

The associations of dynamic pain transitions with osteoarthritis risk and the mediating role of frailty in middle-aged and older adults

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Abstract

As the global population ages, pain and frailty have emerged as increasingly important health concerns among middle-aged and older adults and may contribute to the development and progression of osteoarthritis (OA). However, the longitudinal associations of pain status and its dynamic transitions with OA risk, and the mediating effect of frailty in this association, remain insufficiently understood. Using five international longitudinal cohorts (HRS, CHARLS, SHARE, ELSA, and MHAS) comprising 67,374 adults aged ≥ 50 years, complemented by local hospital data (including 6,538 adults) and bidirectional Mendelian randomization (MR), we examined the associations among pain, frailty, and incident OA. Multistate Markov models showed that transition intensity and probability to OA were higher in individuals with pain than in pain-free individuals, while the intensity of recovering to a pain-free state exceeded that of progressing to OA. Regardless of severity, baseline pain significantly increased the risk of OA, and MR confirmed that pain-free status was linked to a lower risk of knee/hip OA. OA risk was elevated by transitions from pain-free to pain but reduced by recovery from pain to pain-free status, with consistent patterns observed across all pain severity levels. Frailty partially mediated the association between pain and OA (mediation proportions 8.80%–21.70%), primarily through mobility limitations such as difficulty rising from a chair. Cross-lagged panel network analysis identified pain and mobility decline (difficulty stooping or getting up from a chair) as stable prospective predictors of OA. Pain at first period predicted mobility decline at second period, which in turn predicted OA at third period. Subgroups with strong associations included employed/retired individuals and those with unhealthy lifestyles. These findings emphasize the importance of combined strategies for pain management and frailty prevention to alleviate the OA burden in aging populations.

Introduction

Osteoarthritis (OA) represents a complex and heterogeneous joint disease¹. It is one of the main causes of long-term disability in adults and is closely related to high medical expenses². Approximately 595 million people worldwide suffered from osteoarthritis in 2020, accounting for nearly 7.6% of the global population³. Population growth and aging are expected to contribute to a substantial increase in cases over the coming decades⁴. Given the limited availability of effective disease-modifying treatments, identifying potentially modifiable factors that precede clinically recognized OA is important for improving risk stratification and developing preventive strategies in aging populations.

Pain, which is highly prevalent in middle-aged and older adults, has been increasingly recognized as a potential upstream risk factor for OA rather than merely a symptom of existing joint pathology⁵. Several biological and behavioral pathways may contribute to this association. At the systemic level, sustained pain upregulates pro-inflammatory mediators such as C-reactive protein and interleukin-6, which have been directly implicated in cartilage matrix degradation and synovial inflammation—two core processes in OA pathogenesis^{6–8}. At the behavioral level, individuals experiencing chronic pain frequently adopt activity-avoidance patterns⁹, leading to physical inactivity, muscle deconditioning, and altered joint

loading, which can accelerate degenerative processes within articular tissues^{10,11}. Therefore, studying the relationship between pain and OA is important to elucidate the disease mechanism and provide a reference for public health policies aimed at preventing or alleviating OA. However, pain is not necessarily a static exposure. Over time, individuals may remain pain-free, develop new pain, experience persistent pain, or recover from pain to a pain-free state. Most previous studies have primarily evaluated pain measured at a single time point, thereby providing limited insight into whether transitions in pain status are accompanied by corresponding changes in subsequent OA risk. In particular, whether the onset of pain is associated with an increased risk of OA and whether recovery from pain is associated with a lower risk remain insufficiently characterized. Evaluating these transitions may therefore provide information beyond that obtained from baseline pain status alone and may help identify potentially modifiable periods of musculoskeletal vulnerability.

Frailty is a multidimensional state characterized by the accumulation of health deficits and reduced physiological reserve¹². Pain and frailty are closely intertwined in aging populations. Pain can drive progressive physical inactivity¹³, nutritional compromise, and psychological distress¹⁴, all of which accelerate the accumulation of frailty deficits. Moreover, frailty-related inflammation may exacerbate pain-induced cartilage degradation and synovial inflammation¹⁵, while muscle weakness and impaired proprioception can cause joint instability and abnormal loading, contributing to structural joint damage¹⁶. Thus, frailty is not merely a coexisting condition with pain but may function as a critical mediator that translates the experience of chronic pain into tangible joint pathology. Nevertheless, previous studies have generally examined pain, frailty, and OA separately or have focused on their baseline associations^{17,18}. Therefore, whether frailty mediates the relationship between pain status, its transitions, and subsequent OA risk remains uncertain.

Accordingly, using five large population-based longitudinal aging cohorts from different countries, together with an independent local hospital dataset, we aimed to comprehensively investigate the longitudinal relationships among pain, frailty, and OA in middle-aged and older adults. Specifically, we sought to: (1) examine the association of baseline pain status with subsequent OA risk; (2) determine whether transitions in pain status, particularly the onset of pain and recovery from pain to a pain-free state, were associated with subsequent OA risk; (3) determine whether frailty mediated the associations of pain status and its transitions with subsequent OA risk. We additionally examined pain severity and transitions across different pain severity levels to further characterize these relationships. Multistate models were used to describe transitions among pain-free, pain, and OA states, while complementary Mendelian randomization and cross-lagged panel network analyses were performed to further evaluate the robustness, temporal relationships, and potential pathways underlying the observed associations. By considering pain as a time-varying condition rather than a single baseline exposure, this study may provide a more comprehensive understanding of the relationship between pain and OA and clarify the potential role of frailty in this longitudinal process (Fig. 1).

Results

Baseline characteristics

Demographic characteristics, including mean age, sex distribution, and pain status, were summarized across cohorts (Supplementary Tables 4 and 5 to 9). The mean ages for the five cohorts were as follows: HRS, 65.38 years; CHARLS, 61.94 years; SHARE, 65.98 years; ELSA, 64.94 years; and MHAS, 61.20 years. Females represented 46.7%-54.6% of participants, with baseline pain prevalence of 12.6%-35.4% and follow-up OA incidence of 22.7%-54.2%. Across countries, the United States exhibited the lowest baseline pain prevalence (12.56%), and Israel had the lowest incidence of subsequent OA (2.75%). By contrast, the highest values for these two measures were recorded in Slovenia and the United States (Supplementary Table 10). As depicted in Fig. 2A-E, Supplementary Fig. 7, and Supplementary Table 11, the proportion of pain was significantly higher among the participants who later developed OA than among those who remained non-OA across all five cohorts. This pattern was consistent across different countries.

Transitions among pain-free, pain, and OA

The mean follow-up times for the five cohorts were as follows: HRS, 9.30 years; CHARLS, 6.64 years; SHARE, 5.52 years; ELSA, 7.58 years; and MHAS, 10.80 years. Supplementary Table 12 summarizes the transitions observed from each state to the next at follow-up. Among the participants with pain, the proportions transitioning to OA at the subsequent assessment were 24.51% (HRS), 13.30% (CHARLS), 20.42% (SHARE), 27.26% (ELSA), and 14.45% (MHAS). Correspondingly, 39.97%, 40.98%, 30.47%, 29.76%, and 41.91% reverted to pain-free status.

The transition intensity among pain-free, pain, and OA is shown in Fig. 1L and Supplementary Table 13. In HRS, the transition intensity to a pain-free state (0.322, 95% CI 0.299–0.345) was 1.84 times higher than that to OA (0.175, 95% CI 0.156–0.197) among individuals with pain. In CHARLS, the intensity of reverting to pain-free (0.340, 95% CI 0.323–0.358) was 2.70 times the intensity of progressing to OA (0.126, 95% CI 0.121–0.132). In SHARE, the transition intensity to pain-free (0.211, 95% CI 0.205–0.217) was 1.85 times that of OA onset (0.114, 95% CI 0.111–0.118). In ELSA, the intensity to pain-free (0.211, 95% CI 0.198–0.224) was 1.04 times that to OA (0.203, 95% CI 0.189–0.217). In MHAS, the intensity to pain-free (0.322, 95% CI 0.305–0.341) was 5.65 times that to OA (0.057, 95% CI 0.051–0.063). As illustrated in Fig. 2F-K and Supplementary Figs. 8–9, the cumulative probability of progressing to OA increased steadily over follow-up in the pain-free group and group with pain, and individuals with pain consistently exhibited higher probabilities than pain-free participants did.

Baseline pain status or degree, and OA risk

Cross-sectional logistic regression analyses revealed that pain was significantly associated with OA (Fig. 3A and Supplementary Tables 14 and 16). For example, in the fully adjusted Model 4, the ORs were 4.47 (95% CI, 4.12–4.84) for HRS, 3.44 (95% CI, 3.19–3.72) for CHARLS, 5.03 (95% CI, 4.79–5.29) for

SHARE, 2.54 (95% CI, 2.28–2.84) for ELSA, 3.01 (95% CI, 2.74–3.31) for MHAS, and 2.81 (95% CI, 2.74–2.90) for the pooled cohort. Similar result was obtained from the local hospital dataset (OR 1.72, 95% CI 1.06–2.81) (Fig. 3A and Supplementary Tables 15).

These curves showed that the participants with any pain and those in each pain severity category had a significantly higher risk of OA than the pain-free participants did (Supplementary Figs. 10 and 11). We further applied Cox proportional hazards models to examine the associations of baseline pain status and degree with incident OA. Across all levels of adjustment, the participants with baseline pain remained at significantly higher OA risk than the pain-free participants did. For instance, the fully adjusted Model 4 yielded HRs of 1.72 (1.58, 1.88) in HRS, 1.71 (1.56, 1.87) in CHARLS, 2.05 (1.96, 2.13) in SHARE, 2.59 (2.39, 2.82) in ELSA, 1.69 (1.55, 1.85) in MHAS, and 1.94 (1.88, 1.99) in the pooled cohort (Fig. 3B and Supplementary Tables 17). The finding was uniformly consistent in most countries, demonstrating that baseline pain conferred a significantly elevated risk of incident OA (Supplementary Table 18). In all cohorts, a consistently elevated risk of OA was observed across all pain severity levels relative to the pain-free group, and the risk increased progressively with pain severity (Fig. 3C and Supplementary Table 19).

Using bidirectional two-sample MR, we found that absence of pain in the past month was associated with a significantly low risk of knee and hip OA (IVW, OR 0.077, 95% CI 0.013–0.473), while the reverse direction showed no significant effect (Supplementary Fig. 20). Sensitivity analyses confirmed the robustness of these findings (Fig. 3D-E and Supplementary Tables 21–22).

Transitions of pain status or severity, and OA risk

The participants who transitioned from pain-free to pain had a significantly elevated risk of developing OA than those who remained pain-free did (HRS: 1.80 [1.58, 2.05]; CHARLS: 1.86 [1.56, 2.22]; SHARE: 1.66 [1.52, 1.81]; ELSA: 1.83 [1.53, 2.17]; MHAS: 1.88 [1.57, 2.25]; pooled: 1.63 [1.54, 1.73]) (Fig. 4A and Supplementary Table 23). This finding was consistent with the meta-analytic pooled estimate, which showed no significant heterogeneity (pooled HR 1.75, 95% CI 1.65–1.86; $I^2 = 0\%$) (Supplementary Fig. 13). By contrast, the participants who transitioned from pain to pain-free status exhibited a significantly reduced OA risk relative to those with persistent pain (HRS: 0.72 [0.58–0.88]; CHARLS: 0.67 [0.53–0.86]; SHARE: 0.69 [0.63–0.76]; ELSA: 0.71 [0.56–0.90]; MHAS: 0.69 [0.57–0.84]; and pooled cohort: 0.69 [0.64–0.74]) (Fig. 4A and Supplementary Table 23). The pooled meta-analysis confirmed this association, showing an HR of 0.69 (95% CI, 0.65–0.74) without evidence of heterogeneity ($I^2 = 0\%$).

Compared with the participants who remained pain-free, those who shifted from pain-free to mild pain (pooled HR 1.65, 95% CI 1.43–1.92; $I^2 = 64\%$), moderate pain (pooled HR 1.90, 95% CI 1.75–2.06; $I^2 = 0\%$), or severe pain (pooled HR 1.82, 95% CI 1.46–2.27; $I^2 = 51\%$) experienced a significantly elevated OA risk (Fig. 4H and Supplementary Fig. 13). These findings were consistent with the results from the pooled cohort, with HRs of 1.45 (95% CI 1.33–1.58) for transition to mild pain, 1.81 (95% CI 1.67–1.95) for moderate pain, and 1.62 (95% CI 1.41–1.86) for severe pain (Fig. 4G and Supplementary Table 24).

Meanwhile, the participants who shifted from mild pain to pain-free (pooled HR 0.75, 95% CI 0.60–0.94; $I^2 = 37\%$), from moderate pain to pain-free (pooled HR 0.69, 95% CI 0.60–0.81; $I^2 = 18\%$), or from severe pain to pain-free (pooled HR 0.62, 95% CI 0.50–0.76; $I^2 = 0\%$) all exhibited a significantly lower OA risk compared with those who remained at the corresponding baseline pain severity (Fig. 4H and Supplementary Fig. 13). These findings were consistent with the results from the pooled cohort, which yielded HRs of 0.80 (95% CI 0.68–0.94), 0.68 (95% CI 0.61–0.76), and 0.58 (95% CI 0.47–0.72) for transitions from mild to pain-free, moderate to pain-free, and severe to pain-free, respectively (Fig. 4G and Supplementary Table 24). The remaining patterns of transition in pain severity showed significant associations with OA risk only in individual cohorts. For example, compared with those who remained consistently at mild pain, a significantly elevated OA risk was observed exclusively in SHARE and ELSA among the participants who transitioned from mild pain to severe pain (SHARE: HR 1.61, 95% CI 1.07–2.41; ELSA: HR 2.32, 95% CI 1.01–5.34) (Fig. 4 and Supplementary Table 24).

Mediation analysis

The results indicated that frailty partially mediated this relationship with the following mediation proportions: HRS, 8.80%; CHARLS, 16.70%; SHARE, 12.20%; ELSA, 18.30%; MHAS, 21.70%; and pooled, 15.56% (Fig. 5). Furthermore, the transition from pain-free to pain was mediated by frailty in the pathway to OA in HRS (9.60%), SHARE (18.20%), and the pooled cohort (18.18%) (Fig. 4). Frailty acted as a mediator in the relationship between transitioning from pain to pain-free and OA within SHARE (20.60%) and the pooled cohort (11.80%) (Fig. 5).

Cross-lagged panel network analysis

Across all five cohorts, pain at T1 and T2, together with certain mobility limitations (specifically, difficulty in stooping and getting up from a chair), prospectively predicted incident OA at T2 and T3 (Fig. 6 and Supplementary Fig. 16). Moreover, T1 pain predicted subsequent worsening in these mobility functions at T2 in all cohorts, suggesting an indirect pathway: T1 pain → T2 difficulty in stooping/getting up → T3 OA. Supplementary Tables 25–34 provide the edge weights, expressed as regularized logistic regression coefficients. Stability analyses were additionally performed for the network models, confirming their robustness (Supplementary Figs. 14–15 and 17–18).

We also examined the mediating effects of individual frailty components on the relationship between baseline pain and incident OA (Supplementary Tables 35–37). The results showed that the components with significant mediating effects were predominantly mobility-related items. Among them, difficulty in getting up from a chair exhibited a significant mediating effect across all five cohorts, with proportions of 4.74% in HRS, 11.05% in CHARLS, 4.40% in SHARE, 11.49% in ELSA, and 9.28% in MHAS. In addition, stooping, kneeling, or crouching exhibited a significant mediating effect in four cohorts (CHARLS: 13.62%; SHARE: 5.50%; ELSA: 14.22%; MHAS: 11.91%) (Fig. 6F and Supplementary Table 37).

Subgroup analysis

Supplementary Table 38 presents the subgroup-specific associations between baseline pain status and incident OA. Across most cohorts, these associations were stronger among employed or retired participants and individuals with unhealthy lifestyles.

Sensitivity analyses

We performed sensitivity analyses to test the robustness of our results. After incident OA cases occurring within the first 2 years of follow-up (Supplementary Tables 39 and 40); participants who had joint pain at baseline from the CHARLS, SHARE, and ELSA cohorts (Supplementary Tables 41–44); and participants lost to follow-up (Supplementary Tables 45–48) were excluded, reanalysis yielded results consistent with the primary findings. When death was treated as a competing risk for OA (Supplementary Tables 49–52) and PSM was applied to minimize potential residual confounding (Supplementary Figs. 19–21 and Supplementary Tables 53–56), the significant associations of pain status and severity and their transitions, persisted with subsequent OA risk.

Discussion

Using five large population-based longitudinal ageing cohorts, complemented by an independent hospital dataset and multiple analytical approaches, we found consistent associations of pain status and its transitions with subsequent OA risk among middle-aged and older adults. Baseline pain was associated with a substantially higher risk of OA across all five cohorts. More importantly, transitions in pain status provided additional prognostic information beyond a single baseline assessment: the development of pain among initially pain-free individuals was consistently associated with increased OA risk, whereas recovery from pain to a pain-free state was associated with a markedly lower risk compared with persistent pain. Similar patterns were observed across pain-severity categories. Frailty partially mediated the association between pain and OA, with mobility-related deficits, particularly difficulty getting up from a chair, making important contributions to this pathway. The cross-lagged analyses further identified a temporal sequence linking earlier pain, subsequent mobility deterioration, and later OA. Together, these findings indicate that pain is not only associated with future OA but also represents a dynamic and potentially modifiable risk state, and that frailty, particularly mobility-related functional decline, may constitute an important pathway linking pain with OA.

Accumulating evidence has linked pain to OA. However, most studies focused on pain as a concomitant symptom following the onset of OA^{19–21}. To date, only one recent study examined the longitudinal association between pain and OA using data from the UK Biobank; it identified multisite pain as an independent risk factor for OA and demonstrated an independent causal relationship through MR⁵. Although this study employed a prospective design and adjusted for numerous confounders, the generalizability of their findings is somewhat limited by reliance on a single data source and the use of

pain data from a single time point. Our findings substantially extend this evidence. Baseline pain was associated with OA risk across five international aging cohorts, despite differences in sociodemographic and cultural characteristics. Furthermore, elevated OA risk was observed across different levels of pain severity, suggesting that the relationship of pain and OA is not restricted to individuals with severe pain. The multistate analyses similarly showed that individuals with pain had consistently higher probabilities of progressing to OA than pain-free individuals. The MR findings further strengthened the longitudinal observational evidence by supporting a potential causal relationship between pain status and OA risk, while the absence of a significant reverse association provided additional support for the temporal direction observed in the cohort analyses. Collectively, these findings support pain as an important early risk marker for OA and emphasize the potential value of pain assessment before the clinical onset of OA.

Several biological mechanisms may help explain the observed association between pain and subsequent OA. Chronic pain can significantly activate the hypothalamic–pituitary–adrenal axis, leading to persistently elevated serum cortisol levels (the primary glucocorticoid in humans)^{22,23}. In turn, elevated glucocorticoids directly induce chondrocyte apoptosis and exacerbate cartilage degradation in OA^{24,25}. Chronic pain can also promote the release of neuropeptides, such as substance P from nociceptors²⁶, which subsequently activate immune cells to release interleukin-6 and tumor necrosis factor- α ²⁷, thereby aggravating cartilage degradation and inflammation²⁸. These biological pathways provide a plausible basis for the observed longitudinal association between pain and OA and further support pain as an important early risk marker for OA.

A major contribution of the present study is the demonstration that transitions in pain status are strongly associated with subsequent OA risk. Most previous epidemiological studies have treated pain as a fixed baseline exposure, despite the fact that pain frequently fluctuates over time. Our findings show that such an approach may overlook clinically meaningful changes in risk. Individuals who transitioned from pain-free to pain consistently experienced a higher subsequent risk of OA than those who remained pain-free, whereas individuals who recovered from pain to pain-free status had a substantially lower risk than those with persistent pain. These opposing patterns were observed across all five cohorts and were corroborated by the meta-analytic estimates. Similar results were obtained across pain-severity categories: transitions from pain-free status to mild, moderate, or severe pain were associated with increased OA risk, whereas recovery from different levels of pain severity to a pain-free state was consistently associated with lower risk. These findings demonstrate that pain status is dynamic and that its transitions carry clinically relevant information beyond baseline pain alone.

The multistate analyses provide further support for this dynamic perspective. Among individuals with pain, the transition intensity toward a pain-free state was higher than that toward OA in all five cohorts, indicating that pain is not necessarily a persistent or irreversible state in middle-aged and older adults. Importantly, the favorable association observed among individuals who recovered to a pain-free state highlights the potential value of maintaining or restoring a pain-free state in OA prevention. Taken together, these findings support pain status as a potentially modifiable risk marker and suggest that changes in pain may reflect corresponding changes in musculoskeletal vulnerability. Repeated

monitoring of pain status may therefore help identify individuals whose OA risk is increasing and provide opportunities for earlier preventive strategies. In particular, preventing the development or persistence of pain and promoting recovery to a pain-free state may represent promising targets for reducing OA risk in ageing populations.

This study further examined the mediating role of frailty in the relationship between pain and OA. The results from most cohorts indicated the significant mediating effect of frailty on the association between pain and OA. Previous research utilizing MR analysis demonstrated a significant positive causal effect of frailty on the risk of developing OA¹⁷, which is largely consistent with our findings. Further analysis revealed that across the five longitudinal cohorts, this mediating effect of frailty was primarily attributable to mobility-related items, such as difficulty rising from a chair, suggesting that mechanical factors play a predominant role. Pain can lead to reduced physical activity and altered gait^{29,30}, and these abnormal behavioral patterns can cause joint instability and aberrant mechanical loading^{31,32}, which directly contribute to structural joint damage³³. Moreover, cross-lagged panel network analysis revealed that pain and mobility decline (difficulty squatting and rising from a chair) stably predicted OA incidence at subsequent follow-up. In particular, pain at first period positively predicted mobility decline (difficulty squatting and rising from a chair) at second period, which in turn positively predicted OA at third period. These results indicate a possible indirect pathway linking pain at the first period to OA at the third period through mobility decline at the second period, supporting our previous mediation findings. Moreover, the pooled cohort analysis showed a significant mediating effect of frailty on the relationship between pain transitions and OA risk. Hence, interventions targeting frailty may represent an effective strategy for the prevention of OA.

Our subgroup analyses revealed that the association between baseline pain and incident OA was consistently pronounced in individuals who were employed or retired participants and individuals with unhealthy lifestyles (smoking, drinking, and low physical activity frequency). One possible explanation is that unhealthy lifestyle factors may promote systemic low-grade inflammation and accelerate muscle loss, thereby rendering joints vulnerable to pain-induced damage^{34–36}. These findings highlight the need for targeted risk reduction strategies in high-risk subgroups, such as promoting smoking cessation and physical activity among individuals with pain. A series of sensitivity analyses confirmed the robustness of our primary results. Excluding OA cases occurring within the first 2 years of follow-up and participants with joint pain at baseline did not materially alter the hazard ratios, arguing against substantial reverse causation. Further analyses excluding those lost to follow-up, treating death as a competing risk, and applying PSM to minimize residual confounding all yielded effect estimates consistent with the main analysis. Collectively, these sensitivity analyses support that our observed associations are not driven by early preclinical disease or differential loss to follow-up, thereby strengthening the validity and generalizability of our conclusions.

Several limitations of this study should be acknowledged. First, pain and frailty were assessed by self-report in most cohorts, which may introduce recall bias. Nonetheless, the consistent findings across

the five international cohorts with different cultural and linguistic settings argue against substantial bias, and self-reported pain is widely accepted in large-scale epidemiological studies. Second, the pain assessment tools varied slightly across the cohorts, potentially limiting direct comparability. However, all instruments have been cross-culturally validated, and the direction and magnitude of associations were strikingly similar across cohorts. Third, we did not distinguish between acute and chronic pain at baseline. Given the longitudinal design, baseline pain likely reflects chronic or recurrent pain in most participants, but residual misclassification cannot be entirely excluded. Fourth, death may act as a competing risk for OA, especially in older populations. When we treated death as a competing event in sensitivity analyses, the results remained virtually unchanged, indicating that our main findings are robust to competing risks. Fifth, our study populations were predominantly middle-aged and older adults, hence, the findings may not be generalizable to younger individuals. However, this age range represents the population at highest risk for OA, making the results clinically relevant. Sixth, despite extensive adjustment for potential confounders and the use of PSM and MR to strengthen causal inference, residual confounding by unmeasured factors (e.g., genetic susceptibility and detailed occupational history) cannot be completely ruled out. Finally, loss to follow-up may compromise the representativeness of the sample, particularly when those who withdraw differ systematically from those who remain.

In summary, this study elucidates the complex relationships among pain, frailty, and OA. By highlighting the mediating role of frailty and employing cross-lagged panel network analysis, providing guidance for OA prevention through improved pain management in older adults.

Methods

Ethics and Inclusion

The final five cohorts included survey waves as follows: HRS 2000–2022, CHARLS 2011–2020, SHARE 2013–2021, ELSA 2004–2018, and MHAS 2001–2018. The HRS, CHARLS, SHARE, ELSA, and MHAS were approved by the Ethics Review Committees of University of Michigan Institutional, Peking University, Ethics Council of the Max Planck Society, London Multi-Centre Research, and National Institute of Public Health in Mexico, respectively. The local data were collected under ethical approval granted by the Second Affiliated Hospital of Wenzhou Medical University, with the clinical trial registration number ChiCTR2600118307 and the ethics approval number 2025-K-193-03. All participants provided written informed consent.

Study design and data sources

Data from the following five population-based longitudinal ageing cohorts were integrated: HRS³⁷, CHARLS³⁸, SHARE³⁹, ELSA⁴⁰, and MHAS⁴¹. Eligible participants were aged 50 years or older and were free of OA at the analytical baseline. The primary longitudinal analyses included 67,374 participants.

Cross-sectional health examination data from the Second Affiliated Hospital of Wenzhou Medical University and publicly available GWAS summary statistics for pain status and knee/hip OA were additionally used⁴². Detailed data processing procedures for each database are provided in the Supplementary Method 1, Supplementary Figs. 1–6.

Measures

Assessment of pain: Pain-related questionnaires from the five cohorts were used to assess pain status and degree⁴³. Pain status was classified as pain-free and pain, and pain severity was categorized as pain-free, mild pain, moderate pain, and severe pain⁴⁴. The dynamics of pain status and degree were evaluated as changes observed between the first two waves.

Assessment of frailty: Frailty was quantified using FI, a measure that accumulates age-related health deficits⁴⁵. Drawing on previous research, the FI for HRS, CHARLS, and ELSA comprised 27 components; SHARE included 26; and MHAS contained 25. These components encompassed chronic illnesses (excluding OA), self-rated health, functional limitations, and cognitive function. With the exception of cognition, all components were binary (1 = deficit present, 0 = absent)⁴⁶. A cutoff of 0.25 was applied to classify participants as non-frail (FI below 0.25) or frail (FI of 0.25 and above)⁴⁷.

Assessment of OA: Incident OA was identified by self-report of a physician's diagnosis or use of OA-related medication^{48,49}. Covariates included age, sex, education, employment, marital status, smoking, alcohol consumption, social engagement, and physical activity. Detailed cohort-specific definitions and harmonization procedures are provided in Supplementary Methods 2–3 and Supplementary Tables 1–3.

Statistical analyses

Continuous and categorical variables were summarized as mean (SD) and count (percentage), respectively.

MSM models in continuous time were fitted using the MSM package in R version 4.4.0⁵⁰ and then used to estimate transition intensities and probabilities among pain-free, pain, and OA states, with OA treated as an absorbing state. Logistic regression was used for cross-sectional analyses, and Cox proportional hazards models were applied to estimate associations of pain status and severity with subsequent OA risk. Relationships of transitions in pain status and severity with subsequent OA were assessed using the same longitudinal framework. Cohort-specific estimates were synthesized using random-effects meta-analysis and compared with the estimates obtained from the pooled individual-participant dataset (Supplementary Method 4).

A bidirectional two-sample MR analysis was conducted in R 4.4.0 using the “TwoSampleMR” package⁵¹ to evaluate the potential genetic relationship between pain status and OA⁵². After the exposure and

outcome datasets were aligned, the inverse-variance weighted (IVW) method was employed as the primary analysis to combine single nucleotide polymorphism (SNP)-specific effect estimates⁵³. Detailed analysis methods are provided in Supplementary Methods 4.

Longitudinal mediation analyses were performed to evaluate whether frailty partially accounts for the associations of pain status and its transitions with subsequent OA risk⁵⁴. Two cross-lagged panel network analyses were conducted using the data from the first and second waves and from the second and third waves, respectively, to identify the complex interrelationships and temporal dynamics among pain, frailty, and OA indicators (Supplementary Method 4).

Subgroup analyses were conducted across demographic, socioeconomic, and behavioral characteristics. Sensitivity analyses excluded early OA cases and participants with baseline joint pain, restricted the sample to participants with complete follow-up, accounted for death as a competing event, and applied propensity score matching (PSM). Effect estimates were reported with 95% confidence intervals. All tests were two-sided, with statistical significance defined as $P < 0.05$. Additional model specifications are provided in the Supplementary Method 4.

Declarations

Competing interests

The authors declare no competing interests.

Author contributions

Y.H.Z. and W.Y.X. conceptualized the study, conducted data analysis and drafted the manuscript. W.Q.X. participated in data cleaning and organization. Q.H.Y. and X.Y.S. were responsible for data validation and visualization. Z.J.Z. participated in manuscript editing and critical revision. X.Q.W., Y.H.Z., S.C.W. and W.Y.Z. supervised the study, provided methodological guidance and approved the final version of the manuscript. All authors reviewed and approved the final manuscript.

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Data availability

The datasets analyzed in this study were obtained from the following publicly available sources: the Health and Retirement Study (HRS; <https://hrs.isr.umich.edu/>), the China Health and Retirement Longitudinal Study (CHARLS; <https://charls.pku.edu.cn/>), the Survey of Health, Ageing and Retirement in Europe (SHARE; <https://share-eric.eu/>), the English Longitudinal Study of Ageing (ELSA; <https://www.elsa-project.ac.uk/>), and the Mexican Health and Aging Study (MHAS; <https://mhasweb.org/Home/index.aspx>). These datasets are accessible to researchers upon registration and compliance with the respective data use agreements.

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Figures

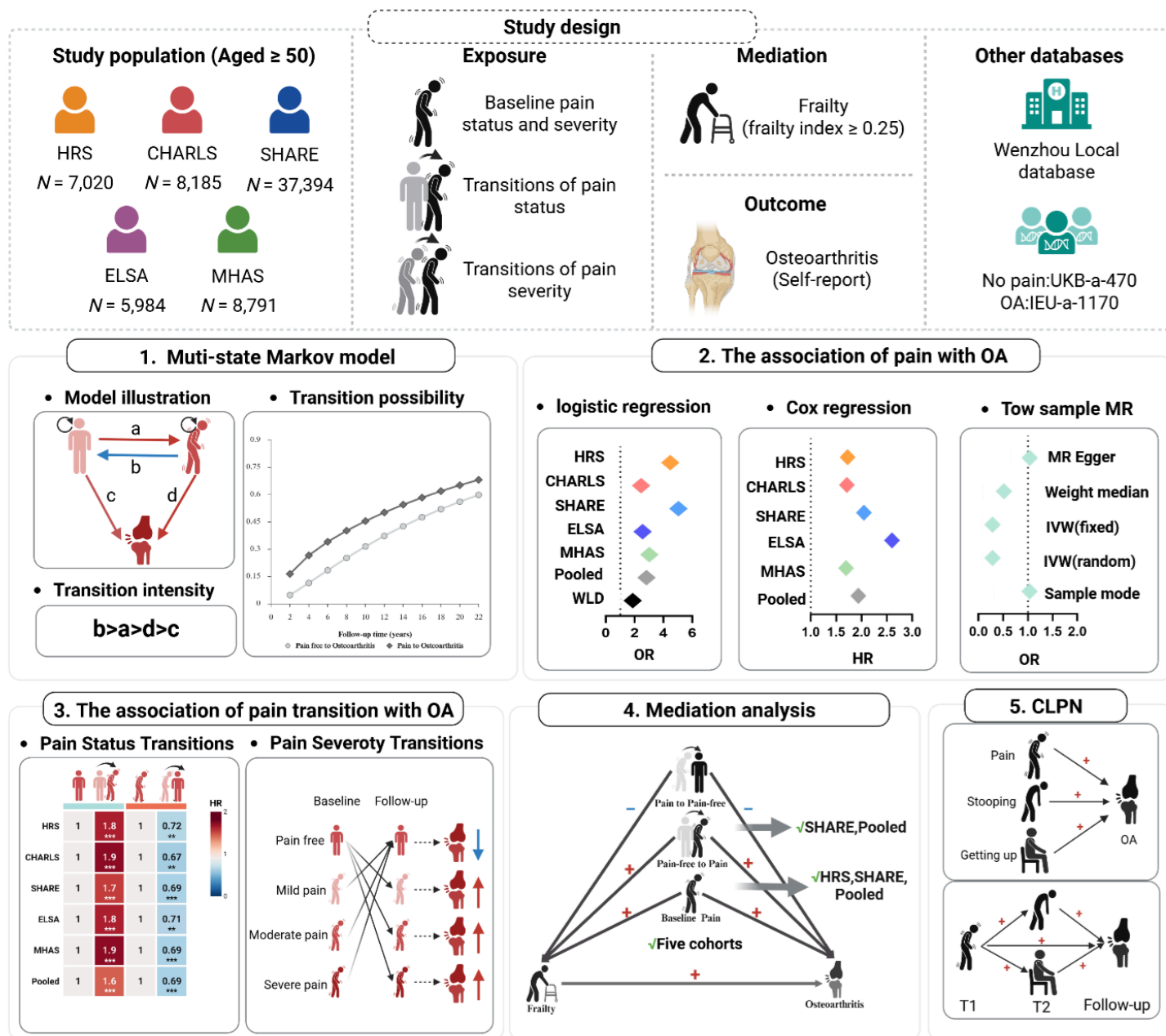


Figure 1

Study workflow

Top: This study used data from 67,374 participants aged 50 years and older from the United States, China, the United Kingdom, Mexico, and 28 other European countries. The exposure was pain status, pain severity and their transitions; the mediator was frailty status (derived from 28 sub-items covering chronic diseases, basic and instrumental activities of daily living, and cognitive function, with frailty defined as a frailty index ≥ 0.25); the outcome was osteoarthritis. Local cross-sectional data (from the Second Affiliated Hospital of Wenzhou Medical University) and GWAS data (ukb-a-470 and ieu-a-170) were also incorporated. Results Part 1: Multi-state Markov models were applied to analyze transition intensities and transition probabilities among the states of no pain, pain, and osteoarthritis. Part 2: Cox

regression, logistic regression, and two-sample Mendelian randomization were used to investigate the longitudinal, cross-sectional, and genetic-level associations between pain and osteoarthritis. Part 3: Cox regression and random-effects meta-analysis were performed to examine the longitudinal associations of transitions in pain status and severity with osteoarthritis. Part 4: Mediation models were used to evaluate the mediating effect of frailty on the associations of pain and changes in pain status with osteoarthritis. Part 5: Cross-lagged panel network analysis and frailty component mediation analysis were employed to investigate the predictive relationships among pain, frailty factors, and osteoarthritis, as well as the potential mechanisms underlying these relationships. GWAS, genome-wide association study.

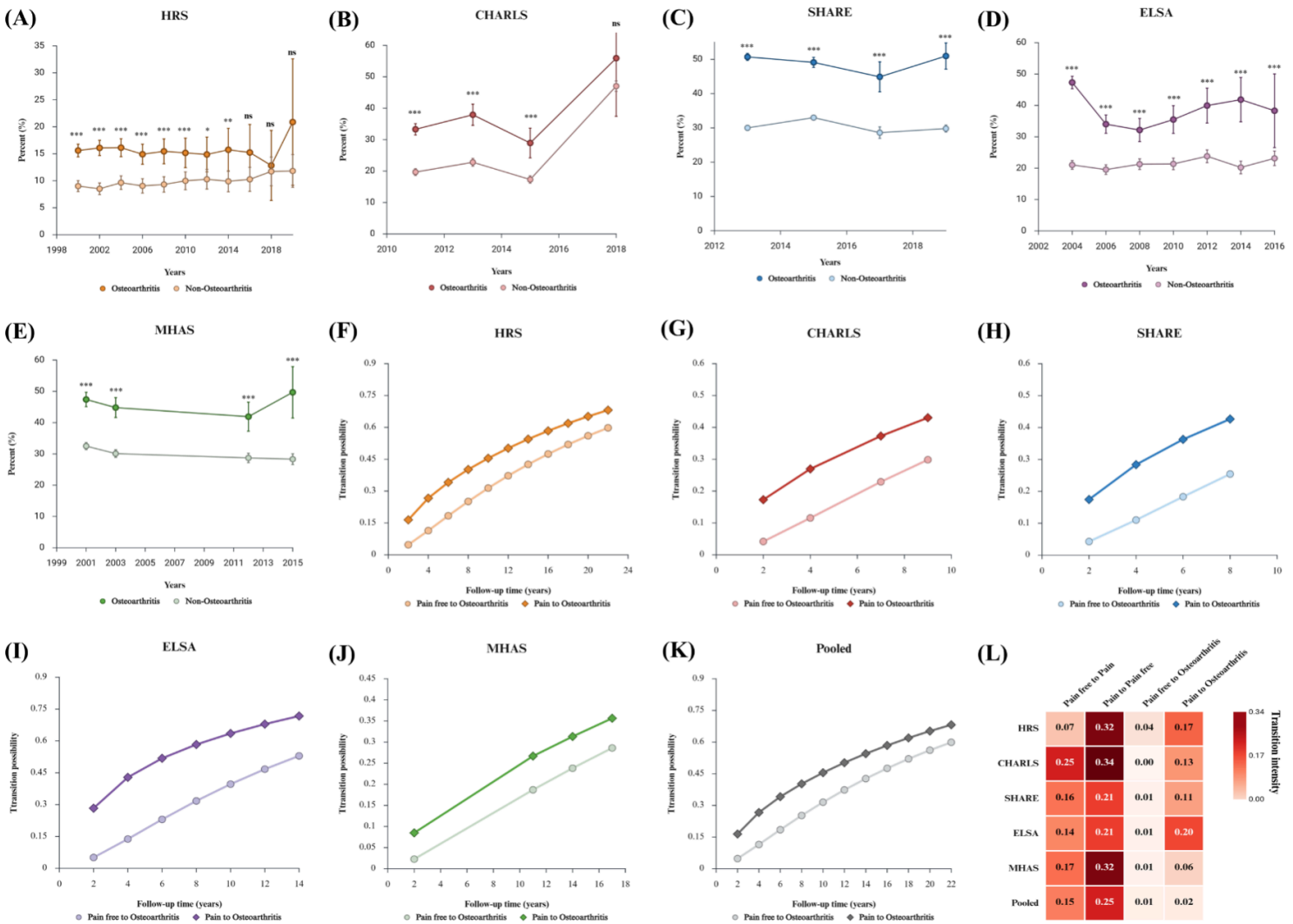


Figure 2

Differences in pain prevalence by OA status and transition probabilities from different pain status to OA

HRS Health and Retirement Study, CHARLS China Health and Retirement Longitudinal Study, SHARE Survey of Health, Ageing and Retirement in Europe, ELSA English Longitudinal Study of Ageing, MHAS Mexican Health and Aging Study. The images A, B, C, D and E illustrated the differences in osteoarthritis incidence rates across pain status by survey year in the following studies: HRS, MHAS, CHARLS, ELSA,

and SHARE, respectively. The chi-square test was used to compare the trends in pain incidence rates and osteoarthritis across different survey waves. The years corresponding to the horizontal coordinates in images A, B, C, D, and E represented the pain incidence rates using this survey period and the incident osteoarthritis at follow-up (e.g., The 2000 results in HRS corresponded to the use of pain incidence rates for 2000 and the prevalence for 2002-2020, and so on). The images F, G, H, I, J and K illustrated the estimated possibility of pain free state and pain state transitions to osteoarthritis by Markov model. The images L illustrated the transition intensity between different pain status by Markov model.

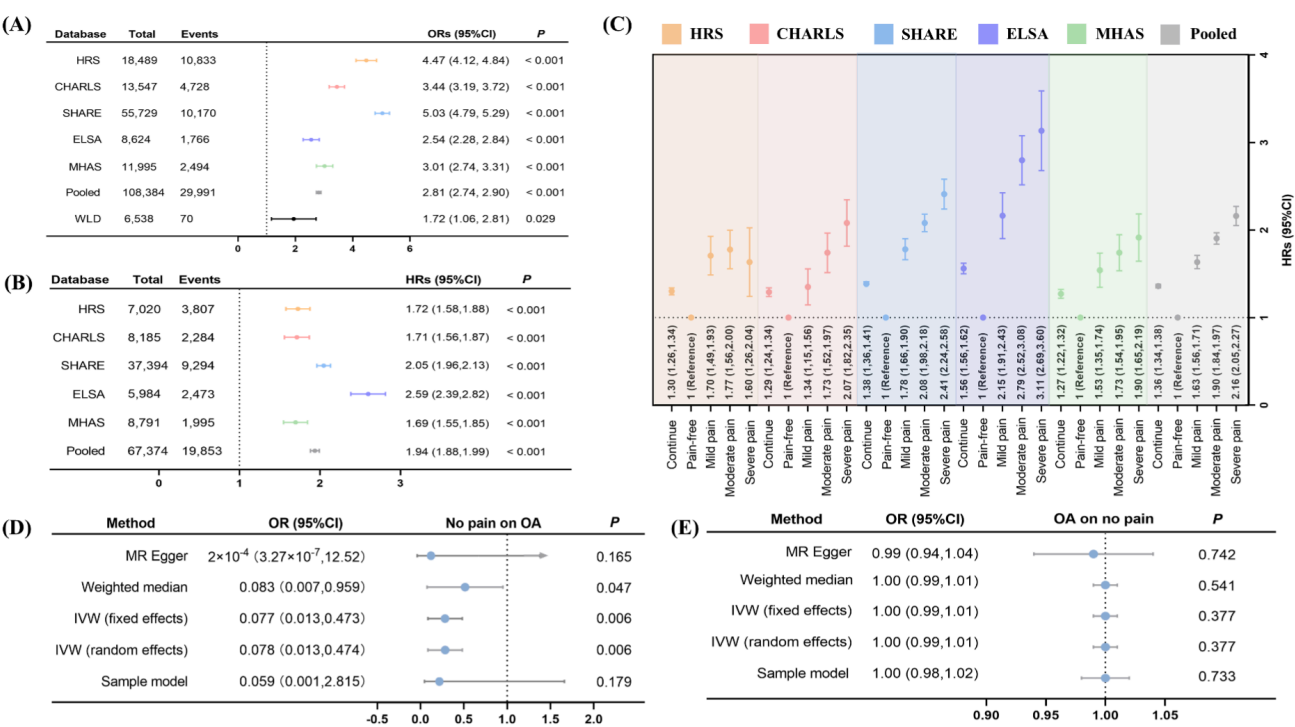


Figure 3

The association of pain status or severity with risks of osteoarthritis

HRS Health and Retirement Study, CHARLS China Health and Retirement Longitudinal Study, SHARE Survey of Health, Ageing and Retirement in Europe, ELSA English Longitudinal Study of Ageing, MHAS Mexican Health and Aging Study, WLD Wenzhou local database. Fig. A illustrates the cross-sectional associations between pain status and osteoarthritis across five independent databases and the local database. Fig. B illustrates the longitudinal associations between pain status and osteoarthritis across five cohorts. Fig. C illustrates the longitudinal associations between different pain severity and osteoarthritis across five cohorts. Fig. D and E illustrate the two sample mendelian randomization in ukb-a-470 and ieu-a-1170. OR, odds ratio; HR, hazard ratio; OA, osteoarthritis.

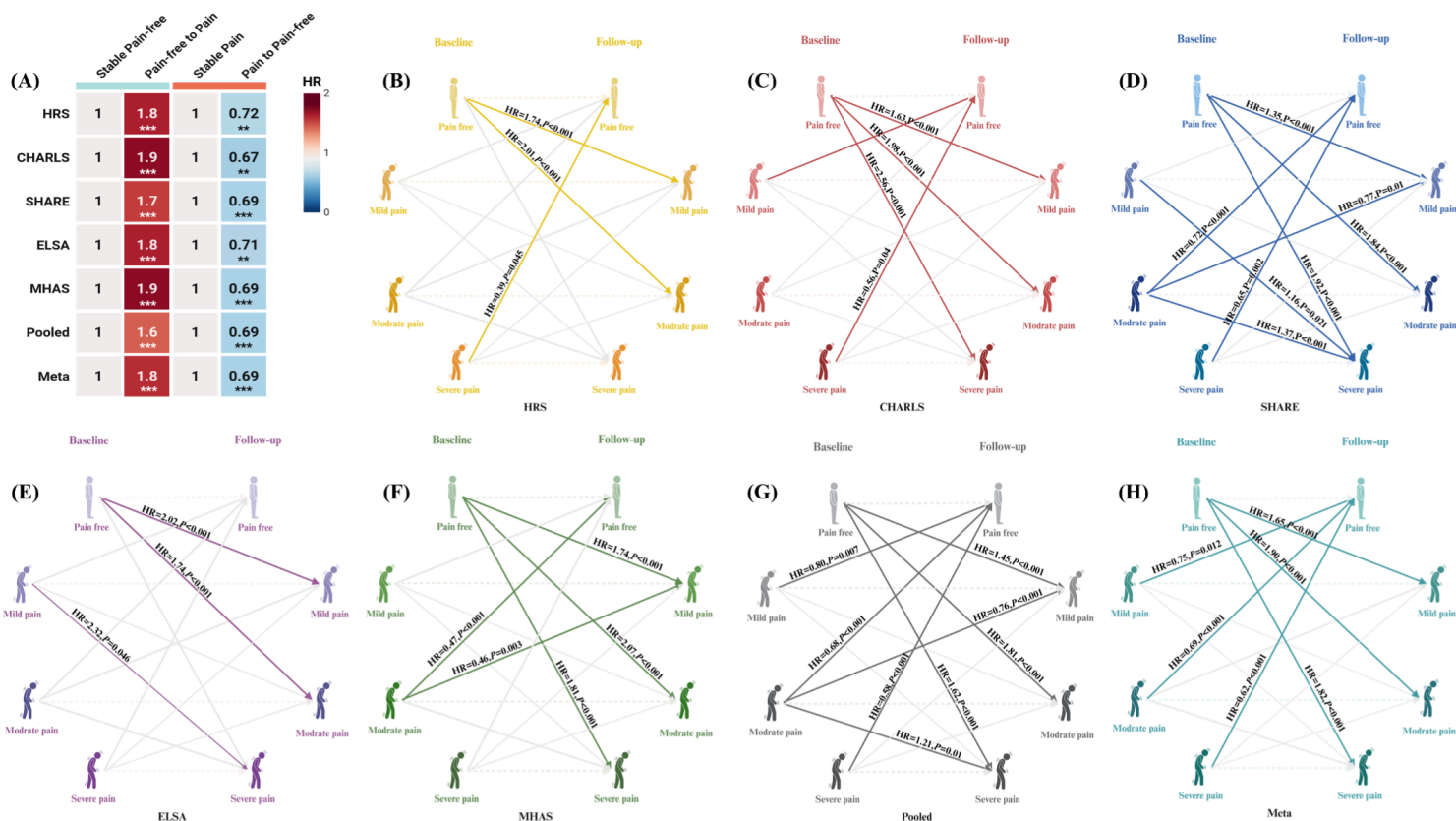


Figure 4

The association of change of pain status and degree with risks of incident osteoarthritis

HRS Health and Retirement Study, CHARLS China Health and Retirement Longitudinal Study, SHARE Survey of Health, Ageing and Retirement in Europe, ELSA English Longitudinal Study of Ageing, MHAS Mexican Health and Aging Study, Pooled. The images A illustrated the association of change of pain status with risks of incident osteoarthritis. The images B-H illustrated the association of change of pain degree with risks of incident osteoarthritis. In images B-H, the left side shows pain degree at baseline, and the right side shows pain degree at the next follow-up wave. The dashed line represents the reference group, and the gray solid line indicates $p > 0.05$; only HR values with $p < 0.05$ are displayed in the Figure.

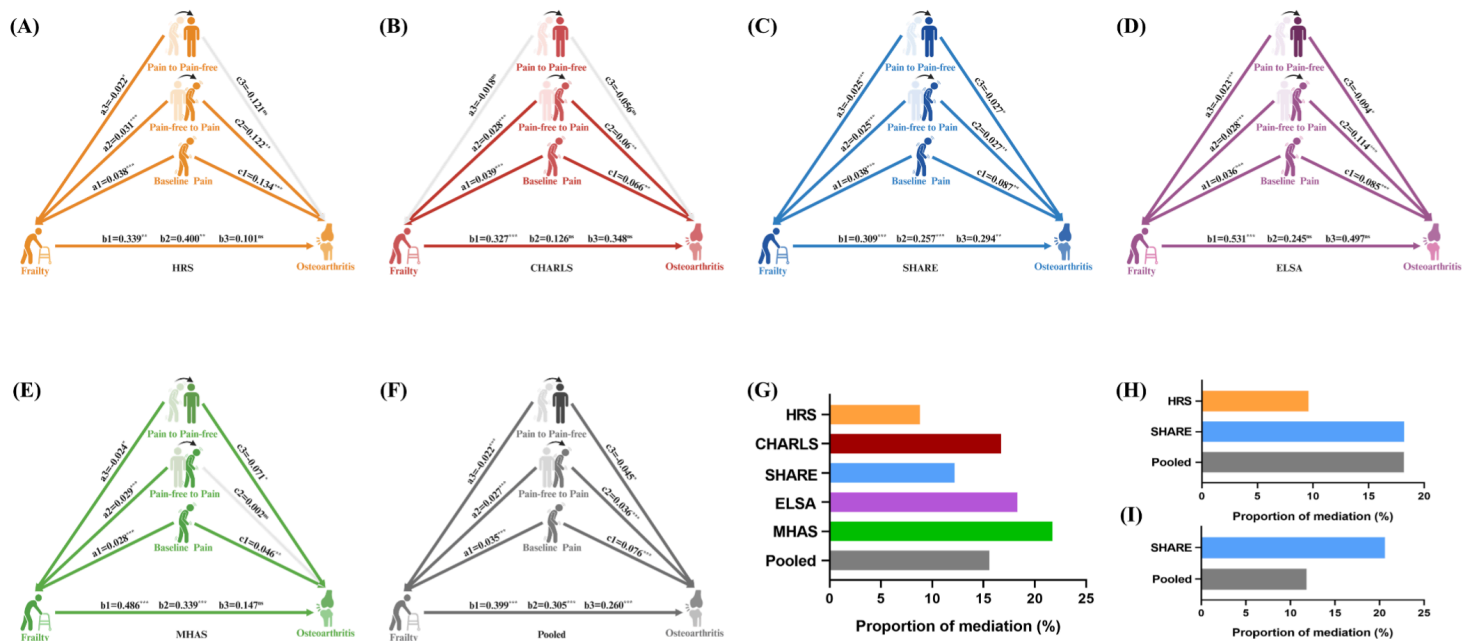


Figure 5

Association between baseline pain status, frailty and osteoarthritis

Note: FI, frailty index; (A) HRS, Health and Retirement Study; (B) CHARLS, China Health and Retirement Longitudinal Study; (C) SHARE, Survey of Health, Ageing and Retirement in Europe; (D) ELSA, English Longitudinal Study of Ageing; (E) MHAS, Mexican Health and Aging Study; (F) Pooled; (G) Mediating proportion of frailty in the association between baseline pain and osteoarthritis; (H) Mediating proportion of frailty in the association between pain-free to pain and osteoarthritis; (I) Mediating proportion of frailty in the association between pain to pain-free and osteoarthritis. In the mediation model, path coefficient a represents the effect of pain status or changes in pain status on frailty; path coefficient b represents the effect of frailty on osteoarthritis; and path coefficient c represents the total effect of pain status or changes in pain status on osteoarthritis. All analyses have been adjusted for age, sex, education, employment, marital status, smoking, drinking, social activity, and physical activity. In the SHARE and Pooled cohorts, we controlled the different country.

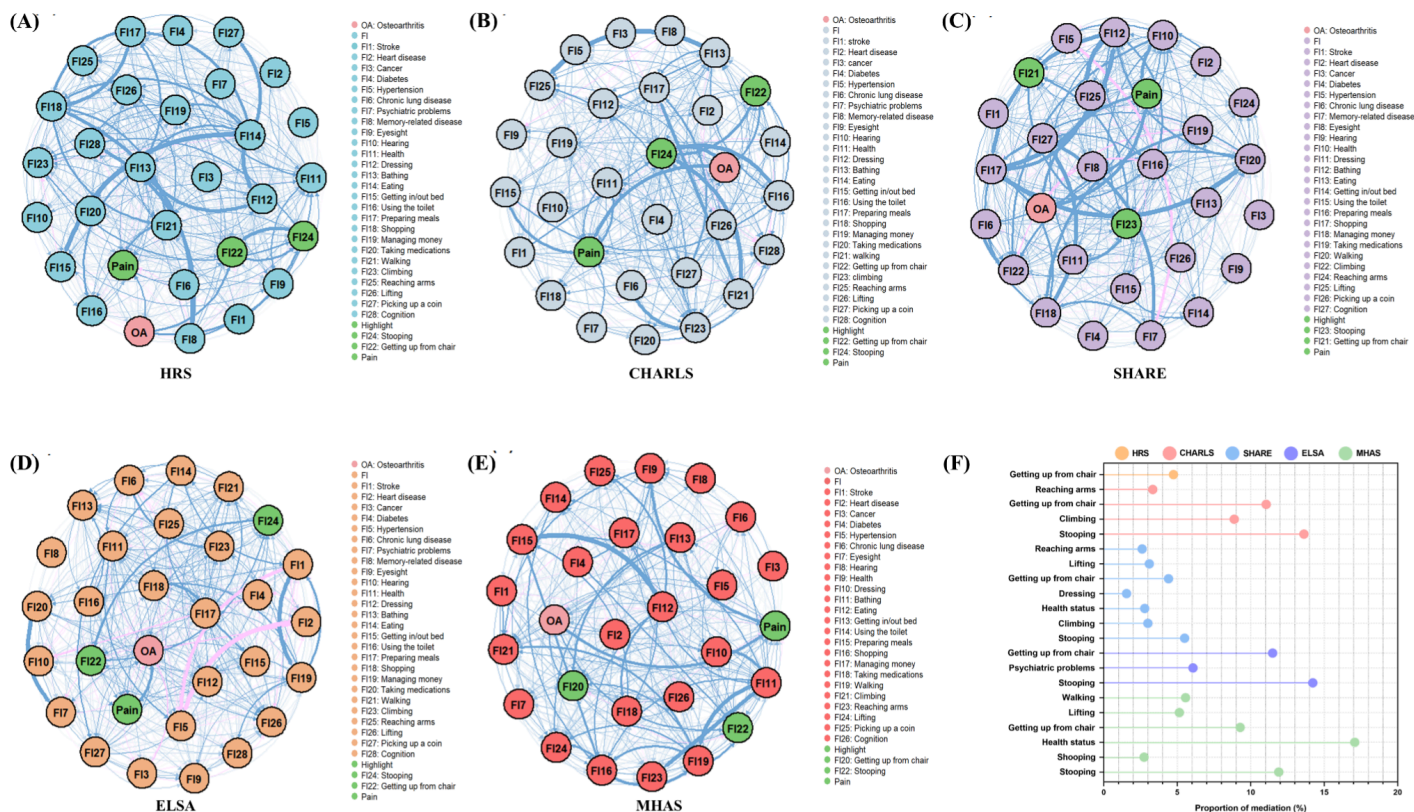


Figure 6

Network structures across HRS, CHARLS, SHARE, ELSA, and MHAS.

Note: (A) HRS: Health and Retirement Study; (B) CHARLS: China Health and Retirement Longitudinal Study; (C) SHARE: Survey of Health, Ageing and Retirement in Europe; (D) ELSA: English Longitudinal Study of Ageing; (E) MHAS: Mexican Health and Aging Study; (F) The mediating proportion of the frailty factor. All analyses were adjusted age, sex, education, employment, marital status, smoking, drinking, social activity, and physical activity. In the SHARE, we further controlled the different country. The lines in the figures A-E represented odds ratios (OR), with values greater than 0 shown in blue and values less than 0 shown in red. Thicker lines indicate larger OR values. To enhance clarity, autoregressive effects and covariates were not displayed in the figure.

Supplementary Files

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