Association between pain and frailty among Chinese community-dwelling older adults: depression as a mediator and its interaction with pain

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Abstract

Pain and frailty are both prevalent and have severe health impacts among older adults. We conducted a cross-sectional observational study to examine the association between pain and frailty, and depression as a mediator and its interaction with pain on frailty among 1788 Chinese community-dwelling older adults. Physical frailty, pain intensity, and depressive symptoms were assessed using the Frailty Phenotype, the Faces Pain Scale-revised, and the 5-item Geriatric Depression Scale, respectively. We found that both pain (odds ratio [OR] = 1.61; 95% confidence interval [CI]: 1.32-1.97) and depressive symptoms (OR = 4.67; 95% CI: 3.36-6.50) were positively associated with physical frailty (OR = 1.61; 95% CI: 1.32-1.97), and depressive symptoms were associated with pain (OR = 1.94; 95% CI: 1.15-3.39), attenuating the association between pain and physical frailty by 56.1%. Furthermore, older adults with both pain and depressive symptoms (OR = 8.13; 95% CI: 5.27-12.53) had a higher risk of physical frailty than those with pain (OR = 1.41; 95% CI: 1.14-1.76) or depressive symptoms (OR = 3.63; 95% CI: 2.25-5.85) alone. The relative excess risk of interaction, the attributable proportion due to interaction, and the synergy index (S) were 4.08, 0.50, and 2.34, respectively. These findings suggest that the positive association of pain with frailty is persistent and partially mediated by depression, and comorbid depression and pain have an additive interaction on physical frailty. It has an implication of multidisciplinary care for frail older adults with pain.

Keywords: Frailty, Pain, Depression, Older adults, China

1. Introduction

With the development of the global population aging, frailty has already become an increasing challenge. Frailty is a state in which older adults have diminished physiological reserves and increased risk to adverse outcomes such as hospitalization, institutionalization, and death.\textsuperscript{6,15,26,48} A systematic review indicates that the prevalence of physical phenotype frailty in community-dwelling older adults ranged from 4.0% to 17.0% in 14 studies from different countries.\textsuperscript{17} Recognizing modifiable risk factors related to the development or deterioration of frailty will help formulate impactful targeted interventions to prevent onset or delay progression of frailty.

Pain is a particularly common symptom in clinical practice that seriously impairs health, and more than 50% of community-dwelling older adults experience persistent pain.\textsuperscript{28} Recently, some studies proposed that pain could contribute to frailty by acting as a stressor and found that older adults with pain were more likely to be frail,\textsuperscript{7,57,68} but other studies found that the association between pain and frailty was not significant.\textsuperscript{13,69} Thus, whether pain could contribute to frailty needs explicit attention. Although it is not entirely clear how pain contributes to the development of frailty, it has been proposed that the relationship between pain and frailty might be caused by a third factor, such as the presence of pain-associated conditions (eg, sleep disturbances, depression, and decreased socialization).\textsuperscript{36} Therein, depression is prevalent among older adults and frequently co-occurs with pain.\textsuperscript{7,20,47} Moreover, an Australian study showed that accounting for depressed mood ameliorated the association between frailty and intrusive pain.\textsuperscript{1} However, this study just emphasized depressed mood as a key role in central pain processing and did not examine the association between depressed mood and frailty, which precludes an inference of depressed mood as a mediator linking pain with frailty. Yet, recent other studies have found that depressive symptoms increased the onset of frailty in older adults.\textsuperscript{42,67} Given the links between pain, depression, and frailty found in separate studies, it seems reasonable to hypothesize that depression mediates the association between pain and frailty. However, this hypothetical explanation is not yet empirically examined. Furthermore, it is worth mentioning that pain is interrelated with depression, and the presence or increase in severity of 1 condition often results in the development or deterioration of the other one.\textsuperscript{29} The treatment of pain is partially or completely ineffective for some patients with chronic pain due to comorbid depression that is often undertreated.\textsuperscript{65} Meanwhile, joint exposure of pain and depression has been associated with greater disability of activities of daily living and heavier economic burdens than 1 condition alone.\textsuperscript{25} These findings indicate that pain may interact with depression on health outcomes. Therefore,
we further hypothesize that interaction between pain and depression may occur when they act together in causing frailty.

This study investigates the relationship between pain and frailty as well as depression as a mediator and its interaction with pain on frailty, which might provide a new insight to multidisciplinary care for frail older adults with pain.

2. Methods

2.1. Setting and participants

2.1.1. Participant recruitment

During August 2015 to December 2016, a cross-sectional study was conducted in Jinan, the capital city of Shandong Province, China. First, the 9 districts under the jurisdiction of Jinan city were divided into 3 groups according to socioeconomic development: high-, moderate-, and low-economic-level group. Next, we selected 1 district randomly from each group. Finally, we selected 7 to 8 communities within each district, resulting in a total of 22 communities. Communities were selected on the basis of availability of the older population and approval from the community residents’ committees. We distributed flyers with relevant information about our study to community residents aged 60 years and over, inviting them to participate in the study. Of 2800 individuals invited, 848 refused to participate in the study, 35 were excluded for severe cognitive impairment, severe visual, or hearing problems, and serious physical deficits, which can preclude the accomplishment of the necessary physical performance measures. Therefore, a total of 1917 participants were enrolled in the study. More details about participant recruitment are presented in Figure 1.

2.1.2. Data collection

The investigators consisting of nursing postgraduates had received standardized training on conducting interviews and physical performance assessments. Older adults were provided with face-to-face culturally appropriate structural questionnaire interviews and physical performance assessments at their affiliated community centers. All participants were informed of the relevant information of our study and signed written informed consent. The study was approved by the Institutional Review Board of Shandong University, Jinan, China.

2.2. Measurements

2.2.1. Physical frailty

Physical frailty was identified using the Frailty Phenotype, which has been widely used and extensively validated. This measure purely includes 5 physical phenotype components: weight loss, weakness, exhaustion, slowness, and low physical activity. The total frailty score was calculated from the 5 components. Participants who met 0 components were categorized as robust, 1 to 2 components as prefrail, and 3 to 5 components as frail. For each frailty component, the measurements were performed as follows:

(1) **Weight loss**: defined as unintentional weight loss over the past year equal to or greater than 5% of the body weight in the previous year. Weight loss over the past year was calculated by subtracting the body weight of last year from the current body weight. Current body weight was measured at the interview directly and the body weight of last year was self-reported.

(2) **Weakness**: maximal grip strength in the dominant hand was measured with a handheld dynamometer 3 times. Adjusted for sex and body mass index, the average value of 3 measurements was used to assess weakness.

(3) **Exhaustion**: assessed using 2 items of the Center for Epidemiologic Studies Depression Scale (CES-D). Exhaustion was considered present if the response to either 1 of the questions below is “3-4 days” or “4-7 days”: I feel everything I did was an effort in the last week; I could not get going in the last week.

(4) **Slowness**: measured by time to walk 15 feet adjusting for sex and height.

(5) **Low physical activity**: assessed by weekly energy expenditure using the IPAQ-SF (International Physical Activity Questionnaire-Short Form). The measures and the cut-point criteria of frailty components used in this study were the same as the original phenotype frailty, with an exception of low physical activity. The IPAQ-SF was substituted for the Minnesota Leisure Time Activity Questionnaire (MLTA-Q) in the original phenotype frailty because the IPAQ-SF has been widely used and proved to have good reliability and validity in China.

2.2.2. Pain

The Faces Pain Scale-revised (FPS-R) was used to measure pain intensity. It is a visual scale consisting of 6 faces scored 0-2, 2-4, 4-6, 6-8, 10 from left to right successively and showing increasing pain. A score of 2 or greater indicates the presence of pain. Respondents were asked to point to the face that best describes how much he or she hurts right now. It does not contain any language related to pain, which make it a cross-cultural instrument for the measurement of pain intensity. The FPS-R has strong correlations with the colored analog scale (r = 0.84) and the visual analog scale (r = 0.93). It measures pain intensity in older Chinese adults.

2.2.3. Depressive symptoms

In the present study, depressive symptoms were assessed with the 5-item Geriatric Depression Scale (GDS-5). The GDS-5 is less time-consuming and demonstrates the same good performance as the 15-item Geriatric Depression Scale. It measures depressive symptoms over the past week and contains 5 questions: (1) Are you basically satisfied with your life?; (2) Do you often feel bored?; (3) Do you often feel helpless?; (4) Do you prefer to stay at home rather than going out and doing new things?; (5) Do you feel pretty worthless the way you are now? Positive answers for depression screening are yes to questions 2, 3, 4, and 5 and no to question 1. The total score ranges from 0 to 5, and participants scoring 2 and above are considered to have
depressive symptoms. It has been proved to be a sensitive and specific screening tool for depressive symptoms.\textsuperscript{33,43,53}

2.2.4. Covariates

We collected data including age, sex, education, monthly income, living arrangement (living alone or not), cognitive function, and number of chronic diseases. Cognitive function was assessed using the Short Portable Mental Status Questionnaire (SPMSQ).\textsuperscript{50} with 8 or more errors indicating cognitive impairment. The reliability and validity of the SPMSQ have been established in detecting the presence of cognitive impairment in previous studies.\textsuperscript{50,50} The self-reported doctor-diagnosed chronic diseases included hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, stroke, arthritis, asthma, chronic obstructive pulmonary disease, chronic renal disease, and cancer.

2.3. Statistical methods

Descriptive statistical analyses were conducted using mean values (SDs) and percentages to describe characteristics of the participants. Chi-square test and analysis of variance were used to compare the sample characteristics and the prevalence of pain and depressive symptoms according to frailty status. Furthermore, the effect size index $f$ for the analysis of variance and the effect size index $w$ for the $\chi^2$ test were calculated using $G \times Power$ 3.1. According to Cohen criteria,\textsuperscript{16} $f = 0.10$, $f = 0.25$, and $f = 0.40$ indicate small, medium and large effect size, respectively, and $w = 0.10$, $w = 0.30$ and $w = 0.50$ indicate small, medium and large effect size, respectively.

To estimate the mediation effect of depressive symptoms, we first conducted an informal procedure testing by performing a series of binomial or ordinal logistic regression models. Then, we performed a series of linear regression models based on the formal procedure outlined by Baron and Kenny.\textsuperscript{5} The first equation regressed the outcome variable (physical frailty) on the independent variable (pain). The second equation regressed the presumed mediator (depressive symptoms) on the independent variable (pain). The third equation regressed the outcome variable (physical frailty) on the independent variable (pain) and the presumed mediator (depressive symptoms). According to Baron and Kenny,\textsuperscript{5} the following criteria must be met to establish a mediation effect: (1) the independent variable must be significantly related to the outcome variable; (2) the independent variable must be significantly related to the presumed mediator; (3) the presumed mediator must be significantly related to the outcome variable; and (4) when the presumed mediator is included in the regression model, the association between the independent and outcome variables must be attenuated. Finally, the Sobel test\textsuperscript{7} was conducted to examine whether the mediating effect of depressive symptoms on the relationship between pain and physical frailty was significant.

To assess the additive interaction between pain and depressive symptoms, we calculated the 3 indicators of interaction on an additive scale: relative excess risk of interaction (RERI), the relative excess risk due to interaction; the attributable proportion due to interaction; and S, the synergy index.\textsuperscript{36} If RERI and AP are equal to 0 and S is equal to 1, it means that there is no additive interaction. According to the method described by Andersson et al.,\textsuperscript{1} we first created a new composite variable with 4 categories: (1) exposure to neither pain nor depressive symptoms; (2) exposure only to pain; (3) exposure only to depressive symptoms; and (4) joint exposure to both pain and depressive symptoms. Using the new composite variable as an independent variable and physical frailty as a dependent variable, we carried out ordinal logistic regression analyses adjusting for covariates. The unexposed group is set up as the reference category. Finally, we used an Excel sheet (available from http://epinet.se/default.htm) to calculate the 3 indicators of an additive interaction and their 95% confidence intervals (CIs) based on the data from the logistic regression analyses.

3. Results

Of the 1917 older adults included, 129 (6.7%) had missing values on the Frailty Phenotype and were excluded from data analyses. Therefore, 1788 community-dwelling older adults were introduced for data analyses. The analyzed sample (n = 1788) was not different in sociodemographic characteristics and physical (the number of chronic diseases and the presence of pain), cognitive, and psychological (depressive symptoms) functioning from the whole sample included (n = 1917).

Table 1 shows the characteristics of the total analyzed sample and by frailty status. The mean age was 69.1 years and 66.9% were women. Of the 1788 participants, 39.6% reported the presence of pain and 10.9% had depressive symptoms. The prevalence of frailty and prefrailty were 4.4% and 43.5%, respectively, whereas 52.1% were robust. There were significant differences in sociodemographic and health characteristics by frailty status, with the exception of sex and incomes ($P < 0.001$). Older adults with more frailty reported a higher prevalence of pain ($w = 0.29$, $P < 0.001$, nearly medium effect) and depressive symptoms ($w = 0.79$, $P < 0.001$, large effect). In addition, participants with more frailty were more likely to be older, have less years of schooling, live alone, have cognitive impairment, and have more chronic diseases.

Table 2 presents the results from sequential logistic regression models adjusting for covariates, addressing the mediation effect of depressive symptoms linking pain with physical frailty. The presence of pain increased the risk of physical frailty (odds ratio [OR] = 1.61; 95% CI: 1.32-1.97). Depressive symptoms were associated with pain (OR = 1.94; 95% CI: 1.15-3.39) and increased the risk of physical frailty (OR = 4.67; 95% CI: 3.36-6.50). With adjustment for depressive symptoms, the risk of physical frailty associated with pain was attenuated but persistent (OR = 1.49; 95% CI: 1.21-1.83).

Figure 2 presents the results of mediation analysis using hierarchical linear regression models adjusting for covariates. Pain intensity was positively associated with (equation 1: $Y = i + c X + e_1$) frailty components ($\beta = 0.161$, $P < 0.001$) and with (equation 2: $M = i + a X + e_2$) depressive symptoms ($\beta = 0.198$, $P < 0.001$). With the inclusion of depressive symptoms (equation 3: $Y = i + c' X + b M + e_3$), the association of pain intensity with increased frailty components was ameliorated but significant ($\beta = 0.103$, $P < 0.001$); depressive symptoms ($\beta = 0.232$, $P < 0.001$) linked to more frailty components (equation 4: $Y = i + c' X + b M + e_4$). These results suggest that depressive symptoms partially mediated the relationship between pain and physical frailty, which was further confirmed by the Sobel test ($z = 7.09$, $P < 0.001$). The mediate effect of depressive symptoms accounted for 56.1% of the total effect of pain with physical frailty.

Table 3 presents the interaction effect of depressive symptoms with pain on physical frailty using an ordinal logistic regression model. For those exposed only to pain or depressive symptoms, the adjusted OR of frailty is 1.41 and 3.63, respectively; however, for those exposed to pain and depressive symptoms simultaneously, the adjusted OR of physical frailty significantly increased to 8.13. The RERI was 4.08 (95% CI: 0.41-7.75); the attributable proportion due to interaction was 0.50 (95% CI: 0.22-0.79); and
Although this study cannot explore physiological mechanisms underlying the link between pain and physical frailty, we found that the relationship between pain and physical frailty was mediated by depressive symptoms, which may provide a mechanistic interpretation of how pain contributes to the development of physical frailty from the standpoint of psychology.

Using mediation analysis, our results showed that depressive symptoms partially mediated the association between pain intensity and physical phenotype frailty, attenuating the association by 56.1%. This finding is similar to previous research indicating that depression acts as a mediator of the relationship between pain and functional limitations. Empirical studies on pain–depression comorbidity have shown that depression is usually a consequence of pain, whereas depression is a risk factor for pain onset. Pain and depression share brain areas (eg, hippocampus), neurobiological pathways (eg, HPA axis), and neurochemicals (eg, 5-HT and norepinephrine). When pain occurs, depression might be induced or exacerbated. From the standpoint of psychology, for individuals having chronic pain, the factors that act synergistically to increase the risk of physical frailty. Figure 3 visually presents the ORs of frailty with contributions from different exposure categories marked (pain and depressive symptoms).

4. Discussion

In line with previous studies, we found that pain was significantly associated with physical frailty. It is not difficult to understand their positive association in view of the substantial evidence that pain has been linked to poorer physical function outcomes such as weaker grip strength, slower gait speed, malnutrition, and lower physical activity, which are essential components of physical phenotype frailty. Previous studies have shown that pain, especially chronic pain as a stressor, may overactivate the hypothalamic pituitary adrenal (HPA) axis and ultimately results in a dysfunctional HPA axis, which cannot effectively respond to stress, and thus, predisposes to frailty development. Although this study cannot explore physiological mechanisms underlying the link between pain and physical frailty, we have found that the relationship between pain and physical frailty was mediated by depressive symptoms, which may provide a mechanistic interpretation of how pain contributes to the development of physical frailty from the standpoint of psychology.

Using mediation analysis, our results showed that depressive symptoms partially mediated the association between pain intensity and physical phenotype frailty, attenuating the association by 56.1%. This finding is similar to previous research indicating that depression acts as a mediator of the relationship between pain and functional limitations. Empirical studies on pain–depression comorbidity have shown that depression is usually a consequence of pain, whereas depression is a risk factor for pain onset. Pain and depression share brain areas (eg, hippocampus), neurobiological pathways (eg, HPA axis), and neurochemicals (eg, 5-HT and norepinephrine). When pain occurs, depression might be induced or exacerbated. From the standpoint of psychology, for individuals having chronic pain, the factors that act synergistically to increase the risk of physical frailty. Figure 3 visually presents the ORs of frailty with contributions from different exposure categories marked (pain and depressive symptoms).

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (1788)</th>
<th>Robust (932)</th>
<th>Prefrail (777)</th>
<th>Frail (79)</th>
<th>P</th>
<th>Effect size*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.1 ± 4.9</td>
<td>67.6 ± 4.6</td>
<td>70.6 ± 6.9</td>
<td>73.4 ± 6.9</td>
<td>&lt;0.001</td>
<td>0.25</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>591 (33.1%)</td>
<td>325 (34.9%)</td>
<td>245 (31.5%)</td>
<td>21 (26.6%)</td>
<td>0.157</td>
<td>0.10</td>
</tr>
<tr>
<td>Years of education</td>
<td>8.7 ± 4.2</td>
<td>9.2 ± 3.9</td>
<td>8.3 ± 4.4</td>
<td>6.5 ± 4.9</td>
<td>&lt;0.001</td>
<td>0.15</td>
</tr>
<tr>
<td>Live alone</td>
<td>218 (12.2%)</td>
<td>83 (8.9%)</td>
<td>118 (15.2%)</td>
<td>17 (21.5%)</td>
<td>&lt;0.001</td>
<td>0.34</td>
</tr>
<tr>
<td>Low income†</td>
<td>1251 (71.6%)</td>
<td>642 (70.9%)</td>
<td>556 (72.8%)</td>
<td>53 (67.9%)</td>
<td>0.530</td>
<td>0.06</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>108 (6.0%)</td>
<td>42 (4.5%)</td>
<td>52 (6.7%)</td>
<td>14 (17.7%)</td>
<td>&lt;0.001</td>
<td>0.35</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td>1.5 ± 1.3</td>
<td>1.3 ± 1.2</td>
<td>1.8 ± 1.3</td>
<td>2.5 ± 1.3</td>
<td>&lt;0.001</td>
<td>0.24</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>195 (10.9%)</td>
<td>46 (4.9%)</td>
<td>111 (14.3%)</td>
<td>38 (48.1%)</td>
<td>&lt;0.001</td>
<td>0.79</td>
</tr>
<tr>
<td>Pain (FPS-R ≥ 2)</td>
<td>708 (39.6%)</td>
<td>311 (33.4%)</td>
<td>347 (44.7%)</td>
<td>50 (63.3%)</td>
<td>&lt;0.001</td>
<td>0.29</td>
</tr>
</tbody>
</table>

* The effect size of 1-way analysis of variance is the index f^2 and the effect size of the χ² test is the index of w^2.
† The criterion of lower income was household per capita disposable income of Jinan, China, in 2014 less than the median of 3200 yuan (498.44 US $). Forty participants had missing data for income.
FPS-R, Faces Pain Scale-revised; GDS-5, 5-item Geriatric Depression Scale; SPMSQ, the Short Portable Mental Status Questionnaire.

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frailty (model without depressive symptoms)</th>
<th>Frailty (model with depressive symptoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
</tr>
<tr>
<td>Pain</td>
<td>1.61 (1.32-1.97) &lt;0.001</td>
<td>1.69 (1.21-1.83) &lt;0.001</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.92 (1.05-1.09) &lt;0.001</td>
<td>1.08 (1.06-1.09) &lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.98 (0.78-1.23) 0.887</td>
<td>0.79 (0.78-1.23) 0.841</td>
</tr>
<tr>
<td>Years of education</td>
<td>0.97 (0.94-0.99) 0.011</td>
<td>0.97 (0.95-1.00) 0.036</td>
</tr>
<tr>
<td>Live alone</td>
<td>1.25 (0.93-1.69) 0.142</td>
<td>1.08 (0.84-1.40) 0.530</td>
</tr>
<tr>
<td>Low income*</td>
<td>1.11 (0.87-1.43) 0.409</td>
<td>1.30 (0.85-1.98) 0.219</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>1.61 (1.32-1.97) 0.250</td>
<td>1.30 (1.20-1.41) 0.001</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td>1.35 (1.25-1.46) &lt;0.001</td>
<td>1.49 (1.21-1.83) &lt;0.001</td>
</tr>
</tbody>
</table>

* The criterion of lower income was household per capita disposable income of Jinan, China, in 2014 less than the median of 3200 yuan (498.44 US $).
Cl, confidence interval; NA, not applicable; OR, odds ratio.
repeated unsuccessful coping efforts may lead to a feeling of helplessness, further exacerbating depression.48,55 Depression can cause changes in behavior and social engagement, resulting in frailty. For example, depression is often associated with sedentary behavior56 and noncompliance to medical treatment recommendations such as following a diet,21,30 thus bringing about a higher risk of frailty. Moreover, depression is often accompanied by social isolation preventing people from getting possible social support, which increases the odds of frailty worsening.25 However, considering the multifaceted nature of pain, depression is unlikely to be the single dominant mediator between pain and frailty. Associated conditions of pain such as loss of appetite56 and poor sleep24 may also contribute to this process, which needs to be further explored.

Furthermore, we found a significant additive interaction between pain and depressive symptoms on physical frailty. Older adults having both pain and depressive symptoms had higher odds of physical frailty than those with either condition alone. Many factors are likely involved in possible mechanisms underlying the hypothesis of interaction between pain and depressive symptoms on physical frailty. For example, depression may enhance the pain experience by impairing the function of the endogenous descending inhibitory system,36 which plays an important role in the modulation of nociceptive transmission.39 Thus, when individuals with pain have comorbid depression, they may develop more severe pain which in turn worsens the depression. In addition, many health care providers are often concerned with somatic symptoms first, and depression is commonly seen as secondary importance.14 Thus, both under-diagnosis and undertreatment of depression may exist in the co-occurrence of pain and depression.3 This undertreatment of depression could impair the treatment effect of pain. It may even result in ineffective treatment when pain is purely a physical symptom of depression rather than when correlated with organic diseases. These phenomena can combine to increase the risk of frailty.

This study has several implications for frailty intervention in older people with pain. First, effective pain management should remain a high priority to slow down the progress of frailty. Although treatable, pain is commonly under-reported and undertreated in older adults.3,27,35,40 Prompt attention to pain complaints, adequate pain assessment, and comprehensive treatment including pharmacologic and nonpharmacologic methods are crucial to pain management. Second, the important role of depression in the development of frailty indicates that psychological treatment is also indispensable to frailty intervention in older people with pain. Attention should be paid to the assessment and treatment of depression. It is worth noting that sometimes depression initially appears as unexplained pain complaints, which may affect the diagnosis of depression.36,52 Thus, the possibility of depression should be considered when individuals present with unexplained pain. This is, in fact, a clear example of the advantage of a multidisciplinary team, including specialists in pain medicine and psychology, in the likelihood of identifying and appropriately treating older patients.

The current study explored the complex relationship between pain, depressive symptoms, and physical frailty using robust measures. It is worth mentioning that the Frailty Phenotype purely focuses on the physical domains. There are also other measures of frailty which not only focus on physical domains but also focus on psychological, cognitive, and social domains.62 However, the Frailty Phenotype is one of the most popular and conventional measurements of frailty in clinical practice and research.8 And this purely physical frailty measurement may be more appropriate to explicate the relationship of frailty with depression because multidimensional frailty instruments usually contain some psychological frailty items, which are overlapped with measurements of depression. Besides, another concern is that the GDS-5 used in this study is just a tool for screening, but not for the diagnosis of depression. The GDS-5 only assessed recent depressive symptoms, which may not only be attributable to psychopathology but also

**Table 3**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain and no depressive symptoms</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Pain only</td>
<td>1.41 (1.14-1.76)</td>
<td>0.002</td>
</tr>
<tr>
<td>Depressive symptoms only</td>
<td>3.63 (2.25-5.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain &amp; depressive symptoms</td>
<td>8.13 (5.27-12.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.08 (1.00-1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.97 (0.77-1.22)</td>
<td>0.810</td>
</tr>
<tr>
<td>Years of education</td>
<td>0.97 (0.95-1.00)</td>
<td>0.036</td>
</tr>
<tr>
<td>Live alone</td>
<td>1.11 (0.82-1.50)</td>
<td>0.512</td>
</tr>
<tr>
<td>Low income*</td>
<td>1.09 (0.85-1.41)</td>
<td>0.488</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>1.31 (0.86-2.00)</td>
<td>0.208</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td>1.30 (1.20-1.41)</td>
<td>&lt;0.001</td>
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</table>

Model fit

<table>
<thead>
<tr>
<th>−2Loglikelihood = 2617.99</th>
<th>P &lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudo R² = 0.205</td>
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*The criterion of lower income was household per capita disposable income of Jinan, China, in 2014 less than the median of 3200 yuan (498.44US $). CI, confidence interval; OR, odds ratio.**
to medical illness or medication side effects. Therefore, this measurement strategy may hinder an inference to depression as a risk factor for frailty. Nonetheless, the 5-item GDS has been widely validated against clinical diagnosis and achieved significant agreement with depression diagnosis (kappa = 0.74-0.81) and showed an excellent diagnostic accuracy (AUC = 0.87-0.90). This relatively high diagnosis accuracy of the GDS-5 may ensure the reliability of inference to depression as a risk factor for frailty and generalizability in clinical practice. Last, the FPS-R only measured the intensity of pain. Several components including pain site, pain duration, and pain treatment should be considered in future research to deepen our understanding.

It should also be noted that our study had some limitations. First, the cross-sectional design did not allow us to examine the temporal association and draw a causal inference. The present exploratory study was just a starting point, which sought to generate strong hypotheses about the potential causal role of depression on frailty to be tested in future longitudinal studies. The recent MacArthur approach, which modified the Baron and Kenny criteria for the definitions of mediators and moderators, may be more appropriate to be applied in longitudinal studies for accurately detecting the causality between pain, depression, and frailty. Second, the participants were enrolled in 1 city of China, which limits the findings generalizable to the entire aged Chinese population. Another limitation of the study was that a large number of participants (30.2%) refused to participate in this study. Last, measures of chronic diseases and some components of physical phenotype (such as loss of weight) were based on the participants’ self-report, which leads to recall bias and missing data (eg, 80 participants did not recall the body weight of last year). However, to our knowledge, this is the first study to explore depression as a mediator linking pain to frailty and its additive interaction with pain on frailty.

In summary, pain is associated with increased physical frailty among Chinese community-dwelling older adults and this relationship is partially mediated by depressive symptoms. Furthermore, the comorbidity of depressive symptoms and pain has an additive interaction on physical frailty. Further research is warranted to explore beneficial interventions of frailty in older people with pain and depression.

Conflict of interest statement
The authors have no conflicts of interest to declare.

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References


