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Epidemiology and clinical researches on neuropsychiatric disorders in aging

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Published in
Frontiers in Psychiatry

ISSN 1664-8714
ISBN 978-2-83251-536-5
DOI 10.3389/978-2-83251-536-5

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Epidemiology and clinical researches on neuropsychiatric disorders in aging

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Citation

Xie, W., Zhong, B.-L., Liang, L., Cai, Y. S., eds. (2023). *Epidemiology and clinical researches on neuropsychiatric disorders in aging*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-536-5

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frontiers | Frontiers in Psychiatry

TYPE Editorial
PUBLISHED 18 January 2023
DOI 10.3389/fpsyt.2023.1108474

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

RECEIVED 26 November 2022
ACCEPTED 04 January 2023
PUBLISHED 18 January 2023

CITATION
Xie W, Zhong B, Liang L and Cai YS (2023) Editorial: Epidemiology and clinical researches on neuropsychiatric disorders in aging. *Front. Psychiatry* 14:1108474. doi: 10.3389/fpsyt.2023.1108474

Editorial: Epidemiology and clinical researches on neuropsychiatric disorders in aging

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KEYWORDS

aging, depression, cognitive function, epidemiology, clinical research

Editorial on the Research Topic
Epidemiology and clinical researches on neuropsychiatric disorders in aging

With the rising aging population in a global range, related neuropsychiatric disorders such as depression and dementia, have emerged and caused a tremendous disease burden. Over the past decades, many risk factors have been identified (1–12), and advances have been made in developing prevention and intervention strategies. However, there still exist challenges to be addressed. These challenges include but are not limited to early detection and prediction of neuropsychiatric disorders, comorbidities of both neuropsychiatric and non-neuropsychiatric aspects, identifying novel indicators for disease progression and prognosis, as well as investigating potential mediating mechanisms. Facing unprecedented challenges, we launched this Research Topic to promote healthy aging and longevity from the neuropsychiatric perspective, *via* collaboration from a number of professional disciplines.

In this topic, Qiu et al. conducted a pooled analysis of two national aging cohort studies to explore a bidirectional relationship between body pain and depressive symptoms. This study detected bidirectional longitudinal influence, while most of the previous studies only explored a cross-sectional or unidirectional longitudinal association. The results indicated that medical practitioners should be aware of the bidirectional relationship and carry out early assessments or event interventions to reduce the possibility of depression in people with pain or to prevent pain in people with depressive symptoms.

Liu et al. performed a resting-state functional MRI study to investigate the altered intrinsic brain activity (IBA) in patients suffering from late-life depression (LLD) using a percent amplitude of fluctuation (PerAF) method. This study mainly found that compared with the normal control group, the late-life depression (LLD) group demonstrated decreased PerAF differences in the bilateral superior frontal gyrus, orbital part (Frontal_Sup_Orb), and bilateral anterior cingulate cortex (ACC), which was closely related to their attention control defects.

In a cross-sectional study published in this topic, Pan Y. et al. identified an association between poor socioeconomic status (SES) and increased prevalence of dependency personality disorder (DPD), and the results of this work represent preliminary evidence that perceived social status has a stronger association with DPD than objective SES. The impact of subjective SES on DPD is possibly associated with the perception of position in the social hierarchy. However, there is abundant room for further progress in determining the pathways of subjective SES and DPD to fully understand the complicated causality and provide targeted support strategies to reduce or delay the dependency of elderly people.

Pan W. et al. conducted a pilot study to identify cognitive function processes that may be associated with treatment response in LLD. In this study, first-episode LLD patients treated with 8-week of escitalopram or sertraline demonstrated improvement of depression and partial cognitive function including immediate memory, language, and delayed memory. The preliminary findings suggested that working memory, attention, visuospatial, and language function should be examined further as a means of providing the useful objective biomarkers of treatment response.

In a longitudinal cohort study, Han et al. examined the relationship between depressive symptoms and the changes in serum cystatin C levels, and they found that baseline persistent depressive symptoms were significantly associated with an increased rate of serum cystatin C levels during the 10-year follow-up. This study indicated that the level of serum cystatin C should be monitored in the elderly with persistent depressive symptoms. Potential mechanisms of the relationship between kidney dysfunction and depression need to be further characterized.

In another large-scale longitudinal cohort study, Wang et al. found that sustained or increasing physical activity was linked to slower declines in motor function and lower risk of incident frailty. These findings are encouraging, not confined to participants with persistently active participation in physical activity, who can still gain substantial benefits in the quality of life by becoming more physically active irrespective of past physical activity levels, providing further evidence to the broad public health benefits of physical activity.

Xiao and Huang performed a cross-sectional study based on the data from the National Health and Nutrition Examination Survey, and found that high levels of dietary inflammatory index were associated with depression and suicidal ideation in older adults. In another cross-sectional study among 769 elderly primary care attenders from 13 primary care clinics in Wuhan, Zhu et al. reported that 12-month prevalence of suicidal ideation was 16.6%, which indicates the potentially high and urgent needs for suicide prevention and crisis intervention in Chinese older adults receiving primary care. Due to the rapid social changes and accelerating aging in recent decades, mental health problems and suicidal behaviors have been significant public health challenges for the older adults (13–17). Recognizing older adults with suicidal ideation in primary care settings could facilitate the early prevention of suicide in the elderly population.

In the last article published in this topic, Feng et al. presented the 17-year temporal trend in anxiety and/or depression prevalence in patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in Beijing, which included 382,125 records from a city-wide representative database of hospitalizations. Three segments in the temporal trend were observed, with a mild increase during 2004–2009 (from 0.4 to 0.6%), followed by a sharp increase during 2009–2012 (from 0.6 to 2.5%), then stabilized at about 3% during 2012–2020. They also reported that patients with anxiety and/or depression had longer hospital stays, more medical costs and higher risks of readmission for AECOPD. These results show that anxiety and/or depression are undoubtedly important burdens for people with AECOPD, the health care systems and the medical insurance systems. Providing appropriate diagnosis and effective treatment of anxiety and/or depression for patients with AECOPD needs to be strengthened in clinical practice.

To conclude, the articles published in this topic provide additional evidence from epidemiology and clinical researches for current literature on neuropsychiatric disorders in aging. In the future, high-quality epidemiology and clinical researches, especially randomized controlled trials are needed to develop effective strategies of prevention and intervention for neuropsychiatric disorders in aging.

Author contributions

WX writing original draft of this editorial. All authors contributed to this topic design and manuscript editing efforts. All authors contributed to the article and approved the submitted version.

Acknowledgments

We thank the authors for their cutting-edge works, and also express our gratitude to all the reviewers for their generously devoted time and highly valuable comments. Finally, we hope that the reader will enjoy these articles.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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ORIGINAL RESEARCH
published: 26 April 2022
doi: 10.3389/fpsyt.2022.881779

Bidirectional Relationship Between Body Pain and Depressive Symptoms: A Pooled Analysis of Two National Aging Cohort Studies

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

Received: 23 February 2022
Accepted: 17 March 2022
Published: 26 April 2022

Citation:
Qiu Y, Ma Y and Huang X (2022) Bidirectional Relationship Between Body Pain and Depressive Symptoms: A Pooled Analysis of Two National Aging Cohort Studies. Front. Psychiatry 13:881779. doi: 10.3389/fpsyt.2022.881779

Aims: To investigate the bidirectional longitudinal association between pain and depressive symptoms and explore whether gender modifies the association.

Methods: This study used data of 17,577 participants without depressive symptoms and 15,775 without pain at baseline from waves 1–8 (2002/2003 to 2016/2017) of the English Longitudinal Study of Aging (ELSA) and waves 1 to 3 [2011–2015] of the China Health Retirement Longitudinal Study (CHARLS). Cox regression models were performed at the cohort level to evaluate the potential longitudinal associations, and then random-effect meta-analyses were conducted to pool the results. The potential modifying effect was detected by Z-test.

Results: During 103,512 person-years of follow-up in participants without depressive symptoms, baseline pain intensity was associated with incident depressive symptoms. Compared with individuals who reported no pain at baseline, the pooled adjusted hazard ratio (HR) of incident depressive symptoms for participants with mild to moderate pain and for those with severe pain was 1.37 (95% CI: 1.22–1.55, $p < 0.001$) and 1.52 (95% CI: 1.34–1.73, $p < 0.001$), respectively. During 81,958 person-years of follow-up in participants without pain, baseline depressive symptoms were associated with a significantly higher incidence of pain, and the pooled adjusted HR of incident pain was 1.71 (95% CI: 1.60–1.82, $p < 0.001$). These associations were not modified by gender.

Conclusions: A bidirectional longitudinal association between pain and depressive symptoms was demonstrated, not modified by gender. Family doctors should be aware of the bidirectional association and advice individuals with pain or depressive symptoms to be screened for both kinds of symptoms.

Keywords: pain, depressive symptoms, nationally representative aging cohorts, prospective study, association between pain and depressive symptoms

INTRODUCTION

Both pain and depression are considerable health-related concerns that draw increasing attention globally (1). As indicated by a study that covered 17 countries, nearly two-fifths of adults reported chronic pains during the previous year, and it is noteworthy that the figure is rising in line with the population aging (2). Depression is another age-related disease that affects 322 million individuals worldwide (3). The annual financial costs of pain and depression had been up to $560 billion and $210.5 billion in the US, respectively (4, 5). The comorbidity of these two diseases is quite common. Pain conditions were complained by more than half of depression patients (6). In turn, more than 50% of patients with chronic pain suffered from depressive symptoms (7). The pain in depressive patients affected the treatment and prognosis of depression and vice versa (7). Thus, a thorough understanding of the association between pain and depressive symptoms is necessary.

Most of the previous studies on the association between pain and depression used cross-sectional data or only researched unidirectional longitudinal association. There have been several prospective studies on the bidirectional relationship between pain and depression, while these studies yielded inconsistent conclusions and were limited by representativeness, follow-up duration, or other methodological pitfalls (1, 8–12). The evidence from community-based large cohorts is still lacking. Moreover, the gender difference in the potential bidirectional longitudinal association remains unclear.

The English Longitudinal Study of Aging (ELSA) (13) and the China Health Retirement Longitudinal Study (CHARLS) (14) are two nationally representative aging cohorts that involved pain and depressive symptoms at multiple waves. These two cohorts provided an opportunity to investigate the longitudinal associations between pain and depressive symptoms. Our aims were (1) to examine the bidirectional longitudinal association between pain and depressive symptoms in community-based aging populations and (2) to explore whether gender modifies the association.

MATERIALS AND METHODS

Participants

The data were derived from the ELSA and the CHARLS, both of which are community-based and nationally representative aging cohorts. The ELSA and the CHARLS were approved by London Multicentre Research Ethics Committee and Peking University Institutional Review Board, respectively (13–15). Written informed consent forms were obtained from all participants in both cohorts.

The CHARLS cohort was of individuals who aged 45 years and older and were living in China (14). Multistage probability sampling was used in the CHARLS to ensure the nationally representativeness. The present study used the data from wave 1 (2011) as a baseline and considered waves 2–3 (2013–2015) as a follow-up period. The ELSA sample was from the Health Survey for England, which randomly enrolled individuals who aged 50 years or older and were living in England using the postcode (13, 16). The baseline of the ELSA cohort was wave 1 (2002/2003) and the follow-up waves included waves from 2 to 8 (2004/2005 to 2016/2017) (17).

Figure 1 shows the flow chart of participant selection for the present study. In the analysis of the association between baseline pain intensity and incident depressive symptoms, 17,577 participants (9,566 from the CHARLS and 8,011 from the ELSA) free of depressive symptoms at baseline and with ≥1 remeasurement of depressive symptoms were included in the present study (**Figure 1**). To analyze the association between baseline depressive symptoms and incident pain, this study included 15,775 participants (9,224 from the CHARLS and 6,551 from the ELSA) free of pain at baseline and with ≥1 reassessment of pain (**Figure 1**).

Assessments

Assessment of Pain

In both cohorts, pain intensity at baseline and each follow-up wave were assessed. In the CHARLS cohort, baseline pain intensity was categorized into three groups: no pain, mild to moderate pain, and severe pain. If there were more than one pain location, the most severe one among them was recorded. Fifteen specific common pain locations have been assessed in the CHARLS: head, shoulders, arms, wrist, fingers, chest, stomach, back, waist, buttocks, legs, knees, ankles, toes, and neck (18). In the ELSA cohort, pain intensity was measured based on pain intensity scores ranging from 0 to 10 (0 was no pain and 10 was severe or excruciating pain). Four specific pain locations have been evaluated in the ELSA: back, hips, knees, and feet (17). For pooling analyses in this study, we divided the ELSA participants into three categories of pain intensity according to the pain intensity scores: no (scored 0), mild to moderate (scored 1–7), and severe pain (scored 8–10). The cutoff points were established according to Boonstra et al. (19). The most severe one among the four locations was used in our analyses.

In the longitudinal association analysis of baseline pain and incident depressive symptoms, pain intensity was used as a potential risk factor. In turn, incident self-reported pain that includes mild to severe pain was used as the outcome when analyzing the association between baseline depressive symptoms and incident pain.

Assessment of Depressive Symptoms

Depressive symptoms were assessed by an eight-item version of the Center for Epidemiologic Studies Depression Scale (CES-D) in the ELSA (20). One point was given for each item, and the total scores were ranged from 0 to 8. According to previous studies, a score of 4 or more was defined as depressive symptoms (20, 21). The CHARLS used CES-D (ten-item version) to assess depressive symptoms (22). Three points were given for each item. Thus, the scores were ranged from 0 to 30. Depressive symptoms were defined as a score ≥12 according to prior validation studies (22, 23).

Covariates

Covariates that were selected in our study include demographics (age and gender), socioeconomic status (education in years

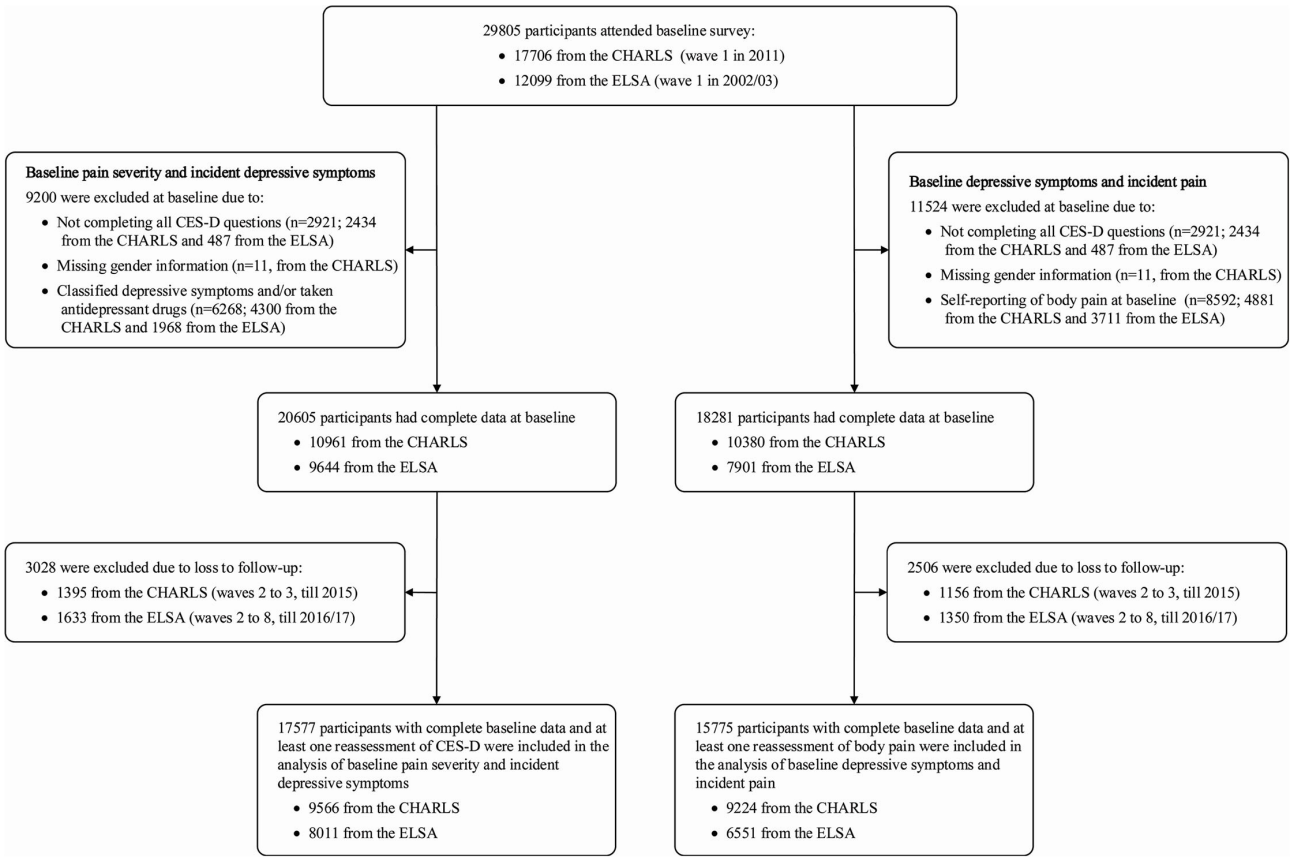

FIGURE 1 | Flow chart of inclusion of this study population.

and cohabitation status), lifestyle factors (smoking and alcohol consumption), and relevant clinical characteristics (self-reported physician-diagnosed history of hypertension, diabetes, coronary heart disease, stroke, cancer, and chronic lung disease) (15). Education levels of ≥senior high school in the CHARLS and ≥level 1 national vocational qualification or General Certificate of Education Advanced level in the ELSA were defined as a high level of education (24). Cohabitation status was defined as currently living alone or not. Only current smokers were defined as smokers.

Statistical Analysis

The results are presented as percentages for categorical variables and means ± standard deviation (SD) for continuous variables. Data were firstly analyzed at cohort level according to the following uniform protocol. We used Cox regression models to evaluate the relationship between baseline pain category and incident depressive symptoms and the association between baseline depressive symptoms and incident pain. After adjustment for the covariates mentioned above, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were reported. Then, pooled analyses were performed to estimate the pooled effect and 95% CIs with random-effect meta-analyses, which took heterogeneity of the two cohorts into consideration. The I^2 statistic was used to present the extent of variability between the two studies that were attributable to heterogeneity. To assess the potential modifying effects of gender on the bidirectional relationship, a *Z*-test was performed to compare the coefficients between two subgroup analyses, with the method proposed by Altman and Bland (25). To evaluate the stability of our main results, we performed longitudinal analyses of baseline pain and incident depressive symptoms repeatedly and restricted to participants with baseline CES-D scores ≤1 (median) in the ELSA and ≤5 (median) in the CHARLS to control the reverse causality.

Regression analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Meta-analyses were performed using STATA (version 11; Stata Corp, College Station, TX, USA). All analyses were two-sided with a threshold value of *p*- equals to 0.05 for statistical significance.

RESULTS

Baseline Characteristics

A total of 17,577 individuals (9,566 from the CHARLS and 8,011 from the ELSA) without depressive symptoms at baseline were included in the pooled analysis of the association between pain intensity and incident depressive symptoms, and 15,775

TABLE 1 | Characteristics of participants in the China Health Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Aging (ELSA) at baseline.

Characteristics	Participants without depressive symptoms at baseline		Participants without pain at baseline	
	CHARLS (n = 9,566)	ELSA (n = 8,011)	CHARLS (n = 9,224)	ELSA (n = 6,551)
Age (years)	57.8 ± 9.2	63.2 ± 10.3	58.2 ± 9.5	62.9 ± 10.5
Women (%)	4,656 (48.7)	4,357 (54.4)	4,491 (48.7)	3,554 (54.3)
Pain severity (%)				
No pain	7,460 (78.0)	5,827 (72.7)	9,224 (100.0)	6,551 (100.0)
Mild to moderate pain	1,465 (15.3)	1,564 (19.5)	0 (0.0)	0 (0.0)
Severe pain	641 (6.7)	620 (7.7)	0 (0.0)	0 (0.0)
Depressive symptoms (%)	0 (0.0)	0 (0.0)	1,554 (16.9)	724 (11.1)
CES-D scores*	5.1 ± 3.3	0.81 ± 0.97	6.6 ± 5.3	1.16 ± 1.70
High level of education (%)	1,427 (14.9)	2,631 (32.8)	1,349 (14.6)	2,264 (34.6)
Living alone (%)	864 (9.0)	2,310 (28.8)	990 (10.7)	2,022 (30.9)
Current smoking (%)	3,059 (32.0)	1,314 (16.4)	2,939 (31.9)	1,104 (16.9)
Alcoholic drink ≥once per week (%)	1,727 (18.1)	4,994 (62.3)	1,624 (17.6)	4,197 (64.1)
Hypertension (%)	2,176 (22.8)	2,842 (35.5)	2,031 (22.0)	2,222 (33.9)
Diabetes (%)	481 (5.0)	484 (6.0)	451 (4.9)	357 (5.5)
Coronary heart disease (%)	942 (9.9)	799 (10.0)	862 (9.4)	587 (9.0)
Stroke (%)	141 (1.5)	244 (3.1)	133 (1.4)	191 (2.9)
Cancer (%)	70 (0.7)	434 (5.4)	62 (0.7)	352 (5.4)
Chronic lung disease (%)	770 (8.1)	400 (5.0)	696 (7.6)	273 (4.2)
Asthma (%)	242 (2.5)	819 (10.2)	219 (2.4)	646 (9.9)

The results are presented as mean ± SD or n (%).
**The ranges of CES-D scores in the CHARLS and the ELSA were different.*

participants free of pain (9,224 from the CHARLS and 6,551 from the ELSA) at baseline were included in this analysis of the association between depressive symptoms and incident pain. **Table 1** presents the baseline characteristics of the two cohorts separately.

Baseline Pain Intensity and Incident Depressive Symptoms

During 103,512 person-years of follow-up (the CHARLS: 33,586 and the ELSA: 69,926), we identified 2,140 participants (22.4%) in the CHARLS and 2,060 (25.7%) in the ELSA who have had incident depressive symptoms. The incidence of depressive symptoms was significantly increased by pain intensity in both cohorts (**Figure 2** and **Supplementary Table 1** in Supplementary File).

Compared with individuals who reported no pain at baseline, the pooled adjusted HR of incident depressive symptoms for participants with mild to moderate pain and for those with severe pain was 1.37 (95% CI: 1.22–1.55, $p < 0.001$) and 1.52 (95% CI: 1.34–1.73, $p < 0.001$), respectively (**Table 2**).

Baseline Depressive Symptoms and Incident Pain

During 81,958 person-years of follow-up (the CHARLS: 30,946 and the ELSA: 51,012), 3,209 individuals (34.8%) from the CHARLS cohort and 2,646 (40.4%) from the ELSA cohort reported incident pain. Compared with participants without depressive symptoms, individuals with baseline depressive symptoms at baseline had a significantly higher incidence of pain in both cohorts (**Figure 2** and **Supplementary Table 2** in Supplementary File).

Compared to participants without baseline depressive symptoms, those with depressive symptoms at baseline had a significantly higher incidence of pain in both cohorts after multivariable adjustment (pooled HR 1.71, 95% CI: 1.60–1.82, $p < 0.001$; **Table 3**).

Non-Response Analyses

Among the baseline population, 1,395 (12.7%) participants from the CHARLS and 1,633 (16.9%) from the ELSA with complete baseline data were excluded from the analyses on the association between baseline pain intensity and incident depressive symptoms for loss to follow-up. The excluded participants in both cohorts were older, had a higher percentage of living alone, smoking, coronary heart disease, self-reported diabetes, stroke, and chronic lung disease, and had a lower percentage of alcohol consumption (**Supplementary Tables 3**, **4** in Supplementary File). Similarly, individuals who were excluded from the analyses on the association between baseline depressive symptoms and incident pain also had higher levels of the major risk factors than those who were included in this study (data not shown).

Subgroup Analyses by Gender

We performed repeated analyses by gender and found that the associations between baseline pain severity and incident

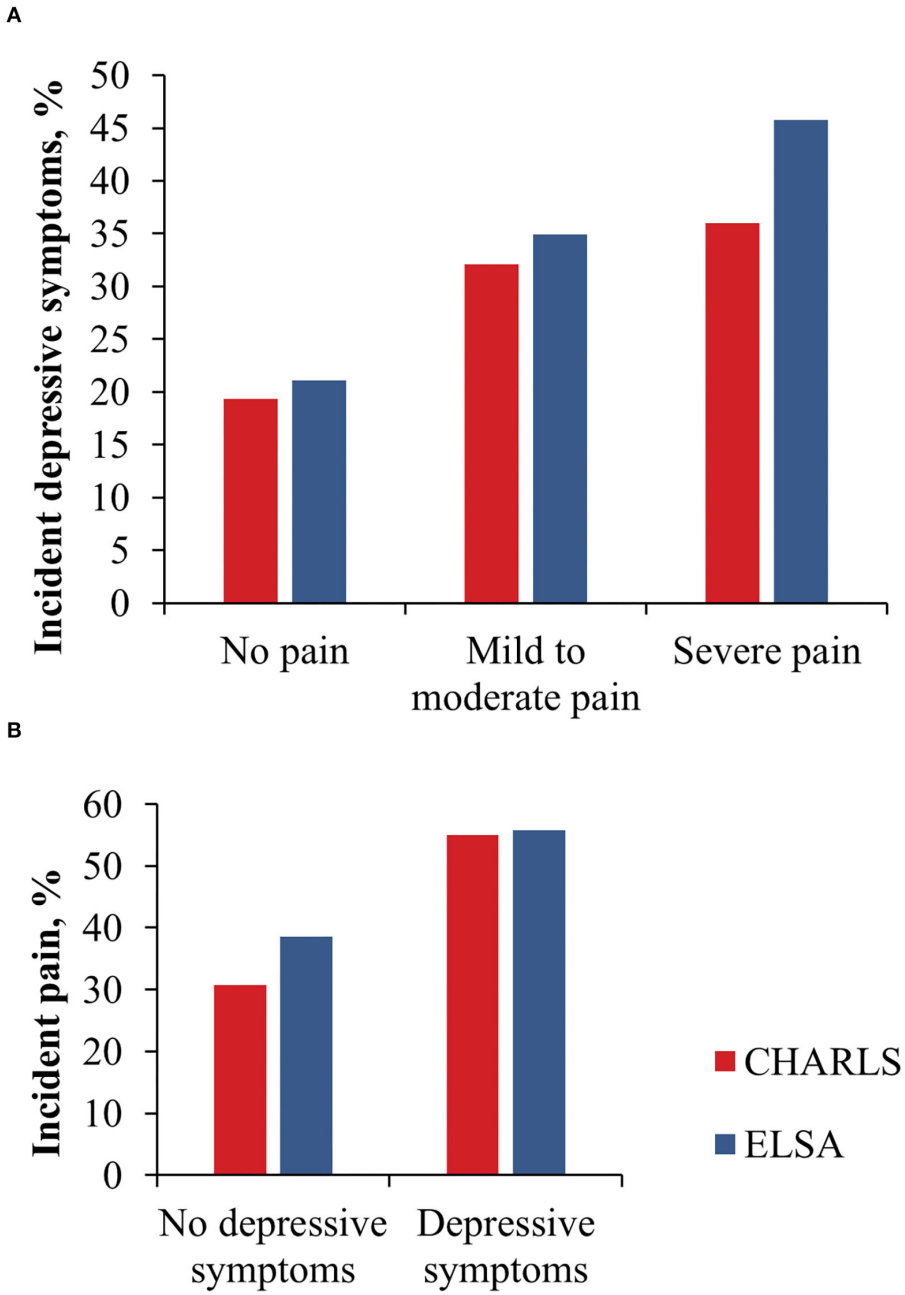

FIGURE 2 | Incident depressive symptoms by baseline pain severity **(A)** and incident pain by baseline depressive symptoms **(B)**.

depressive symptoms were still significant in both men and women (**Supplementary Tables 5**, **6** in Supplementary File). **Table 4** shows the summarized results of pooled analyses by gender, and we found that these associations were not modified by gender.

Sensitivity Analyses

We restricted analyses to participants with baseline CES-D scores ≤5 in the CHARLS and ≤1 in the ELSA. The results show that the associations between pain categories and incident depressive symptoms became stronger (**Supplementary Table 7** in Supplementary File).

DISCUSSION

In this pooled study of two nationally representative aging cohorts, we detected a significant bidirectional longitudinal association between pain and depressive symptoms after

TABLE 2 | Association between baseline pain severity and incident depressive symptoms, using Cox regression models.

Pain category	CHARLS (n = 4,656)		ELSA (n = 4,357)		Meta-analysis (n = 9,013)			
	HR (95% CI)*	*P* value*	HR (95% CI)*	*P* value*	Pooled HR (95% CI)	*P* value	I^2 (%)	*P* value
No pain	Ref	/	Ref	/	Ref	/	/	/
Mild to moderate pain	1.29 (1.16–1.44)	<0.001	1.46 (1.32–1.62)	<0.001	1.37 (1.22–1.55)	<0.001	62.3	0.103
Severe pain	1.42 (1.23–1.64)	<0.001	1.62 (1.41–1.85)	<0.001	1.52 (1.34–1.73)	<0.001	41.3	0.192
Per category increase	1.22 (1.14–1.30)	<0.001	1.31 (1.23–1.39)	<0.001	1.27 (1.18–1.36)	<0.001	58.6	0.120

**After adjusting for baseline CES-D scores, gender, age, education, marital status, current smoking, alcohol consumption, self-reported hypertension, diabetes, coronary heart disease, stroke, cancer, chronic lung disease, and asthma.*

TABLE 3 | Association between baseline depressive symptoms and incident pain, using Cox regression model.

Depressive symptoms	CHARLS (n = 9,224)		ELSA (n = 6,551)		Meta-analysis (n = 15,775)			
	HR (95% CI)*	*P* value*	HR (95% CI)*	*P* value*	Pooled HR (95% CI)	*P* value	I^2 (%)	*P* value
No	Ref	/	Ref	/	Ref	/	/	/
Yes	1.74 (1.61–1.89)	<0.001	1.65 (1.48–1.84)	<0.001	1.71 (1.60–1.82)	<0.001	0.0	0.441

**After adjusting for gender, age, education, marital status, current smoking, alcohol consumption, self-reported hypertension, diabetes, coronary heart disease, stroke, cancer, chronic lung disease, and asthma.*

TABLE 4 | Modifying effects of sex on the association between baseline pain intensity and incident depressive symptoms, and on the association between baseline depressive symptoms and incident pain.

	Pooled HR (95% CI)*	*P* for interaction
Baseline pain intensity and incident depressive symptoms		
No Pain	Ref	/
Mild to moderate pain		
Women	1.33 (1.09–1.62)	0.436
Men	1.46 (1.29–1.66)	
Severe pain		
Women	1.51 (1.25–1.83)	1.000
Men	1.51 (1.28–1.78)	
Per category increase		
Women	1.25 (1.12–1.41)	0.734
Men	1.28 (1.19–1.38)	
Baseline depressive symptoms and incident pain		
No depressive symptoms	Ref	/
Depressive symptoms		
Women	1.63 (1.48–1.80)	0.075
Men	1.86 (1.67–2.07)	

**After adjusting for baseline CES-D scores (when analyzing the association between baseline pain intensity and incident depressive symptoms), age, education, marital status, current smoking, alcohol consumption, self-reported hypertension, diabetes, coronary heart disease, stroke, cancer, chronic lung disease, and asthma.*

adjustment for potential confounders. This bidirectional association was not modified by gender. To the knowledge of the authors, the present study is one the of largest cohort studies on this topic.

Our study provided additional evidence for the bidirectional association between pain and depression from community-based middle-aged and elderly people. Magni et al. firstly investigated and found the bidirectional relationship in a prospective study among patients with pain or depression in 1993, while they found the association was small in magnitude (8). Some short-term studies, which lasted only 1 or 2 years, found a bidirectional association between lower back pain and depression (9, 10, 26). Besides the limited follow-up period, these three studies were conducted among patients from outpatient or healthcare plans, thus the representativeness limited their power to demonstrate the association in the general population. In 2006, Chou analyzed the 2-year data of the ELSA and found the bidirectional longitudinal association between pain and depression (1). While this study did not perform a subgroup study according to gender and was limited by the short period, as Chou admitted (1). In a long-term cohort of 2,028 seniors, the bidirectional influence was also noticed but did not remain after adjustment for covariates (11). Recently, a large-sampled study proved a stronger bidirectional association between pain and mental illness than what we found (12). Nevertheless, this study only employed data from a register system, which not only caused selection bias but also limited its ability to investigate the temporal association between pain and depression, since patients with pain or depression did not necessarily go to see a doctor at the onset. Moreover, the registered study did not differentiate between depression and anxiety (12).

Some researchers suggested that female depression patients were more likely to be affected by chronic pain than male patients (27, 28). Besides, previous studies also observed that women were more sensitive to pain and pain-related distress in both real life and experiment (28–30). Thus, we assumed that gender might modify the bidirectional association between pain and depressive symptoms. However, our study did not find this modifying effect. It probably resulted from the age category, for all the participants

who were above 45 in China and above 50 in England, around or after menopause. This population was nearly free from the effect of sex hormones. Consequently, future research could extend the population to younger individuals to investigate the potential gender difference of the bidirectional association between pain and depression.

The precise mechanisms that link pain and depression remain unclear. An adequate understanding of the bidirectional relationship and underlying mechanism may contribute to screening approach and prevention strategies for pain in patients with depressive symptoms and vice versa. The following potential mechanisms might explain the bidirectional relationship. It has been proved that neuroinflammation was of pivotal importance in the pathogenesis of both chronic pain and depression. High levels of corticosterone and cytokines induced microglial activation (31). This activation probably suppresses neurogenesis and neuroplasticity, leading to depressive symptoms (28, 32). Meanwhile, microglial activation has been identified as a key role in chronic pain development and maintenance (33). Thus, pain and depression probably share neuropathological mechanisms. Moreover, psychological factors that include self-perceived health-related quality of life might also mediate the bidirectional association between pain and depression (33).

The major strength of our study is the large long-term community-based cohorts. Both the ELSA and the CHARLS were nationally representative of two countries with substantial cultural differences and provided free premium multiwave data that cover depressive scores, pain severities, and covariates measurement. Second, this study detected bidirectional longitudinal influence, while most of the previous studies only explored across-sectional or unidirectional longitudinal association.

However, the presented study has several limitations. First, it is an observational study, which inevitably limited its ability to demonstrate the causal association. Thus, further mechanisms or experimental studies that focus on the bidirectional association are required. Second, over 10% of individuals were excluded in both cohorts due to loss to follow-up. These excluded individuals had higher levels of risk factors than those included in this study, which may limit the generalization of our results to the original populations (24). Third, it is noteworthy that the scales of pain intensity and depressive symptoms used in the ELSA and CHARLS were different. However, the consistent results under the different scales might be more persuasive than under a uniform scale. Fourth, pain and depressive symptoms used in this study were self-reported but not doctor-diagnosed, which might have biased our results. Fifth, current confounding might exist even though we have adjusted for a series of potential covariates. For example, the rural/urban differences in China might bias the bidirectional association between pain and depressive symptoms without a certain direction, while the consistency of the findings between the two cohorts indicated the magnitude of the bias might be small. Finally, there was small heterogeneity between the results of the ELSA and the CHARLS, which had been located as the influence of baseline depressive symptom scale on later incident pain for women.

CONCLUSIONS

This pooled analysis of two national aging cohort studies provides further evidence that supports the bidirectional association between pain and depressive symptoms. Individuals with pain had a higher risk of incident depressive symptoms and vice versa. Gender does not modify the bidirectional association. This study suggested that family doctors should be aware of the bidirectional relationship and carry out early assessments or event interventions to reduce the possibility of depression in people with pain or to prevent pain in people with depressive symptoms. Future studies are necessary to explore the potential mechanisms underneath the bidirectional association.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: http://charls.pku.edu.cn/; https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=200011.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by London Multicentre Research Ethics Committee and Peking University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YQ and YM conducted the statistical analysis and drafted the original manuscript. XH conceived the study and revised the manuscript. All authors had final responsibility for the submission and all of them read and approved the final version of the manuscript.

FUNDING

This study was supported by the Capital Health Research and Development of Special Fund Program (No. 2018-2-4114) and Self-exploration Project of National Clinical Research Center for Mental Disorders (No. NCRC2020Z05).

ACKNOWLEDGMENTS

The authors thank the original data creators, copyright holders, depositors, the funders of the data collections for the use of

data from the China Health Retirement Longitudinal Study: Waves 1–3, and the English Longitudinal Study of Aging: Waves 1–8. The original data creators, copyright holders or depositors bear no responsibility for the current data analysis or interpretation.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.881779/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 20 May 2022
doi: 10.3389/fpsyt.2022.916041

Prediction of Antidepressant Efficacy by Cognitive Function in First-Episode Late-Life Depression: A Pilot Study

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The response rate of treatment for late-life depression (LLD) is only 25–60%. The cognitive impairment associated with LLD often affects the effectiveness of antidepressants and may has the potential ability to predict response. This study seeks a biomarker for baseline cognitive function to predict efficacy of antidepressants. Sixty patients diagnosed with LLD received escitalopram or sertraline treatment for 8 weeks. Clinical symptom was measured using Hamilton Depression Rating Scale-17 (HAMD-17) and cognitive function was measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Trail Making Test (TMT) before and after 8-week treatment. Patients were divided into treatment effective group (TE) and treatment ineffective group (TI) according to reduction rate in scores of HAMD-17 after treatment. Thirty-eight matched healthy controls (HC) were assessed using RBANS and TMT. There was significant decrease of score of RBANS and increase of score of TMT in patients with LLD compared with HC. Regression analysis revealed that change in HAMD-17 score was significantly positively associated with baseline score of picture naming, figure copy, digit span, and delayed memory. The preliminary findings suggested that working memory, attention, visuospatial, language function, and delayed memory should be examined further as a means of providing the useful objective biomarkers of treatment response.

Clinical Trials Registration: [www.ClinicalTrials.gov], identifier [ChiCTR2100042370].

Keywords: treatment response, remission, aging population, major depression (MDD), cognitive predictors, cognitive function

OPEN ACCESS

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Specialty section:
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

Received: *08 April 2022*
Accepted: *02 May 2022*
Published: *20 May 2022*

Citation:
Pan W, Liu C, Zhu D, Liu Y, Mao P, Ren Y and Ma X (2022) Prediction of Antidepressant Efficacy by Cognitive Function in First-Episode Late-Life Depression: A Pilot Study. Front. Psychiatry 13:916041. doi: 10.3389/fpsyt.2022.916041

INTRODUCTION

Late-life depression (LLD) can be defined as major depressive disorder that occurs for 60 years of age or older (1, 2). The global prevalence of LLD is 13.3%, which is significantly higher than that of depression in younger age (3). The response rate of treatment for late-life depression (LLD) is only 25–60% (4). Because treatment effects may be delayed during antidepressant treatment, the guideline continues to recommend 4–6 weeks of treatment until treatment failure. This approach to

medication selection contributes to treatment failure and unnecessarily exposes patients to lengthy and inadequate treatment trials, prolonging patient morbidity (5). Identifying predictors of early efficacy for antidepressants is an important issue to be solved and have great clinical significance because it will enable clinicians to determine as early as possible whether patients will benefit from specific types of treatment (4, 5). In addition, the prediction of antidepressant efficacy could improve treatment sensitivity, which would help reduce unnecessary drug exposure (6). Treatment-resistant depression is detected promptly and antidepressant therapy can be optimized as early as possible (7) which could improve the patient's quality of life, reduce the medical burden, and even reduces the risk of suicide of patients (8).

Cognitive dysfunction, such as decreased ability to think and concentrate, and difficulty in making decisions, is one of the main clinical manifestations of depression and a diagnostic item in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (9). LLD has a particularly prominent cognitive impairment compared with youth depression (10). Cognitive symptoms in LLD are mainly manifested as functional impairments in executive function, memory, and information processing speed, which are risk factors affecting social functional outcomes (5, 10, 11). There was discrepancy of the relationship for cognitive function and response to antidepressant therapy in LLD. Several studies suggested that cognitive symptoms appeared in the acute periods of depression, which would affect the effective rate of antidepressant treatment (12, 13). A recent meta-analysis investigated the relationship between antidepressant efficacy in LLD and attention, suggesting that executive function deficits in LLD are associated with poor prognosis (5). It is generally believed that the impairment of executive function in LLD affects the efficacy of antidepressants (10). Morimoto et al. (14) found that baseline TMT scores (indicative of greater executive dysfunction) predicted percent change of Montgomery Asberg Depression Rating Scale (MADRS) over the 4 weeks in LLD. The result appeared to distinguish verbal perseveration from verbal initiation as the cognitive process that was most associated with poor treatment response. Similarly, in the largest positive study, Potter et al. (15) found that perseverative responses during verbal initiation tasks that fewer perseverative errors on the Controlled Oral Word Association Task and better performance on Digit Span significantly predicted better remission status in LLD (n = 110). Another meta-analysis (17 studies) analyzed the prediction of antidepressant efficacy by different cognitive impairments (90 cognitive assessment tools) found that impairment of working memory and delayed recall were associated with poor antidepressant efficacy (16). This finding was also reported by Sheline et al. (17), who found that baseline episodic memory, language, working memory predicted percent change of MADRS in LLD. In accordance with the present results, previous study had demonstrated that best prose recall at baseline exhibited the greatest treatment response at follow-up (18). It was inconsistent about the relationship of cognitive function impairment and antidepressant efficacy in LLD. Pimontel et al. (4) concluded from a meta-analysis of cognitive testing in LLD, that only planning and organization (measured by a subtest of the Dementia Rating Scale) were associated with antidepressant efficacy. Other studies have found that there was no association between executive function and antidepressant efficacy (19–21). Several other studies have suggested no correlation between verbal learning and memory performance in LLD and antidepressant efficacy (22–24).

Although there is emerging evidence indicating that there might be potential cognitive function to predict treatment response in LLD, conclusions from these studies are limited by the using of unequally treatment, inadequate follow-up time and frequency, small sample size subjects, and only assessed one or a small number of cognitive domains, which resulting in inconsistent information to identify the cognitive function on prediction of response of treatment. In addition, some studies included relapsed patients, which is difficult to differentiate the effect on cognition of previous use of antidepressant drugs from the factors of the disease itself (5). Especially, patients with LLD are a heterogeneous group, including individuals with early-onset depression in whom the initial depression manifesting occurs earlier in life, and individuals with late-onset depression who had a first depressive episode after age 60 years (1, 2). Late-onset depression has a particularly prominent cognitive impairment compared with early-onset depression (10). To the best of our knowledge, it is still unclear which cognitive function best predicts antidepressant response of first-episode, drug naive LLD patients.

In this study, we discuss how cognitive dysfunction may contribute to the treatment response in late-onset depression. During this longitudinal study, we measured Trail Making Test A (TMT-A), Trail Making Test B (TMT-B) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), to determine whether the baseline measures of these could be used to predict response after 8 weeks of antidepressant treatment. The association between baseline cognitive testing (TMT-A, TMT-B, and RBANS) score and percent change in 17-item Hamilton Depression (HAMD-17) score after antidepressant was assessed.

We hypothesized that LLD was widespread cognitive function impairment affect disease prognosis. The purpose of the current study was to identify cognitive function processes that may be associated with treatment response in LLD. One goal was to further examine the roles of cognitive function as predictor of treatment response. Moreover, we aimed to identify the role of cognitive function, such as immediate memory, delayed memory, visuospatial, language, and executive function, that might influence treatment response in LLD.

MATERIALS AND METHODS

Participants

Eighty LLD patients were recruited from the outpatient clinic of Beijing Anding Hospital, Affiliated Capital Medical University from January 2021 to November 2021. LLD patients met the following inclusion criteria: (1) age $\geq$ 60 years old, with an education level more than 6 years; (2) first episode of depression

occurred after the age of 60; (3) met the criteria for major depression according the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (4) HAMD-17 score $\geq$ 17; (5) not taking antidepressants when enrollment. Twenty of these patients did not complete the study. Thus, the final analysis consisted of sixty LLD patients. Thirty-eight healthy controls (HC) were recruited from the communities in Beijing, China. The inclusion criteria for HCs as follows: (1) age $\geq$ 60 years old; (2) no psychiatric disorder, cognitive function is normal; (3) no psychotropic drug treatment. The exclusion criteria of all participants were as follows: (1) participants with previous manic or hypomanic episode; (2) comorbid dementia, psychiatric or medical conditions; (3) serious medical illnesses like cardiovascular, hepatic, renal, etc.; (4) history of brain injury; (5) substance abuse or dependence; (6) score of Minimum Mental State Examination (MMSE) more than 20 for primary education level, or score of MMSE more than 24 for equal to and over middle school education level over middle school (25, 26).

The study was approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University (2020-Scientific Research-97). All participants or their family members were required to provide written informed consent before entering the study. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2100042370).

Antidepressant Treatment and Efficacy Assessment

Patients diagnosed with LLD received 8-week antidepressant treatment with escitalopram or sertraline. The dosage of the drug was adjusted by doctor according the patient's clinical conditions. Patients with severe sleep disturbance, anxiety or agitation may be treated with short-term benzodiazepines. During the 8-week treatment period, none of the patients received neurostimulation therapy such as electroconvulsive therapy or transcranial magnetic stimulation therapy. The clinical symptom was measured using the HAMD-17 at baseline and 8-week after treatment.

Rates of response was defined as a $\geq$ 50% reduction in HAM-17 total score from baseline to post 8-week treatment. The percent changes in HAMD-17 were determined using: (baseline HAMD-17– posttreatment HAMD-17)/baseline HAMD-17 $\times$100%. The patients with LLD were divided into two groups based on change of HAMD-17. Treatment effective group (TE) was defined as the changes in HAMD-17 score 50% or higher and treatment ineffective group (TI) was defined as changes in HAMD-17 score less than 50%.

Cognitive Function Assessment

TMT and RBANS were used to assess cognitive function. The TMT-A test connects the circles with numbers (1$\sim$25) written in sequence, and the TMT- B test connects the numbers and Chinese characters in an alternating manner. The operation time and error number of TMT-A test reflects the visuospatial scanning and writing ability of the subjects, and the operation time and error number of TMT-B test reflects the ability of the subjects to transform between different sequences. The longer the time spent and the more errors, the lower the cognitive flexibility of the subjects. The test reflects executive function, attention, and information processing speed. RBANS consists of 12 test tasks (12 items) to assess 5 cognitive function indicators (5 factors): Immediate Memory: assessed by list learning and story memory; Visuospatial: composed of figure copy and line orientation; Language: including picture naming and semantic fluency; Attention: consisted of digital span and coding; Delayed Memory: composed of list recall, list recognition, story recall and figure recall. RBANS is easy to perform and takes nearly 20 min to administer. The mean of the RBANS index score and subscale score is 100 in each instance, with the standard deviation of each instance is 15.

LLD patients were assessed for cognitive function at baseline and after 8-week treatment. HC participants completed the cognition test once when entering the trial.

Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences version 23.0 (IBM SPSS 23.0, Chicago, IL, United States). Data were tested for normality using Kolmogorov-Smirnov test. The non-parametric data were compared by Wilcoxon-Mann-Whitney test. Between the NC group and LLD group, we examined differences in demographics, cognitive testing using t-test for continuous variables and χ^2-test for categorical variables. The difference of change in cognitive testing (TMT-A, TMT-B and RBANS) score and HAMD-17 score between TE and TI group were examined using repeated-measures ANCOVAs. Multiple linear regression analysis was performed to analyze potential impact on response rate of various risk factors including cognitive function, clinical characteristic, and sociodemographic data. Binary logistic regression analysis was performed to analyze the predictors of efficacy. Receiver operating characteristic (ROC) curve was used to evaluate the predictive ability of the model constructed by logistic regression analysis. $p < 0.05$ was considered statistically significant. The significance level was set to $p < 0.05$, two-tailed.

RESULTS

Participants

A total of eighty LLD patients and 38 HC were recruited. Twenty of LLD patients did not complete the study. Thus, the final analysis consisted of sixty LLD patients and 38 HC. There were no significant differences in age, gender, and education level between two groups (see **Table 1**).

The scores of TMT-A (z = 4.259, $p < 0.001$) and TMT-B (z = 5.042, $p < 0.001$) in LLD group were significantly higher than those in HC group. There were significant differences in immediate memory (t = −38.977, $p < 0.001$), visuospatial (t = −40.824, $p < 0.001$), language (z = −8.319, $p < 0.001$), attention (t = −75.350, $p < 0.001$), delayed memory (t = −30.671, $p < 0.001$), and RBANS total score (z = −4.871, $p < 0.001$) between LLD and HC groups, with the LLD patient group being worse overall (see **Table 2**).

TABLE 1 | The demographic and clinical characteristics of the LLD and HC group.

Variables	LLD (n = 60)	HC (n = 38)	t/χ^2-value	p-value
Age (years)	67.75 ± 4.732	65.92 ± 4.122	1.957	0.053
Sex (male/%)	19 (31.7%)	15 (39.5%)	0.626	0.429
Education years	10.32 ± 3.311	10.97 ± 1.881	−1.113	0.268

LLD, late life depression; HC, healthy control.

TABLE 2 | Comparison of cognitive function between LLD and HC group.

Cognitive task	LLD (n = 60)	HC (n = 38)	t/z-value	p-value
TMT-A	54.27 ± 20.98	36.7 ± 11.36	4.259*	<0.001
TMT-B	95.24 ± 39.3	58.77 ± 19.08	5.042*	<0.001
RBANS total score	119.34 ± 14.44	147.05 ± 28.97	−4.871*	<0.001
Immediate memory	24.27 ± 7.81	112.16 ± 14.48	−38.977	<0.001
List learning	17.23 ± 4.79	24.32 ± 6.19	−5.123*	<0.001
Story memory	7.08 ± 3.91	10.71 ± 3.76	−4.542	<0.001
Visuospatial	31.5 ± 8.56	107.61 ± 9.64	−40.824	<0.001
Figure copy	15.18 ± 3.79	16.97 ± 2.77	−2.726*	0.006
Line orientation	13.37 ± 3.35	16.05 ± 2.61	−3.940*	<0.001
Language	28.53 ± 5.5	107.39 ± 6.36	−8.319*	<0.001
Picture naming	9.15 ± 1.49	9.79 ± 0.41	−2.898*	0.004
Semantic fluency	16.8 ± 4.46	22.47 ± 4.05	−5.445*	<0.001
Attention	25.9 ± 5.15	123.11 ± 7.63	−75.35	<0.001
Digit span	13.35 ± 2.83	15 ± 1.43	−2.997*	0.003
Coding	23.98 ± 9.61	38.47 ± 10.01	−7.155	<0.001
Delayed memory	36.8 ± 11.4	105.74 ± 9.88	−30.671	<0.001
List recall	2.98 ± 4.01	4.68 ± 2.27	−4.246*	<0.001
List recognition	17.03 ± 1.96	18.84 ± 1.35	−4.955*	<0.001
Story recall	3.17 ± 2.25	5.42 ± 2.34	−4.213*	<0.001
Figure recall	8.63 ± 4.87	11.58 ± 4.45	−3.017	<0.001

*LLD, late life depression; HC, healthy control; TMT, trial making test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status. *z-test.*

Effects of Clinical Symptoms and Impact on Cognitive Function of Antidepressant Treatment in Late-Life Depression Group

In the LLD group, compared with baseline, there was a significant improvement in the HAMD (t = 13.925, p < 0.001) after 8-week treatment. The reduction rates (%) of HAMD was 58.091 ± 24.495.

Compared with baseline, there were statistically significant differences in immediate memory (t = −3.389, p = 0.001), language (t = −2.160, p = 0.035), delayed memory (t = −4.946, p < 0.001), and RBANS total score (t = −5.238, p < 0.001) after treatments in the LLD group.

Comparison of Cognitive Performance Between Treatment Effective Group and Treatment Ineffective Group in Late-Life Depression Group

A total of 39 cases (65%) were responsive (TE) and 21 LLD patients (35%) were non-responsive (TI) after 8-week treatment. There was no significant difference between the TE and TI group in age, gender, education level, age of onset, duration of disease, antidepressant drugs, and baseline scores of HAMD-17 (see **Table 3**).

There was no significant difference of baseline TMT and RBANS (all $p > 0.05$) between TE and TI patients. All differences in the change of TMT and RBANS after treatment were not statistically significant between TE and TI patients (all $p > 0.05$). Repeated-measure ANCOVA analysis showed that there was no significant time and group interaction for the TMT and RBANS score between TE and TI patients (all $p > 0.05$).

Predictors of Baseline Cognitive Performance on Efficacy in Late-Life Depression Group

Multiple linear regression analysis showed that the change in HAMD-17 score after treatment was significantly correlated with baseline score of picture naming (B = 0.043; p = 0.04), figure copy (B = −0.025; p = 0.004), and digit span (B = 0.028; p = 0.027) in the LLD group (see **Table 4** and **Figure 1**).

Binary logistic regression analysis was performed with response or non-response (TE = 1, TI = 0) as the dependent variable and the baseline cognitive function including TMT and RBANS scores as independent variables. The results showed that

TABLE 3 | The demographic and clinical characteristics of the TE and TI group.

Variables	TE (*n* = 39)	TI (*n* = 21)	*t*/χ^2-value	*p*-value
Age (years)	67.79 ± 4.98	67.67 ± 4.35	−0.099	0.921
Sex (male, *n*, /%)	13 (33.3%)	6 (28.6%)	0.143	0.705
Education years	10.18 ± 3.07	10.57 ± 3.79	−1.113	0.268
Age of onset (years)	66.18 ± 5.20	65.48 ± 4.43	−0.525	0.601
Disease duration (months)	5.33 ± 5.27	8.05 ± 7.61	1.622	0.11
With or without etiology (*n*, %)	24 (61.5%)	15 (71.4%)	0.587	0.444
Types of antidepressant drugs				
Escitalopram (*n*, %)	21 (53.8%)	15 (71.4%)	1.758	0.185
Sertraline (*n*, %)	18 (46.2%)	6 (28.6%)		
Antidepressant dosage (mg/day)				
Escitalopram	13.81 ± 4.445	16.33 ± 4.419	−1.684	0.101
Sertraline	102.78 ± 3.907	116.67 ± 18.960	1.422	0.169
HAMD-17	21.52 ± 3.53	21.79 ± 3.53	−0.284	0.778

TE, treatment effective group; TI, treatment ineffective group; HAMD, Hamilton Depression Rating Scale.

TABLE 4 | Multiple linear regression analysis of predictors of antidepressant efficacy in LLD.

Variable	B	Std. error	Beta	*t*-value	*p*-value
(Constant)	0.196	0.202		0.973	0.335
Picture naming	0.043	0.02	0.269	2.101	0.04
Figure copy	−0.025	0.008	−0.397	−2.98	0.004
Digit span	0.028	0.012	0.325	2.282	0.027

LLD, late life depression.

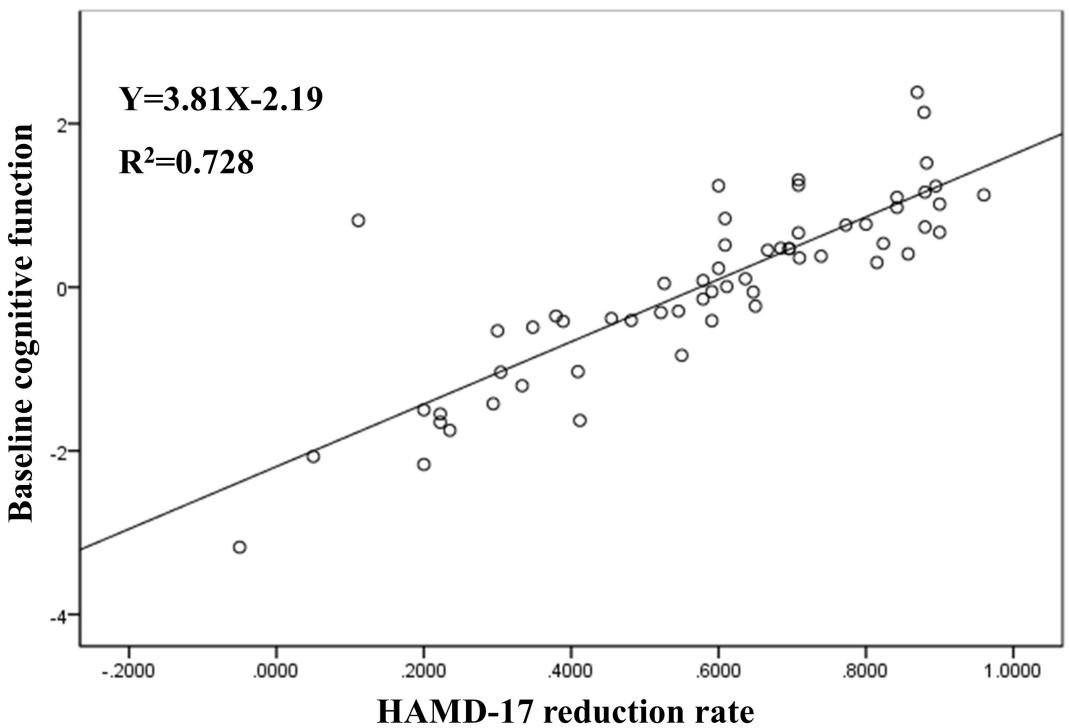

FIGURE 1 | Predictors of the cognitive function on HAMD-17 reduction rate in LLD.

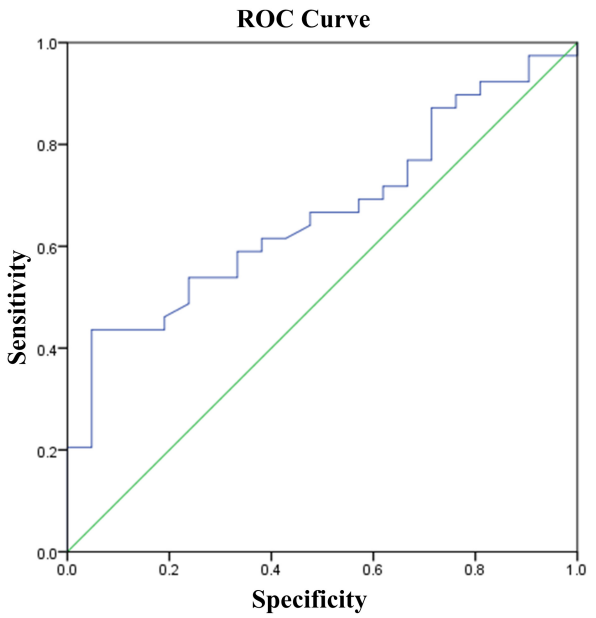

FIGURE 2 | Prediction model of treatment effectiveness of LLD.

the higher of the delayed memory score, the better of the efficacy (OR = 1.107, 95% confidence interval: 1.026–1.199, p = 0.009). The area under the ROC curve suggested that the predicting efficacy of delayed memory was 0.665 (95% confidence interval: 0.529–0.802, p = 0.036), and the sensitivity was 0.436, specificity was 0.952, and Youden index was 0.388 when the optimal cut-off value was taken (see **Figure 2**).

DISCUSSION

In this study, first-episode LLD patients treated with 8-week of escitalopram or sertraline demonstrated improvement of depression and partial cognitive function including immediate memory, language, and delayed memory. Patients with lower level of baseline cognitive function, including figure copy, picture naming, digital span, delayed memory had poorer response after 8-week treatment. This finding suggested that cognitive function may be a predictor of 8-week antidepressant treatment outcome.

The results of this study showed that there was broad cognitive function impairment in first-episode, drug naïve LLD patients and supports evidence from previous observations. Recent studies have found that cognitive deficits are a core feature of depression in elderly, and cognitive complaints in older adults with depression include learning difficulties, slow processing, and executive dysfunction (13, 27).

Digital span consisted of digit span forward and digit span backward. Digit span forward was used to assess working memory (28). Working memory involves holding information in mind and mentally working with it (29). A deficit in working memory may correlate with functional difficulties in maintaining mental set in the face of distracting affective input during depressive episode. A positive relationship between digit span forward and treatment remission was reported that LLD patients with poorer working memory performance was slower to remit at the end of treatment (15). Another study had demonstrated that poorer working memory was associated with poorer response at 4 weeks fluoxetine treatment in 72 youth depressed patients (30). Furthermore, this study demonstrated that poor working memory was related with worse efficacy in LLD patients.

Digit span backward was used to assess sustained attention. Shiroma et al. (31) found that people with good concentration at baseline were more likely to better treatment respond. Etkin et al. (20) analyzed predictors of efficacy in patients with youth depression (n = 1,008; 665 completers) and found that impaired attention was associated with antidepressant efficacy. This study also supported that attention was a predictor of response to antidepressant treatment.

This study confirms that figure copy was also correlated with treatment response. Figure copy was used to assess visuospatial function including stereopsis vision. Stereopsis vision with binocular disparity mainly through the three-dimensional reconstruction of depth-related information in the visual cortex, and stereopsis was considered a visual perception that may affect cognitive-related tasks, including visual memory, visual attention (32). A previous large scale retrospective study reported that visuospatial was significantly related to eventual reduction of depression severity in youth depression patients (33). Another finding was that youth depression patients obtained rehabilitation of psychosocial function by improving cognitive ability in spatial structure (34). This study suggested that visuospatial also played an important role in predicting the efficacy of LLD patients.

We also observed that picture naming and delayed memory could be serve as a significant predictor of treatment response. Picture naming was used to reflect language function. Several studies suggested that language function has the potential to predict antidepressant efficacy in geriatric depression (18, 35). A study found that 25 patients with depression performed significantly worse delayed memory than non-responders after a single injection of ketamine (36). Decreased verbal function may have a "top-down" negative impact on verbal episodic memory performance and may predict remission rates in geriatric depression (35, 37).

Cognitive impairments in LLD maybe related with the alteration in neuroimaging. Cognitive impairment in LLD may be associated with cerebral abnormalities in the prefrontal, medial prefrontal, and parietal cortex (38). Imaging studies of LLD identified microstructural abnormalities in white matter tracts that connect the prefrontal cortex with subcortical and posterior cortical regions, which have been linked to cognitive dysfunction (10, 39). Low white matter integrity in distributed networks tracts supporting executive function was associated with poor response in LLD patients (10). Functional neuroimaging study has shown that the increased functional connectivity of the left dorsolateral prefrontal cortex and bilateral prefrontal regions was associated with the severity of depression and executive function and working memory in LLD (40). Memory impairment is typical of medial temporal region involvement, especially

where hippocampal atrophy has been found in LLD (41). Several reports have shown that decreased cognitive task-related activity in the prefrontal cortex in LLD prior to treatment, which is normalized following treatment (42). Increased cognitive control network functional connectivity and decreased default mode network functional connectivity were observed in LLD with remission, but not in patients with ineffective treatment (43). The functional connectivity between cingulate cortex and ventromedial prefrontal lobe in default mode network, and between dorsal anterior cingulate gyrus and insular lobe in Salience Network was enhanced in LLD with treatment response (44). It could be deduced that the mechanism of cognitive impairment maybe overlapped with the pathophysiology of efficacy. Cognitive function would be used as a potential biomarker for efficacy prediction in LLD patients.

There were several limitations in this study. First, the sample size was relatively small. Second, the drop-out rate (25%) was relatively high which limited the exploration of the trajectory of cognitive ability changes between TE and TI group. Third, participants visited only twice (baseline and after 8-week treatment) which limited the investigation of group difference in cognitive function at early phase of treatment. The results of this pilot study should be interpreted with caution. Future study may need to recruit larger sample size of participants, combine more cognitive indicators and frequent follow-up visits to find a prediction model with high sensitivity and specificity.

CONCLUSION

This study found that lower level of baseline cognitive function had poorer antidepressant response after 8-week treatment in LLD patients. Cognitive function may be used as a predictor of antidepressant treatment outcome, especially working memory, attention, visuospatial, and language function. The results of this pilot study should be interpreted with caution because of the small sample size. Further studies using larger sample sizes are needed to assess these preliminary results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WP contributed to study design, data analysis, investigation, and writing—original draft. WP and DZ contributed to prescribing and administering antidepressant drugs, depression rating, and cognitive text. CL and YL contributed to patients recruitment and consenting, analyzed and interpreted the data, and revised the manuscript. PM contributed to funding acquisition, project administration, writing—review, and editing. YR and XM contributed to conceptualization, methodology, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Beijing Municipal Science and Technology Commission (No. Z191100006619105).

ACKNOWLEDGMENTS

We thank all the participants for participating in this study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor LL declared a shared parent affiliation with the authors at the time of review.

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ORIGINAL RESEARCH
published: 23 May 2022
doi: 10.3389/fpsyt.2022.894646

Altered Intrinsic Brain Activity in Patients With Late-Life Depression: A Resting-State Functional MRI Study

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Objectives: To investigate the altered intrinsic brain activity (IBA) in patients suffering from late-life depression (LLD) using a percent amplitude of fluctuation (PerAF) method.

Methods: In total, fifty patients with LLD and 40 non-depressed controls (NCs) were recruited for the present research. Participants underwent the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test and resting-state functional MRI (rs-fMRI) scans. The RBANS test consists of 12 sub-tests that contribute to a total score and index scores across the following five domains: immediate memory, visuospatial/constructional, language, attention, and delayed memory. The PerAF method was used for data analysis to detect changes in neural activity in the relevant brain regions. A receiver operating characteristic (ROC) curve was conducted to evaluate the ability of the RBANS test and proposed the PerAF method in distinguishing the two groups. The relationships between altered IBA and neuropsychologic deficits were determined by the Pearson correlation analysis.

Results: A significant difference existed in RBANS total score, immediate memory, visuospatial/constructional, language, attention, and delayed memory between groups ($P < 0.05$). Compared with the NCs group, the LLD group demonstrated decreased PerAF differences in the bilateral superior frontal gyrus, orbital part (Frontal_Sup_Orb), and bilateral anterior cingulate cortex (ACC). The PerAF method and RBANS test exhibited an excellent discriminatory power with the area under curve (AUC) values in distinguishing the two groups. In addition, the attention score of the RBANS test positively correlated with the PerAF values of the bilateral Frontal_Sup_Orb and bilateral ACC.

Conclusion: The changes of PerAF in the bilateral Frontal_Sup_Orb and bilateral ACC are related to an increased risk of developing LLD. Moreover, the PerAF method could be used as an underlying sensitivity biomarker to identify the psychiatric disorder.

Keywords: intrinsic brain activity, late-life depression, percent amplitude of fluctuation, receiver operating characteristic, biomarker

OPEN ACCESS

Edited by:
Lirong Liang,
Capital Medical University, China

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Specialty section:
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

Received: *12 March 2022*
Accepted: *25 April 2022*
Published: *23 May 2022*

Citation:
Liu C, Pan W, Zhu D, Mao P, Ren Y and Ma X (2022) Altered Intrinsic Brain Activity in Patients With Late-Life Depression: A Resting-State Functional MRI Study. Front. Psychiatry 13:894646. doi: 10.3389/fpsyt.2022.894646

INTRODUCTION

Depression after 60–65 is generally called late-life depression (LLD), affecting 4%−10% of the elderly (1, 2). Compared with the depression observed in the younger generation, LLD is often related to aging-associated neurodegeneration, cognitive impairment, or somatic complaints, increasing the risk for dementia, disability, and mortality (3). Exploring changes in the functional

and structural connectivity in brain networks in association with emotional and cognitive symptoms may contribute to understanding the neural mechanisms underlying LLD, whereas the specific brain regions engaged with such changes are still unclear.

Recently, the modern brain neuroimaging techniques have developed rapidly. Functional magnetic resonance imaging (fMRI) has appeared as a popular technology because of its being non-invasive and does not require exposure to radioactive tracers, and provides new insights into the pathophysiology of depression. According to the collection status, fMRI is divided into task-state fMRI (ts-fMRI) and resting-state fMRI (rs-fMRI). In terms of the ts-fMRI study, hypoactivation of the anterior cingulate cortex (ACC) in the elderly patients experienced multiple depressive episodes in a verbal fluency task (4). However, another study did not observe the abnormal activation of ACC in response to an explicit sequence learning task, and they discovered diminished activation in the dorsolateral prefrontal cortex (DLPFC) bilaterally while increased activation in the right caudate and putamen (5). Confounds associated with illness chronicity, such as the number of episodes and prolonged exposure to antidepressants, may be inconsistent across studies (6). Compared with the studies including patients with a long course of depression, few studies have investigated first-episode, treatment-naive patients with LLD. The study of the first-episode, drug-naive patients with LLD may be significant for elucidating the core pathogenesis of this illness. In addition, another issue pertains to the task-related functional neuroimaging studies that require patients to follow complicated cognitive tasks, and thus, the performance may confound the results (7).

Rs-fMRI has been considered a feasible and widely accepted method since the study of Biswal et al. (8). They first reported that the spontaneous low-frequency (0.01-0.08 Hz) fluctuations were closely associated with the intrinsic brain activity (IBA) and physiological meaning. IBA indicates sustained neural activity, which affects brain functions (9). In rs-fMRI studies of depression, most of the current work has focused on the major depressive disorder (MDD), regional brain activity in the frontal, temporal, occipital, and cerebellar lobes, and also in the thalamus and insula, displays reduced local synchronization among patients with MDD (10–12). The amplitude of low-frequency fluctuations (ALFFs), fractional ALFF (fALFF), and regional homogeneity (ReHo) constitute three major rs-fMRI approaches in testing IBA (13, 14). An rs-fMRI study using ALFF to investigate first-episode, drug-naive patients with LLD revealed that compared with the control group, the left superior temporal gyrus activation increased while the activation of the bilateral superior frontal gyrus decreased (15). However, another study using ReHo demonstrated that the left Crus I of the cerebellum increased while the activation of the right precuneus decreased (16). The population criteria of the two studies aforementioned are similar, and the inconsistent results may be related to the fact that ALFF and ReHo methods are susceptible to high-frequency physiological cardiac and respiratory noises (17). As a novel approach, percent amplitude of fluctuation (PerAF) exhibits optimal performance in-degree centrality, ALFF, and regional homogeneity (18). Thus, the PerAF approach makes it possible to enhance sensitivity and lower bias while dealing with the IBA changes related to LLD. However, there is still a lack of research on LLD.

Research demonstrates that the severity of depressive symptomatology among patients with LLD contributes to neurocognitive decline (19), while the latest cross-sectional and longitudinal surveys have not recognized any prominent correlation between depression symptoms with cognitive impairments (20–22). Therefore, we hypothesized that compared with non-depressed controls, widespread IBA alternations occurred in patients with LLD. These changes were associated with depression symptoms or cognitive impairment, providing a good understanding of the neurobiological mechanisms that underlay LLD.

MATERIALS AND METHODS

Participants

The present research recruited 50 patients suffering from LLD and 40 non-depressed controls (NCs) between February 2021 and October 2021. All the participants presented informed consent. The study protocols gained approval from the institutional review board of the Beijing Anding Hospital. All the subjects were 60–75 years old and right-handed, first episode and no previous treatment with psychotropic drugs, confirmed by a certified geriatric psychiatrist through Axis I major depressive episode according to the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) through the diagnostic interview (23, 24). Besides, no cases were diagnosed with additional Axis I major psychiatric disorders, except for anxiety disorders. Patients enrolled in the study had the least 17-item Hamilton depression rating scale (HAMD) (17). In addition, the participants were all requested to get the least Mini-Mental State Examination (MMSE) scale scores of 24 (excluding the presence of dementia) (25). Patients conforming to the following standards were excluded, including major neurocognitive decline, major head trauma history, Parkinson's disease, stroke, serious cardiovascular, respiratory, immune, and other systemic diseases.

Cognitive Assessment

This study performed a cognitive assessment with the Repeatable Battery in the Assessment of Neuropsychological Status (RBANS) by well-trained clinicians (26). It contains 12 standardized cognitive tests categorized into the 5 following fields: visuospatial/constructional (line orientation and figure copy), immediate memory (story memory and list learning), attention (digit symbol coding and digit span), language (semantic fluency and picture naming), and delayed memory (list recognition, list recall, figure recall, and story recall). A higher RBANS score suggests superior cognitive performance. Former research has proved RBANS as a helpful screener to evaluate cognitive impairments in psychiatric patients (27).

Rs-fMRI Protocol and Data Analysis

Each participant was scanned using the Siemens 3T scanner (Siemens, Erlangen, Germany), and the head was tightly fastened

using foam pads and straps to avoid motion. This study initially captured images in T1 image (excluding intracranial organic diseases preliminary, such as tumor-like lesion or absence), and then the rs-fMRI was made (around 7 min). When collecting resting-state fMRI data, each participant was asked to relax with eyes closed, lie still, and keep awake. The T1 images was gathered with the T1-weighted sagittal 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence: TE = 1.85 ms; TR = 2530 ms; FOV = 256 × 256 mm^2; FA = 9°; voxel size = 1.0 × 1.0 × 1.0 mm^3; thickness = 1.0 mm and matrix size = 256 × 256. Then, images were gathered in resting-state axially with the echo-planar imaging (EPI) sequence under the following parameters, echo time (TE) = 30 ms; repetition time (TR) = 2,000 ms; field of view (FOV) = 256 × 256 mm^2; flip angle (FA) = 90°; axial slices = 33; matrix size = 64 × 64; slice thickness = 3.5 mm, voxel size = 3.1 × 3.1 × 3.5 mm^3; and a total of 200 time points.

We classified and studied functional images with MRIcro software (www.MRIcro.com). Data were pre-processed with RESTplus V1.2 (http://www.restfmri.net) toolbox based on the MATLAB R2018b platform (28). Initially, the first ten functional volumes were excluded to acquire balanced measurement signals. Then, it was followed by form transformation (DICOM to NIFTI), slice timing, correction of head motion, Montreal Neurological Institute (MNI) space normalization (using T1 image unified segmentation), and re-sample data at 3×3×3 mm^3 resolution, smoothing (full-width Gaussian kernel = 6×6×6 mm^3), and also linear detrending and filtering (0.01–0.08 Hz) (29). In total, 11 of them were excluded due to head movement over 3-mm translocation or over 3° rotation toward each direction in scanning (5 in the LLD group and 6 in the NCs group). This study referenced Friston's 24 head-motion parameters as covariates in regressing the head motion effects. Linear regression was adopted for removing covariates for white matter, global mean signal, cerebrospinal fluid signal, and head motion. In addition, the PerAF approach indicates the ratio of frequency-domain in blood oxygen level-dependent signal in the resting-state to average signal strength for a specific period. Following the pre-processing, the PerAF method was computed (30).

$$PerAF = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{x_i - \mu}{\mu}\right| \times 100 \quad (1)$$

$$\mu = \frac{1}{n}\sum_{i=1}^{n} x_i \quad (2)$$

where "X" represents the signal intensity of the time point, "n" refers to the total number of time points of the time course, and "μ" represents the mean value of the time course.

Statistical Analysis

In this study, statistical analyses were conducted with SPSS 26.0 (SPSS, Chicago, IL, USA). The independent descriptive variables (age) were expressed as mean ± SD, whereas categorical variables (sex) were expressed as counts and percentages. Comparison for continuous variables was conducted by performing an independent t-test, and comparison for categorical variables was made with chi-square or Mann–Whitney U test. Statistical test differences between the LLD and NCs groups showed statistical significance with P-values < 0.05. The 'Statistical Analysis' module of the RESTplus V1.2 toolbox was adopted to compare the average PerAF values of the LLD group and the NCs group. To maintain the balance between the two groups. Some covariates, such as age, gender, and education level, were regressed. For the preliminary comparison results of the average PerAF values between the two groups, the multiple-comparison correction based on the Gaussian random field theory (GRF, two-tailed, cluster-wise $p < 0.05$, voxel-wise $p < 0.001$) was further conducted (30). Previous studies reported that, compared with the Bonferroni correction and false discovery rate (FDR), GRF could reduce the false-positive rate and improve statistical power by utilizing the spatial information of fMRI data (31). Subsequently, the "Viewer" module displayed the brain regions with different perAF values between the two groups. Then, the brain regions with different PerAF values were further made into masks, and the PerAF values of altered brain regions of patients with LLD were extracted using the "Extract ROl Signals" module in RESTplus V1.2 toolbox for the next analysis. Here, we adopted the receiver operating characteristic (ROC) curves for identifying the presented PerAF method's ability to distinguish the two groups compared with the RBANS test. The correlations of the PerAF values for the region of interests (ROIs) with clinical symptoms (HAMD-17 and RBANS score) were assessed through Pearson correlation analysis.

RESULTS

Demographics and Neuropsychologic Data

Upon removing patients with head motion above 3° rotation or 3 mm translocation (5 in the LLD group, 3 men and 2 women; 6 in the NCs group, 2 men and 4 women), 45 in the LLD group and 34 in the NCs group were eventually recruited for the current research. Patients with the LLD and NCs were aged 67.04 ± 4.51 and 65.12 ± 3.98, respectively. No differences in age, gender, and educational level could be observed. However, differences in the RBANS total score were observed in immediate memory, visuospatial/constructional, language, attention, and delayed memory between groups ($P < 0.05$). More details are illustrated in **Table 1**.

PerAF Differences

As shown in between-group statistical maps, by contrast to the NCs group, the LLD group showed decreased PerAF differences in the bilateral superior frontal gyrus, orbital part (Frontal_Sup_Orb) [Brodmann area (BA) 11], and bilateral anterior cingulate cortex (ACC, BA24) (**Table 2**, **Figure 1A**). **Figure 1B** displayed the mean PerAF signal value of altered brain regions between the two groups.

ROC Curve Analysis

Receiver operating characteristic curve analysis and further diagnostic analysis were performed to evaluate the ability of

TABLE 1 | Demographics and neuropsychologic data of the LLD group and the NCs group.

Characteristic	LLD group (n = 45)	NCs group (n =34)	Statistics t/x^2	P-value
Sex (male/female)	15/30	16/18	1.530	0.216
Age (years)	67.04 ± 4.51	65.12 ± 3.98	1.976	0.052
Education (years)	9.47 ± 3.15	10.79 ± 3.22	1.837	0.071
RBANS total score	94.62 ± 12.62	119.65 ± 14.85	8.084	< 0.001
Immediate memory	95.27 ± 12.12	113.18 ± 15.24	5.820	< 0.001
Visuospatial/Constructional	97.09 ± 11.2	108.44 ± 9.38	4.769	< 0.001
Language	94.58 ± 10.52	106.47 ± 5.95	5.913	< 0.001
Attention	106.80 ± 13.51	123.26 ± 8.08	6.301	< 0.001
Delayed memory	91.78 ± 11.1	105.32 ± 10.17	5.552	< 0.001

LLD, late-life depression; NCs, non-depressed controls; RBANS, repeatable battery for assessing neuropsychological status.

TABLE 2 | Brain regions with significantly different PerAF values of the LLD group and the NCs group.

Brain regions of peak coordinates	MNI Coordinates			BA	Number of Voxels	t-value
	X	Y	Z			
LLD group < NCs group						
Bilateral Frontal_Sup_Orb	−9	39	−21	11	46	−4.2726
Bilateral ACC	6	15	−6	24	130	−4.7104

Frontal_Sup_Orb_L, superior frontal gyrus, orbital part, this anatomical name originates from Automated anatomical labeling atlas (32); Bilateral ACC, bilateral anterior cingulate cortex; MNI, Montreal neurological institute; BA, Brodmann's area.

the RBANS test and PerAF method in distinguishing the two groups, and higher area under curve (AUC) value indicated higher diagnostic accuracy. As for the RBANS test, AUC value for RBANS total score reached 0.899 ($P < 0.001$; 95% CI: 0.834–0.964, sensitivity: 0.794, specificity: 0.844), and AUC values of immediate memory, visuospatial/constructional, language, attention, and delayed memory were 0.809 ($P < 0.001$; 95% CI: 0.711–0.908, sensitivity: 0.676, specificity: 0.844), 0.781 ($P < 0.001$; 95% CI: 0.679–0.883, sensitivity: 0.794, specificity: 0.689), 0.852 ($P < 0.001$; 95% CI: 0.770–0.935, sensitivity: 0.912, specificity: 0.711) 0.866 ($P < 0.001$; 95% CI: 0.788–0.945, sensitivity: 0.882, specificity: 0.711), and 0.818 ($P < 0.001$; 95% CI: 0.725–0.911, sensitivity: 0.618, specificity: 0.889) (**Figure 2A**, **Table 3**), respectively. As a comparison, AUC value for bilateral Frontal_Sup_Orb reached 0.770 ($P < 0.001$; 95% CI: 0.667 −0.873, sensitivity: 0.559, specificity: 0.867), and AUC value of the bilateral ACC was 0.782 ($P < 0.001$; 95% CI: 0.676–0.887, sensitivity: 0.676, specificity: 0.867) (**Figure 2B**, **Table 3**).

Correlation Analysis

Linear correlation analysis only observed the positive correlation between the attention score of RBANS test and the bilateral Frontal_Sup_Orb ($r = 0.344$, $p = 0.021$, $n = 45$, **Figure 3A**) and bilateral ACC ($r = 0.313$, $p = 0.036$, $n = 45$, **Figure 3B**) in the LLD group, respectively. It is worth noting that the current correlation results did not passed the multiple-comparison correction.

DISCUSSION

The current work performed a novel and more feasible method, namely, PerAF, which was also helpful in lowering the impact of BOLD signal strength, aiming to investigate the IBA in patients suffering from LLD. The findings indicated that the PerAF values of bilateral Frontal_Sup_Orb and bilateral ACC were significantly lower than those of the NCs. The RBANS test and PerAF values in the aforementioned altered brain regions exhibited a quite good discriminatory power with the AUC values in distinguishing the two groups.

Compared with the NCs group, patients with LLD exhibited poor-cognitive performance in all domains such as in the previous studies (33). Many hypotheses are present on the pathogenesis of LLD, one of which is depression executive dysfunction syndrome (DED). The main features of DED include decreased pleasure, intellectual disability, and lack of insight (34). In some cognitive tests, compared with the normal elderly, patients suffering from DED tend to score lower, such as language fluency, reaction inhibition, novelty problem solving, cognitive flexibility, and working memory, which are consistent with the destruction frontal-subcortical functional network. The disorder of subcortical structure, such as ACC, insula, and hippocampus, often occurs in patients with LLD, leading to abnormal IBA and projection to the pre-frontal cortex (PFC) (35).

Most researchers have demonstrated a declined metabolism within pre-frontal, parietal and temporal cortices and cingulate regions among patients suffering from major depression disorder

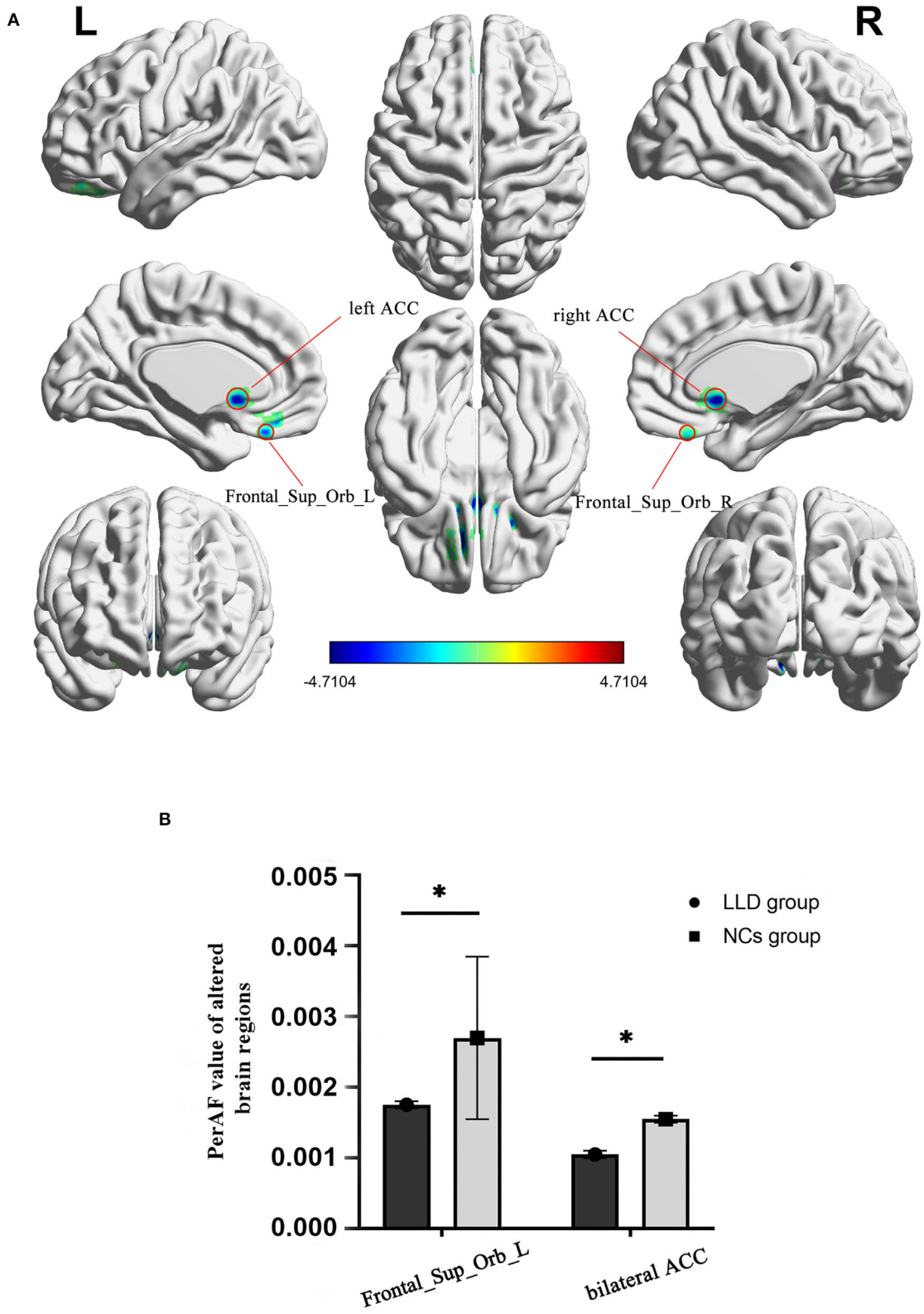

FIGURE 1 | Altered brain regions in PerAF of the LLD group and the NCs group. **(A)** A comprehensive view; Blue color, decreased PerAF areas R, right; L, left; PerAF, percent amplitude of fluctuation; by contrast to the NCs group, the LLD group showed decreased PerAF differences in the bilateral superior frontal gyrus, orbital part (Frontal_Sup_Orb) [Brodmann area (BA) 11] and bilateral anterior cingulate cortex (ACC, BA24). **(B)** The mean PerAF signal value of bilateral Frontal_Sup_Orb and bilateral ACC between the two groups. Bilateral Frontal_Sup_Orb, bilateral superior frontal gyrus, orbital part; bilateral ACC, bilateral anterior cingulate cortex. *indicates that the difference between groups is statistically significant.

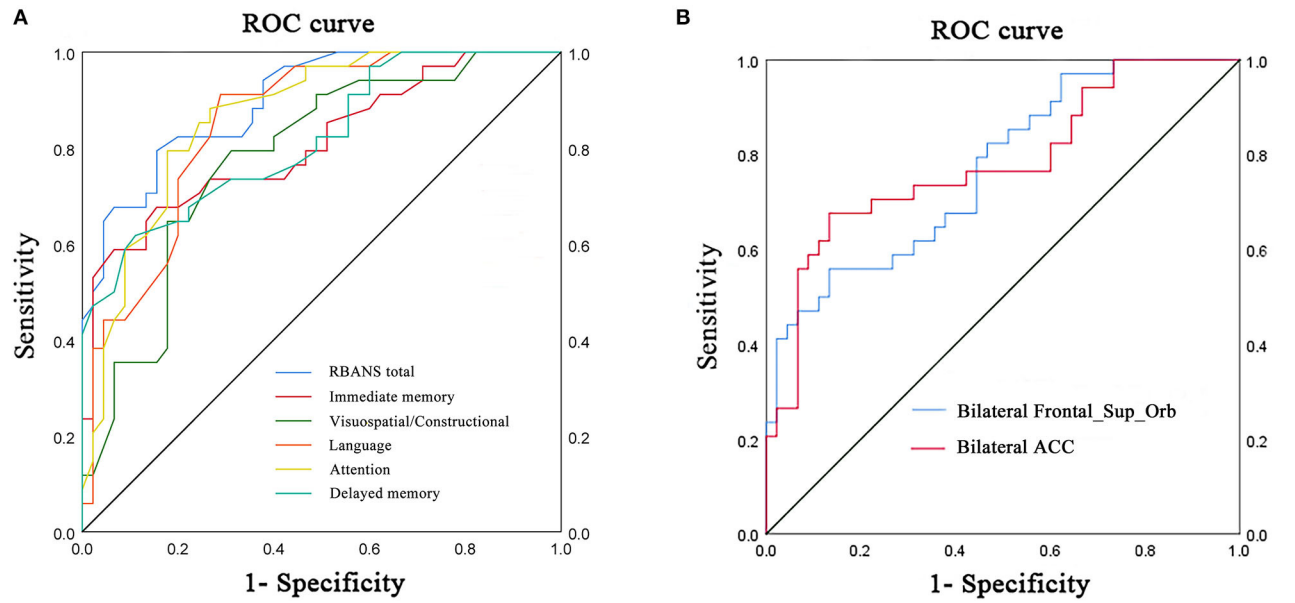

FIGURE 2 | ROC curve analysis of RBANS test and PerAF values of altered brain regions in distinguishing LLD group from NCs group. **(A)** ROC curve analysis of RBANS total, immediate memory, visuospatial/constructional, language, attention, and delayed memory. **(B)** ROC curve analysis of bilateral Frontal_Sup_Orb and bilateral ACC. ROC, receiver operating characteristic; bilateral Frontal_Sup_Orb, bilateral superior frontal gyrus, orbital part; bilateral ACC, bilateral anterior cingulate cortex.

TABLE 3 | ROC curve analysis of RNANS test and PerAF values of altered brain regions in distinguishing the LLD group from the NCs group.

Variables	AUC, 95%CI	Sensitivity, %	Specificity, %	Cut off Point[a]
RBANS total	0.899 (0.834–0.964)	0.794	0.844	108
Immediate memory	0.809 (0.711–0.908)	0.676	0.844	122
Visuospatial/constructional	0.781 (0.679–0.883)	0.794	0.689	108
Language	0.852 (0.770–0.935)	0.912	0.711	102
Attention	0.866 (0.788–0.945)	0.882	0.711	121
Delayed memory	0.818 (0.725–0.911)	0.618	0.889	114
Bilateral Frontal_Sup_Orb	0.770 (0.667–0.873)	0.559	0.867	0.0047
Bilateral ACC	0.782 (0.676–0.887)	0.676	0.867	0.0016

[a]*Cut off point mean RBANS test score or PerAF signal value.*

(MDD) (36). According to the literature, frontal regions (ACC included) exert a key role in MDD-related ReHo pathophysiology. Similarly, our study also discovered that the IBA detected by the proposed PerAF method in bilateral Frontal_Sup_Orb and bilateral ACC of patients with LLD was decreased in contrast to the NCs group. Former research showed that, relative to controls, IBA of superior frontal gyrus among patients suffering from remitted geriatric depression was mitigated (37), and interestingly, the patients incorporated in our research suffered from moderate to severe depressive disorder. It suggests that the decreased IBA superior frontal gyrus does not recover with the relief of depression, which may be an inherent attribute of IBA in some patients suffering from LLD. However, these two studies are all cross-sectional designs.

Moreover, the current finding needs further support from large-scale longitudinal research. In addition, the ROC curve showed that the PerAF method was lower than the RBANS test in discriminatory power for differentiating the two groups. Indeed, the RBANS test, including immediate memory, visuospatial/constructional, language, attention, and delayed memory, is commonly used in the neuropsychological tests, it makes judgments based on the symptomatic characteristics of LLD, and the heterogeneity of the results varies greatly. The advantage of the PerAF method is that it is based on hemodynamics at the resting state. The results are objective and repeatable. From the observed perspective, it could be considered that bilateral Frontal_Sup_Orb and bilateral ACC both exhibited a quite good discriminatory power in differentiating the two groups, indicating that the PerAF method was potentially a neuroimaging indicator in identifying the individuals with depression among the elderly.

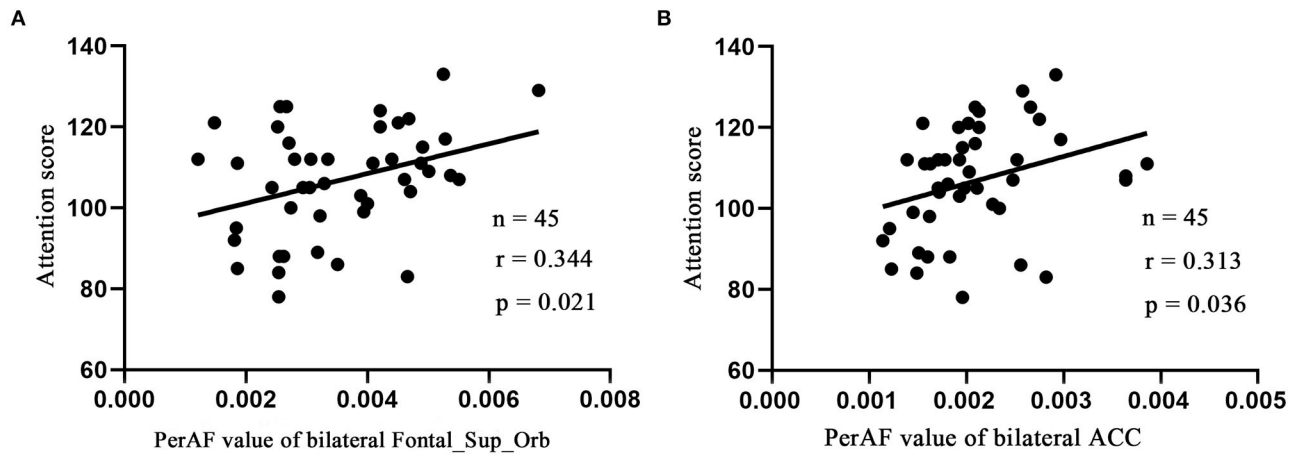

FIGURE 3 | Pearson's correlation. Correlations were between attention score and bilateral Frontal_Sup_Orb **(A)**, bilateral ACC **(B)**. Bilateral Frontal_Sup_Orb, superior frontal gyrus, orbital part; bilateral ACC, bilateral anterior cingulate cortex.

From the perspective of anatomical labeling atlas, Frontal_Sup_Orb is a part of the orbital frontal gyrus (OFC), which belongs to Brodmann area 11. Guo et al. (10) discovered that compared with the control group, the activation of the left superior temporal gyrus increased, while the activation of bilateral superior frontal gyrus decreased among first-episode, drug-naive patients with LLD (15). Similarly, an rs-fMRI study of late-life subthreshold depression (StD) revealed that, compared with the controls, subjects with StD displayed a lower ReHo value in the right OFC (38). OFC is considered to play a key role in the pathophysiology of depression (39). A study demonstrated that patients with LLD exhibited smaller OFC volumes and positively correlated with white-matter lesion volume (40). A study exhibited that compared with patients with LLD without odor identification (OI) impairment and normal controls, patients with LLD with OI impairment exhibited increased functional connectivity (FC) between the left OFC and left calcarine gyrus, between the left OFC and right lingual gyrus, between the right OFC and right rectus gyrus (41). Odor identification (OI) impairment increases the risk of Alzheimer's disease in patients with LLD (42). Hypoactivity in the superior frontal gyrus may partially result in non-response to initial antidepressants in patients with LLD (43). Reports on OFC indicate that abnormal resting-state activity in Frontal_Sup_Orb or OFC may be related to the persistence of depressive symptoms in some patients with LLD, which should also arouse the attention of the elderly with StD.

The ACC connects structurally and functionally with various brain areas, including the lateral pre-frontal cortex, OFC, parietal cortex, amygdala, superior temporal gyrus (STG), nucleus accumbens, hypothalamus, insula, raphe nucleus, and hippocampus (44, 45). In addition, the ACC is thought to play a crucial role in allocating attentional resources in situations of conflicting cognitive and emotional demands (46). One study revealed that patients with LLD in the depressed and remitted phases showed significantly smaller gray matter volume in the left ACC and left posterior STG than healthy subjects (47). In addition, they also discovered that remitted patients with LLD showed lower functional ACC-pSTG connectivity than healthy subjects and positively correlated with lower global function during remission. Liu et al. (48) applied a novel analytical method, named coherence-based regional homogeneity (Cohe–ReHo), to assess regional IBA during the resting state in 15 first-episode, treatment-naive patients with LLD and demonstrated that, compared with the healthy controls, the LLD group showed significantly decreased Cohe–ReHo in right ACC (48). Thus, our finding that decreased PerAF in the bilateral ACC is compatible with these previous studies. These findings suggest that functional alteration in ACC is deeply involved in depression.

Executive function processes, such as focusing attention, organizing, and strategizing, are representative symptoms of LLD, fully demonstrated to be maintained by frontotemporal brain regions (49). The superior frontal gyrus is conventionally considered the frontal eye field. However, functional research has revealed the major contribution of this region to executive function, working memory, and attention (50, 51). As a major function of cognition, attention is essential to perception, language, and memory. Individuals with MDD exhibited impairment in emotion and attention control. The regulation of emotion is vital for adaptive behavior in a social environment. The different strategies may be adopted to achieve successful emotion regulation, ranging from attentional control (e.g., distraction) to cognitive change (e.g., reappraisal). A study revealed that the OFC is involved in distinguishing presently relevant from previously relevant information and was activated for reappraisal only (52, 53).

In contrast, the attentional control condition is characterized by orienting attention away from the emotional stimulus to a cognitive task, the commitment of resources to the processing of this task, and the detection of potential conflicts between task processing and emotional activation. The dorsal portion

of the ACC has been widely discussed as a major node in the attentional control network, for the monitoring of conflict between opposing activations (54). Loeffler et al. (55) thought that attention control and emotion regulation are conceptually similar and might share common mechanisms (55), which indicate that emotional disturbances among patients suffering from LLD can be ameliorated through interventions with target attention control.

In this study, the attention score of the RBANS test is positively correlated with the PerAF values in Frontal_Sup_Orb_L and bilateral ACC. During the cognitive assessment of the RBANS test, the Attention test contains two subtests, respectively, Digit Span Test and Symbol-Digit Coding Test. The former can reflect working memory capacity to a certain extent, while the latter is closely related to psychomotor speed and cognitive flexibility (56, 57), which also reflects the inherent complexity and hierarchy of advanced cognitive function. Attention, interference control, and working memory are essential components of executive function. Executive dysfunction is one of the representative symptoms of patients with LLD. Therefore, it can be speculated that in future intervention studies, if bilateral Frontal_Sup_Orb and bilateral ACC can be used as therapeutic targets, it may be conducive to improving the executive function of LLD.

However, the research has some limitations. First, the participants all come from or around Beijing, near our hospital, which decides the small sample size. Second, adequate attention must be paid to potential confounders, such as diabetes and hypertension, often co-morbid with LLD. Personality and special skills also affect resting-state hemodynamic fluctuations, thus, requiring further evaluation and control in future research. Third, changes in cognitive impairment severity result in confounding bias though average MMSE scores of the two groups are all >24. Finally, research has demonstrated that the neuroendocrine stress and subjective reactions resulting from MRI involvement affect brain functioning, which relates to adverse reactions, such as dizziness, phosphenes, and head ringing (58). To solve the existing problem, a several-minute habituation time is recommended for the participants by the scanner in MRI research before the actual examination, particularly, for female participants (59).

CONCLUSION

Notwithstanding the limitations mentioned earlier, the research showed that changes of PerAF in bilateral Frontal_Sup_Orb and bilateral ACC are related to an increased risk of developing LLD. Moreover, the PerAF method could be used as an underlying sensitivity biomarker to identify the psychiatric disorders.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Anding Hospital Affiliated to Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CL and WP conceived and designed the research protocol. CL completed the data analyses. DZ and PM assisted with neuropsychological assessment and data processing. YR and XM checked the rs-fMRI data and revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

The present work was supported by Beijing Municipal Science & Technology Commission (No. Z191100006619105).

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frontiers | Frontiers in Psychiatry

ORIGINAL RESEARCH
published: 03 June 2022
doi: 10.3389/fpsyt.2022.917082

Persistent Depressive Symptoms and the Changes in Serum Cystatin C Levels in the Elderly: A Longitudinal Cohort Study

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Background: The burden of depression in the elderly is increasing worldwide with global aging. However, there is still a lack of research on the relationship between depressive symptoms and the progression of renal function. Our aim is to evaluate the longitudinal association between baseline depressive symptoms and the changes in serum cystatin C levels over 10 years' follow-up period.

Methods: We used longitudinal data from the Health and Retirement Study (HRS), an existing community based nationally representative aging cohort study which enrolled individuals over age 50 in the USA. Depressive symptoms were determined using an eight-item version of the Center for Epidemiologic Studies Depression Scale (CESD) at wave 7 (2004) and wave 8 (2006). Persistent depressive symptoms were defined as both CESD scores measured at waves 7 and 8 were ≥3; episodic depressive symptoms were defined as CESD scores ≥3 at wave 7 or wave 8. A linear mixed model was used to evaluate the correlation between baseline depressive symptoms and future changes in cystatin C levels.

Results: The mean age of the 7,642 participants was 63.8 ± 10.8 years, and 60.9% were women. Among the participants, 1,240 (16.2%) had episodic depressive symptoms and 778 (10.2%) had persistent depressive symptoms. Compared with participants with no depressive symptoms at both waves, a significant increase in serum cystatin C levels was found among those with persistent depressive symptoms.

Conclusions: Our results showed that baseline persistent depressive symptoms were significantly associated with an increased rate of serum cystatin C levels. The level of serum cystatin C should be monitored in the elderly with persistent depressive symptoms.

Keywords: persistent depressive symptoms, serum cystatin C, longitudinal cohort study, the HRS, renal function

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

Received: *10 April 2022*
Accepted: *05 May 2022*
Published: *03 June 2022*

Citation:
Han T, Zhang L, Jiang W and Wang L (2022) Persistent Depressive Symptoms and the Changes in Serum Cystatin C Levels in the Elderly: A Longitudinal Cohort Study. Front. Psychiatry 13:917082. doi: 10.3389/fpsyt.2022.917082

INTRODUCTION

In worldwide, all the governments need to face the social problem of depression in older people, as it might lead to increasing burdens and costs to individuals and society. To explore the modifiable risk factors and effective prevention for depression is needed. Accumulating evidences from studies suggest that depression can regulate the response of angiogenesis and immune state, which may

cause increased mortality (1). Although depression is a common health problem in the middle-aged and elderly (2, 3), it is reported that depression is also common in patients with Chronic Kidney Disease (CKD) (4).

However, in recent years, there is limited research on the progress of renal function failure and depression in the elderly. Recently, a cross-sectional study reported the association between depression and renal function measured by estimated glomerular filtration rate (eGFR) (5). In addition, the manifestations of depression in various comorbidities are obesity, diabetes, and cardiovascular diseases. It may further predict poor renal prognosis (6, 7). However, the longitudinal relationship between baseline depression or depressive symptoms and future age-related renal impairment (from mild to moderate) is unclear.

Although serum or plasma creatinine have become the most commonly used serum marker of renal function, these are often misleading in the elderly, because muscle mass declines with aging, creatinine metabolism could be also changed (8). Cystatin C is a member of the type 2 cystatin superfamily of cysteine protease inhibitors. It is a small protein produced by almost all human cells and can be obtained in all body fluids (9). With freely filtered through the glomerulus, then reabsorbed and completely catabolized without secretion or subsequent reabsorption into the circulation (10), the characteristic is less dependent on muscle mass than creatinine, so that Cystatin C may be more accurate in kidney function's evaluation (9, 11).

The objectives of the current analysis were 1) to investigate whether depressive symptoms are associated with the levels of serum cystatin C at the baseline; and 2) to develop a better understanding of the potential relevance between baseline depressive symptoms and future changes of cystatin C levels in the elderly.

METHODS

Study Population

We used longitudinal data from the Health and Retirement Study (HRS), an existing community based nationally representative aging cohort study which is freely available to all researchers. Since 1992, HRS has randomly recruited individuals over the age of 50 in the United States through a multistage regional probability sampling design (12). The cohort was in accordance with the Helsinki Declaration and approved by the Institutional Review Committee for Health Sciences and behavioral sciences at the University of Michigan (HUM00061128). Written informed consent was obtained from all participants.

Figure 1 shows the flow chart of the current participant analysis. In our study, wave 8 (2006) in HRS was regarded as the baseline. A total of 18,469 participants participated in the wave 8 survey of HRS. The exclusion standard included: (1) missing completion at the wave 7 or wave 8 of the Center for Epidemiologic Studies Depression Scale (CESD) scores, (2) no data of serum cystatin C at the baseline, (3) history of CKD at baseline, or (4) additional 2,082 individuals without follow-up during wave 10 to wave 13.

Depressive Symptoms

Depressive symptoms were measured by the eight-item version of the Center for Epidemiological Studies Depression scale (CESD-8). This is a widely used self-report measure of depressive symptoms, which has been used in many population-based studies to identify people at risk of depression (13). Participants were asked to think about the past time and feelings, and then distinguish whether the following statements are more similar to them: you feel depressed; You find everything difficult; Your sleep is disturbed; You are happy; You feel lonely; You enjoy life; You feel sad; You can't go. To select Yes or No. The CESD version has internal consistency and factor structure, which is equivalent to the longer version of the scale (14). Although there were scores $\geq$4, according to the relevant survey, people were considered to have depressive symptoms (15, 16). In our study, depressive symptoms were defined as three or more of eight, which is a threshold used to indicate the clinical diagnosis of depression (17). People with depressive symptoms at wave 7 or wave 8 were classified as having episodic depressive symptoms, and those with depressive symptoms in both waves were classified as persistent depressive symptoms.

Measurement of Serum Cystatin C

In the wave 8 (2006) survey of HRS, half of the participants were randomly preselected for blood collection, wave 9 (2008) included the other half. So that both wave surveys decided the baseline serum cystatin C data. Blood specimens were collected by dried blood spot. Serum cystatin C was detected in these two waves using a BNII nephelometer (Siemens, Inc., Deerfield, IL) at the University of Vermont. The equivalent value of serum cystatin C in the national health and Nutrition Examination Survey recommended by HRS researchers was used in our analysis.

Definition of CKD and All-Cause Death

Renal function was defined by using the CKD Epidemiology Collaboration (CKD-EPI) equation, the new CKD-EPI equation was first published in 2012 with cystatin C alone or combined with creatinine (10). The most basic application of cystatin C is for GFR estimation. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) recommended that cystatin C be measured in adults with creatinine eGFR from 45–60 mL/min/1.73m^2 but lack of other markers of renal damage to confirm the diagnosis of CKD (18). The mortality data were taken from the tracker file with verification from family members.

Assessment of Covariates

Covariates included clinical and demographic characteristics. Clinical characteristics included hypertension and diabetes. As for demographic characteristics, sex, race, age (years), and body mass index (kg/m^2) were selected for our analysis.

Hypertension was identified as a patient's systolic blood pressure $\geq$ 140 mmHg and / or diastolic blood pressure $\geq$ 90 mmHg, or if the participant was currently using relative antihypertensive drugs. Body mass index was defined as weight (kg)/height^2 (m^2). The definition for Diabetes as hemoglobin A1c

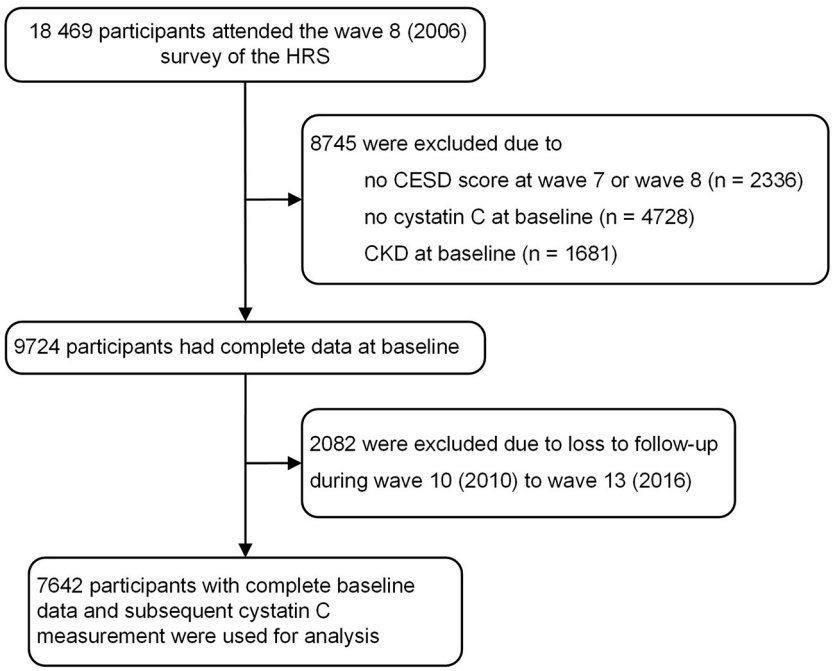

FIGURE 1 | Flow chart of participant selection for this study.

TABLE 1 | Characteristics of the study participants at baseline.

Characteristic	Depressive symptoms at waves 7 and 8			*P* for trend[a]
	Persistent (*n* = 778)	Episodic (*n* = 1,240)	No (*n* = 5,624)	
Women (%)	556 (71.5)	864 (69.7)	3,231 (57.5)	<0.001
White (%)	573 (73.7)	961 (77.5)	4,833 (85.9)	<0.001
Age (Year)	63.0 ± 10.0	63.5 ± 9.4	65.3 ± 9.2	<0.001
Body mass index (kg/m2)	31.1 ± 6.8	29.8 ± 5.8	29.0 ± 5.4	<0.001
Hypertension (%)	440 (56.6)	626 (50.6)	2,592 (46.1)	<0.001
Diabetes (%)	186 (23.9)	241 (19.5)	737 (13.1)	<0.001
Cystatin C (mg/L)	0.97 (0.84–1.11)	0.94 (0.82–1.11)	0.93 (0.80–1.07)	0.006

Data are presented as mean ± standard deviation, n (%), or median (quartiles 1–3).
[a]*Calculated by using a linear regression analysis or* χ^2 *test for trend.*

>6.5%, fasting blood glucose >7 mmol/L, or currently used for anti-diabetic treatment (16).

Statistical Analysis

Characteristics of the overall sample were described using means and standard deviations (SD) or median (quartile range) for continuous data, and *n* (%) for categorical data.

Linear regression models were used to evaluate the cross-sectional associations between baseline status of depressive symptoms and serum cystatin C levels. Then, we used linear mixed model to perform longitudinal associations between sum of CES-D scores and the changes of serum cystatin C levels. We also ran longitudinal analyses to explore the association between baseline status of depressive symptoms and future changes of serum cystatin C levels, using participants without depressive symptoms as the reference. Linear mixed models use all available data during follow-up, considering that repeated measurements of the same participant are interrelated, and can deal with missing data (16). Cox regression models were used to analyze the longitudinal associations of baseline persistent depressive symptoms with incident CKD and all-cause mortality. Model 1 was adjusted for age and gender, and Model 2 was further adjusted for race, body mass index, hypertension, and diabetes.

All analyses were performed by using SAS (version 9.4; SAS Institute Inc). All tests were bilateral, the value is 0.05 as the threshold of statistical significance.

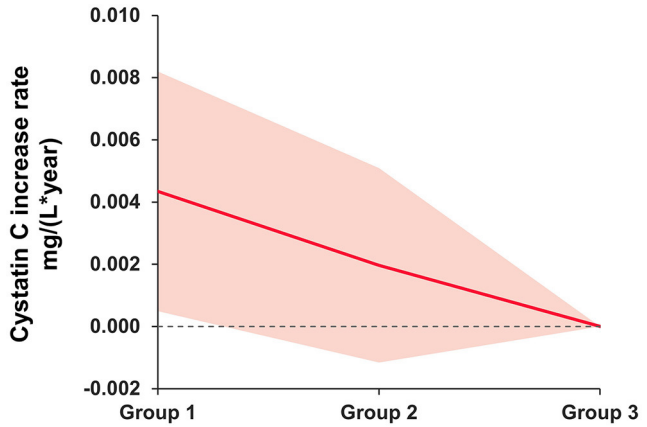

FIGURE 2 | Mean difference rate of change in serum cystatin C (mg/L) between baseline depressive symptom groups. Group 1 as persistent depressive symptoms. Group 2 as episodic depressive symptoms. Group 3 as no depressive symptoms. The group 3 was the reference group. Solid lines represent mean differences in serum cystatin C (mg/L) after adjusting for age, sex, race, body mass index, hypertension, and diabetes. The shadows represent the 95% CIs. The detailed results are presented in **Table 3**.

RESULTS

Participant Selection and Characteristics

A total of 18,469 participants were included. Detailed process of participant selection was shown in **Figure 1**. Among these, 7,642 participants with complete baseline data and subsequent cystatin C measurement were used for our analysis. 778 participants (10.2%) were classified as experiencing persistent depressive symptoms, the other 1,240 participants (16.2%) were classified as experiencing episodic depressive symptoms.

Table 1 shows the baseline characteristics of participants according to the baseline status of depressive symptoms. The mean age of included participants for the HRS was 63.8 ± 10.8 years. In generally speaking, participants who reported a longer duration of depressive symptoms were significantly less well characterized than those who did not. Study participants reporting longer duration had higher body mass index, were more likely to be female, and had a higher prevalence of hypertension and diabetes mellitus.

Cross-Sectional Association Between Depressive Symptoms and Serum Cystatin C

As seen in **Figure 2**, solid lines represent mean differences in serum cystatin C (mg/L) after adjusting for age, sex, race, body mass index, hypertension, and diabetes. The shadows represent the 95% confidence intervals (CI). Compared with participants with no depressive symptoms at both waves, a significant increase in serum cystatin C levels was found among those with persistent depressive symptoms.

Longitudinal Association Between Depressive Symptoms and Serum Cystatin C

As shown in **Table 2**, the longitudinal correlation between the sum of CESD scores and the rate of change in serum cystatin C. After multivariable adjustment, an increase of one unit in the total score of CESD was associated with a faster increase in serum cystatin C levels in patients with persistent and episodic depressive symptoms (0.004 mg/L, 95% CI: 0.001 to 0.008, $P = 0.025$; 0.002 mg/L, 95% CI: −0.001 to 0.005, $P = 0.288$), respectively, compared with participants without depressive symptoms. Besides, our analyses found that per 3-point increase in CESD scores was associated with a higher rate of change in serum cystatin C levels (0.003 mg/L, 95% CI: 0.001 to 0.005, $P = 0.003$), after multivariable adjustment.

Longitudinal Associations of Depressive Symptoms With Incident CKD and All-Cause Death

As shown in **Table 3**, the risks of CKD and all-cause death in participants with persistent depressive were significantly or marginally significantly higher, compared with those without depressive symptoms. Similarly, CESD scores, as a continuous variable, was always significantly correlated with new onset CKD and all-cause death after multivariate adjustment.

DISCUSSION

This ongoing cohort study of an elderly American populations investigate the temporal association between episodic or persistent depressive symptoms and the level of cystatin C in a large general population based on previous assessments of depressive symptoms. After extensive adjustment for covariates, persistent depressive symptoms were significantly associated with the change of kidney dysfunction, incident CKD, and all-cause mortality. These associations were not related to gender, age, race, body mass index, hypertension, and diabetes.

Emerging evidences suggest that depression and CKD may both affect most of the world's population, depression is more common in CKD patients than without CKD (19). In general, depressive symptoms can cause active inflammation and impaired immune response which may lead to poor clinical outcomes (20). Even if all patients with depression receive the best treatment of evidence-based intervention, residual symptoms and dysfunction are still common (21). Therefore, some previous studies have evaluated relationship between depressive symptoms and rapid eGFR decrease or progression to renal failure (22–26). Considering the adverse clinical results caused by depressive symptoms, the high prevalence of these symptoms in elderly maintained the importance of our study.

There are many mechanisms for the relationship between depressive symptoms and serum cystatin C. Although etiology and pathogenesis of depression are not fully understood, there are consistent and strong empirical evidences that neuronal injury and immune inflammation are important factors related to depression (27–31). Cystatin C is an important endogenous

TABLE 2 | Association between baseline depressive symptoms and rate of change in serum cystatin C (mg/L): longitudinal analyses using linear mixed models.

Depressive symptoms at waves 7 and 8	Model 1[a]		Model 2[b]	
	β (95% CI)	*P*-value	*β* (95% CI)	*P*-value
Persistent	0.004 (0.001 to 0.008)	0.025	0.004 (0.000 to 0.008)	0.027
Episodic	0.002 (−0.001 to 0.005)	0.288	0.002 (−0.001 to 0.005)	0.218
No	Reference		Reference	
Per 3-point increase[c]	0.003 (0.001 to 0.005)	0.004	0.003 (0.001 to 0.005)	0.004

[a]*Model 1: adjusted for age and sex.*
[b]*Model 2: adjusted for age, sex, race, body mass index, hypertension, and diabetes.*
[c]*Per 3-point increasement of the mean CESD score at wave 7 and wave 8.*

TABLE 3 | Association between baseline depressive symptoms and risk of incident CKD and all-cause mortality.

		Model 1[a]		Model 2[b]	
	Events/Total	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
CKD					
Persistent	243/492	1.512 (1.318 to 1.735)	<0.001	1.283 (1.061 to 1.552)	0.010
Episodic	339/1,240	1.268 (1.128 to 1.425)	<0.001	1.093 (0.928 to 1.288)	0.286
No	1,327/5,624	Reference		Reference	
Per 3-point increase[c]		1.350 (1.258 to 1.449)	<0.001	1.178 (1.065 to 1.304)	0.002
All-cause death					
Persistent	148/492	1.567 (1.314 to 1.868)	<0.001	1.267 (0.991 to 1.620)	0.059
Episodic	205/1,240	1.289 (1.106 to 1.503)	0.001	1.226 (0.997 to 1.507)	0.054
No	896/5,624	Reference		Reference	
Per 3-point increase[c]		1.365 (1.242 to 1.501)	<0.001	1.246 (1.093 to 1.420)	<0.001

[a]*Model 1: adjusted for age and sex.*
[b]*Model 2: adjusted for age, sex, race, body mass index, hypertension, and diabetes.*
[c]*Per 3-point increasement of the mean CESD score at wave 7 and wave 8.*

inhibitor of cysteine protease activity (32), which is also closely related to the nerve injury and immune inflammation (33, 34). Another possible mechanism is that cystatin C is close to oxidative stress, which can play a significant role in the process of depression (35). Last but not least, apoptosis may be an important risk factor for depression, it can also influence on the level of Cystatin C by changing the concentration of active caspinase-9 protein (36, 37). However, most investigations by now laid the emphasis on the relationship about higher cystatin C concentration appear to present with high risk of depression (38, 39). Different from previous studies, in this large cohort study of older Americans, persistent depressive symptoms were significantly associated with elevated serum cystatin C levels.

To our knowledge, this study is the largest general population-based investigation exploring the relationship between depressive symptoms and level of serum cystatin C with a long-term follow-up of 10 years. In our research, we showed that patients with higher depression events correlated with higher serum levels of cystatin C, then had an increased CES-D score at baseline. Our results imply that the prospective association between depressive symptoms and rapid kidney function decline in the general population, serum cystatin C might be a more sensitive biomarker for CKD.

What is more, we guaranteed comprehensive follow-up and strict adjudication of depression events, so that the results are reliable. Then, the determination method of serum cystatin C assay chosen for this study is both widely available and stable (coefficient of variation of precision < 5%). The serum index is simple, reliable, and convenient for clinical promotion.

Several potential limitations need to be mentioned. The study sample comes from a single cohort, and the sample size may be larger. Additionally, the time courses of cystatin C levels were not evaluated and amended, especially the information for serum cystatin C level was absent in wave 7. By evaluating the time course of cystatin C, further research is necessary to consolidate the clinical significance of depressive symptoms. In addition, HRS enrolled only middle-aged and older persons, and as such, we do not know whether this association is suitable for younger person.

Several researchers have already evaluated the potential link between cystatin C levels and depression (38–40). A study which enrolled 1,440 Chinese elders (>60 years old) found a harmful relationship between high serum cystatin C levels and risk of depression (38). Another prospective cohort study of 11,847 Chinese people (>45 years old) demonstrated that high levels of serum cystatin C were associated with an increased risk of depression (40). They computed the risk of depression by using

modified Poission regression models, found that the association between serum cystatin C levels and the risk of depression remained significant after adjusting for multiple covariance. Consistent with the above findings, our results show that serum cystatin C not only is associated with depression, but also severity of depressive symptoms is closely related to change of serum cystatin C. This association persists after controlling for multiple potentially confounding variables. We indicate that cystatin C should be monitored in the pathogenesis of depression among all the kidney function markers.

CONCLUSIONS

Our results showed that baseline persistent depressive symptoms were significantly correlated with an increased rate of serum cystatin C levels. The level of serum cystatin C should be monitored in the elderly with persistent depressive symptoms. Potential mechanisms of the relationship between kidney dysfunction and depression need to be further characterized. If further confirmed, our data could be the evidence for depressive symptoms' screening and effective psychosocial intervention to improve the primary prevention of CKD and all-cause death.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Committee for Health Sciences and Behavioral Sciences at the University of Michigan (HUM00061128). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TH and LZ conceived the study and designed the statistical analyses. TH, LZ, and LW did the statistical analyses and prepared the draft of the manuscript. TH, WJ, LZ, and LW substantively revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

The National Natural Science Foundation of China (81901125) have contributed to analysis and interpretation of data.

ACKNOWLEDGMENTS

The authors thank the HRS research team and the field team for collecting and providing the data. The authors also thank all volunteers and staff involved in this research.

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frontiers | Frontiers in Psychiatry

ORIGINAL RESEARCH
published: 29 June 2022
doi: 10.3389/fpsyt.2022.898686

Socioeconomic Status Association With Dependency From Objective and Subjective Assessments: A Cross-Sectional Study

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OPEN ACCESS

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Specialty section:
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

Received: *17 March 2022*
Accepted: *31 May 2022*
Published: *29 June 2022*

Citation:
Pan Y, Aierken A, Ding X, Chen Y and Li Y (2022) Socioeconomic Status Association With Dependency From Objective and Subjective Assessments: A Cross-Sectional Study. Front. Psychiatry 13:898686. doi: 10.3389/fpsyt.2022.898686

Background: The effect of socioeconomic status (SES) on dependency is still complex and not fully clear. The purposes of this study are to assess the association between SES and dependency personality disorder (DPD) using both objective and subjective assessments.

Methods: A cross-sectional study was conducted in 27 locations in China among 1,276 general residents aged 60 years and above through a complex multistage sampling design. Data were collected using a questionnaire by well-trained investigators through face-to-face interviews. The DPD was assessed using a standardized Chinese version of the Minnesota Multiphasic Personality Inventory-II scale. Objective SES was assessed by the combination of education levels, individual income, preretirement occupation, and medical insurance. Subjective SES was measured using the MacArthur Scale. The logistic regression analysis was used to evaluate the association between objective SES and DPD. Analysis of covariance was conducted to compare the mean of DPD scores in different levels of SES.

Results: The results of the chi-squared test showed that the levels of objective SES were associated with DPD, depression, social resources, and region. The logistic regression analysis showed a significant negative association between the levels of objective SES and DPD. The odds ratio was 1.84 (95% confidence interval, 1.07–3.18) after adjusting for important confounding factors. The analysis of covariance showed differences in the mean of DPD scores among different groups defined by different levels of SES.

Conclusion: The levels of SES were negatively associated with DPD, and subjective SES had a stronger association with DPD than objective SES. The effect of subjective SES on DPD is possibly associated with the perception of position in the social hierarchy.

Keywords: dependency, socioeconomic status, social resources, objective and subjective assessments, elderly people

INTRODUCTION

With economic and social development, the increasing number of elderly people worldwide results in the increasing challenge of health and social care demand in the next few decades (1, 2). Owing to the general reductions in social and economic resources and physical function decline, dependency is generally regarded as the inevitable result of aging and has become an important public health problem (3).

Dependency is a personality disorder, and its primary feature was identified as "a pervasive and excessive need to be taken care of, or meet their emotional and physical needs which lead to the gradual loss of autonomy and clinging behavior." Dependency has historical roots far preceding the seminal volume of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (4, 5).

The different dependency objects, such as substances, behaviors, and people, can lead to alcohol dependency, sleep dependency, and nursing dependency. Dependency personality disorder (DPD) manifests differently at various points in a human life span; in children, it is characterized by helplessness, indecisiveness, and a tendency to cling to a supportive parent. In adolescents, it may manifest as close relationships with valued peers rather than with their parents. As the individual changes from adolescence to adulthood, the primary object of dependency may change again from peers to a mentor or figure of authority. The elderly with DPD often show psychopathological symptoms, such as loss of motivation, feelings of loneliness, and a sense of helplessness, which can bring about severe depressive symptoms and other health-related problems (6). In old age, with the impairment of physical function, cognitive decline, and the lack of social and environmental resources, the objects that cause dependency among elderly people become increasingly complex. Those elderly people with disability and cognitive impairment are associated with increased length of hospital stay and dependency for caregivers. Other older people with low income are financially dependent on their adult children. The appearance of dependent behaviors seems to be an adaptive response to debilitating socioeconomic circumstances. Epidemiological studies have confirmed that a high level of dependency is related to the risk of nutritional deficiency, depression, suicide, and increased all-cause mortality (7–9). In addition, high levels of dependency are associated with excessive use of healthcare services and increased healthcare expenditures, thus giving rise to medical burdens. DPD may have a negative impact on life satisfaction, as societal costs of increasing dependency increase over time (10).

A previous study has shown that socioeconomic factors, such as gender inequality, residence, age trends, and occupations, have a significant predictive power for an impending onset of dependency (11). A longitudinal study conducted on elderly people in Taiwan that has shown subjective socioeconomic status (SES) assessments seems to be more favorable than the objective SES assessment as a predictor of health outcomes (12). Subjective social status (SSS) can capture more comprehensive and dynamic attributes of SES than objective SES (13). Subjective SES reflects the relative rather than the absolute status in the social hierarchy. In addition, the perception of subordinate status in the social hierarchy is believed to have a destructive effect on health outcomes (14).

To the best of our knowledge, the impact of SES on dependency is understudied, particularly for subjective SES. The main objectives of this study include assessing the association between DPD and SES, using both objective and subjective measurements, and further determining the modifiable risk factors for future intervention studies.

MATERIALS AND METHODS

Study Design

The data for this study were drawn from the project titled, "Accessibility Evaluation of Health-related Resources for the Elderly" using a cross-sectional design. Informed consent was obtained from each participant before participation. This study was approved by the institutional review board at the School of Medicine, Zhejiang University.

Participants

A total of 1,276 general residents aged 60 years and above were selected using a complex multistage sampling design. According to the geographical distribution of China, sampling was conducted in four provinces (Zhejiang, Heilongjiang, Xinjiang, and Sichuan) from July 2019 to September 2021. In total, 27 locations (urban/rural) with good managerial and organizational capabilities were selected from five cities (Hangzhou, Harbin, Tulufan, Yining, and Chongqing), and **Figure 1** shows the third sampling units. We computed the total sample size required based on the events per variable method. Potentially eligible participants were recruited through mobile phones by local staff members, followed by extensive publicity campaigns.

Among them, 271 participants were interviewed about the subjective SES using the SSS Scale. Participants who failed to complete the questionnaire were excluded.

Data Collection

Data were collected on-site by well-trained investigators through face-to-face interviews to ensure true answers. The duration of each interview lasted 45–60 min or longer. The questionnaire consisted of fifteen parts comprising 520 items. The main content comprised demographic characteristics, psychological status, cognitive status, resource utilization, and personality.

Measurements

Objective Socioeconomic Status

We combined the following measurements as a comprehensive measurement of objective SES: education level, individual income, pre-retirement occupation, and medical insurance. Education level was measured as completed years of schooling (0, ≤6, 7–9, 10–12, 13–17, and ≥18 years) with a value of 0–5, respectively. Individual income was measured by self-reported monthly income, which was divided into <¥2,000, 2,000–3,999, 4,000–5,999, 6,000–7,999, and more than ¥8,000, ranging from 0 to 4, respectively. The preretirement occupation was classified with reference to the empirical study (15), which were

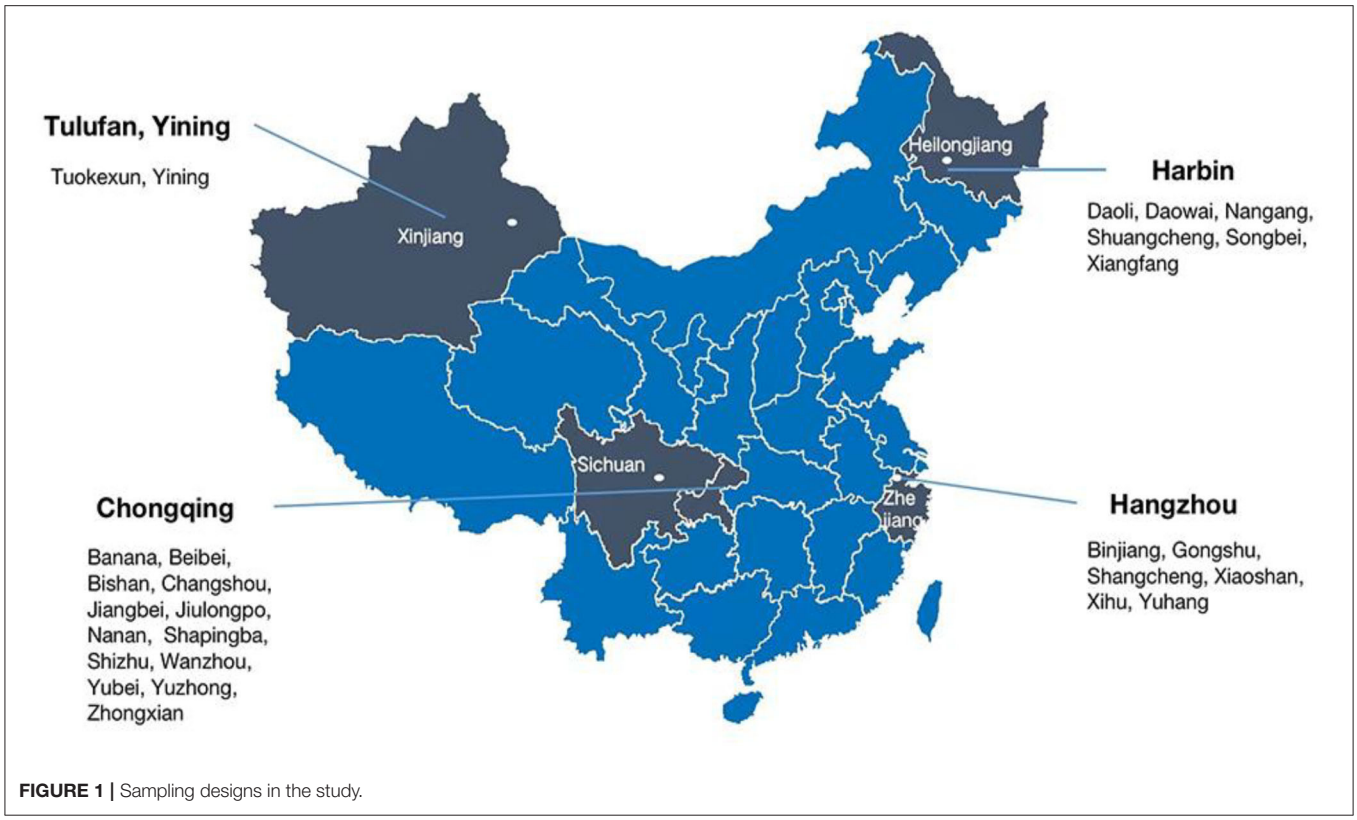

FIGURE 1 | Sampling designs in the study.

divided into two categories with values of 0 and 1 according to manual (unemployed workers, temporary workers, factory workers, transportation personnel, housework, and labor in agriculture, fishery, and animal husbandry) and non-manual (staff of state agencies and institutions, service and sales workers, medical and health personnel, educators, and self-employed). Medical insurance was categorized into rural cooperative medical care, social basic medical insurance, and free medical care, each assigned a value of 1–3 points. If participants had commercial health insurance, an additional point would be added. 0 represents those with no health insurance. The objective SES scores ranged from 0 to 13 points; the higher the score, the higher the objective SES. In addition, it was divided into two categories with a cutoff point value of 3 based on quartiles (50th percentile), such as low objective SES and high objective SES (16).

Subjective Socioeconomic Status

Meanwhile, subjective SES can be defined as an individual's common sense perception of their social standing (17, 18). The MacArthur scale was applied to assess the SSS (12, 19–21). The instructions of the MacArthur scale are more complex linguistically speaking because they have long periods and subordinate constructions and thus require substantially greater cognitive skills (22). Based on the previous study (23), we changed the original reference group of these two questions into "Provinces" and "people around" due to the large socioeconomic differences in China's provinces and the unformed concept of "community" in the same sense (**Figure 2**). Respondents who had put their marks in between two rungs were assigned to the higher levels of these rungs. Each item was counted as 1–10 points, and the total score was 20 points. Higher scores were considered to have higher subjective SES. Based on the scores of 271 participants, subjective SES was divided into two categories with a cutoff point value of 11 such as low subjective SES and high subjective SES. This social status indicator is a well-validated measurement with a strong construct validity and retest reliability (24). We identified a pool of six experts to participate in the content validity evaluation, including three gerontologists and three social science experts. These experts were selected for their extensive experience in gerontology and sociology, respectively. The relevance scale, which inspected the optimal collocation among four different reference groups ("China" and "Community;" "China" and "People around;" "Province" and "Community;" and "Province" and "People around"), along with the introduction, was sent *via* email to these experts. Each of the items was assessed with the following criteria: 1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, and 4 = highly relevant. With the data obtained, we established the content validity index (CVI) for the item level (I-CVI) by dividing the number of experts rated 3 or 4 by the total number of experts. Meanwhile, we established the CVI indicator for the scale level (S-CVI) by summing the number of items rated 3 or 4 and dividing the total number of items. I-CVI reflected the degree of agreement among experts, while S-CVI represented the consensus of all experts. When the number of experts was >5, I-CVI $\geq$ 0.78 and S-CVI $\geq$ 0.80 were

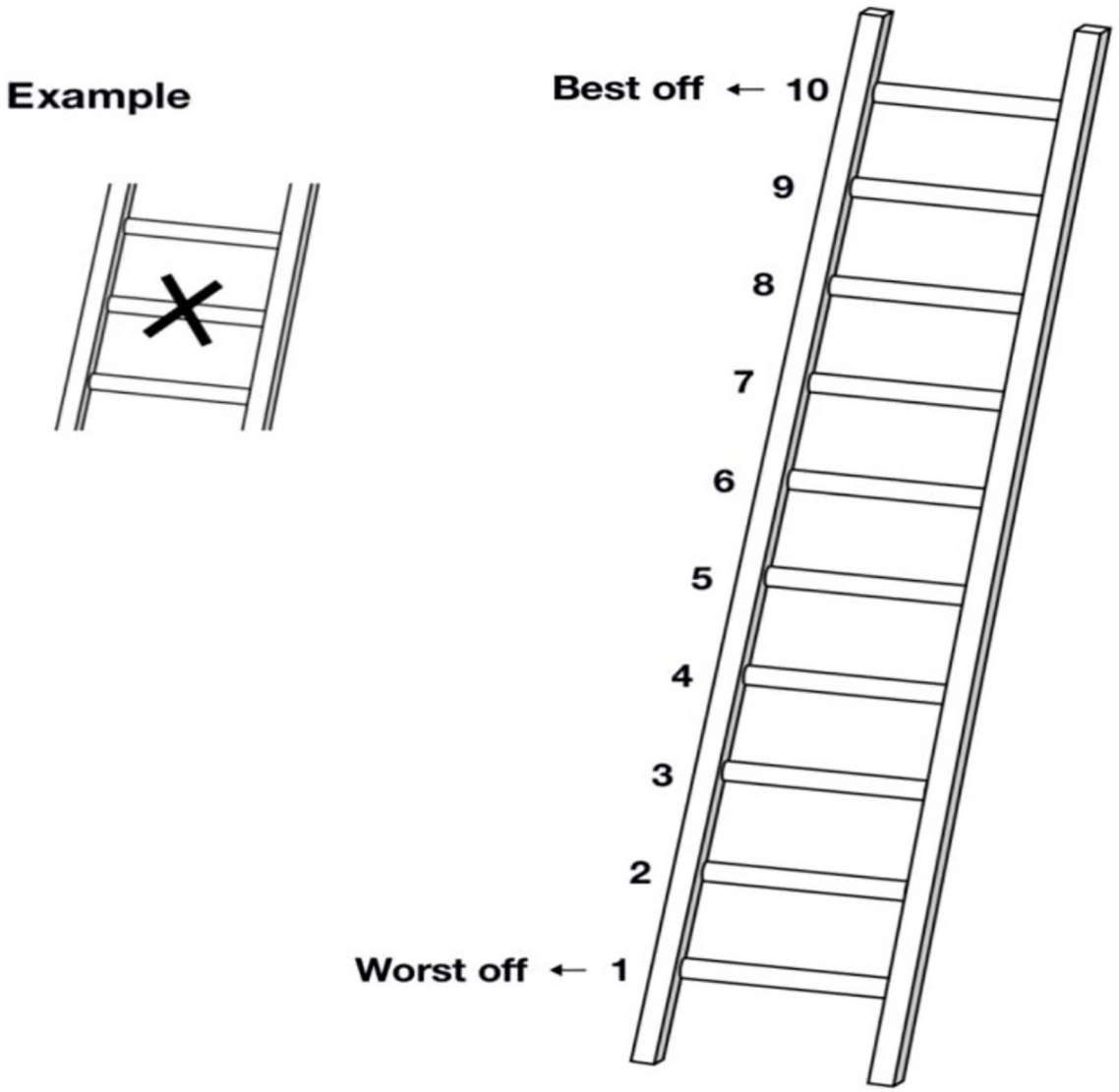

FIGURE 2 | The subjective social status was measured using the MacArthur scale. (1) Here is a ladder. Think of this ladder representing where people stand in Zhejiang Province. At the top of the ladder are the people who are the best off—those who have the most money, the most education, and the most respected jobs. At the bottom are the people who are the worst off—who have the least money, the least education, and the least respected jobs or no jobs. The higher up you are on this ladder, the closer you are to the people at the very top, and the lower you are, the closer you are to the people at the very bottom. If you consider your current situation and compare it with all other people in Zhejiang Province, where would you place yourself on this ladder? Please mark an X on the rung that best represent your situation. (2) Here is another ladder. Think of this ladder as representing where people stand in the people around them. At the top of the ladder are the people who are the best off—those who have the most money, most education, and best jobs. At the bottom are the people who are the worst off—those who have the least money, least education, and worst jobs or no job. If you consider your current situation and compare it with all the people around you, where would you place yourself on this ladder? Please mark an X on the rung that best represent your situation.

acceptable. Finally, the subjective SES indicator based on the "Province" and "People around" was selected because it had the best content validity.

Dependency Personality Disorder

Dependency personality disorder was assessed by the standardized Minnesota Multiphasic Personality Inventory-II scale. The DPD scale comprised 57 items. The raw score was calculated and converted into a standardized T-score. A score of 60 or above was indicated as the diagnostic criteria for DPD.

Cognitive Function

Cognitive function was measured using the Chinese version of the Dementia Assessment Sheet for Community-Based Integrated Care System 21 items (DASC-21) through which we had identified the reliability and validity for elderly people

in the Chinese community (25). The DASC-21 comprised two introductory items and 21 assessment items.

Social Support

Social support was measured by the Chinese version of the questionnaires of the Older American Resources and Services (OARS). The ratings were summed to yield a total score. High scores indicated high levels of social support.

Community Service Resources

Social resources were assessed using four questions as follows: "Does your community have emergency services like an emergency call?," "Can you get timely treatment when you are seriously ill?," "Does your community regularly ask about your current condition or do you receive follow-up calls regularly after seeing a doctor?," and "Do you regularly attend physical examinations?" If respondents responded with "No," then, the answer was coded as "0;" otherwise, it was coded as "1".

Other Measurements

Depressive symptoms were measured using the 15-item Geriatric Depression Scale. Participants' personality characteristics were assessed by the Eysenck Personality Questionnaire (EPQ).

Statistical Analysis

Statistical analysis was restricted to the 1,217 participants who had complete questionnaires, objective SES, and DPD assessment data. The demographic characteristics of the participants were described using percentage.

Bivariate analysis for the level of objective SES and related factors was used for the chi-squared test. The participants were divided into two groups, namely, high level of SES and low level of SES.

A logistic regression analysis was performed to identify the association between DPD and objective SES. Individuals with a T-score on the DPD scale ≥60 points were regarded as DPD individuals and expressed as "1;" otherwise, "0" for those score lower than 60 points. As a binary variable, objective SES was divided into high and low groups, and the high group was used as the control group. The logistic regression model was adjusted for age, gender, marital status, chronic disease status, social support, DASC-21, community service resources, GDS-15, and personality.

We conducted the analysis of covariance to evaluate the DPD scores among different SES groups such as high objective SES score and high subjective SES score group (objective high-subjective high), low objective SES score and high subjective SES score group (objective low-subjective high), high objective SES score and low subjective SES score group (objective high-subjective low), and low objective SES score and low subjective SES score group (objective low-subjective low) by using the general linear model procedure with the SAS program PROC glm. A variance homogeneity test and normality test were performed. We calculated the mean and standard error for the DPD score for the four groups, and the linear trend was tested for the means of four groups. Comparisons were conducted among the four groups by using an F test with a significance level of 0.05.

Statistical analysis was performed using SAS for Windows (version 9.4) and statistical package SPSS version 26.0 (IBM Corporation, Armonk, NY, USA). All statistical tests were two-sided with $\alpha = 0.05$.

RESULTS

Table 1 shows the demographic characteristics of the study participants. The average age of the participants was 68.5 years. Among all the participants, 486 (39.9%) were men, and 731 (60.1%) were women. Those who lived in rural areas accounted for 58.0 and 42.0% for those in the cities. More than half of the participants had equal or <6 years of schooling or no schooling. A total of 70.5% of participants self-reported having one or more chronic diseases. No statistically significant differences existed in DPD by gender ($p = 0.234$). However, DPD scores increased with age ($p < 0.001$). In addition, DPD scores were different in urban (*Mean* = 39.5, *SD* = 11.3) and rural (*Mean* = 44.5, *SD* =12.5) areas ($p < 0.001$).

Table 2 shows the results of the levels of objective SES and related risk factors in the chi-squared test. In rural areas, 82.7% had a low level of objective SES ($p < 0.001$). Failure to receive any timely treatment or emergency service had a greater likelihood of a low level of objective SES. The low level of objective SES group compared with the counterpart had a higher proportion of individuals with depressive symptoms (GDS-15 scores ≥ 5, $p < 0.001$) and DPD (T-score ≥ 60, $p = 0.005$).

Table 3 shows the association between the levels of objective SES and DPD status by binary logistic regression analyses after adjusting for depression, personality, community resources related to DPD, cognitive status, social support, and other covariates. The objective SES was significantly negatively associated with the levels of DPD, with odds ratio of 1.84 (95% CI, 1.07–3.18; $p = 0.028$).

Table 4 presents the mean DPD scores among different SES groups in 271 participants. The objective high-subjective low group had higher DPD scores than the objective high-subjective high group. The objective low-subjective low group had the highest score among the four groups. Although the mean DPD score of the objective low-subjective high group was higher than the reference group, no statistical significance existed between the two groups. Based on the results of analysis of covariance (ANCOVA), the DPD score means of these groups increased gradually with a significant linear trend ($p = 0.005$). Then, they were adjusted for gender, marital status, chronic disease status, 2-week prevalence, alcohol use, mobile use, DASC-21 points, living spaces, and EPQ.

DISCUSSION

This study observed the association between SES and DPD among the elderly. We found that the levels of objective SES were negatively associated with the DPD scores by logistic regression.

TABLE 1 | Demographic characteristics of the study participants by sex in the study.

Variables	Men (*N* = 486)		Women (*N* = 731)	
	n	%	*n*	%
Age (year)				
60–69	275	56.6	462	63.2
70–79	186	38.3	223	30.5
≥80	25	5,1	46	6.3
Education (year)				
0–6	248	51.0	412	56.3
7–9	132	27.2	173	23.7
10–12	61	12.5	95	13.0
≥13	45	9.3	51	7.0
Marital status				
Non-married	44	9.1	183	25.0
Married	442	90.9	548	75.0
Smoking status				
Yes	147	30.2	7	1.0
No	339	69.8	724	99.0
Alcohol use				
Yes	207	42.6	70	9.6
No	279	57.4	661	90.4
Physical activity				
Yes	214	44.0	391	53.5
No	272	56.0	340	46.5
Individual income				
¥ 0–1,999	232	47.7	317	43.4
¥ 2,000–3,999	125	25.7	290	39.7
¥ 4,000–5,999	84	17.3	91	12.4
¥ 6,000 and over	45	9.3	33	4.5
Chronic disease status				
Yes	353	72.6	505	69.1
No	133	27.4	226	30.9
Measured variables (Mean, SD)				
Dependency scores	42.9	11.05	42.1	12.9
SES scores	4.3	2.6	4.1	2.49
GDS-15 scores	2.9	2.9	3.1	3.1
EPQ scores	45.7	8.7	46.2	9.8
DASC-21 scores	27.5	6.3	28.5	7.1

SES, Socioeconomic Status; GDS, Geriatric Depression Scale; EPQ, Eysenck Personality Questionnaire; DASC-21, Dementia Assessment Sheet for Community-based Integrated Care System 21-items.

TABLE 2 | The level of socioeconomic for characteristics of participants in chi-squared test.

Variables	Low SES (*N* = 724)		High SES (*N* = 493)		*P*-value
	n	%	*n*	%	
Region					
Rural	584	82.7	122	17.3	<0.001
City	140	27.4	371	72.6	
Age (year)					
60–69	418	56.7	319	43.3	0.015
≥70	306	63.7	174	36.3	
Marital status					
Non-married	151	66.5	76	33.5	0.017
Married	573	57.9	417	42.1	
Social support					
≤13	394	68.8	179	31.2	<0.001
≥14	330	51.2	314	48.8	
Timely treatment					
Yes	692	58.8	485	41.2	0.007
No	32	80.0	8	20.0	
Emergency service					
Yes	316	55.4	254	44.6	0.007
No	408	63.1	239	36.9	
GDS-15					
0–4	510	54.0	435	46.0	<0.001
≥5	214	78.7	58	21.3	
Dependency					
Yes	91	71.1	37	28.9	0.005
No	633	58.1	456	41.9	

SES, Socioeconomic Status; GDS, Geriatric Depression Scale.

Further results showed that the subjective SES was more strongly associated with DPD than objective SES.

Our results show that SES is associated with places of residence, emergency services, timely treatment, and social support. The majority of the elderly with low objective SES live in rural areas. The increased risk of DPD at a lower level of objective SES may be due to greater stress exposure and reduced resources that buffer its effects (26). Stress exposure is often invoked as important pathways linking lower objective SES to poorer health (27). At the same time, individuals with fewer social and economic resources have added difficulty in obtaining general medical care information and services, including preventive health services such as screening. Under this state of inequality, they tend to choose emergency departments and small clinics to acquire timely treatment and emergency services, thus observing dependency. A previous study has confirmed that, compared with areas with higher objective SES, areas with lower objective SES have a higher incidence of external cardiac arrest due to insufficient emergency resources, such as automatic external defibrillators, thus contributing to dependency (28). Resources include not only material resources that individuals can obtain and use but also psychosocial resources that are intangible but significant. Compared with people who are not dependent, the feeling of inequality in material and psychosocial resources among dependent people will exacerbate their dependency and drive them to rely on relevant resources to acquire support (29). Gallo et al. (30) observed a significant and moderate correlation between higher levels of objective SES and higher psychosocial resources in middle-aged Mexican American women. People with low objective SES encounter more negative life events and chronic stressors (31). The lack of coping resources, especially psychosocial resources, such as social support, will further lead to adverse effects on individuals with low objective SES (32). In addition, psychosocial resources can operate through cognitive and emotional states, such as self-efficacy and self-control, which

TABLE 3 | The odd ratios of socioeconomic status for dependency by logistic regression model.

Variables	Dependency status			
	OR	95% CI		*P*-value
Socioeconomic status (High/Low)	1.84	1.07	3.18	0.028
EPQ score	1.14	1.11	1.17	<0.001
GDS-15 (High/Low)	0.29	0.17	0.51	<0.001
Regular physical examination (No/Yes)	0.46	0.26	0.83	0.010
Age (60–69/≥70)	1.45	0.87	2.42	0.154
Gender (Male/Female)	1.42	0.84	2.38	0.188
Marital status (Non-married/Married)	0.99	0.56	1.79	0.993
Chronic disease status (No/Yes)	1.17	0.67	2.05	0.584
Social support (High/Low)	1.19	0.71	2.00	0.518
Timely treatment (No/Yes)	2.08	0.84	5.18	0.115
Regular follow-up (No/Yes)	0.93	0.58	1.50	0.755
DASC-21 score	1.01	0.98	1.05	0.442

EPQ, Eysenck Personality Questionnaire; GDS, Geriatric Depression Scale; DASC-21, Dementia Assessment Sheet for Community-based Integrated Care System 21-items.

TABLE 4 | The mean and standard error for dependency scores in different groups of SES and SSS by the analysis of covariance.

Variable categories	Dependency			
	n	*Mean*	*SE*	*P*-value
Socioeconomic status-subjective social status				
High-high	83	35.62	1.03	
Low-high	71	37.84	1.13	0.160
High-low	40	39.19	1.52	0.048
Low-low	77	39.29	1.07	0.017
	P for trend	0.005		

Adjusted for gender, marital status, chronic disease status, 2-week prevalence, alcohol use, mobile use, DASC-21 points, living spaces and EPQ. SES, Socioeconomic Status; SSS, Subjective Social Status; DASC-21, Dementia Assessment Sheet for Community-based Integrated Care System 21-items; EPQ, Eysenck Personality Questionnaire.

are inherently related to DPD (33). Social support has a protective effect on the dependency of the elderly with low levels of objective SES. Research shows that people with larger social networks are also more likely to have an active lifestyle and a better state of health. However, previous research has pointed out that the elderly in a community environment may improve positive connections with other people to reduce loneliness and increase security, which may lead to further dependency. Additional research is needed to determine the dividing point between adaptive and maladaptive dependency in the future.

The association between SES and DPD was also observed by using subjective measurement tools. Regardless of the objective SES, subjective SES has a stable association with DPD. The analysis of association between DPD and different groups of SES showed that those individuals with low objective SES and low subjective SES had the highest DPD scores. Moreover, participants with high levels of objective SES and high perceived social status had the lowest DPD scores. For those individuals with high subjective SES, no statistical significance exists between objective SES and DPD. These results suggest that subjective perceptions of SES have a stronger effect on DPD than objective measurements, and a high perceived social status can reduce the risk of DPD.

Among individuals with high subjective SES, we found that they can be characterized by better self-perceived health, better perceived financial status, and higher self-efficacy compared with their peers (results not shown), resulting in positive evaluation and higher self-satisfaction. Senectitude is a special period of life, and previous achievements and status are no longer important in this period (34). A study reported that well-adjusted elderly people are more resilient in suffering from objective status forfeiture compared with middle-aged adults (35). These individuals are able to accept positive or negative lives and have higher adaptive flexibility in coping with age-related losses and restrictions, achieving the balance between dependency and autonomy. These elderly people who are emotionally adaptive tend to have a low level of dependency. Based on the psychosocial hypothesis, psychological stress is related to adverse perception, which is detrimental to health (36). We can interpret this hypothesis as follows: the elderly people with high subjective SES can reduce DPD through the positive perception of objective conditions, which protects their mental health.

Subjective SES has a stronger correlation with DPD than objective SES, that is, subjective SES can be regarded as the "cognitive average," which includes the evaluation of education and socioeconomic factors obtained in the past and future development prospects (37). Subjective SES not only evaluates previously obtained traditional measurements, such as education, income, and occupation status, but also assesses the self-perceived esteem and social capital from others (38). Evidence suggests that the subjective assessment of SES at the individual level may be a better assessment than any objective SES indicator.

The majority of these studies focus on the association between subjective SES and health. To the best of our knowledge, few studies have explored the association between subjective SES and DPD. We attempt to clarify the association between subjective SES and DPD by the perception of position in the social hierarchy. This perception will generate cognitive and emotional responses that will mediate the detriment of low subjective SES to DPD. Individuals with higher levels of dependency may be more vulnerable to negative emotions. This DPD is operated by the negative emotion and stress mechanism of psychoneurobiology (39). Given the persistent or recurring negative emotions and stress responses caused by perceived low social status, lower subjective SES may lead to higher risks of DPD (40).

The main strength of this study is that we collect comprehensive data so that we not only can explore the variables that captured our interest but also fully adjusted potential risk factors, including cognition, personality, and depression, eliminating their effect on the association between DPD and subjective and objective SES. In addition, we tested the content validity of the objective SES index to further confirm the validity of the scale. Our study also has several limitations. First, the cross-sectional research design limits us to determine the causality between the SES and DPD. Thus, the complex and changing trends of behavior factors and the risk of DPD over time cannot be evaluated. Although a significant linear trend exists in the four

categories of deterrent SES by using GLM to evaluate the DPD scores, we could not assess precisely the cause and effect between DPD and the levels of SES. In further studies, a longitudinal study design is needed to clarify possible causality. Second, owing to the limitations of the sample size of subjective SES, we still need to verify the mechanism of the association between DPD and subjective SES.

CONCLUSION

This study determined the association between poor SES and increased risk of DPD, and the results of this work represent preliminary evidence that perceived social status has a stronger association with DPD than objective SES. The effect of subjective SES on DPD is possibly associated with the perception of position in the social hierarchy. However, several questions remain unanswered and represent promising directions for future work. There is abundant room for further progress in determining the pathways of subjective SES and DPD to fully understand the complicated causality and provide targeted support strategies to reduce or delay the dependency of elderly people.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by all participants provided informed consent before participation. The study was approved by the Institutional Review Board at the School of Public Health, Zhejiang University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YP and YL were the principal investigators and involved in the study design, conception, and manuscript preparation. AA, XD, and YC performed data collection and analysis. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (2019R01007) and in part by the Key Laboratory of Intelligent Preventive Medicine of Zhejiang Province (2020E10004).

ACKNOWLEDGMENTS

We thank Xia Gao, Songsong Han, Dongbin Hu, and Xuanting Liu for their assistance with survey setup.

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ORIGINAL RESEARCH
published: 05 July 2022
doi: 10.3389/fpsyt.2022.944154

Association of Dietary Inflammatory Index With Depression and Suicidal Ideation in Older Adult: Results From the National Health and Nutrition Examination Surveys 2005–2018

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

Received: *14 May 2022*
Accepted: *09 June 2022*
Published: *05 July 2022*

Citation:
Xiao Y and Huang W (2022) Association of Dietary Inflammatory Index With Depression and Suicidal Ideation in Older Adult: Results From the National Health and Nutrition Examination Surveys 2005–2018. Front. Psychiatry 13:944154. doi: 10.3389/fpsyt.2022.944154

Background: The relationship between diet and psychological disorders in older adults has attracted considerable attention as the global trend of aging. This study examines the relationship between Dietary inflammatory index (DII) and the risk of depression and suicide in older adults using the National Health and Nutrition Examination Survey (NHANES) as a large cross-sectional study.

Methods: The data were extracted from NHANES from 2005 to 2018, and cross-sectional studies were conducted on older adults (age $\geq$ 60 years). According to their median DII, participants were classified into High-DII (DII $\geq$ 1.23) and Low-DII (DII $<$ 1.23) groups. Depression was the primary outcome, and suicidal ideation was a secondary outcome. Utilizing multi-factor logistic regression to correlate DII with outcomes.

Results: There were 10,956 elderly participants included in the analysis. In comparison to Low-DII group, High-DII group exhibited a higher rate of depression (8.9% vs. 6.7%; $P < 0.001$) and higher ideation to commit suicide (3.7% vs. 3.0%; $P = 0.039$). Moreover, in terms of gender ratio, men accounted for 44% of the High-DII group, which was significantly lower than 56.2% of the Low-DII group ($P < 0.001$). Furthermore, logistic regression revealed that High-DII group had a higher risk of depression in the previous 2 weeks (OR = 1.358, 95% CI: 1.180–1.564; $P < 0.001$) and a higher risk of suicidal ideation (OR = 1.244, 95% CI: 1.010–1.532; $P = 0.040$). Additionally, after adjusting for demographic covariates such as age, gender and race, High-DII group still had a higher risk of depression (OR = 1.293, 95% CI: 1.121–1.493; $P < 0.001$) and suicidal ideation (OR = 1.261, 95% CI: 1.021–1.55; $P = 0.031$). Furthermore, after adjusting for various covariates like demographic, social factors, and comorbidities, the High-DII group remained at higher risk for depression (OR = 1.178, 95% CI: 1.019–1.363; $P = 0.027$), and the risk of comorbid suicidal ideation remained high (OR = 1.136, 95% CI: 0.917–1.408), but the difference was not significant ($P = 0.243$).

Conclusion: In older adults, high levels of DII are associated with depression and suicidal ideation. Multiple factors affect the mental health of older adults, and it is unknown to what extent a pro-inflammatory diet contributes to depression and suicidal thoughts in older adults. Nonetheless, daily dietary management in older adults should be emphasized.

Keywords: Dietary inflammatory index, depression, suicide ideation, older adults, NHANES

INTRODUCTION

The mental health of the elderly is gradually becoming a critical global public health issue as the global aging trend develops. As of 2013, nearly 10% of the world's population (approximately 615 million) suffers from a psychiatric disorder, with more than 20% of the older population over the age of 60 suffering from a psychiatric disorder, of which depression is one of the most common (1). Many factors, including widowhood, living alone, reduced intergenerational communication, declining physical function, and various chronic diseases, are increasing the elderly's mental health risks, seriously impacting their daily lives, and lowering their quality of life in their later years (2, 3). The most frequent mental illness in the elderly is depression (4). Research conducted in Germany (5). According to a population-based survey, it is reported that 28.7% of older adults had depressive symptoms, among them, 6.6% were severe depression, and the older the person, the higher the prevalence of depressive symptoms. Another study (6) conducted in Greece found that 34.4% of older adults had impaired cognitive functions, and 32.3% experienced depressive symptoms. In addition, a large cross-sectional study (7) from China indicated that the prevalence of somatic symptom disorders in older adults was 63.2%, significantly higher than in the non-elderly population (45.3%); similarly, the risk of depression or anxiety was 3.7 times that of the general population. Furthermore, patients with chronic depressive symptoms are prone to suicidal thoughts, with up to 15% of depressed patients reportedly preferring suicide ideation (8).

There is research evidence that depression is significantly associated with chronic systemic inflammation (9). Chronic inflammation can mediate a permanent reorganization of inflammatory neurotransmitter pathways, resulting in the transition from acute to chronic pain and promoting depression, anxiety, and sleep disturbances (10–12). The association between diet and chronic systemic inflammation is quite close, and an inappropriate dietary structure or pattern is a significant source of chronic systemic inflammation in the organism (13). Dietary inflammatory index (DII) is a novel tool for assessing the subversive potential of the diet and the amount of pro-inflammatory food components in an individual's dietary composition (14). DII is strongly associated with mental illness, compared to controls, patients with schizophrenia appeared to have higher DII scores (1.99 ± 1.39 vs. 1.60 ± 1.38; $P = 0.009$), and each unit increase in DII score was associated with a 62% increase in the odds of developing schizophrenia (OR = 1.62; 95% CI 1.17–2.26) (14). Chronic systemic inflammation can significantly increase with high levels of DII (15). Several studies (16, 17) have found that pro-inflammatory dietary patterns are significantly associated with an elevated risk of depression in adults, as high levels of DII increase the risk of depressive symptoms. Nonetheless, these studies have been limited to specialized populations, like medical personnel. However, these were only single-center studies on specific people, such as medical personnel (18). Furthermore, the relationship between suicide and DII has not been clarified.

There is a scarcity of direct and robust evidence between DII to an increased risk of depression and suicide in the elderly population. Data from large-scale demographic surveys are still required, given the potential economic burden and adverse effects of psychological disorders in older adults on an individual and societal level and the guiding significance of a rational daily dietary pattern. It is essential to investigate the relationship between psychological disorders and nutritional habits in the elderly, emphasizing daily dietary interventions.

Abbreviations: DII, dietary inflammatory index; NHANES, National Health and Nutrition Examination Survey; PHQ-9, patient health questionnaire-9; BMI, body mass index.

MATERIALS AND METHODS

Included Population

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey conducted by the National Center for Health Statistics and the Centers for Disease Control and Prevention, utilizing data from a nationally representative sample of the U.S. civilian population. This study's dataset was constructed using NHANES public data files from 2005 to 2018, and the study population comprised all NHANES respondents.

Dietary Inflammatory Index Evaluation and Grouping

The key exposure variable in this study was DII, and the types and amounts of food and beverages consumed by the participants in 24 h were extracted. As documented in the literature (19), DII was calculated and briefly explained as follows: DII for each nutrient or dietary ingredient = [(daily intake of that nutrient or dietary ingredient - global per capita daily intake of that nutrient or dietary ingredient)/that nutrient or dietary ingredient Standard deviation of global per capita daily intake] × inflammatory effect index of that nutrient or dietary ingredient, and the sum of DII of each nutrient or dietary ingredient was the total DII score of individual study subjects (see **Supplementary Table 1** for specific

nutrients and their inflammation indexes). According to the median DII of all included subjects, the participating population was classified into a High-DII group (DII ≥ median) and a Low-DII group (DII < median).

Outcomes

This study's primary outcome was depression. NHANES questionnaire yielded Patient Health Questionnaire-9 (PHQ-9) data. They consisted of nine clinical depression symptom items for the past 2 weeks, with scores ranging from zero to three for each item, with zero indicating no symptoms during the period, one suggesting a few days of symptoms, two showing more than half of the days with symptoms, and three describing symptoms almost every day. The cumulative PHQ-9 score was used to determine the presence and severity of clinical depressive symptoms in the previous 2 weeks. According to prior studies (20), when the total PHQ-9 score = 10, there was good sensitivity and specificity for major depression. Therefore, the study participant population with PHQ-9 < 10 was considered non-depressed patients and PHQ-9 ≥ 10 as depressed patients.

Even though the proportion of elderly suicides is relatively low compared to depressive symptoms, it is important to focus on the study of suicidal ideation in the elderly, considering that suicide is mainly secondary to severe depressive symptoms and the heavy burden on society. Consequently, suicidal ideations were chosen as the secondary outcome in this study, and item nine of the PHQ-9 (Scoring rules are in **Supplementary Table 2**) explicitly asked respondents if they had had suicidal thoughts in the past 2 weeks, which was demonstrated to be a valid predictor of future attempted or completed suicide (21).

Covariates

Covariates were chosen to influence depression-related factors that have previously been reported. Age, gender, and race, for example, were included as demographic characteristics. Social factors include education level, marital status, household income up to the poverty level, health insurance coverage, and data on everyday health-related behaviors such as smoking and alcohol consumption. In addition, medical comorbidity variables such as Body mass index (BMI), diabetes, and cancer were collected.

Data Analysis

Quantitative data were examined using the *t*-test or Analysis of Variance, and data for categorical variables were analyzed using the $\chi 2$ test for differences in cohort characteristics between exposure groups. The preliminary analysis employed multi-factor logistic regression to determine the relationship between the exposure group and the outcome variable. All descriptive studies were assessed for significance using two-sided tests at the $P < 0.05$ level of energy. Eventually, a Generalized additive model was employed to test for non-linear relationships between the outcome variables and exposure factors. All data analyses were performed utilizing Empower Stats software[1] (X&Y solutions, Inc., Boston MA, United States) and R.3.5.2.[2]

RESULTS

First, initial survey data were obtained from 70,190 participants. After eliminating individuals who lacked outcome, exposure, or covariate data (with the exceptions noted above), the analysis included 10,956 older participants (**Figure 1**).

Essential Characteristics of Participants in High-Dietary Inflammatory Index and Low-Dietary Inflammatory Index Groups

All elderly subjects' median DII was calculated to be 1.23. As a result, the subjects were classified into the High-DII group (DII ≥ 1.23) and Low-DII group (DII < 1.23), with 5,478 participants in each group. **Table 1** depicts the distribution of cohort characteristics stratified by DII level. In the preliminary analysis, the average age of participants in the High DII group was (70.0 ± 7.0) years, whereas the average age of participants in the Low-DII group was (69.9 ± 7.0) years. There was no statistically significant difference between the groups ($P > 0.05$). Furthermore, regarding gender ratio, males accounted for 44% of the High-DII group, significantly lower than 56.2% of the Low-DII group ($P < 0.001$), indicating that men tend to have a lower DII. Similarly, in terms of social factors, the High-DII group had a higher proportion ratio of family income to poverty ≤ 2.9," "Married or living with a partner," and "Never married" compared to the Low-DII group ($P < 0.05$). Furthermore, the differences in BMI, hypertension, diabetes and tumor history were statistically significant ($P < 0.05$).

[1] www.empowerstats.com
[2] http://www.R-project.org

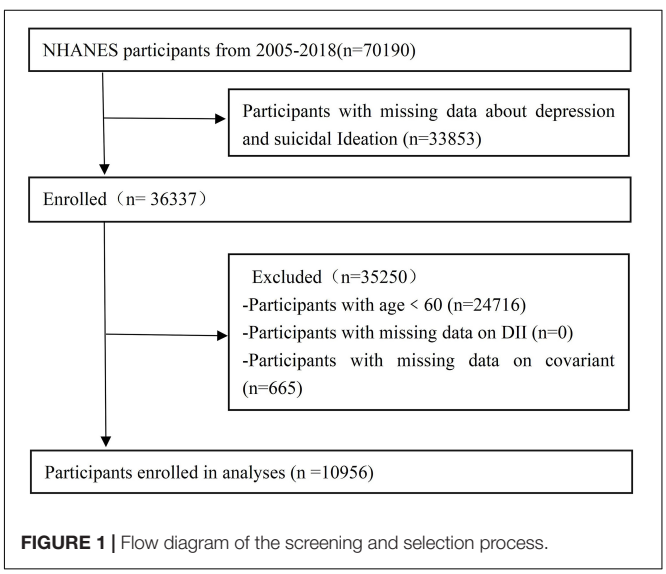

FIGURE 1 | Flow diagram of the screening and selection process.

TABLE 1 | Characteristics of participants enrolled in the study from the NHANES (2005 to 2018).

Characteristic	Low-DII (DII < 1.23, *N* = 5,478)	High-DII (DII ≥ 1.23, *N* = 5,478)	*P*-value
Age (y)	69.9 ± 7.0	70.0 ± 7.0	0.587
Male sex	3080 (56.2)	2413 (44.0)	<0.001
Race			<0.001
Hispanic	3353 (61.2)	3183 (58.1)	
Non-Hispanic white	707 (12.9)	682 (12.4)	
Non-Hispanic black	928 (16.9)	1288 (23.5)	
Other	490 (8.9)	325 (5.9)	
Education beyond high school	4100 (74.8)	3603 (65.8)	<0.001
Marital status			<0.001
Never married	253 (4.6)	282 (5.1)	
Married or living with partner	3405 (62.2)	3006 (54.9)	
Divorced, separated, or widowed	1820 (33.2)	2190 (40.0)	
Ratio of family income to poverty level			<0.001
<1.0	1229 (22.4)	1490 (27.2)	
1.0∼2.9	2200 (40.2)	2523 (46.1)	
≥3	2049 (37.4)	1465 (26.7)	
Health insurance coverage	5099 (93.1)	4987 (91.0)	<0.001
BMI (kg/m2)			<0.001
<25	1517 (27.7)	1322 (24.1)	
25∼29	2004 (36.6)	1938 (35.4)	
≥30	1957 (35.7)	2218 (40.5)	
eGFR, ml/min per 1.73 m^2	75.0 ± 18.4	74.5 ± 19.0	0.120
ALT (U/L)	23.0 ± 16.1	21.6 ± 13.7	<0.001
AST (U/L)	25.4 ± 12.0	24.9 ± 12.0	0.038
HbA1c	6.0 ± 1.1	6.1 ± 1.2	<0.001
Alcohol user	3250 (59.3)	2643 (48.2)	<0.001
Smoker	2811 (51.3)	2830 (51.7)	0.716
Hypertension	3769 (68.8)	4061 (74.1)	<0.001
Cancer	1150 (21.0)	1049 (19.1)	0.016
Diabetes	1756 (32.1)	1987 (36.3)	<0.001
Suicidal ideation	166 (3.0)	205 (3.7)	0.039
Depressed	367 (6.7)	487 (8.9)	<0.001

All values are displayed as n (%). χ^2 analysis is used to test significance between groups for categorical variables. BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated Hemoglobin, type A1C; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The Relationship Between Dietary Inflammatory Index and Depression and Suicidal Ideation

Both Depression and Suicidal Ideation Were Higher in the High-Dietary Inflammatory Index Group Than in the Low-Dietary Inflammatory Index Group Participants

The High-DII group had 487 (8.9%) participants with comorbid depression and 205 (3.7%) with comorbid suicidal ideation, while the Low-DII group had 367 (6.7%) participants with comorbid depression and 166 (3.0%) with comorbid suicidal ideation. Therefore, depression and suicidal ideation were higher in the High-DII group than in the Low-DII group, and the differences were statistically significant ($P < 0.05$).

Dietary Inflammatory Index Is a Sole Risk Factor for Depression and Suicidal Ideation

As indicated in **Table 2**, in an unadjusted multivariate logistic regression analysis, high DII was an independent risk factor for depression (OR = 1.358, 95% CI: 1.180–1.564; $P < 0.001$) and suicidal ideation (OR = 1.244, 95% CI: 1.010–1.532; $P = 0.040$) in the previous 2 weeks. After adjusting for demographic covariates like age, sex, and race, high DII was still associated with a higher risk of depression (OR = 1.293, 95% CI: 1.121–1.493; $P < 0.001$) and suicidal ideation (OR = 1.261, 95% CI: 1.021–1.55; $P = 0.031$). In addition, after adjusting for various covariates like demographic, social factors, and comorbidities, high DII remained an independent risk factor for depression (OR = 1.178, 95% CI: 1.019–1.363; $P = 0.027$). However, it was not a risk factor for suicidal ideation (OR = 1.136, 95% CI: 0.917–1.408; $P = 0.243$).

Moreover, subgroup logistic regression analyses by gender revealed that women with high DII were more likely to have comorbid suicidal ideation (OR = 1.355, 95% CI: 1.004–1.829; $P = 0.047$), while men were not (**Table 3**).

Dose-Response Relationship Between Dietary Inflammatory Index and the Risk of Depression and Suicide in the Elderly

Figure 2 depicts the dose-response relationship between DII and outcome indicators. DII was positively associated with the risk of depressive symptoms, and the overall risk of depression in older adults tended to increase progressively with increasing DII (**Figure 2A**). Similarly, the relationship between DII and the risk of comorbid suicidal ideation also increased progressively with DII levels (**Figure 2B**).

DISCUSSION

Using a nationally representative cross-sectional study of older adults, this study demonstrated a significant relationship between high levels of DII and depression in older adults

TABLE 2 | Multi-factor logistic regression analysis for associations DII high-level and outcomes.

	Depressed		Suicidal ideation	
DII high-level	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Un- adjusted	1.358 (1.180–1.564)	<0.001	1.244 (1.010–1.532)	0.040
Model 1	1.293 (1.121–1.493)	<0.001	1.261 (1.021–1.557)	0.031
Model 2	1.191 (1.030–1.377)	0.018	1.182 (0.955–1.462)	0.124
Model 3	1.178 (1.019–1.363)	0.027	1.136 (0.917–1.408)	0.243

Model 1 was adjusted for age, sex, and race.
Model 2 was adjusted for age, sex, race, education level, marital status, ratio of family income to poverty level, and health insurance coverage.
Model 3 was adjusted for age, sex, race, education level, marital status, family income to poverty level, health insurance coverage, BMI, smoker, alcohol user, hypertension, cancer, and diabetes.

TABLE 3 | Subgroup multi-factor logistic regression analysis for the association between DII high-level and outcomes.

	Depressed			Suicidal ideation		
	OR (95%CI)	***P*-value**	**Interaction *P*-value**	**OR (95%CI)**	***P*-value**	**Interaction *P*-value**
Sex			0.374			0.409
Female	1.219 (1.013–1.467)	0.036		1.355 (1.004–1.829)	0.047	
Male	1.399 (1.123–1.744)	0.003		1.135 (0.843–1.527)	0.403	
BMI			0.306			0.237
<25	1.372 (1.022–1.842)	0.035		1.316 (0.872–1.987)	0.192	
25∼29	1.549 (1.189–2.020)	0.001		1.520 (1.058–2.184)	0.023	
≥30	1.196 (0.976–1.466)	0.084		1.007 (0.728–1.393)	0.967	
Alcohol user			0.277			0.558
Yes	1.145 (1.147–1.747)	0.001		1.283 (0.945–1.743)	0.110	
No	1.028 (0.998–1.463)	0.053		1.132 (0.851–1.507)	0.394	
Smoker			0.606			0.410
Yes	1.315 (1.092–1.585)	0.004		1.160 (0.889–1.512)	0.274	
No	1.418 (1.142–1.760)	0.002		1.389 (0.991–1.946)	0.057	
Hypertension			0.833			0.217
Yes	1.328 (1.130–1.562)	<0.001		1.143 (0.898–1.455)	0.278	
No	1.376 (1.031–1.838)	0.030		1.542 (1.022–2.327)	0.039	
Cancer			0.421			0.786
Yes	1.530 (1.105–2.118)	0.010		1.184 (0.767–1.828)	0.445	
No	1.319 (1.128–1.543)	<0.001		1.268 (1.000–1.608)	0.050	
Diabetes			0.878			0.599
Yes	1.343 (1.088–1.657)	0.006		1.306 (0.946–1.803)	0.104	
No	1.313 (1.084–1.590)	0.005		1.166 (0.887–1.534)	0.271	

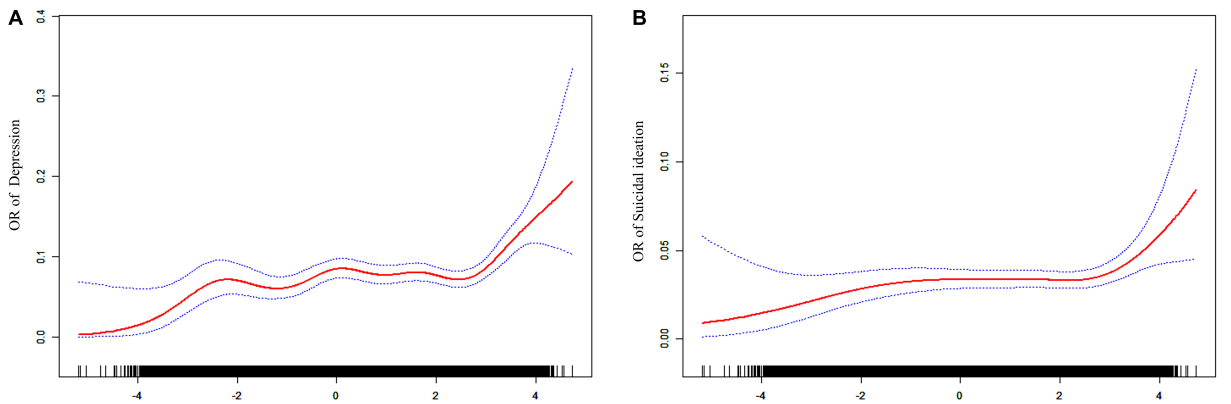

FIGURE 2 | Dose-response association between **(A,B)** OR of depression and suicidal ideation and DII (adjusted for age, sex, race, smoker, alcohol user, glucocorticoid user, hypertension, cancer, and diabetes).

and a relationship with suicidal ideation in the past 2 weeks.

These outcomes are consistent with earlier studies (16) on the relationship between diet and depression; a high intake of pro-inflammatory foods significantly increases the risk of depressive symptoms. Those at the highest risk for depression had significantly lower consumption of meat, fish, and eggs, higher consumption of added sugars, and relatively lower consumption of fruits, vegetables, and fiber (16, 18). Furthermore, a study of medical personnel (18) found a significant positive correlation between high PHQ-9 scores and high DII levels when gender, psychiatric diagnosis, physical activity, and mental exercise were all taken into account ($P < 0.01$). Another study (22) of residential female undergraduates discovered that higher DII was significantly associated with an increased likelihood of stress symptoms (OR = 1.41, 95% CI: 1.12–1.77; $P = 0.003$) and anxiety symptoms (OR = 1.35, 95% CI: 1.07–1.69; $P = 0.01$). The relationship between dietary patterns and depression remains significant, and strong epidemiological evidence proposes that poor diet may hurt mental health disorders (23). However, after adjusting for marriage, education, and family poverty to income ratios, the significance of DII concerning the risk of suicide in

older patients decreased significantly. Diet may have a lesser impact on suicidal ideation than social factors. Indeed, according to earlier surveys, unhappy marriages, inadequate education, and economic poverty are significant social factors contributing to older adults' suicide (24, 25).

Furthermore, our gender stratification results indicate that both men and women in the High-DII group are at higher risk of developing depression than those in the Low-DII group. Women with high DII are more likely to experience suicidal ideation. The differential results for suicidal ideation may be driven primarily by the female population. Although women generally have lower rates of committing suicide than men, they have higher suicidal ideation and attempt rates, especially in women over the age of 75 (26). This could be related to the unstable nature of the female elderly, who are emotional in situations and have weak resistance to stress and a relative lack of social support. When confronted with unexpected situations, they are more prone to depression and anxiety symptoms (27, 28).

In short, the relationship between diet and mental health is complicated. Even though our observational studies reveal that high levels of DII may be related to depressive mood and suicidal ideation, there are many biological, psychological and social factors involved. As the global trend of population aging develops, numerous aspects of demographic changes increase socioeconomic pressures, and declining somatic functionality further complicates the discussion linked to mental health in the elderly population. The previous study has focused on the association between social factors and mental health in older adults.

However, there are some limitations of the present work. First, it is difficult to elaborate on the causal relationship between an inflammatory diet and depression/suicide in the present cross-sectional study. Because the NHANES study collected data at a single time point, nutritional data were recorded only once for all participants, and PHQ-9 scores, as well as suicidal ideation questionnaires, were measured only once, which resulted in some possible bias in DII scores and PHQ-9 scores. In addition, this study may also have overlooked some relevant factors that influence depression/suicidal ideation in older adults, such as the presence of major life changes, chronic pain, family atmosphere, etc. Therefore, in the future, we need to conduct a multicenter longitudinal clinical trial to confirm our findings, dynamically assess changes in each of the factors that may influence depression/suicidal ideation in older adults, and conduct a long follow-up to investigate how inflammatory diet specifically affects the onset and progression of depression in older adults.

Nonetheless, studies of dietary patterns and cognitive problems in older adults are scarce and primarily single-centered with small sample sizes. As our understanding of the factors influencing mental health in the elderly population improves, we should carefully evaluate dietary patterns' long-term benefits and harms to mental disease in future studies and develop appropriate nutritional patterns for the elderly.

CONCLUSION

By analyzing a nationally representative sample, we discovered that high levels of DII were related to moderate to severe clinical depression and suicidal ideation in older adults. This relationship is complicated, and further studies are required to understand it fully. However, the extent to which a pro-inflammatory diet leads to significant depressive symptoms and suicidal ideation is complicated and requires further research to demonstrate this relationship.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

ETHICS STATEMENT

Before being interviewed or examined, all survey participants provided informed consent, and the NCHS Ethics Review Board approved the data collection protocol.

AUTHOR CONTRIBUTIONS

YX and WH carried out the acquisition and interpretation of data and was the major contributor to drafting the manuscript and participated in drawing tables and diagrams. YX carried out the clinical data collection and analysis. WH contributed to the ideas of the article and reviewed the manuscript. Both authors provided final approval for publishing the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.944154/full#supplementary-material

Supplementary Table 1 | Forty five nutrients included in DII calculation.

Supplementary Table 2 | PHQ-9 score.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 09 September 2022
DOI 10.3389/fpsyt.2022.1003810

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

RECEIVED 26 July 2022
ACCEPTED 23 August 2022
PUBLISHED 09 September 2022

CITATION
Zhu X-M, Xu Y-M, Wang Z-Q and Zhong B-L (2022) Prevalence and correlates of suicidal ideation among older adults attending primary care clinics in Wuhan, China: A multicenter cross-sectional study.
Front. Psychiatry 13:1003810.
doi: 10.3389/fpsyt.2022.1003810

Prevalence and correlates of suicidal ideation among older adults attending primary care clinics in Wuhan, China: A multicenter cross-sectional study

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Background: Primary care represents an ideal setting for screening for and managing suicidal older adults but the clinical epidemiology of suicidal ideation in Chinese older primary care patients remains unclear. This study investigated the prevalence and correlates of suicidal ideation in older Chinese adults receiving primary care.

Methods: This multicenter cross-sectional survey included a total of 769 older adults (≥65 years) from seven urban and six rural primary care clinics in Wuhan, China. The presence of depressive symptoms and suicidal ideation was assessed with the Geriatric Depression Scale and a single-item question "In the past 12 months, did you think about ending your life?," respectively.

Results: The 12-month prevalence of suicidal ideation in older primary care patients was 16.6%. Significant correlates of suicidal ideation were poor economic status (vs. good, OR = 2.80, $P = 0.008$), heart disease (OR = 2.48, $P = 0.005$), chronic gastric ulcer (OR = 3.55, $P = 0.012$), arthritis (OR = 2.10, $P = 0.042$), and depressive symptoms (OR = 11.29, $P < 0.001$).

Conclusions: Suicidal ideation is common among older adults attending Chinese primary care clinics. It is necessary to integrate psychological crisis intervention into primary care to prevent late-life suicide.

KEYWORDS

older adults, primary care, suicidal ideation, cross-sectional survey, China

Introduction

Despite the declining time-trend in national elderly suicide rates in recent decades, suicide in older adults remains a significant public health concern in China because of its higher elderly suicide rate compared to most major East Asian and Western countries/regions, largest number of older adults in the world, and rapid increase of

aging population (1–6). Given the complexity of late-life suicide, a multi sectoral suicide prevention strategy is needed for effective suicide prevention in older adults (7–9).

In Western countries, Hong Kong SAR, and mainland China, as high as 60–80% of the older suicide completers visited their primary care physicians (PCPs) in the preceding month before committing suicide (10–13). Given the wide availability of primary care services and the frequent contacts between PCPs and older adults, primary care represents an ideal setting for screening for and managing suicidal older adults (14–16). Accordingly, one essential component of the national strategies for suicide prevention of most countries in the world, as recommended by the World Health Organization, is to provide and maintain gatekeeper training programs to PCPs to improve their capacity to identify persons who are at-risk of suicide and refer them to mental health specialists when necessary (7).

To facilitate the timely detection, suicide risk assessment, and early initiation of the intervention of suicidal older adults in primary care settings, it is necessary to understand the clinical epidemiology of suicidal behaviors in older primary care patients. Until now, suicidal behaviors, in particular suicidal ideation, have been extensively studied in older primary care adults in Western countries (17–23). These studies assessed the presence of suicidal ideation with various instruments (i.e., suicidality subscale of the Depressive Symptom Inventory and suicidal item of the nine-item Patient Health Questionnaire) and reported a wide range of prevalence estimates (0.7–23.3%) (18, 21, 23). A variety of factors were found to be significantly associated with suicidal ideation in this population, including male sex, living alone, financial strain, family history of suicide, depressive symptoms, pain, and poor physical health (17, 18, 23).

Findings from psychological autopsy studies in both Western countries and China have reported the greater risk of suicide in older adults with physical illnesses (24, 25); for example, congestive heart failure, chronic obstructive lung disease (COPD), seizure disorder, and urinary incontinence are associated with 1.7-, 1.6-, 3.0-, and 2.0-fold increases in odds of suicide in older adults, respectively. However, one significant knowledge gap of the above studies is that few data are available regarding the risk of suicidal behaviors in older primary care patients according to physical conditions, which may help the identification of high-risk subgroups in this physically ill population. In addition, accumulating empirical evidence has shown the important role of social disconnectedness-related factors in the etiology of later-life suicide, which are potentially modifiable and include lack of close friends, living alone, feelings of loneliness, no trusted friends, insufficient number family relatives, and inadequate social support (12, 26–30). Nevertheless, few prior studies have examined the contributions of these factors to suicidal behaviors in older primary care patients.

Although suicidal ideation is less prevalent in old age-group than younger age-groups, older adults, once they have suicidal thoughts, are more likely to commit suicide with greater suicidal intention and by using more immediately lethal means (1, 31–34). These data suggest that screening for suicidal ideation is the first essential step toward effective prevention of late-life suicide. However, to the best of our knowledge, few studies have investigated the clinical epidemiology of suicidal ideation in older adults undergoing primary care services in China. This study filled the above-mentioned knowledge gaps by investigating the prevalence of suicidal ideation and its associated factors in older primary care patients in Wuhan, the largest city in Hubei province and the most populous city in Central China (35). Factors to be examined included major medical conditions and some social disconnectedness-related factors.

Methods

Sampling and subjects

Subjects were 791 older adults who were consecutively recruited from 13 district-center public primary care clinics (seven urban and six rural) in Wuhan, 65 years old or over, receiving outpatient treatment at these selected clinics during the survey period from October 2015 to November 2016, and voluntary to participate in this study. Details of the sampling and subject inclusion have been described elsewhere (14, 36–38). Wuhan has 13 districts: seven urban and six rural. Considering the geographic representativeness of the study sample, we purposively selected one primary care clinic from each district, which was located in or nearest to the center of the most populous area of the district.

Prior to the formal study, the survey protocol was approved by the Institutional Review Board of Wuhan Mental Health Center (approval number: WMHC-IRB-S065). All subjects and their guardians (if necessary) provided informed consent before the interview.

Procedures and instruments

Trained PCPs collected the questionnaire data *via* face-to-face interviews with the older primary care patients. Demographic factors in the questionnaire included sex, age, educational attainment, marital status, self-rated economic status (good, fair, poor), main occupation engaged in before the older adulthood (physical vs. mental), and current residence place (urban vs. rural).

Lifestyle factors included currently smoking and the habit of regular physical activity (36). We used a checklist to assess the presence of 11 major medical conditions and two sensory impairments: hypertension, diabetes, heart diseases, stroke and other cerebrovascular diseases, COPD, tuberculosis, chronic

gastric ulcer, Parkinson's disease, anemia, hepatitis cirrhosis, arthritis, hearing impairment, and vision impairment. Hearing impairment was present if the interviewer must speak more loudly than normal to let the patients know what the interviewer was saying, while vision impairment was present if the patient endorsed having difficulties in watching movies or TV shows (32, 36).

Social disconnectedness-related factors included number of living adult children, the status of living alone, feelings of loneliness, self-rated relationship with family members (good, fair, poor), and self-rated relationship with non-family associates (good, fair, poor). A single-item question was used to assess feelings of loneliness: "How often do you feel lonely?" with five response options: always, often, sometimes, seldom, and never. Respondents who reported felt lonely at least sometimes were those having feelings of loneliness (38).

Depressive symptoms were evaluated with validated Chinese version of the Geriatric Depression Scale with a total score of five or greater denoting clinically significant depressive symptoms (37, 39). One-year suicidal ideation was assessed with a single question "In the past 12 months, did you think about ending your life?"(40).

Statistical analysis

Prevalence of suicidal ideation was calculated. Chi-square test was used to compare rates of suicidal ideation between/across subgroups according to demographic and other characteristics. Unconditional binary logistic regression was used to identify correlates of suicidal ideation, which included all significant factors from the Chi-square test as the independent variables and employed backward elimination to select the final set of correlates. Associations between correlates and suicidal ideation were measured by using Odds Ratios (ORs) and their 95% confidence intervals (95% CIs). SPSS software, version 16.0, was used for analyzing the data. A two-sided $P < 0.05$ was defined as statistically significant.

Results

In total, 791 older primary care adults were invited to join the study and 769 completed the survey questionnaire. Reasons for non-completion of the survey included: refusal to join in the survey ($n = 10$), very severe cognitive impairment ($n = 5$), the withdrawal of informed consent ($n = 6$), and missing data on variables of interest ($n = 1$). The average age of the study sample was 72.9 years (standard deviation = 6.1, range = 65–97) and 414 (53.8%) were women. Table 1 displays the characteristics of the survey sample and prevalence rates of suicidal ideation by sample characteristics.

Altogether, 128 older adults endorsed suicidal ideation during the past year and the corresponding 1-year prevalence of suicidal ideation was 16.6%.

Results from Chi-square test (Table 1) show that significantly higher rates of suicidal ideation were observed in illiterate respondents (vs. middle school and above), in respondents with poor economic status (vs. good), in respondents who engaged in physical labor (vs. mental labor) before the older adulthood, in respondents suffering heart disease (vs. no), in respondents suffering stroke and other cerebrovascular diseases (vs. no), in respondents suffering chronic gastric ulcer (vs. no), in respondents suffering arthritis (vs. no), in respondents with fair and poor family relationship (vs. good), in respondents having feelings of loneliness (vs. no), and in respondents having depressive symptoms (vs. no).

Multiple logistic regression analysis identified five factors significantly associated with suicidal ideation in older primary care patients (Table 2): poor economic status (vs. good, OR = 2.80, $P = 0.008$), heart disease (OR = 2.48, $P = 0.005$), chronic gastric ulcer (OR = 3.55, $P = 0.012$), arthritis (OR = 2.10, $P = 0.042$), and depressive symptoms (OR = 11.29, $P < 0.001$).

Discussion

Given the limited mental health service and crisis intervention resources in China, empirical data on the clinical epidemiology of suicidal ideation in older primary care patients would inform the development of late-life suicide prevention programs in Chinese primary care settings. To the best of our knowledge, this is the first study in China that examined the prevalence and correlates of suicidal ideation among older Chinese adults receiving primary care. The main findings of this study are the 16.6% prevalence of 1-year suicidal ideation and its significant associations with poor economic status, heart disease, chronic gastric ulcer, arthritis, and depressive symptoms.

Compared to the 2.6 and 5.7% prevalence of 1-year suicidal ideation in urban and rural community-residing older Chinese adults, respectively (41, 42), our study found a much higher prevalence of suicidal ideation in older primary care adults in China. The high risk of suicidal ideation in older Chinese adults attending primary care clinics should be primarily due to their prevailing physical health problems, because poor physical health has been associated with poor mental health, i.e., acute stress caused by the fracture and post-stroke depression, which in turn results in the elevated risk of suicidal behaviors (1, 14, 24, 25). Further, there is evidence that the treatment rate of major depression in older adults receiving primary care in China is extremely low, <1% (43). Therefore, the much higher prevalence of suicidal ideation might be the result of untreated late-life depression in primary care settings in China.

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TABLE 1 Characteristics of the sample of older primary care patients and prevalence rates of suicidal ideation by sample characteristics.

	Characteristics	No. of older adults	No. of older adults with suicidal ideation	Prevalence (%)	χ^2	*P*-value
Sex	Male	355	56	15.8	0.360	0.548
	Female	414	72	17.4		
Age (years)	65–74	493	85	17.2	0.352	0.553
	75+	276	43	15.6		
Education	Illiterate	181	43	23.8	10.944	0.004
	Primary school	217	38	17.5		
	Middle school and above	371	47	12.7		
Marital status	Married	534	87	16.3	0.157	0.692
	Others*	235	41	17.4		
Self-rated financial status	Good	137	18	13.1	33.770	<0.001
	Fair	543	76	14.0		
	Poor	89	34	38.2		
Main occupation before older adulthood	Mental labor	223	26	11.7	5.627	0.018
	Manual labor	546	102	18.7		
Residence place	Urban	414	63	15.2	1.317	0.251
	Rural	355	65	18.3		
Current smoking	No	647	109	16.8	0.120	0.729
	Yes	122	19	15.6		
Regular physical activity	No	438	66	15.1	1.823	0.177
	Yes	331	62	18.7		
Hypertension	No	397	65	16.4	0.044	0.834
	Yes	372	63	16.9		
Diabetes	No	653	104	15.9	1.611	0.204
	Yes	116	24	20.7		
Heart disease	No	688	105	15.3	9.009	0.003
	Yes	81	23	28.4		
Stroke and other cerebrovascular diseases	No	705	110	15.6	6.631	0.010
	Yes	64	18	28.1		
Chronic obstructive pulmonary disease	No	724	120	16.6	0.044	0.833
	Yes	45	8	17.8		
Cancer	No	764	127	16.6	0.041	0.840
	Yes	5	1	20.0		
Tuberculosis	No	767	127	16.6	1.608	0.205
	Yes	2	1	50.0		
Chronic gastric ulcer	No	744	119	16.0	6.977	0.008
	Yes	25	9	36.0		
Parkinson's disease	No	764	126	16.5	1.979	0.160
	Yes	5	2	40.0		

(Continued)

10.3389/fpsyt.2022.1003810

TABLE 1 (Continued)

	Characteristics	No. of older adults	No. of older adults with suicidal ideation	Prevalence (%)	χ^2	*P*-value
Anemia	No	761	126	16.6	0.407	0.524
	Yes	8	2	25.0		
Hepatitis cirrhosis	No	767	127	16.6	1.608	0.205
	Yes	2	1	50.0		
Arthritis	No	709	110	15.5	8.366	0.004
	Yes	60	18	30.0		
Hearing impairment	No	739	125	16.9	0.994	0.319
	Yes	30	3	10.0		
Vision impairment	No	692	112	16.2	1.054	0.305
	Yes	77	16	20.8		
Self-rated family relationship	Good	605	86	14.2	12.075	0.001
	Fair and poor**	164	42	25.6		
Self-rated non-family relationship	Good	535	82	15.3	2.201	0.138
	Fair and poor**	234	46	19.7		
Feelings of loneliness	No	566	67	11.8	35.717	<0.001
	Yes	203	61	30.0		
Living alone	No	686	116	16.9	0.321	0.571
	Yes	83	12	14.5		
Number of living adult children	0	20	6	30.0	3.807	0.283
	1	87	17	19.5		
	2	233	34	14.6		
	3+	429	71	16.6		
Depressive symptoms	No	531	30	5.6	149.5	<0.001
	Yes	238	98	41.2		

*"Others" included never married, separated, divorced, widowed, cohabitating, and remarried.
**Because of the very small numbers of the category of "poor" relationship ($n < 10$), "poor" and "fair" were merged into one category.

In line with earlier studies (17, 18, 23, 40, 44), we confirmed significant associations between poor financial status, depressive symptoms, and suicidal ideation in Chinese older primary care patients. Nevertheless, this study did not find significant associations of suicidal ideation with disconnectedness-related factors in the final step of multiple logistic regression model despite significant associations between fair and poor family relationship and feelings of loneliness and suicidal ideation in the Chi-square test. We speculate that this does not indicate that disconnectedness-related factors did not contribute to suicidal ideation; rather, the effects of these factors may be relative weak and be masked by the prevailing physical health problems of this population.

The elevated risk of suicidal ideation in individuals with heart disease, peptic ulcers, and arthritis in the general population has been previously reported (45–47). Because depression can be viewed as an antecedent for suicidal ideation and these chronic diseases have been associated with depression (45, 48, 49), our findings on the three major medical conditions as significant correlates of suicidal ideation are expected. Nevertheless, it seems that depression is not the only bridge that links major medical conditions and suicidal ideation together because both depressive symptoms and major medical conditions were significant and independent correlates in the final regression model. We speculated that major medical conditions might increase the risk of suicidal ideation *via* other pathways such as pain and psychological distress.

The main limitation of this study is the methodology of cross-sectional survey, which cannot ascertain the causality between identified correlates and suicidal ideation. The second limitation is no assessment of the mental health-help seeking behaviors of suicidal older adults, which is essential for the

TABLE 2 Correlates of suicidal ideation in older primary care patients.

Factor	Risk level	Reference level	Co-efficient	Standard error	χ^2	*P*-value	OR (95% CI)
Self-rated financial status	Poor	Good	1.028	0.389	6.982	0.008	2.80 (1.30, 5.99)
Heart disease	Yes	No	0.909	0.320	8.061	0.005	2.48 (1.33, 4.65)
Chronic gastric ulcer	Yes	No	1.265	0.505	6.275	0.012	3.55 (1.32, 9.54)
Arthritis	Yes	No	0.740	0.364	4.145	0.042	2.10 (1.03, 4.28)
Depressive symptoms	Yes	No	2.424	0.240	102.159	<0.001	11.29 (7.06, 18.07)

planning of crisis intervention in primary care settings in China. Third, some modifiable factors that are potentially associated with suicidal ideation in older adults such as pain and social support were not measured in this study.

In summary, in Chinese primary care settings, suicidal ideation is common among older patients. Given the potentially high risk of suicide in suicidal older adults, it is necessary to integrate psychological crisis intervention into primary care to prevent late-life suicide. Services in primary care settings in China should include routinely screening for older adults at-risk of suicide, suicide risk assessment, psychosocial support, antidepressant treatment, and referral to mental health specialists when necessary. In addition, the elevated risk of suicidal ideation in older adults with several major medical conditions suggests that effective management of major medical conditions should be considered as a component of the late-life suicide prevention strategy in primary care settings.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Wuhan Mental Health Center (approval number WMHC-IRB-S065). The patients/participants provided their written informed consent to participate in this study.

Author contributions

X-MZ acquisition and analysis of data for the study, drafting the paper, and interpretation of data for the study. Y-MX and Z-QW design and acquisition of data for the study. X-MZ and B-LZ drafting the paper, revising the paper for important intellectual content, and interpretation of data for the study. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by National Natural Science Foundation of China (grant number: 71774060), 2015 Irma and Paul Milstein Program for Senior Health Awards from the Milstein Medical Asian American Partnership Foundation, Wuhan Health and Family Planning Commission (grant numbers: WX17Q30, WG16A02, and WG14C24), and Suzhou Medical Talents Program from Suzhou Health Commission (grant number: GSWS2021052).

Acknowledgments

The authors thank all the research staff for their team collaboration work and all the older adults and primary healthcare physicians involved in this study for their co-operation and support.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 26 October 2022
DOI 10.3389/fpsyt.2022.939310

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

RECEIVED 09 May 2022
ACCEPTED 03 October 2022
PUBLISHED 26 October 2022

CITATION
Wang Y, Li C, Ma Y, Zheng F and Xie W (2022) Associations of physical activity participation trajectories with subsequent motor function declines and incident frailty: A population-based cohort study. *Front. Psychiatry* 13:939310. doi: 10.3389/fpsyt.2022.939310

Associations of physical activity participation trajectories with subsequent motor function declines and incident frailty: A population-based cohort study

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Background: Maintaining physical function and delaying frailty are of significant importance in both quality of life and health longevity for successful aging. The objective of this study is to investigate whether different trajectories of long-term physical activity (PA) participation are associated with subsequent motor function declines and incident frailty in middle-aged and elderly adults.

Materials and methods: Data from 8,227 aged ≥ 50 years adults enrolled in the English Longitudinal Study of Aging were analyzed. Long-term PA participation trajectories were assessed using group-based trajectory modeling over the first 6-year period from wave 1 (2002–2003) to wave 4 (2008–2009). The longitudinal associations of PA trajectories with motor function declines and incident frailty were evaluated by a linear mixed model and Cox regression model, respectively, with follow-up of 10 years from wave 4 to wave 9 (2018–2019).

Results: Five distinct trajectories of long-term PA participation were identified in the aging cohort, including persistently low-active trajectory (*N* = 2,039), increasing active trajectory (*N* = 1,711), declining active trajectory (*N* = 216), persistently moderate-active trajectory (*N* = 2,254), and persistently high-active trajectory (*N* = 2,007). Compared with the persistently low-active group, the participants in persistently moderate- and high-active groups experienced significantly decelerated grip strength decline, decreased gait speed decline, and faster chair rises after multiple-adjustment. Similarly, participants maintaining moderate- and high-active PA were also associated with a lower risk of incident frailty (multiple-adjusted hazard ratio: 0.70, 95% confidence interval: 0.62–0.80, and 0.42, 95% CI: 0.36–0.49, respectively), compared with

those with persistently low PA. Notably, the participants with the increasing active trajectory got similar health benefits as those with persistently moderate and high levels of PA.

Conclusion: In addition to persistent PA, increasing PA was linked to a slower decline in motor function and lower risk of incident frailty in the cohort. Our findings suggest that regular PA is never too late.

KEYWORDS

physical activity, trajectory, incident frailty, group-based trajectory modeling, grip strength, gait speed, chair rise

Highlights

- Trajectories of long-term participation in physical activity can be varied among middle and older adults.
- Persistently moderate-, high-active, and increasing participation in physical activity were associated with decelerated motor function decline and reduced risk of incident frailty.
- Strategies focusing on maintaining or increasing active physical activity might promote healthy aging.
- It's never too late to start or enhance regular physical activity for middle-aged and elderly adults.

Introduction

The world's population aged 60 years or older will increase from 841 million in 2013 to more than two billion by 2050 (1). The aging process is characterized by a decline in functional performance and an increase in morbidity, which, although they are two separate conditions, are both related to disability. The total sum of global years lived with disability increased from 562 million to 853 million from 1990 to 2017 (2). Impaired physical functions, such as muscle strength, balance, and gait performance deficits, are common underlying traits among disability. The transition from robustness to disability is a long-lasting, continuous and insidious process that may take years (3). A stage in the transition is referred to as frailty characterized by a decline in functioning across multiple physiological systems and accompanied by an increased vulnerability to stressors (4, 5). Frailty is multidimensional, with physical and psychosocial factors playing a part in its development, an extreme consequence of the normal aging process and dynamic, which means that an individual can fluctuate between states of severity of frailty (6). It is potentially preventable, up to a probable point of no return when it becomes a pre-death phase with profound implications for clinical practice and public health (6). Growing evidence shows that frailty increases the risks of falls, hospitalization, admission to long-term care and mortality (4, 5). In clinical practice, frailty can help clinicians identify patients who may benefit from aggressive interventions and those who might suffer harm from them (7). Together, maintaining function and delaying frailty are of significant importance in both quality of life and longevity.

Increasing evidence reports the benefits yielded by regular physical activity (PA) on the motor function in older people by preserving mobility, muscle strength, and balance (8–10). However, there is a methodological limitation that PA are evaluated at single time-point (primarily the baseline level) or short time-scales without considering the long-term dynamic nature of PA behavior. Group-based trajectory modeling (GBTM) allows grouping of subjects presenting with similar baseline values and longitudinal patterns of change according to their direction and magnitude (11). Using this method, some studies have detected different PA trajectories among older adult cohorts (12–14). Three studies examined the association of PA trajectories with mortality in older adults (15–17). One study investigated the relationship between PA trajectories with contemporaneous physical performance changes in older men (18). But, there isn't an investigation of the temporal association of long-term PA participation trajectories with subsequent motor function changes and incident frailty.

Therefore, the main objectives of this study were to investigate different trajectories of long-term PA participation over a 6-year span by the GBTM and evaluate their associations with subsequent motor function decline and incident frailty in middle-aged and elderly adults. Our hypotheses are that older adults maintaining PA over time will have a slower motor function decline and a lower risk of incident frailty compared with persistently inactive subjects or those reducing PA levels, and that increasing PA even at older ages promotes healthy aging characterized by reduced motor function decline and incident frailty.

Materials and methods

Study population

The English Longitudinal Study of Ageing (ELSA) is a biennial, ongoing prospective, nationally representative cohort study of community-based English adults aged 50 years and older, which collected data in 2002–2003 (wave 1) and follow-up assessments were conducted until 2018–2019 (wave 9). Briefly, this is a population-based prospective cohort study examining the determinants and consequences of frailty. Detailed design and methods of the study have been published previously (19).

Data from wave 1 to wave 4 (2008–2009) were analyzed to evaluate PA participation trajectories, and wave 4 to wave 9 to assess incident frailty and changes of motor function. Wave 4 was the baseline assessment of frailty and motor function. Excluded participants were those who: (1) developed frailty at wave 4; (2) failed to follow-up from wave 4 to wave 9. Participant selection process of the present study was described in **Figure 1**.

The ELSA was approved by the London Multicenter Research Ethics Committee (MREC/01/2/91). All participants provided written informed consent.

Physical activity assessments

The frequency of mild, moderate and vigorous PA was measured by self-reported questionnaire in the ELSA, with a card describing different types of activities presented for participants when being asked about these questions. Further details are provided in the **Supplementary methods**.

The scoring system for assessing PA consisted of the three-stage approach in the present study. Firstly, the frequency of participating in mild, moderate and vigorous activities was assigned a score of 1 (hardly ever or never), 2 (one to three times per month), 3 (at least once per week), respectively (20). Secondly, the standardized Z scores of assigned scores were generated by subtracting the corresponding mean and dividing by standard deviation (SD), separately. Lastly, a weighted global activity Z scores were calculated to evaluate different intensities of PA. The weights were chosen based on metabolic equivalent of tasks (MET) (21). After calculation, mild, moderate, and vigorous intensity of PA were assigned MET weights of 2.3, 4.4, and 7.2, respectively. **Supplementary Table 1** provides the detailed information for MET weights calculation that agreed with previous studies (22).

Assessment of incident frailty

The frailty index based on an accumulation of age-related deficits and was generated according to a standard procedure (23). Deficits in health were included in the frailty index in the present study if they matched the following criteria: the deficit represented multiple physiological systems; the prevalence of deficits increased with age; the deficit was not too universal in middle-age and the prevalence of the deficit should not be less than 1%.

After screening baseline data of the ELSA, 32 variables were selected to calculate the frailty index, including diseases (based on self-reports or physical measurements), disability in activities of daily living (ADL) and signs of psychological unhealthy (**Supplementary Table 2**). All variables were recoded, with "0" and "1" indicating the absence and the presence of a deficit, respectively. An additional value of "0.5" for variables with an intermediate response (e.g., "sometimes" or "suspect") was added. The frailty score was generated for each participant according to the number of deficits present in a person divided by the 32 deficits considered. The frailty score was a continuous variable ranging from 0 to 1, with greater scores indicating higher degree of frailty. The frailty score ≥ 0.25 had been proposed to indicate frailty, with reference to previous studies (6).

Assessment of motor function

Grip strength was measured three times for each hand using a Smedley dynamometer in the ELSA, and the maximum measurements were used in our analyses. The measurement method of grip strength is consistent with the recent similar study (24). In addition, some studies have found similar test-retest reliability with the mean of two or three trials and the maximum of three trials (25).

Gait speed was measured by asking the participants to walk at their usual pace and use any assistive devices at an 8 ft (2.44 m) marked course. The mean of two trails (m/s) was calculated. The method of measuring gait speed is consistent with previous research (26).

The time (in seconds) it takes to get up and sit down is known as the timed chair rise. Participants sit in a chair and cross their arms over the chest with feet resting on the floor. They were asked to stand up and sit down five times as quickly as possible without using their arms. The complete time was recorded in the five-repetition chair stand test (CS-5). According to previous research, chair rises measurement method is valid (26).

The changes in grip strength, gait speed and timed five chair rises from wave 4 to wave 9 (2002–2003 to 2018–2019) were taken as dependent variables.

Covariates

Covariates included demographic and health factors were collected at wave 4. The covariates were selected on basis

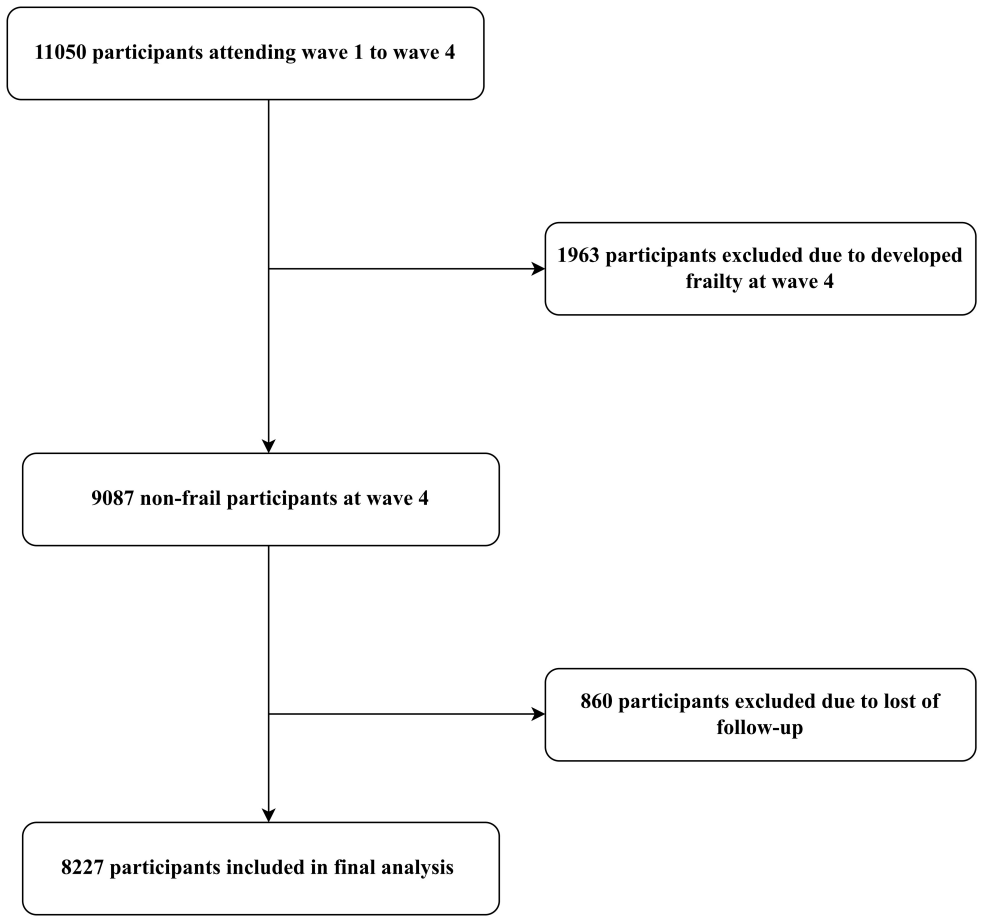

FIGURE 1
Flow chart of participants selection.

of potential cofounders known to be related with frailty and motor function, including demographic factors (age, sex, ethnicity, educational background, cohabitation status), health behaviors (current smoking, alcohol consumption, and vigorous exercise), and health condition (hypertension, diabetes, stroke, cardiovascular diseases, cancer, chronic lung diseases, depressive symptoms, functional limitations, body mass index [BMI], and physical function measurements). The detailed information of covariates was described in the **Supplementary methods**.

Statistical analysis

The GBTM was performed by the SAS Proc Traj procedure to distinguish potential trajectories of long-term PA participation based on weighted Z scores of PA across a 6-year period from waves 1 to 4 in the ELSA. The GBTM used maximum likelihood estimation to identify participants sharing similar trajectory of weighted Z scores, which can process data distributions including censored normal, Poisson and Bernoulli, and was an appropriate option when handling non-monotonic trajectories (27). Then, the most appropriate trajectory group was determined for each participant, which was included in further multivariate analysis as the independent variable. In the **Supplementary methods**, a detailed description of trajectory modeling was presented.

For the primary analysis, linear mixed models were used to assess the longitudinal associations between PA trajectories and subsequent motor function changes, with the intercept and slope of time fitted as random effects to account for inter-individual differences. Considering capability of linear mixed models in handling response data missing at random, we didn't implement imputation methods. The longitudinal association between PA trajectories and incident frailty was evaluated using proportional hazard regression (Cox regression) model. Detailed descriptions of the statistical models were provided in the **Supplementary methods**.

In addition, an exploratory analysis was performed separately in the mild, moderate and vigorous intensity PA trajectories to find out the influence of different intensity PA

on the primary results. Several sensitivity analyses were carried out to examine the robustness of the conclusions of the primary analysis. To address reverse causation, the participants who reported difficulties with daily life activities such as bathing, dressing, eating, getting in/out of bed and walking across a room were excluded, during waves 1 to 4.

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, United States). A two-tailed alpha of 0.05 was referred to as statistically significant level.

Results

Baseline characteristics

A total of 8,227 frailty-free participants from the ELSA were included in the analysis. Detailed description of participant selection was shown in Figure 1. Of the included participants, the mean age was 57.8 ± 9.2 years and 45.9% were male.

Physical activity participation trajectories from wave 1 to 4

Five trajectories of long-term PA participation based on weighted activity Z scores were identified from waves 1 to 4 of the ELSA. The five trajectories were shown in Figure 2, including: (1) persistently low-active trajectory (N = 2,039), representing low participation in PA during waves 1 to 4; (2) increasing active trajectory (N = 1,711), representing initially low participation in PA but turned to elevating afterward; (3) declining active trajectory (N = 216), representing high participation at early stages but turned to decreasing afterward; (4) persistently moderate-active trajectory (N = 2,254), representing constantly moderate participation; (5) persistently high-active trajectory (N = 2,007), representing highly participation.

Table 1 displays the baseline characteristics of the study participants by five PA trajectories. Compared with the other PA trajectory groups, participants in the persistently high-active and increasing active trajectory groups were more likely to be men, had lower BMI, frailty index and better motor function performance.

Physical activity participation trajectories and subsequent motor function changes

The longitudinal associations of the PA trajectories with subsequent motor function changes are shown in Table 2. After multiple-adjustment, the participants with persistently moderate and high PA trajectories experienced decelerated grip strength decline (β = 0.999 kg, 95% confidence interval [CI]: 0.314–1.684, P = 0.004; β = 1.334 kg, 95% CI: 0.641–2.026, $P < 0.001$), decreased gait speed decline (β = 4.655 cm/s, 95% CI: 1.582–7.727, P = 0.003; β = 7.949 cm/s, 95% CI: 4.783–11.116, $P < 0.001$), and faster chair rises (β = −0.519 s, 95% CI: −0.812 to −0.226, P = 0.001; β = −0.904 s, 95% CI: −1.199 to −0.608, $P < 0.001$) compared with participants with the persistently low-active trajectory. Notably, the increasing active trajectory was associated with subsequent motor function comprehensive improvement (grip strength: β = 1.799 kg, 95% CI: 1.009–2.589, $P < 0.001$; grip speed: β = 5.012 cm/s, 95% CI: 1.475–8.548, P = 0.005; timed five chair rises: β = −0.904 s, 95% CI: −1.199 to −0.608, $P < 0.001$), while the longitudinal associations of the declining active trajectory with motor function changes were not found.

Further analyses were conducted in the mild, moderate and vigorous intensity PA (Supplementary Table 3). Similar to global PA trajectories, five trajectories were identified for mild and moderate intensity PA, while four trajectories were identified for vigorous intensity PA, as shown in Supplementary Figures 1–3. The subgroup analyses found similar results to the global PA results, although the significant association was mainly observed in the vigorous intensity PA.

Physical activity participation trajectories and subsequent incident frailty

There were 1,866 incidents of frailty during a 10-year follow-up period, data summarized in Table 3. In contrast to subjects with the persistently low-active trajectory, participants with persistently moderate and high trajectories had a significant lower risk of incident frailty, with a multivariate-adjusted HR of 0.70 (95% CI: 0.62–0.80, $P < 0.001$) and 0.42 (95% CI: 0.36–0.49, $P < 0.001$), respectively (Table 3). Importantly, similar to the longitudinal associations of PA trajectories with motor function changes, participants with increasing active trajectory also had a significantly lower risk of incident frailty (HR = 0.60, 95% CI: 0.50–0.72, $P < 0.001$), while the association of the declining active trajectory with the risk of incident frailty was not identified (Table 3). The subgroup analyses with different intensities of PA remain generally consistent with our primary findings (Supplementary Table 4).

Sensitivity analyses

According to the sensitivity analyses that excluded participants who reported daily activities difficulties during waves 1–4, the associations of PA trajectories with motor function declines and incident frailty remained the same as those from the main analyses (Supplementary Tables 5, 6).

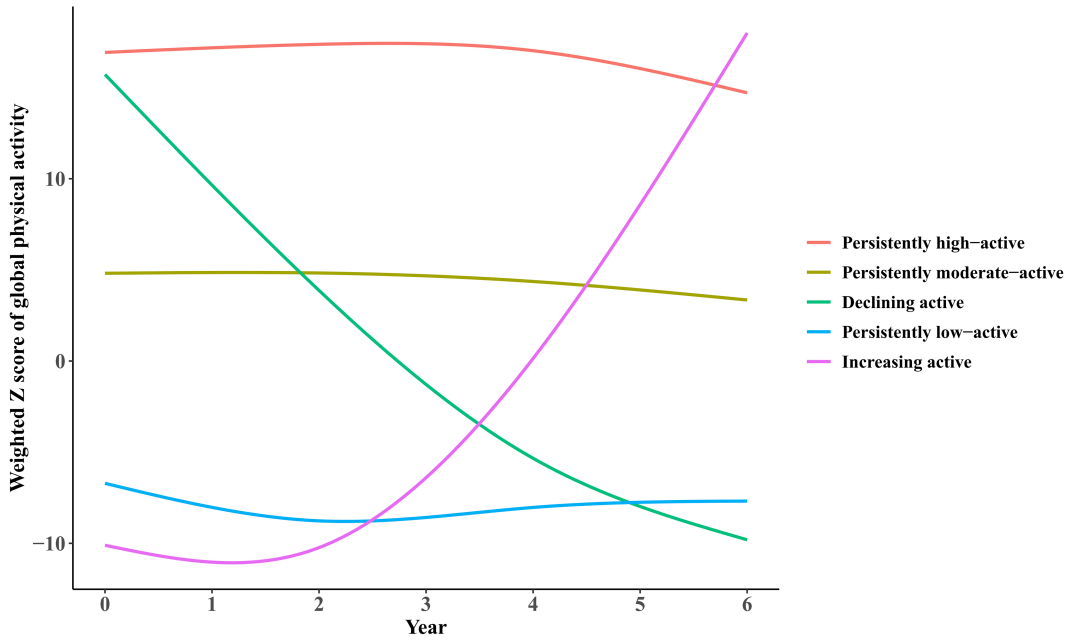

FIGURE 2
Trajectories of participation in global physical activities by participants from the ELSA over a 6-year span. (1) Persistently low-active trajectory (*N* = 2,039), representing low participation in physical activity (PA) during waves 1–4; (2) increasing active trajectory (*N* = 1,711), representing initially low participation in PA but turned to elevating afterward; (3) declining active trajectory (*N* = 216), representing high participation at early stages but turned to decreasing afterward; (4) persistently moderate-active trajectory (*N* = 2,254), representing constantly moderate participation; (5) persistently high-active trajectory (*N* = 2,007), representing highly participation.

TABLE 1 Baseline characteristics of study population according to physical activity trajectories.

Characteristics[a]	All *N* = 8,227	Increasing active *N* = 1,711	Persistently low *N* = 2,039	Declining active *N* = 216	Persistently moderate *N* = 2,254	Persistently high *N* = 2,007	*P-value*[b]
Male (%)	3,780 (45.9%)	872 (51.0%)	872 (42.8%)	90 (41.7%)	949 (42.1%)	997 (49.7%)	<0.001
Age (years)	57.8 ± 9.2	52.1 ± 7.5	56.2 ± 9.8	64.0 ± 9.6	61.6 ± 8.8	59.4 ± 7.5	<0.001
White (%)	7,945 (96.6%)	1,635 (95.6%)	1,919 (94.1%)	207 (95.8%)	2,205 (97.8%)	1,979 (98.6%)	<0.001
High level education (%)	2,810 (34.2%)	585 (34.2%)	389 (19.1%)	60 (27.8%)	779 (34.6%)	997 (49.7%)	<0.001
Living alone (%)	1,400 (17.0%)	39 (2.3%)	197 (9.7%)	64 (29.6%)	637 (28.3%)	463 (23.1%)	<0.001
Current smoking (%)	757 (9.2%)	26 (1.5%)	116 (5.7%)	36 (16.7%)	362 (16.1%)	217 (10.8%)	<0.001
Drinking ≥ once per week (%)	3,353 (40.8%)	84 (4.9%)	274 (13.4%)	125 (57.9%)	1,407 (62.4%)	1,463 (72.9%)	<0.001
Depressive symptoms (%)	496 (6.0%)	15 (0.9%)	86 (4.2%)	30 (13.9%)	245 (10.9%)	120 (6.0%)	<0.001
Hypertension (%)	2,545 (30.9%)	62 (3.6%)	329 (16.1%)	117 (54.2%)	1,156 (51.3%)	881 (43.9%)	<0.001
Diabetes (%)	209 (2.5%)	2 (0.1%)	35 (1.7%)	10 (4.6%)	101 (4.5%)	61 (3.0%)	<0.001
Stroke	91 (1.1%)	2 (0.1%)	25 (1.2%)	5 (2.3%)	39 (1.7%)	20 (1.0%)	<0.001
Cardiovascular disease (%)	353 (4.3%)	16 (0.9%)	62 (3.0%)	22 (10.2%)	153 (6.8%)	100 (5.0%)	<0.001
Chronic lung disease (%)	168 (2.0%)	6 (0.4%)	28 (1.4%)	12 (5.6%)	80 (3.5%)	42 (2.1%)	<0.001
Cancer (%)	239 (2.9%)	5 (0.3%)	27 (1.3%)	13 (6.0%)	96 (4.3%)	98 (4.9%)	<0.001
BMI (kg/m^2)	27.7 ± 4.8	27.4 ± 4.6	28.6 ± 5.3	28.2 ± 4.9	27.9 ± 4.7	27.0 ± 4.3	<0.001
Frailty index	0.07 (0.04–0.13)	0.05 (0.03–0.10)	0.10 (0.05–0.16)	0.12 (0.06–0.18)	0.08 (0.04–0.14)	0.05 (0.02–0.09)	<0.001
Grip strength (kg)	33.0 ± 11.2	36.5 ± 11.3	31.7 ± 11.3	27.9 ± 10.5	30.7 ± 10.5	34.5 ± 10.8	<0.001
Gait speed (cm/s)	98.4 ± 28.0	103.8 ± 28.7	90.3 ± 27.5	82.0 ± 23.4	95.5 ± 26.6	106.8 ± 27.4	<0.001
Timed 5 chair rises (s)	10.9 ± 3.6	9.8 ± 2.9	11.4 ± 4.0	12.4 ± 3.9	11.6 ± 3.7	10.4 ± 3.2	<0.001

[a]Data are presented as mean ± SD, *n* (%), or median (quartile 1–quartile 3). [b]*P*-value reported for differences between trajectory groups using analysis of variance, chi-square test, or Kruskal-Wallis test.

Besides, "The subgroup analyses based on gender and age range were performed. Findings in subgroup analyses were consistent with the results of previous analyses (**Supplementary Tables 8–15**)."

Discussion

By following a longitudinal cohort of 8,227 middle-aged and older adults from the ELSA, we identified five distinct trajectories of long-term PA participation over a 6-year span and observed prospective associations of PA trajectories with subsequent 10-year incident frailty and motor function performance declines, including grip strength, gait speed and timed five chair rises. Compared with those in the persistently low-active group, individuals in all other trajectories, except for those with the declining active trajectory, had slower motor function declines and a lower risk of incident frailty. Importantly, individuals with an increasing active trajectory had similar or even lower physical performance declines and risk of incident frailty than those with a persistently moderate or high active trajectory. Our findings are encouraging, not confined to participants with persistently active participation in PA, who can still gain substantial benefits in the quality of life by becoming more physically active irrespective of past physical activity levels, providing further evidence to the broad public health benefits of PA. In clinical practice, the elderly is encouraged to exercise regularly to reduce the incidence of frailty that help clinicians identify patients who may benefit from aggressive interventions and increases the risks of falls, hospitalization, admission to long-term care and mortality (4, 5). To our knowledge, this is the first study to evaluate temporal associations of long-term PA participation trajectories with subsequent motor function declines and incident frailty in middle-aged and elderly adults.

Previous studies on the relationship between long-term PA participation trajectories and motor function changes are lack of prospectiveness and applied to some certain populations (18, 28). Laddu et al. identified three PA groups using the GBTM approach only in older men and demonstrated that men in moderate and high activity trajectory groups had contemporaneous higher performance outcomes and experienced smaller declines in nearly each performance outcome than men in the low activity trajectory group (18). Pettee Gabriel et al. used latent class growth analysis, identified five PA trajectory groups only in middle-aged women and found that women included in the middle and highest physical activity groups demonstrated ≥ 5% better physical functioning performance in late midlife than those who maintained low physical activity levels (28). Despite different approaches, we both demonstrated five similar trends in PA trajectory and found that increasing active participation in PA could reduce the rate of physical performance declines, even for those who were physically inactive at an early age. But neither of the previous studies could verify the temporal correlation between

TABLE 2 Mean differences of changes in physical function between global physical activity trajectories.

Global physical activity trajectories	Grip strength (kg)		Gait speed (cm/s)		Timed 5 chair rises (s)	
	β (95% CI)[a]	*P-value*	β (95% CI)[a]	*P-value*	β (95% CI)[a]	*P-value*
Persistently low-active	Reference		Reference		Reference	
Increasing active	1.799 (1.009, 2.589)	<0.001	5.012 (1.475, 8.548)	0.005	−0.513 (−0.789, −0.236)	<0.001
Declining active	0.785 (−0.683, 2.253)	0.295	2.789 (−4.083, 9.662)	0.426	−0.072 (−0.727, 0.582)	0.829
Persistently moderate-active	0.999 (0.314, 1.684)	0.004	4.655 (1.582, 7.727)	0.003	−0.519 (−0.812, −0.226)	0.001
Persistently high-active	1.334 (0.641, 2.026)	<0.001	7.949 (4.783, 11.116)	<0.001	−0.904 (−1.199, −0.608)	<0.001

[a]Adjusted for age, sex, ethnicity, education, cohabitation status, current smoking, alcohol consumption, depressive symptoms, hypertension, diabetes, stroke, cardiovascular diseases, chronic lung diseases, cancer, functional limitations, BMI, and physical function measurements at wave 4.

TABLE 3 Hazard ratios and 95% confidence intervals of incident frailty by global physical activity trajectories.

Global physical activity trajectories	Events/Total	Risk for incident frailty[a]	
		HR (95% CI)	*P-value*
Persistently low-active	596/2,039	Reference	
Increasing active	202/1,711	0.60 (0.50, 0.72)	<0.001
Declining active	89/216	0.93 (0.73, 1.17)	0.527
Persistently moderate-active	668/2,254	0.70 (0.62, 0.80)	<0.001
Persistently high-active	311/2,007	0.42 (0.36, 0.49)	<0.001

[a]Adjusted for age, sex, ethnicity, education, cohabitation status, current smoking, alcohol consumption, depressive symptoms, hypertension, diabetes, stroke, cardiovascular diseases, chronic lung diseases, cancer, functional limitations, and BMI.

PA trajectories and the physical performance declines. With the prospective design, we confirm and expand upon observations by Pettee Gabriel et al. (28) and other investigators (18, 29–31) by prospectively assessing associations of PA trajectories with subsequent motor changes in men and women aged 50 years and older. And our findings also provide encouraging information that individuals with increasing active participation in PA had minimal and comparable rates of motor function declines to those with persistently active participation in PA. Our findings suggest that regular physical activity is never be too late.

In the current study, gait speed, grip strength, and timed five chair rises were used as indicators of motor function. Gait speed has been considered to be an invaluable health functional vital sign and a core indicator of many health outcomes especially mortality and disability (32, 33). Although the decline of gait speed in this study didn't reach the risk-effect reduction of 10 cm/s confirmed by the systematic review of association between gait speed with mortality and cardiovascular disease (33), the differences observed among the PA trajectories in this study met a threshold of meaningful change in gait speed (4–6 cm/s) (34, 35). Slower gait speed declines may reflect the enhancement of multi-system organ function by being physically active. The grip strength can represent global muscle strength in older people in the community (36). Of note, faster grip strength decline may reveal immediacy of death rather than age-related decline, and be more accurate at detecting the risk of mortality in very old adults (37, 38). Peterson et al. found that each 0.1 decrease in normalized grip strength was associated with a 15 and 12% increased risk of mortality in older Mexican American men and women, respectively (39). The chair rise test can be commonly used as a proxy for the power and strength of the lower limbs. The results of a previous study indicated that participants who performed poorly on the timed five chair rise test at baseline were at a significantly higher risk of developing disability (40). Additionally, it is one of the preferred ways to assess physical function in sarcopenia (41). The effect of regular physical activity on these meaningful indicators of motor function suggests the health benefits of regular physical activity.

Physical activity is known to preserve or improve physical function and delay or reverse frailty (42). Data from UK cohort study showed that active participants had a lower risk of frailty compared with inactive participants (43). Borda et al. also reported that PA was significantly associated with a lower risk of developing frailty in the Mexican Health and Aging Study cohort (44). Based on mobile healthcare and wearable technologies, Li et al. found that for 1 SD decrease in the temporal activity (more random activity fluctuations) correlations the risk of frailty increased by 31%; the risk of disability increased by 15–25%; and the risk of death increased by 26% (45). More recently, Yamada et al. found that older adults are more likely to experience incident frailty/disability due to decreased PA during the COVID-19 pandemic (46). Although previous studies have advanced our knowledge regarding PA and incident frailty, there isn't an investigation of the temporal association between long-term PA trajectories and incident frailty, thus providing an incomplete picture of the total evidence base on this subject. The current study confirmed previous findings and provided new evidence for a temporal association between long-term PA participation trajectories and subsequent incident frailty. This study showed that lower risks of incident frailty were obtained not only by persistently moderate or high active older adults but also by those who become more physically active regardless of their baseline level.

Our study has several strengths that make our findings more valid and robust. First, we prospectively assessed a temporal association of PA trajectories with subsequent motor function declines and incident frailty in a relatively large and nationally-representative sample with a long follow-up of 10 years. Such a prospective cohort design improves the ability to draw casual conclusions. Second, we explored all possible patterns of PA over the span of 6 years using the novel GBTM method that could address limitations of only considering activity participation at a single time point by efficiently incorporating measurements of activity participation at multiple time points. Finally, we used validated measures for assessing motor function and replicated results with relatively small heterogeneity by controlling confounding factors and sensitivity analysis.

Notwithstanding these strengths, our study has several limitations. Firstly, the ELSA's regional basis may limit our ability to generalize our results across ethnically diverse populations. Secondly, we used self-reported PA frequency when evaluating PA trajectories, thus recall errors are inevitable especially in older adults. Over-reporting of PA levels, if present, would lead to an underestimation of the actual effect of PA (47). In addition, we did not consider duration of PA when assessing PA trajectories. Thirdly, a total of 2,823 (25.55%) individuals were excluded from the analysis due to loss during follow up or develop frailty at wave 4. Individuals who were excluded were older and had higher percentages of living alone and higher prevalence of chronic diseases at baseline, compared with included older adults (**Supplementary Table 7**). Hence, selection bias could restrict the generalizability of our results. Fourthly, GBTM method inherently simplifies the variability of individual trajectories within classes. Individuals may show more change than others within the same group, and conclusions about individual outcomes should be approached with caution (11). Fifthly, our study is based on observation, and reverse causality cannot be excluded. PA trajectories may be influenced by health status. To address the issue, we performed sensitivity analyses in that participants reported daily activities difficulties during waves 1–4 were further excluded and observed consistent results. Finally, there may still be confounding bias due to unmeasured confounding factors such as pro-inflammatory cytokine interleukin-6 (48).

Conclusion

In summary, this study demonstrated that not only persistently active participation in PA, but also gradually improved PA were associated with subsequent a slower decline in motor function and a lower risk of incident frailty in middle-aged and older adults. Strategies focusing on maintaining or increasing PA may promote healthy aging and longevity.

Data availability statement

Access to original ELSA datasets can be obtained by visiting the website (https://www.elsa-project.ac.uk/).

Ethics statement

The ELSA was approved by the London Multicenter Research Ethics Committee (MREC/01/2/91). The patients/participants provided their written informed consent to participate in this study.

Author contributions

FZ and WX: had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. YW, FZ, and WX: study concept, design, and drafting of the manuscript. YW, CL, FZ, and WX: acquisition, analysis, or interpretation of data. YW, CL, and WX: statistical analysis. WX: obtained funding, administrative, technical, or material support, and supervision. All authors critical revision of the manuscript for important intellectual content and approved the submitted version.

Funding

This work was supported by the National Natural Science Foundation of China (project no. 81974490), the Newton International Fellowship from the Academy of Medical Sciences, UK (project no. NIF001-1005-P56804), and 2019 Irma and Paul Milstein Program for Senior Health Research Project Award. The funding sources had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

Acknowledgments

We thank the original data creators, depositors, copyright holders, the funders of the data collections, and their contributions for access of data from the English Longitudinal Study of Aging. The original data creators, depositors, or copyright holders bear no responsibility for the current analysis or interpretation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.939310/full#supplementary-material

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frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 31 October 2022
DOI 10.3389/fpsyt.2022.996451

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

RECEIVED 17 July 2022
ACCEPTED 29 September 2022
PUBLISHED 31 October 2022

CITATION
Feng L, Li J, Lv X, Chu S, Li C, Zhang R, Cao X and Liang L (2022) Temporal trends in anxiety and depression prevalence and their association with adverse outcomes in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease in Beijing, China, from 2004 to 2020.
Front. Psychiatry 13:996451.
doi: 10.3389/fpsyt.2022.996451

Temporal trends in anxiety and depression prevalence and their association with adverse outcomes in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease in Beijing, China, from 2004 to 2020

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Aims: To investigate the temporal trend in anxiety and/or depression prevalence in patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in Beijing and their association with adverse outcomes.

Materials and methods: Hospital admission records from 2004 to 2020 with a primary discharge diagnosis of AECOPD were retrieved from Beijing Public Health Information Centre database. The anxiety and depression were identified from discharge diagnoses of each record. Joinpoint regression was used to analyze the temporal trend and calculate the annual percentage change (APC) for the prevalence of anxiety and/or depression. Generalized linear model was used to analyze the associations between anxiety and/or depression and patients' adverse outcomes.

Results: A total of 382,125 records were included, most of which were male (66.0%) and aged ≥ 75 years (59.7%). Three segments in the temporal trend were observed, with a mild increase during 2004–2009 (APC: 5.9%, 95% CI: -14.9 to 31.7%), followed by a sharply increase during 2009–2012 (APC: 60.4%, 95% CI: 10.6 to 132.7%), then stabilized at about 3% during 2012–2020 (APC: 1.9%, 95% CI: -0.4 to 4.3%). On average, anxiety, and/or depression was more prevalent in females, the aged and those admitted in secondary

hospitals (all $P < 0.001$). Patients with anxiety and/or depression had lower in-hospital mortality (IHM) (OR = 0.74, 95% CI: 0.63–0.88), but longer hospital stay (OR = 1.10, 95% CI: 1.07–1.13), more medical costs (OR = 1.12, 95% CI: 1.08–1.17) and higher risks of readmission for AECOPD at 30-, 90-, 180-day, and 1-year (ORs ranged from 1.22 to 1.51).

Conclusion: The prevalence of anxiety and/or depression in patients hospitalized for AECOPD in Beijing stabilized at approximately 3% after 2012. Anxiety and/or depression is associated with a heavier burden on patients, health care, and medical insurance systems. Appropriate diagnosis and effective treatment of anxiety and depression is crucial for patients with AECOPD.

KEYWORDS

anxiety, depression, chronic obstructive pulmonary disease, temporal trend, influence, China

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the top three global causes of death and top ten global causes of disability-adjusted life years (DALYs) (1). Anxiety and depression are common in patients with COPD, with an estimated prevalence of 6–74% and 8–80%, respectively (2–7). As important comorbidities in COPD, anxiety and depression are associated with increased risks of exacerbations (2, 8), emergency care use (9), and medical costs (10), contributing to a substantial disease burden of COPD (6).

It's worth noting that most of results reported in previous studies related to the prevalence, associated factors and influences of depression and/or anxiety were restricted to stable COPD patients from outpatient or community settings (2, 9, 11). Different from those with stable COPD, patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) are often in a severer physical condition and worse quality of life (12), which are closely related to the occurrence of depression and/or anxiety symptoms (3). Meanwhile the presence of depression and/or anxiety could also worsen the condition of COPD as well as the quality of life of patients (13–15). Accordingly, the anxiety and depression could be more prevalent among patients hospitalized for AECOPD than those with stable COPD, but limited data has been reported in the previous study.

Apart from the point prevalence, the temporal trends of anxiety and depression prevalence in AECOPD are also of paramount importance in understanding the changes in mental health status over time, which has significant implications for health policy and healthcare provision in systematically influencing clinical practice (16). Although of high priority (12, 17), the existing literature fails to assess the temporal trends in the prevalence of anxiety and depression among those hospitalized for AECOPD.

In the meantime, there is still controversy regarding the impact of anxiety and depression on the prognosis of patients hospitalized for AECOPD. Some authors have reported a worse disease progression (18–20), while others have failed to find any link between anxiety nor depression and a worse prognosis (8, 21). More evidence from large-sample representative study is needed.

Therefore, the present study focused on patients hospitalized for AECOPD with two aims: (1) to describe the temporal trends of anxiety and/or depression prevalence among patients hospitalized for AECOPD in Beijing; (2) to estimate the associations between comorbid anxiety and/or depression and the in-hospital outcomes as well as the risks of readmission for AECOPD within 1-year after discharge.

Materials and methods

Study design

This study is a city-wide electronic medical records (EMR) -based study of patients hospitalized for AECOPD in Beijing, with a cross-sectional study design to describe the temporal trends of the prevalence of anxiety and/or depression, along with a retrospective cohort study design to estimate the associations between anxiety and/or depression and the in-hospital outcomes as well as the risks of readmission for AECOPD at 30-, 90-, 180-days, and 1-year.

The present study was approved by the Research Ethics Board of Beijing Chaoyang Hospital (2018-ke-303). Data were de-identified before analysis. It is impossible to identify patients

at the individual level either in this article or in the retrieved database. Given the anonymous and mandatory nature of the data, informed consent was not required or necessary.

Data source

AECOPD hospitalization records were retrieved form a hospital discharge database operated by the Beijing Public Health Information Centre. This database covers discharge records from all secondary- and tertiary-level hospitals in Beijing. As only secondary- and tertiary-level hospitals could provide inpatient service, this database provides good representative of hospitalized patients in Beijing and can be used to analyze hospitalization outcomes. These patient-level records contain data on patient's demographic characteristics, hospital name, date of admission, discharge diagnoses along with corresponding International Classification of Diseases, 10th Revision (ICD-10) codes, and so on. All hospitalization records for patients aged $\geq$ 20 years with a primary discharge diagnosis of AECOPD (ICD-10 codes of J44.0–J44.9) from January 1st 2004 to December 30th 2020 were included in the current analyses.

Measurement

Anxiety (ICD-10 codes of F40.0-F40.9, F41.1-F41.9) and depression (ICD-10 codes of F32.0-F32.9, F33.0-F33.9, F41.2) were identified from discharge diagnoses in each hospitalization record. Patients with only anxiety diagnosis, only depression diagnosis, both anxiety and depression diagnoses were considered as in the only anxiety subtype, only depression subtype, and both anxiety and depression subtype. The other combined diseases were also identified from discharge diagnoses and the corresponding Charlson Comorbidity Index (CCI) was calculated (22). Use of mechanical ventilation (MV), including non-invasive MV and invasive MV, was determined using ICD-10 code J15.501, which was available in the dataset from 2012 to 2020. The length of hospital stay (LOHS) was defined as days from admission to discharge of each record. The medical cost was total cost during each hospitalization and was converted into 2020 Chinese Yuan (CNY) values (1 CNY = 0.145 US dollar) based on the year-specific health care consumer price index of China (23). The readmission for acute exacerbation was defined as another hospitalization with a primary diagnosis of AECOPD (ICD-10 codes of J44.0–J44.9) happened afterward (within 30-, 90-, 180-days, 1-year), which was identified in our hospital discharge database.

Statistical analysis

Descriptive statistics were presented as means and standard deviations or medians and interquartile ranges for continuous variables with or without normal distributions and as frequencies and percentages for categorical variables. Characteristics between groups were compared using χ^2-test or Fisher's exact test for nominal categorical data, the Mantel-Haenszel Chi-Square test for ordered categorical data, and the Wilcoxon rank sum test or Kruskal-Wallis test for continuous variables without normal distribution, respectively.

The prevalence of anxiety and/or depression and the subtypes (only depression, only anxiety, both anxiety and depression) were presented annually in the total hospitalization records for AECOPD as well as the subgroups defined by gender, age group and institute level. The temporal trend analyses were conducted using Joinpoint Regression Program developed by United States National Cancer Institute. The turning points in the temporal trend of the prevalence of anxiety and/or depression could be identified and the annual percentage change (APC) for each time segment could be calculated. The program assumes that proportions changed at a constant percentage every year on a log scale in each time segment. The average annual percent change (AAPC)—a weighted average of APCs from the Joinpoint models, with weights equal to the length of the APC interval—was also computed as a summary measure of the trend over the whole observation period.

The generalized linear models were used to investigate the associations between co-diagnosis of anxiety and/or depression and patients' prognoses, with a random effect to account for multiple hospitalization records of one patient. The binominal distribution and logit link were used to investigate the associations between co-diagnosis of anxiety and/or depression and receiving MV, in-hospital mortality (IHM) and readmission for AECOPD after discharge. The gamma distribution and log link were used to investigate the associations between co-diagnosis of anxiety and/or depression and LOHS, medical costs. Model covariates included admission year, gender, age, CCI, and institute level. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set as two-sided $P < 0.05$.

Results

Patients' characteristics and the prevalence of anxiety and/or depression

A total of 382,125 patient discharge records were identified, submitted by 78 tertiary hospitals and 77 secondary hospitals. Most patients (59.6%) were 75 years old or older and 66.0% of them were male. The types of anxiety and depression diagnosis and the corresponding ICD-10 code were shown in **Supplementary Table 1**. As shown in **Table 1**, a total of 2.1% (7,912 of 382,125) patients had a co-diagnosis of anxiety and/or depression. The prevalence of anxiety and/or depression was higher for females than for males and increased with age,

TABLE 1 The characteristics and the prevalence of anxiety and/or depression among patients hospitalized for AECOPD from 2004 to 2020 in Beijing, China.

	Total	With anxiety and/or depression	*P*
Overall	382,125	7,912 (2.1%)	
Gender			
Male	252,055	4,438 (1.8%)	<0.001
Female	130,070	3,474 (2.7%)	
Age			
Median (IQR)	77.0 (69.0–83.0)	79.0 (72.0–84.0)	
20–59 years	28,893	367 (1.3%)	<0.001
60–74 years	125,190	2,145 (1.7%)	
≥ 75 years	228,042	5,400 (2.4%)	
P trend			<0.001
Institute level			
Secondary hospitals	108,861	2,424 (2.2%)	<0.001
Tertiary hospitals	269,824	5,368 (2.0%)	
Charlson comorbidity index			
0	148,424	3,182 (2.1%)	0.012
1	128,378	2,656 (2.1%)	
≥ 2	105,157	2,074 (2.0%)	
P trend			0.003

IQR, interquartile range; Institute level missing (n = 3,440), Charlson Comorbidity Index missing (n = 166).

with the highest prevalence seen among patients aged ≥ 75 years (all $P < 0.001$). Details about the prevalence of its subtypes are showed in Supplementary Table 2.

Trends of anxiety and/or depression in patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease 2004–2020

Figure 1A shows the prevalence of anxiety and/or depression and its subtypes among patients with AECOPD for each calendar year. During the observation period, the prevalence increased significantly from 0.3% in 2004 to 3.1% in 2020. Trends in the prevalence of three subtypes exhibit different patterns (Figure 1B). During 2004–2012, the prevalence of only anxiety increased continuously, and then stabilized at about 1%. The prevalence of only depression and the prevalence of both anxiety and depression stayed at about 0.1% during 2004–2011. In 2012, the former increased sharply and stabilized at about 1%, while the latter has been increasing since 2011 and reaching about 1% in 2020. The annual prevalence data are in Supplementary Table 3.

The temporal trends in the prevalence of anxiety and/or depression were compared by subgroups and the corresponding results are displayed in Figure 2. The prevalence for female patients were close to those for male patients from 2004 to 2011, and then became almost twice as those for male patients. The prevalence for three age groups all fluctuated during study period, and mainly manifested as the older age the higher the prevalence. However, the prevalence for patients aged 20–59 years old exceeded that for patients aged 60–74 years old in 2020. The temporal trends in the prevalence for patients in secondary hospitals and for those in tertiary hospitals were similar during study period, with sharp increases in 2011 and 2012. The temporal trends in the prevalence of three subtypes stratified by subgroups are showed in Supplementary Figures 1–3.

In Joinpoint Regression, the prevalence of anxiety and/or depression increased significantly during study period with an AAPC of 12.3% [95% confidence interval (CI): 3.1 to 22.3%]. Two turning points with three segments were observed in the temporal trend of prevalence, with a mild increase during 2004–2009 (APC: 5.9%, 95% CI: -14.9 to 31.7%), followed by a sharply increase during 2009–2012 (APC: 60.4%, 95% CI: 10.6 to 132.7%), and then stabilized during 2012–2020 (APC: 1.9%, 95% CI: -0.4 to 4.3%). In subgroups, APCs for female patients increased during 2012–2020 with 5.8% (95% CI: 2.6 to 9.0%) while male patients did not have a significant change during that period (APC: 0.6%, 95% CI: -1.9 to 3.1%). Over the entire observation period, patients aged 20–59 had a continuous upward trend without a significant turning point; while in 2012, one turning point was found in those aged 60–74; and in 2009 and 2012, two turning points were found in those aged ≥ 75. During 2009–2012, the APC of secondary hospitals was higher than that of tertiary hospitals (73.1% vs. 54.9%) (details in Table 2).

The associations of anxiety and/or depression and patients' outcomes

As shown in Table 3, patients with anxiety and/or depression had lower IHM (2.1% vs. 3.0%), longer LOHS (13.0 days vs. 12.5 days), more medical cost (19,515 CNY vs. 17,004 CNY), but similar mechanical ventilation rates (5.5% vs. 5.2%, $P = 0.356$). Among those alive at discharge and followed up at least for 1 year, patients with anxiety and/or depression had higher risks of readmission for AECOPD at 30-day (20.5% vs. 16.9%), 90-day (32.95 vs. 25.7%), 180-day (42.2% vs. 33.2%), and 1-year (53.6% vs. 43.3%) (all $P < 0.001$). Patients in three different subtypes had different mechanical ventilation rates, LOHS and risks of readmission for AECOPD after discharge (all $P < 0.001$).

After multivariate adjustment, patients with anxiety and/or depression still had a lower risk of IHM (OR = 0.74, 95% CI: 0.63 to 0.88), but longer LOHS (OR = 1.10, 95% CI: 1.07 to 1.13), more medical costs (OR = 1.12, 95% CI: 1.08 to 1.17) and higher

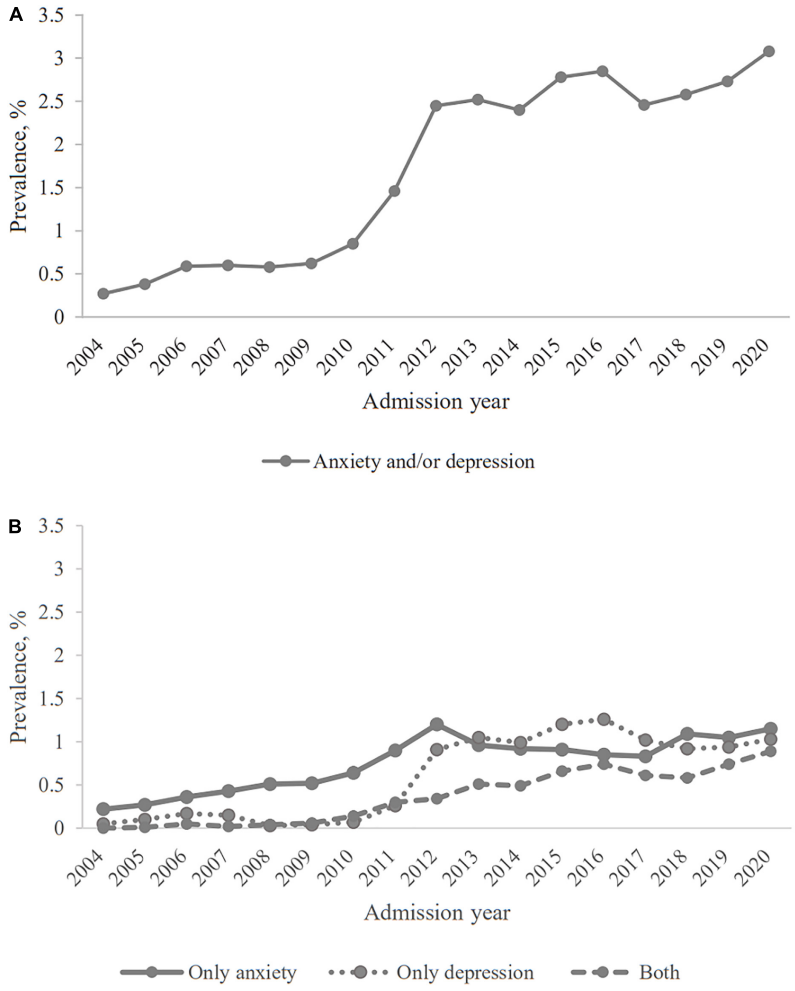

FIGURE 1
The prevalence of anxiety and/or depression among patients hospitalized for AECOPD in Beijing. **(A)** Anxiety and/or depression; **(B)** three subtypes of anxiety and/or depression.

risks of readmission for AECOPD after discharge at 30-day (OR = 1.22, 95% CI: 1.04 to 1.43), 90-day (OR = 1.39, 95% CI: 1.24 to 1.55), 180-day (OR = 1.44, 95% CI: 1.31 to 1.59) and 1-year (OR = 1.51, 95% CI: 1.38 to 1.64). Details in Table 4.

The multivariate analyses of only depression, only anxiety, both depression and anxiety on the in-hospital outcomes and readmission for AECOPD were shown in Supplementary Table 4. No significant difference was observed among three different subtypes except for the LOHS (*P* for interaction, 0.020).

Discussion

During the observation period of this EMR-based observational study, the prevalence of anxiety and/or depression increased sharply from 2009 to 2012, before stabilizing at approximately 3%. The prevalence of subtypes of anxiety and/or depression and subgroups stratified by gender, age group and institute level all increased, however, they showed varying temporal patterns. Anxiety and/or depression was more prevalent among the elderly, female patients and those hospitalized in secondary hospitals. Patients with anxiety and/or depression had a lower risk of IHM, but longer LOHS and higher medical costs, as well as higher risks of readmission for AECOPD after discharge within 1 year.

During 2009–2012, the prevalence of anxiety and/or depression among AECOPD inpatients increased sharply. An improvement of the regional mental health service system leading by local government could be responsible for this increase (24). All general hospitals in Beijing were required to establish psychiatric departments (25). Psychiatric specialists provided extensive training to clinicians in general hospitals, and marked increases in psychiatric beds and psychiatric professionals were observed (25).

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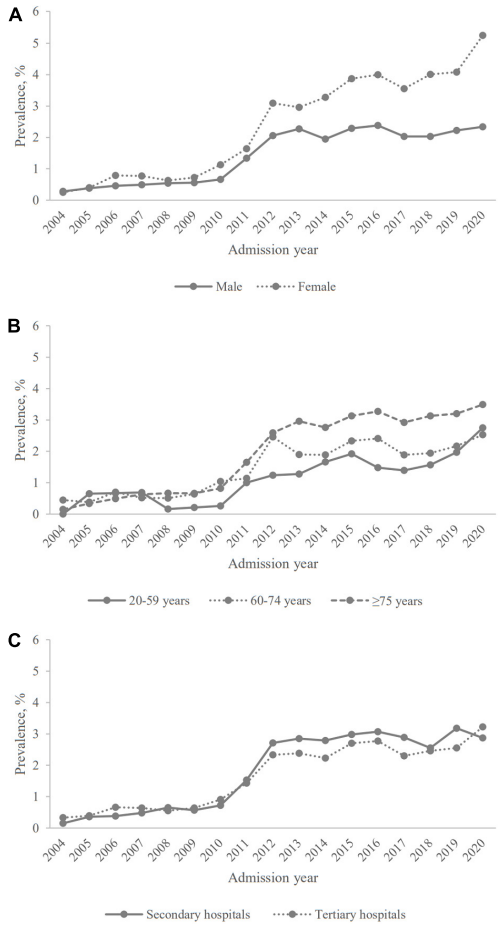

FIGURE 2
The prevalence of anxiety and/or depression among patients hospitalized for AECOPD in Beijing, stratified by gender, age group, and institute level. **(A)** Gender; **(B)** age group; **(C)** institute level.

Our results indicate that the systemic improvement in the diagnostic capacity of common mental disorders in general hospitals, particularly in secondary hospitals. Since 2012, the prevalence of depression and/or anxiety among AECOPD inpatients has remained stable, fluctuating between 2.4 and 3.1%. This may be indicative of the true prevalence of comorbid anxiety and depression among AECOPD inpatients.

Diagnosis of anxiety and depression is essential to delivering effective psychiatric treatments for AECOPD patients. In recent years, approximately 3% AECOPD inpatients were co-diagnosed with anxiety and/or depression in Beijing, which is lower than those reported in Taiwan (depression: 9.0%) and the United States (anxiety: 9.6%; depression: 14.2%) (19, 21). This difference can be attributed to several factors. It relates, in part, to the difficulty in identifying and diagnosing anxiety and depression among AECOPD inpatients. Symptoms of these mental disorders are similar to those of AECOPD,

TABLE 2 Trend analysis of the prevalence of anxiety and/or depression among patients hospitalized for AECOPD by gender, age group and institute level from 2004 to 2020.

	Overall trend		Trend segment 1[a]			Trend segment 2			Trend segment 3	
	AAPC (95% CI)	*P*	Period	APC (95% CI)	*P*	Period	APC (95% CI)	*P*	Period	APC (95% CI)	*P*
Overall	12.3 (3.1, 22.3)	0.008	2004–2009	5.9 (−14.9, 31.7)	0.570	2009–2012	60.4 (10.6, 132.7)	0.018	2012–2020	1.9 (−0.4, 4.3)	0.093
Gender											
Male	11.6 (1.6, 22.6)	0.023	2004–2009	6.1 (−15.9, 33.8)	0.577	2009–2012	60.1 (4.4, 145.6)	0.035	2012–2020	0.6 (−1.9, 3.1)	0.605
Female	14.1 (2.3, 27.3)	0.018	2004–2009	4.6 (−22.0, 40.2)	0.738	2009–2012	61.7 (2.5, 155.3)	0.041	2012–2020	5.8 (2.6, 9.0)	0.002
Age group											
20–59	10.1 (4.9, 15.6)	0.001	2005–2020[b]	10.1 (4.9, 15.6)	<0.001						
60–74	14.7 (9.4, 20.2)	< 0.001	2004–2012	29.6 (17.6, 42.9)	<0.001	2012–2020	1.4 (−2.1, 5.1)	0.399			
≥ 75	14.1 (5.7, 23.1)	0.001	2004–2009	8.7 (−11.9, 34.2)	0.391	2009–2012	63.5 (20.6,121.7)	0.005	2012–2020	2.7 (0.8, 4.6)	0.009
Institute level											
Secondary	14.5 (5.4, 24.3)	0.001	2004–2009	9.1 (−12.2, 35.6)	0.387	2009–2012	73.1 (21.9,145.7)	0.006	2012–2020	1.0 (−1.0, 3.1)	0.281
Tertiary	11.5 (−0.6,25.0)	0.062	2004–2009	4.9 (−21.6, 40.4)	0.717	2009–2012	54.9 (−6.2,155.8)	0.080	2012–2020	2.3 (−0.9, 5.7)	0.143

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval.
[a]Trend segment identified by Joinpoint regression.
[b]No patient aged 20–59 year diagnosed with depression and/or anxiety in 2004.

TABLE 3 The differences in in-hospital outcomes and the risks of readmission for AECOPD after discharge between those with anxiety and/or depression and those without.

	With anxiety and/or depression			Subtypes			
	Yes *N* = 7,912	NO *N* = 37,4213	*P*	Only depression *N* = 2,911	Only anxiety *N* = 3,288	Both *N* = 1,713	*P*
Receiving mechanical ventilation, *n* (%)[a]	384 (5.5)	13,678 (5.2)	0.356	146 (5.3)	180 (6.8)	58 (3.7)	<0.001
In-hospital mortality, *n* (%)[b]	162 (2.1)	10,708 (3.0)	<0.001	55 (1.9)	77 (2.4)	30 (1.8)	0.265
Length of hospital stay, day, median (IQR)	13.0 (9.0–18.0)	12.5 (8.9–17.2)	<0.001	12.9 (9.0–17.0)	13.0 (9.0–19.8)	13.0 (9.0–17.0)	<0.001
Medical cost, CNY[c], median (IQR)	19,515 (13,127–30,160)	17,004 (11,445–25,808)	<0.001	19,148 (12,978–28,924)	19,653 (13,046–31,224)	19,783 (13,700–30,407)	0.064
30–day readmission for AECOPD, *n* (%)[d]	1,493 (20.5)	5,8970 (16.9)	<0.001	625 (21.9)	597 (18.6)	364 (21.6)	0.003
90-day readmission for AECOPD, *n* (%)[d]	2,404 (32.9)	8,9939 (25.7)	<0.001	954 (33.4)	993 (30.9)	601 (35.7)	0.002
180-day readmission for AECOPD, *n* (%)[d]	3,080 (42.2)	11,6129 (33.2)	<0.001	1,225 (42.9)	1,260 (39.2)	768 (45.65)	<0.001
1-year readmission for AECOPD, *n* (%)[d]	3,910 (53.6)	15,1169 (43.3)	<0.001	1,511 (52.9)	1,636 (51.0)	949 (56.4)	0.001

IQR, interquartile range; Fisher's exact test for binary variables; Wilcoxon rank sum test and Kruskal-Wallis test for continuous variables.
[a]Hospitalization recodes in 2012–2020, *N* = 268,456.
[b]Hospitalization recodes in 2007–2020, *N* = 361,776.
[c]Converted to CNY 2020.
[d]Hospitalization recodes alive at discharge in 2004–2019, *N* = 356,862.

TABLE 4 The multivariate analyses of the associations between depression or anxiety and patients' in-hospital outcomes and the risks of readmission for AECOPD after discharge.

	Model 1		Model 2	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Receiving mechanical ventilation[a]	1.06 (0.74, 1.51)	0.759	1.09 (0.76, 1.56)	0.648
In-hospital mortality[b]	0.73 (0.62, 0.86)	<0.001	0.74 (0.63, 0.88)	<0.001
Length of hospital stay	1.09 (1.05, 1.12)	<0.001	1.10 (1.07, 1.13)	<0.001
Medical cost	1.10 (1.05, 1.15)	<0.001	1.12 (1.08, 1.17)	<0.001
30-day readmission for AECOPD[c]	1.11 (0.94, 1.30)	0.214	1.22 (1.04, 1.43)	0.015
90-day readmission for AECOPD[c]	1.28 (1.14, 1.43)	<0.001	1.39 (1.24, 1.55)	<0.001
180-day readmission for AECOPD[c]	1.35 (1.22, 1.48)	<0.001	1.44 (1.31, 1.59)	<0.001
1-year readmission for AECOPD[c]	1.43 (1.31, 1.56)	<0.001	1.51 (1.38, 1.64)	<0.001

Model 1: adjusted for admission year.
Model 2: adjusted for sex, continuous age, continuous Charlson Comorbidity Index, institute level and admission year.
CI, confidence interval.
[a]Hospitalization recodes in 2012–2020, *N* = 268,456.
[b]Hospitalization recodes in 2007–2020, *N* = 361,776.
[c]Hospitalization recodes alive at discharge in 2004–2019, *N* = 356,862.

including dyspnea, oppression in chest, palpitations, fatigue, sleep disturbances, loss of appetite, reduced physical activity, and hopelessness (4, 26). Therefore, there is a need for more experienced psychiatric professionals as well as a well-established system to improve future diagnosis capabilities. On the other hand, in previous studies, psychological scales such as the Hospital Anxiety and Depression Scale (HADS) and Hamilton Anxiety Rating Scale (HAMA) were used to detect AECOPD patients suffering from anxiety and/or depression (3, 8, 20). Accordingly, these studies reported higher prevalence of anxiety and depression than we did (ranging from 44.4 to 68.2%) (3, 8). It should be noted, however, that anxiety and depression based on scales may be affected by AECOPD symptoms (27), these measures are not comparable to the clinical diagnoses (28).

The results of another EMR-based study of 26,591 veterans with AECOPD admissions in the United States, of whom 97% were male, showed that those with anxiety and/or depression were younger than those without psychiatric comorbidity, who had an average age of 61.9 years and 3.1 comorbid diagnoses on average (18). By contrast, anxiety and/or depression was more prevalent among the elderly in our study. Perhaps this is due to the difference in the study populations, as veterans may be more likely to get anxiety and depression from their prior war experience (29). Moreover, similar to a previous study, female patients with AECOPD were more likely to experience anxiety and depression (18). This could be explained as female patients are more sensitive to respiratory symptoms, experiencing more negative emotions, thus leading to higher risks of anxiety and depression (30). Furthermore, female COPD patients are more likely to face barriers to receiving appropriate treatment (31). Poor female COPD management may also contribute to the progression of the disease, increasing their risk of depression and anxiety. In addition, an increasing prevalence of anxiety and depression in patients with AECOPD aged 20–59 years in recent years was observed. There is still much uncertainty about the causes, but more attentions should be paid to mental health among young and middle-aged people and explore their influences.

After the COVID-19 pandemic outbreak, the prevalence of anxiety and/or depression increased by about 15% (from 2.7 to 3.1%). This slight increase could be due to a number of factors. As a result of the uncertainties and fears of the virus infection, mass lockdowns and economic recession, people have higher psychological distress during the COVID-19 pandemic (32, 33). Furthermore, COPD patients are more likely to experience disorders of mental illness during COVID-19 pandemic because of worse access to necessary medical care for COPD (34, 35). In view of the fact that our study period ended in 2020, more data in subsequent years are required to determine whether the COVID-19 pandemic has a profound impact on the prevalence of anxiety and depression among patients hospitalized for AECOPD.

In a retrospective study of Taiwan's health insurance database, which included 4,204 first-ever AECOPD patients, 73% were male and the mean age was 75 years, those dying in hospital (7.4%) had less depression than those survived (9.1%) (21). Similarly, we found AECOPD patients with anxiety and/or depression was associated with a lower risk of IHM. This association has not been fully elucidated. According to previous studies, COPD patients suffering from anxiety and/or depression could not objectively evaluate their condition and might experience subjectively worsening lung disease (36, 37). AECOPD inpatients with anxiety and/or depression may overestimate the severity of an exacerbation and, therefore, are not in as severe physical condition as those without anxiety nor depression. Due to the lack of severity measurements, neither our study nor the other study in Taiwan were able to evaluate this hypothesis. For a more conclusive conclusion, a prospective cohort study is required. Moreover, we observed patients with anxiety and/or depression had longer LOS and spent more money in the hospital. This association was also observed in a prospective cohort study that excluded patients who died during their hospitalization (38). The explanation for this association is still unclear. Even so, anxiety and depression are undoubtedly important burden for AECOPD patients, the health care systems and the medical insurance systems.

In our prospective study of 504 patients with stable COPD, anxiety and depression were associated with an increased risk of acute exacerbations in the following year (11). Similarly, our present study demonstrates that comorbid anxiety and/or depression is associated with increased the risks of 30-, 90-, 180-days, and 1-year readmission for AECOPD in patients hospitalized for AECOPD, which has not been reported before. There are several mechanisms that linking anxiety and depression to the prognosis of COPD. Physiologically, anxiety and depression can activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, leading to a weakened immune system and increased vulnerability to respiratory infection and exacerbation of COPD (39, 40). Psychologically, COPD patients with anxiety and/or depression have decreased self-efficacy, resulting in insufficient management of their diseases manifested as poor medication adherence and participation in pulmonary rehabilitation (41–43).

Anxiety and depression are extra-pulmonary treatable traits of COPD patients (17). In current clinical guideline, there is no evidence that anxiety and depression should be treated differently in the presence of COPD (12). Moreover, recent studies showed that some COPD treatments such as mind-body exercise, breathing-based walking, and pulmonary rehabilitation could also improve patients' anxiety and depression symptoms (44–46). Multidisciplinary disease management for COPD patients with psychological assessment and follow-up by clinical psychologist also showed promising preliminary results (47). Consequently, it is imperative to identify anxiety and depression in COPD patients, especially those with acute exacerbations, in order to provide them with adequate psychological treatment and ultimately improve their prognosis.

Strengths and limitations

This is, to the best of our knowledge, the first and largest long-term study conducted in a city over a 17-year period, using a representative database of AECOPD hospitalizations. Additionally, we used the Joinpoint Regression Program to identify points where these trends changed and

to estimate the APC to uncover underlying causes, such as changes in policy or program implementation at specific points in time. There are also several limitations should be noted. First, as with all studies utilizing medical records, it was impossible for us to determine whether a hospitalization record was for a patient experiencing their first episode of anxiety and/or depression or for a patient experiencing recurrent episodes. The lack of data in our database also prevented us from examining the potential effects of socioeconomic status, smoking, or alcohol consumption, exacerbation severity, and pharmaceutical treatments on comorbid anxiety and/or depression. Second, anxiety and/or depression is likely to be underdiagnosed in our study population, resulting in systematically underestimated prevalence rates in AECOPD inpatients. And the temporal trends in our study mixed the changes of prevalence and improvements in diagnostic capability. Taken together, our temporal trend does not accurately reflect the "true" epidemic trend in anxiety and/or depression in patients hospitalized for AECOPD. However, we provide with useful information for policymakers regarding the prevalence of anxiety and depression among patients hospitalized with AECOPD. Third, no temporal trend analysis for only anxiety, only depression, both anxiety and depression was conducted because their prevalence are too low to fit the Joinpoint regression model. Fourth, there is inevitably survivor bias in a retrospective cohort, which may lead to a null interpretation for anxiety and depression being associated with patients' prognoses, particularly IHM. Finally, the data are from Beijing, and our findings may not be generalizable to patients with AECOPD in other provinces of China. Future studies using nationwide records are warranted to better reflect the burden of this condition in China as a whole.

Conclusion

Our study showed that the prevalence of anxiety and/or depression among patients hospitalized for AECOPD in Beijing stabilized at approximately 3% after a sharp increase during 2009–2012. Anxiety and/or depression is associated with a longer LOS, more medical cost, and higher risk of readmission for AECOPD. It is imperative to identify anxiety and depression in AECOPD patients, and to provide them with adequate psychological treatment and ultimately to reduce the disease burden on patients, health care and medical insurance systems.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Board of Beijing Chaoyang Hospital (2018-ke-303). The ethics committee waived the requirement of written informed consent for participation.

Author contributions

LF and LL designed the analysis. LL acquired the data resource, supervised the work, and edited the final version of the manuscript. LF analyzed the data and wrote the first draft. JL, XL, SC, CL, RZ, and XC provided expertise as well as edited the contents of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants from the Beijing Municipal Science and Technology Commission (grant no. Z201100005520028).

Acknowledgments

We thank the data collection teams.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.996451/full#supplementary-material

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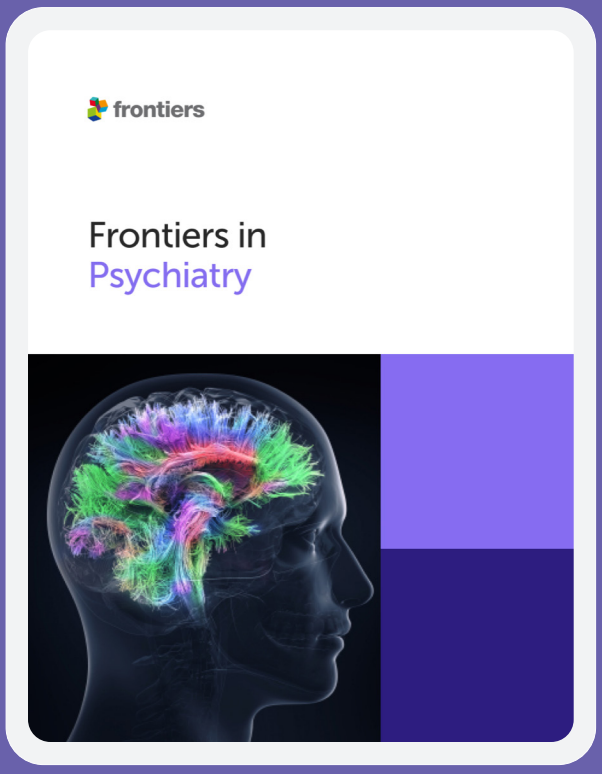

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