

Association Between Frailty Status Transitions and Incident Pain Risk in Older Adults: A Prospective Cohort Study Across Three Countries

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Title Page

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Association Between Frailty Status Transitions and Incident Pain Risk in Older Adults: A Prospective Cohort Study Across Three Countries

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22 **Association Between Frailty Status Transitions and Incident Pain Risk in Older**

23 **Adults: A Prospective Cohort Study Across Three Countries**

24 **Abstract**

25 **Objective:** Frailty and pain frequently co-occur in older adults, yet evidence linking dynamic frailty transitions to
26 incident pain across cultures is scarce. We examined associations of the Frailty Index (FI), frailty transitions, and
27 cumulative frailty burden with incident pain in three countries.

28 **Methods:** Adults aged ≥ 50 from CHARLS (China, $n = 6,473$), HRS (USA, $n = 5,401$), and ELSA (UK, $n = 6,865$) were
29 included. A 28-item FI (covering chronic diseases, sensory impairment, physical functioning, depressive symptoms, and
30 cognition) classified participants as robust ($FI < 0.10$), pre-frail ($0.10 \leq FI < 0.25$), or frail ($FI \geq 0.25$). Frailty transitions
31 were assessed by comparing baseline and second-wave status (approximately 2 years apart). Pain was ascertained via a
32 single self-reported item; participants free of pain at baseline were followed until incident pain, death, or last survey wave
33 (up to 7–15 years). Cox proportional hazards models estimated HRs (95% CIs) with adjustment for demographics,
34 socioeconomic factors, and health behaviors; missing covariate data were imputed using multiple imputation by chained
35 equations(MICE). Kaplan–Meier(KM) curves visualized cumulative pain risk by transition group, and smoothed curves
36 assessed non-linear FI–pain relationships.

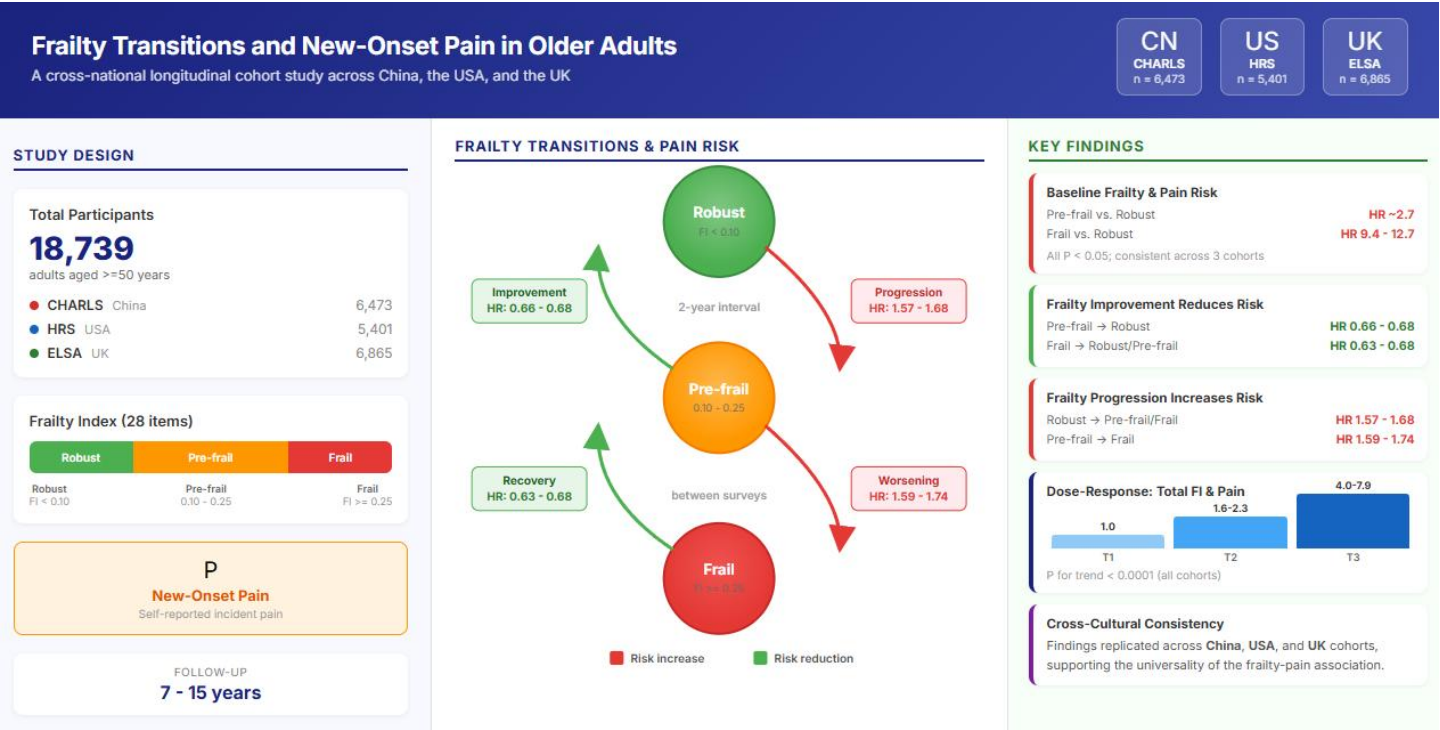
37 **Results:** Among 18,739 participants, baseline pre-frailty and frailty conferred ~ 2.7 -fold and 9–13-fold excess pain risk,
38 respectively. In transition analysis ($n = 10,486$), frailty progression elevated pain risk (CHARLS: HR 1.57; ELSA: HR
39 1.68; HRS: HR 1.11, NS). Pre-frail to frail worsening consistently increased risk (HR 1.59–1.74). Improvement reduced
40 risk: pre-frail to robust (HR 0.66–0.70) and frail to less-frail (HR 0.63–0.76). KM curves showed early divergence and
41 progressive separation across trajectories. Total FI tertiles demonstrated a significant dose–response gradient (highest
42 tertile: HR 3.95–7.88; all P for trend < 0.0001), corroborated by smoothed curves showing a consistent positive FI–pain
43 relationship across cohorts.

44 **Conclusion:** Frailty transitions are bidirectionally associated with incident pain risk across China, the U.S., and England.
45 Preventing frailty progression and promoting recovery may reduce pain burden in aging populations.

46 **Keywords:** Frailty; Incident pain; Frailty status transition; Older adults; Prospective cohort study

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48 **GRAPHICAL ABSTRACT**



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50

51 **Introduction**

52 As the global population ages rapidly, the health of older adults has become a more significant concern in public health.
53 Frailty and chronic pain are two common health issues among older adults, significantly affecting functional
54 independence, quality of life, and public health systems^[1]. Frailty is a condition seen in older adults that involves a
55 decrease in the body's ability to function across multiple systems and a lower capacity to handle stress. It is linked to
56 increased disability, higher rates of hospitalization, greater mortality, and a lower quality of life^[2,3]. Pain is also a common
57 health issue among older adults. Chronic pain significantly affects daily activities and social interactions. It is also
58 associated with various negative outcomes, such as depression, cognitive difficulties, and increased mortality^[4]. Previous
59 research has indicated that frailty and pain frequently occur together in older populations, with around 45%–70% of frail
60 older adults experiencing chronic pain^[5]. Persistent pain is a separate factor that can predict the onset of frailty^[6], and
61 increased severity of frailty is linked to a higher risk of having additional pain conditions^[7,8].

62 However, most longitudinal studies have concentrated solely on the relationship between static baseline frailty status and
63 the risk of developing pain, overlooking the predictive significance of changes in frailty status—specifically, progression
64 or recovery—for the onset of new pain^[9,10]. Frailty has a certain level of reversibility: some older adults may move from
65 a frail or pre-frail condition to a healthier state over time. If improving frailty can lead to a decrease in pain risk, this
66 would create a significant foundation for research on interventions^[7]. Second, many current studies rely on samples from
67 only one country or region and do not include systematic comparisons across different cultures and countries^[11]. This
68 limitation makes it challenging to assess whether the observed relationships are universal or influenced by particular
69 socio-cultural contexts. Third, previous research has used varying methods for assessing frailty. The Fried frailty
70 phenotype is based on five criteria related to physical performance impairment, while the Frailty Index (FI) proposed by
71 Rockwood and Mitnitski is the most commonly used method^[12]. Additionally, these studies have differed significantly
72 in their adjustment for covariates, resulting in considerable variability between studies that makes meaningful
73 comparisons challenging^[13,14].

74 To address these gaps, the current study used data from three large prospective cohort studies from China, the United
75 States, and the United Kingdom—the China Health and Retirement Longitudinal Study (CHARLS), the Health and

76 Retirement Study (HRS), and the English Longitudinal Study of Ageing (ELSA)^[1,15]. The study aimed to systematically
77 evaluate the relationships between the FI, transitions in frailty status (including progression and improvement), and
78 cumulative frailty burden (total FI) with the risk of developing pain, while also comparing the consistency of these
79 relationships across different socio-cultural contexts. We proposed that, in all three groups, higher FI and worsening
80 frailty status would be linked to an increased risk of developing pain, while improvement in frailty status would be
81 connected to a decreased risk of pain^[7].

82 **Methods**

83 **Study Design and Population**

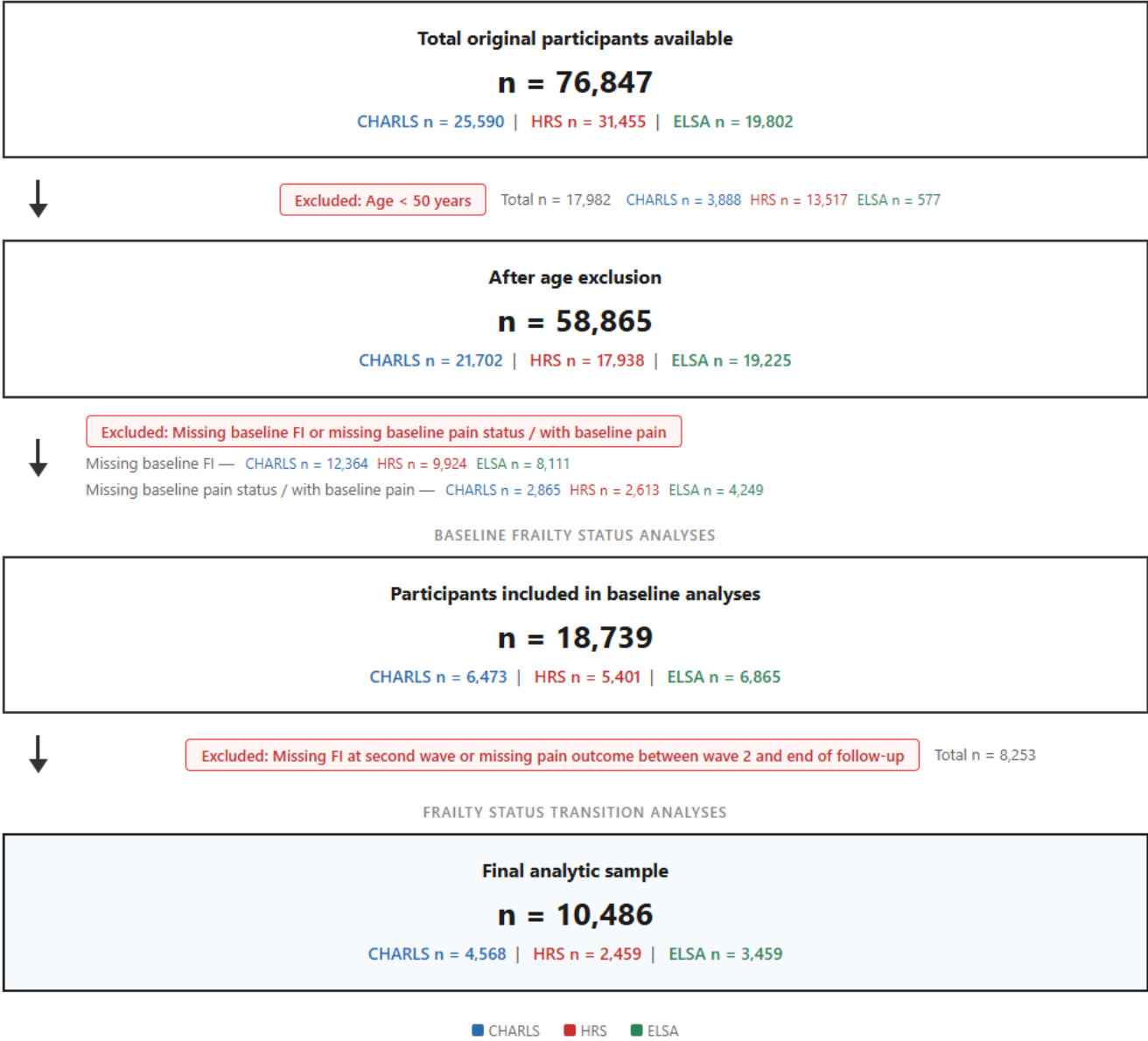
84 Data for this study were obtained from three nationally representative prospective cohort studies: CHARLS^[16], HRS^[17]
85 , and ELSA^[18]. Detailed study designs of these cohorts are included in the Supplementary Methods. CHARLS Wave 1
86 (2011), HRS Wave 8 (2006), and ELSA Wave 1 (2002–2003) were used as the baseline data sources. To monitor follow-
87 up outcomes, participants were tracked using the most recent survey waves: CHARLS Wave 4 (2018), HRS Wave 15
88 (2020), and ELSA Wave 9 (2018–2019). All three studies have similar design characteristics, such as the same survey
89 intervals (about every two years) and uniform evaluations of functioning and health-related factors. CHARLS, ELSA,
90 and HRS obtained ethical approval from the Institutional Review Boards of Peking University, the London Multi-Centre
91 Research Ethics Committee, and the University of Michigan, respectively. Informed consent in writing was acquired
92 from all participants in each group.

93 **Screening and Sample Size**

94 Figure 1 presents the participant screening process for each cohort. Across the three cohorts, a total of 76,847 original
95 participants were available (CHARLS: 25,590; HRS: 31,455; ELSA: 19,802). First, participants younger than 50 years
96 were excluded (CHARLS: n = 3,888; HRS: n = 13,517; ELSA: n = 577). Participants with missing baseline FI (CHARLS:
97 n = 12,364; HRS: n = 9,924; ELSA: n = 8,111) or missing baseline pain status/with baseline pain (CHARLS: n = 2,865;
98 HRS: n = 2,613; ELSA: n = 4,249) were further excluded. A total of 18,739 participants were ultimately included in the
99 baseline frailty status analyses (CHARLS: 6,473; HRS: 5,401; ELSA: 6,865). For frailty status transition analyses,

100 building upon the baseline sample, we further excluded participants with missing FI at the second survey wave and those
101 with missing pain outcome data between the second wave and the end of follow-up, yielding a final analytic sample of
102 10,486 participants (CHARLS: 4,568; HRS: 2,459; ELSA: 3,459).

103 **Figure 1 Selection process of the study population.** CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of
104 Ageing; HRS, Health and Retirement Study; FI, frailty index



105

106 **Assessment of Frailty Index**

107 The FI was developed using the deficit accumulation model^[19-21], which includes 28 health deficit items related to chronic

diseases, sensory impairment, self-rated overall health, physical functioning, depressive symptoms, and cognitive function. Items 1 to 27 were assigned scores of 0 (indicating no deficit) or 1 (indicating a deficit present), while Item 28 (cognition) was measured as a continuous variable with values ranging from 0 to 1. The FI was determined by summing individual deficit scores and dividing by 28, resulting in a value between 0 and 1, where higher values reflect greater severity of frailty. Participants were categorized based on established cut-off values as robust ($FI < 0.10$), pre-frail ($0.10 \leq FI < 0.25$), or frail ($FI \geq 0.25$)^[22,23]. The 28 deficit items are outlined in Supplementary Table S1.

Definition of Frailty Status Transition

Frailty status transitions were assessed by comparing the frailty status category at the beginning with that at the second survey wave (CHARLS Wave 2, 2013; HRS Wave 9, 2008; ELSA Wave 2, 2004–2005). The data and ratios of participants in each transition type are presented in Table 3. Additionally, the total FI (baseline FI plus second-wave FI)^[24] was calculated and divided into tertiles to assess the relationship between cumulative frailty burden and the risk of developing pain, thus reflecting the changing aspects of frailty status.

Outcome Ascertainment and Follow-up

The primary outcome was incident pain. Pain was assessed via a single self-reported item: participants were asked, "Are you often troubled by bodily pain?" (CHARLS) or "Are you often troubled with pain?" (HRS, ELSA), with responses of "yes" or "no" indicating whether they were currently experiencing pain. Participants who reported pain at baseline were excluded; only those free of pain at baseline were included, ensuring that all outcomes represented incident pain. In baseline frailty status analyses, follow-up started from the baseline wave; in frailty status transition analyses, follow-up started from the second survey wave. The follow-up endpoint was the first occurrence of pain, death, or the last available survey wave (censoring), whichever occurred first.

Covariates

Covariates included age, sex, marital status, education level, employment status, residential area (not collected in ELSA), living with children, smoking status, and alcohol consumption. In the CHARLS study, life satisfaction (satisfied/dissatisfied) was also included as a covariate. To ensure comparability across cohorts, marital status was

standardized as a binary variable: "married/partnered" versus "other marital status" (which includes separated, divorced, never married, or widowed). Comprehensive definitions of covariates and the harmonization method used across cohorts can be found in the Supplementary Methods.

Statistical Analysis

Baseline characteristics were described by frailty category (robust/pre-frail/frail). Continuous variables were presented as mean $\pm$ standard deviation (SD), and categorical variables as frequency (percentage). Cox proportional hazards regression models were used to estimate the association between frailty and incident pain risk, with results expressed as Hazard Ratios (HRs) and 95% Confidence Intervals (CIs). The analyses comprised three components: (1) association between baseline frailty status and incident pain risk in the second-wave population (Supplementary Table S3); (2) association between frailty status transitions and incident pain risk (Table 4), with Kaplan-Meier (KM) curves illustrating cumulative incidence by transition group (Figure 2); and (3) association between total FI tertiles and incident pain risk, with trend tests conducted by entering the median value of each tertile as a continuous variable in the regression model (Table 5). We additionally computed the mean of the baseline FI and the second-wave FI and performed smoothed curve fitting to examine the non-linear relationship between mean FI and incident pain risk (Figure 3). For each analysis, two models were constructed: Model 1 was unadjusted; Model 2 adjusted for all covariates listed above. Missingness rates for covariates are shown in Supplementary Table S2. As detailed in the Supplementary Methods, missing covariate data were handled using multiple imputation by chained equations (MICE). Proportional hazard assumptions for these Cox regression models were confirmed by the Schoenfeld residual^[25,26].

Sensitivity Analyses

We conducted the following sensitivity analyses: (1) To further examine the association between frailty status transitions and incident pain, we separated the combined "pre-frail/frail" group from the "robust/pre-frail" group in the transition analyses (Supplementary Table S4). (2) Given ongoing debate regarding the FI thresholds for defining frailty status, we adopted an alternative set of widely accepted cut-off values (frail: $FI > 0.21$; pre-frail: $0.10 < FI \leq 0.21$; robust: $FI \leq 0.10$)^[24] to reclassify frailty status (Supplementary Table S5), thereby verifying the robustness of the primary results.

156 All analyses were performed using R version 4.1.2 and Empower® software. A two-sided $P < 0.05$ was considered
157 statistically significant.

158 **Results**

159 **Baseline Characteristics of the Study Population**

160 Following the screening process, the baseline frailty status analytic sample included 6,473 participants from CHARLS,
161 5,401 from HRS, and 6,865 from ELSA. Table 1 shows the basic characteristics of the participants. The proportions of
162 robust, pre-frail, and frail participants were 56.99%, 38.44%, and 4.57% in CHARLS; 5.72%, 61.51%, and 32.74% in
163 HRS; and 46.38%, 44.80%, and 8.83% in ELSA. In all three groups, increased frailty severity was consistently linked to
164 older age, a higher percentage of women, a greater number of unmarried individuals, and a lower chance of being
165 employed. For the analyses of frailty status transitions, based on the pre-defined criteria, 4,568 participants from
166 CHARLS, 2,459 participants from HRS, and 3,459 participants from ELSA were included. The baseline characteristics
167 of the participants are presented in Table 2, and the analogous trends observed were comparable to those displayed in
168 Table 1.

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Table 1 Baseline characteristics of participants for baseline frailty status analyses

Variables	CHARLS(n=6473)			HRS(n=5401)			ELSA(n=6865)		
	Robust	Pre-frail	Frail	Robust	Pre-frail	Frail	Robust	Pre-frail	Frail
Number, n(%)	3689(56.99)	2488(38.44)	296(4.57)	309(5.72)	3323(61.51)	1769(32.74)	3184(46.38)	3075(44.80)	606(8.83)
Age, mean ±SD, years	60.13 ± 7.33	63.02 ± 8.23	65.58 ± 8.39	72.83 ± 7.37	72.49 ± 6.36	75.45 ± 7.44	61.17 ± 8.83	66.05 ± 10.01	73.48 ± 10.19
Gender, n(%)									
Female	1493 (40.47)	1172 (47.11)	173 (58.45)	110 (35.60)	1730 (52.06)	1148 (64.90)	1573 (49.40)	1646 (53.53)	346 (57.10)
Male	2196 (59.53)	1316 (52.89%)	123 (41.55)	199 (64.40)	1593 (47.94)	621 (35.10)	1611 (50.60)	1429 (46.47)	260 (42.90)
Marital status, n(%)									
Unmarried/divorced /widowed/others	368 (9.98)	385 (15.47)	58 (19.59)	112 (36.25)	1147 (34.52)	860 (48.62)	854 (26.82)	1066 (34.67)	340 (56.11)
Married/with a partner	3321 (90.02)	2103 (84.53)	238 (80.41)	197 (63.75)	2176 (65.48)	909 (51.38)	2330 (73.18)	2009 (65.33)	266 (43.89)
Working, n(%)									
No	1302 (35.29)	1063 (42.73)	173 (58.45)	213 (68.93)	2389 (71.89)	1515 (85.64)	1411 (44.32)	1999 (65.01)	549 (90.59)
Yes	2387 (64.71)	1425 (57.27)	123 (41.55)	96 (31.07)	934 (28.11)	254 (14.36)	1773 (55.68)	1076 (34.99)	57 (9.41)
Residential area, n(%)									
Urban Community	1753 (47.52%)	1134 (45.58)	127 (42.91)	225 (72.82)	2338 (70.36)	1184 (66.93)	/	/	/
Rural Village	1936 (52.48)	1354 (54.42)	169 (57.09)	84 (27.18)	985 (29.64)	585 (33.07)	/	/	/
Co-residence with children, n(%)									
No	1545 (41.88)	1158 (46.54)	145 (48.99)	229 (74.11)	2693 (81.04)	1314 (74.28)	2256 (70.85)	2405 (78.21)	523 (86.30)
Yes	2144 (58.12)	1330 (53.46%)	151 (51.01)	80 (25.89)	630 (18.96)	455 (25.72)	928 (29.15)	670 (21.79)	83 (13.70)
Smoking ,n(%)									
No	2319 (62.86)	1694 (68.09)	223 (75.34)	258 (83.50)	3053 (91.87)	1592 (89.99)	1326 (41.65)	1072 (34.86)	184 (30.36)
Yes	1370 (37.14)	794 (31.91)	73 (24.66)	51 (16.50)	270 (8.13)	177 (10.01)	1858 (58.35)	2003 (65.14)	422 (69.64)
Drinking, n(%)									
No	2228 (60.40)	1642 (66.00%)	231 (78.04)	154 (49.84)	1442 (43.39)	996 (56.30)	203 (6.38)	290 (9.43)	103 (17.00)
Yes	1461 (39.60)	846 (34.00)	65 (21.96)	155 (50.16)	1881 (56.61)	773 (43.70)	2981 (93.62)	2785 (90.57)	503 (83.00)
Satisfaction with life,n(%)									
Dissatisfied	2720 (73.73)	1887 (75.84)	246 (83.11)	/	/	/	/	/	/
Satisfied	969 (26.27)	601 (24.16)	50 (16.89)	/	/	/	/	/	/

CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; ELSA, English Longitudinal Study of Ageing.
Continuous variables were expressed as mean±standard deviation (SD) in case of normal distribution, and categorical variables are presented as counts (percentages).

Table 2 Baseline characteristics of participants for changes in frailty status analyses

Variables	CHARLS(n=4568)			HRS(n=2459)			ELSA(n=3459)		
	Robust	Pre-frail	Frail	Robust	Pre-frail	Frail	Robust	Pre-frail	Frail
Number, n(%)	2049(44.85)	2153(47.13)	366(8.02)	108 (4.39)	1499 (60.96)	852 (34.65)	1291(37.33)	1682(48.61)	486(14.05)
Age, mean ±SD, years	59.59 ± 6.89	61.89 ± 7.58	64.42 ± 8.29	71.25 ± 6.00	70.96 ± 4.82	72.72 ± 5.75	59.33 ± 7.48	63.09 ± 8.78	68.87 ± 10.29
Gender, n(%)									
Female	758 (36.99)	968 (44.96)	205 (56.01)	41 (37.96%)	841 (56.10%)	589 (69.13%)	641 (49.65)	925 (54.99)	307 (63.17)
Male	1291 (63.01)	1185 (55.04)	161 (43.99)	67 (62.04%)	658 (43.90%)	263 (30.87%)	650 (50.35)	757 (45.01)	179 (36.83)
Marital status, n(%)									
Unmarried/divorced /widowed/others	179 (8.74)	263 (12.22)	66 (18.03)	29 (26.85%)	477 (31.82%)	352 (41.31%)	313 (24.24)	515 (30.62)	233 (47.94)
Married/with a partner	1870 (91.26)	1890 (87.78)	300 (81.97)	79 (73.15%)	1022 (68.18%)	500 (58.69%)	978 (75.76)	1167 (69.38)	253 (52.06)
Working, n(%)									
No	634 (30.94)	840 (39.02)	205 (56.01)	75 (69.44%)	1009 (67.31%)	664 (77.93%)	491 (38.03)	926 (55.05)	390 (80.25)
Yes	1415 (69.06)	1313 (60.98)	161 (43.99)	33 (30.56%)	490 (32.69%)	188 (22.07%)	800 (61.97)	756 (44.95)	96 (19.75)
Residential area, n(%)									
Urban Community	914 (44.61)	1004 (46.63)	164 (44.81)	78 (72.22%)	1057 (70.51%)	547 (64.20%)	/	/	/
Rural Village	1135 (55.39)	1149 (53.37)	202 (55.19)	30 (27.78%)	442 (29.49%)	305 (35.80%)	/	/	/
Co-residence with children, n(%)									
No	851 (41.53)	971 (45.10)	153 (41.80)	79 (73.15%)	1204 (80.32%)	652 (76.53%)	858 (66.46)	1258 (74.79)	410 (84.36)
Yes	1198 (58.47)	1182 (54.90)	213 (58.20)	29 (26.85%)	295 (19.68%)	200 (23.47%)	433 (33.54)	424 (25.21)	76 (15.64)
Smoking ,n(%)									
No	1261 (61.54)	1438 (66.79)	279 (76.23)	94 (87.04%)	1403 (93.60%)	786 (92.25%)	563 (43.61)	644 (38.29)	169 (34.77)
Yes	788 (38.46)	715 (33.21)	87 (23.77)	14 (12.96%)	96 (6.40%)	66 (7.75%)	728 (56.39)	1038 (61.71)	317 (65.23)
Drinking, n(%)									
No	1225 (59.79)	1337 (62.10)	269 (73.50)	43 (39.81%)	598 (39.89%)	442 (51.88%)	73 (5.65)	108 (6.42)	71 (14.61)
Yes	824 (40.21)	816 (37.90)	97 (26.50)	65 (60.19%)	901 (60.11%)	410 (48.12%)	1218 (94.35)	1574 (93.58)	415 (85.39)
Satisfaction with life,n(%)									
Dissatisfied	1490 (72.72)	1654 (76.82)	284 (77.60)	/	/	/	/	/	/
Satisfied	559 (27.28)	499 (23.18)	82 (22.40)	/	/	/	/	/	/

CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; ELSA, English Longitudinal Study of Ageing. Continuous variables were expressed as mean±standard deviation (SD) in case of normal distribution, and categorical variables are presented as counts (percentages).

185 Frailty Status Transitions between Baseline and the Second Wave

186 Table 3 shows the frequencies and proportions of changes in frailty status from the baseline to the second survey wave
187 (approximately two years) across the three cohorts. In CHARLS, 60.97% of participants who were robust at baseline

188 remained robust in the second wave, 36.12% progressed to pre-frail, and 2.91% progressed to frail. Among baseline pre-
189 frail participants, 23.76% improved to robust, 64.18% remained pre-frail, and 12.06% worsened to frail. Among the
190 baseline frail participants, 5.17% transitioned to robust, 48.28% moved to pre-frail, and 46.55% continued to be frail. In
191 HRS, the persistence of frailty status was notable: 77.32% of participants who were frail at baseline continued to be frail
192 at the second wave, while only 0.27% improved to robust. Among those who were pre-frail at baseline, 79.21% remained
193 in the pre-frail category. In ELSA, 65.89% of participants who were robust at baseline continued to be robust, 77.82%
194 of those who were frail at baseline remained frail, and only 0.38% improved to a robust state.

Table 3 Number and percentage of the changes in frailty status

Baseline	The second survey	CHARLS n(%)	HRS n(%)	ELSA n(%)
	Robust	1632(60.97%)	55(40.74%)	1047(65.89%)
Robust	Pre-frail	967(36.12%)	74(54.82%)	512(32.24%)
	Frail	78(2.91%)	6(4.44%)	30(1.89%)
	Robust	408(23.76%)	51(3.20%)	243(15.15%)
Pre-frail	Pre-frail	1102(64.18%)	1261(79.21%)	1112(69.33%)
	Frail	207(12.06%)	280(17.59%)	249(15.52%)
	Robust	9(5.17%)	2(0.27%)	1(0.38%)
Frail	Pre-frail	84(48.28%)	164(22.40%)	58(21.80%)
	Frail	81(46.55%)	566(77.32%)	207(77.82%)

The time interval between baseline and the second survey was two years in the CHARLS, ELSA, and HRS.

CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; ELSA, English Longitudinal Study of Ageing

196 **Association between Baseline Frailty Status and Incident Pain Risk in the Second-Wave Population**

197 In the analyses of baseline frailty status based on the second-wave population (Supplementary Table S3), both pre-frail
198 and frail statuses were linked to a significantly higher risk of developing incident pain compared to robust status. After
199 adjusting for covariates, pre-frail participants had about 2.7 times the risk of pain compared to robust participants across
200 all three cohorts (CHARLS: HR = 2.79, 95% CI 2.36–3.30; HRS: HR = 2.69, 95% CI 1.16–6.25; ELSA: HR = 2.66, 95%
201 CI 2.19–3.23). Frail participants had a risk that was approximately 9 to 13 times greater (CHARLS: HR = 9.85, 95% CI
202 7.71–12.5; HRS: HR = 9.37, 95% CI 4.04–21.73; ELSA: HR = 12.7, 95% CI 9.7–16.66). The associations showed a high
203 level of consistency across all three groups.

204 **Association between Frailty Status Transitions and Incident Pain Risk**

205 Table 4 shows the relationships between changes in frailty status and the risk of developing pain. Among baseline robust
206 participants, those who progressed to pre-frail or frail exhibited a significantly higher risk of pain compared to those who
207 remained robust (CHARLS: HR = 1.57, 95% CI 1.40–1.75, Model 2; ELSA: HR = 1.68, 95% CI 1.48–1.89, Model 2).
208 The association showed a consistent direction in HRS but did not achieve statistical significance (HR = 1.11, 95% CI
209 0.71–1.73, P = 0.64, Model 2). Among baseline pre-frail participants, those who improved to robust status showed
210 significantly lower pain risk compared to those who remained pre-frail (CHARLS: HR = 0.66, 95% CI 0.56–0.77, Model
211 2; ELSA: HR = 0.68, 95% CI 0.58–0.80, Model 2; HRS: HR = 0.70, 95% CI 0.48–1.03, P = 0.07, directionally consistent
212 but not significant). Conversely, participants who worsened to frail status exhibited significantly higher risk (CHARLS:
213 HR = 1.59, 95% CI 1.34–1.89, Model 2; HRS: HR = 1.66, 95% CI 1.46–1.89, Model 2; ELSA: HR = 1.74, 95% CI 1.50–
214 2.02, Model 2), with consistent direction across all three cohorts. Among baseline frail participants, those who improved
215 to a less frail state (pre-frail or robust) exhibited a lower risk of pain compared to those who remained frail. The results
216 were as follows: CHARLS: HR = 0.63, 95% CI 0.43–0.92, P = 0.017, Model 2; HRS: HR = 0.68, 95% CI 0.56–0.82,
217 Model 2; ELSA: HR = 0.76, 95% CI 0.56–1.02, P = 0.07, Model 2.

Table 4 Association of changes in frailty status with risk of pain

	CHARLS					HRS					ELSA				
	event/n	HR1(95%CI)	P1	HR2(95%CI)	P2	event/n	HR1(95%CI)	P1	HR2(95%CI)	P2	event/n	HR1(95%CI)	P1	HR2(95%CI)	P2
Stable robust	700/1632	1(reference)		1(reference)		35/55	1(reference)		1(reference)		689/1047	1(reference)		1(reference)	
Robust to pre-frail/frail	608/1045	1.59 (1.42, 1.77)	<0.001	1.57 (1.40, 1.75)	<0.001	52/80	1.10 (0.71, 1.68)	0.674	1.11 (0.71, 1.73)	0.6449	451/542	1.72 (1.53, 1.94)	<0.001	1.68 (1.48, 1.89)	<0.001
Stable pre-frail	729/1102	1(reference)		1(reference)		798/1261	1(reference)		1(reference)		978/1112	1(reference)		1(reference)	
Pre-frail to robust	210/408	0.67 (0.58, 0.78)	<0.001	0.66 (0.56, 0.77)	<0.001	27/51	0.74 (0.50, 1.09)	0.1229	0.70 (0.48, 1.03)	0.0697	182/243	0.67 (0.57, 0.78)	<0.001	0.68 (0.58, 0.80)	<0.001
Pre-frail to frail	168/207	1.60 (1.35, 1.90)	<0.001	1.59 (1.34, 1.89)	<0.001	242/280	1.82 (1.60, 2.07)	<0.001	1.66 (1.46, 1.89)	<0.001	241/249	1.85 (1.60, 2.14)	<0.001	1.74 (1.50, 2.02)	<0.001
Stable frail	70/81	1(reference)		1(reference)		518/566	1(reference)		1(reference)		205/207	1(reference)		1(reference)	
Frail to robust/pre-frail	46/93	0.73 (0.53, 1.02)	0.0647	0.63 (0.43, 0.92)	0.0170	132/166	0.67 (0.56, 0.82)	<0.001	0.68 (0.56, 0.82)	<0.001	59/59	0.75 (0.56, 1.01)	0.0556	0.76 (0.56, 1.02)	0.0679

CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; ELSA, English Longitudinal Study of Ageing.
HR1 and P1 were unadjusted
HR2and P2 were adjusted for age、Gender、Marital status、Education、Working、Residential area(Exclude ELSA)、Co-residence with children、Smoking、Drinking、Satisfaction with life（Exclude HRS and ELSA）

218

219 Figure 2 shows the Kaplan-Meier cumulative risk curves for the three groups, organized by initial frailty status and

220 categorized by the direction of frailty status change. A clear pattern was observed in all three groups: as the frailty

221 trajectory moved toward progression, the cumulative incidence of new pain increased more quickly. The curves for each

222 group began to diverge early in the follow-up period and continued to separate as time progressed. Among baseline robust

223 participants, the stable robust group exhibited the lowest cumulative risk, while the group that progressed to pre-frail or

224 frail status demonstrated a significantly higher cumulative risk. In the baseline pre-frail participants, a distinct three-way

225 divergence was noted: the group that improved to robust had the lowest cumulative risk, the stable pre-frail group had an

226 intermediate risk, and the group that worsened to frail exhibited the highest cumulative risk, with the most significant

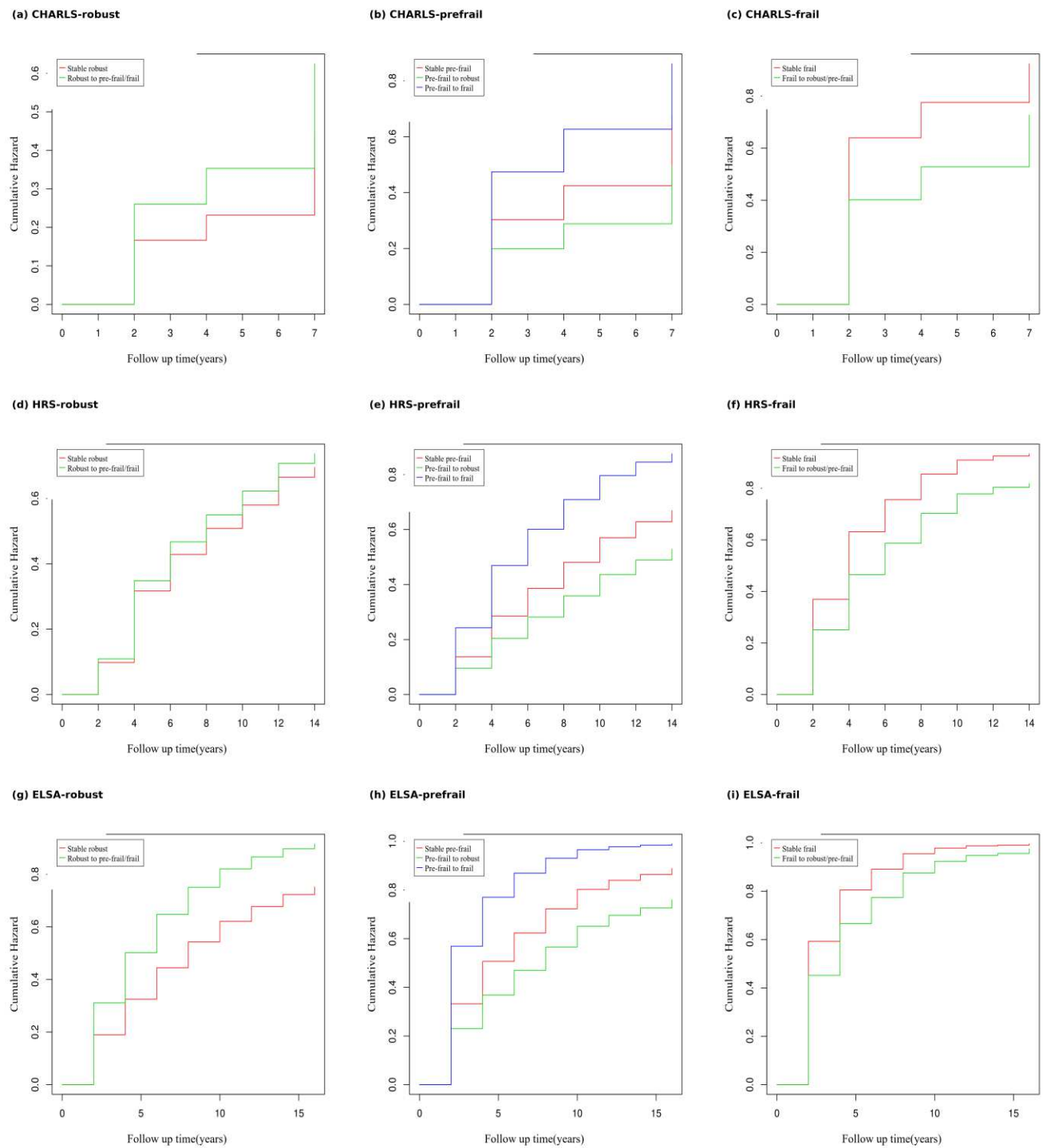
227 increase. Among baseline frail participants, the stable frail group exhibited the highest cumulative risk, while

228 improvement to a less frail state was linked to a noticeably lower cumulative risk.

229

230

231 **Figure 2. Cumulative hazard of new-onset pain among individuals with different frailty state transitions**



235 **Dose–Response Relationship between Total FI and Incident Pain Risk**

236 The total FI was calculated by adding the baseline FI to the FI from the second survey, and the data were organized into
237 tertiles, the risk of incident pain increased significantly with higher total FI, showing a clear dose–response relationship
238 (P for trend < 0.0001, consistent across all three cohorts, Table 5). After adjusting for covariates, the middle tertile
239 exhibited an increased risk of pain compared to the lowest total FI tertile (CHARLS: HR = 1.57, 95% CI 1.40–1.75,
240 Model 2; HRS: HR = 2.28, 95% CI 1.84–2.83, Model 2; ELSA: HR = 1.86, 95% CI 1.53–2.26, Model 2). The highest
241 tertile demonstrated an even greater risk (CHARLS: HR = 3.95, 95% CI 3.36–4.63, Model 2; HRS: HR = 5.71, 95% CI
242 4.37–7.46, Model 2; ELSA: HR = 7.88, 95% CI 5.72–10.85, Model 2).

Table 5 Association of total frailty index with risk of pain

	CHARLS					HRS					ELSA				
	event/n	HR1(95%CI)	P1	HR2(95%CI)	P2	event/n	HR1(95%CI)	P1	HR2(95%CI)	P2	event/n	HR1(95%CI)	P1	HR2(95%CI)	P2
T1 of total FI	631/1518	1(reference)		1(reference)		448/805	1(reference)		1(reference)		772/1151	1(reference)		1(reference)	
T2 of total FI	806/1520	1.59 (1.37, 1.83)	<0.001	1.57 (1.40, 1.75)	<0.001	620/829	2.38 (1.93, 2.93)	<0.001	2.28 (1.84, 2.83)	<0.001	924/1146	2.04 (1.69, 2.47)	<0.001	1.86 (1.53, 2.26)	<0.001
T3 of total FI	1124/1530	3.89 (3.34, 4.53)	<0.001	3.95 (3.36, 4.63)	<0.001	736/825	6.51 (5.02, 8.43)	<0.001	5.71 (4.37, 7.46)	<0.001	1109/1162	10.27(7.6, 13.89)	<0.001	7.88 (5.72, 10.85)	<0.001
P for trend test		<0.001		<0.001			<0.001		<0.001			<0.001		<0.001	

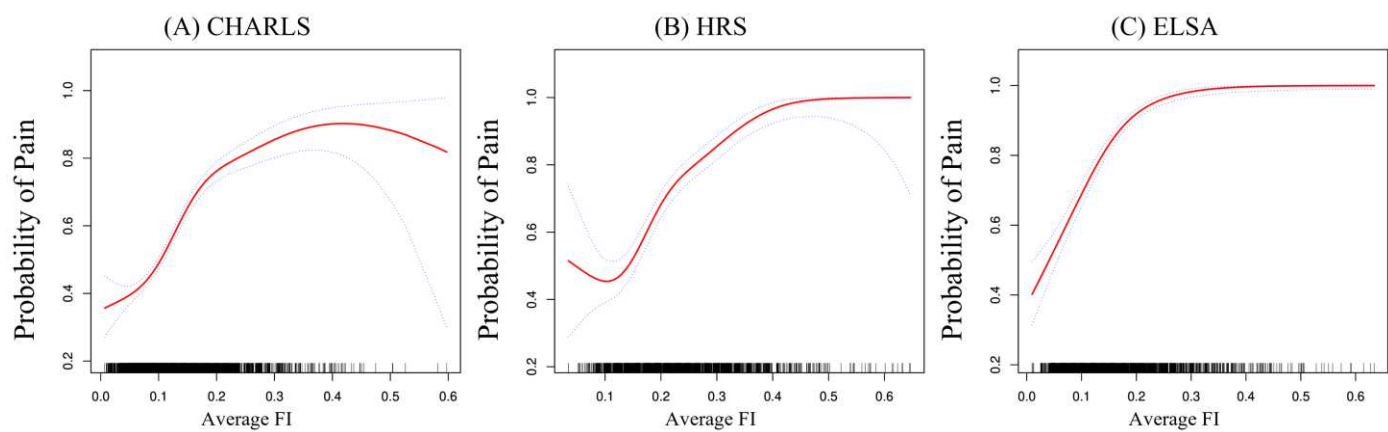
CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; ELSA, English Longitudinal Study of Ageing.
HR1 and P1 were unadjusted
HR2and P2 were adjusted for age、 Gender、 Marital status、 Education、 Working、 Residential area(Exclude ELSA)、 Co-residence with children、 Smoking、 Drinking、 Satisfaction with life（Exclude HRS and ELSA）

243

244 To better understand the continuous shape of the FI–pain probability relationship, we created smoothed fitting curves
245 using the mean of baseline FI and second-wave FI (Figure 3). In general, all three groups showed a positive relationship
246 between higher average FI and an increased likelihood of developing pain, which aligns with the findings presented in
247 Table 5. In CHARLS, there was a nearly linear relationship between FI and pain probability. As FI increased from 0 to
248 around 0.35, the probability of experiencing pain rose from about 0.35 to roughly 0.90. After an FI of approximately 0.4,
249 the curve levelled off, indicating that FI was a strong predictor of pain risk across nearly the entire range of FI values in
250 this population. In HRS, the curve showed a threshold pattern: when FI was below 0.15, the probability of pain stayed
251 around 0.5. However, once FI surpassed this point, the risk increased sharply toward about 1.0, suggesting that only

252 higher levels of FI significantly raised the risk of pain in HRS. In ELSA, the curve increased quickly within the FI range
253 of 0.0–0.2 to about 1.0 and then levelled off, indicating that in this older group, once FI surpassed a relatively low
254 threshold, the risk of pain reached a near maximum. The variations in the absolute levels of the curves among the cohorts
255 (CHARLS < HRS < ELSA) aligned with the differences in follow-up duration and the baseline age structure seen in the
256 KM curves. Despite the variation in curve shapes resulting from different baseline characteristics of the populations, the
257 strong positive relationship between FI and pain probability was consistently observed in all three cohorts.

258 **Figure 3. Dose-response relationships between the average frailty index and the probability of developing pain.**



260 **Sensitivity Analyses**

261 Analyses that separated the "pre-frail/frail" group from the "robust/pre-frail" group showed that a decline in frailty status
262 was linked to a higher risk of developing pain, while an improvement in frailty status was connected to a lower risk
263 (Supplementary Table S4). Additionally, due to the debate regarding the FI thresholds that determine frailty status, we
264 utilized a different set of commonly accepted cut-offs. After redefining frailty status with the alternative FI thresholds
265 (frail: $FI > 0.21$; pre-frail: $0.10 < FI \leq 0.21$; robust: $FI \leq 0.10$), the direction and statistical significance of all primary
266 analyses did not change (Supplementary Table S5). These sensitivity analyses provide additional support for the
267 reliability of the main findings.

268 **Discussion**

269 In this study, we carefully examined the relationships between the FI changes in frailty status, and the overall frailty
270 burden (total FI) with the risk of developing pain in older adults from three large prospective cohorts: China (CHARLS),
271 the United States (HRS), and the United Kingdom (ELSA). The main findings are as follows. Initially, a greater level of
272 baseline frailty was linked to an increased risk of developing pain, showing a clear graded effect. Second, changes in
273 frailty status were significantly predictive of pain: participants whose frailty worsened had a higher risk of pain, while
274 those whose frailty improved had a lower risk. This bidirectional relationship was further supported by the Kaplan-Meier
275 cumulative risk curves (Figure 2). Third, total FI and pain risk showed a significant dose–response relationship, and the
276 smoothed fitting curves of mean FI (Figure 3) indicated a consistent positive association between higher FI and increased
277 pain probability across all three cohorts. Fourth, these associations were consistent across three countries with different
278 socio-cultural backgrounds, indicating that the frailty–pain association has cross-cultural generalizability. These findings
279 enhance our understanding of the relationship between frailty and pain in both directions. They also broaden the research
280 focus from fixed associations to changing patterns, offering important evidence over time for intervention strategies.

281 Our findings about baseline frailty status and pain risk align with earlier studies. Several cross-sectional studies have
282 shown that frailty is an independent risk factor for chronic pain, indicating a significant positive relationship between the
283 two^[27-29]. However, previous studies have mostly focused on a single group or country. By conducting analyses in three
284 countries with varying cultural and economic contexts, this study confirms the consistency of this association across
285 cultures, significantly improving the external validity of the findings.

286 This study also includes the changes in frailty status over time within the analytical framework. While earlier studies
287 have looked into the prevalence of frailty and its relationships with health outcomes at a single point in time, there is a
288 lack of research that includes the long-term patterns of frailty development. A meta-analysis by Kojima et al. showed
289 that almost half of older adults living in the community experienced changes in their frailty status during follow-up^[30],
290 suggesting that frailty is not a permanent condition. In this study, we discovered that baseline pre-frail participants who
291 transitioned to robust status after about two years had a 32%–34% lower risk of developing pain compared to those who
292 stayed pre-frail (CHARLS and ELSA; a similar trend was noted in HRS, although it was not statistically significant). On

the other hand, participants who deteriorated from pre-frail to frail exhibited a 59%–74% increase in pain risk. A similar two-way relationship was noted among participants who were frail at baseline. The Kaplan-Meier cumulative risk curves (Figure 2) show the pattern of divergence in cumulative risk over time among different frailty trajectory groups: the improvement group had the lowest cumulative risk, the progression group had the highest, and the stable group was in an intermediate position. The curves started to separate early in the follow-up period and continued to diverge over time, suggesting that the impact of frailty trajectory on pain risk is not a temporary occurrence but a long-term cumulative process^[31]. This finding indicates that reversing the frailty trajectory through specific interventions may be an effective approach for alleviating pain in older adults, providing clear objectives for future research on interventions.

The current study systematically examined the dose–response relationship between cumulative frailty burden^[24] and pain risk by stratifying total FI tertiles (Table 5) and using smoothed fitting curves of mean FI (Figure 3). Results from Table 5 indicate that, in comparison to the lowest total FI tertile, the highest tertile was linked to a pain risk that was approximately 4 to 8 times greater (CHARLS: HR = 3.95; HRS: HR = 5.71; ELSA: HR = 7.88), with all trend tests achieving statistical significance. The smoothed fitting curves in Figure 3 show a consistent positive relationship between FI and pain probability across all three cohorts, although the shapes of the curves varied due to differences in population characteristics. In ELSA, pain probability reached a plateau at relatively low FI levels, likely due to the older baseline age and higher frailty severity in this group. In CHARLS, the curve covered a wider FI range and displayed an approximately linear increase, indicating that in populations with milder frailty, the ability of FI to indicate pain risk can extend into higher FI ranges. Despite the variation in curve shape, the positive association between FI and pain probability was consistently observed in all three cohorts, further supporting the generalizability of the frailty and pain relationship across different cultures.

Regarding potential mechanisms, the connection between frailty and pain likely involves several interconnected biological and behavioral pathways^[32,33]. From a biological viewpoint, chronic low-grade inflammation, such as increased levels of interleukin-6 (IL-6) and C-reactive protein (CRP), is a fundamental mechanism that contributes to both the onset and advancement of frailty, as well as the processes of central and peripheral pain sensitization. Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and oxidative stress have also been associated with both conditions^[34,35]. From a functional and behavioral viewpoint, declines in muscle strength related to frailty, along with

319 reduced physical activity and fear of falling, can result in decreased mobility and social participation. This, in turn, may
320 lower pain thresholds, creating a harmful cycle of "frailty–pain–disability"^[4]. Additionally, chronic pain can speed up
321 the progression of frailty by limiting physical activity, disrupting sleep, and influencing mood, thus creating a mutually
322 reinforcing cycle.

323 The strengths of this study include the following: (1) the use of a large-sample prospective cohort design across three
324 countries shows the consistency of the findings across cultures; (2) the analysis of frailty status transitions included both
325 improvement and worsening directions, offering a thorough understanding of the relationship between frailty trajectories
326 and pain risk; (3) a standardized 28-item FI was used, and covariates were systematically adjusted, which minimized
327 differences between studies; and (4) several sensitivity analyses were conducted, which confirmed the reliability of the
328 results.

329 Several limitations of this study should be recognized. First, the observational design cannot eliminate residual
330 confounding, and causal inference is still not possible^[36]. Second, pain outcomes were evaluated using a single self-
331 reported item that did not measure pain intensity, location, or type, which could lead to some level of misclassification
332 bias^[5]. Third, frailty status transitions were assessed using only two time points (baseline and the second wave), which
333 may not reflect shorter-term changes. Fourth, mortality data in ELSA were available only up to Wave 6, which may lead
334 to informative censoring. Fifth, unmeasured covariates, such as genetic factors, detailed medication history, and analgesic
335 use, may have contributed to residual confounding^[37].

336

337 **Conclusion**

338 In summary, this study, which is based on three representative multinational prospective cohorts, shows that frailty status
339 and its changes are independently and consistently linked to the risk of developing pain in older adults: an increase in
340 frailty raises the risk of pain, while an improvement in frailty status lowers it. These associations were confirmed in older
341 adult populations in China, the United States, and the United Kingdom. This highlights the importance of including frailty
342 assessment in regular screenings for pain risk in older adults and focusing on improving frailty or delaying its progression

343 to prevent pain. Future research should focus on interventional studies, such as randomized controlled trials involving
344 physical exercise, nutritional support, and comprehensive management by multiple disciplines. These studies aim to
345 assess whether enhancing frailty status can effectively decrease pain incidence in older adults and to investigate the
346 potential benefits of pain management in slowing the progression of frailty.

347 **List of abbreviations**

348 CHARLS China Health and Retirement Longitudinal Study

349 CI Confidence Interval

350 CRP C-reactive protein

351 ELSA English Longitudinal Study of Ageing

352 FI Frailty Index

353 HPA Hypothalamic – Pituitary – Adrenal

354 HR Hazard Ratio

355 HRS Health and Retirement Study

356 IL-6 Interleukin-6

357 KM Kaplan – Meier

358 MICE Multiple Imputation by Chained Equations

359 SD Standard Deviation

360 **Declarations**

361 **Generative AI and AI-assisted technologies**

362 During the composition of this work, no generative AI and AI-assisted technologies was employed.

363 **Consent for publication**

364 This manuscript does not contain any individual person's data in any form (including individual details, images, or videos),
365 and therefore consent for publication is not applicable

366 **Ethics approval and consent to participate**

CHARLS received approval from the Ethics Review Committee of Peking University. HRS received approval from the University of Michigan. ELSA received approval from London Multi-Centre Research. All individuals signed informed consent. All procedures performed in the studies involving human participants were in accordance with the Declaration of Helsinki-Ethical Principles for Medical Research.

Availability of data and materials

Data supporting the results of this study are available from official websites of China Health and Retirement Longitudinal Study (<http://charls.pku.edu.cn>), English Longitudinal Study of Ageing (<https://ukdataservice.ac.uk>), and Health and Retirement Study (<https://hrs.isr.umich.edu>)

Competing interests

No potential conflicts of interest relevant to this article were reported.

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Authors' contributions

Siyu Liao: Conceptualization, Methodology, Formal Analysis, Writing - Original Draft Preparation.

Xin Hua.: Data Curation, Software, Validation, Writing - Review & Editing.

Haorui Li: Investigation, Resources, Visualization.

Senda Zhong: Supervision, Writing - Review & Editing, Project Administration.

All authors have read and agreed to the published version of the manuscript.

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388 **Clinical Trial Number**

389 Not applicable

390

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