Clinical Interventions in Aging

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

# Association Between Pain and Frailty in Middle-Aged and Older Patients: The Mediating Roles of Sleep and Mood

Hua-Peng Wang[1,*], Tao Wang[1,*], Hao-Tian Ye[1], Yong-Yan Dong[1], Shi-Jie Zhao[1], Qing-Ren Liu[2], Xiao-Yi Hu[3], Mu-Huo Ji[3], Jian-Jun Yang[1]

[1]Department of Anesthesiology, Pain and Perioperative Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, People's Republic of China; [2]Department of Anesthesiology, Xishan People's Hospital of Wuxi City, Wuxi, Jiangsu, People's Republic of China; [3]Department of Anesthesiology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jian-Jun Yang, Department of Anesthesiology, Pain and Perioperative Medicine, The First Affiliated Hospital of Zhengzhou University, No. 1, Longhu Zhonghuan Road, Jinshui District, Zhengzhou, Henan Province, 450018, People's Republic of China, Email yjyangjj@126.com; Mu-Huo Ji, Department of Anesthesiology, The Second Affiliated Hospital of Nanjing Medical University, No. 262, North Zhongshan Road, Gulou District, Nanjing, Jiangsu Province, 210003, People's Republic of China, Email jimuhuo2009@sina.com

Clinical Interventions in Aging downloaded from https://www.dovepress.com/
For personal use only.

**Purpose:** Pain and frailty are significantly social concerns negatively affecting physical and mental health in middle-aged and older population. This study aimed to investigate the association between pain and frailty, with a particular focus on the mediating roles of sleep and mood.

**Patients and Methods:** A cross-sectional study was conducted involving 244 middle-aged and older participants in local hospital. Their pain, frailty, sleep and mental health conditions were assessed through face-to-face interviews. Linear regression analysis was used to examine the association between pain and frailty. Simple and serial mediation models were employed to investigate the complex mediation effects of sleep and mood on pain and frailty.

**Results:** Significant effects were observed in both the pain-frailty nexus and the frailty-pain nexus. For simple mediation models, we identified significant mediation effects of sleep ($\beta_{Sleep}$=0.049, 95% CI: 0.011, 0.094), anxiety ($\beta_{Anxiety}$=0.054, 95% CI: 0.023, 0.094), and depression ($\beta_{Depression}$=0.093, 95% CI: 0.049, 0.150) in the pain-frailty nexus. Similarly, in the frailty-pain nexus, sleep ($\beta_{Sleep}$=0.096, 95% CI: 0.043, 0.162), anxiety ($\beta_{Anxiety}$=0.085, 95% CI: 0.029, 0.156), and depression ($\beta_{Depression}$=0.126, 95% CI: 0.056, 0.208) continued to be significant mediators, while sleep and depression had more significant mediating effects than anxiety. Serial mediation models revealed that sleep and depression jointly played a sequential mediation role in the frailty-pain nexus ($\beta_a$=0.020, 95% CI: 0.002, 0.044; $\beta_b$=0.043, 95% CI: 0.014, 0.081).

**Conclusion:** Our research provided evidence supporting the robust association between pain and frailty and offered new sights into potential strategies by enhancing sleep quality and mental health for preventing and managing both pain and frailty.

**Keywords:** pain, frailty, sleep, mood, middle-aged and older adults

## Introduction

Frailty is frequently characterized as an augmented susceptibility to stressors, which compromises various interconnected physiological systems and leads to diminishing reserves with deteriorating homeostasis.[1,2] A recent systematic review and meta-analysis using multidimensional approaches found that the overall prevalence of pre-frailty and frailty was 63% in older population, while the prevalence in hospital settings could reach up to 70%.[3] Pain represents a significant medical and social burden that negatively impacts both physical and psychological well-being. Studies suggest that approximately 60–75% of individuals aged 65 and older experience pain, with a notably higher prevalence observed among residents in assisted living facilities and nursing homes.[4] Pain and frailty often coexist in older adults. Recently, a possible reciprocal impact was reported between pain and frailty.[5,6] Pain might act as a significant stressor that depletes bodily resources and induces unnecessary stress responses, consequently contributing to frailty.[6] Conversely, frailty itself



Received: 1 January 2025
Accepted: 18 May 2025
Published: 4 June 2025

© 2025 Wang et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

can exacerbate pain perception through descending inhibitory neural circuits.[7] While the impact of pain on frailty has been extensively studied,[8–16] less attention has been paid to investigating the effect of frailty on pain.[5,14] In particular, this has not been explored in hospital environments.

In recent years, there has been an increasing recognition of sleep and mental health, which were probably potential neuropsychic mechanisms in the association between pain and frailty. Studies indicated that depression and poor sleep quality served as significant mediators in the link between pain and frailty.[16–19] Pain may increase the risk of depression and sleep disturbances, which in turn accelerate the progression of frailty.[16–19] Additionally, anxiety, often co-occurring with depression and sleep disorders, is prevalent in hospital settings but has not been thoroughly examined in mediation analyses. To our knowledge, there is no study investigating the mediating effects among sleep, anxiety and depression in both the pain-frailty nexus and the frailty-pain nexus.

In this study, we aim to investigate the association between pain and frailty in hospitalized middle-aged and older adults, as well as the mediation effects of sleep, anxiety and depression on pain and frailty through both simple and serial mediation models. The objective of our study is to explore whether poor sleep and mental health are associated with the onset or aggravation of pain and frailty. Ultimately, our work may provide foundation for developing efficacious interventions to avert or postpone the emergence of these conditions.

# Methods

## Study Design

This study was a single-center, cross-sectional, observational investigation conducted from May 2024 to August 2024, which was approved by the Institutional Scientific Research and Clinical Trails Ethics Committee of the First Affiliated Hospital of Zhengzhou University (number 2024-KY-0580-001) and performed in accordance with the Helsinki Declaration. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was followed, and the study was registered with http://www.chictr.org.cn, ChiCTR2400084481. All participants provided written informed consent before the study commenced.

## Participants and Procedures

Participants were recruited sequentially based on their order of admission in the Department of Pain Medicine, The First Affiliated Hospital of Zhengzhou University, provided they met the following inclusion criteria: (1) aged 50 years and older;[20] (2) reported pain with a Numerical Rating Scale (NRS) score above 0. The exclusion criteria were as follows: (1) Severe visual and hearing impairment, speech and communication impairment, not able to complete the assessment; (2) Mini-Mental State Examination (MMSE)<20 to exclude dementia.[21] All the recruited participants were assessed on the day of admission including demographics, sleep, mental health conditions, cognition, lifestyle factors, diseases, pain and frailty. All assessments were performed face-to-face by a professionally trained investigator.

## Measures

### Pain

NRS was used to assess current pain intensity (0=no pain, 10=worst imaginable pain) at admission. Otherwise, two subscales of the Brief Pain Inventory (BPI) were used: the 4-item pain severity subscale and the 7-item pain interference subscale. Two subscales provide two scores: a pain severity score and a pain interference score.[22] The pain severity score is calculated based on four items related to pain severity (worst, least, average in the past 24h, and current pain) ranging from 0 to 40.[22] Accordingly, score≥21 indicates severity pain, and score<21 indicates mild-to-moderate pain.[23] The pain interference score consists of seven items that assess how pain interferes with daily life, with each item scored from 0 to 10 (total score range: 0–70).[22] In line with the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommendations, BPI pain interference score was proposed as a main measure of pain.[24] A previous comment has demonstrated two subscales of BPI showed great reliability and internal consistency.[22] Moreover, the characteristics of pain including duration (acute or chronic),[8] type (neuropathic, nociceptive or mixed),[9] and location (head and neck, back, bones and joints, legs, arms or other sites) were recorded.[10]

### Sleep

The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality, which consisted of 19 self-reported items and 7 component scores (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction).[25] Each component is scored 0–3 points, resulting in a total PSQI score 0–21 points. PSQI score>5 indicates poor sleep quality.[25] PSQI is widely used, which has been proved to be a reliable and valid measure to assess sleep quality.[26]

### Mood

The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression; It is composed of 14 items, with 7 items allocated to each subscale: the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) and the Hospital Anxiety and Depression Scale-Depression subscale (HADS-D). Each item is scored from 0 to 3, and the scores are summed for each subscale. A score of 8 or above indicates a diagnosis of anxiety or depression.[27] In terms of discrimination ability, the scale has a moderate to high rating, with specificity and sensitivity both exceeding 0.80, respectively.[28]

### Frailty

As previously described by Wade et al, frailty was defined using a Frailty Index (FI) consisted of 51 variables, which quantified age-related deficits including functional mobility, disability, comorbidities, and cognitive function.[11] In spite of the fact that the deficits were used differently for constructing the FI between studies, a minimum of 30 variables were needed for the FI to be considered significant.[29] For binary variables, we assigned the score according to the presence of the deficit (no=0; yes=1). Ordinal variables were transformed into a score between 0 and 1. The FI for each participant was calculated as the sum of the deficits present divided by the total number of variables considered, resulting in a continuous score varying from 0 to 1. The FI was categorized according to a previous study: individuals with FI scores≤0.08 were considered robust, while 0.08–0.25 and ≥0.25 were classified as prefrail and frail.[30]

### Other Variables

Variables as potential confounders in the association between pain and frailty including socio-demographic characteristics (age, sex, education, BMI), cognition (MMSE), lifestyle factors (smoking and drinking), and diseases (age-adjusted Charlson Comorbidity Index, hypertension, diabetes, coronary heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, cancer) were also collected.

## Sample Size

The sample size was determined using the formula $N = Z^2{}_{\alpha/2}P(1-P)(DEEF)/d^2$,[16] with the test level α of 0.05, statistic $Z_{\alpha/2}$ of 1.96 and margin of error (d) of ±10%. The preliminary experiment indicated a 60% incidence of frailty or severity pain in middle-aged and older patients. Considering a design effect (DEEF) of 2, the minimum sample size required for the study was calculated to be 222 participants, accounting for a 20% drop-out rate.

## Statistical Analysis

Continuous variables were summarized as mean (standard deviation) or median (interquartile range) if not normally distributed, and categorical variables were presented as number (percent). Student's T-tests or Mann–Whitney *U*-tests were used as appropriate. Categorical variables were compared with Pearson's Chi-square or Fisher exact tests. Linear regression analyses were conducted to investigate the relationships between pain scores, frailty, and potential mediators such as sleep, anxiety and depression. Various models were performed to examine these associations adjusting for different variables such as age, sex, education, pain duration, pain type, pain location, PSQI, HADS-A and HADS-D. The SPSS PROCESS macro by Hayes et al,[31] version 4.3, specifically models 4 and 6, was utilized to assess the mediating roles of sleep, anxiety and depression in the relationship between pain and frailty. The macro employed a bootstrapping method to assess the significance of indirect effects, with each test being resampled 5000 times to calculate 95% confidence intervals. Significance was determined if zero was not included in the interval. In order to standardize effect size comparisons, we transformed β coefficients from linear regression into Cohen's d metrics, as outlined in a prior research study.[32] This conversion allowed for the interpretation of effect sizes as small (0.2), moderate (0.5), or large

(0.8) based on established criteria.[33] In the sensitivity analysis, the forest plot was used to illustrate the resilience of the relationship between pain and frailty in two nexuses. Additionally, linear regression analyses were employed to explore the impact of pain related parameters including pain duration, pain type and pain location on frailty. The statistical significant level was set at two-sided P<0.05. Data analysis was conducted using IBM SPSS v25.0 software (SPSS Inc., Chicago, IL, USA).

# Results

## Demographics and Clinical Characteristics

A total of 310 participants with pain were initially enrolled in this study; Of those, 16 refused to participated, 12 had severe visual, hearing and communication impairment, 38 had MMSE scores<20 indicating dementia. Therefore, 244 middle-aged and older adults were included in the data analyses (Supplementary Figure S1). Among these, 136 (55.7%) were female and 108 (44.3%) were male, with a median (IQR) age of 64 (57,70) years. Based on their FI scores, participants were categorized into the prefrail (38.5%), and frail (61.5%) groups. Significant differences were observed between the prefrail and frail groups in terms of age, education, MMSE scores, and prevalence of diseases. Frail participants exhibited poorer sleep quality, higher levels of anxiety and depression. BPI pain severity score was positively correlated to frailty severity, whereas NRS pain intensity score was not. Frail individuals reported more mixed pain and locations of pain compared to prefrail individuals. According to BPI pain severity score, participants were classified as mild-to-moderate pain group (43.9%) and severity pain group (56.1%). Severity pain was associated with poorer sleep, worse anxiety and depression, and higher levels of frailty (Table 1).

**Table 1** Demographics, Sleep, Mental Health Conditions, Cognition, Lifestyle Factors, Diseases, Pain and Frailty According to Frailty Status and BPI Pain Severity Score

| Characteristics | Overall (n=244) | Grouped According to Frailty Status | | | Grouped According to BPI Pain Severity Score | | |
|---|---|---|---|---|---|---|---|
| | | Prefrail (n=94) | Frail (n=150) | P value | Mild-to-Moderate Pain (n=107) | Severity Pain (n=137) | P value |
| Age (years) | 64 (57,70) | 60 (56,66) | 66 (59,71) | <0.001 | 64 (58,71) | 64 (56,69) | 0.124 |
| Female | 136 (55.7) | 53 (56.4) | 83 (55.3) | 0.872 | 64 (59.8) | 72 (52.6) | 0.257 |
| Education (years) | 7 (6,9) | 9 (6,12) | 6 (4,9) | 0.003 | 9 (5,9) | 6 (6,9) | 0.884 |
| PSQI | 11 (6,15) | 9 (5,13) | 13 (8,16) | <0.001 | 10 (6,14) | 13 (8,16) | <0.001 |
| HADS-A | 10 (7,12) | 9 (6,12) | 10 (8,13) | 0.002 | 9 (6,11) | 10 (8,13) | 0.003 |
| HADS-D | 8 (6,11) | 7 (5,9) | 9 (6,13) | <0.001 | 7 (5,8) | 9 (6,13) | <0.001 |
| MMSE | 24 (22,27) | 26 (24,28) | 23 (21,26) | <0.001 | 24 (23,28) | 24 (22,27) | 0.377 |
| BMI | 24.03 (21.61,26.14) | 24.18 (22.05,26.50) | 23.96 (21.53,26.00) | 0.358 | 24.22 (21.45,26.67) | 23.88 (21.81,26.04) | 0.698 |
| Smoking | 44 (18.0) | 19 (20.2) | 25 (16.7) | 0.483 | 17 (15.9) | 27 (19.7) | 0.441 |
| Drinking | 30 (12.3) | 12 (12.8) | 18 (12.0) | 0.859 | 12 (11.2) | 18 (13.1) | 0.650 |
| aCCI | 4 (2,5) | 2 (2,3) | 4 (3,6) | <0.001 | 3 (2,4) | 4 (2,7) | 0.033 |
| Hypertension | 85 (34.8) | 23 (24.5) | 62 (41.3) | 0.007 | 38 (35.5) | 47 (34.3) | 0.844 |
| Diabetes | 58 (23.8) | 11 (11.7) | 47 (31.3) | <0.001 | 26 (24.3) | 32 (23.4) | 0.864 |
| Coronary heart disease | 31 (12.7) | 3 (3.2) | 28 (18.7) | <0.001 | 12 (11.2) | 19 (13.9) | 0.537 |
| Cerebrovascular disease | 42 (17.2) | 12 (12.8) | 30 (20.0) | 0.145 | 21 (19.6) | 21 (15.3) | 0.378 |
| COPD | 9 (3.7) | 1 (1.1) | 8 (5.3) | 0.170 | 2 (1.9) | 7 (5.1) | 0.322 |
| Cancer | 40 (16.4) | 4 (4.3) | 36 (24.0) | <0.001 | 6 (5.6) | 34 (24.8) | <0.001 |
| NRS Pain intensity score | 8 (6,9) | 8 (6,8) | 8 (6,9) | 0.577 | 6 (5,7) | 8 (8,9) | <0.001 |
| BPI Pain severity score | 21 (18,25) | 20 (17,23) | 22 (19,26) | <0.001 | 17 (16,19) | 24 (22,27) | <0.001 |
| BPI Pain interference score | 40 (35,46) | 35 (29,40) | 44 (39,49) | <0.001 | 38 (31,41) | 45 (38,49) | <0.001 |
| Pain duration | | | | 0.366 | | | 0.029 |
| Acute pain | 65 (26.6) | 22 (23.4) | 43 (28.7) | | 21 (19.6) | 44 (32.1) | |
| Chronic pain | 179 (73.4) | 72 (76.6) | 107 (71.3) | | 86 (80.4) | 93 (67.9) | |
| Pain type | | | | <0.001 | | | 0.003 |
| Neuropathic | 70 (28.7) | 50 (53.2) | 20 (13.3) | | 28 (26.2) | 42 (30.7) | |
| Nociceptive | 82 (33.6) | 31 (33.0) | 51 (34.0) | | 48 (44.9) | 34 (24.8) | |
| Mixed | 92 (37.7) | 13 (13.8) | 79 (52.7) | | 31 (29.0) | 61 (44.5) | |

(*Continued*)

**Table 1** (Continued).

| Characteristics | Overall (n=244) | Grouped According to Frailty Status | | | Grouped According to BPI Pain Severity Score | | |
|---|---|---|---|---|---|---|---|
| | | Prefrail (n=94) | Frail (n=150) | P value | Mild-to-Moderate Pain (n=107) | Severity Pain (n=137) | P value |
| Pain location | | | | 0.001 | | | 0.157 |
| 1–2 pain sites | 183 (75.0) | 81 (86.2) | 102 (68.0) | | 85 (79.4) | 98 (71.5) | |
| ≥3 pain sites | 61 (25.0) | 13 (13.8) | 48 (32.0) | | 22 (20.6) | 39 (28.5) | |
| Frailty index | 0.28 (0.20,0.36) | 0.18 (0.14,0.22) | 0.34 (0.29,0.40) | <0.001 | 0.25 (0.18,0.31) | 0.30 (0.22,0.38) | 0.001 |

**Notes**: Categorical variables were presented as number (%) and continuous variables were summarized as mean (SD) or median (IQR). Student's T-tests or Mann–Whitney *U*-tests were used for continuous variables. Categorical variables were compared using Pearson's Chi-square or Fisher exact tests.

**Abbreviations**: BPI, Brief Pain Inventory; PSQI, Pittsburgh Sleep Quality Index; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; MMSE, Mini-Mental State Examination; BMI, Body Mass Index; aCCI, age-adjusted Charlson Comorbidity Index; COPD, Chronic Obstructive Pulmonary Disease; NRS, Numerical Rating Scale; SD, Standard Deviation; IQR, Interquartile Range.

## Linear Regression Analyses for the Relationships Between Pain, Mediators, and Frailty

The linear regression analyses for the relationships among pain, mediators and frailty were shown in Figures 1 and 2. Significant effects were observed in all nexuses including pain-frailty, frailty-pain, pain-mediators, frailty-mediators, mediators-pain, and mediators-frailty. These positive associations were persistent even after adjusting for different covariates. Effect sizes were consistently moderate to large (Cohen's d>0.5).

## Simple Mediation Models

Figure 3 showed the simple mediation effects of sleep, anxiety and depression in both the pain-frailty nexus and the frailty-pain nexus after controlling for age, sex, education, pain duration, pain type and pain location. We identified significant mediation effects of sleep, anxiety, and depression in these two nexuses, while sleep and depression had stronger mediating effects compared to anxiety in the frailty-pain nexus (Mediated proportion $_{Sleep}$=19.2%, Mediated proportion $_{Depression}$=25.1%, Mediated proportion $_{Anxiety}$=17.0%). More details could be found in Supplementary Table S1.

## Serial Mediation Models

The serial mediation models revealed a significant total indirect effect accounting for 31.7% of the total effect (Supplementary Table S2). The indirect effect paths, specifically the path (Frailty→Sleep→Depression→Pain), as well

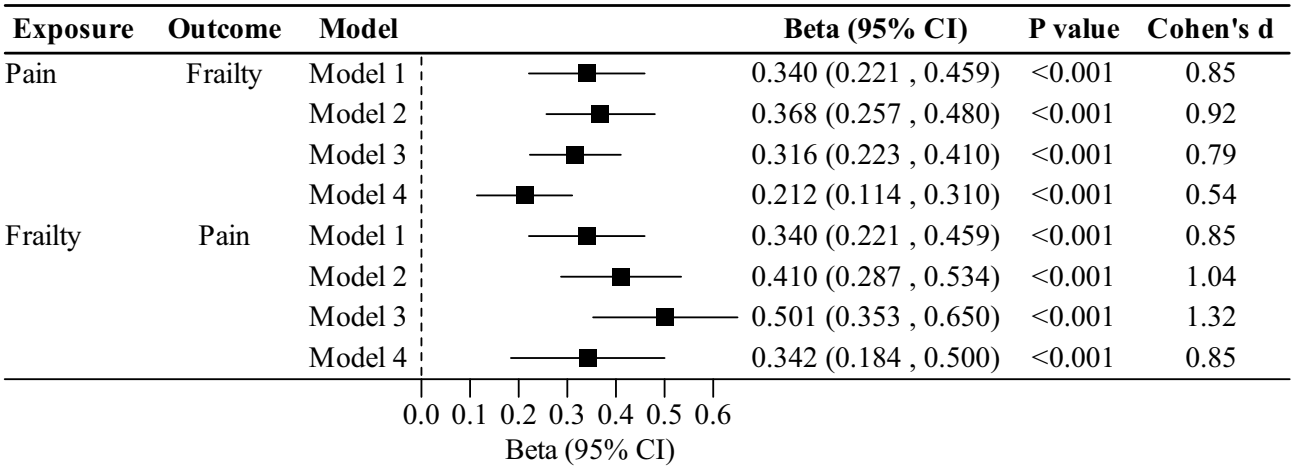


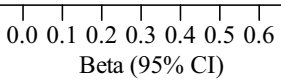

**Figure 1** Linear regression of the association between pain and frailty in two nexuses. Beta refers to standardized coefficient. Cohen's d was evaluated to demonstrate the effect sizes. All models 1 were unadjusted. All models 2 were adjusted for age, sex and education. All models 3 were adjusted for age, sex, education, pain duration, pain type and pain location. All models 4 were adjusted for age, sex, education, pain duration, pain type, pain location, PSQI, HADS-A and HADS-D.

**Abbreviations**: CI, Confidence Interval; PSQI, Pittsburgh Sleep Quality Index; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale.


https://doi.org/10.2147/CIA.S515294

**A**

| Exposure | Mediator | Model | Beta (95% CI) | P value | Cohen's d |
|---|---|---|---|---|---|
| Pain | Sleep | Model 1 | 0.386 (0.270 , 0.503) | <0.001 | 0.97 |
| | | Model 2 | 0.395 (0.277 , 0.513) | <0.001 | 0.99 |
| | | Model 3 | 0.350 (0.231 , 0.469) | <0.001 | 0.87 |
| Pain | Anxiety | Model 1 | 0.334 (0.214 , 0.453) | <0.001 | 0.83 |
| | | Model 2 | 0.333 (0.215 , 0.450) | <0.001 | 0.83 |
| | | Model 3 | 0.318 (0.196 , 0.440) | <0.001 | 0.79 |
| Pain | Depression | Model 1 | 0.390 (0.274 , 0.507) | <0.001 | 0.98 |
| | | Model 2 | 0.400 (0.284 , 0.516) | <0.001 | 1.01 |
| | | Model 3 | 0.364 (0.243 , 0.484) | <0.001 | 0.91 |
| Frailty | Sleep | Model 1 | 0.366 (0.248 , 0.484) | <0.001 | 0.91 |
| | | Model 2 | 0.407 (0.282 , 0.532) | <0.001 | 1.03 |
| | | Model 3 | 0.364 (0.211 , 0.517) | <0.001 | 0.91 |
| Frailty | Anxiety | Model 1 | 0.258 (0.135 , 0.380) | <0.001 | 0.65 |
| | | Model 2 | 0.365 (0.242 , 0.488) | <0.001 | 0.91 |
| | | Model 3 | 0.402 (0.248 , 0.556) | <0.001 | 1.01 |
| Frailty | Depression | Model 1 | 0.390 (0.273 , 0.507) | <0.001 | 0.98 |
| | | Model 2 | 0.476 (0.357 , 0.596) | <0.001 | 1.24 |
| | | Model 3 | 0.537 (0.390 , 0.684) | <0.001 | 1.45 |




**B**

| Mediator | Outcome | Model | Beta (95% CI) | P value | Cohen's d |
|---|---|---|---|---|---|
| Sleep | Frailty | Model 1 | 0.366 (0.248 , 0.484) | <0.001 | 0.91 |
| | | Model 2 | 0.361 (0.250 , 0.471) | <0.001 | 0.90 |
| | | Model 3 | 0.235 (0.136 , 0.333) | <0.001 | 0.59 |
| Anxiety | Frailty | Model 1 | 0.258 (0.135 , 0.380) | <0.001 | 0.65 |
| | | Model 2 | 0.341 (0.226 , 0.457) | <0.001 | 0.85 |
| | | Model 3 | 0.253 (0.156 , 0.349) | <0.001 | 0.64 |
| Depression | Frailty | Model 1 | 0.390 (0.273 , 0.507) | <0.001 | 0.98 |
| | | Model 2 | 0.431 (0.323 , 0.540) | <0.001 | 1.10 |
| | | Model 3 | 0.336 (0.244 , 0.428) | <0.001 | 0.84 |
| Sleep | Pain | Model 1 | 0.386 (0.270 , 0.503) | <0.001 | 0.97 |
| | | Model 2 | 0.390 (0.273 , 0.506) | <0.001 | 0.98 |
| | | Model 3 | 0.358 (0.236 , 0.479) | <0.001 | 0.89 |
| Anxiety | Pain | Model 1 | 0.334 (0.214 , 0.453) | <0.001 | 0.83 |
| | | Model 2 | 0.347 (0.225 , 0.469) | <0.001 | 0.87 |
| | | Model 3 | 0.317 (0.195 , 0.438) | <0.001 | 0.79 |
| Depression | Pain | Model 1 | 0.390 (0.274 , 0.507) | <0.001 | 0.98 |
| | | Model 2 | 0.403 (0.286 , 0.521) | <0.001 | 1.02 |
| | | Model 3 | 0.361 (0.242 , 0.480) | <0.001 | 0.90 |

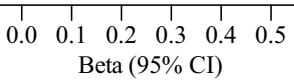



**Figure 2** Linear regression of the associations between pain, frailty and mediators. (**A**) The effect of exposure on each mediator. (**B**) The effect of each mediator on outcome. Beta refers to standardized coefficient. Cohen's d was evaluated to demonstrate the effect sizes. All models 1 were unadjusted. All models 2 were adjusted for age, sex and education. All models 3 were adjusted for age, sex, education, pain duration, pain type and pain location.
**Abbreviation** CI, Confidence Interval.

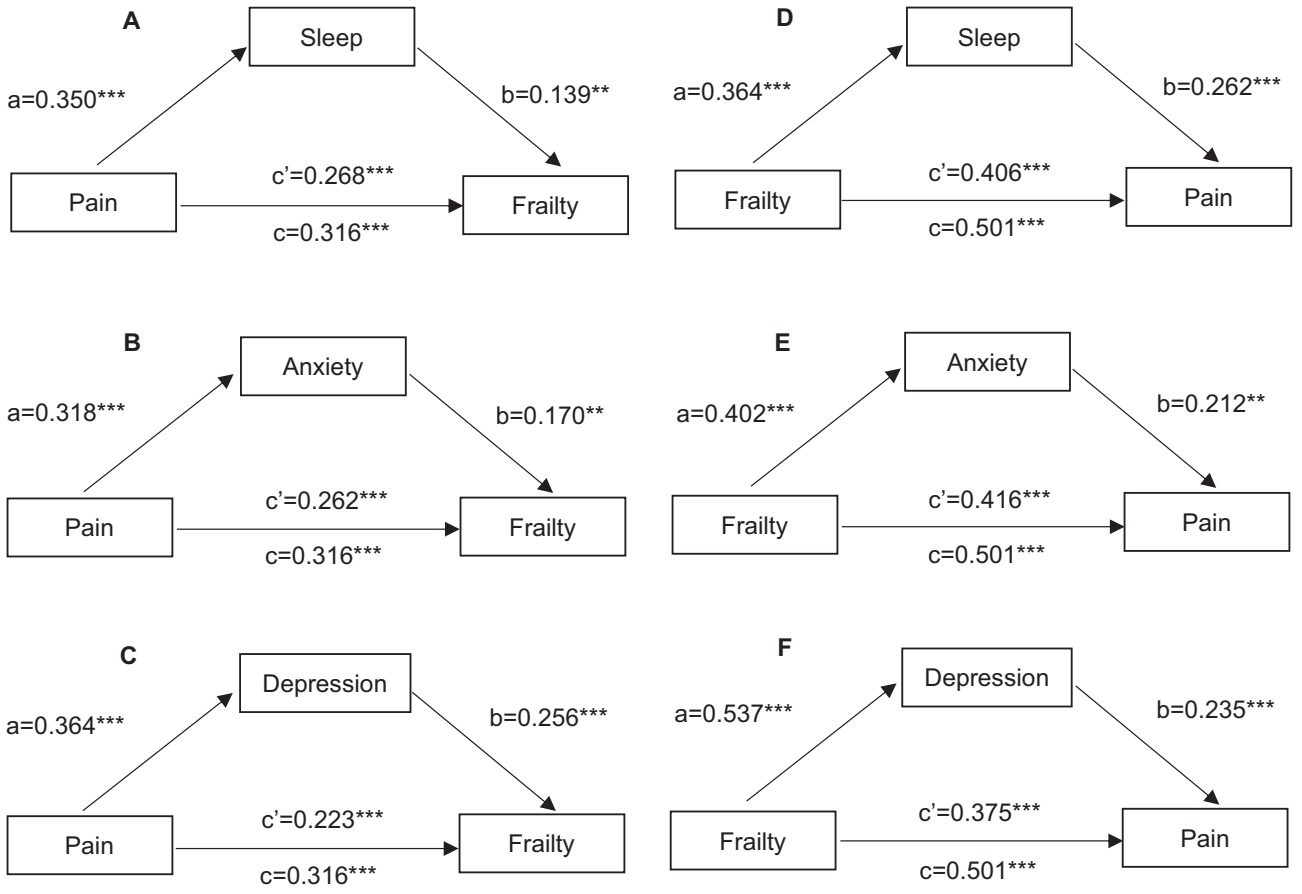



**Figure 3** The simple mediation roles of sleep, anxiety and depression in both the pain-frailty nexus and frailty-pain nexus. Beta refers to standardized coefficient. All mediator analyses were adjusted for age, sex, education, pain duration, pain type and pain location. Models (**A**–**C**) show the mediator models of sleep, anxiety and depression in the pain-frailty nexus. Models (**D**–**F**) show the mediator models of sleep, anxiety and depression in the frailty-pain nexus. "c" is the total effect; "a×b" is the indirect effect; "c'" is the direct effect. *Significant at the 0.05 level (2-tailed); **Significant at the 0.01 level (2-tailed); ***Significant at the 0.001 level (2-tailed).

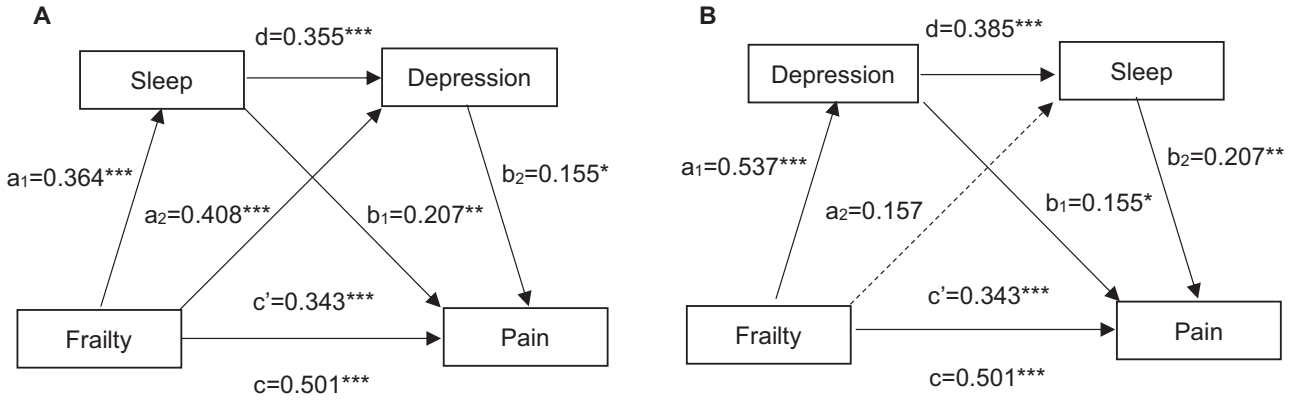



**Figure 4** The serial mediation roles of sleep and depression in the frailty-pain nexus. Beta refers to standardized coefficient. All mediator analyses were adjusted for age, sex, education, pain duration, pain type and pain location. Serial mediation models included Model (**A**) (Frailty→Sleep→Depression→Pain) and Model (**B**) (Frailty→Depression→Sleep→Pain). "c" is the total effect; "$a_1 \times b_1$", "$a_2 \times b_2$", "$a_1 \times d \times b_2$" are the indirect effects; "c'" is the direct effect. *Significant at the 0.05 level (2-tailed); **Significant at the 0.01 level (2-tailed); ***Significant at the 0.001 level (2-tailed).


https://doi.org/10.2147/CIA.S515294

as the alternative path (Frailty→Depression→Sleep→Pain) were found to be statistically significant (Figure 4), suggesting that the progression of frailty led to an increase in sleep disturbance or depressive symptoms, which subsequently contributed to the escalation of pain severity.

## Sensitivity Analysis

The consistent relationship between pain and frailty was found across various subgroups in two nexuses. Nociceptive pain, mixed pain, and the presence of three or more pain sites appeared to amplify the impact of frailty on pain (pain type: p for interaction=0.001; pain location: p for interaction=0.048) (Figure 5). Additionally, nociceptive and mixed pain rather than neuropathic pain, together with pain sites, were positively correlated with frailty (Supplementary Figure S2).

# Discussion

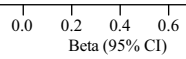
This study provided evidence of the robust relationship between pain and frailty among middle-aged and older hospitalized patients. Simple mediation models showed that sleep, anxiety and depression acted as individual mediators in both two nexuses. Serial mediation models demonstrated that sleep and depression co-played mediating effects in the frailty-pain nexus. Nociceptive pain, mixed pain, and the presence of three or more pain sites were found to exacerbate the effects of frailty on pain. Nociceptive and mixed pain, together with pain sites, were positively correlated with frailty.

Our study identified the stable positive association between pain and frailty as reported previously.[5,6,34] In the pain-frailty nexus, numerous observational studies confirmed that pain was a risk factor for frailty, with majority of them conducted in community settings,[9–15] and only a few studies investigated in hospital settings.[8,16] The strong correlation could be attributed to the fact that pain was associated with lower physical activity, malnutrition and musculoskeletal diseases, all of which were essential components of frailty. Previous studies suggested that pain might serve as an important stressor, which led to the depletion of body reserves and overactivated the HPA axis, ultimately contributing to frailty.[17] In the frailty-pain nexus, limited research has been undertaken to investigate the potential role of frailty as a precursor to the development of pain. Dai et al conducted a two-sample Mendelian randomization study which suggested that frailty might elevate the likelihood of experiencing pain.[5] Chaplin et al demonstrated that baseline frailty was a predictor of increased pain at one year, using a two-wave cross-lagged path modeling approach.[34] Conversely, a prospective cohort study by Megale et al did not observe the significant effect of frailty on pain.[14] These discrepancies might be ascribed to variations in the assessment tools used to measure frailty and high rates of loss to follow-up in the longitudinal study. Frailty may function as a potential risk factor in the modulation of pain through descending inhibitory pathways,[7] reinforcing the hypothesis that frailty influences pain. A shared basis in molecular mechanisms, such as genetic and epigenetic factors, immune system responses, and inflammation was observed in both pain and frailty,[6] which implied that these two might interact synergistically in a vicious cycle, wherein each condition exacerbated the progression of the other. Nevertheless, the current recommendations issued by NHS England[35] on frailty prevention do not include pain, and similarly, the NICE guidelines[36] for pain management do not consider frailty. Our findings indicate that increased awareness of the interrelated risks of pain and frailty may enhance public health interventions. Moreover, this robust positive association was observed exclusively when the BPI pain severity score was used to assess pain, whereas it was not evident with the NRS pain intensity score. The BPI pain severity score encompasses indicators of pain from multiple dimensions and temporal points, rendering it particularly suitable for evaluating the relationship between pain and frailty, considering that frailty is a process characterized by chronic progression.

The current study showed that sleep, anxiety and depression mediated the reciprocal relationship between pain and frailty in the simple mediation models. In line with previous studies,[17–19] depression was found to be a more significant mediator compared to anxiety and sleep. Empirical investigations into pain-depression comorbidity indicated that pain served as a risk factor for depression,[37] while also being a consequence of depression,[38] and the conclusion was further corroborated by animal experiments and neuroimaging studies.[39,40] Pain and depression are interconnected sharing neural substrates including brain areas (eg, amygdala, hippocampus, prefrontal cortex, and anterior cingulate cortex), neurotransmitters (eg, serotonin, norepinephrine, glutamate and GABA), as well as neurobiological pathways (eg, HPA axis).[37] Depression has been consistently linked with social isolation and increased incidence of physical illnesses, leading to the development of frailty.[41] Consequently, individuals with a high burden of illnesses may experience heightened frailty,

**A**

| Subgroup | Patients (n/N) | Beta (95% CI) | P value | Cohen's d | P for interaction |
|---|---|---|---|---|---|
| All patients | 244 | 0.316 (0.223 , 0.410) | <0.001 | 0.79 | |
| **Age** | | | | | 0.883 |
| 50-64 years | 126/244 | 0.307 (0.180 , 0.434) | <0.001 | 0.76 | |
| ≥65 years | 118/244 | 0.323 (0.159 , 0.487) | <0.001 | 0.80 | |
| **Sex** | | | | | 0.928 |
| Male | 108/244 | 0.336 (0.178 , 0.494) | <0.001 | 0.84 | |
| Female | 136/244 | 0.327 (0.216 , 0.439) | <0.001 | 0.81 | |
| **Education** | | | | | 0.862 |
| Primary school and below (≤6 years) | 122/244 | 0.321 (0.187 , 0.456) | <0.001 | 0.80 | |
| Junior high school and above (>6 years) | 122/244 | 0.284 (0.143 , 0.424) | <0.001 | 0.71 | |
| **Pain duration** | | | | | 0.735 |
| Acute pain | 65/244 | 0.289 (0.097 , 0.481) | 0.004 | 0.72 | |
| Chronic pain | 179/244 | 0.333 (0.225 , 0.442) | <0.001 | 0.83 | |
| **Pain type** | | | | | 0.399 |
| Neuropathic | 70/244 | 0.213 (0.003 , 0.423) | 0.047 | 0.55 | |
| Nociceptive | 82/244 | 0.383 (0.226 , 0.539) | <0.001 | 0.96 | |
| Mixed | 92/244 | 0.355 (0.208 , 0.502) | <0.001 | 0.89 | |
| **Pain location** | | | | | 0.317 |
| 1-2 pain sites | 183/244 | 0.269 (0.160 , 0.379) | <0.001 | 0.67 | |
| ≥3 pain sites | 61/244 | 0.466 (0.299 , 0.633) | <0.001 | 1.20 | |
| **PSQI** | | | | | 0.781 |
| ≤5 scores | 46/244 | 0.492 (0.228 , 0.756) | 0.001 | 1.29 | |
| >5 scores | 198/244 | 0.276 (0.174 , 0.378) | <0.001 | 0.69 | |
| **HADS-A** | | | | | 0.927 |
| <8 scores | 74/244 | 0.294 (0.137 , 0.450) | <0.001 | 0.73 | |
| ≥8 scores | 170/244 | 0.262 (0.145 , 0.380) | <0.001 | 0.66 | |
| **HADS-D** | | | | | 0.728 |
| <8 scores | 112/244 | 0.327 (0.196 , 0.459) | <0.001 | 0.81 | |
| ≥8 scores | 132/244 | 0.253 (0.122 , 0.385) | <0.001 | 0.64 | |




**B**

| Subgroup | Patients (n/N) | Beta (95% CI) | P value | Cohen's d | P for interaction |
|---|---|---|---|---|---|
| All patients | 244 | 0.501 (0.353 , 0.650) | <0.001 | 1.32 | |
| **Age** | | | | | 0.849 |
| 50-64 years | 126/244 | 0.529 (0.310 , 0.748) | <0.001 | 1.42 | |
| ≥65 years | 118/244 | 0.376 (0.185 , 0.567) | <0.001 | 0.94 | |
| **Sex** | | | | | 0.742 |
| Male | 108/244 | 0.450 (0.239 , 0.662) | <0.001 | 1.15 | |
| Female | 136/244 | 0.636 (0.419 , 0.853) | <0.001 | 1.89 | |
| **Education** | | | | | 0.316 |
| Primary school and below (≤6 years) | 122/244 | 0.512 (0.298 , 0.726) | <0.001 | 1.36 | |
| Junior high school and above (>6 years) | 122/244 | 0.432 (0.218 , 0.647) | <0.001 | 1.10 | |
| **Pain duration** | | | | | 0.928 |
| Acute pain | 65/244 | 0.476 (0.160 , 0.793) | 0.004 | 1.24 | |
| Chronic pain | 179/244 | 0.533 (0.360 , 0.706) | <0.001 | 1.44 | |
| **Pain type** | | | | | 0.001 |
| Neuropathic | 70/244 | 0.287 (0.004 , 0.570) | 0.047 | 0.72 | |
| Nociceptive | 82/244 | 0.628 (0.371 , 0.884) | <0.001 | 1.84 | |
| Mixed | 92/244 | 0.601 (0.353 , 0.850) | <0.001 | 1.72 | |
| **Pain location** | | | | | 0.048 |
| 1-2 pain sites | 183/244 | 0.440 (0.261 , 0.619) | <0.001 | 1.12 | |
| ≥3 pain sites | 61/244 | 0.796 (0.510 , 1.082) | <0.001 | 3.17 | |
| **PSQI** | | | | | 0.664 |
| ≤5 scores | 46/244 | 0.565 (0.262 , 0.869) | 0.001 | 1.56 | |
| >5 scores | 198/244 | 0.478 (0.302 , 0.654) | <0.001 | 1.24 | |
| **HADS-A** | | | | | 0.965 |
| <8 scores | 74/244 | 0.607 (0.284 , 0.930) | <0.001 | 1.74 | |
| ≥8 scores | 170/244 | 0.411 (0.227 , 0.595) | <0.001 | 1.04 | |
| **HADS-D** | | | | | 0.973 |
| <8 scores | 112/244 | 0.585 (0.350 , 0.820) | <0.001 | 1.64 | |
| ≥8 scores | 132/244 | 0.417 (0.200 , 0.633) | <0.001 | 1.06 | |

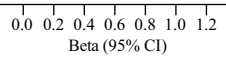



**Figure 5** Subgroup analyses of the association between pain and frailty in two nexuses. (**A**) Pain effect on frailty by subgroup. (**B**) Frailty effect on pain by subgroup. Beta refers to standardized coefficient. Cohen's d was evaluated to demonstrate the effect sizes. All analyses were adjusted for age, sex, education, pain duration, pain type and pain location.

**Abbreviations**: CI, Confidence Interval; PSQI, Pittsburgh Sleep Quality Index; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale.


https://doi.org/10.2147/CIA.S515294

which in turn exacerbates their depression.[42] Moreover, two Mendelian randomization studies demonstrated evidence for bidirectional relationships between depression and both pain and frailty.[43,44] Zhang et al illustrated that sleep partially mediated the association between pain and frailty in older cancer patients.[16] Neurobiological evidence also showed a causal relationship between pain and sleep disturbances, with the latter leading to heightened sensitivity to painful stimuli and exacerbating pain, thereby impacting sleep quality.[45] In older population, sleep disorders may contribute to the loss of muscle mass and function, ultimately leading to decreased physical activity, which are key components of frailty.[46]

We subsequently investigated the serial mediation models in both the pain-frailty nexus and the frailty-pain nexus, consisted with current results of effect sizes (Cohen's d), only two models demonstrated the significance (Frailty→Sleep→Depression→Pain and Frailty→Depression→Sleep→Pain), suggesting that sleep and depression co-played a mediation role in the relationship between frailty and pain. Previous studies showed that sleep and depression separately mediated the association between pain and frailty.[16–19] Our findings provided a new sight of these complicated relation, which declared the interaction effect between sleep and depression. Zhang et al considered the reciprocal influence of sleep and depression, revealing a bidirectional mediation of these two factors on their associations with frailty.[47] Another cross-sectional study illustrated that pain, difficulty initiating sleep, and depressive symptoms were each independently linked to pre-frailty and frailty in older adults.[48] Furthermore, the depressive symptom interacted with pain and difficulty initiating sleep resulted in a synergistic effect that had a greater impact on pre-frailty and frailty than their individual effects.[48]

A prospective cohort study found that the intensity and localization of pain were significant risk factors for frailty.[10] Additionally, Ardoino et al conducted a study on a sizable cohort of older hospitalized individuals experiencing pain from various causes, revealing that chronic rather than acute pain, widespread rather than localized pain, somatic rather than visceral and neuropathic pain were more commonly linked to an elevated frailty status.[8] Nociceptive pain, mixed pain and widespread pain are closely associated with high level of systemic inflammation, depression and sleep disorders, which collectively contribute to the exacerbation of frailty.[8] In contrast, our study did not identify a significant correlation between chronic pain and frailty. This discrepancy may be attributed to variations in frailty assessment and the universal presence of pain symptoms among all participants in our study, leading to a high prevalence of frailty. Moreover, subgroup analyses revealed a positive correlation between pain and frailty in both middle-aged and older adults, suggesting that increased attention should be directed towards middle-aged adults. Similarly, a population-based study from the UK Biobank corroborated this perspective, highlighting the significance of frailty, particularly among middle-aged adults, for whose mental health might be more adversely impacted by frailty compared to their older counterparts.[32] Conversely, Chiou et al reported no significant association between pain and frailty among middle-aged individuals, attributing this finding to their study's focus on cognitively and functionally sound community-dwelling adults.[18] A meta-analysis indicated that females exhibited higher FI scores compared to males across all age groups.[49] However, our analysis did not reveal any significant difference within sex-stratified subgroups, which was consistent with findings from a recent cross-sectional study conducted in China.[47]

This study elucidates the robust association between pain and frailty. Our findings suggest that interventions targeting both sleep and psychological symptoms are crucial in managing pain and frailty, which represents a significant advancement in comprehending the underlying mechanisms linking pain and frailty.

However, it is important to acknowledge certain limitations when interpreting our findings. Firstly, the cross-sectional design utilized in this study precluded the ability to assess temporal associations and establish causality. Nevertheless, our results offered a compelling hypothesis for potential bidirectional relationship between pain and frailty that could be explored in future longitudinal studies. Secondly, our study solely incorporated participants experiencing pain and included only two frailty status: prefrail and frail, potentially introducing bias into the results. Thirdly, given the distinct pathophysiological mechanisms underlying cancer-related pain, future research should prioritize differentiating cancer pain from non-cancer pain. Lastly, the restriction to participants from a tertiary care hospital might limit the generalizability of our findings to community-based settings.

## Conclusions

Our findings indicated the stable relationship between pain and frailty, as well as the mediation roles of sleep, anxiety and depression. Nociceptive and mixed pain, as opposed to neuropathic pain, and the quantity of pain sites were positively associated with frailty. Acknowledging the co-occurrence of frailty and pain presents an opportunity to enhance patient care in hospital settings. Future research should integrate strategies for managing sleep and mental health as well as developing strategies in mitigating the progression of pain and frailty.

## Data Sharing Statement

The raw data generated or analyzed during this study can be made available by the corresponding author upon reasonable request.

## Ethics Approval and Informed Consent

This study was approved by the Institutional Scientific Research and Clinical Trails Ethics Committee of the First Affiliated Hospital of Zhengzhou University (number 2024-KY-0580-001) and performed in accordance with the Helsinki Declaration. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was followed. All participants provided written informed consent before the study commenced.

## Acknowledgments

We would like to express our gratitude to all the participants in this study. We also thank Prof. Daqing Ma, Professor of Anaesthesia, Imperial College London for his critical comments during manuscript preparation. An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was supported by grant U23A20421 from the National Natural Science Foundation of China.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752–762. doi:10.1016/S0140-6736(12)62167-9
2. He Y, Cheng J, Qin H, et al. Effects of dexmedetomidine on perioperative brain protection in elderly frail patients. *J Anesth Transl Med*. 2023;2(3):29–33. doi:10.58888/2957-3912-2023-03-04
3. Veronese N, Custodero C, Cella A, et al. Prevalence of multidimensional frailty and pre-frailty in older people in different settings: a systematic review and meta-analysis. *Ageing Res Rev*. 2021;72:101498. doi:10.1016/j.arr.2021.101498
4. Molton IR, Terrill AL. Overview of persistent pain in older adults. *Am Psychol*. 2014;69(2):197–207. doi:10.1037/a0035794
5. Dai Z, Wu Y, Chen J, Huang S, Zheng H. Assessment of relationships between frailty and chronic pain: a bidirectional two-sample Mendelian randomisation study. *Age Ageing*. 2024;53(1):afad256. doi:10.1093/ageing/afad256
6. D'Agnelli S, Amodeo G, Franchi S, et al. Frailty and pain, human studies and animal models. *Ageing Res Rev*. 2022;73:101515. doi:10.1016/j.arr.2021.101515
7. Karp JF, Shega JW, Morone NE, Weiner DK. Advances in understanding the mechanisms and management of persistent pain in older adults. *Br J Anaesth*. 2008;101(1):111–120. doi:10.1093/bja/aen090

8. Ardoino I, Franchi C, Nobili A, Mannucci PM, Corli O. Pain and frailty in hospitalized older adults. *Pain Ther*. 2020;9(2):727–740. doi:10.1007/s40122-020-00202-3
9. Saraiva MD, Suzuki GS, Lin SM, et al. Persistent pain is a risk factor for frailty: a systematic review and meta-analysis from prospective longitudinal studies. *Age Ageing*. 2018;47(6):785–793. doi:10.1093/ageing/afy104
10. Rodríguez-Sánchez I, García-Esquinas E, Mesas AE, et al. Frequency, intensity and localization of pain as risk factors for frailty in older adults. *Age Ageing*. 2019;48(1):74–80. doi:10.1093/ageing/afy163
11. Wade KF, Marshall A, Vanhoutte B, et al. Does Pain Predict Frailty in Older Men and Women? Findings from the English Longitudinal Study of Ageing (ELSA). *J Gerontol a Biol Sci Med Sci*. 2017;72(3):403–409. doi:10.1093/gerona/glw226
12. Shega JW, Dale W, Andrew M, et al. Persistent pain and frailty: a case for homeostenosis. *J Am Geriatr Soc*. 2012;60(1):113–117. doi:10.1111/j.1532-5415.2011.03769.x
13. Wade KF, Lee DM, McBeth J, et al. Chronic widespread pain is associated with worsening frailty in European men. *Age Ageing*. 2016;45(2):268–274. doi:10.1093/ageing/afv170
14. Megale RZ, Ferreira ML, Ferreira PH, et al. Association between pain and the frailty phenotype in older men: longitudinal results from the Concord Health and Ageing in Men Project (CHAMP). *Age Ageing*. 2018;47(3):381–387. doi:10.1093/ageing/afy012
15. Sodhi JK, Karmarkar A, Raji M, et al. Pain as a predictor of frailty over time among older Mexican Americans. *Pain*. 2020;161(1):109–113. doi:10.1097/j.pain.0000000000001711
16. Zhang Q, Yu M, Tang R, et al. A pathway model of chronic pain and frailty in older Chinese cancer patients: the mediating effect of sleep. *Geriatr Nurs*. 2023;50:215–221. doi:10.1016/j.gerinurse.2023.01.015
17. Tian X, Wang C, Qiao X, et al. Association between pain and frailty among Chinese community-dwelling older adults: depression as a mediator and its interaction with pain. *Pain*. 2018;159(2):306–313. doi:10.1097/j.pain.0000000000001105
18. Chiou J-H, Liu L-K, Lee W-J, Peng L-N, Chen L-K. What factors mediate the inter-relationship between frailty and pain in cognitively and functionally sound older adults? A prospective longitudinal ageing cohort study in Taiwan. *BMJ Open*. 2018;8(2):e018716. doi:10.1136/bmjopen-2017-018716
19. Tomás JM, Sentandreu-Mañó T, Martínez-Gregorio S. Does depression mediate the pain-frailty relationship? Latent variables approach. *Geriatr Nurs*. 2023;51:388–393. doi:10.1016/j.gerinurse.2023.04.006
20. Theou O, Blodgett JM, Godin J, Rockwood K. Association between sedentary time and mortality across levels of frailty. *CMAJ*. 2017;189(33):E1056–E1064. doi:10.1503/cmaj.161034
21. Zhang J, Basnet D, Du X, et al. Does cognitive frailty predict delayed neurocognitive recovery after noncardiac surgery in frail elderly individuals? Probably not. *Front Aging Neurosci*. 2022;14:995781. doi:10.3389/fnagi.2022.995781
22. Poquet N, Lin C. The Brief Pain Inventory (BPI). *J Physiother*. 2016;62(1):52. doi:10.1016/j.jphys.2015.07.001
23. Im DD, Jambaulikar GD, Kikut A, Gale J, Weiner SG. Brief pain inventory-short form: a new method for assessing pain in the emergency department. *Pain Med*. 2020;21(12):3263–3269. doi:10.1093/pm/pnaa269
24. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1–2):9–19. doi:10.1016/j.pain.2004.09.012
25. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213. doi:10.1016/0165-1781(89)90047-4
26. Black DS, O'Reilly GA, Olmstead R, Breen EC, Irwin MR. Mindfulness meditation and improvement in sleep quality and daytime impairment among older adults with sleep disturbances: a randomized clinical trial. *JAMA Intern Med*. 2015;175(4):494–501. doi:10.1001/jamainternmed.2014.8081
27. Kovacs AH, Luyckx K, Thomet C, et al. Anxiety and depression in adults with congenital heart disease. *J Am Coll Cardiol*. 2024;83(3):430–441. doi:10.1016/j.jacc.2023.10.043
28. Beekman E, Verhagen A. Clinimetrics: hospital anxiety and depression scale. *J Physiother*. 2018;64(3):198. doi:10.1016/j.jphys.2018.04.003
29. Bray NW, Pieruccini-Faria F, Witt ST, et al. Frailty and functional brain connectivity (FBC) in older adults with mild cognitive impairment (MCI): baseline results from the SYNERGIC trial. *Geroscience*. 2023;45(2):1033–1048. doi:10.1007/s11357-022-00702-4
30. Maharani A, Sinclair DR, Chandola T, et al. Household wealth, neighbourhood deprivation and frailty amongst middle-aged and older adults in England: a longitudinal analysis over 15 years (2002-2017). *Age Ageing*. 2023;52(3):afad034. doi:10.1093/ageing/afad034
31. Hayes AF. *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. 3rd ed. New York: The Guilford Press; 2022.
32. Jiang R, Noble S, Sui J, et al. Associations of physical frailty with health outcomes and brain structure in 483 033 middle-aged and older adults: a population-based study from the UK biobank. *Lancet Digit Health*. 2023;5(6):e350–e359. doi:10.1016/S2589-7500(23)00043-2
33. Barber KE, Zainal NH, Newman MG. The mediating effect of stress reactivity in the 18-year bidirectional relationship between generalized anxiety and depression severity. *J Affect Disord*. 2023;325:502–512. doi:10.1016/j.jad.2023.01.041
34. Chaplin WJ, McWilliams DF, Millar BS, Gladman JRF, Walsh DA. The bidirectional relationship between chronic joint pain and frailty: data from the investigating musculoskeletal health and wellbeing cohort. *BMC Geriatr*. 2023;23(1):273. doi:10.1186/s12877-023-03949-4
35. Preventing Frailty. NHS England; 2022. Available from: https://www.england.nhs.uk/ourwork/clinical-policy/older-people/frailty/preventing-frailty/. Accessed 2022.
36. Carville S, Constanti M, Kosky N, Stannard C, Wilkinson C. Chronic pain (primary and secondary) in over 16s: summary of NICE guidance. *BMJ*. 2021;373:n895. doi:10.1136/bmj.n895
37. Goesling J, Clauw DJ, Hassett AL. Pain and depression: an integrative review of neurobiological and psychological factors. *Curr Psychiatry Rep*. 2013;15(12):421. doi:10.1007/s11920-013-0421-0
38. Carroll LJ, Cassidy JD, Côté P. Depression as a risk factor for onset of an episode of troublesome neck and low back pain. *Pain*. 2004;107(1–2):134–139. doi:10.1016/j.pain.2003.10.009
39. Bravo L, Mico JA, Rey-Brea R, et al. Depressive-like states heighten the aversion to painful stimuli in a rat model of comorbid chronic pain and depression. *Anesthesiology*. 2012;117(3):613–625. doi:10.1097/ALN.0b013e3182657b3e
40. Zheng CJ, Van Drunen S, Egorova-Brumley N. Neural correlates of co-occurring pain and depression: an activation-likelihood estimation (ALE) meta-analysis and systematic review. *Transl Psychiatry*. 2022;12(1):196. doi:10.1038/s41398-022-01949-3

41. Alexopoulos GS. Depression in the elderly. *Lancet*. 2005;365(9475):1961–1970. doi:10.1016/S0140-6736(05)66665-2
42. Read JR, Sharpe L, Modini M, Dear BF. Multimorbidity and depression: a systematic review and meta-analysis. *J Affect Disord*. 2017;221:36–46. doi:10.1016/j.jad.2017.06.009
43. Tang B, Meng W, Hägg S, Burgess S, Jiang X. Reciprocal interaction between depression and pain: results from a comprehensive bidirectional Mendelian randomization study and functional annotation analysis. *Pain*. 2022;163(1):e40–e48. doi:10.1097/j.pain.0000000000002305
44. Sang N, Li B-H, Zhang M-Y, et al. Bidirectional causal relationship between depression and frailty: a univariate and multivariate Mendelian randomisation study. *Age Ageing*. 2023;52(7):afad113. doi:10.1093/ageing/afad113
45. Haack M, Simpson N, Sethna N, Kaur S, Mullington J. Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. *Neuropsychopharmacology*. 2020;45(1):205–216. doi:10.1038/s41386-019-0439-z
46. Buchmann N, Spira D, Norman K, et al. Sleep, muscle mass and muscle function in older people. *Dtsch Arztebl Int*. 2016;113(15):253–260. doi:10.3238/arztebl.2016.0253
47. Zhang Y, Yu G, Bai W, et al. Association of depression and sleep quality with frailty: a cross-sectional study in China. *Front Public Health*. 2024;12:1361745. doi:10.3389/fpubh.2024.1361745
48. Liu M, Hou T, Nkimbeng M, et al. Associations between symptoms of pain, insomnia and depression, and frailty in older adults: a cross-sectional analysis of a cohort study. *Int J Nurs Stud*. 2021;117:103873. doi:10.1016/j.ijnurstu.2021.103873
49. Gordon EH, Peel NM, Samanta M, et al. Sex differences in frailty: a systematic review and meta-analysis. *Exp Gerontol*. 2017;89:30–40. doi:10.1016/j.exger.2016.12.021

**Clinical Interventions in Aging**

**Dovepress**
Taylor & Francis Group

**Publish your work in this journal**

Clinical Interventions in Aging is an international, peer-reviewed journal focusing on evidence-based reports on the value or lack thereof of treatments intended to prevent or delay the onset of maladaptive correlates of aging in human beings. This journal is indexed on PubMed Central, MedLine, CAS, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

**Submit your manuscript here:** https://www.dovepress.com/clinical-interventions-in-aging-journal