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ORIGINAL RESEARCH

Association Between Cognitive Frailty and Depression: A Prospective Cohort Study of Adults Aged 45 Years and Older in China

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Background: The interplay between cognitive frailty and depression remains inadequately understood, with a paucity of evidence from prospective cohort studies. Our study aims to elucidate the relationship between cognitive frailty and the risk of incident depression.

Methods: Utilizing data from the China Health and Retirement Longitudinal Study (CHARLS) spanning 2011, 2013, and 2015, subjects were classified according to cognitive frailty criteria established by an international consensus panel. Multiple logistic regression models were employed to examine the cross-sectional and longitudinal associations between frailty, cognitive impairment, cognitive frailty, and depression. Subgroup analyses and interaction tests were conducted to identify potential effect modifiers.

Results: In 2011, the study encompassed 4514 participants, with 2330 individuals followed up through 2015. Cross-sectional analyses revealed that participants classified in frailty, cognitive impairment, and cognitive frailty exhibited multivariable-adjusted odds ratios (ORs) for depression of 1.87 (95% CI 1.60–2.18; P < 0.001), 1.97 (95% CI 1.58–2.47; P < 0.001), and 3.38 (95% CI 2.66–4.29; P < 0.001), respectively, compared to no diseased group. Longitudinal analyses from 2011 to 2015 indicated that participants in frailty, cognitive impairment, and cognitive frailty had multivariable-adjusted ORs of 1.28 (95% CI 1.05–1.58; P = 0.0165), 1.39 (95% CI 1.01–1.91; P = 0.0411), and 1.57 (95% CI 1.05–2.35; P = 0.0273), respectively, for new-onset depression relative to no diseased group.

Limitations: The definition of depression relied solely on self-reported data.

Conclusion: In the middle-aged and elderly Chinese population, patients with cognitive frailty have a higher risk of depression than those with only frailty and cognitive impairment. This may suggest that health care providers should pay more attention to the mental health of those patients with cognitive frailty.

Keywords: cognitive frailty, cognitive impairment, physical frailty, depression, CHARLS

Introduction

The global demographic shift towards an aging population is accompanied by an increased prevalence of health concerns, notably cognitive frailty (CF) and depression, which significantly contribute to the overall disease burden.[1] CF is characterized as a geriatric syndrome involving the concurrent presence of frailty and cognitive impairment, exclusive of dementia, Parkinson's disease, or other neurodegenerative conditions.[2] Research suggests that the prevalence of CF among community-dwelling elderly is approximately 9%, with a rising trend in recent data.[3] Both physical frailty and

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cognitive impairment are common among older adults, with frailty being a marker of accelerated aging across multiple organ systems.[4] Studies in other countries and regions have shown that debilitated patients tend to have a higher risk of financial exploitation (FE), anxiety, and hypertension.[5–7] Cognitive impairment, often an early stage of dementia, impairs daily functioning.[8] Recently, a great number of studies had reported that cognitive frailty had an impact on the adverse outcome among older people, such as increased the risk of falls, depression, fractures, disability and mortality. Among these adverse outcomes, depression was considered as an important issue among older people that attracted by many researchers.

Depression, a prevalent mental disorder affecting over 264 million individuals globally, significantly contributes to the global disease burden.[9] Studies indicate that older adults with depressive symptoms have higher mortality rates compared to those without.[10,11] Identifying risk factors associated with depression in older adults is crucial for timely interventions and improving quality of life in this demographic.

Previous studies have shown a strong association between frailty and depression.[12,13] Cross-sectional research has also linked cognitive frailty (CF) with depression, suggesting that interventions targeting CF may help mitigate depressive symptoms.[14] A recent meta-analysis by Zou et al, which included 15 relevant studies, found that geriatric CF was associated with a higher risk of depression.[15] However, the existing literature is predominantly cross-sectional, with a notable lack of longitudinal studies examining the relationship between CF and depression. This study aims to address this gap by investigating the association between CF and depression in middle-aged and older adults in China. We hypothesize that individuals with CF are at a higher risk of developing depression compared to those with frailty or cognitive impairment alone. We believe that our findings could provide valuable insights for the prevention of depression in individuals with cognitive frailty, emphasizing the importance of early detection and intervention for physical frailty and cognitive impairment to prevent further disease progression.

Methods

Study Population

The China Health and Retirement Longitudinal Study (CHARLS) is a large-scale interdisciplinary survey initiative managed by the National Development Institute of Peking University and executed by the China Social Science Survey Center of Peking University. This high-quality microdata project represents the households and individuals of middle-aged and older adults in China, specifically those aged 45 years and older.

CHARLS has conducted surveys and interviews across 150 counties and 450 communities (including villages) in 28 provinces, autonomous regions, and municipalities during four distinct waves: 2011 (Wave 1), 2013 (Wave 2), 2015 (Wave 3), and 2018 (Wave 4). The National Baseline Survey, initiated in 2011, followed participants for two years, collecting data from 23,000 respondents across 12,400 households.

For this study, we analyzed CHARLS data collected from the baseline (2011) through the third wave (2015). The inclusion criteria for this analysis were: (1) participants aged 45 years or older, (2) a clear definition of frailty and cognitive impairment. Exclusion criteria were: (1) individuals with a history of dementia and (2) those with missing data for cognitive frailty or depression. After follow-up, 4514 participants were included in the analysis. In the second phase, 2330 participants were included after excluding those with missing depression data in Waves 2 and 3, as well as those with depression in Wave 1 (Figure 1).

Frailty, Cognitive Impairment, and Cognitive Frailty

Frailty was measured using a modified version of Fried's Body Frailty Phenotyping Method.[4] The five criteria included: atrophy, weakness, slowness, low physical activity, and exhaustion. Atrophy was defined as a body mass index (BMI) of ≤ 18.5 kg/m^2 or self-reported weight loss of ≥ 5 kg over the past year. Weakness was assessed by a grip strength test.[12] The cut-off points for low grip strength were < 28 kg for men and < 18 kg for women. Slowness was determined by the 2.5 m pace or chair stand test as described in Wu et al's study.[16] Low physical activity was defined as walking no more than 10 minutes continuously during a usual week. Fatigue was assessed using two items from the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10): "I felt everything I did was an effort" and "I could not get going".

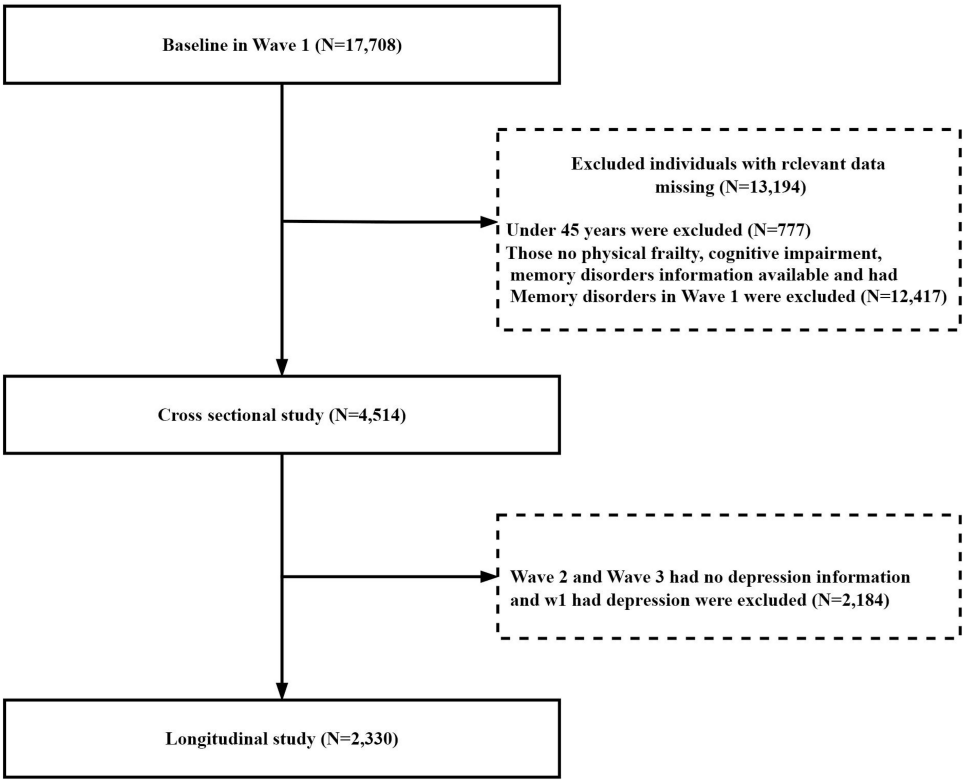

Figure 1 Flowchart of the sample selection process.

Participants who responded "sometimes or half of the time (3–4 days)" or "most of the time (5–7 days)" to either item were classified as self-reported exhaustion. In our analysis, we modified Fried's criteria by replacing "unintentional weight loss" with "Atrophy" to better reflect available data in the CHARLS database. Additionally, to ensure the robustness of the results, we excluded the exhaustion criterion due to its strong association with depression. Participants meeting two or more of the above criteria were classified as frail; those meeting fewer than two criteria were classified as non-frail.

Cognitive impairment was assessed using the cognitive status telephone interview (TICS-10), word recall, and picture drawing.[17] The total score ranged from 0 to 21, with higher scores indicating better performance.[18] Participants scoring more than one standard deviation below the mean for their age were defined as cognitively impaired; otherwise, they were considered cognitively normal.[19]

Participants were divided into four groups based on the presence of physical frailty and cognitive impairment: no disease, frailty, cognitive impairment, and cognitive frailty (CF). Following the definition set by the International Consensus Group, CF was defined as the co-occurrence of both physical frailty and cognitive impairment, consistent with prior studies.[20] Participants with memory disorders were excluded. Frailty, cognitive impairment, and CF were considered independent variables in this analysis, with participants exhibiting CF excluded from both the frailty and cognitive impairment groups.

Depression

Depressive symptoms were assessed using the CES-D-10, validated for the Chinese elderly population, with satisfactory reliability and validity.[21] The CES-D-10 contains 10 items with 4 response options: 1) little or none of the time (< 1 day); 2) some or a little of the time (1–2 days); 3) occasionally or a moderate amount of the time (3–4 days); and 4) most or all of the time (5–7 days). Each item is scored from 0 to 3, with the total score ranging from 0 to 30. Higher scores indicate more severe depressive symptoms. A cut-off score of ≥ 10 points was used to identify respondents with

significant depressive symptoms.[22] In the longitudinal study, new-onset depression was defined as either wave2 or wave3 having depression in any year. (Details of all administered tests can be found in Supplementary information 1).

Covariates

At baseline, trained interviewers collected information on demographic and health-related factors using a structured questionnaire. These include age, sex, education level (illiterate, primary school or below, junior high school or above), marital status (married/cohabiting, divorced/widowed/separated, unmarried), place of residence (urban or rural), smoking and alcohol consumption (yes or no), diastolic and systolic blood pressure, diabetes, hypertension, dyslipidemia, kidney disease, and social activity (yes or no).

Statistical Analysis

Baseline characteristics were described as mean ± SD for continuous variables or number and percentage for categorical variables. Continuous variables were compared using the One-way analysis of variance (ANOVA), while categorical variables were compared using the Chi-square test. Univariate analysis was used to screen for confounding factors affecting baseline depression in 2011 (wave 1), and multivariate logistic regression analysis established three models to examine the relationship between frailty, cognitive impairment, CF, and depression. Model I did not adjust for any variables; Model II adjusted for age, sex, education, marital status, and residence; Model III adjusted for covariates identified from univariate analysis, including age, sex, education, marital status, residence, smoking, alcohol consumption, diastolic blood pressure, diabetes, hypertension, kidney disease, and social activities.

To explore the longitudinal association between CF and new depression, we used univariate analysis to derive confounding factors for the primary longitudinal outcome of new depression based on longitudinal data from 2011 to 2015. We developed three models using multivariate logistic regression analysis: Model I was unadjusted, Model II adjusted for age, sex, education, and residence; Model III included covariates from univariate analysis such as sex, education, residence, smoking status, drinking status, and social activities. Results of logistic regression analysis were presented as odds ratios (ORs) and 95% confidence intervals (CIs).

We also stratified longitudinal outcomes according to age, sex, educational level (illiterate, below middle school and above, middle school and above), marital status (married/cohabiting, divorced/widowed/separated, unmarried), residence (agricultural, other), drinking status (yes or no), current smoking status (yes or no), diabetes (yes or no), hypertension (yes or no), dyslipidemia (yes or no), kidney disease (yes or no), and social activities (yes or no) to assess whether potential confounding variables influenced the association between CF and new depression, and to test for interactions. A two-sided P-value < 0.05 was required for statistical significance. All analyses were performed using R version 4.1.0 and EmpowerStats version 4.1 (www.empowerstats.com; X&Y Solutions Inc).

Results

Table 1 shows the baseline characteristics of the 2011 (wave 1) participants' cross-sectional profiles, including 4514 participants (2329 men and 2185 women) with a mean age of 60.37 ± 9.29 years. The prevalence rates of frailty, cognitive impairment, CF, and depression were 29.42%, 9.44%, 8.99%, and 35.67%, respectively. The prevalence of depressive symptoms in patients with frailty, cognitive impairment, and CF was 41.34%, 46.71%, and 59.61%, respectively. The differences in sociodemographic and health behavior variables among the four groups were statistically significant, except for hypertension, dyslipidemia and kidney disease, as shown in Table 1. Further, Supplementary Table 1 describes the number and proportion of frailty, cognitive impairment, and cognitive frailty by age group. Frailty, cognitive impairment, and cognitive frailty were 698 (22.63%), 340 (11.02%), and 200 (6.48%) in the age range of 45 to 65 years, respectively.

Results of the longitudinal univariate analysis from 2011 to 2015 (wave 1 – wave 3) are presented in Table 2. Only five variables showed a significant univariate association with new onset depression ($p < 0.05$) and were therefore included in the multivariate model for the longitudinal study from 2011 to 2015: sex, education level, residence, smoking status, and social activities.

Table 1 Baseline Characteristics of the Study Participants According to Variables Related to Cognitive Failty in Cross-Sectional Study

	Total	No Diseased	Frailty	Cognitive Impairment	Cognitive Frailty	Effect Sizes	P-value
N	4514	2354 (52.15%)	1328 (29.42%)	426 (9.44%)	406 (8.99%)		
Age, mean ± SD	60.37 ± 9.29	57.82 ± 8.34	64.29 ± 8.82	57.57 ± 8.90	65.28 ± 9.95	215.34[a]	<0.001
Age, n (%)						459.49[b]	<0.001
Age<65	3085 (68.34%)	1847 (78.46%)	698 (52.56%)	340 (79.81%)	200 (49.26%)		
Age≥65	1429 (31.66%)	507 (21.54%)	630 (47.44%)	86 (20.19%)	206 (50.74%)		
Sex, n (%)						128.07[b]	<0.001
Male	2329 (51.60%)	1283 (54.50%)	758 (57.08%)	127 (29.81%)	161 (39.66%)		
Female	2185 (48.40%)	1071 (45.50%)	570 (42.92%)	299 (70.19%)	245 (60.34%)		
Education level, n (%)						735.31[b]	<0.001
Uneducated	1015 (22.49%)	320 (13.59%)	243 (18.30%)	211 (49.53%)	241 (59.36%)		
Below middle school	2030 (44.97%)	1028 (43.67%)	693 (52.18%)	162 (38.03%)	147 (36.21%)		
Middle school or above	1469 (32.54%)	1006 (42.74%)	392 (29.52%)	53 (12.44%)	18 (4.43%)		
Married status, n (%)						38.70[b]	<0.001
Married/cohabit	3743 (82.92%)	2015 (85.60%)	1082 (81.48%)	342 (80.28%)	304 (74.88%)		
Widowed/divorced/ separated with partner	732 (16.22%)	327 (13.89%)	232 (17.47%)	79 (18.54%)	94 (23.15%)		
Never married/unmarried	39 (0.86%)	12 (0.51%)	14 (1.05%)	5 (1.17%)	8 (1.97%)		
Residence, n (%)						83.39[b]	<0.001
Agriculture	2731 (60.50%)	1306 (55.48%)	816 (61.45%)	302 (70.89%)	307 (75.62%)		
Others	1783 (39.50%)	1048 (44.52%)	512 (38.55%)	124 (29.11%)	99 (24.38%)		
Smoking status, n (%)						63.80[b]	<0.001
No	2576 (57.07%)	1339 (56.88%)	677 (50.98%)	307 (72.07%)	253 (62.32%)		
Yes	1938 (42.93%)	1015 (43.12%)	651 (49.02%)	119 (27.93%)	153 (37.68%)		
Drinking status, n (%)						34.82[b]	<0.001
No	2672 (59.19%)	1330 (56.50%)	776 (58.43%)	295 (69.25%)	271 (66.75%)		
Yes	1842 (40.81%)	1024 (43.50%)	552 (41.57%)	131 (30.75%)	135 (33.25%)		
SBP, mean ± SD	130.77 ± 21.77	129.53 ± 19.98	131.14 ± 22.85	132.23 ± 23.99	135.26 ±24.80	9.14[a]	<0.001
DBP, mean ± SD	75.51 ± 12.11	76.04 ± 11.69	74.45 ± 12.41	76.51 ± 12.71	74.83 ± 12.59	6.28[a]	<0.001
Diabetes, n (%)						13.40[b]	0.004
No	4204 (93.13%)	2216 (94.14%)	1212 (91.27%)	403 (94.60%)	373 (91.87%)		
Yes	310 (6.87%)	138 (5.86%)	116 (8.73%)	23 (5.40%)	33 (8.13%)		
Hypertension, n (%)						6.39[b]	0.094
No	3263 (72.29%)	1737 (73.79%)	929 (69.95%)	305 (71.60%)	292 (71.92%)		
Yes	1251 (27.71%)	617 (26.21%)	399 (30.05%)	121 (28.40%)	114 (28.08%)		
Dyslipidemia, n (%)						4.72[b]	0.193
No	4057 (89.88%)	2098 (89.12%)	1196 (90.06%)	389 (91.31%)	374 (92.12%)		
Yes	457 (10.12%)	256 (10.88%)	132 (9.94%)	37 (8.69%)	32 (7.88%)		
Kidney disease, n (%)						6.69[b]	0.083
No	4259 (94.35%)	2239 (95.11%)	1236 (93.07%)	401 (94.13%)	383 (94.33%)		
Yes	255 (5.65%)	115 (4.89%)	92 (6.93%)	25 (5.87%)	23 (5.67%)		
Social activities, n (%)						40.27[b]	<0.001
No	1068 (45.84%)	1046 (44.44%)	711 (52.82%)	225 (52.82%)	226 (55.67%)		
Yes	1262 (54.16%)	1308 (55.56%)	617 (46.46%)	201 (47.18%)	180 (44.33%)		
Depression, n(%)						115.84[b]	<0.001
No	2904 (64.33%)	1734 (73.66%)	779 (58.66%)	227 (53.29%)	164 (40.39%)		
Yes	1610 (35.67%)	620 (26.34%)	549 (41.34%)	199 (46.71%)	242 (59.61%)		

Notes: Continuous variables were expressed as mean ± standard deviation (SD) in case of normal distribution and compared between two groups by KruskalWallis rank sum test. If the count variable had a theoretical number < 10, Fisher's exact probability test was used. Categorical variables are presented as counts (percentages) and compared by Chi-square test. Measurement data were analyzed by one-way analysis of variance, expressed as a; enumeration data were analyzed by chi-square test, expressed as b.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2 Univariate Analysis for Depression of Longitudinal Study

	Statistics	OR (95% CI)	P-value
Age, mean ± SD	59.58 ± 8.88	1.00 (0.99, 1.01)	0.9895
Age, n (%)			
Age<65	1663 (71.37%)	1.00	
Age≥65	667 (28.63%)	0.99(0.82, 1.20)	0.9439
Sex, n (%)			
Male	1293 (55.49%)	1.00	
Female	1037 (44.51%)	1.70 (1.43, 2.02)	<0.0001
Education level, n (%)			
Uneducated	471 (20.21%)	1.00	
Below middle school	1021 (43.82%)	0.79 (0.63, 0.99)	0.0371
Middle school or above	838 (35.97%)	0.49 (0.38, 0.62)	<0.0001
Married status, n (%)			
Married/cohabit	2022 (86.78%)	1.00	
Widowed/divorced/separated with partner	294 (12.62%)	1.13 (0.88, 1.46)	0.3286
Never married/unmarried	14 (0.60%)	1.44 (0.50, 4.18)	0.4974
Residence, n (%)			
Agriculture	1407 (60.39%)	1.00	
Others	923 (39.61%)	0.70 (0.59, 0.84)	<0.0001
Smoking status, n (%)			
No	1299 (55.75%)	1.00	
Yes	1031 (44.25%)	0.69 (0.58, 0.82)	<0.0001
Drinking status, n (%)			
No	1335 (57.30%)	1.00	
Yes	995 (42.70%)	0.70 (0.58, 0.83)	<0.0001
SBP, mean ± SD	130.34 ± 20.99	1.00 (1.00, 1.01)	0.1366
DBP, mean ± SD	75.68 ± 11.79	1.00 (1.00, 1.01)	0.2392
Diabetes, n (%)			
No	2201 (94.46%)	1.00	
Yes	129 (5.54%)	1.25 (0.87, 1.80)	0.2255
Hypertension, n (%)			
No	1731 (74.29%)	1.00	
Yes	599 (25.71%)	1.12 (0.93, 1.36)	0.2400
Dyslipidemia, n (%)			
No	2110 (90.56%)	1.00	
Yes	220 (9.44%)	0.98 (0.73, 1.31)	0.8695
Kidney disease, n (%)			
No	2232 (95.79%)	1.00	
Yes	98 (4.21%)	1.21 (0.80, 1.83)	0.3744
Social activities, n (%)			
No	1068 (45.84%)	1.00	
Yes	1262 (54.16%)	0.77 (0.65, 0.92)	0.0034

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; OR, Odds ratio; CI, confidence interval.

Cross-sectional and longitudinal associations between frailty, cognitive impairment, CF, and depression are shown in Table 3. Multiple logistic regression analysis of the association between depression risk and baseline status of frailty, cognitive impairment, and CF is presented in Table 3. Compared to participants without frailty or cognitive impairment at baseline, the multivariable-adjusted ORs of depression for participants with baseline frailty, cognitive impairment, and CF were 1.87 (95% CI 1.60–2.18; P < 0.001), 1.97 (95% CI 1.58–2.47; P < 0.001), and 3.38 (95% CI 2.66–4.29; P < 0.001), respectively. Compared to participants without frailty or cognitive impairment at baseline, the multivariable-

Table 3 Association (ORs, 95% CI) Between Cognitive Frailty and Depression in Cross Sectional and Longitudinal Study

	Model I		Model II		Model III	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Cross sectional Study						
Class 1 (52.15%)	Ref		Ref		Ref	
Class 2 (29.42%)	1.97 (1.71, 2.27)	<0.0001	1.93 (1.65, 2.24)	<0.0001	1.87 (1.60, 2.18)	<0.0001
Class 3 (9.44%)	2.45 (1.98, 3.03)	<0.0001	1.99 (1.59, 2.48)	<0.0001	1.97 (1.58, 2.47)	<0.0001
Class 4 (8.99%)	4.13 (3.32, 5.13)	<0.0001	3.46 (2.73, 4.39)	<0.0001	3.38 (2.66, 4.29)	<0.0001
Longitudinal study						
Class 1 (60.47%)	Ref		Ref		Ref	
Class 2 (25.84%)	1.34 (1.10, 1.64)	0.0041	1.30 (1.06, 1.59)	0.0128	1.28 (1.05, 1.58)	0.0165
Class 3 (8.67%)	1.81 (1.34, 2.44)	0.0001	1.41 (1.03, 1.94)	0.0331	1.39 (1.01, 1.91)	0.0411
Class 4 (5.02%)	2.13 (1.46, 3.12)	<0.0001	1.61 (1.08, 2.40)	0.0198	1.57 (1.05, 2.35)	0.0273

Notes: Class 1: not suffer from physical frailty or cognitive impairment; class 2: only physical frailty; class 3: only cognitive impairment, class 4: cognitive frailty (both physical frailty and cognitive impairment). Cross sectional study: Model I: unadjusted; Model II: adjusted for age, sex, education level, married status, residence; Model III: adjusted for age, sex, education level, married status, residence, smoking status, drinking status, DBP, diabetes, social activities. Longitudinal study: Model I: unadjusted; Model II: adjusted for sex, education level, residence; Model II: adjusted for sex, education level, residence, smoking status, social activities.
Abbreviations: OR, Odds ratio; CI, confidence interval; Ref, Reference.

adjusted ORs of new depression for participants with baseline frailty, cognitive impairment, and CF were 1.28 (95% CI 1.05–1.58; P = 0.0165), 1.39 (95% CI 1.01–1.91; P = 0.0411), and 1.57 (95% CI 1.05–2.35; P = 0.0273), respectively.

We performed subgroup analyses to investigate the relationship between CF and depressive events stratified by potential risk factors. As shown in Figure 2, subgroup analyses based on normal subjects, frailty, cognitive impairment, and CF showed that Age less than 65 years, female, illiterate, married, non-alcoholic and no comorbidities were associated with a higher risk of depression than other subgroups. CF did not interact with subgroup variables.

Discussion

To the best of our knowledge, this is the first study to examine the longitudinal association between CF and depression among the elderly population aged over 45 years in Chinese communities using nationally representative data. In a cross-sectional analysis, we found a significant positive association between CF and depression. Further, individuals aged 45 to 65 years with CF were more likely to develop new-onset depression in a longitudinal analysis. Both cross-sectional and cohort studies have confirmed that people with CF are more likely to suffer from depression.

The participants in this study consisted of middle-aged and elderly individuals aged 45 years and older in China. Numerous studies indicate that frailty is a complex and multifaceted clinical condition associated with advancing age, emphasizing that it should not be exclusively focused on the elderly.[23,24] The prevalence of cognitive frailty (CF) in this study was found to be 8.99%, aligning with findings from research examining CF prevalence among individuals aged 60 years and older.[3] This further underscores the importance of recognizing frailty as a concern not only within the elderly population but also among middle-aged adults. A study conducted across 17 countries demonstrated that individuals with cognitive impairment exhibited a higher risk of mortality compared to those with frailty alone.[25] Our findings similarly indicate that CF significantly elevates the risk of depression in comparison to individuals experiencing only cognitive impairment or frailty. The absence of longitudinal studies on this subject limit the capacity for direct comparisons with our results. Nevertheless, several cross-sectional studies assessing the relationship between CF and depression have yielded findings consistent with those presented in this study.[14,26]

For instance, one community-based cross-sectional study explored the impact of CF on depression and reported that individuals with CF faced a significantly heightened risk of depressive symptoms.[14] In this study, frailty and CF were

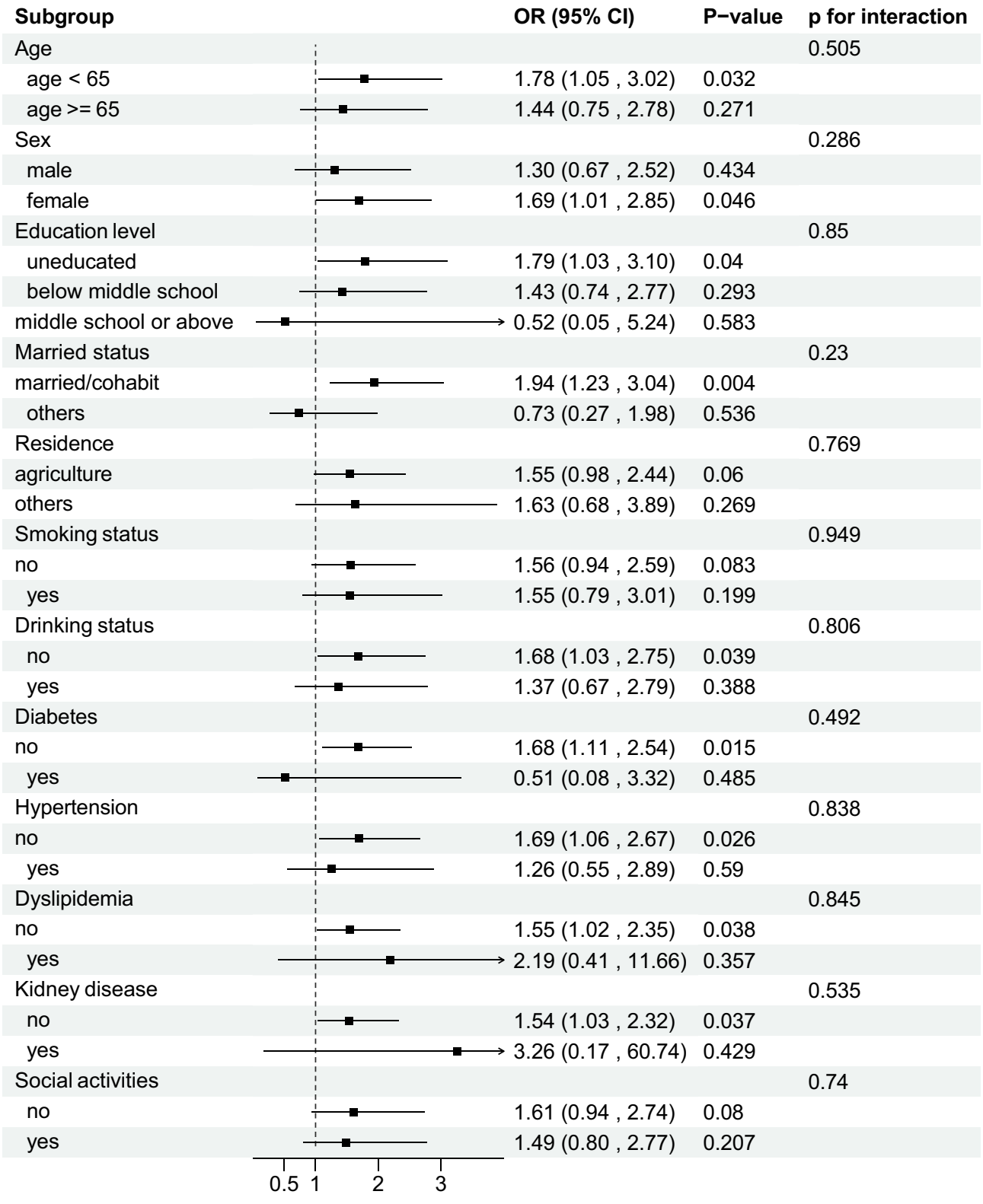

Figure 2 Association between cognitive frailty and depression by the subgroup of participants in longitudinal study.

linked to an increased risk of depression, whereas mild cognitive impairment (MCI) did not demonstrate a similar association. This lack of association may be attributed to the small total sample size, which included only 24 participants in the control group and 14 individuals with MCI. The substantial imbalance in participant numbers across groups,

particularly the limited representation within the MCI cohort, may have compromised the statistical power needed to detect potential differences between MCI patients and healthy controls.

In a Rotterdam population aged 55 years and older, Marina De Rui et al assessed the relationship between MCI and depression. They found that mild cognitive impairment was a risk factor for dementia, depression, and anxiety disorders. This is consistent with the results of our cross-sectional and cohort studies. Another observational cohort study showed that worsening levels of frailty nearly doubled the risk of developing depression.[27] This underscores the important clinical value of frailty reversal in the field of depression prevention. A meta-analysis of 24 studies reported that frailty in older adults was bidirectionally associated with depression, with each condition associated with an increased prevalence and incidence of the other.[12] Among them, the conclusion that frailty leads to an increased incidence of depression is consistent with our findings. Three Mendelian randomisation studies have found bidirectional associations between frailty and depression from a genomic association perspective.[28–30] Previous cross-sectional studies have not been able to determine the causal relationship between CF and depression. However, our cohort studyhave demonstrated that CF significantly increases the risk of new depression.

The mechanisms underlying the association between CF and depression involve multiple aspects, including pathophysiological changes and the accumulation of behavioral risk factors. First, frailty is a multifactorial geriatric syndrome, which may be influenced by pain, mobility and balance problems, frailty, and poor endurance. All of these risk factors can lead to disability or functional dependence.[31] Negative psychological states are more likely to emerge in these individuals, and the deterioration of psychological conditions exacerbates the reduction in social support due to cognitive impairment. Reduced social support is associated with the emergence of depressive mood and reduced quality of life,[32] which leads to depression. Second, frailty reflects biological aging, which is associated with molecular markers of aging such as DNA methylation, oxidative stress,[33] endoplasmic reticulum stress, chronic inflammation, proteostasis, and mitochondrial dysfunction.[34] Among these, oxidative stress, chronic inflammation, and mitochondrial dysfunction are risk factors for depression.[15,35,36] Forgetfulness, gradual inability to perform daily tasks, and fear of developing dementia may be sufficient to trigger depressive symptoms in vulnerable individuals with mild cognitive impairment.[26] Third, frailty can lead to decreased levels of physical activity, and lack of physical activity is a known risk factor for depression. Cognitive impairment can further limit individuals' physical activities that are complex or require cognitive participation. Fourth, cognitively frail individuals face the management of multiple chronic diseases simultaneously, and the pressure of this management may increase the risk of depression.

This study has significant implications for clinical practice. Research indicates that patients with cognitive frailty (CF) are at a greater risk of developing depression compared to those who only experience cognitive impairment or frailty. This finding underscores the need for clinicians to extend their focus beyond patients with just frailty and cognitive impairment, emphasizing the importance of early intervention for those identified as cognitively frail.

While CF is theoretically characterized by its potential reversibility, there is a scarcity of intervention trials specifically targeting cognitively frail older adults to date. Existing literature suggests that resistance training has a positive and substantial impact on enhancing both cognitive and physical functions.[37] Additionally, a study conducted in China highlights the significance of dynamic dietary diversity in preventing CF and promoting the overall health of older adults.[38]

Furthermore, a recent large-scale study spanning multiple countries and regions demonstrated that digital exclusion negatively affects cognitive impairment.[39] Similarly, another comprehensive study revealed that internet use may offer protective benefits against frailty.[40] These findings suggest that promoting internet usage could have a beneficial impact on cognitively frail patients, enhancing their overall health outcomes.

Our study has many strengths. First, to our knowledge, this is the first longitudinal study to investigate the relationship between CF and depression in middle-aged and elderly Chinese adults. Previous studies have generally focused on the fact that changes in depression can reduce the risk of CF.[15] Limited literature has investigated the risk of CF and depression,[14] and there has previously been a lack of academic consensus on the causal relationship between CF and depression. After adjusting for multiple potential confounders in our study, the results of logistic regression provide further empirical support to investigate the causal relationship between CF and depression. Second, we found that CF participants had a higher risk of new-onset depression compared to those with mild cognitive

impairment or frailty alone. This suggests that an effective intervention strategy for depression is to delay the development of individuals with mild cognitive impairment or frailty and prevent them from further evolving into CF by supplementing nutrition or providing psychological intervention. In addition, our study included a diverse and representative sample from different regions of China, aged 45 years and older, including the middle-aged and elderly population.

Our study has several limitations. While we adjusted for many potential confounding factors, we could not control for all possible variables. First, the CHARLS database does not include data on physician-diagnosed depression; therefore, depression was defined solely based on self-reported data, which may introduce recall bias. Second, we did not account for the influence of the APOE ε4 allele, a known genetic risk factor for Alzheimer's disease, which may affect the development of cognitive impairment. Cognitive impairment can be an early or prodromal symptom of Alzheimer's disease.[41] Additionally, we employed a modified version of Fried's Frailty Phenotyping Method, which may have resulted in a higher number of frail participants, potentially affecting the interpretation of the results. This modification may also impact the generalizability of the findings to other countries. Finally, excluding participants with CF and those missing depression data resulted in a loss of some of the target population, which could impact the outcome. However, the proportion of follow-up failures was statistically acceptable.

Conclusion

In the middle-aged and elderly Chinese population, individuals exhibiting cognitive impairment, frailty, and cognitive frailty (CF) are at an increased risk of experiencing depressive symptoms. It is crucial to prioritize the mental health of patients with cognitive impairment and frailty, particularly those identified as cognitively frail, to ensure timely and appropriate interventions. Future research is necessary to further elucidate the relationship between CF and depression in different countries and regions, enabling the development of tailored preventive measures.

Ethics Approval

The studies involving humans were approved by Institutional Review Board (IRB) of Peking University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because The IRB approval number for the main household survey including anthropometrics is IRB00001052-11015, and the IRB approval number for biomarker collection is IRB00001052-11014. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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Author Contributions

All authors made substantial contributions to the work, including in the conception and study design, data acquisition, analysis, and interpretation. They actively participated in drafting, revising, or critically reviewing the manuscript, provided final approval of the version to be published, agreed on the journal for submission, and committed to being accountable for all aspects of the work.

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