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Association between the depressive symptom trajectories and all-cause mortality in Chinese middle-aged and elderly adults

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Previous studies reported that depressive symptoms were associated with a high risk of all-cause mortality. However, the effect of different long-term depressive symptom trajectory patterns on the risk of all-cause mortality has not been evaluated. Our research aimed to explore the association between different depressive symptom trajectories and the risk of all-cause mortality in Chinese adults. The data we used were from the China Health and Retirement Longitudinal Study. In total, 13,624 subjects aged over 45 years were ultimately included in the analysis. Group-based trajectory modeling was used to identify the different trajectories of depressive symptoms. The multivariable Cox regression model was used to examine the association between long-term depressive symptom trajectories and all-cause mortality. The results show that a total of five depressive symptom trajectories were identified in our study, including stable-low, stable-moderate, increasing, decreasing and stable-high. Compared with individuals in the stable-low depressive symptom trajectories group, those in the increasing and stable-high trajectory groups possessed a greater mortality rate, with a multivariable-adjusted hazard ratio (95% CIs) for mortality were 1.30 (1.06, 1.60) and 1.59 (1.26, 2.02), respectively. In addition, we have not identified the significant risk of all-cause mortality in people with decreased and stable-moderate symptom trajectories. Moreover, the risk of all-cause mortality had an increasing trend among the different trajectory groups. In the sensitivity analysis, the association was robust in most of the subgroups. In conclusion, people with increasing and persistent higher depressive symptom trajectories were associated with an increased risk of all-cause mortality.

Keywords Depressive symptom, Trajectory, CHARLS, GBTM, CESD-10

Depression has become a common problem and major public health concern worldwide. Moreover, the prevalence of depression has increased to a higher level[1]. One meta-analysis showed that 34% of adolescents globally are at risk of developing clinical depression[2]. According to studies in China, the prevalence of clinically significant depressive symptoms was 18% in a month-long observation period[3]. It has been confirmed to increase the risk for cardiovascular disease, dementia, and suicidal ideation[4–6]. Moreover, the combination of these illnesses and depression can worsen existing medical issues. The Global Burden of Disease Study in 2019 reported that over 45 million all-age disability-adjusted life-years (DALYs) were contributed by depression[7]. Thus, the effect of depression or depressive symptoms on mortality has also been evaluated in recent decades. Lots of population-based cohort studies indicated that depressive symptoms were significantly associated with higher mortality[8–11]. In this study, the definition of a depressive state was only based on one-time measured depressive symptoms. However, depressive symptoms may fluctuate over the lifetime of people. As we all know depressive symptoms frequently improve with treatment, remission periods, and personal resilience. Moreover, the course of depression is inherently variable, influenced by factors such as life events, social support, and biological changes. One previous study showed that almost 20% of the total participants had great depressive symptom changes in a 4 years follow-up survey[12]. Nevertheless, few studies have evaluated the effect of long-term trajectories of depressive symptoms on mortality.

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Therefore, our study aimed to present the different long-term trajectories of depressive symptoms, and explored their effect on all-cause mortality in Chinese middle-aged and elderly adults. We hypothesized that individuals with low to high depressive symptoms, high to low depressive symptoms, and persistent high depressive symptoms were significantly associated with all-cause mortality.

Methods

Data sources and study population

In the current study, the data we used were obtained from the China Health and Retirement Longitudinal Study (CHARLS), a nationwide, ongoing cohort of Chinese adults aged 45 years or older. The CHARLS was designed to assess changes in the social, economic and health circumstances of community residents. As a longitudinal study, the national baseline survey was conducted in June 2011 and March 2012, which included 17,708 respondents from 10,257 households. To date, CHARLS researchers have conducted four follow-up surveys in 2013, 2015, 2018 and 2020. The details of the design and sampling methods of the CHARLS have been described elsewhere[13].

Data from the five survey waves, which were conducted from 2011 to 2020, were used in the current study. After excluding participants without follow-up tracking data or depressive symptom data, those under 45 years old, and those without the death information, 13,624 subjects were ultimately included in the analysis. The participant selection flow chart is shown in Fig. 1. All the participants signed informed consent forms, and all methods were performed in accordance with the relevant guidelines and regulations. This study was approved by the Ethics Review Committee of Peking University.
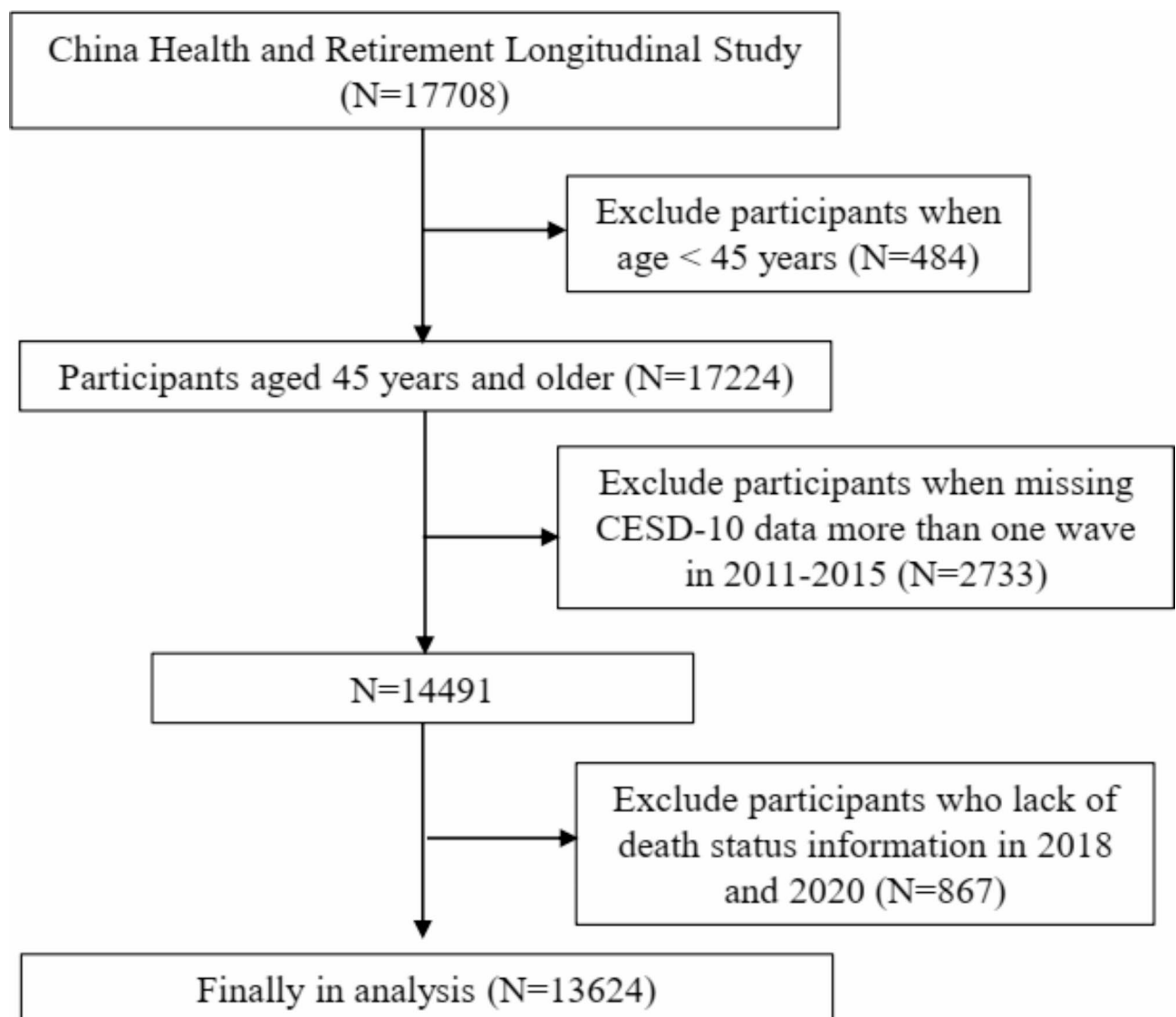

Fig. 1. The participant selection flowchart.

Depressive symptoms and trajectories

Depressive symptoms were evaluated by the Center of Epidemiologic Studies Depression Scale-10 (CESD-10). The CESD-10 has been validated and widely used in the measurement of depression symptoms in China[14,15]. The CESD-10 consists of 10 items, including optimistic and negative states. Every item had four response levels, which were recorded as 0, 1, 2 and 3; thus, the sum scores of the CESD-10 ranged from 0 to 30, with a higher score indicating a greater level of depression. In our study, the trajectories of depressive symptoms surveyed in 2011, 2013 and 2015 were defined as the exposed variable, and whether participants died in 2018 and 2020 was defined as the outcome, details are shown in Fig. 2.

Assessment of mortality and covariates

We divided the participants into two groups based on their mortality status in 2018 and 2020 (alive or dead). The residential location was also divided into two groups based on the household living region of the population: urban and rural. Education levels were divided into three levels: college or above, middle or high school, and elementary school or below. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, self-reported hypertension, or taking antihypertensive medication. Diabetes was defined as Hab1c $\geq$ 6.5, self-reported diabetes, or receiving any medical treatment[16]. Smoking status and alcohol consumption were defined according to whether residents have engaged in these behaviors at any point (yes/no). BMI (kg/m^2) was calculated as weight divided by height squared. In addition, the diagnosis of other diseases, including cancer, diabetes, heart disease, and stroke was based on self-reported information.

The survival time was calculated based on the time from wave 3 to wave 5 when people were alive. If participants die, the survival time is calculated from wave 3 to the time of death. If participants died and lacked a specific time of death, the death time was defined as the median of two adjacent wave intervals.

Statistical analysis

Data analysis was conducted by using the statistical analysis software package SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Group based trajectory modeling (GBTM) can identify latent clusters of individuals who are following similar trajectories of a particular indicator of interest[17]. In our study, GBTM for participants was performed by the PROC TRAJ procedure, and those without all three waves of depressive symptom survey data were handled under the missing-at-random assumption. When GBTM was used to identify the different trajectories of depressive symptoms, we started from one trajectory model to six trajectory models and fit those trajectories up to the optimal number by comparing the Bayesian information criterion. Moreover, the number of participants in every trajectory group was greater than 5% of the total number of participants in each trajectory group.

Continuous and categorical variables are presented as the mean $\pm$ standard deviation (SD) and frequency (percentage), respectively. Continuous variables were compared between participants with different depressive symptom trajectories by ANOVA or the Kruskal-Wallis test. A chi-square test was used to detect significant differences in categorical variables. The hazard ratio (HR) and 95% confidence interval (CI) for mortality were calculated by using a multivariable Cox regression model, with the trajectory of the stable-low symptoms group as the reference. Additionally, we investigated a potential dose-response relationship (P trend) based on median values of CESD-10, employing HRs and 95% CI. The significance level was set at 0.05 (two-sided).

Results

Baseline characteristics and depressive symptom trajectories

In the present research, 13,624 participants (6496 men and 7128 women) were included in the analysis, and the average age was 58.4 $\pm$ 9.0 years. A total of five depressive symptom trajectories were identified in our study (Fig. 3). Trajectory 1 (stable-low symptoms trajectory) included 4894 participants (35.9%) with an average CESD-10 score consistently < 3.5 during follow-up. Trajectory 2 (stable-moderate symptoms trajectory) included 5250 participants (38.5%) whose average CESD-10 score was consistently stable between 8.3 and 7.8 during the follow-up. Trajectory 3 (increasing symptoms trajectory) included 1193 participants (8.8%) with an average CESD-10 score that increased from 9.4 to 18.8. Trajectory 4 (decreasing symptoms trajectory) included 1539 participants (11.3%) whose average CESD-10 score decreased from 18.1 to 10.6. Trajectory 5 (stable-high symptoms trajectory) included 748 participants (5.5%) with an average CESD-10 score consistently > 19.8 during follow-up. All of the baseline characteristics were not balanced between the different groups (Table 1).
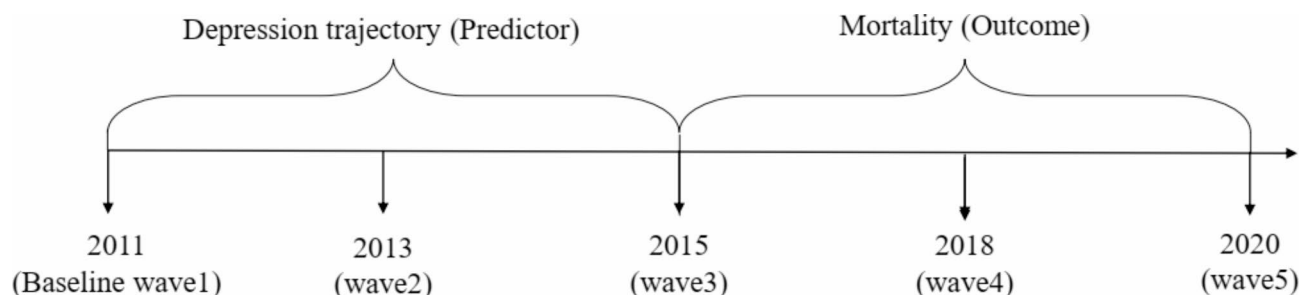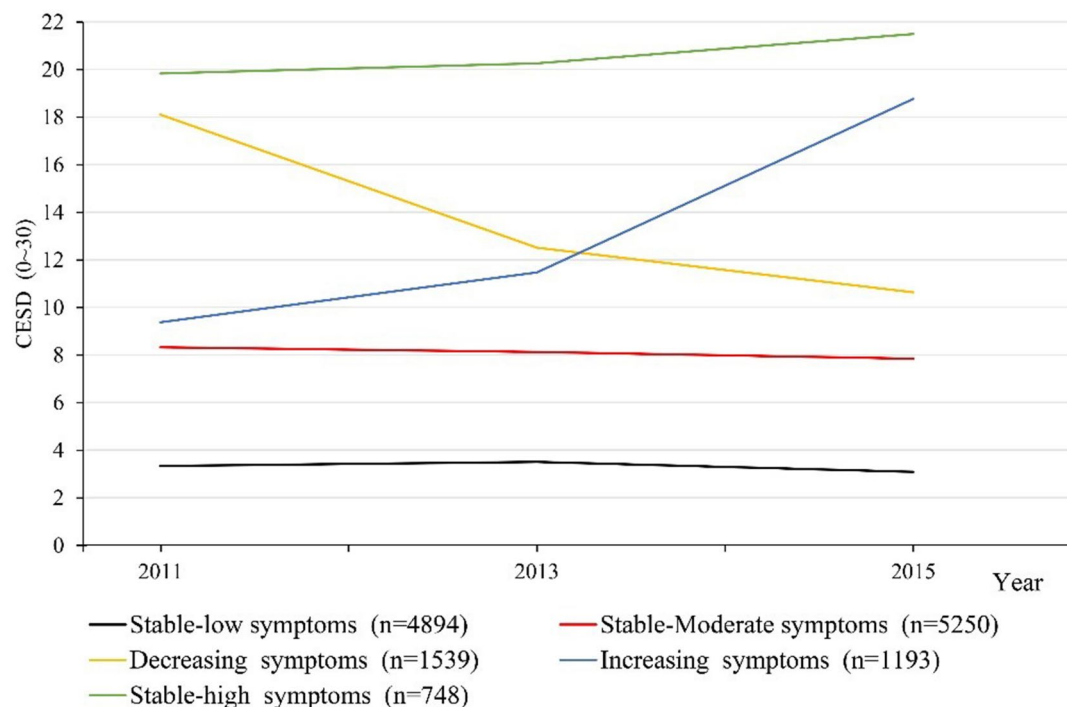

Fig. 2. Timeline of exposure and follow-up assessment.

Fig. 3. Trajectory grouping of depressive symptoms during 2011, 2013 and 2015.

Characteristics	Total	Stable-low	Stable-moderate	Increasing	Decreasing	Stable-high	P value
N	13,624	4894	5250	1193	1539	748	
Age (years)	58.4 ± 9.0	57.7 ± 8.9	58.4 ± 9.1	59.0 ± 8.9	59.8 ± 9.3	59.0 ± 8.5	< 0.0001
Male (n,%)	6496 (47.7)	2821 (57.6)	2484 (47.3)	431 (36.1)	569 (37.0)	191 (25.5)	< 0.0001
BMI (kg/m^2)	23.6 ± 3.9	24.0 ± 3.9	23.6 ± 4.0	23.4 ± 4.1	23.2 ± 3.9	23.1 ± 3.8	< 0.0001
Urban (n,%)	2622 (19.3)	1294 (26.4)	935 (17.8)	154 (12.9)	170 (11.1)	69 (9.2)	< 0.0001
Education level (n,%)							< 0.0001
Elementary school or below	9211 (67.6)	2764 (56.5)	3651 (69.5)	935 (78.4)	1222 (79.4)	639 (85.4)	
Middle or high school	3880 (28.5)	1803 (36.8)	1441 (27.5)	233 (19.5)	297 (19.3)	106 (14.2)	
College or above	533 (3.9)	327 (6.7)	158 (3.0)	25 (2.3)	20 (1.3)	3 (0.4)	
Smoked (n,%)	5368 (39.4)	2148 (43.9)	2082 (39.7)	404 (33.9)	529 (34.4)	205 (27.4)	< 0.0001
Alcohol (n,%)	5355 (39.3)	2154 (44.0)	2042 (38.9)	397 (33.3)	544 (35.4)	218 (29.1)	< 0.0001
Hypertension (n,%)	5275 (38.7)	1798 (36.7)	2031 (38.7)	515 (43.2)	641 (41.7)	290 (38.8)	< 0.0001
Diabetes (n,%)	1046 (7.7)	337 (6.9)	390 (7.4)	119 (10.0)	124 (8.1)	76 (10.2)	0.0004
Cancer (n,%)	134 (1.0)	31 (0.6)	62 (1.2)	11 (0.9)	19 (1.2)	11 (1.5)	0.0252
Heart disease (n,%)	1698 (12.5)	435 (8.9)	629 (12.0)	192 (16.1)	283 (18.4)	159 (21.3)	< 0.0001
Stroke (n,%)	328 (2.4)	75 (1.5)	119 (2.3)	40 (3.4)	56 (3.6)	38 (5.1)	< 0.0001
Follow-up time (months)	56.6 (10.5)	57.0 (9.7)	56.6 (10.7)	56.3 (11.0)	55.9 (11.5)	55.9 (11.6)	< 0.0001
Median survival time (months)	59.9	59.9	59.9	59.9	59.9	59.9	0.2975

Table 1. Baseline characteristics of participants according to depressive symptom trajectories. The *P*-value displays the characteristics of whether there are significant differences between various trajectories.

Association between depressive symptom trajectories and all-cause mortality risk

The HRs (95% CIs) for the risk of all-cause mortality according to the depressive symptom trajectories are shown in Table 2. During the follow-up period from 2015 to 2020, 1194 deaths were reported, for a mortality rate of 8.7%. Subjects with increasing and stable-high depressive symptom trajectories possessed a greater mortality risk than those with stable-low depressive symptom trajectories. After adjusting for age, sex and other covariates, the multivariable-adjusted HRs (95% CIs) for mortality risks were 1.30 (1.06,1.60) and 1.59 (1.26,2.02) among participants in the increasing and stable-high trajectory groups, respectively. Moreover, the risk of mortality had an increasing trend among the different trajectory groups, and we have not identified the significant risk of

	Stable-low	Stable-moderate	Increasing	Decreasing	Stable-high	P trend
Dead cases/ person-years	356/23,257	463/24,755	124/5594	161/7165	90/3486	
Model 1	1.00 (Ref)	1.22 (1.06, 1.40)	1.44 (1.18, 1.77)	1.47 (1.22, 1.77)	1.68 (1.34, 2.12)	< 0.0001
Model 2	1.00 (Ref)	1.17 (1.01, 1.34)	1.47 (1.19, 1.80)	1.33 (1.10, 1.60)	1.83 (1.45, 2.32)	< 0.0001
Model 3	1.00 (Ref)	1.13 (0.98, 1.30)	1.40 (1.13, 1.72)	1.25 (1.03, 1.51)	1.71 (1.35, 2.20)	< 0.0001
Model 4	1.00 (Ref)	1.10 (0.96, 1.27)	1.30 (1.06, 1.60)	1.17 (0.96, 1.41)	1.59 (1.26, 2.02)	0.0004

Table 2. HR (95% CI) of depressive symptom trajectories and mortality during 2015–2020. Model 1 is not adjusted for any variables. Model 2 is adjusted for age, sex and BMI. Model 3 is adjusted for age, sex, BMI, education, location, smoking and drinking. Model 4 is adjusted for age, sex, BMI, education, location, smoking, drinking, hypertension, diabetes, cancer, heart disease and stroke. *P* value trend was to assess whether there is an increased trend in HR among the five groups.

Characteristics	Stable-low	Stable-moderate	Increasing	Decreasing	Stable-high	P trend
Sex						
Male	1.00 (Ref)	1.16 (0.98, 1.38)	1.53 (1.17, 2.01)	1.18 (0.91, 1.53)	1.86 (1.32, 2.61)	0.0007
Female	1.00 (Ref)	1.03 (0.81, 1.31)	1.10 (0.80, 1.53)	1.17 (0.87, 1.56)	1.40 (0.99, 1.96)	0.0454
Age						
< 60	1.00 (Ref)	1.09 (0.82, 1.45)	1.31 (0.84, 2.04)	1.35 (0.90, 2.02)	1.48 (0.87, 2.53)	0.0498
≥ 60	1.00 (Ref)	1.12 (0.95, 1.32)	1.22 (0.97, 1.55)	1.16 (0.93, 1.44)	1.53 (1.17, 2.00)	0.0050
BMI						
< 24	1.00 (Ref)	1.00 (0.84, 1.19)	1.42 (1.11, 1.82)	1.17 (0.93, 1.47)	1.74 (1.33, 2.29)	0.0001
≥ 24	1.00 (Ref)	1.37 (1.08, 1.74)	1.08 (0.73, 1.61)	1.19 (0.83, 1.69)	1.25 (0.76, 2.06)	0.2959
Hypertension						
Yes	1.00 (Ref)	1.20 (0.99, 1.46)	1.21 (0.91, 1.62)	1.27 (0.98, 1.64)	1.95(1.42, 2.69)	0.0005
No	1.00 (Ref)	1.01 (0.82, 1.23)	1.43 (1.06, 1.92)	1.05 (0.78, 1.40)	1.25 (0.87, 1.79)	0.1583
Diabetes						
Yes	1.00 (Ref)	1.23 (0.81, 1.89)	0.88 (0.44, 1.77)	1.49 (0.88, 2.54)	1.38 (0.70, 2.71)	0.2183
No	1.00 (Ref)	1.08 (0.93, 1.25)	1.35 (1.09, 1.68)	1.12 (0.91, 1.38)	1.64 (1.27, 2.12)	0.0008
Smoked						
Yes	1.00 (Ref)	1.20 (0.93, 1.35)	1.44 (1.08, 1.92)	1.06 (0.81, 1.40)	1.53 (1.06, 2.20)	0.0464
No	1.00 (Ref)	1.08 (0.88, 1.33)	1.18 (0.87, 1.59)	1.28 (0.98, 1.68)	1.65 (1.20, 2.27)	0.0017
Alcohol						
Yes	1.00 (Ref)	1.09 (0.89, 1.33)	1.42 (1.05, 1.91)	1.11 (0.83, 1.47)	1.47 (0.99, 2.16)	0.0517
No	1.00 (Ref)	1.12 (0.92, 1.36)	1.22 (0.91, 1.63)	1.22 (0.94, 1.59)	1.68 (1.24, 2.28)	0.0020

Table 3. Subgroup analysis of HR (95% CI) of depressive symptom trajectories for mortality during 2015–2020. *P* value trend was to assess whether there is an increased trend in HR among the five groups.

all-cause mortality in people with decreased and stable-moderate symptom trajectories. In addition, the Kaplan-Meier survival curve showed individuals in the stable-high depressive symptom trajectories had the highest risk of mortality (Supplementary Fig. 1).

Stratified analyses of depressive symptom trajectories and all-cause mortality
In the sensitivity analysis, we explored the associations between different depressive symptom trajectories and the risk of mortality in the subgroup of sex, age BMI, hypertension, diabetes, smoking and alcohol status (Table 3). After adjusting a series of covariates, most of the results were consistent with those in Table 2.

Discussion
In this longitudinal study, we discovered heterogeneous depressive symptom trajectory patterns in a large cohort of 13,624 middle-aged and elderly people in China, and 5 unique depressive symptom trajectory groups were identified through the three investigations from 2011 to 2015. We found that subjects with the increasing and stable-high depressive symptoms trajectories possessed higher all-cause mortality than those with the stable-low depressive symptoms trajectory. Furthermore, we have not identified the significant risk of all-cause mortality in people with decreased and stable-moderate symptom trajectories.

Previous studies have indicated that significant positive relationship between depressive symptoms and the risk of all-cause mortality[18–20]. These researches provide important evidence about the impact of depression states at a single time point on the risk of all-cause mortality. However, the definition of a depressive state was only based on one-time measured depressive symptoms, which was always determined by the first survey. The

process of depression in different populations is unique and varies with changes in influencing factors. Thereby, the study of the relationship between depressive symptoms and outcomes should utilize the process of depressive symptoms rather than a single measurement result.

Currently, few studies have reported the association between the long-time trajectories of depressive symptoms and all-cause mortality. In a previous cohort study in the United States, five depressive symptom trajectories were identified among 7810 US residents aged 50 years and older. It showed that when compared to the non-depressive trajectory group, the group with depressive symptoms trajectory had a significantly greater risk of all-cause mortality[21]. Nevertheless, the percentage of participants in the persistent depressive trajectory group and the improving depressive trajectory group were both less than 5%, which is seriously unbalanced and may affect the results. Another longitudinal cohort study from London used a population-based trajectory model to determine the trajectory of depression and concluded that an increase in depressive symptoms is associated with higher mortality rates[22]. These findings in stroke patients are consistent with our results. In our study, the individuals with high-stable trajectories (CESD-10 score > 19.8) have the highest risk of mortality, which increased by 59%. One prospective cohort study also reported there was a graded positive association between depressive symptoms and mortality[23]. Moreover, previous research shows that approximately 13.2% of patients with depression have a chronic course of more than two years[24]. Meanwhile, individuals with long-term high-level depressive symptoms are more likely to be diagnosed with depression or anxiety, indicating that individuals with this trajectory either already suffer from clinical depression or will continue to suffer in the future[25]. Thus, from a clinical perspective, this group is highly noteworthy. Drug intervention, resistance exercise training, improvements in quality of life, and positive psychological intervention can all improve depressive symptoms[26–29]. Importantly, in our study, we have not identified the risk of all-cause mortality in people with decreased symptom trajectories, when their average CESD-10 score decreased from 18 to 10.8. The all-cause mortality risk of this population could have been overestimated in previous studies. Meanwhile, our results show people with increasing depression symptom trajectories have a high risk of all-cause mortality. Those individuals did not reach the cut-off point for depression symptoms assessment with a CESD-10 score in the first survey, and this group of people is often regarded as normal. Importantly, such individuals usually overlook the risk of all-cause mortality in most single depression assessments. For this reason, our research better elucidated the association between long-term depression and all-cause mortality in Chinese adults. It indicates that through extensive long-term follow-up, a more comprehensive understanding of residents' depression status and its evolving trends can facilitate timely interventions, potentially leading to a significant reduction in all-cause mortality associated with depression.

The potential mechanisms linking depressive symptoms trajectories and all-cause mortality could be attributed to several arguments. First, from a biological perspective, depression and depressive symptoms are usually accompanied by dysregulation of biofeedback mechanisms, such as disturbances in the activity of the HPA axis[30,31], which can contribute to cardiovascular mortality, cancer and suicide behavior, all of these can increase the risk of all-cause mortality[32–34]. Second, the interaction between long-term depression and inflammation may increase the risk of all-cause mortality. Depression can prime larger cytokine responses to pathogens or stressors, leading to immune dysregulation and activation of the inflammatory response system (IRS)[35]. Meanwhile, proinflammatory cytokines, such as interleukin (IL)-1β, IL-2, IL-6 and interferon-gamma, can contribute directly to the development of depressive symptoms[36]. More importantly, these cytokines can facilitate the development of chronic diseases, such as inflammatory bowel disease, by causing tissue damage and triggering persistent inflammation[37]. And the formation of this comorbidity undoubtedly increases the risk of death. Third, individuals with depression may have a higher likelihood of engaging in unhealthy behaviors, including physical inactivity and unfavourable dietary intake[38,39], all of which are recognized as the leading causes of all-cause mortality. Thus, the long-term high depressive symptoms could greatly increase the risk of all-cause mortality through these possible mechanisms and pathways.

The strengths of this study include the large sample size of participants in a national cohort. Additionally, our study provides a valid appraisal of the association between long depressive symptom trajectories and all-cause mortality in Chinese adults. Moreover, a lot of potential confounders were adjusted in the multivariable models. However, several limitations also exist in our study. First, the depression states of participants were defined based on the CESD, which may have led to information bias. However, the reliability of CESD has been proven, and the scale has been widely used in the assessment of depression. Second, some participants were lost to follow-up and were excluded, which may have caused selection bias. Third, self-reported hypertension and diabetes information were dependent on participants' memory and awareness, which lacked clinical verification and may lead to inaccuracies.

In conclusion, people with increasing (from normal to high) and persistent higher depressive symptom trajectories were associated with an increased risk of mortality, while the risk of individuals with decreasing depressive symptoms is probably overestimated. Moreover, it is worth noting that multiple waves of surveys for depressive symptoms can provide some new understanding for specialists and the government regarding the association between long-term depression and mortality.

Data availability
The datasets analysed during the current study are available in the CHARLS repository, www.g2aging.org.

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Y. F, D. H and C. G designed the research; Y. F and C. G analyzed the data; Y. F, D. H and L. C wrote the manuscript; Y. F, D. H, L. C and C. G revised the manuscript. All the authors have approved the final version of this manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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