolic dysregulation(40). However, the risk plateaus beyond an FI of 0.32. This "saturation effect" suggests that 0.32 could serve as a clinical alert threshold; individuals exceeding this point are at maximal risk and should be prioritized for intensive multimodal interventions, such as physical therapy and nutritional support. This plateau at high frailty levels might reflect a "competing risk" or significantly reduced mobility in severely frail individuals, which paradoxically limits further mechanical wear on the knees. These findings offer a nuanced perspective compared to Western cohorts, where frailty is often described as a linear risk factor(41), potentially reflecting differences in lifestyle, physical activity patterns, or healthcare access between populations.

The finding that phenotypic frailty significantly increases incident KOA risk in individuals under 60, males, current smokers, and married individuals highlight critical demographic and lifestyle modifiers. First,

the stronger association in adults <60 years suggests that early-onset frailty may represent a phenotype of "accelerated aging," characterized by premature metabolic and inflammatory dysregulation that hastens joint degeneration(42). Clinically, this highlights the urgent need for targeted prevention in middle-aged populations showing early signs of deficit accumulation. Second, the heightened risk in males may be attributed to occupational patterns in the Chinese population. As a significant proportion of our sample resides in rural areas, men are more likely to engage in heavy physical labor, which compounds mechanical joint stress in the presence of frailty. This effect may be further amplified by biological factors, where lower testosterone levels contribute to susceptibility(43). Third, smoking has been linked to both increased inflammation and impaired cartilage repair mechanisms(44) ; the interaction between smoking and frailty likely compounds these deleterious effects. Fourth, for married individuals, social factors including potential caregiving burdens and physical inactivity may exacerbate frailty, leading to greater vulnerability(45). Finally, beyond identifying high-risk subgroups, our analysis demonstrated the incremental predictive value of the FI. Comparison with a base model (age, sex, BMI) revealed that incorporating the FI significantly improved predictive performance, confirming that frailty assessment provides critical prognostic information for clinical decision-making(46).

In summary, this study elucidates the complex relationship between frailty and incident KOA, highlighting a distinct dose-response pattern and the mediating role of social isolation. These findings expand our understanding of the interplay between mental health, metabolic dysregulation, and chronic disease development, providing evidence to support integrated geriatric interventions for preventing KOA in middle-aged and elderly populations. However, several limitations must be acknowledged. First, the diagnosis of KOA relied on self-reported physician diagnosis and knee pain rather than objective radiographic assessment (e.g., Kellgren-Lawrence grading). While this definition aligns with previous large-scale epidemiological studies, it is susceptible to recall bias and potential misclassification(27). To mitigate this, we performed sensitivity analyses excluding early-onset cases, which confirmed the robustness of our results. Second, despite adjusting for multiple covariates, residual confounding from unmeasured factors, such as specific dietary habits or medication use, cannot be ruled out. Third, applying the robust causal mediation framework revealed that the mediating effect of social isolation was not statistically significant (P = 0.074). This reinforces the hypothesis that the link between frailty and KOA is predominantly driven by direct physiological mechanisms, such as

chronic low-grade inflammation or sarcopenia, rather than behavioral pathways associated with social isolation. Future research should incorporate objective inflammatory markers (e.g., CRP, IL-6) and muscle mass assessments to explore these pathways further(41, 47) . Fourth, as the CHARLS cohort consists exclusively of Chinese adults, the generalizability of these findings to other ethnic groups remains limited. Finally, attrition bias is a concern in longitudinal studies. We compared the baseline characteristics of the retained participants versus those excluded due to missing data or loss to follow-up. The results indicated that the excluded participants were significantly older and had a higher frailty index compared to the included population. Since these high-risk individuals were more likely to be excluded, this differential attrition may have led to a conservative estimate (underestimation) of the true association between frailty and KOA, suggesting that our findings are robust.

Our study found a significant association between frailty and the risk of incident KOA, with social isolation serving as a minor mediator in this relationship. These findings suggest that interventions targeting frailty and social isolation in middle-aged and elderly populations could be effective in reducing the incidence of KOA. Given regional disparities in

rehabilitation resources, particularly in rural areas, public health strategies should prioritize frailty screening and KOA prevention programs in underserved communities. We recommend a comprehensive geriatric health policy that integrates both medical and psychological interventions, focusing on improving the overall well-being of middle-aged and elderly individuals, thus mitigating the risk of chronic diseases such as KOA.

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Abbreviations

CHARLS: China Health and Retirement Longitudinal Study

FI: Frailty index

KOA: Knee Osteoarthritis

BMI: Body mass index

OR: Odds ratio

CI: Confidence Interval

ROC: Receiver Operating Characteristic

AUC: Area Under the Curve

Author contributions

JL and GY set the overall goal, set up the outline of the manuscript, and performed data analysis. HZ, JL, and WL produced figures, completed the first draft of the article, and revised the paper. HZ and JL assisted in determining the direction of research, data description, and quality control of the paper. All authors provided feedback on the manuscript and reviewed the manuscript.

Data availability

Support the results of data could be available at "https://charls.pku.edu.cn".

Declarations

Ethics approval and consent to participate

CHARLS has received ethical approval from the Institutional Review Board (IRB) of Peking University. The IRB approval number for the primary participant survey (including anthropometric measurements) was

IRB00001052-11015 and the IRB approval number for Biomarker collection was IRB00001052-11014. All the participants had signed their written informed consent. The study methods were conducted in accordance with the approved guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Table 1. Baseline Characteristics Stratified by Frailty in the CHARLS Cohorts

	Overall (n=14079)	**No Frailty (n=12581)**	**Frailty (n=1479)**	***P value***
Body mass index, mean±SD	23.53±3.85	23.55±3.81	23.33±4.15	<0.05
BMI category, n (%)				0.497
<25	9678 (68.7)	8642 (68.7)	1036 (69.2)	
≥25□<30	3700 (26.3)	3320 (26.4)	380 (25.4)	
> 30	701 (5.0)	619 (4.9)	82 (5.5)	
Age, years, mean±SD	58.63±9.51	57.81±9.09	65.46±10.18	<0.05
Age category, n (%)				<0.05
<60	8283 (58.8)	7810 (62.1)	473 (31.6)	
≥60	5796 (41.2)	4771 (37.9)	1025 (68.4)	
Smoking status, n (%)				<0.05
Current smoker	8520 (60.5)	7525 (59.8)	995 (66.4)	
Ex-smoker	4339 (30.8)	4010 (31.9)	329 (22.0)	
Non-smoker	1220 (8.7)	1046 (8.3)	174 (11.6)	
Alcohol drinker status, n (%)				<0.05
Less than once a month	1223 (8.7)	1148 (9.1)	75 (5.0)	
More than once a month	3044 (21.6)	2847 (22.6)	197 (13.2)	
None of these	9812 (69.7)	8586 (68.2)	1226 (81.8)	
Sex, n (%)				<0.05
Female	7022 (49.9)	6138 (48.8)	884 (59.0)	

Male	7057 (50.1)	6443 (51.2)	614 (41.0)	
Education, n (%)				<0.05
College or above	663 (4.7)	621 (4.9)	42 (2.8)	
High school	4236 (30.1)	4034 (32.1)	202 (13.5)	
Primary school or below	9180 (65.2)	7926 (63.0)	1254 (83.7)	
Marital, n (%)				<0.05
Married	1679 (11.9)	1319 (10.5)	360 (24.0)	
Non-married	12400 (88.1)	11262 (89.5)	1138 (76.0)	
Regular physical activity, n (%)				<0.05
No	9143 (64.9)	8092 (64.3)	1051 (70.2)	
Yes	4936 (35.1)	4489 (35.7)	447 (29.8)	
Location (%)				<0.05
City/town	3133 (22.3)	2856 (22.7)	277 (18.5)	
Village	10946 (77.7)	9725 (77.3)	1221 (81.5)	
Frailty index, mean±SD	0.12±0.11	0.09±0.06	0.36±0.10	<0.05

The data are presented as mean (SD) for continuous variables or n (%) for categorical variables. P values were calculated using one-way ANOVA for continuous variables and Chi-square tests for categorical variables.

Abbreviations: SD, standard deviation; BMI, body mass index.

Table 2. Associations of frailty and frailty index with the risk for incident KOA in the CHARLS cohorts

Outcome	Expose	Total NO. of Participants (%)	NO. of KOA cases (%)	Model 1 HR (95% Cl)	Model 2 HR (95% Cl)
KOA	**Frailty**				
	No	3534 (25.10)	766 (6.09)	1 (reference)	1 (reference)
	Yes	3511 (24.94)	192 (12.82)	2.44 (2.08-2.86)	2.10 (1.78-2.48)
	P for trend			**<0.05**	**<0.05**
	Frailty index				
	Quartile 1	3534 (25.10)	102 (2.89)	1 (reference)	1 (reference)
	Quartile 2	3511 (24.94)	177 (5.04)	1.81 (1.42-2.31)	1.74 (1.36-2.22)
	Quartile 3	3538 (25.13)	270 (7.63)	2.84 (2.26-3.57)	2.62 (2.08-3.30)
	Quartile 4	3496 (24.83)	409 (11.70)	4.73 (3.81-5.88)	4.17 (3.33-5.22)
	P for trend			**<0.05**	**<0.05**

Quartiles: Patients were divided into 4 quartiles, quartiles 1-4 (Q1-4) based on nine adiposity-related markers measures across quartiles.

Model 1: (crude model) was unadjusted;

Model 2: adjusted for age, sex, BMI, smoking status, drinking status, race, education, location, marital, regular physical activity.

Abbreviations: HR, hazard ratio; CI, Confidence Interval; KOA, Knee Osteoarthritis.

Bold indicates statistical significance at the $p < 0.05$ level.

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Figure 1. Flowchart of the study participants.

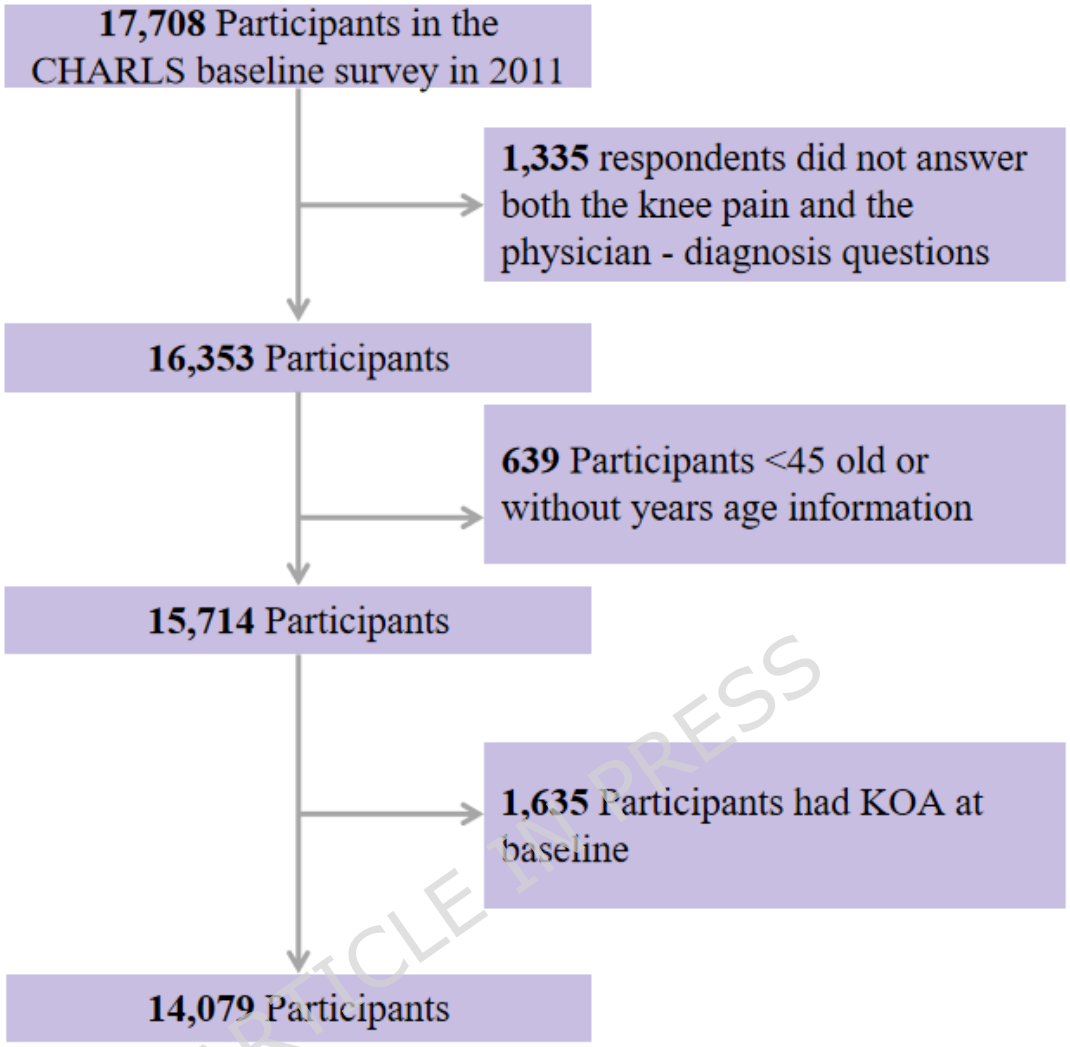
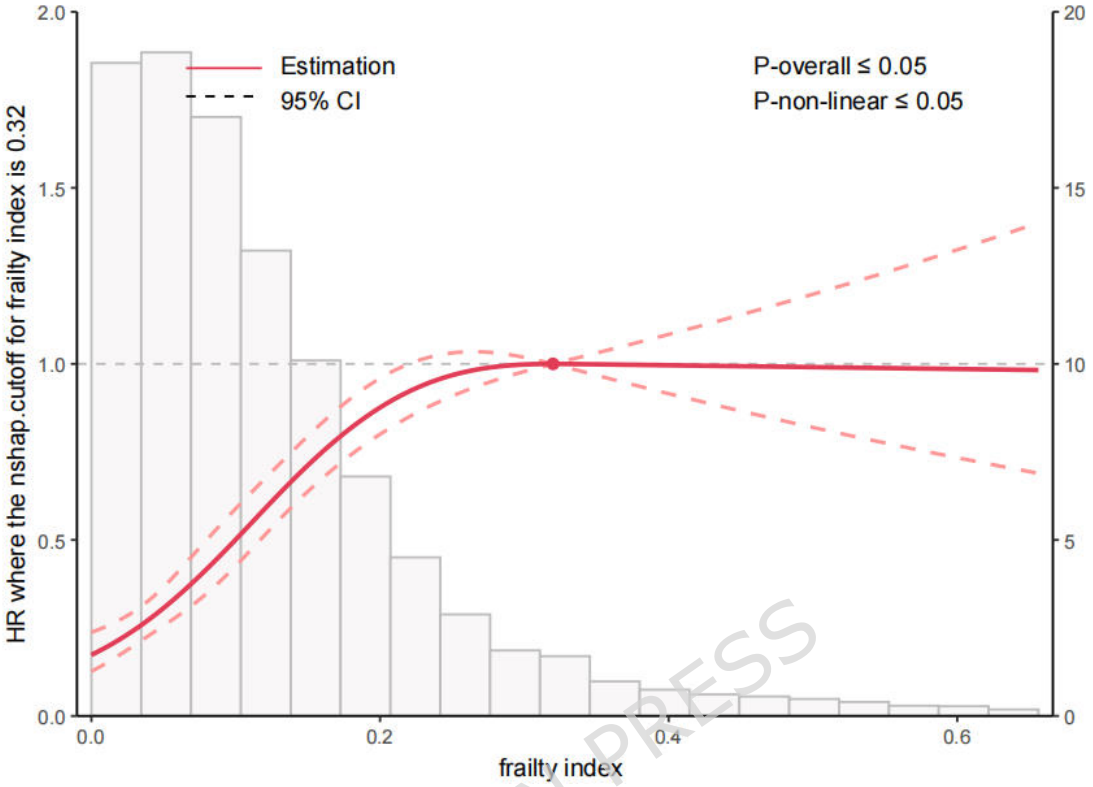


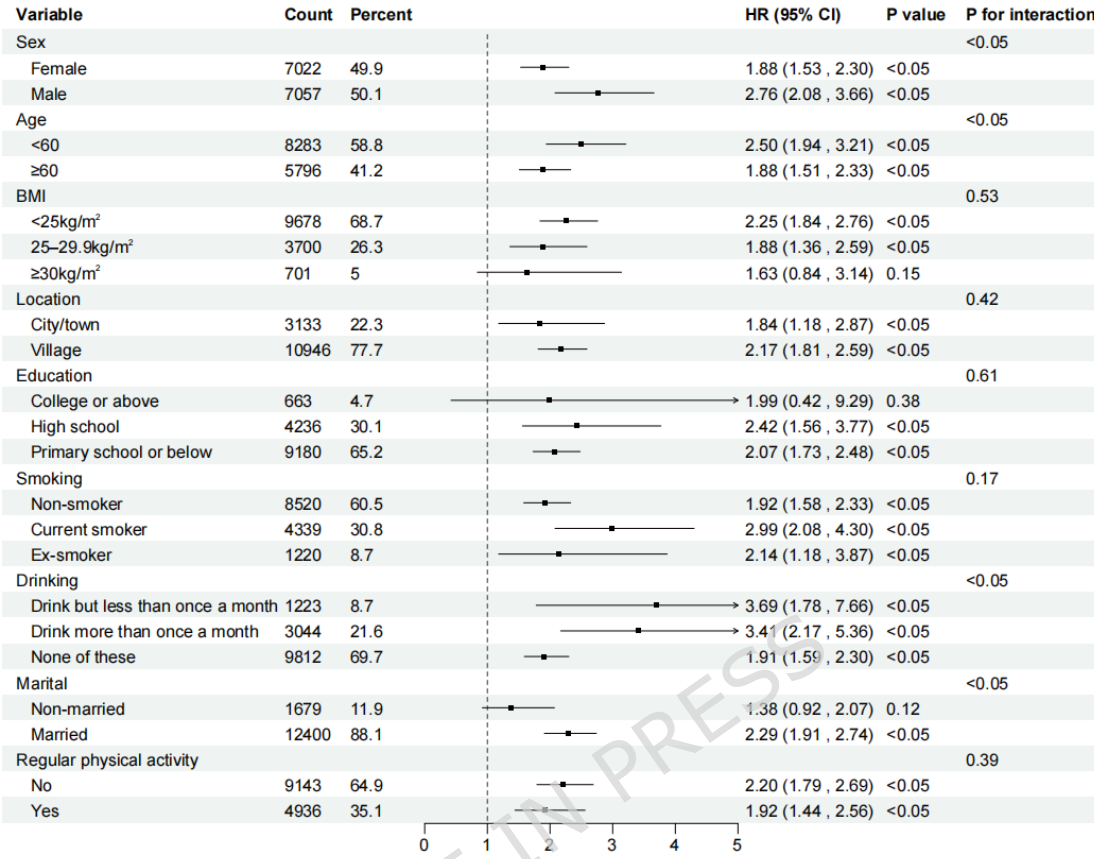
Figure 2. Dose-response relationship between frailty index and KOA using RCS.



Adjusted for age, sex, BMI, smoking status, drinking status, race, education, location, marital, regular physical activity.

Abbreviations: KOA, Knee Osteoarthritis; RCS, Restricted Cubic Spline.

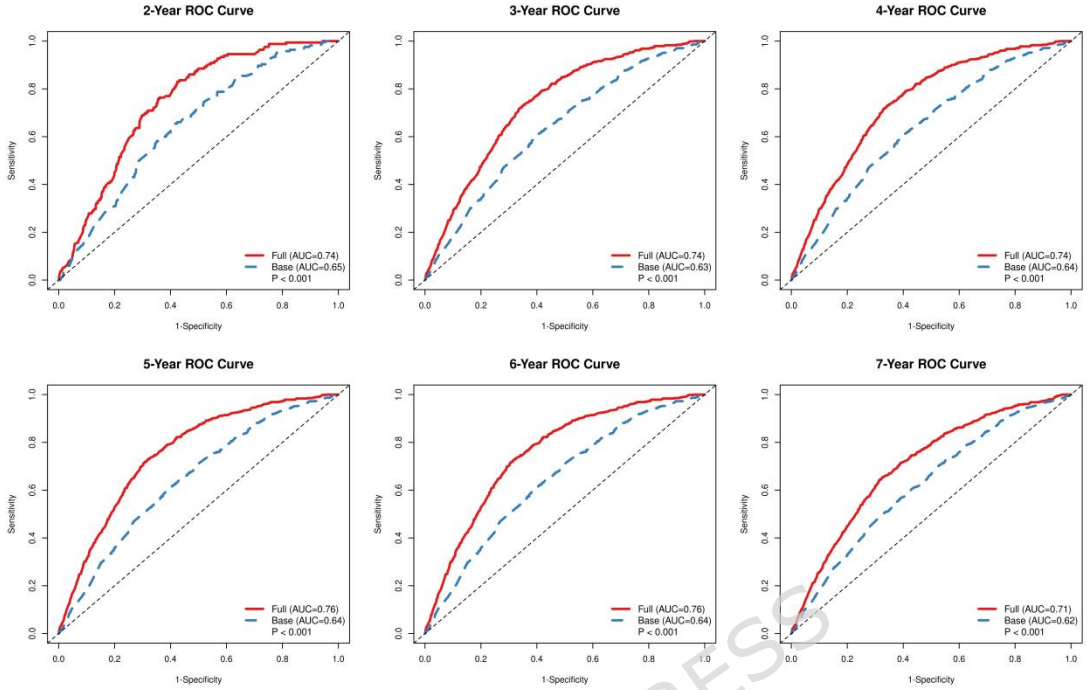
Figure 3. Subgroup analysis of the association between frailty and the risk of incident KOA (Cox proportional hazards model)



Abbreviations: HR, hazard ratio; CI, confidence interval; KOA, knee osteoarthritis.

Adjusted for age, sex, BMI, smoking status, drinking status, race, education, location, marital, regular physical activity.

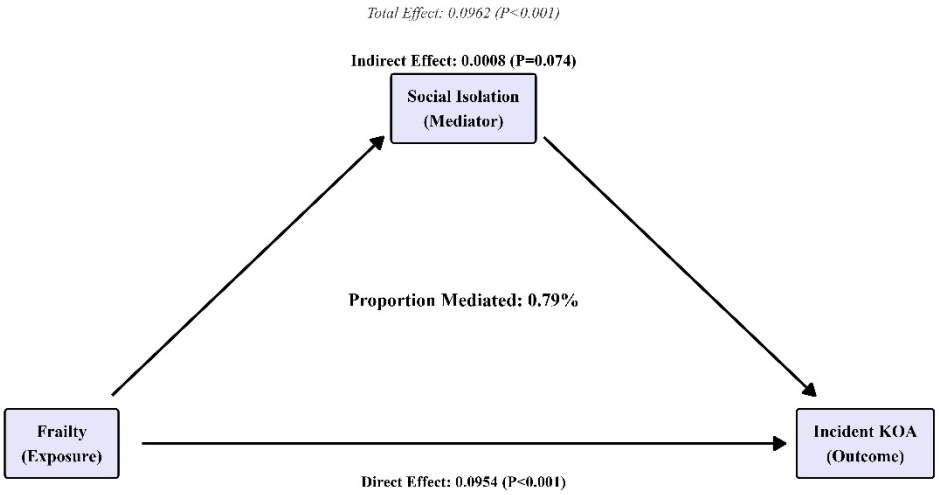
Figure 4. Time-dependent ROC curves comparing the predictive performance of the Base Model and the Full Model over a 2 to 7



The red solid lines represent the Full Model (incorporating the Frailty Index), while the blue dashed lines represent the Base Model (conventional risk factors only).

The Base Model was adjusted for age, sex, BMI, smoking, drinking, marital status, education, location, and regular physical activity. The

Figure 5. The mediation effect of social isolation on phenotypic



Abbreviations: KOA, Knee Osteoarthritis.