The Journal of Frailty & Aging 14 (2025) 100087

Contents lists available at ScienceDirect

The Journal of Frailty & Aging

journal homepage: www.elsevier.com/locate/tjfa

The bidirectional relationship between knee osteoarthritis and frailty in China: A longitudinal study

Ziwei Tian [a], Huimin Zhao [a], Yanping Zhai [b], Zhilan Yang [a,*]

[a] College of Nursing, Shanxi University of Chinese Medicine, Jinzhong 030619, China
[b] Third Hospital of Shanxi Medical University, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Taiyuan 030032, China

ARTICLE INFO

Keywords:
Knee osteoarthritis
Frailty
Bidirectional relationship
Cross-lagged panel model
Longitudinal study

ABSTRACT

Background: Knee osteoarthritis is a common disease that causes disability and loss of independence in middle-aged and older adults, and may interact with frailty through shared pathways. Understanding their bidirectional relationship is clinically meaningful for early intervention. This study aimed to investigate the associations between knee osteoarthritis and frailty among middle-aged and older adults in China.

Methods: The data for this study came from three waves (baseline 2011, follow-up 2013 and 2015) of the China Health and Retirement Longitudinal Study (CHARLS). A total of 3560 participants were included. Frailty was assessed with the Frailty Index. Knee osteoarthritis was defined as physician-diagnosed arthritis with self-reported knee pain. Longitudinal bidirectional relationships were found using cross-lagged panel models and random-intercept cross-lagged panel models.

Results: A longitudinal bidirectional relationship between knee osteoarthritis and frailty was observed, with a stronger effect of frailty on subsequent knee osteoarthritis (Wald $\chi^2 = 11.416$, $P < 0.001$). At the between-person level, individuals with knee osteoarthritis also tend to have a higher risk of frailty ($\beta = 0.454$, $P < 0.001$). At the within-person level, the predictive effect of knee osteoarthritis on frailty was significant only in the long term ($\beta = 0.055$, $P < 0.05$). Subgroup analyses showed that this longitudinal bidirectional relationship was particularly strong among females as well as those with low education levels.

Conclusions: This study reveals a longitudinal bidirectional relationship between knee osteoarthritis and frailty in middle-aged and older adults. In particular, the dominant role of frailty in the development of knee osteoarthritis was found, as well as the negative impact of knee osteoarthritis accumulation on frailty over time. This result suggests that targeting frailty early interventions in an ageing society may help to interrupt the vicious cycle of knee osteoarthritis and reduce the risk of disability. It provides a scientific basis for public health strategies.

1. Introduction

As global ageing accelerates, frailty, as an important clinical syndrome associated with aging, has become one of the world's most significant challenges [1]. Frailty is a geriatric syndrome characterized by declining physiological reserves, multi-system dysfunction, and reduced stress capacity [2]. Frailty is commonly associated with a range of adverse health consequences, including falls, disability, hospitalization, and mortality [3]. Research has shown that frailty is dynamically reversible [4]. Therefore, early identification and targeted interventions can effectively prevent the occurrence of frailty in older people and achieve healthy aging.

Frailty is closely related to musculoskeletal health [5]. Knee osteoarthritis (KOA) as a common musculoskeletal disease in middle-aged and older adults, is characterized by articular cartilage destruction and subchondral bone hyperplasia, with joint pain as the main symptom [6]. According to the Global Burden of Disease study [7], the number of KOA patients worldwide has reached 303 million and is expected to exceed 594 million by 2050. In China, the prevalence of KOA in middle-aged and older adults is as high as 36.4 percent, and the total number of KOA cases in China is expected to increase by 74.9 percent by 2050. Meanwhile, KOA is the fourth most disabling disease, with nearly 100 million people worldwide disabled by it [8]. The years lived with disability (YLD) of KOA is 18.9 million person-years and accounts for 2.2 percent of the global burden of all diseases. The high prevalence, disability, and disease burden of KOA have a great impact on

* Corresponding author.
E-mail addresses: 737156605@qq.com (Z. Tian), 3173627973@qq.com (Z. Yang).

https://doi.org/10.1016/j.tjfa.2025.100087
Received 19 June 2025; Received in revised form 18 August 2025; Accepted 19 August 2025
Available online 23 August 2025

both human health and quality of life [9].

There is an association between KOA and frailty. From KOA to frailty, chronic joint pain and mobility limitations not only directly reduce physical activity (aligning with the key criteria of Fried's frailty phenotype) but also trigger systemic functional decline through prolonged disuse [10–13]. Moreover, KOA-related local inflammation (elevated IL-6/TNF-α) may release these cytokines into systemic circulation, exacerbating age-related inflammaging via NF-κB activation, which disrupts muscle protein balance, accelerating sarcopenia development and ultimately leading to frailty [14].

Meanwhile, frailty status significantly exacerbates KOA progression, with physical frailty playing a particularly prominent role. Sarcopenia, a core component of frailty, not only reduces lower limb muscle strength but also alters knee joint biomechanical stability and increases joint loading, directly supporting the "muscle-joint functional unit" theory emphasized in OARSI guidelines [15,16]. Furthermore, the "metabolic-inflammatory" axis plays a crucial role in osteoarthritis progression: frailty-associated metabolic disorders, including insulin resistance and vitamin D deficiency, may promote joint degeneration by disrupting cartilage metabolism and bone remodeling processes [17].

Taken together, most studies focus on the unidirectional association between KOA and frailty, with limited exploration of their long-term bidirectional dynamics [10–13,15,16]. Elucidating the bidirectional frailty-chronic disease relationship captures their vicious cycle, providing more comprehensive insights than unidirectional models [18,19]. Although Mendelian randomization studies have provided evidence for bidirectional causal relationships between KOA and frailty, these have primarily involved European populations and focused on genetic predisposition, with limited consideration of non-genetic factors, thus restricting their clinical applicability [20,21]. Thus, while KOA and frailty are linked, their bidirectional reinforcement needs confirmation through multi-wave longitudinal studies.

China is one of the countries with the largest older population and the fastest aging speed in the world [22]. As the population ages, the burden of KOA and frailty will increase further. Clarifying the bidirectional relationship between KOA and frailty in the Chinese population can help to reveal their complex causal interplay. The findings also provide a scientific basis for early identification of people at high risk of frailty and the development of comprehensive intervention strategies [23]. This has important public health implications for achieving healthy ageing and reducing the healthcare burden. In addition, this study can reflect the mechanism between KOA and frailty under the Chinese medical system and family support model, providing a new perspective for global public health practice and a reference for other developing countries.

Therefore, we utilized data from the China Health and Retirement Longitudinal Study (CHARLS) to examine bidirectional KOA-frailty relationships at both between-person and within-person levels. This approach provides novel insights into the chronic disease-frailty cycle while addressing key limitations of previous unidirectional or cross-sectional analyses.

2. Methods

2.1. Data sources and study population

This study uses data from the CHARLS, a nationally representative survey of Chinese residents aged 45 and above conducted by the National School of Development at Peking University. CHARLS employs a multistage probability sampling design, encompassing over 10,000 households across 150 counties and 450 villages in 28 provinces, and including assessments of the social, economic, and health circumstances of community residents. Following the 2011 baseline survey, participants were followed biennially, in 2013 (wave 2), 2015 (wave 3), and 2018 (wave 4). Data from 2011 (wave 1) to 2015 (wave 3) were selected for this study. Participants were considered eligible for this study if they met the following criteria: (1) aged 45 years or older; (2) provided three repeated measures of KOA and frailty from wave 1 to wave 3; and (3) had no missing covariate data. Ultimately, 3560 participants were included in this study (see supplementary eFig. 1).

2.2. Assessment of KOA

According to the definitions used in several previous CHARLS-based studies [24–27], KOA was defined as the presence of physician-diagnosed arthritis and pain in one or both knees. A diagnosis of symptomatic KOA can be confirmed if a participant answers "Yes" to the following two questions and specifies "knee" as the affected body part in response to the third question: (1) Have you been diagnosed with arthritis or rheumatism by a doctor? (2) Do you frequently experience physical pain? (3) On what part of your body do you feel pain? (Please list all parts of body you are currently feeling pain).

2.3. Assessment of frailty

In the present study, we used the Frailty Index (FI) to assess frailty, which is defined as the accumulation of age-related health problems. Drawing on previous research whilst considering data availability [28,29], we selected 32 items encompassing diseases, disabilities, physical functions, depressive symptoms, and cognitive measures, with detailed variable specifications provided in Supplementary eTable 1. Except item 32, each item was categorized as 0 or 1 according to specific criteria, where 0 means no defects and 1 means defects. Item 32 (cognitive function) was derived from questionnaire assessments by normalizing the sum of memory test score (immediate and delayed word recall, range 0–10) and orientation test score (range 0–4) to a 0–1 scale (total/14), with higher scores indicating poorer cognitive ability. In addition, to balance data completeness with quality control, we allowed up to 20 % missing items ($\leq$6 items) in the FI calculation. If a participant has more than 6 missing items on these indicators, their FI will be considered missing and excluded [30]. FI is a continuous variable ranging from 0 to 1. Higher values indicate more severe frailty, and the frailty state is defined as a value of 0.25 or higher [29].

2.4. Covariates

In wave 1, covariates such as sociodemographic characteristics and health-related indicators were collected [31,32]. Sociodemographic characteristics included age (categorized as 45–59 years and $\geq$60 years), gender (male/female), education level (primary school or below, junior/senior high school, and junior college or above), marital status (married and unmarried [including separated, divorced, widowed, and never married]), and residence (urban/rural). Health-related indicators included sleep duration (continuous, self-reported nightly hours), sarcopenia (defined per AWGS 2019 criteria as low muscle mass [estimated by anthropometric equation], low muscle strength [estimated by handgrip strength] or poor physical performance [5-time chair stand test]), visual impairment (yes/no), and hearing impairment (yes/no).

2.5. Statistical analysis

The study used R 4.4.2 for data cleaning and collation, SPSS 27.0 for descriptive statistics and cross-sectional analysis, and Mplus 8.3 for longitudinal modelling.

Continuous variables were expressed as mean ± standard deviation (SD), and *t*-test was used for comparison between groups. Categorical variables were expressed as N (%), and then the χ^2 test was used to check the statistical differences between the groups.

2.5.1. Cross-sectional correlation analysis

Binary logistic regression was used to explore the covariates affecting KOA and frailty at wave 1. Chi-square test was used to explore the

correlation between KOA and frailty at three time points. Immediate relationships can be understood to provide a basis for subsequent dynamic model analysis.

2.5.2. Longitudinal bidirectional analyses

The cross-lag panel model (CLPM) and the random-intercept cross-lag panel model (RI-CLPM) were used to investigate the differences between-person effects and within-person effects.

First, we used the CLPM to examine the interconnections of KOA and frailty between-person. The CLPM analysis was estimated using the mean and variance-adjusted weighted least squares estimator (WLSMV), resulting in the construction of four different models [33]. Checking the fit indices of the model: Comparative Fit Index (CFI) >0.90, Tucker-Lewis Index (TLI) >0.90, Standardized Root Mean Square Residual (SRMR) <0.05, and Root Mean Square Error of Approximation (RMSEA) <0.05 indicate a good model fit [34].

In addition, to distinguishing between-person stable differences and within-person dynamic changes, we performed RI-CLPM analyses using the same CLPM variables. The RI-CLPM introduces a random intercept latent variable to the CLPM, capturing stable between-person differences in the study variable across all time points [34]. All factor loadings were fixed to 1, and residual variances of observed variables were set to zero. Subsequently, two arbitrary intercepts (one for KOA and the other for frailty) were merged. The correlation between random intercepts indicates the stable, trait-like differences between-person on KOA and frailty [34].

2.5.3. Subgroups and sensitivity analyses

To assess potential effects, we performed subgroup analyses. We stratified participants by: age (45–59 years/≥60 years), gender (male/female), and education level (low education level/high education). Participants with an education level below primary school belonged to the "low education" group, while those with an education level of lower secondary school and above were categorized as the "higher education" group. All p-values were two-sided, and statistical significance set at 0.05. We conducted supplementary CLPM analyses using the wave 1-wave 2 complete-case population. This approach evaluated whether the observed associations persisted over shorter time intervals. Furthermore, we stratified the FI into three domains (physiological, physical functional, and cognitive-social) and analyzed their differential predictive effects on frailty progression.

3. Results

3.1. Characteristics of the participants

In 2011 (wave 1), among 3560 middle-aged and older adults, 1064 (29.89 %) suffered from KOA and 1676 (47.10 %) from frailty. The prevalence of KOA differed significantly across multiple sociodemographic and health-related factors (all $P < 0.05$), including age, gender, residence, education level, visual and hearing impairments, sleep duration, and sarcopenia (see Table 1). Similarly, frailty showed comparable associations with these factors, with additional significant associations observed for marital status.

3.2. Correlation analysis between KOA and frailty at three time points

Binary logistic regression analysis showed that the prevalence of KOA was higher in females, older age, hearing impairment, and sarcopenia($P < 0.05$). Age, gender, residence, marital status, visual and hearing impairment, sarcopenia, and sleep duration influenced the prevalence risk of frailty ($P < 0.05$). (see Supplementary eTable2)

Correlation analyses showed that KOA was significantly and positively correlated with frailty at the three time points. The variables showed significant temporal stability and cross wave correlation, providing preliminary support for cross-lagged panel modeling to examine their dynamic interplay (see Table 2).

3.3. The CLPM analysis between KOA and frailty

The study investigated the correlation between KOA and frailty using CLPM. Various covariates were adjusted for at the start of the study, and the relationships between variables and the accuracy of the model remained largely consistent (see Table 3). The standardized path coefficients for the final model (Model 4) were shown in Fig. 1. Model fit CLPM was acceptable: CFI = 0.987, TLI = 0.954, RMSEA = 0.040 (90 %

Table 1
Baseline characteristics of different knee osteoarthritis and frailty in 2011.

Characteristics	N	Knee osteoarthritis			Frailty		
		Yes	No	*P*	Yes	No	*P*
Age (years)				<0.001			<0.001
45–59 years	1896	506(26.69 %)	1390(73.31 %)		698(36.81 %)	1198(63.19 %)	
≥60 years	1664	558(33.53 %)	1106(66.47 %)		978(58.77 %)	686(41.23 %)	
Gender				<0.001			<0.001
Male	1364	349(25.6 %)	1015(74.4 %)		578(42.4 %)	786(57.6 %)	
Female	2196	715(32.56 %)	1481(67.44 %)		1098(50 %)	1098(50 %)	
Residence				0.020			<0.001
Urban	3395	1028(30.3 %)	2367(69.7 %)		1623(47.8 %)	1772(52.2 %)	
Rural	165	36(21.8 %)	129(78.2 %)		53(32.1 %)	112(67.9 %)	
Marital status				0.101			<0.001
Married	3108	914(29.4 %)	2194(70.6 %)		1385(44.6 %)	1723(55.4 %)	
Unmarried	452	150(33.2 %)	302(66.8 %)		291(64.4 %)	161(35.6 %)	
Education level				0.003			<0.001
Primary school or below	2802	875(31.2 %)	1927(66.8 %)		1423(50.8 %)	1379(49.2 %)	
Junior/senior high school	740	186(25.1 %)	554(74.9 %)		249(33.6 %)	491(66.4 %)	
Junior college or above	18	3(16.7 %)	15(83.3 %)		4(22.2 %)	14(77.8 %)	
Visual impairment				0.009			<0.001
Yes	3109	953(30.7 %)	2156(69.3 %)		1543(49.6 %)	1566(50.4 %)	
No	451	111(24.6 %)	340(75.4 %)		133(29.5 %)	318(70.5 %)	
Hearing impairment				<0.001			<0.001
Yes	2420	788(32.6 %)	1632(67.4 %)		1287(53.2 %)	1133(46.8 %)	
No	1140	276(24.2 %)	864(75.8 %)		389(34.1 %)	751(65.9 %)	
Sleep duration		5.60±2.08	6.01±2.02	<0.001	6(4.5,7.5)	6(4.5,7.5)	<0.001
Sarcopenia				<0.001			<0.001
Yes	865	341(39.42 %)	524(60.58 %)		498(57.57 %)	367(42.43 %)	
No	2695	723(26.83 %)	1972(73.17 %)		1178(43.71 %)	1517(56.29 %)	

Table 2
Cross-wave bivariate associations between knee osteoarthritis and frailty: Phi coefficients from three waves (2011, 2013, 2015).

	KOA (wave 1)	Frailty (wave 1)	KOA (wave 2)	Frailty (wave 2)	KOA (wave 3)	Frailty (wave 3)
KOA (wave 1)	1					
Frailty (wave 1)	0.258***	1				
KOA(wave 2)	0.453***	0.253***	1			
Frailty (wave 2)	0.187***	0.413***	0.238***	1		
KOA(wave 3)	0.403***	0.244***	0.575***	0.245***	1	
Frailty (wave 3)	0.176***	0.423***	0.217***	0.492**	0.239***	1

Note: KOA= knee osteoarthritis, Phi coefficients were used for associations between binary variables. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

Table 3
Model fit indices and standardized path coefficients for cross-lagged models between knee osteoarthritis and frailty, CHARLS (n = 3560), 2011–2015.

Paths	Model 1		Model 2		Model 3		Model 4	
	β	SE	β	SE	β	SE	β	SE
Autoregressive paths								
KOA1 → KOA2	0.544***	0.012	0.709***	0.018	0.705***	0.018	0.698***	0.017
KOA2 → KOA3	0.767***	0.016	0.772***	0.017	0.772***	0.017	0.771***	0.017
Frailty1 → Frailty2	0.507***	0.014	0.638***	0.024	0.636***	0.025	0.628***	0.024
Frailty2 → Frailty3	0.710***	0.018	0.675***	0.019	0.029***	0.024	0.667***	0.020
Cross-lagged paths								
KOA1 → Frailty2	0.099***	0.018	0.035	0.028	0.041	0.028	0.056*	0.027
Frailty1 → KOA2	0.177***	0.018	0.131***	0.028	0.150***	0.029	0.181***	0.028
KOA2 → Frailty3	0.117***	0.025	0.112***	0.025	0.110***	0.025	0.112***	0.024
Frailty2 → KOA3	0.124***	0.023	0.119***	0.024	0.117***	0.025	0.121***	0.025
Residual correlations								
KOA1 with Frailty1	0.258***	0.014	0.388***	0.025	0.369***	0.026	0.344***	0.026
KOA2 with Frailty2	0.177***	0.030	0.100*	0.044	0.089	0.045	0.049	0.045
KOA3 with Frailty3	0.010	0.051	0.016	0.051	0.021	0.051	0.004	0.051
Model fit indices								
CFI	0.987		0.992		0.992		0.987	
TLI	0.951		0.973		0.971		0.954	
SRMR	0.024		0.024		0.023		0.037	
RMSEA	0.090		0.039		0.036		0.040	

Note: Model 1 was constructed without any modifications; Model 2 controlled for age, gender, residence, education level, and marital status; Model 3 was adjusted to account for vision and hearing impairments; Model 4 adds sleep duration and sarcopenia based on Model 3. KOA1, KOA2, and KOA3 = knee osteoarthritis at waves 1, 2, and 3; Frailty1, Frailty2, and Frailty3 = frailty at waves 1, 2, and 3. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

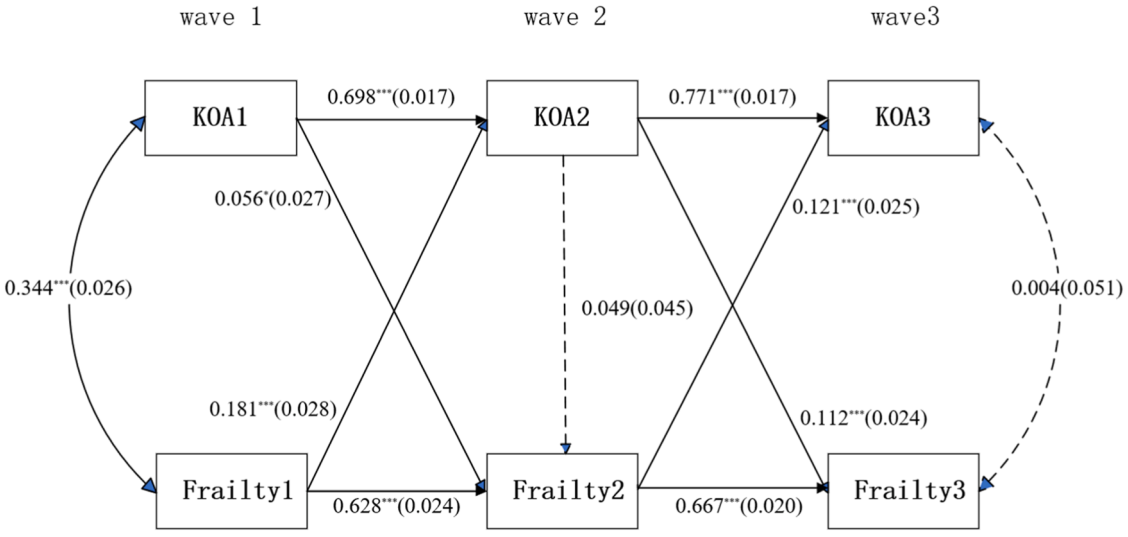

Fig. 1. Standardized path diagram of cross-lagged panel models between knee osteoarthritis and frailty, CHARLS (n = 3560), 2011–2015.
Note: For brevity, all covariates and residuals were estimated in the analysis but are not shown in the diagram. Models were adjusted for age, gender, residence, education level, marital status, visual impairment, hearing impairment, sleep duration, and sarcopenia. KOA1, KOA2, and KOA3 = knee osteoarthritis at waves 1, 2, and 3; Frailty1, Frailty2, and Frailty3 = frailty at waves 1, 2, and 3. Non-effective paths were represented with dotted lines and significant paths with solid lines. ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

CI: 0.034 - 0.047), SRMR = 0.037.

Both KOA and frailty showed statistically significant autoregressive effects across all three time points (all $P < 0.001$). Standardized path estimates showed consistent stability for both KOA (0.698–0.771) and frailty (0.628–0.667). Cross-lagged analysis showed that wave 1 KOA significantly predicted wave 2 frailty ($\beta = 0.056$, $P < 0.05$), while higher

wave 1 frailty predicted increased wave 2 KOA (β=0.181, $P < 0.001$). Similarly, bidirectional relationships were observed between wave 2 and wave 3 (all $P < 0.001$).

The study further compared standardized path coefficients to evaluate the relative strength of bidirectional relationships between KOA and frailty across waves. Wald tests demonstrated that wave 1 frailty had significantly stronger predictive effects on wave 2 KOA than wave 1 KOA on wave 2 frailty (Waldχ^2 (1) = 11.416, $P < 0.001$). No significant differences were found between wave 2 and wave 3 pathways.

3.4. The RI-CLPM analysis between KOA and frailty

This study examined the dynamic relationships between KOA and frailty using RI-CLPM. The model demonstrated good fit indices. As presented in Table 3 and Supplementary eTable3, the model fit indices demonstrated superior performance of RI-CLPM (CFI = 0.996, TLI = 0.950, SRMR = 0.012, RMSEA = 0.033) compared to CLPM (CFI = 0.987, TLI = 0.954, SRMR = 0.037, RMSEA = 0.040).

The longitudinal relationship between KOA and frailty operated at both within-person and between-person levels. At the within-person level, autoregressive effects indicated that the variables are somewhat stable at the within-person level, that is, the value at the previous point in time is predictive of the value at the subsequent point in time. This stability was significant at all three time periods in KOA, whereas frailty was significant only from wave 2 to wave 3. The RI-CLPM results revealed bidirectional but asymmetric relationships between KOA and frailty. Frailty consistently showed stronger predictive effects on subsequent KOA across all waves. In contrast, KOA only significantly predicted frailty from wave 2 to wave 3 (β = 0.055, $P < 0.05$). KOA and frailty are significantly and positively correlated ($P < 0.05$) at each time point. Complete RI-CLPM results are presented in Fig. 2.

At the between-person level, the random intercepts of KOA and frailty showed a strong positive correlation (β = 0.454, SE = 0.039, $P <$ 0.001). This suggests a positive correlation between initial levels of KOA and frailty. Individuals also differed significantly in baseline levels of KOA and frailty, which were positively correlated, suggesting that individuals at high risk of KOA prevalence also tended to be at higher risk of frailty.

3.5. Subgroups and sensitivity analyses

No significant age-group differences were observed (P = 0.5098) (see supplementary eFig. 2). Gender-stratified analyses revealed significant between-group differences in path coefficients (P = 0.0031) (see supplementary eFig. 3). Males showed balanced bidirectional relationships, whereas stronger effects were shown in the bidirectional relationship between both KOA and frailty in females. Education level-stratified analyses revealed significant between-group differences in path coefficients (P = 0.004) (see supplementary eFig. 4). Those with low levels of education showed stronger effects in the bidirectional relationship between both in KOA and frailty. The protective effect of those with high levels of education was mainly characterized by lower frailty stability and non-significant partial pathways.

In supplementary CLPM analyses using complete cases from waves 1–2 (N = 3863), the results showed: (1) significant short-term prediction from KOA to frailty (β = 0.105, $P < 0.001$); and (2) stronger short-term prediction from frailty to KOA (β = 0.183, $P < 0.001$). This is consistent with the findings of the main results (see supplementary eFig. 5). The results showed that among the three dimensions of frailty, physical dysfunction (β = 0.233, $P < 0.05$) significantly positively predicted the progression of frailty, while physiological and cognitive dimensions had weaker predictive effects.

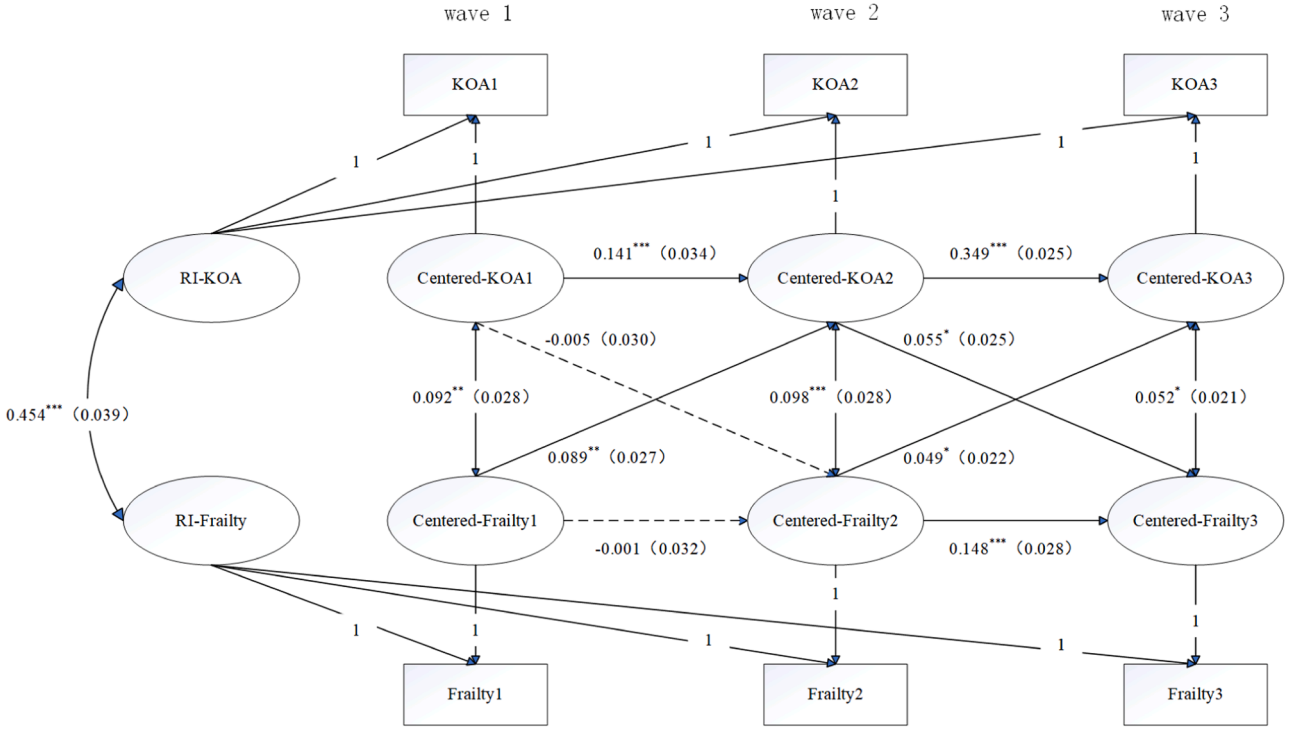

Fig. 2. Random-intercept cross-lagged panel model results for the knee osteoarthritis and frailty, CHARLS (n = 3560), 2011–2015.
Note: For brevity, all covariates and residuals were estimated in the analysis but are not shown in the diagram. Models were adjusted for age, gender, residence, education level, marital status, visual impairment, hearing impairment, sleep duration, and sarcopenia. KOA1, KOA2, and KOA3 = knee osteoarthritis at waves 1, 2, and 3; Frailty1, Frailty2, and Frailty3 = frailty at waves 1, 2, and 3; RI = random intercepts. Non-effective paths were represented with dotted lines and significant paths with solid lines. ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

4. Discussion

4.1. Principal findings

This study established a longitudinal bidirectional relationship between KOA and frailty for the first time. We found a positive correlation between KOA and frailty. Moreover, the effect of frailty on KOA was more significant than that of KOA, suggesting that frailty plays a dominant role in the bidirectional relationship between KOA and frailty among people. Third, at the within-person level, the prediction of frailty by KOA was only significant in later stages.

The results of the cross-lag panel model suggest a potential correlation between KOA and frailty. Previous studies have mostly examined unidirectional relationships between KOA and frailty, and our findings may provide new insights [10,12,14]. The study found that frailty was a stronger predictor of KOA than the effect of KOA on frailty. This view is supported by a 9-year prospective cohort, which suggests that frailty can predict the long-term trajectory of knee pain, with the main drivers likely to be exhaustion and slow gait speed [35]. There are several potential mechanisms by which frailty predicts KOA. Frail patients often develop sarcopenia, which may lead to decreased joint stability, resulting in abnormal joint load and increased susceptibility to biomechanical damage [36]. In addition, a previous study showed that frailty is often accompanied by chronic low-grade inflammation [37]. Pro-inflammatory cytokines (e.g., IL-6, CRP, TNF-α) may accumulate in joints, promoting low-grade inflammation and cartilage degradation [38]. This also confirms that early functional impairment may be the core factor driving long-term frailty in the results of this study, suggesting that clinical intervention should prioritize the functional status of KOA patients.

Stratified results showed that the longitudinal bidirectional relationship between frailty and KOA showed a stronger effect in women. This may reflect women's heightened pain sensitivity in KOA, promoting activity avoidance and accelerated muscle loss [39]. Moreover, the decline in estrogen in women after menopause accelerates muscle loss and exacerbates frailty [40]. Within the educational level subgroup, low educational level showed a stronger effect. It may be that low educators are less likely to receive standardized treatment, leading to poor control of KOA and frailty [41]. And the chronic stress faced promotes muscle breakdown and inflammation through elevated cortisol, accelerating KOA and frailty [42]. In contrast, a high level of education level as a protective factor, with health awareness and counterpart resources, and is more likely to adopt a healthy diet and regular exercise to slow the progression of frailty [43]. This result suggests targeting women and low-education KOA patients for early intervention and prioritizing prevention of frailty.

To the best of our knowledge, the study is the first to utilize RI-CLPM to investigate the longitudinal bidirectional relationship between KOA and frailty. The results of the RI-CLPM also show a dynamic interaction between KOA and frailty. The stronger effect of frailty on KOA corroborates the CLPM results. However, some differences remain. The RI-CLPM revealed a positive and strong association between KOA and frailty at the baseline level in the population. This has been confirmed by several studies, suggesting that attention needs to be paid to early intervention in high-risk groups [44,45].

KOA showed significant time persistence within individuals and the effect was stronger at later ages, suggesting that the progression of KOA may accelerate with age. The results are highly consistent with the biological mechanisms of aging [46], suggesting that clinical attention needs to be focused on early intervention in elderly patients. This was mentioned in a longitudinal cohort study where age was a significant risk factor for KOA and the incidence and severity of KOA increased significantly with age [26]. However, age subgroups were not significantly different at the time of subgroup analyses in this study. It is possible that KOA progression accelerates significantly after 60–70 years of age, but the difference is smaller before 60 years of age, and the subgroups mask the thresholds to bias [26].

Another notable current finding was that the KOA's prediction of frailty was only significant in the later stages, which was not reflected in the CLPM. Possibly due to the cumulative effects of KOA, such as reduced activity due to chronic pain, it takes longer to affect the frailty. Our findings are supported by a longitudinal survey involving 3053 participants from multiple centers, which suggests that unilateral knee pain gradually shifts to bilateral knee pain over time, and that bilateral knee pain is strongly associated with an increased risk of a debilitating state [10]. On the other hand, the Kellgren-Lawrence (K-L) classification plays a role in this, with frailty being more pronounced in patients with a higher K-L classification [44]. This result is similarly confirmed by a longitudinal study in the UK, which showed that knee pain at baseline was not significantly associated with future debilitating states in the short term and became more significant in the long term [47].

Our findings indicate that frailty positioning it not merely as a consequence, but as a modifiable upstream driver of KOA. With rapid population aging, multidisciplinary collaboration across rheumatology, geriatrics and rehabilitation medicine, along with integrating frailty into national disease prevention programs, is crucial for maintaining functional ability and quality of life in older adults.

These findings provide important preventive medicine insights across three levels. First, primary prevention through routine frailty screening in middle-aged and older adults (particularly women and less-educated individuals) could enable early interventions like nutrition and exercise programs to prevent KOA onset [48]. Second, secondary prevention for early KOA patients should focus on holistic functional optimization through tailored exercise programs that simultaneously improve strength, balance, and joint loading [49]. Third, tertiary prevention requires preoperative frailty assessment in advanced KOA cases, with prehabilitation programs combining protein supplementation and resistance training to improve surgical outcomes and maintain independence [50]. This multilevel approach highlights the need to integrate frailty management throughout KOA care.

4.2. Strengths and limitations

The use of a representative national sample in this study allows our results to be generalized to the Chinese middle-aged and older adults. Moreover, we used CLPM and RI-CLPM to examine longitudinal relationships between KOA and frailty, looking at both between-person and within-person levels, which is an innovative aspect of the article. Evidence can be provided for subsequent studies of debilitating interventions in patients with KOA.

However, we also recognize that there are some inherent limitations. Firstly, this study was observational, which could lead to biased relationships due to confounding factors. To address this issue, we considered various covariates based on previous studies. Second, the information weakened in CHARLS is only available at the first three time points (2011, 2013, and 2015). Therefore, the follow-up period of this study was limited to four years. In addition, our definition of KOA, based on patient-reported physician diagnoses combined with knee pain, may underestimate the true prevalence of the disease. Future studies incorporating objective assessment methods (such as imaging or physical examination) are needed to validate these findings. Finally, it is worth noting that this study only focuses on Chinese individuals, and further research is needed to verify the applicability of our findings to different nationalities.

5. Conclusions

Our study demonstrates, for the first time, a reciprocal and facilitative association between KOA and frailty at the between-person level in middle-aged and older Chinese adults. Furthermore, frailty plays a prominent role in this bidirectional relationship. Patients with KOA are at higher risk of developing frailty later in life. Based on these findings,

we suggest that frailty management should be incorporated early into the routine treatment of patients with KOA, as well as timely control of the disease and delay of progression in patients with KOA. This study provides an empirical basis for the clinical development of targeted preventive and comprehensive interventions. In particular, it highlights the importance of focusing on both joint health and functional maintenance in an ageing society. It provides a new perspective on the management of chronic disease co-morbidities in an ageing society worldwide. Future validation is needed in different healthcare settings and socio-cultural contexts.

Author contributions: credit

Ziwei Tian: Data curation, Software, Writing - original draft. Huimin Zhao, Yanping Zhai: Methodology, Project administration, Supervision. Zhilan Yang: Writing - review and editing

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Ziwei Tian: Writing – original draft, Software, Data curation. **Huimin Zhao:** Supervision, Project administration, Methodology. **Yanping Zhai:** Supervision, Project administration, Methodology. **Zhilan Yang:** Writing – review & editing.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the National Development Research Institute of Peking University and the China Social Science Survey Center of Peking University for providing the CHARLS data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2025.100087.

References

[1] Hoogendijk EO, Afilalo J, Ensrud KE, et al. Frailty: implications for clinical practice and public health. Lancet 2019;394(10206):1365–75. https://doi.org/10.1016/S0140-6736(19)31786-6.
[2] Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146–56. https://doi.org/10.1093/gerona/56.3.m146.
[3] Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet 2013;381(9868):752–62. https://doi.org/10.1016/S0140-6736(12)62167-9.
[4] Kolle AT, Lewis KB, Lalonde M, et al. Reversing frailty in older adults: a scoping review. BMC Geriatr 2023;23(1):751. https://doi.org/10.1186/s12877-023-04309-y.
[5] McGuigan FE, Bartosch P, Åkesson KE. Musculoskeletal health and frailty. Best Pract Res Clin Rheumatol 2017;31(2):145–59. https://doi.org/10.1016/j.berh.2017.11.002.
[6] Chinese Society of Physical Medicine and Rehabilitation, West China Hospital of Sichuan University. Chinese guideline for the rehabilitation treatment of knee osteoarthritis (2023 edition). J Evid-Based Med 2024;24(01):1–14. https://doi.org/10.7507/1672-2531.202306145.
[7] Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the global burden of disease study 2021. Lancet 2024;403(10440):2133–61. https://doi.org/10.1016/S0140-6736(24)00757-8.
[8] Safiri S, Kolahi A, Smith E, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the global burden of disease study 2017. Ann Rheum Dis 2020;79(6):819–28. https://doi.org/10.1136/annrheumdis-2019-216515.
[9] Long H, Zeng X, Liu Q, et al. Burden of osteoarthritis in China, 1990-2017: findings from the global burden of disease study 2017. Lancet Rheumatol 2020;2(3):e164–72. https://doi.org/10.1016/S2665-9913(19)30145-6.
[10] Bindawas SM, Vennu V, Stubbs B. Longitudinal relationship between knee pain status and incident frailty: data from the osteoarthritis initiative. Pain Med 2018;19(11):2146–53. https://doi.org/10.1093/pm/pnx296.
[11] Veronese N, Maggi S, Trevisan C, et al. Pain increases the risk of developing frailty in older adults with osteoarthritis. Pain Med 2017;18(3):414–27. https://doi.org/10.1093/pm/pnw163.
[12] Wanaratna K, Muangpaisan W, Kuptniratsaikul V, et al. Prevalence and factors associated with frailty and cognitive frailty among community-dwelling elderly with knee osteoarthritis. J Community Health 2019;44(3):587–95. https://doi.org/10.1007/s10900-018-00614-5.
[13] Zhang LY, Zhang Q, Liu Q, et al. Relationship between symptomatic knee osteoarthritis and frailty among elderly people in China. Chin J Geriatr 2023;42(9):1117–22. https://doi.org/10.3760/cma.j.issn.0254-9026.2023.09.017.
[14] Greene MA, Loeser RF. Aging-related inflammation in osteoarthritis. Osteoarth Cartil 2015;23(11):1966–71. https://doi.org/10.1016/j.joca.2015.01.008.
[15] Segal NA, Glass NA, Torner J, et al. Quadriceps weakness predicts risk for knee joint space narrowing in women in the MOST cohort. Osteoarth Cartil 2010;18(6):769–75. https://doi.org/10.1016/j.joca.2010.02.002.
[16] Veronese N, Stefanac S, Koyanagi A, et al. Lower limb muscle strength and muscle mass are associated with incident symptomatic knee osteoarthritis: a longitudinal cohort study. Front Endocrinol 2021;12:804560. https://doi.org/10.3389/fendo.2021.804560.
[17] Li Z, Yin S, Zhao G, et al. Association between sarcopenic obesity and osteoarthritis: the potential mediating role of insulin resistance. Exp Gerontol 2024;197:112611. https://doi.org/10.1016/j.exger.2024.112611.
[18] Bhattarai U, Bashyal B, Shrestha A, et al. Frailty and chronic diseases: a bi-directional relationship. Aging Med 2024;7(4):510–5. https://doi.org/10.1002/agm2.12349.
[19] Zhou K, Wang A, Yi K. Cardiometabolic multimorbidity and frailty in middle-aged and older adults: a cross-nationally harmonized study. Front Public Health 2025;13:1565682. https://doi.org/10.3389/fpubh.2025.1565682.
[20] Zhou J, Li Y, Lin Y, et al. The genetic causal association between hip or knee osteoarthritis and frailty: a two-sample mendelian randomization analysis. Arch Med Sci 2024;20(3):938–46. https://doi.org/10.5114/aoms/176741. AMS.
[21] Pan SX, Wu SF, Wei YT, et al. Exploring the causal relationship between inflammatory cytokines and inflammatory arthritis: a mendelian randomization study. Cytokine 2024;173:156446. https://doi.org/10.1016/j.cyto.2023.156446.
[22] World Health Organization. Ageing and health - China. Retrieved August 18, 2025, from y.
[23] Tian Z.W., Yang Z.L., Zhao H.M., et al. Frailty in knee osteoarthritis:a scoping review. Chin General Prac. doi: 10.12114/j.issn.1007-9572.2025.0012.
[24] Ren Y, Hu J, Tan J, et al. Incidence and risk factors of symptomatic knee osteoarthritis among the Chinese population: analysis from a nationwide longitudinal study. BMC Public Health 2020;20(1):1491. https://doi.org/10.1186/s12889-020-09611-7.
[25] Tang X., Wang S., Zhan S., et al. The prevalence of symptomatic knee osteoarthritis in China: results from the China health and retirement longitudinal study. 2016,68(3):648–53. doi: 10.1002/art.39465.
[26] Wang L, Lu H, Chen H, et al. Development of a model for predicting the 4-year risk of symptomatic knee osteoarthritis in China: a longitudinal cohort study. Arthritis Res Ther 2021;23(1):65. https://doi.org/10.1186/s13075-021-02447-5.
[27] Zhou S, Wu L, Si H, et al. Association between nighttime sleep duration and quality with knee osteoarthritis in middle-aged and older Chinese: a longitudinal cohort study. Arch Gerontol Geriatr 2024;118:105284. https://doi.org/10.1016/j.archger.2023.105284.
[28] Fan J, Yu C, Guo Y, et al. Frailty index and all-cause and cause-specific mortality in Chinese adults: a prospective cohort study. Lancet Public Health 2020;5(12):e650–60. https://doi.org/10.1016/S2468-2667(20)30113-4.
[29] He D, Wang Z, Li J, et al. Changes in frailty and incident cardiovascular disease in three prospective cohorts. Eur Heart J 2024;45(12):1058–68. https://doi.org/10.1093/eurheartj/ehad885.
[30] Sun L, Deng G, Lu X, et al. The association between continuing work after retirement and the incidence of frailty: evidence from the China health and retirement longitudinal study. J Nutr Health Aging 2024;28(12):100398. https://doi.org/10.1016/j.jnha.2024.100398.
[31] Szilagyi IA, Waarsing JH, van Meurs JBJ, et al. A systematic review of the sex differences in risk factors for knee osteoarthritis. Rheumatology 2023;62(6):2037–47. https://doi.org/10.1093/rheumatology/keac688.
[32] Fisher DE, Ward MM, Hoffman HJ, et al. Impact of sensory impairments on functional disability in adults with arthritis. Am J Prev Med 2016;50(4):454–62. https://doi.org/10.1016/j.amepre.2015.07.014.
[33] Muthén B., Asparouhov T., Witkiewitz K. Cross-lagged panel modeling with binary and ordinal outcomes. Psychol Methods. doi:10.1037/met0000701.
[34] Grimm KJ, Helm J, Rodgers D, et al. Analyzing cross-lag effects: a comparison of different cross-lag modeling approaches. New Dir Child Adolesc Dev 2021;2021(175):11–33. https://doi.org/10.1002/cad.20401.
[35] Cai G, Zhang Y, Wang Y, Li X, et al. Frailty predicts knee pain trajectory over 9 years: results from the osteoarthritis initiative. Pain Med 2023;24(12):1364–71. https://doi.org/10.1093/pm/pnad097.

[36] Pegreffi F, Balestra A, De Lucia O, et al. Prevalence of sarcopenia in knee osteoarthritis: a systematic review and meta-analysis. J Clin Med 2023;12(4). https://doi.org/10.3390/jcm12041532.
[37] Pan Y, Ma L. Inflammatory markers and physical frailty: towards clinical application. Immun Age 2024;21(1):4. https://doi.org/10.1186/s12979-023-00410-3.
[38] Wen S, Cai Y, Zhang Q, et al. Immunological insights into the causal link between arthritis, osteoarthritis, and frailty: an integrated analytical study. Int J Med Sci 2025;22(3):616–29. https://doi.org/10.7150/ijms.104476.
[39] Franke M, Mancino C, Taraballi F. Reasons for the sex bias in osteoarthritis research: a review of preclinical studies. Int J Mol Sci 2023;24(12). https://doi.org/10.3390/ijms241210386.
[40] Sipilä S, Törmäkangas T, Sillanpää E, et al. Muscle and bone mass in middle-aged women: role of menopausal status and physical activity. J Cachexia Sarcopenia Muscle 2020;11(3):698–709. https://doi.org/10.1002/jcsm.12547.
[41] Unevik E, Abbott A, Fors S, et al. Sociodemographic inequalities in outcomes of a Swedish nationwide self-management program for osteoarthritis: results from 22,741 patients between years 2008-2017. J Clin Med 2020;9(7). https://doi.org/10.3390/JCM9072294.
[42] Knezevic E, Nenic K, Milanovic V, et al. The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. Cells 2023;12(23). https://doi.org/10.3390/cells12232726.
[43] Dong Y, Yan Y, Zhou J, et al. Evidence on risk factors for knee osteoarthritis in middle-older aged: a systematic review and meta analysis. J Orthop Surg Res 2023;18(1):634. https://doi.org/10.1186/s13018-023-04089-6.
[44] Salaffi F, Di Carlo M, Carotti M, et al. Frailty prevalence according to the survey of health, ageing and retirement in Europe-frailty instrument (SHARE-FI) definition, and its variables associated, in patients with symptomatic knee osteoarthritis: findings from a cross-sectional study. Aging Clin Exp Res 2021;33(6):1519–27. https://doi.org/10.1007/s40520-020-01667-0.
[45] Joo SH, Song JW, Shin K, et al. Knee osteoarthritis with a high grade of Kellgren-Lawrence score is associated with a worse frailty status, KNHANES 2010-2013. Sci Rep 2023;13(1):19714. https://doi.org/10.1038/s41598-023-46558-2.
[46] Loeser RF, Collins JA, Diekman BO. Ageing and the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2016;12(7):412–20. https://doi.org/10.1038/nrrheum.2016.65.
[47] Chaplin WJ, McWilliams DF, Millar BS, et al. The bidirectional relationship between chronic joint pain and frailty: data from the investigating musculoskeletal health and wellbeing cohort. BMC Geriatr 2023;23(1):273. https://doi.org/10.1186/s12877-023-03949-4.
[48] Dent E, Dalla Via J, Bozanich T, et al. Frailty increases the long-term risk for fall and fracture-related hospitalizations and all-cause mortality in community-dwelling older women. J Bone Miner Res 2024;39(3):222–30. https://doi.org/10.1093/jbmr/zjad019.
[49] Zeng CY, Zhang ZR, Tang ZM, et al. Benefits and mechanisms of exercise training for knee osteoarthritis. Front Physiol 2021;12:794062. https://doi.org/10.3389/fphys.2021.794062.
[50] Moyer R, Ikert K, Long K, et al. The value of preoperative exercise and education for patients undergoing total hip and knee arthroplasty: a systematic review and meta-analysis. JBJS Rev 2017;5(12):e2. https://doi.org/10.2106/JBJS.RVW.17.00015.