

# Social Connection and Chronic Pain: A Cohort Study to Explore the Association of Social Isolation and Loneliness with Chronic Pain Among Older Adults in China

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**Background:** As societies worldwide experience rapid aging, social isolation and loneliness are as prevalent and impactful on health outcomes of older adults as other well-recognized risk factors. This study investigates the association of social isolation and loneliness on the prevalence of chronic pain among Chinese older adults.

**Methods:** Participants from waves of the Chinese Health and Retirement Longitudinal Study (CHARLS) with no chronic pain in baseline 2011, and their conditions of chronic pain in wave 2018, were analyzed. The exposure factors were social isolation and loneliness. Social isolation was assessed by a comprehensive multi-factor measure, while loneliness and the outcome variable, chronic pain, were self-reported. The association of the exposure factors on the prevalence of chronic pain was conducted by logistic regression.

**Results:** Adults 60 years old and over who did not suffer from chronic pain at baseline in 2011 were enrolled, of whom 1669 participants (53.68%) developed chronic pain, and 1440 did not develop chronic pain, over a span of seven years. The results showed that social isolation (OR: 1.21, 95% CI: 1.01–1.45) and loneliness (OR: 1.61, 95% CI: 1.36–1.92) were associated with an elevated risk of chronic pain over seven years. It showed no statistically significant interaction associations between social isolation and feelings of loneliness.

**Conclusion:** Older adults with social isolation or loneliness tended to experience chronic pain, emphasizing the importance of incorporating social support and community engagement into chronic pain treatment strategies.

**Keywords:** social isolation, loneliness, chronic pain, cohort study

## Introduction

Chronic pain persists for months or years and may progress as a disease with its own clinical course.<sup>1,2</sup> Pain is defined by the International Association for the Study of Pain (IASP) in 2020 as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”.<sup>3</sup> And chronic pain often refers to the pain that lasts for over three or six months.<sup>4,5</sup> Chronic pain affects around 40% of older adults in some demographically representative provinces of China<sup>6–8</sup> and is one of the major risk factors for increasing disability-adjusted life years, disease burden, and health expenditure in China and globally.<sup>9</sup> Besides the commonly recognized causes of pain,

including genetics, age, and lifestyle,<sup>10–12</sup> increasing evidence indicates that psychosocial factors can elevate the prevalence of chronic pain.<sup>13–15</sup>

Over the last century, global attention has increasingly focused on the potential health impact of social connection or its absence.<sup>16–18</sup> Loneliness and social isolation are concepts related to social connections, but with distinct definitions. Loneliness is a self-perceived or subjective feeling of being disconnected from social relationships<sup>19</sup> while social isolation is an objective condition, measured by the number of relationships, participation in social activities, and frequency of social engagements.<sup>20,21</sup> With population aging, the over-60s will increase from 20% of the Chinese population today to 30% by 2035, with the consequent increase in the disease burden and medical care costs.<sup>22,23</sup> Coupled with declining fertility, breakdown in the extended Chinese family and rural-to-urban migration leaving older parents in the countryside, the high-risk older population face social disengagement, loneliness, and separation from their children.<sup>21,24</sup> The prevalence of social isolation among older adults in China, estimated at 25% to 40%,<sup>25</sup> is comparable to that of older populations in other countries.<sup>26–28</sup> Biopsychosocial modeling has identified loneliness and social isolation, as well as depression, anxiety, and education,<sup>29–31</sup> as factors impacting a range of chronic diseases, such as hypertension,<sup>21</sup> cardiovascular diseases,<sup>20,32</sup> digestive disease,<sup>33</sup> and diabetes.<sup>20</sup>

But current studies on how loneliness and social isolation correlate with chronic pain have failed to draw uniform conclusions. Some research indicates a correlation between social isolation and pain and between loneliness and pain.<sup>34,35</sup> Most studies of social isolation and loneliness correlating with pain have concentrated on developed countries, such as the UK and Japan. The relationship between loneliness, social isolation, and chronic pain, focusing on Chinese older adults has not been fully elucidated. Whether loneliness and social isolation act independently or collectively on chronic pain will not only reveal the potential mechanisms between social isolation, loneliness, and pain, but have practical implications for preventing and alleviating chronic pain in older individuals.

To address this research gap, our study investigated the association between loneliness, social isolation, and chronic pain in Chinese adults aged 60 years and older. Based on nationally representative longitudinal data, we provide empirical evidence on the relationship between social connection and chronic pain and suggest early prevention and intervention strategies. Our findings highlight the importance of addressing social and emotional factors in the management of chronic pain among older adults, which will contribute to the development of targeted interventions that improve the well-being of older adults in China.

## Methods

### Study Design

Designing empirical models, our study asks the following questions: was social isolation associated with chronic pain, and was loneliness associated with chronic pain?; was there an interaction between social isolation, loneliness, and chronic pain?; and did social isolation and loneliness separately or jointly associate with chronic pain?

### Sample

This cohort study sourced its participants from the Chinese Health and Retirement Longitudinal Study (CHARLS), which is a nationwide longitudinal survey, using a multistage stratified probability-proportionate-to-size sampling method to track individuals aged 45 and above, throughout 150 counties and 450 communities, spanning 28 provinces in China. Anonymized individual data include health status, socio-economic situation, and family relationships at intervals of 2–3 years after the 2011 baseline survey. The ethical approval of CHARLS is provided by the Institutional Review Board (IRB) of Peking University (IRB00001052-11015).

CHARLS has released five national survey datasets corresponding to the years 2011, 2013, 2015, 2018, and 2020. However, the datasets from 2013 and 2015 do not include measurements of chronic pain and its severity, and the 2020 dataset was seriously affected by the COVID-19 pandemic. Therefore, we examined data from both the 2011 and 2018 waves of CHARLS, comprising a total of 17,710 participants at the 2011 baseline. The study excluded 2011 individuals who were not tracked in 2018 ( $n=4142$ ). Our study's focus is on older adults, who were more likely to be isolated from society and to experience loneliness than younger adults. Following the definition of older adults by

the World Health Organization,<sup>36</sup> we restricted the sample to individuals aged 60 and above. We removed individuals under 60 years old (n=8188); those with chronic pain in 2011 (n=1940); and those with missing data at the 2011 baseline and 2018 follow-up (n=14). After interpolating 2018 missing data from the 2011 baseline data, remaining incomplete baseline information on loneliness and social isolation (n=209) and on demographic socio-economics data (n=109) were also excluded. After applying these criteria, a total of 3109 participants were included in the study as shown in Figure 1.

## Social Isolation and Loneliness Measures

Following previous studies,<sup>21,25,37</sup> social isolation was assessed using a five-point measure adapted from the Steptoe Social Isolation Index,<sup>38</sup> incorporating marital status, cohabitation status of family members, frequency of participation in social activities, frequency of contact or meeting with their children, and residential urban or rural areas. While originally developed in Western settings, this index has been previously applied and adapted in studies using the CHARLS dataset to assess social isolation among older Chinese adults.<sup>21,25</sup> Although a fully validated scale for the Chinese population is still evolving, the index has demonstrated construct relevance in the context of aging studies in China. Social isolation in CHARLS was measured by scoring one point for participants' subjective perceptions: single (including never married, separated, divorced, or widowed), living alone, infrequent or no involvement in social activities in the last month (including socializing with friends, playing chess or cards, going to the community room, dancing or exercising, offering help to others, participating in club activities, voluntary or charitable activities, caring for the sick, training, speculating on stocks, surfing the Internet), no weekly face-to-face meetings with children, no weekly contact with children (via phone calls, text messages, letters or emails), and living in a rural area.<sup>39,40</sup> We used the median of the total social isolation score to categorize participants into a low ( $\leq 2$  points) and a high ( $> 2$  points) social isolation group.<sup>21,38</sup> From the Centre for Epidemiological Studies Depression Scale (CESD) in CHARLS, loneliness was assessed by asking the question "How frequently did you experience feelings of loneliness within the past week?". Respondents who responded they were lonely rarely or none of the time were classified into the no loneliness group and all other respondents were classified as lonely. Using the single question on loneliness from the CESD has been widely used and the results are consistent with those using the UK Biobank questionnaires and the UCLA loneliness scale.<sup>20,24,41</sup> While this single-item measure of loneliness reflects recent use, it may not fully capture the depth or emotional complexity of loneliness. To understand how social isolation and loneliness relate to chronic pain, we established four dummy variables: low social isolation and not lonely, low social isolation and lonely, high social isolation and not lonely, and high social isolation and lonely.

## Pain Measure

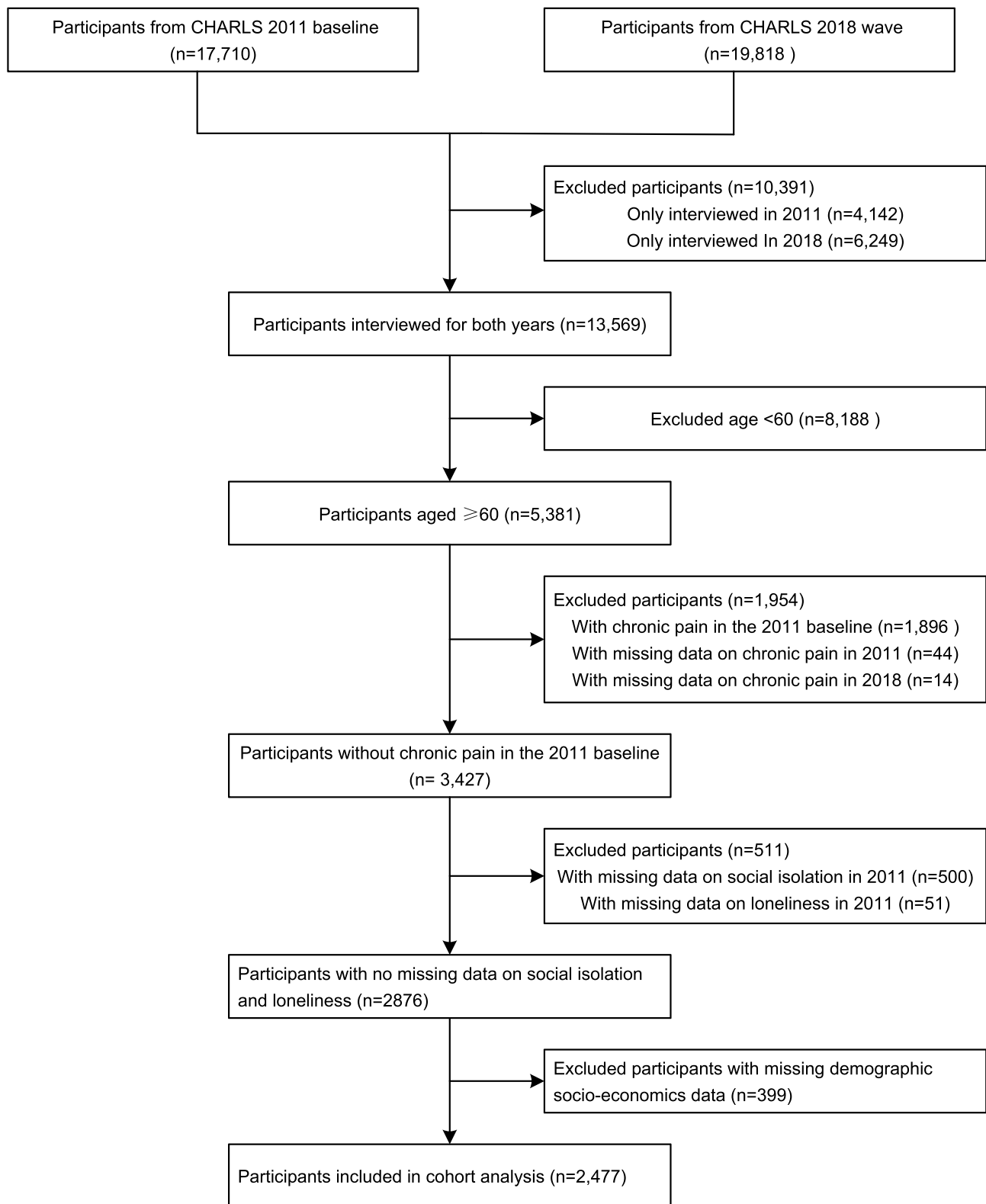
Chronic pain was our primary outcome variable, measured through the question "Are you often troubled with any body pains?" or answering specific questions about the part of the body experiencing pain or the level of the pain.<sup>42,43</sup> The question in CHARLS is often used to measure chronic pain, as the term "often troubled with" distinguishes it from acute pain.<sup>43-45</sup> The participants with mild, moderate, or severe chronic pain were coded as 1, while those with no pain were coded as 0.

## Covariates

Based on the existing published literature and clinical experience, Table 1 shows the definition of the demographic socio-economic covariates collected from the 2011 CHARLS baseline, including sex, age, education, household income level,<sup>46</sup> health status (sleep level, smoke-ever, drink-ever, and chronic diseases). Total household income (including individuals' and household members' wages, pensions, government transfers, financial income, agricultural income, and other incomes) was categorized into low-income ( $< \text{US}\$415$ ) and middle-to-high income ( $\geq \text{US}\$415$ ).<sup>46</sup> Rural residency is one of our five-point composite measures of social isolation; therefore, urban-rural residency is not treated as a separate covariate.

## Statistical Analysis

Hypothesis tests were conducted on baseline continuous and categorical variables using the two-sample Wilcoxon rank-sum test and Chi-square tests. To test the underlying relationships between social isolation, loneliness, and chronic pain,



**Figure 1** Flowchart of participants' selection process.

binary logistic regression was utilized and all regression outcomes were performed as Odds Ratio (OR) with 95% confidence intervals (CI). Three logistic regression models were estimated. To examine the relationship between social isolation and chronic pain, as well as loneliness and chronic pain, we designed Model 1, which includes control variables

**Table 1** Sample Baseline Characteristics

Variables	All (N = 3109)	Social Isolation		P value	Loneliness		P value
		Low (Score≤2) (N=2429)	High (Score>2) (N=680)		Not Lonely (N=2357)	Lonely (N=752)	
Sex, %							
Male	1683 (54.13)	1370 (56.40)	313 (46.03)	<0.001	1330 (56.43)	353 (46.94)	<0.001
Female	1426 (45.87)	1059 (43.60)	367 (53.97)		1027 (43.57)	399 (53.06)	
Age, M (SD)	66.98 (5.94)	66.57 (5.67)	68.45 (6.64)	<0.001	66.90 (5.87)	67.24 (6.15)	0.458
Education <sup>a</sup> , %				<0.001			<0.001
No formal education	1516 (48.76)	1300 (53.53)	216 (31.76)		1207 (51.21)	309 (41.09)	
Formal education	1593 (51.24)	1129 (46.48)	464 (68.24)		1150 (48.79)	443 (58.91)	
Household income level, %				<0.001			0.001
Low (<US\$415)	911 (29.30)	654 (26.92)	257 (37.79)		655 (27.79)	256 (34.04)	
Medium-high (>US\$414)	2198 (70.70)	1775 (73.08)	423 (62.21)		1702 (72.21)	496 (65.96)	
Sleep level, %				0.009			<0.001
≤4 hours	458 (14.73)	346 (14.24)	112 (16.47)		298 (12.64)	160 (21.28)	
4-8 hours	2382 (76.62)	1889 (77.77)	493 (72.50)		1868 (79.25)	514 (68.35)	
>8 hours	269 (8.65)	194 (7.99)	75 (11.03)		191 (8.10)	78 (10.37)	
Smoke-ever, %				0.827			0.244
Yes	1351 (43.45)	1058 (43.09)	293 (43.09)		1038 (44.04)	313 (41.62)	
No	1758 (56.55)	1371 (56.44)	387 (56.91)		1319 (55.96)	439 (58.38)	
Drink-ever, %				0.305			0.365
Yes	783 (25.18)	622 (25.61)	161 (23.68)		603 (25.58)	180 (23.94)	
No	2326 (74.82)	1807 (74.39)	519 (76.32)		1754 (74.42)	572 (76.06)	
Chronic diseases <sup>b</sup> , %				0.003			0.127
Yes	2100 (67.55)	1673 (68.88)	427 (62.79)		1575 (66.82)	525 (69.81)	
No	1009 (32.45)	756 (31.12)	253 (37.21)		782 (33.18)	227 (30.19)	

**Notes:** <sup>a</sup>Education was classified as no formal education and formal education (basic literacy skills, elementary, middle, and high school, vocation school, and attainment of degrees ranging from associate to Ph.D.). <sup>b</sup>Chronic diseases were categorized as either present or absent, based on whether participants had been diagnosed by a doctor with one or more of the following conditions: hypertension, dyslipidemia, diabetes, cancer, chronic lung diseases, liver disease, heart problems, stroke, kidney disease, digestive diseases, emotional or psychiatric problems, memory-related disease, arthritis, or asthma.

and tests both associations separately. Then, we developed Model 2, based on Model 1, with the interaction of social isolation and loneliness to examine whether exposure factors interacted with chronic pain. We designed Model 3 to explore the combined effects of social isolation and loneliness by incorporating four dummy variables: low social isolation and not lonely, high social isolation and lonely, high social isolation and not lonely, and low social isolation and lonely. We conduct subgroup analyses of social isolation and loneliness with the risk of developing chronic pain. Finally, we conducted two sensitivity analyses. First, to further predict the association between the degree of chronic pain and the future loneliness of the older adults, we substituted the outcome variable, chronic pain, with moderate and severe chronic pain levels using the original data.<sup>47</sup> Next, we focused on a subset of the sample where social isolation or loneliness remained consistent in 2011 and 2018 (individuals who were either socially isolated or not socially isolated in both years), to examine whether persistently isolated or persistently lonely individuals are at higher risk of developing chronic pain. We performed logistic regression analyses on this sample to explore the enduring effects, considering the stability of social isolation and loneliness.

Statistical analyses were conducted via Stata version 17 and R 4.4.0, with statistical significance by the two-sided <0.05 P-value.

## Results

### Sample Baseline Characteristics

Our national sample consisted of 3109 older adults free of chronic pain at the 2011 baseline. The average age of participants was 66.98 years (SD = 5.94), with a broadly even distribution of males (54.13%) and females (45.87%). In our sample, 1940 (62.40%) individuals experienced low social isolation and were not lonely; 489 (15.73%) experienced

low social isolation but were lonely; 417 (13.41%) experienced high social isolation but were not lonely; and 263 (8.46%) experienced both high social isolation and loneliness. The social isolation average score was  $1.8 \pm 1.0$ . As shown in Table 1, 680 (21.87%) were in the > 2 social isolation score group, which consisted of a larger proportion of females, older aged, those with formal education, medium-to-high income families, 4–8 hours sleep time, and a high prevalence of chronic diseases. According to the self-assessment response in CHARLS, 752 (24.19%) were lonely. Lonely participants had lower rates of smoking and drinking, but higher rates of chronic diseases compared to non-lonely participants.

### Social Isolation and Loneliness Association with Chronic Pain

CHARLS 2018 had 1669 individuals (or 53.68%) who developed chronic pain since the CHARLS 2011 baseline. Figure 2 depicts the relationship of social isolation with chronic pain and loneliness with chronic pain. We conducted Model 1 estimation where both social isolation and loneliness were concurrently included in the evaluation, the results showed that baseline social isolation and loneliness were correlated with a higher risk of 7-years-later chronic pain (social isolation: OR: 1.21, 95% CI: 1.01 to 1.45; loneliness: OR: 1.61, 95% CI: 1.36 to 1.92). Next, we conducted the Model 2 to explore the interaction correlation of social isolation and loneliness. In Figure 2, the results showed no observed interaction relationship. This suggests that the association between each factor and chronic pain operates independently in our sample.

To explore whether objective social isolation or subjective loneliness had a stronger association with chronic pain, we generated four dummy variables: low social isolation and not lonely, high social isolation and lonely, high social isolation and not lonely, and low social isolation and lonely. Figure 3 shows that compared to the older adults with low social isolation and no loneliness, those with high social isolation and high loneliness (OR: 1.93, 95% CI: 1.46 to 2.55), and those with low social isolation and high loneliness (OR: 1.49, 95% CI: 1.21 to 1.83), had a higher likelihood of chronic pain. Further, individuals concurrently experiencing high social isolation and high loneliness had the highest OR among the four groups. Older adults with high social isolation and no loneliness had no significant correlation with chronic pain (OR: 1.05, 95% CI: 0.84 to 1.31), suggesting that subjective loneliness has a more important relationship with chronic pain.

### Subgroup Analyses

Subgroup analyses based on the basic model are presented in Figure 4, classified by sex, education, household income level, drinking and smoking status, sleep level, and chronic diseases to estimate potential interactions that might influence the relationship between social isolation and chronic pain. Social isolation was associated with an increased risk of chronic pain among several subgroups: no formal education (OR: 1.26, 95% CI: 1.00 to 1.58), non-drinkers (OR: 1.23, 95% CI: 1.00 to 1.52), and non-smokers (OR: 1.29, 95% CI: 1.01 to 1.65).

As shown in Figure 5, subgroup analyses for the association of loneliness and chronic pain showed loneliness was associated with an elevated risk of chronic pain among several subgroups: non-smokers (OR: 1.96, 95% CI: 1.55 to

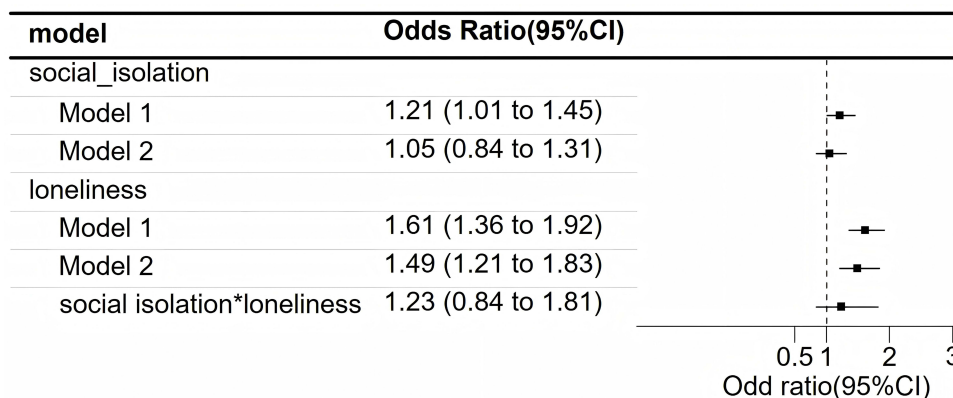
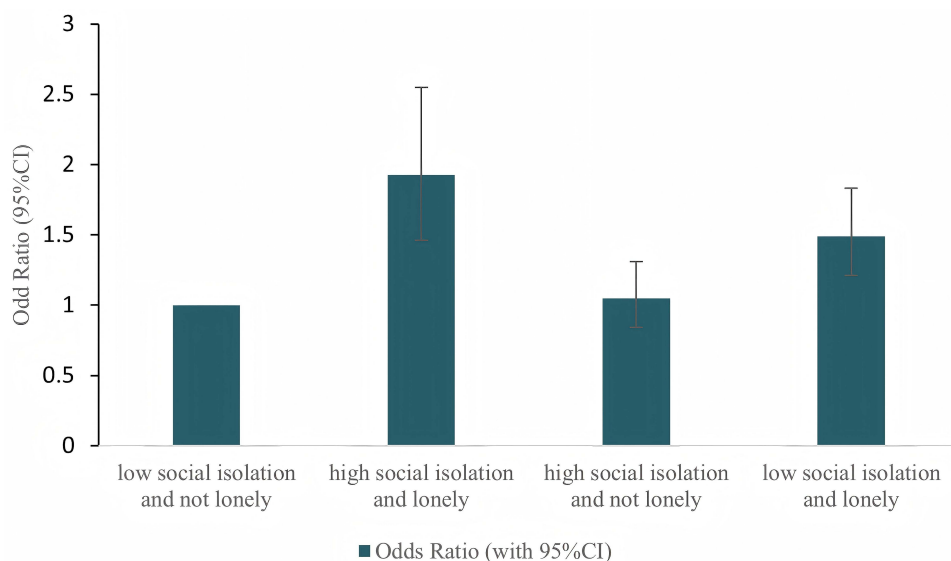
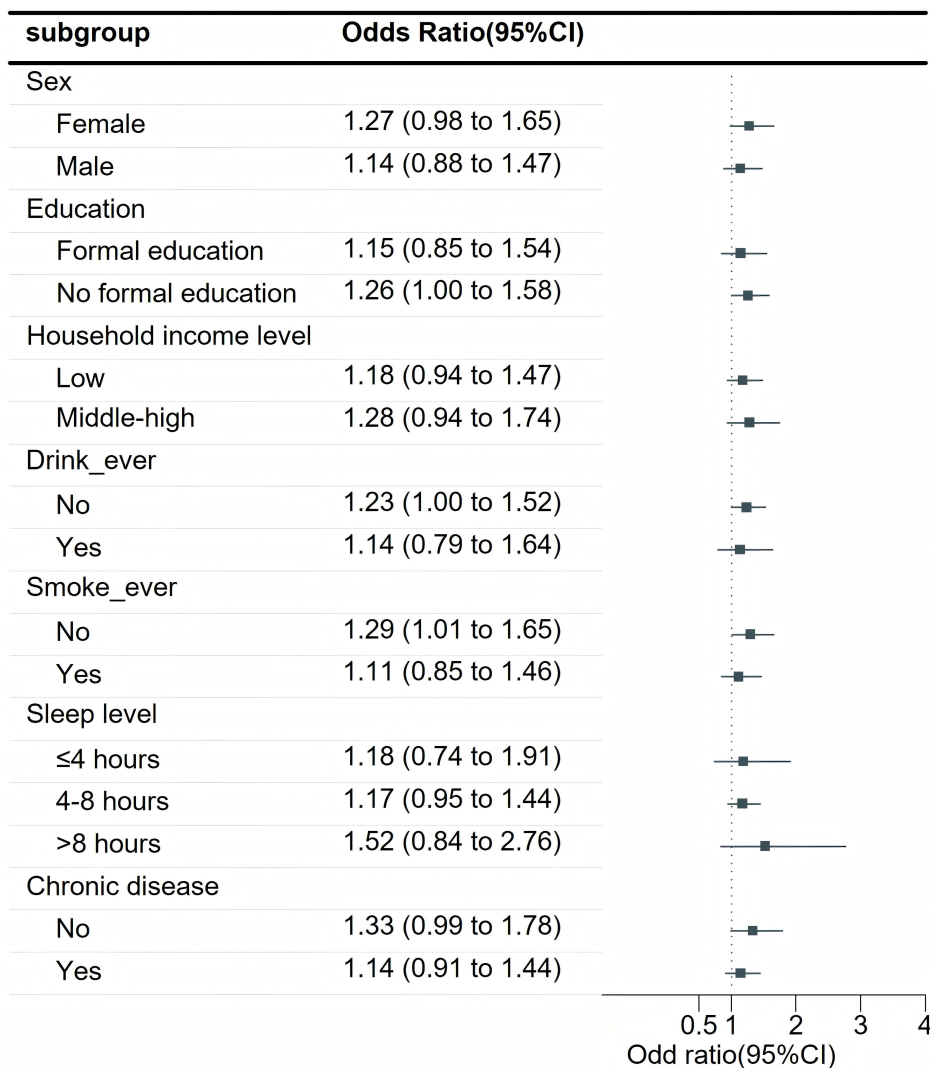


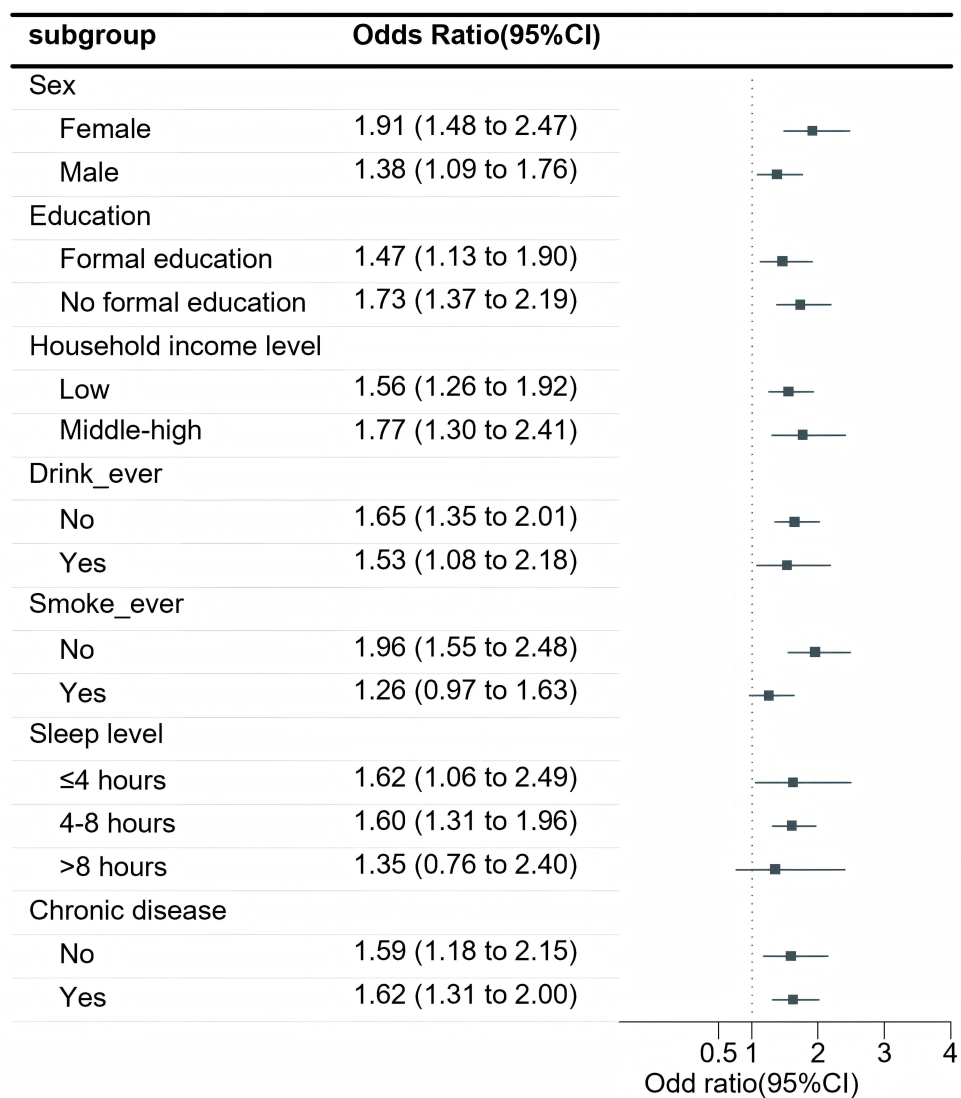
Figure 2 Social isolation and loneliness association with chronic pain.



**Figure 3** Social isolation and loneliness association with chronic pain: model 3.



**Figure 4** Social isolation and chronic pain: Subgroup analysis.



**Figure 5** Loneliness and chronic pain: Subgroup analysis.

2.48), and ≤8 hours sleep. Loneliness was also consistently associated with pain across categories of sex, education, household income level, never drinking, and chronic conditions.

## Sensitive Analyses

To avoid potential bias due to the measurement methods of the chronic pain variable and the long follow-up interval, we conducted sensitivity analyses for robustness. Replacing chronic pain with moderate and severe self-report pain in [Table S1](#) yielded similar regression results to the basic model. Compared to the benchmark regression, the sensitivity analysis indicated that the greater the degree of chronic pain in the elderly, the higher the predicted probability of future loneliness. Next, we estimated Model 1 in [Table S2](#) and Model 2 in [Table S3](#) on a subset of the sample where the social isolation and loneliness results remained consistent in 2011 and 2018, which confirmed our main findings.

## Discussion

Using a representative sample of the older population aged 60 and above in China, we examined the longitudinal relationships between social isolation and loneliness with chronic pain. The results demonstrated that both baseline social isolation and loneliness were associated with a higher likelihood of chronic pain, while there were no statistically

significant interaction correlations between social isolation and loneliness. Our study identified significant associations between social isolation, loneliness, and chronic pain, although our observational design limits causal inferences.

Social connectivity is essential for human well-being.<sup>48</sup> In our study, 21.87% of the participants were identified as having a high level of social isolation and 24.19% reported self-perceived loneliness according to 2011 baseline characteristics. Degrees of social isolation and loneliness among older adults varied across different country studies partly reflecting different measurement tools, technological access and usage, and cultural differences.<sup>21</sup> For example, some cultures emphasize close family ties while others are more individualistic.<sup>49,50</sup>

In recent decades, strong efforts have been made to understand the connection between social connection and the experiences of pain.<sup>51,52</sup> There are analogous mechanisms underlying both social and physical pain.<sup>53</sup> Several studies have examined associations between social disconnection and pain outcomes. For example, a UK Biobank cross-sectional study (N = 502,528) found that loneliness and social exclusion significantly predicted both acute and chronic pain, though no interaction relationship was found.<sup>54</sup> This consistency with our findings suggests that loneliness and social isolation act as independent risk factors, potentially through different mechanisms. Of course, this finding may reflect limitations in how these constructs were measured. A US midlife study reported that an increase in loneliness was related to a 24% increased likelihood of chronic pain, and a 17% higher risk of the quantity of chronic pain locations during the following-up period, highlighting that social activity indirectly correlated with chronic pain through loneliness.<sup>35</sup> Some studies have specifically examined the link between loneliness and chronic pain, highlighting that loneliness may contribute to an increased risk of chronic pain.<sup>40,47</sup> These studies provide important insights, but were mostly conducted in Western populations, and few simultaneously examined both social isolation and loneliness within the same analytic framework. While consistent with previous studies, our results provide new evidence that both social isolation and loneliness were associated with a higher risk of chronic pain among older individuals in China, and loneliness showed a stronger relationship with chronic pain.

Our subgroup analyses showed similar results to the main models. In the subgroup analyses stratified by sex, loneliness was significantly correlated with an increased risk of chronic pain among females, but not in the social isolation and chronic pain subgroup analysis. Females typically engage more in their local communities than males, and they often act as the key providers of emotional and instrumental support to neighborhood social networks.<sup>55</sup> While such engagement can foster social trust and connectedness, it may also lead to increased relational strain. This duality of network participation—conferring both benefits and burdens—might help explain why social isolation does not show a significant association with chronic pain in females, whereas loneliness, as a subjective emotional state, does. Both social isolation and loneliness were also significantly associated with a higher risk of chronic pain among non-drinkers and non-smokers. Previous studies showed that individuals who do not engage in China's alcohol-drinking culture “pay the price” of isolation from the sociocultural context of normative alcohol consumption.<sup>56</sup> In conclusion, the association of social isolation and loneliness with chronic pain varied by individuals' personal characteristics, necessitating the recognition of the specific social contexts that could exacerbate the relationship.

Given the influence of social contexts on social isolation, loneliness, and pain among older Chinese adults, efforts to enhance community-based care and social interaction facilities may contribute to creating a supportive environment, potentially enabling older adults to age in place, maintain independence, and stay connected to their communities.<sup>57</sup> Community older age facilities offer various social facilities such as game playing, exercise groups, and volunteer work.<sup>35</sup> Time banking is a potential method within the older-aged community to create a positive cycle for giving old age care when young and receiving social interaction services when old.<sup>58</sup> By integrating healthcare, social support, and community resources, a sense of belonging is enhanced with the reduction of social isolation and loneliness. Our finding that loneliness exhibited a strong association with chronic pain further suggests the need to consider mental health as part of comprehensive older-aged care. Integrating mental health support into primary care and community-based services may help address emotional well-being among older adults.<sup>59,60</sup> Previous studies showed that older adults who receive strong family support tend to have better physical and psychological outcomes, such as improving the life quality of older adults with chronic disease and disability.<sup>61</sup> Promoting greater social media interconnectivity, health care, and community organizations can facilitate family involvement with older adults, reducing their feelings of loneliness and social isolation.

While this study highlights important associations between social isolation, loneliness and chronic pain in China, the paper has several limitations. First, some participants were lost from the sample because they had deceased during the study period, and these deceased individuals may have been sicker and thus more likely to experience chronic pain. By including only those aged 60 and above who remained in the survey across the 7-year span, the sample may over-represent healthier individuals compared to those who were excluded. Comparing participants with and without complete information in [Table S4](#), our argument is supported by the mixed statistical results, which show differences in age and chronic diseases. Second, chronic pain was estimated by subjective assessments rather than clinical diagnosis. As a self-reported and subjective question, it may also be influenced by individual differences in perception, interpretation, or reporting bias. While this measure has been applied in prior studies using the same dataset, its validity in fully capturing pain chronicity remains uncertain. Third, the study focuses on the context in China; further studies should construct alternative databases to explore the relationship in different regions or countries.

## Conclusions

For older aged Chinese adults, social isolation and loneliness were associated with a higher risk of chronic pain. There was no statistically significant association between social isolation and feelings of loneliness. Our findings underscore the significance of integrating social support and community involvement into chronic pain management approaches.

## Abbreviations

CHARLS, Chinese Health and Retirement Longitudinal Study; CESD, Centre for Epidemiological Studies Depression Scale; SD, Standard deviation; OR, Odds Ratio; 95% CI, 95% confidence intervals.

## Data Sharing Statement

The data used to support this study can be obtained in the Chinese Health and Retirement Longitudinal Study, <https://charls.pku.edu.cn/>.

## Ethics Approval and Consent to Participate

This study is a secondary analysis based on anonymized information data from the publicly available CHARLS database, obtained legally. According to Article 32, Items 1 and 2, of the “Ethical Review Measures for Life Science and Medical Research Involving Human Subjects in China” (February 18, 2023), this research is exempt from ethical approval under the national legislative guidelines. And the ethical approval of CHARLS is provided by the Institutional Review Board (IRB) of Peking University (IRB00001052-11015), which is updated annually. All participants provided informed consent before joining the survey. We confirm that all methods were conducted in accordance with relevant guidelines and regulations.

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## 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.

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## Disclosure

All authors declare no conflicts of interests. This paper has been uploaded to ResearchSquare as a preprint: <https://www.researchsquare.com/article/rs-4550828/v1>.

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