

Adverse Childhood Experiences and Incident Symptomatic Knee Osteoarthritis: The Mediating Role of Frailty in a Nationwide Chinese Cohort

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Abstract

Objectives

To examine the association between adverse childhood experience burden and a newly observed symptomatic knee osteoarthritis proxy phenotype among middle-aged and older Chinese adults, and to assess whether frailty accounts for part of this association.

Methods

We linked CHARLS data from 2011, the 2014 Life History Survey, 2015 and 2018. ACE burden was measured with a nine-item score recalled in 2014. Frailty was measured in 2015 with an arthritis-excluded deficit-accumulation index (FI31). We excluded participants who met the combined knee pain and arthritis/rheumatism diagnosis-history phenotype in 2015. New occurrence of this phenotype in 2018 was the outcome. Logistic regression estimated the ACE–outcome association. Parametric g-computation estimated natural direct and indirect effects through FI31. Model 2 was the primary adjustment set. Uncertainty was estimated with 2,000 community-level bootstrap samples. Biomarker adjustment and FI32 were sensitivity analyses.

Results

Among 5,841 participants, 942 (16.1%) developed the outcome. In the primary adjusted model, each additional ACE was associated with higher outcome odds (odds ratio [OR] 1.18, 95% confidence interval [CI] 1.11–1.25). The model-standardized risk rose from 13.0% (95% CI 11.6%–14.4%) at an ACE score of 0 to 28.0% (95% CI 22.9%–33.1%) at a score of 6. Each additional ACE was also associated with a 0.00905 higher FI31 (95% CI 0.00650–0.01159), and the outcome OR was 1.39 per 0.1 higher FI31 (95% CI 1.31–1.47). After including FI31, the ACE OR was 1.15 (95% CI 1.08–1.22). The natural indirect effect was 0.33 percentage points (95% CI 0.23–0.45), equal to 17.4% of the total effect (95% CI 11.4%–29.4%). Results were directionally consistent after biomarker adjustment and when FI32 replaced FI31.

Conclusions

Greater ACE burden was prospectively associated with the later symptomatic knee outcome. FI31 accounted for a modest, statistically supported part of this association. Most of the estimated effect remained outside the frailty pathway. Accumulated health deficits may therefore be one link between childhood adversity and later knee health.

Background

Knee osteoarthritis (KOA) is a major cause of pain and disability in older adults. The Global Burden of Disease 2021 analysis estimated that 595 million people had osteoarthritis in 2020. It also projected a substantial increase in knee osteoarthritis by 2050 [1]. Changes in joint and periarticular tissues can restrict walking and daily activities [2]. Age, female sex, obesity and joint injury are established risk factors, but they do not fully explain variation in disease occurrence and symptoms [3]. Earlier social and health exposures may also contribute to this variation.

Adverse childhood experiences (ACEs) include harmful experiences within the family and wider social environment. The original ACE study linked cumulative childhood adversity to multiple adult health risks [4]. A recent umbrella review reported associations with physical and psychological health, behaviour and biological dysregulation. Findings varied with the adversity definition and outcome [5]. In China, ACEs have been associated with chronic conditions, including arthritis, among middle-aged and older adults [6]. Less is known about the processes that connect childhood adversity to later knee symptoms.

Frailty may be one such process because it reflects accumulated deficits across several health domains. A systematic review found an association between ACEs and frailty across populations and measurement approaches [7]. CHARLS research has also linked childhood adversity to higher frailty levels and changes in frailty over time [8]. Adults exposed to adversity may reach later life with more functional limitations, psychological problems and chronic diseases. These deficits could reduce their ability to tolerate joint stress and maintain mobility.

The relationship may also operate in the opposite direction. Longitudinal CHARLS research suggests that frailty can precede knee symptoms and that knee disease can contribute to later frailty [9]. Some frailty indices also include arthritis as a deficit. This creates overlap when the index is used as a mediator for an arthritis-related outcome. Both the timing of assessment and the content of the index therefore matter.

We therefore tested two linked questions in CHARLS. The primary question was whether greater ACE burden predicted a new symptomatic knee outcome between 2015 and 2018. The second was whether FI31 measured in 2015 accounted for part of that association. Arthritis/rheumatism was excluded from the primary mediator to reduce content overlap and restored only in sensitivity analysis.

Methods

Study design and participants

CHARLS follows community-dwelling Chinese adults aged 45 years or older and their spouses through multistage sampling, repeated interviews and health measurements [10]. We linked records from the 2011 baseline, 2014 life-history, 2015 and 2018 surveys. Adult covariates were drawn mainly from 2011. ACEs were recalled in 2014, FI31 and baseline knee status were measured in 2015, and the follow-up knee outcome was assessed in 2018. Figure 1 summarizes this temporal and analytic framework.

Participants had to be aged at least 45 years in 2011 and linked to the 2014 life-history survey. They also needed a calculable ACE score and FI31, an observed 2018 outcome, and the variables required for the primary adjustment set. We excluded participants who met the combined knee symptom–diagnosis definition in 2015. Figure 2 presents the sequential selection process.

We used the Strengthening the Reporting of Observational Studies in Epidemiology recommendations to structure the report [11]. We referred to the AGReMA guideline when describing the mediation contrast, effect scale, uncertainty estimates and causal assumptions [12].

Adverse childhood experiences

Based on previous CHARLS research [6], we derived nine ACE indicators from the 2014 Life History Survey. The indicators covered physical abuse, household substance problems, interparental violence, unsafe neighbourhood, bullying, emotional neglect, household mental illness, family disruption and parental death before age 18. Family disruption included caregiver incarceration or parental separation. Each indicator contributed one point to a score ranging from 0 to 9. Only affirmative responses contributed a point for the first eight indicators; parental-death status had to be ascertainable. The score was analysed continuously, with higher values indicating greater adversity.

Frailty assessment

We reconstructed a published 32-item CHARLS frailty framework covering chronic conditions, sensory impairment, self-rated health, function, depressive symptoms and cognition [13]. The index equalled the sum of observed deficit scores divided by the number of observed items [14]. We removed arthritis/rheumatism from the primary index to reduce overlap with the outcome. This 31-item index (FI31) included nine chronic-condition items, vision and hearing, and self-rated health. It also included five basic and five instrumental activities of daily living, seven mobility or physical-task items, depressive symptoms and cognition. All deficits ranged from 0 to 1. Cognition had a graded score; the remaining deficits were binary.

We resolved questionnaire-routing skips using the official 2015 questionnaire [15]. A functional item was scored 0 only when an earlier response or screening item established a no-difficulty skip. Other unobserved responses were left unscored. The same rule was applied to walking, basic activities and whole-module skips.

We checked cognitive coding against the released codebook [16]. Recall counted words correctly reported from ten eligible options, and an explicit report of no recalled words was scored 0. Orientation covered the year, month, date and day of the week. An unanswered component was scored incorrect only when other answers showed that the assessment had been administered. Depressive symptoms were defined as a prorated CESD-10 score of at least 10, based on at least eight valid responses.

FI31 was calculated when at least 28 of 31 items were observed, using the observed items as the denominator. We used continuous FI31 in regression and mediation analyses. The threshold of 0.25 was used only to describe frailty prevalence in Table 1. For sensitivity analysis, arthritis/rheumatism was restored to form FI32, which required at least 29 of 32 observed items.

Table 1
Participant characteristics by follow-up knee outcome

Characteristic	Overall	No outcome	Incident outcome	P value
Number	5841	4899	942	
Age, years	63.60 (8.38)	63.53 (8.47)	63.98 (7.91)	0.119
Female	2789 (47.7)	2235 (45.6)	554 (58.8)	< 0.001
ACE score	1.50 (1.24)	1.45 (1.22)	1.72 (1.30)	< 0.001
FI31	0.148 (0.120)	0.138 (0.115)	0.200 (0.132)	< 0.001
Frailty (FI31 $\geq$ 0.25)	910 (15.6)	656 (13.4)	254 (27.0)	< 0.001
Ethnic minority	466 (8.0)	362 (7.4)	104 (11.0)	< 0.001
Childhood residence: urban	474 (8.1)	415 (8.5)	59 (6.3)	0.027
Parent education: primary	1825 (31.2)	1548 (31.6)	277 (29.4)	0.217
Parent education: secondary+	359 (6.1)	310 (6.3)	49 (5.2)	
Education: high school	531 (9.1)	477 (9.7)	54 (5.7)	< 0.001
Education: college+	84 (1.4)	79 (1.6)	5 (0.5)	
Not married	609 (10.4)	508 (10.4)	101 (10.7)	0.725
Not employed	1568 (26.8)	1325 (27.0)	243 (25.8)	0.673
Disability	198 (3.4)	152 (3.1)	46 (4.9)	0.019
Health insurance	5496 (94.1)	4601 (93.9)	895 (95.0)	0.427
Life dissatisfaction	650 (11.1)	511 (10.4)	139 (14.8)	< 0.001
Sleep duration, h	6.40 (1.85)	6.46 (1.82)	6.09 (1.97)	< 0.001
Smoking	2508 (42.9)	2168 (44.3)	340 (36.1)	< 0.001
Drinking	2032 (34.8)	1761 (35.9)	271 (28.8)	< 0.001

Values are mean (SD) or n (%). The outcome is new knee pain with a self-reported physician diagnosis history of arthritis/rheumatism in 2018, absent as a combination in 2015. Age and FI31 refer to 2015; adult covariates otherwise refer to 2011. Frailty is FI31 $\geq$ 0.25. Smoking denotes ever smoking; drinking denotes any alcohol use in the previous year. Parent education 'primary' includes literate/primary education, and 'secondary+' denotes middle school or above. High school includes vocational education. P values compare full encoded distributions using Welch t, chi-square or simulated Fisher exact tests and are descriptive only. FI31, 31-item frailty index excluding arthritis/rheumatism.

Knee outcome

The outcome combined knee pain with self-reported physician-diagnosed arthritis or rheumatism in 2018. A positive outcome required reported bodily pain, selection of the knee as a painful site and a positive diagnosis history. We excluded participants who met this combination in 2015. Those with an arthritis diagnosis but no knee pain could remain eligible. Thus, the endpoint captured a newly observed symptomatic combination, not necessarily a new diagnosis. We refer to this combination as a symptomatic KOA proxy.

The 2018 diagnosis indicator combined current responses and preloaded prior diagnoses, following the survey questionnaire [17]. Any reliable positive report established a positive history. A negative status required an explicit negative response and no positive history. Diagnosis history was assigned only when at least one source was interpretable. We applied the same approach to 2015. This avoided classifying a routed follow-up question as a negative diagnosis.

The diagnosis question covers arthritis or rheumatism generally. It does not identify the affected joint or distinguish osteoarthritis from inflammatory arthritis, and imaging confirmation was unavailable. Throughout this paper, incidence refers to new occurrence of the combined phenotype among participants free of that combination in 2015.

Covariates

We used three adjustment sets. Model 1 included age in 2015 and sex. Model 2 added parental education, ethnicity and childhood residence. It also included respondent education, marital status, employment, disability, health insurance, life satisfaction, sleep duration, smoking and drinking. These additional adult covariates came from 2011 records, before the mediator assessment. For childhood residence, village was the reference and city/town the comparison category, following the baseline documentation [18].

Smoking denoted ever smoking; drinking denoted any alcohol use in the year before the 2011 interview. Sleep duration referred to reported nightly sleep. Unrecorded categorical covariates were retained as separate levels in Model 2. For sleep duration, the cohort median and an indicator were used when no value was recorded. Table 1 uses short labels, with category definitions and measurement years in its note. Covariates were selected in advance for their relevance to social circumstances and health, and for comparability with previous ageing and knee-health studies. Table 1P values were not used to select covariates.

Model 3 added systolic and diastolic blood pressure, HDL-C, LDL-C, total cholesterol, triglycerides, uric acid, C-reactive protein, blood urea nitrogen and creatinine. Medication indicators covered antihypertensive, lipid-lowering, glucose-lowering and arthritis drugs. Blood pressure was the mean of up to three measurements, and laboratory variables were standardized within the Model 3 subset. Medication indicators included a separate category when no response was recorded. Model 3 was

limited to 3,700 participants with complete blood-pressure and laboratory measurements and was treated as a sensitivity analysis.

Adult covariates were measured before frailty but after childhood adversity. Some may therefore be consequences of ACEs. Broader adjustment assesses the stability of the association; it does not guarantee adequate control of causal confounding.

Statistical analysis

Continuous variables are reported as means and standard deviations. Categorical variables are reported as counts and percentages. Table 1 compares the primary study variables and prespecified Model 2 covariates by 2018 outcome status. Supplementary Table S1 describes the biomarkers and medication indicators used only in Model 3. It documents the smaller biomarker subset and shows how these measurements were distributed by outcome status. These descriptive P values were not used to choose adjustment variables. We used Welch two-sample t tests for continuous variables and Pearson chi-square tests without continuity correction for medication comparisons with observed Yes/No responses. Tests for multi-category variables in Table 1 compared the full encoded distributions. Simulated Fisher exact tests with 10,000 replicates were used when expected counts were small. All P values were descriptive.

Linear regression estimated the ACE–FI31 association. FI31 was multiplied by ten during model fitting, and coefficients were converted back to the 0–1 scale. Logistic regression estimated the ACE–outcome association before and after FI31 adjustment. ACE ORs are reported per one-point increase; FI31 ORs are reported per 0.1 increase. Confidence intervals and P values used HC0 community-cluster robust standard errors. For Fig. 3B, we standardized Model 2 predicted probabilities over the observed covariate distribution at ACE scores 0–6. The same robust covariance matrix was used with the delta method. The only participant with a score of 7 remained in model fitting but was omitted from the curve because support was sparse.

We estimated natural direct and indirect effects using parametric g-computation and standardization [19]. The mediator model was linear and the outcome model logistic. The outcome model did not include an ACE-by-FI interaction. The contrast was ACE score 1 versus 0 under the continuous-score model. We predicted each participant's outcome risk under the required exposure and mediator distributions, then averaged the risks across participants.

Let $R(a, a^*)$ denote the standardized risk when the outcome-model ACE score is set to a and frailty follows its fitted distribution at score a^* . The natural indirect effect was $R(1, 1)$ minus $R(1, 0)$. The natural direct effect was $R(1, 0)$ minus $R(0, 0)$, and the total effect was $R(1, 1)$ minus $R(0, 0)$. We reported these effects as absolute risk differences in percentage points. The mediated proportion was the indirect effect divided by the total effect. It was not calculated from differences in logistic coefficients or odds ratios.

We integrated over the mediator distribution using 21 equally weighted normal-quantile midpoint nodes. Generated FI values were constrained to 0–1. We sampled communities with replacement 2,000 times and refitted both models in each bootstrap sample. We report percentile 95% confidence intervals and two-sided, plus-one-corrected bootstrap sign-tail P values. No P value was calculated for the mediated proportion. Model 2 was the primary mediation model. Sensitivity analyses used Model 3 or substituted FI32 for FI31 under Model 2. The index comparison used each index's eligible sample rather than a paired subset.

A causal interpretation requires consistency, positivity and correct model specification. It also requires no unmeasured confounding of the exposure–outcome, exposure–mediator or mediator–outcome relations, and no exposure-induced mediator–outcome confounding. CHARLS cannot verify these assumptions. We therefore describe the g-computation result as an indirect association compatible with a frailty pathway, rather than proof that frailty is causal. Analyses used R version 4.5.1.

Results

The linked age-eligible cohort comprised 14,164 participants. Among them, 8,542 had a calculable ACE score, 6,595 did not meet the combined knee–outcome definition in 2015, and 5,917 had an observed outcome in 2018. After applying the FI31 and analytical-variable requirements, 5,841 participants from 442 communities were included (Fig. 2).

During follow-up, 942 participants (16.1%) developed the outcome. The mean age in 2015 was 63.60 years (SD 8.38), and 47.7% were women. The mean ACE score was 1.50 (SD 1.24), and the mean FI31 was 0.148 (SD 0.120). Overall, 910 participants (15.6%) had an FI31 of 0.25 or higher.

Compared with participants who remained outcome-free, those who developed the outcome had higher mean ACE scores (1.72 versus 1.45) and FI31 values (0.200 versus 0.138). Frailty was also more common in the outcome group (27.0% versus 13.4%), as was female sex (58.8% versus 45.6%). Mean age was similar between the groups (63.98 versus 63.53 years; $P = 0.119$). Table 1 presents the remaining characteristics. Recorded arthritis medication use was more frequent in the outcome group (31.9% versus 9.6%; $P < 0.001$), whereas the other variables in Supplementary Table S1 did not differ significantly between the groups.

In the adjusted analyses, each additional ACE was associated with higher odds of the follow-up knee outcome. The OR was 1.20 (95% CI 1.13–1.27) in Model 1 and 1.18 (95% CI 1.11–1.25; $P < 0.001$) in the primary Model 2. Each additional ACE was also associated with a 0.00905 increase in FI31 (95% CI 0.00650–0.01159; $P < 0.001$). In turn, each 0.1 increase in FI31 was associated with higher outcome odds (OR 1.39, 95% CI 1.31–1.47; $P < 0.001$). After FI31 was added to Model 2, the ACE association remained significant (OR 1.15, 95% CI 1.08–1.22; $P < 0.001$). Table 2 and Fig. 3A present the estimates across models.

Table 2
Adjusted ACE–outcome association and frailty pathway estimates

Model	Path	Measure	Estimate (95% CI)	P value
Model 1	ACE → FI	FI difference	0.01058 (0.00802 to 0.01314)	< 0.001
Model 1	FI → outcome	Odds ratio	1.40 (1.33 to 1.48)	< 0.001
Model 1	ACE → outcome	Odds ratio	1.20 (1.13 to 1.27)	< 0.001
Model 1	ACE → outcome adjusted for FI	Odds ratio	1.16 (1.10 to 1.23)	< 0.001
Model 2	ACE → FI	FI difference	0.00905 (0.00650 to 0.01159)	< 0.001
Model 2	FI → outcome	Odds ratio	1.39 (1.31 to 1.47)	< 0.001
Model 2	ACE → outcome	Odds ratio	1.18 (1.11 to 1.25)	< 0.001
Model 2	ACE → outcome adjusted for FI	Odds ratio	1.15 (1.08 to 1.22)	< 0.001
Model 3	ACE → FI	FI difference	0.01160 (0.00876 to 0.01443)	< 0.001
Model 3	FI → outcome	Odds ratio	1.39 (1.29 to 1.49)	< 0.001
Model 3	ACE → outcome	Odds ratio	1.15 (1.07 to 1.23)	< 0.001
Model 3	ACE → outcome adjusted for FI	Odds ratio	1.11 (1.03 to 1.19)	0.006
ACE, adverse childhood experience; FI, frailty index excluding arthritis/rheumatism; CI, confidence interval. Linear coefficients are FI differences on the 0–1 scale per one-point ACE increase. Outcome estimates are ORs per one-point ACE increase or per 0.1 higher FI. Model 1: age and sex. Model 2: Model 1 plus parental education, ethnicity, childhood residence, respondent education, marital status, employment, disability, insurance, life satisfaction, sleep, smoking and drinking. Model 3: Model 2 plus blood pressure, lipids, uric acid, CRP, BUN, creatinine and four medication indicators in complete biomarker cases. CIs use community-cluster robust standard errors. The ACE estimate adjusted for FI is a conditional association and is not the natural direct effect.				

On the probability scale, the model-standardized outcome risk increased with the ACE score. It was 13.0% (95% CI 11.6%–14.4%) at a score of 0, 14.9% (95% CI 13.7%–16.1%) at a score of 1, and 28.0% (95% CI 22.9%–33.1%) at a score of 6 (Fig. 3B).

The mediation analysis supported an indirect pathway through FI₃₁. For the ACE-score contrast of 1 versus 0, the Model 2 natural indirect effect was 0.33 percentage points (95% CI 0.23–0.45; $P < 0.001$). The natural direct effect was 1.58 percentage points (95% CI 0.93–2.18; $P < 0.001$), and the total effect was 1.92 percentage points (95% CI 1.27–2.50; $P < 0.001$). The mediated proportion was 17.4% (95% CI 11.4%–29.4%). All 2,000 bootstrap samples contributed to these estimates. The findings were consistent with partial mediation under the fitted models (Table 3 and Fig. 4).

Table 3
Natural direct and indirect effects through FI31

Model	Effect	Estimate (95% CI)	P value
Model 2	Natural indirect effect	0.33 (0.23 to 0.45)	< 0.001
Model 2	Natural direct effect	1.58 (0.93 to 2.18)	< 0.001
Model 2	Total effect	1.92 (1.27 to 2.50)	< 0.001
Model 2	Proportion mediated	17.4% (11.4% to 29.4%)	
Model 3	Natural indirect effect	0.43 (0.30 to 0.59)	< 0.001
Model 3	Natural direct effect	1.23 (0.31 to 1.99)	0.009
Model 3	Total effect	1.66 (0.78 to 2.42)	< 0.001
Model 3	Proportion mediated	26.1% (15.6% to 58.5%)	
Effects are absolute risk differences in percentage points for an ACE score of 1 versus 0 under the continuous-score model. Proportion mediated is the indirect effect divided by the total effect; no P value is assigned to this ratio. Model 2 is primary. Model 3 additionally adjusts for biomarkers and medications in complete biomarker cases. Confidence intervals and P values were derived from 2,000 community-level bootstrap resamples using the percentile interval and the plus-one-corrected two-sided sign-tail calculation.			

The findings remained consistent after additional adjustment for biomarkers and medications. Model 3 included 3,700 participants and 643 outcomes. The ACE–outcome OR was 1.15 (95% CI 1.07–1.23) before FI31 adjustment and 1.11 (95% CI 1.03–1.19) after FI31 adjustment. The ACE–FI31 coefficient was 0.01160 (95% CI 0.00876–0.01443), and the outcome OR was 1.39 per 0.1 increase in FI31 (95% CI 1.29–1.49). The natural indirect effect was 0.43 percentage points (95% CI 0.30–0.59), with a mediated proportion of 26.1% (95% CI 15.6%–58.5%).

Results were also consistent when FI32 replaced FI31. This analysis included 5,837 participants and 941 outcomes. The natural indirect effect was 0.46 percentage points (95% CI 0.34–0.61), the natural direct effect was 1.44 percentage points (95% CI 0.78–2.04), and the total effect was 1.91 percentage points (95% CI 1.25–2.50). The mediated proportion was 24.3% (95% CI 16.6%–40.3%) (Table 4 and Supplementary Figure S1).

Table 4
Sensitivity analysis using FI32

Mediator	Effect	Estimate (95% CI)	P value
Primary FI31	Natural indirect effect	0.33 (0.23 to 0.45)	< 0.001
Primary FI31	Natural direct effect	1.58 (0.93 to 2.18)	< 0.001
Primary FI31	Total effect	1.92 (1.27 to 2.50)	< 0.001
Primary FI31	Proportion mediated	17.4% (11.4% to 29.4%)	
Sensitivity FI32	Natural indirect effect	0.46 (0.34 to 0.61)	< 0.001
Sensitivity FI32	Natural direct effect	1.44 (0.78 to 2.04)	0.002
Sensitivity FI32	Total effect	1.91 (1.25 to 2.50)	< 0.001
Sensitivity FI32	Proportion mediated	24.3% (16.6% to 40.3%)	
Both analyses use Model 2 and the ACE score 1-versus-0 contrast. FI31 excludes arthritis/rheumatism; FI32 includes it. Natural effects are percentage-point risk differences. Each index uses its eligible sample. No formal comparison between indices was performed. A larger FI32 indirect estimate does not by itself quantify bias from including arthritis.			

Discussion

Higher ACE scores predicted greater odds of the symptomatic knee outcome in 2018. The association changed little after adjustment for demographic, early-life, socioeconomic and behavioural factors. It also remained after FI31 adjustment. FI31 accounted for part of the association: the indirect effect was 0.33 percentage points and represented 17.4% of the total effect. Most of the association remained outside the frailty pathway.

FI31 was measured before the 2018 outcome and did not include arthritis/rheumatism. This reduced direct overlap between the mediator and outcome. It did not fully establish temporal order, however, because frailty and baseline knee status were both assessed in 2015. Some functional deficits may have reflected early or intermittent knee problems. Reverse causation therefore remains possible.

Our ACE–frailty result is consistent with reports from other ageing cohorts. In the Canadian Longitudinal Study on Aging, Mian et al. found a graded association between ACE burden and a 76-item frailty index [20]. The association differed across adversity domains and demographic groups. Its appearance with a different frailty measure suggests that the finding is not confined to one item set. Direct comparison of coefficients is difficult because exposure measures, age distributions and adjustment sets differ.

Prospective results have also varied by population. In the Longitudinal Aging Study Amsterdam, the association with incident frailty was clearest among participants aged 70 years or older who were not frail at baseline [21]. A Chinese cohort linked childhood experiences to baseline frailty and later frailty trajectories [22]. These studies suggest that age and follow-up design influence the observed

association. We included middle-aged and older adults but did not estimate mediation separately by age, sex or adversity type.

The FI31 increase associated with one additional ACE was small. The cumulative score also gives the same weight to experiences that may differ in severity and duration. People with equal scores can therefore have very different histories. Our measure describes overall burden; it cannot identify which experience contributes most to later frailty.

Evidence linking frailty to knee health also supports the proposed pathway. A CHARLS study associated an arthritis-excluded 35-item frailty index with prevalent KOA [23]. Another linked frailty trajectories to later symptomatic KOA in postmenopausal women [24]. That study examined change in frailty, whereas we measured FI31 at a single intermediate wave. The designs answer related but different questions.

Other longitudinal studies report similar patterns. Frailty levels predicted subsequent KOA in CHARLS [25], and baseline frailty predicted worse knee-pain trajectories over nine years in the Osteoarthritis Initiative [26]. Associations between frailty and pain have also been found in cohorts from China, England and the United States [27]. Taken together, these studies support a link between accumulated health deficits and musculoskeletal symptoms. They also leave open the possibility that frailty and pain affect each other.

Frailty indices need not contain identical items, but they should cover several health domains. An Osteoarthritis Initiative study used a 31-item index to examine mortality [28]. This shows that a multidomain FI can be used in a musculoskeletal cohort, although it does not validate our FI31. In a mediation analysis, avoiding overlap between mediator and outcome is more important than matching another study's item count.

Several mechanisms could connect childhood adversity with later knee symptoms. One is greater vulnerability to pain. A systematic review linked childhood adversity to chronic pain in adulthood [29]. In 239 patients awaiting knee arthroplasty, childhood abuse was associated with greater pain interference and poorer self-reported function [30]. That clinical sample differs from our community cohort, but the finding suggests that adversity may influence symptom burden as well as joint disease.

Long-term stress responses provide another possible explanation. ACEs have been associated with higher allostatic load, although studies used different exposure definitions and biomarkers [31]. UK Biobank data also linked childhood adversity to faster phenotypic ageing [32]. In a Canadian cohort, social engagement and allostatic load partly mediated the association between ACEs and multimorbidity [33]. Biological stress and social circumstances may therefore contribute to the accumulation of deficits.

Inflammation and health behaviour may also contribute. Chronic low-grade inflammation connects systemic ageing with local joint changes in osteoarthritis [34]. In UK Biobank, unhealthy lifestyle partly accounted for the association between childhood adversity and frailty [35]. Our biomarker-adjusted analysis retained a positive indirect effect. However, biomarkers were included as covariates rather than

mediators, were measured in 2011, and were unavailable for many participants. We therefore cannot attribute the frailty pathway to inflammation or metabolism.

Functional and psychological changes may be relevant as well. A Canadian study found that the association between ACEs and incident sarcopenia differed by depression status [36]. In CHARLS, sarcopenia was associated with later symptomatic KOA [37]. Xiao et al. also linked ACEs and sleep characteristics to lower-extremity function [38]. FI31 includes functional and psychological deficits, but our analysis cannot separate their individual contributions.

Multimorbidity offers a related explanation. Chinese cohort data have linked ACEs to chronic-disease burden and its trajectories [39]. A meta-analysis reported a dose-dependent association between ACE exposure and multimorbidity [40]. Another CHARLS study examined chronic diseases as mediators between ACEs and disability trajectories [41]. FI31 excluded arthritis but retained other diseases and functional deficits. It therefore represents accumulated health problems rather than a single biological mechanism.

The indirect effect should be interpreted in context. Although its confidence interval excluded zero, the absolute difference was only 0.33 percentage points. The mediated proportion of 17.4% applies to the ACE score 1-versus-0 contrast in the Model 2 covariate distribution. It does not mean that frailty caused 17.4% of cases or that treating frailty would prevent that proportion. Other exposure contrasts may produce different mediated proportions.

FI32 produced a larger indirect estimate than FI31. This was expected because FI32 includes arthritis/rheumatism and therefore shares more content with the knee outcome. The two analyses also used slightly different samples. The difference indicates sensitivity to index composition, not a formal estimate of bias. FI31 remains the primary mediator because it avoids direct diagnostic overlap.

Model 3 also yielded a positive indirect effect. Its larger mediated proportion may reflect the broader adjustment set, the smaller biomarker sample, or both. Some adult covariates may lie on pathways from childhood adversity to later health. Adjusting for them can change the target association and may introduce bias. Consistency in direction is useful, but it does not remove the causal assumptions of mediation analysis.

These findings suggest that childhood social history may be relevant when frailty and knee symptoms are assessed together. Current frailty research supports person-centred assessment across several health domains [42]. ACE histories should be discussed sensitively and should not be treated as deterministic predictors. Our results do not define an ACE threshold for knee-outcome screening.

Frailty is dynamic and varies with age, health and the measurement method [43]. Trials indicate that physical activity and some multicomponent programmes can improve frailty outcomes [44]. Whether these changes reduce knee symptoms among people with ACEs is unknown. Future studies should

measure frailty repeatedly before clinically defined knee outcomes. Intervention studies could then test whether benefits differ by adversity history.

This study has several strengths. We linked multiple CHARLS waves and measured FI31 before the follow-up outcome. We excluded participants with the combined knee phenotype in 2015. We also reconstructed questionnaire skip patterns and removed arthritis/rheumatism from the primary mediator. FI31 was right-skewed and increased with age in both sexes, as expected for a deficit-accumulation measure (Supplementary Figure S2). Cluster-robust inference and community-level bootstrap resampling accounted for dependence within communities.

Several limitations should be considered. ACEs were recalled in later adulthood, and retrospective measures may not identify the same people as prospective measures [45]. The nine-item score did not include every adversity domain used in other CHARLS studies. Selection into the life-history survey and survival to later waves may also limit generalisability.

Our outcome was based on knee pain and a nonspecific history of physician-diagnosed arthritis or rheumatism. CHARLS did not provide imaging, joint-specific diagnoses or adjudicated disease type. We could not distinguish structural KOA from inflammatory arthritis. Nor could we distinguish newly reported symptoms from symptoms in people with an earlier diagnosis. The endpoint should therefore be read as a symptomatic KOA proxy rather than clinically confirmed incident KOA.

Frailty and baseline knee status were measured during the same 2015 wave. Functional deficits could therefore reflect subclinical or intermittent knee disease, even among participants without the combined phenotype. Removing arthritis from FI31 reduced direct overlap but did not eliminate this concern. Repeated frailty measurements before a clinically defined knee outcome would offer stronger temporal evidence.

Residual confounding may remain from adiposity, knee injury, occupational loading, physical activity, diet and other unavailable factors. Some adult covariates may also be consequences of ACEs. Model 3 used a smaller biomarker subset, so its estimates may reflect sample selection as well as wider adjustment. We did not apply attrition weighting, and the unweighted incidence estimate is not nationally representative.

The mediator model treated FI31 as approximately linear and normally distributed, although the index was bounded and right-skewed. The outcome model assumed a linear ACE term and no ACE-by-FI interaction. Figure 3B shows this fitted term on the probability scale; support was sparse at high ACE scores. We did not formally assess sensitivity to unmeasured mediator–outcome confounding. The confidence intervals therefore reflect sampling uncertainty under the fitted models, not every source of bias.

Conclusions

Greater ACE burden was prospectively associated with a new symptomatic knee outcome in middle-aged and older Chinese adults. Frailty explained a modest but statistically supported part of this association after arthritis/rheumatism was removed from the primary index. The remaining direct component was larger, indicating that frailty is one pathway rather than a complete explanation. Studies with repeated frailty measures and clinically verified KOA are needed to test this mechanism more directly.

Abbreviations

ACE	adverse childhood experience
ADL	activity of daily living
BUN	blood urea nitrogen
CESD-10	10-item Center for Epidemiologic Studies Depression Scale
CHARLS	China Health and Retirement Longitudinal Study
CI	confidence interval
CRP	C-reactive protein
DBP	diastolic blood pressure
FI	frailty index
FI31	31-item index excluding arthritis/rheumatism
FI32	32-item index including arthritis/rheumatism
HDL-C	high-density lipoprotein cholesterol
IADL	instrumental activity of daily living
KOA	knee osteoarthritis
LDL-C	low-density lipoprotein cholesterol
OR	

odds ratio
SBP
systolic blood pressure
SD
standard deviation.

Declarations

Ethics approval and consent to participate

The original CHARLS study was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent. The present study analysed de-identified secondary data and involved no new participant contact.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Shibao Xiang and Jiaxing Huang contributed equally to this work. Huai Wu, Chunzhu Gong, Shibao Xiang and Jiaxing Huang drafted the manuscript and prepared the figures. All authors contributed to interpretation of the findings and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data Availability

The data supporting the findings of this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS) and are publicly available through the official data-access portal (<https://charls.charlsdata.com/>) following registration and acceptance of the applicable data-use requirements. Participant-level data are not redistributed with this manuscript. The analytical code and supporting aggregate results are available from the corresponding authors upon reasonable request.

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Figures

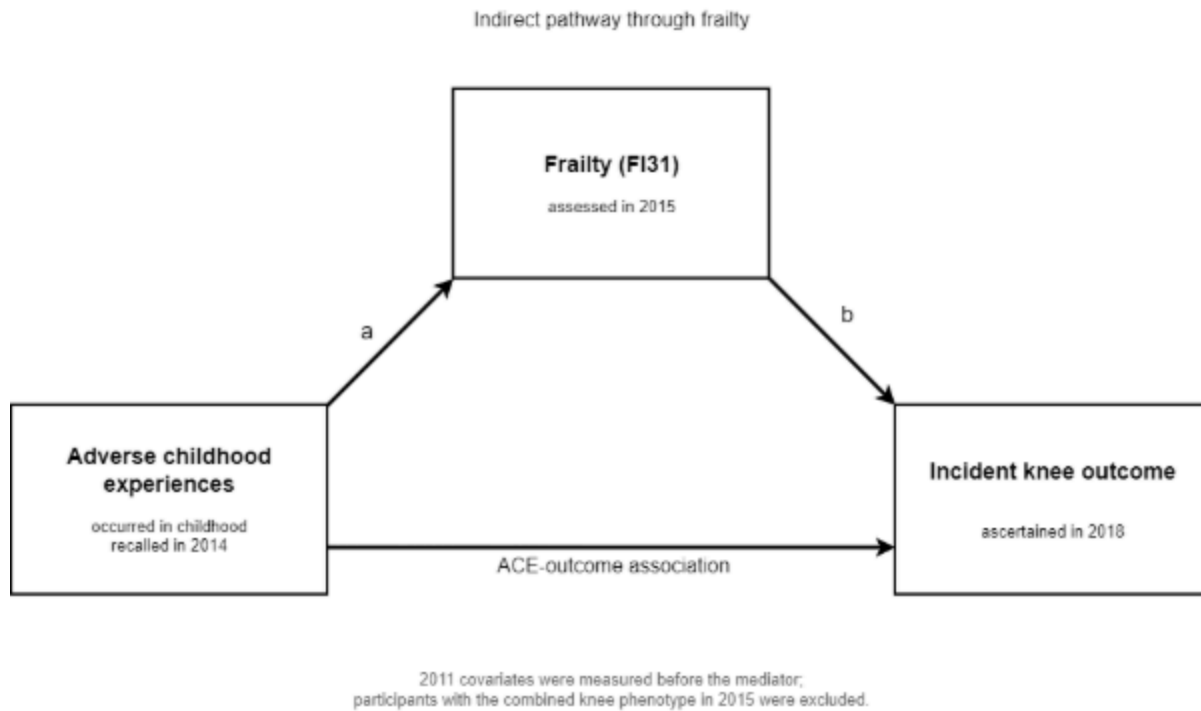
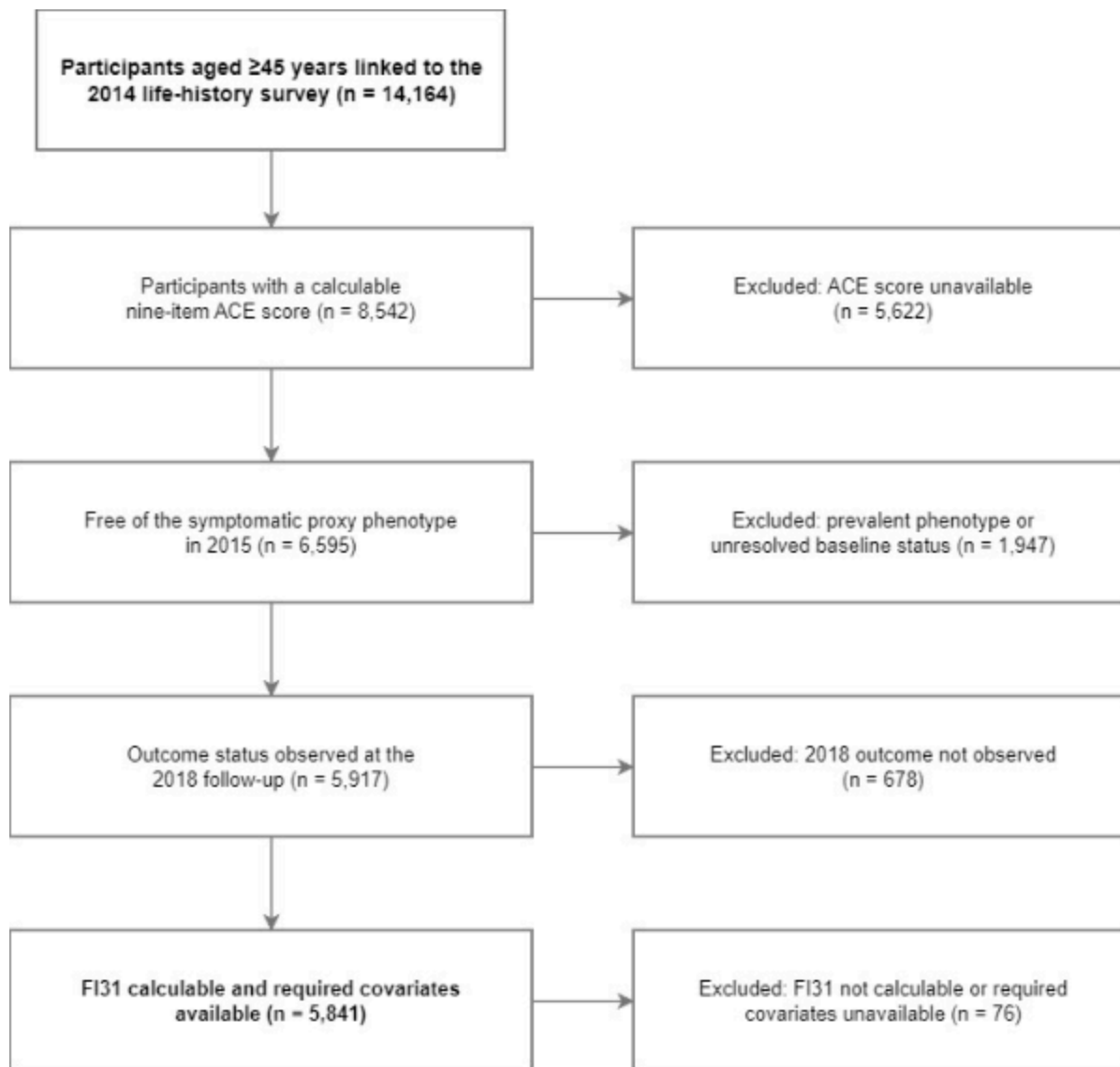


Figure 1

Study timeline and analytic framework

The primary study question was the association between ACE burden and the 2018 knee outcome. The secondary pathway analysis examined FI31 as a mediator. Path a denotes the ACE–FI31 association; path b denotes the FI31–outcome association after ACE adjustment. The horizontal arrow emphasizes the ACE–outcome association. ACEs occurred in childhood and were recalled in 2014, FI31 was measured in 2015, and the outcome was assessed in 2018. Participants with the combined knee phenotype in 2015 were excluded. The figure is conceptual and does not establish causality.



FI31 was calculated when at least 28 of 31 deficits were observed.

Figure 2

Participant selection

Exclusions are sequential. Participants were aged at least 45 years in 2011 and linked to the 2014 life-history survey. The knee outcome combines knee pain with a physician diagnosis history of arthritis/rheumatism. Participants meeting that combination in 2015 were excluded. FI31 required at least 28 of 31 observed deficits after questionnaire-routing correction.

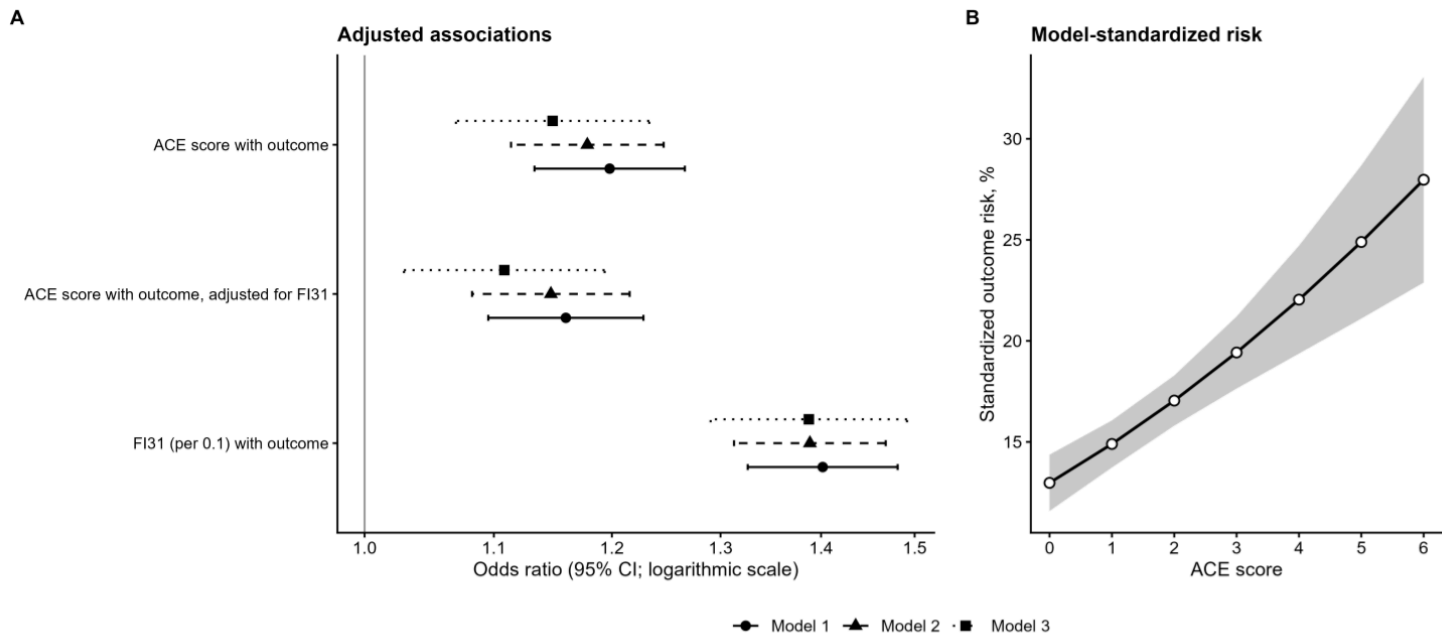


Figure 3

Adjusted associations and model-standardized knee-outcome risk

Panel A shows ORs and 95% CIs for the ACE–outcome association, the ACE–outcome association after FI31 adjustment, and the FI31–outcome association under Models 1–3. ACE estimates are per one-point score increase; FI31 estimates are per 0.1 increase. Panel B shows Model 2 standardized outcome probabilities at ACE scores 0–6 with community-cluster robust delta-method 95% CIs. The score-7 participant was included in model fitting but omitted from the display because $n=1$. The curve is based on a continuous linear ACE term and is not a category-specific analysis.

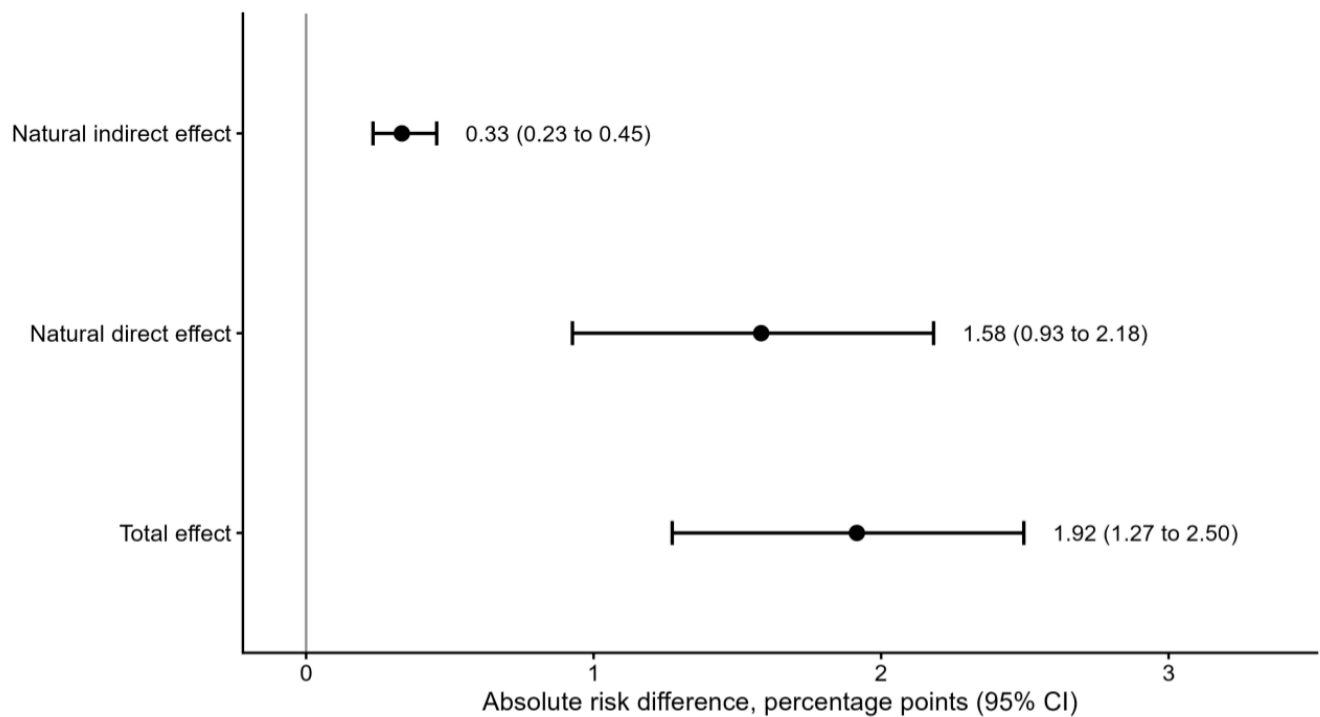


Figure 4

Natural effects through FI31

Points and bars show Model 2 standardized risk differences and percentile 95% CIs for an ACE score of 1 versus 0. The indirect effect was 0.33 percentage points (95% CI 0.23–0.45), and the mediated proportion was 17.4% (95% CI 11.4%–29.4%). Estimates used 2,000 community-level bootstrap resamples. FI31 excludes arthritis/rheumatism.

Supplementary Files

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