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Trajectories of depressive symptoms and risk of chronic liver disease: evidence from CHARLS

Xikun Yang[1,2†], Jiangping Ma[3,4†] and Hui Li[1,2*]

Abstract

Background It is unclear whether there is a association between the long-term depressive symptoms and chronic liver disease(CLD). The aim of present study was to investigate the relationship between the trajectories of depressive symptoms and CLD in middle-aged and older Chinese adults.

Methods The study included data from 7351 Chinese individuals, which from the China Health and Retirement Longitudinal Study (CHARLS). Latent Class Growth Model (LCGM) and Growth Mixture Model (GMM) identified five categories of depressive symptom trajectories from 2011 to 2015. Multiple logistic regression models were used to analyze the relationship between depressive symptom trajectories and CLD in 2015–2020.

Results We identified five distinct trajectories of depressive symptoms characterized by persistent low CES-D scores throughout follow-up (low-stable; 4621 cases [62.86%]); high starting CES-D scores but then declining (high-decreasing; 824 cases [11.21%]); persistent high CES-D scores during follow-up (high-stable; 508 cases [6.91%]); starting moderate CES-D scores but then increasing (moderate-increasing; 844 cases [11.48%]); and low starting CES-D scores that increased and then remitted through follow-up (remitting; 554 cases [7.54%]). A total of 420 (5.71%) participants developed chronic liver disease during follow-up. The ORs (95% CI) for the risk of developing chronic liver disease in participants on the moderate-increasing trajectory, high-decreasing trajectory, and high-stable trajectory were 1.44 (1.05–1.93), 1.59 (1.17–2.12), and 2.25 (1.62–3.08), respectively, compared with participants on the low-stable trajectory.

Conclusion In Chinese middle-aged and older adults, individuals with moderate-increasing, high-decreasing, and high-stable trajectories of depressive symptoms over time had an increased risk of developing CLD.

Keywords Chronic liver disease, Depressive symptoms, Trajectory, CHARLS

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Introduction

Chronic liver disease (CLD), which includes chronic viral hepatitis, autoimmune hepatitis, non-alcoholic fatty liver disease(NAFLD)and cirrhosis, poses a huge burden on the world's healthcare systems due to its high morbidity and mortality. It is estimated that more than 1.6 billion people worldwide suffer from CLD [1]. In China, CLD accounts for more than 20% of the population [2]. Liver disease results in around 2 million deaths annually, accounting for 4% of all fatalities [3]. Cirrhosis and its associated complications contribute to roughly 1.16 million of these deaths [4]. Therefore, in order to take appropriate preventive measures earlier and more precisely and to reduce the burden on the health care system, the analysis of risk factors for CLD is particularly necessary.

It has been established that depression can act as an independent risk factor and is positively associated with NAFLD [5, 6] and cirrhosis [7]. Inflammatory and metabolic mechanisms, viral infections, and lifestyle and social factors are possible explanations for linking depression to CLD. However, most of the available evidence on the relationship between depressive symptoms or depression and the risk of CLD involves only a single measure of baseline depressive symptoms and fails to capture the long-term impact of dynamic changes in depressive symptoms on CLD. Depression or depressive symptoms change dynamically over the course of a person's life and may vary from person to person. Individuals with clinically relevant depressive symptoms may recover briefly or have recurrent relapses with intermittent periods of wellness throughout their lives [8]. Thus, trajectory-based approaches can reveal in greater detail how chronic or fluctuating depressive symptoms interact with the body over time, thereby enhancing the predictive validity of chronic disease. Existing evidence suggests that different trajectories of depressive symptoms confer different risks for sarcopenia [9], diabetes [10], arthritis [11], and cardiovascular disease [12], and that their predictive validity is significantly better than the predictive validity of single baseline depressive symptoms. However, no studies have examined the relationship between depressive symptom trajectories and CLD. Studies based on the association between depressive trajectories and CLD are particularly necessary as the unique mechanisms of inflammation and metabolic disorders, viral infections, and other factors in the pathogenesis of CLD may be differentially influenced by long-term depressive states.

Therefore, the aim of this study was to investigate the predictive value of long-term trajectories of depressive symptoms for the development of CLD using data from the China Health and Retirement Longitudinal Study (CHARLS).

Methods

Study population

The CHARLS is an ongoing prospective study of middle-aged and older adults in China. It mainly collected demographic, economic, lifestyle, and health-related information from adults over the age of 45. The first survey began in 2011 with 17,708 participants recruited, followed by follow-up visits every two years. Subsequent surveys were conducted in 2013, 2015, 2018, and 2020. The Ethics Review Board of Peking University approved the study protocol (Approval No. IRB00001052-11015-01) for the main household survey and biomarker collection. Informed consent and repository consent forms were signed by all participants after being informed of the risks and benefits of participating in the study. The details of the CHARLS data are available at its website (http://charls.pku.edu.cn/en).

For this study, we excluded participants with psychiatric disorders ($n = 4798$) and CLD ($n = 1050$) in the first three waves. We subsequently excluded participants with incomplete data on the Centre for Epidemiology Studies Depression Scales (CES-D) in the first three waves ($n = 1662$), as well as those with a lack of CLD data for 2015–2020 ($n = 1357$) and incomplete data at baseline ($n = 1490$). Ultimately, our analysis included 7,351 participants (Fig. 1).

Measurements of depressive symptom

Depressive symptoms were assessed at each wave through face-to-face interviews. The CES-D scale, which consists of 10 items measuring depressive symptoms in the last week, was used and has been widely employed to detect such symptoms in Chinese adults [13, 14]. Each item is scored from 0 to 3, indicating the frequency of the symptom experienced: little or no time (< 1 day), some or little time (1–2 days), occasional or moderate time (3–4 days), and most or all time (5–7 days). The 10 items on the CES-D include feeling bothered by small things, difficulty concentrating, frustration, feeling that everything is an endeavour, hope for the future, fearfulness, restless sleep, happiness, loneliness, and inability to continue. The total CES-D score ranges from 0 to 30 (positive items were reverse coded), with higher scores indicating more severe depressive symptoms [14].

Measurements of chronic liver disease

CLD was diagnosed by a physician and reported by the patient during each visit. This included viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis, but excludes tumors and cancer. The participants' CLD status was classified as either present or absent.

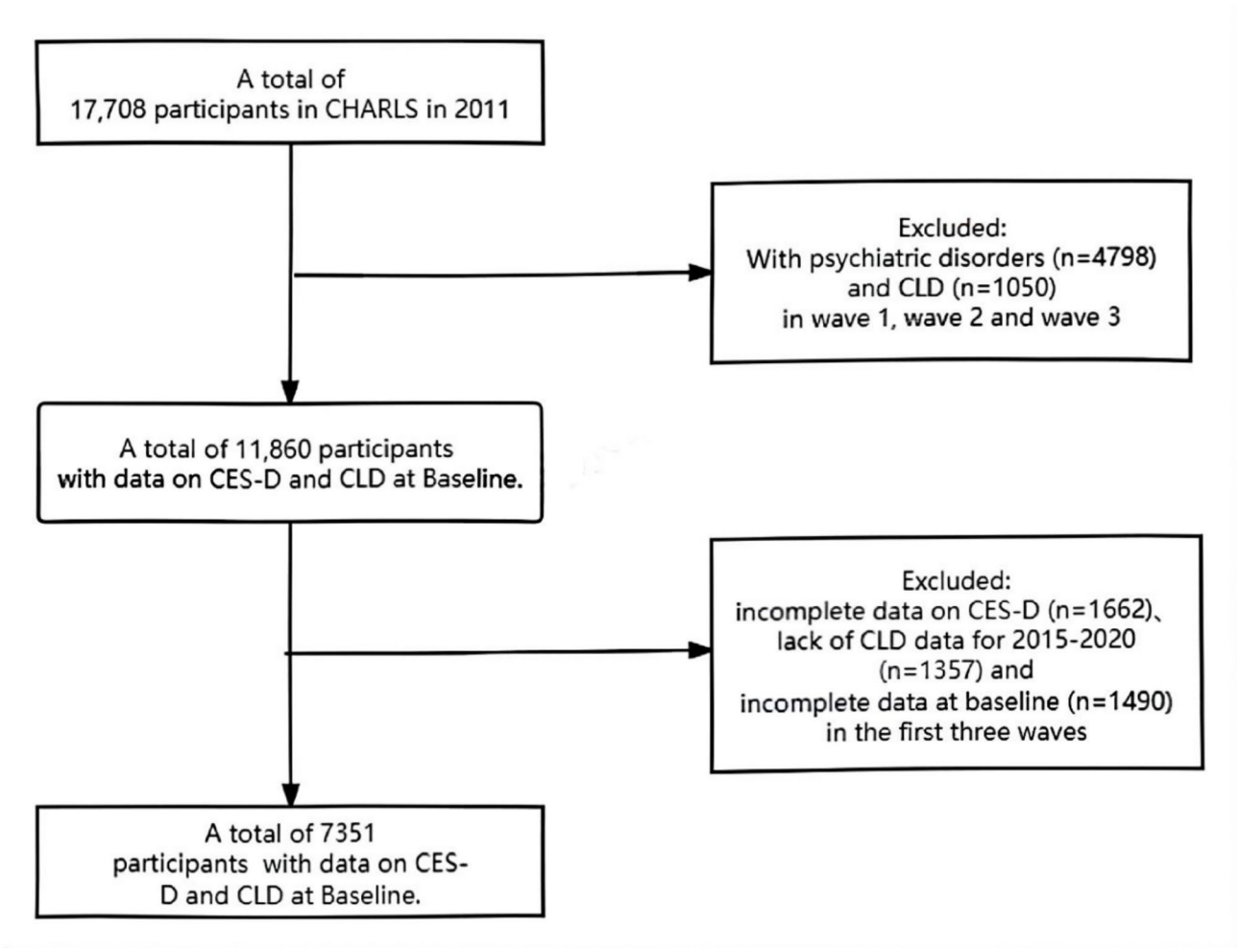

Fig. 1 Flowchart of study participants

Assessment of covariates

At baseline, we collected information on socio-demographic characteristics, lifestyle behaviours, and history of chronic diseases. Covariates were identified based on previous studies [15]. The socio-demographic characteristics of the participants were recorded, including gender, age, educational attainment (categorised as below primary school, secondary to vocational school, and university and above), place of residence (categorised as rural or urban), and marital status (categorised as married or unmarried). Lifestyle behaviours comprise smoking status (never/former/current) and drinking status (never/former/current). History of chronic diseases included hypertension, diabetes, dyslipidaemia, stroke, heart disease (including heart attack, coronary heart disease, angina pectoris, congestive heart failure or other cardiac problems) and kidney disease. Body Mass Index (BMI) was calculated by dividing weight in kilograms by the square of height in metres, the data for which was obtained from body examination.

Depressive symptom trajectories

Depression rating scales were collected for Wave 1-Wave 3 (2011–2015). Latent Class Growth Model (LCGM) andGrowth Mixture Model (GMM) were used to determine the heterogeneity of depressive symptom trajectories. LCGM analyses should be performed to determine the number of latent categories prior to GMM analyses [16]. LCGM was utilized to identify homogeneous clusters of individuals who follow similar developmental trajectories across time [17]. As the relationship between depressive symptom and time may not be linear, we fitted 2–6 sets of depressive symptom trajectories using linear and quadratic functions. Once we identified the optimal LCGM model, we subsequently fitted a GMM model. The number and shape of trajectories were determined optimally based on the following criteria [18]: (1) minimum sample size adjusted for Bayesian Information Criterion (SABIC); (2) mean posterior probability of assignment to each group of trajectory was greater than 0.7; (3) the number of populations in each group accounted for at least 5% of the population; and (4)

the Lo-Mendell-Rubin-adjusted Likelihood Ratio Test (ALRT), the Bootstrap Likelihood Ratio Test (BLRT) and the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR-LRT) had *p*-values less than 0.05.

Statistical analysis

In this study, we initially modeled depressive symptom trajectories from 2011 to 2015 using LCGM and GMM approaches. Later, we compared baseline data among groups with distinct depressive symptom trajectories. Continuous variables were presented as mean ± standard deviation, while categorical variables were shown as percentages. Baseline characteristics for each depressive trajectory type were compared through one-way ANOVA and chi-square tests. We used multifactorial logistic regression to examine the odds ratio (OR) and 95% confidence interval (95% CI) for CLD occurrence across different depressive symptom trajectories. Subgroup analyses and interactive analysis were conducted based on various factors such as age, gender, marital status, education, residential area, smoking, alcohol use, BMI, hypertension, diabetes, stroke, heart disease, dyslipidaemia, and renal issues. To quantify the additive and multiplicative interactions, we additionally included a product term of depressive symptom trajectories and each subgroup variable in the model. Additive interactions emphasize public health relevance (e.g., identifying subgroups with excess risk), whereas multiplicative interactions test biological synergism. The OR with its 95% CI of the product term was the measure of interaction on the multiplicative scale. We assessed additive interactive effects using three distinct metrics: relative excess risk due to interaction (RERI), proportion attributable to interaction (AP), and synergy index (SI). These metrics capture different aspects of interaction, including the part of the effect attributable to interaction, the proportion of the combined effect arising from interaction, and the ratio between the combined effect and individual effects. Specifically, RERI = 0, AP = 0, and SI = 1 indicate the absence of interactive effects between depressive symptom trajectories and each subgroup variable concerning CLD incidence. Conversely, when RERI > 0, AP > 0, and SI > 1, this signifies that the combined effects of depressive symptom trajectories and each subgroup variable on CLD incidence exceed the sum of their individual effects, suggesting synergistic effects. Conversely, if RERI < 0, AP < 0, and SI < 1, it indicates that the combined effects are smaller than the sum of the individual effects of depressive symptom trajectories and each subgroup variable. We computed the corresponding 95% CI for these three metrics using the delta method. And, sensitivity analyses were conducted as follows: (1) conducting analyses after the exclusion of participants who received antidepressant medication or psychotherapy in the first three waves, in order to minimise the effect of antidepressant treatment on the depressive symptom trajectories; (2) calculating E-values to assess the potential impact of unmeasured confounders on conclusions in observational studies; (3) using Cox proportional hazards regression analysis to test the hazard ratios (HR) with 95% confidence intervals (CI) between depressive symptom trajectories and incident CLD; (4) analysing results using complex probability weighting methods; (5) conducting analyses using multiple imputation with chain equations (MICE).

Analysis of depressive symptom trajectories was conducted with Mplus 8.0. Data cleaning and organization were done using SPSS 25.0. Follow-up analysis utilized R 4.2.2 for further data analysis and graphical representation. A two-sided *p*-value < 0.05 was deemed statistically significant.

Results

A total of 7351 participants (3278 males and 4073 females) with a mean age of 57.26 ± 8.73 years were included in this study. We established 5 different categories of depressive symptom trajectories among these 7351 individuals, and although the aBIC of the model for category 6 was reduced compared to category 5, the percentage of some trajectories were less than 5% (Additional file: Table S2). Therefore, we ultimately chose five categories (quadratic) of depressive symptom trajectories for further analysis (Additional file: Table S2). The characteristics of the five categories of trajectories were: low-stable trajectory (low CES-D scores that persisted over the course of follow-up) [4621,62.86%]; high-decreasing trajectory (high starting CES-D scores, but then declining) [824,11.21%]; high-stable trajectory (high CES-D scores that persisted over the course of follow-up) [508,6.91%]; moderate-increasing trajectory (moderate starting CES-D scores, but then increasing) [844,11.48%]; and remitting trajectory (low starting CES-D scores increasing, then moderating through follow-up) [554,7.54%] (Fig. 2).

In the present study, 7351 participants (3278 men and 4073 women) were included in the analysis. A comparison of the baseline characteristics between the participants included in the analysis and those excluded is presented in Additional file: Table S1.

The baseline profile of the participants included in the analysis is shown in Table 1. Among the baseline characteristics, there were statistically significant differences in the distribution of age, sex, marital status, place of residence, education level, history of hypertension, history of stroke, history of dyslipidaemia, history of kidney disease, history of heart disease, smoking, and alcohol consumption among the five trajectories.

During the 2015–2020 follow-up period, a total of 420 (5.71%) of these 7351 participants developed CLD.

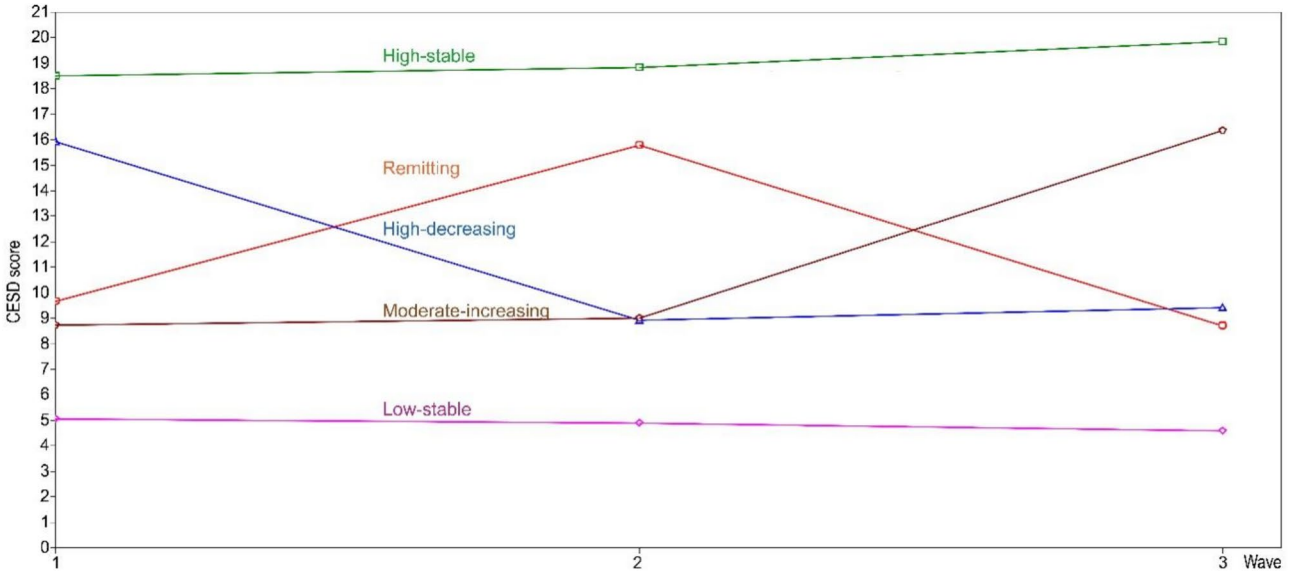

Fig. 2 Trajectories of depressive symptoms from 2011 to 2015

In univariate logistic regression models, the OR (95% CI) for the risk of developing CLD in participants with moderate-increasing trajectory, high-decreasing trajectory, and high-stability trajectory compared with those with low-stability trajectory were 1.44 (1.05–1.93), 1.59 (1.17–2.12), and 2.25 (1.62–3.08), respectively. In the multifactorial logistic regression model, model 1 adjusted for age, gender, education, marital status, and place of residence, model 2 further adjusted for smoking, alcohol consumption, and BMI on the basis of model 1 coming, and model 3 adjusted for history of chronic diseases (hypertension, diabetes mellitus, dyslipidaemia, heart diseases, stroke, and renal diseases) on the basis of model 2, and the results still indicated a moderate-increasing trajectory, a high -decreasing trajectory, and an increased risk of CLD in participants with a high stabilization trajectory compared with a low-stabilization trajectory risk. (Table 2). In subgroup analyses (Table 3), there were significant interactions between depressive symptom trajectories and marital status, smoking status, history of dyslipidaemia and history of heart disease. Specifically, the high-decreasing trajectory exerted a more substantial influence on the incidence of CLD in the married population, the high-stable trajectory exerted a more substantial influence on the incidence of CLD in the smoking population, and the remitting trajectory exerted a more substantial influence on the incidence of CLD in the dyslipidaemia and heart disease population. Furthermore, remitting trajectories may increase the incidence of CLD in individuals under the age of 60 and in those who do not consume alcohol. In interaction analysis (Table 4), no addictive interaction was found between depressive symptom trajectory classes and subgroup variables.

In sensitivity analyses, similar results were found after exclusion of participants who received antidepressant medication or psychotherapy in the first three waves (Additional file: Table S3). The E-values showed the associations of depressive symptom trajectories with CLD were robust (Additional file: Table S4). In the multifactorial Cox regression model, the risk of developing CLD was found to be higher in those with high-stable trajectory, moderate-increasing trajectory, and high-decreasing trajectory, in accordance with the main results (Additional file: Table S5).

Discussion

In our nationally representative prospective cohort study of middle-aged and older Chinese adults, we identified five distinct trajectories of depressive symptoms characterized by: low-stable trajectory (low CES-D scores persisting over follow-up); high-decreasing trajectory (high starting CES-D scores, but then decreasing); high-stable trajectory (high CES-D scores persisting over follow-up); moderate-increasing trajectory (starting moderate CES-D scores, but then rising); and remitting trajectory (i.e., low starting CES-D scores increasing and then moderating through follow-up). We identified five trajectories of depressive symptoms in middle-aged and older Chinese adults by repeated measures of the CES-D using data from the CHARLS from 2011 to 2020. For the first time, the study found that participants with moderate-increasing trajectory, high-decreasing trajectory, and high-stable trajectory were associated with a high risk of developing CLD, whereas participants with typical low stable and remitting trajectories were not at high risk of developing CLD.

Table 1 Baseline characteristics of the study population by depressive symptom trajectories

No. of subjects	All	Low-stable	High-decreasing	High-stable	Moderate increasing	Remitting	*p*.overall
	N = 7351	*N* = 4621	*N* = 824	*N* = 508	*N* = 844	*N* = 554	
Age, years	57.3 ± 8.73	57.0 ± 8.84	58.0 ± 8.92	57.8 ± 8.08	57.7 ± 8.43	57.3 ± 8.53	0.006
Residence, *n* (%)							<0.001
Rural	2385 (32.4%)	1704 (36.9%)	205 (24.9%)	101 (19.9%)	212 (25.1%)	163 (29.4%)	
Urban	4966 (67.6%)	2917 (63.1%)	619 (75.1%)	407 (80.1%)	632 (74.9%)	391 (70.6%)	
Gender, *n* (%)							<0.001
Male	3278 (44.6%)	2380 (51.5%)	308 (37.4%)	116 (22.8%)	289 (34.2%)	185 (33.4%)	
Female	4073 (55.4%)	2241 (48.5%)	516 (62.6%)	392 (77.2%)	555 (65.8%)	369 (66.6%)	
Diabetes, *n* (%)							0.213
No	6985 (95.0%)	4404 (95.3%)	788 (95.6%)	479 (94.3%)	790 (93.6%)	524 (94.6%)	
Yes	366 (4.98%)	217 (4.70%)	36 (4.37%)	29 (5.71%)	54 (6.40%)	30 (5.42%)	
Hypertension, *n* (%)							0.001
No	5659 (77.0%)	3630 (78.6%)	627 (76.1%)	369 (72.6%)	622 (73.7%)	411 (74.2%)	
Yes	1692 (23.0%)	991 (21.4%)	197 (23.9%)	139 (27.4%)	222 (26.3%)	143 (25.8%)	
Stroke, *n* (%)							0.002
No	7227 (98.3%)	4555 (98.6%)	806 (97.8%)	492 (96.9%)	836 (99.1%)	538 (97.1%)	
Yes	124 (1.69%)	66 (1.43%)	18 (2.18%)	16 (3.15%)	8 (0.95%)	16 (2.89%)	
Dyslipidaemia, *n* (%)							0.033
No	6717 (91.4%)	4254 (92.1%)	748 (90.8%)	449 (88.4%)	761 (90.2%)	505 (91.2%)	
Yes	634 (8.62%)	367 (7.94%)	76 (9.22%)	59 (11.6%)	83 (9.83%)	49 (8.84%)	
Chronic kidney disease, *n* (%)							<0.001
No	7021 (95.5%)	4465 (96.6%)	769 (93.3%)	464 (91.3%)	802 (95.0%)	521 (94.0%)	
Yes	330 (4.49%)	156 (3.38%)	55 (6.67%)	44 (8.66%)	42 (4.98%)	33 (5.96%)	
Chronic heart disease, *n* (%)							<0.001
No	6643 (90.4%)	4260 (92.2%)	715 (86.8%)	426 (83.9%)	764 (90.5%)	478 (86.3%)	
Yes	708 (9.63%)	361 (7.81%)	109 (13.2%)	82 (16.1%)	80 (9.48%)	76 (13.7%)	
Drinking status, *n* (%)							<0.001
Never drinker	4959 (67.5%)	2931 (63.4%)	605 (73.4%)	390 (76.8%)	606 (71.8%)	427 (77.1%)	
Former drinker	574 (7.81%)	385 (8.33%)	46 (5.58%)	36 (7.09%)	63 (7.46%)	44 (7.94%)	
Current drinker	1818 (24.7%)	1305 (28.2%)	173 (21.0%)	82 (16.1%)	175 (20.7%)	83 (15.0%)	
Smoking status, *n* (%)							<0.001
Never smokers	4639 (63.1%)	2745 (59.4%)	543 (65.9%)	386 (76.0%)	579 (68.6%)	386 (69.7%)	
Ever smoker	539 (7.33%)	380 (8.22%)	60 (7.28%)	21 (4.13%)	54 (6.40%)	24 (4.33%)	
Current smoker	2173 (29.6%)	1496 (32.4%)	221 (26.8%)	101 (19.9%)	211 (25.0%)	144 (26.0%)	
Marital status, *n* (%)							<0.001
Divorced/separated /widowed/never married	717 (9.75%)	354 (7.66%)	120 (14.6%)	85 (16.7%)	91 (10.8%)	67 (12.1%)	
Married	6634 (90.2%)	4267 (92.3%)	704 (85.4%)	423 (83.3%)	753 (89.2%)	487 (87.9%)	
Education level, *n* (%)							<0.001
Below primary school	5058 (68.8%)	2914 (63.1%)	648 (78.6%)	442 (87.0%)	636 (75.4%)	418 (75.5%)	
Secondary to vocational school	2104 (28.6%)	1542 (33.4%)	172 (20.9%)	64 (12.6%)	198 (23.5%)	128 (23.1%)	
University and above	189 (2.57%)	165 (3.57%)	4 (0.49%)	2 (0.39%)	10 (1.18%)	8 (1.44%)	
Body mass index, kg/m2	24.3 ± 35.3	24.7 ± 43.8	23.3 ± 4.17	23.2 ± 4.12	24.1 ± 16.8	23.7 ± 3.96	0.724

Previous studies have mainly involved the exploration of the relationship between single baseline depressive symptoms and CLD [19, 20]. Kim et al. conducted a cross-sectional study of adults using the 2007–2016 American Health and Nutrition Examination Survey (AHANES) database and found that patients with major depressive disorder (MDD) were 1.6–2.2 times more likely to develop NAFLD than those without MDD [5]. Several other studies utilizing CHARLS have shown that elevated depressive symptoms are associated with an increased risk of CLD [15, 21]. A dose-dependent relationship between the severity of depressive symptoms and the degree of hepatocellular swelling was found by pathologically analyzing the livers of patients with NAFLD, with patients with subclinical MDD being 2.1 times more likely to have hepatocellular swelling and patients with clinical MDD being 3.6 times more likely to have hepatocellular swelling compared to non-depressed

Table 2 Trajectories of depressive symptoms and risk of CLD (multiple logistic regression models)

	Low-stable	Moderate-increasing	High-decreasing	High-stable	Remitting
Case, *n* (%)	218 (4.7)	56 (6.6)	60 (7.3)	51 (10.0)	35 (6.3)
Unadjusted	1.00 (Ref)	1.44 (1.05–1.93)	1.59 (1.17–2.12)	2.25 (1.62–3.08)	1.36 (0.93–1.94)
Age and sex- adjusted	1.00 (Ref)	1.49 (1.09–2.01)	1.63 (1.20–2.18)	2.40 (1.72–3.30)	1.42 (0.96–2.03)
Model1*	1.00 (Ref)	1.53 (1.12–2.07)	1.69 (1.24–2.27)	2.52 (1.79–3.48)	1.45 (0.99–2.08)
Model2**	1.00 (Ref)	1.53 (1.12–2.07)	1.69 (1.24–2.27)	2.52 (1.79–3.49)	1.45 (0.98–2.07)
Model3***	1.00 (Ref)	1.44 (1.04–1.95)	1.55 (1.13–2.09)	2.14 (1.52–2.99)	1.32 (0.89–1.90)

Data are odds ratios (95% CI)

*Model 1 was adjusted for age, sex, education, marital status, residence

**Model 2 was adjusted for BMI, smoking, alcohol consumption and variables in model 1

***Model 3 was adjusted for hypertension, diabetes, stroke, heart disease, kidney disease, dyslipidaemia, and variables in model 2

patients [22]. Depressive symptoms are the result of the interaction of multiple risk and long-term factors, and a single measure of baseline depressive symptoms alone may not adequately reflect an individual's precise depressive state. Therefore, studies of the relationship between depressive symptoms and illness should utilize the long-term course of depressive symptoms. In a prospective study based on an elderly population, three trajectories of depressive symptoms were identified by following 2488 older adults over a 5-year period, during which high and exacerbated depressive symptom trajectories were found to be associated with a significantly increased risk of dementia (OR: 1.94) [23]. The results suggest that depressive symptom trajectory may more accurately predict long-term health status in depressed patients than only a single assessment of depressive symptoms. Similarly, in our study, five depressive symptom trajectories were identified by repeated CES-D measurements in middle-aged and older Chinese adults using data from CHARLS from 2011 to 2020, and for the first time, participants with moderate-increasing trajectory, high-decreasing trajectory, and high-stable trajectory were found to be associated with a high risk of developing CLD.

Although the exact relationship between depressive symptoms and CLD is not known, several studies have found possible explanations in terms of biological mechanisms, lifestyle, and social factors. Persistent chronic inflammatory state, insulin resistance (IR) and hepatitis virus infection and latent reactivation play an important role in the relationship between depression and CLD. It has been found that the levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are significantly elevated in the peripheral blood of depressed patients [24], which suggests that an inflammatory response often accompanies the onset of the disease in depressed patients. The above inflammatory factors can affect the physiological function of the liver through multiple pathways, leading to the occurrence of intrahepatic inflammatory responses and metabolic derangements, which in turn lead to the development of CLD. After binding to its receptor, TNF-α interacts with tumor necrosis factor receptor-associated protein and death structural domain (TRADD), tumor necrosis factor receptor-associated factor 2 (TRAF2), and receptor-interacting protein (RIPK), activating NF-κB, which is the most important cytokine in the liver. interact with each other to activate the NF-κB signaling pathway, forming pro-inflammatory and anti-apoptotic pathways [24], which in turn leads to the development of hepatic inflammatory responses. In addition, TNF-α induces hepatic steatosis by inhibiting amp-activated protein kinase (AMPK) activity, activating sterol regulatory element-binding protein 1 (SREBP-1), and up-regulating the expression of acetyl-coenzyme A carboxylase (ACC) and fatty acid (FA) synthase (FAS), leading to an increase in FA synthesis and an over-accumulation of triglyceride (TG), which in turn leads to hepatic steatosis [25, 26]. TNF-α also induces the production and secretion of IL-6, and the two can combine to cause disease and aggravate NAFLD [26].

Depression has been found to be associated with glucose and insulin metabolism, and depression is positively associated with IR [27]. In the IR state of depressed patients, the insulin signaling pathway is impaired, gluconeogenesis is no longer inhibited, the promotion of hepatic neo-lipogenesis is unabated, and hepatic steatosis is increased, which in turn increases the risk for the development of NAFLD [27]. IR is central to intrahepatic steatosis injury, which damages the liver by permitting excess fatty acids to enter the organ from the adipose tissue, and also by decreasing peripheral glucose uptake in the Liver. Researchers have found that abnormal glucose tolerance and insulin resistance are prevalent in both NAFLD, cirrhosis, and other CLD [28, 29]. Similarly, in our study, we found that in populations with diabetes and moderately increasing trajectories of depressive symptoms, they were strongly associated with a high risk of CLD. Although people with highly decreasing, highly stable depressive trajectories did not have diabetes, their probable IR status and high depressive symptomatic status made it associated with a high risk of CLD.

Previous studies have suggested that depressive symptoms and anxiety can increase the risk of chronic

Table 3 Subgroup analysis of depressive symptoms trajectories for CLD

Characteristics	Low-stable	Moderate-increasing	High-decreasing	High-stable	Remitting	*P* for interaction
Age, years						0.187
< 60	1.00(Ref)	1.55 (1.01–2.30)	1.50 (0.97–2.25)	2.49 (1.57–3.84)	1.62 (1.00-2.53)	
≥ 60	1.00(Ref)	1.31 (0.80–2.09)	1.60 (1.01–2.48)	1.77 (1.03–2.95)	0.94 (0.46–1.73)	
Gender						0.142
Male	1.00(Ref)	1.03 (0.59–1.71)	1.31 (0.80–2.07)	2.84 (1.59–4.82)	1.20 (0.63–2.10)	
Female	1.00(Ref)	1.81 (1.20–2.67)	1.85 (1.22–2.75)	2.07 (1.32–3.18)	1.45 (0.87–2.32)	
Education level						0.068
Below primary school	1.00(Ref)	1.48 (1.02–2.13)	1.68 (1.17–2.37)	2.24 (1.52–3.24)	1.36 (0.85–2.09)	
Secondary to vocational school	1.00(Ref)	1.16 (0.57–2.16)	1.29 (0.63–2.40)	1.78 (0.69-4.00)	1.22 (0.55–2.41)	
University and above	1.00(Ref)	NA	6.00 (1.17–25.15)	NA	2.00 (0.10-12.77)	
Current married						0.007
Yes	1.00(Ref)	1.49 (1.06–2.05)	1.83 (1.33–2.49)	2.38 (1.65–3.39)	1.44 (0.95–2.10)	
No	1.00(Ref)	1.02 (0.37–2.43)	0.37 (0.09–1.09)	1.09 (0.39–2.62)	0.67 (0.16–2.01)	
Residence						0.088
Rural	1.00(Ref)	1.57 (0.88–2.66)	1.22 (0.63–2.19)	1.07 (0.42–2.34)	1.18 (0.58–2.19)	
Urban	1.00(Ref)	1.43 (0.97–2.08)	1.72 (1.19–2.45)	2.58 (1.74–3.75)	1.39 (0.86–2.16)	
Smoking Status						0.004
Never	1.00(Ref)	1.56 (1.06–2.26)	1.89 (1.30–2.70)	1.61 (1.02–2.46)	1.19 (0.72–1.87)	
Former	1.00(Ref)	0.65 (0.14–2.16)	0.66 (0.15–2.07)	1.83 (0.36–6.92)	1.26 (0.19–5.03)	
Current	1.00(Ref)	1.45 (0.75–2.64)	1.13 (0.55–2.14)	4.92 (2.62–8.94)	1.85 (0.89–3.52)	
Drinking Status						0.172
Never	1.00(Ref)	1.47 (1.00-2.11)	1.62 (1.12–2.30)	2.02 (1.33–2.99)	1.56 (1.02–2.32)	
Former	1.00(Ref)	2.62 (0.93–6.78)	2.68 (0.88–7.27)	2.32 (0.60–7.28)	NA	
Current	1.00(Ref)	1.10 (0.50–2.19)	1.13 (0.51–2.25)	3.24 (1.47–6.65)	0.88 (0.26–2.25)	
BMI, kg/m2						0.250
≥ 24	1.00(Ref)	1.11 (0.67–1.78)	1.67 (1.06–2.56)	1.65 (0.94–2.77)	1.24 (0.68–2.10)	
< 24	1.00(Ref)	1.76 (1.15–2.62)	1.48 (0.95–2.25)	2.70 (1.71–4.15)	1.39 (0.81–2.28)	
Hypertension						0.180
Yes	1.00(Ref)	1.51 (0.86–2.55)	1.42 (0.78–2.47)	2.76 (1.56–4.76)	1.50 (0.76–2.77)	
No	1.00(Ref)	1.40 (0.94–2.03)	1.57 (1.08–2.24)	1.86 (1.18–2.84)	1.21 (0.74–1.89)	
Diabetes						0.311
Yes	1.00(Ref)	2.91 (1.04–7.82)	2.68 (0.83–7.83)	2.01 (0.41–7.57)	0.96 (0.14–3.80)	
No	1.00(Ref)	1.36 (0.97–1.88)	1.48 (1.06–2.02)	2.20 (1.54–3.10)	1.34 (0.89–1.95)	
Dyslipidaemia						0.018
Yes	1.00(Ref)	1.99 (0.80–4.61)	1.53 (0.53–3.93)	3.63 (1.48–8.66)	4.29 (1.67–10.46)	
No	1.00(Ref)	1.41 (1.00-1.95)	1.60 (1.15–2.19)	1.99 (1.35–2.88)	1.10 (0.70–1.66)	
Heart disease						0.037
Yes	1.00(Ref)	1.37(0.60–2.92)	1.24(0.59–2.50)	2.13(1.04–4.25)	2.18(1.06–4.32)	
No	1.00(Ref)	1.43(1.01-2.00)	1.60(1.13–2.23)	2.15(1.43–3.14)	1.04(0.64–1.63)	
Stroke						0.367
Yes	1.00(Ref)	4.57 (0.20-54.16)	4.00 (0.45–35.49)	4.57 (0.51–40.86)	NA	
No	1.00(Ref)	1.42 (1.03–1.93)	1.53 (1.11–2.06)	2.12 (1.49–2.96)	1.35 (0.91–1.9)	
kidney disease						0.285
Yes	1.00(Ref)	1.78 (0.54–5.41)	3.24 (1.17–8.84)	3.20 (1.05–9.60)	0.69 (0.10–2.92)	
No	1.00(Ref)	1.42 (1.02–1.95)	1.49 (1.06–2.05)	2.10 (1.44–2.99)	1.40 (0.94–2.03)	

hepatitis B virus infection and reactivation of latent infection. Results of a retrospective study showed that the median time to hepatitis B episode was significantly shorter in the anxious or depressed cohort compared to the control cohort, and by the end of follow-up, the risk of hepatitis B episode was significantly higher in patients with anxiety or depression than in those without (3017/100,000 person-years vs. 2042/100,000 person-years, respectively; $P = 0.003$), and a multifactorial corrected for age and comorbidities factor analysis showed that anxiety or depression was independently associated with an increased risk of hepatitis B episodes [30]. Studies at the level of molecular mechanisms have found higher levels of IL-10 in the peripheral blood of patients

Table 4 Interaction analysis of covariates and depressive symptoms trajectories

	multiplicative interaction	additive interaction		
		RERI	AP	SI
Age, years	1.534(1.005,2.278)	2.553(-1.077,6.182)	0.469(0.194,0.744)	2.350(1.337,4.131)
Gender	1.060(0.605,1.748)	0.859(-2.010,3.728)	0.209(-0.299,0.716)	1.380(0.607,3.138)
Education level	1.482(1.018,2.118)	2.644(-0.694,5.982)	0.475(0.232,0.719)	2.378(1.446,3.911)
Current married	1.026(0.367,2.478)	-0.006(-0.665,0.653)	-0.017(-1.995,1.960)	1.009(0.372,2.734)
Residence	1.605(0.900,2.708)	0.897(-0.960,2.754)	0.393(0.0314,0.754)	3.310(0.717,15.281)
Smoking status	1.572(1.068,2.269)	2.292(-0.733,5.317)	0.478(0.230,0.725)	2.520(1.526,4.164)
Drinking status	1.136(0.516,2.228)	0.752(-3.196,4.700)	0.187(-0.560,0.935)	1.333(0.404,4.401)
BMI, kg/m2	1.694(1.117,2.508)	2.882(-1.026,6.789)	2.882(-1.026,6.789)	2.583(1.487,4.486)
Hypertension	1.382(0.930,1.999)	1.530(-0.715,3.775)	0.392(0.114,0.670)	2.116(1.239,3.615)
Diabetes	1.365(0.971,1.884)	1.794(-0.498,4.086)	0.399(0.153,0.645)	2.055(1.284,3.288)
Dyslipidaemia	1.395(0.988,1.934)	1.782(-0.473,4.037)	0.412(0.171,0.654)	2.156(1.352,3.437)
Heart disease	1.506(0.670,3.137)	2.545(-4.012,9.102)	0.4667(-0.043,0.977)	2.333(0.818,6.657)
Stroke	1.419(1.029,1.928)	1.927(-0.341,4.195)	0.423(0.198,0.648)	2.180(1.408,3.377)
kidney disease	1.426(1.020,1.958)	1.920(-0.424,4.263)	0.422(0.189,0.656)	2.182(1.385,3.439)

with major depression [31], a finding that was similarly confirmed in a meta-analysis [32]. IL-10 is a potent immunosuppressive factor with multidirectional biological activity that alters the body's immune response and the expression of major histocompatibility complex-like antigens, which can lead to HBV-specific suppression of CD8 T-cell responses. Thus, patients with depressive symptoms may have a reduced ability to clear pathogens, thereby increasing the risk of HBV outbreaks.

In lifestyle and social factors. Firstly, certain risky behaviors are more prevalent in individuals with depressive symptoms [33], like reduced physical activity, high-calorie diets, and smoking, all of which could be risk factors for CLD development. Secondly, mental and psychological stress can also escalate the chances of CLD. Intense depressive symptoms heighten mental and psychological stress, placing strain on the nervous, endocrine, and other systems. These physiological reactions might impact liver functions and contribute to the onset and progression of CLD [30, 34].

In the subgroup analyses of the moderated trajectory, we found a correlation with a high risk of CLD in the group aged < 60 years, who had never consumed alcohol, who had dyslipidaemia, and who suffered from heart disease. In interpreting the above results, some explanations can be made in terms of the following possibilities: first, in the age < 60 group, there are fewer risk factors for CLD, so they may be more susceptible to be affected by depression and show an association with a high risk of CLD; Secondly, moderate alcohol consumption can produce a certain degree of relaxation and pleasure, allowing people to escape from stress and depression for a short period of time, so that groups who have never consumed alcohol may be more affected by depression and may be associated with a higher risk of CLD; thirdly, in groups suffering from hyperlipidemia, the adverse effects of blood lipids on the liver may play a dominant role in the outcome of a higher risk of CLD; lastly, the decline in heart function leads to the obstruction of the circulatory system, which then affects the physiological function of the liver and results in the development of CLD, so groups who suffer from cardiovascular disease may show an association with a high risk of CLD.

Based on data from the CHARLS study, we conducted a nationally representative prospective cohort study in China with a long follow-up period. This study utilized a large sample of the Chinese population to describe long-term changes in depression using a latent growth model (group-based trajectory model) after adjusting for a large number of confounders, and performed rich subgroup analyses, sensitivity analyses, and interaction analyses to explore the relationship between depressive symptom trajectories and CLD, providing a valid assessment of the relationship between depressive symptom trajectories and CLD risk; however, the there are some noteworthy limitations of our study as well. First, depressive symptoms were defined according to the CES-D, whereas CLD was assessed using retrospective self-report, which may lead to biased information. Second, the findings are applicable only to the middle-aged and elderly Chinese population, and may have less applicability to other age classes in China and to populations in other countries. Third, the failure to take into account the bidirectional relationship between CLD and depressive symptoms may be a limitation. Fourth, the lack of data on CLD severity, which prevented us from analyzing the relationship between depressive symptoms and CLD severity, may be a limitation.

In summary, in this prospective study based on a Chinese middle-aged and elderly population, we identified five trajectories of depressive symptoms and found that participants with a moderate-increasing trajectory,

a high-decreasing trajectory, and a high-stable trajectory were associated with a high risk of developing CLD. Research into the categorisation of depressive trajectories can help to target treatment for those at high risk of CLD, leading to more effective management. High-risk trajectory suggest the need for earlier and more intensive monitoring and treatment, and can impede the development of CLD to some extent. To reduce the risk of CLD, effective treatments and psychological interventions can be implemented for patients with depressive symptoms.

Conclusion

In this study, five distinct 4-year trajectories of depressive symptoms were identified: the low-stable, high-stable, moderate-increasing, high-decreasing, and remitting depressive symptom trajectories. The high-stable, moderate-increasing, and high-decreasing depressive symptom trajectories may increase the risk of CLD in middle-aged and older adults. However, the remitting depressive symptom trajectory does not appear to have the same effect.

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Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03943-7.

Supplementary Material 1: Table S1 demonstrates the comparison of baseline information for the included/non-included population of this study. Supplementary Material Table S2 demonstrates the comparison of information from different trajectory models. Tables S3, S4, and S5 of the Supplementary Material demonstrate the sensitivity analyses of this study (exclusion of the antidepressant-treated population, assessment of the effect of potential confounders by E-values, or analysis using the COX proportional risk model)

Author contributions

Xikun Yang: Study design, data collection and, Formal analysis, Visualization, Writing an original draft. Jiangping Ma: Study design, data collection and, Formal analysis, Visualization, Writing an original draft. Hui Li: Supervision, Project administration, Writing a review & editing, All authors read and approved the final manuscript.

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Data availability

The datasets utilised in this investigation are available in online repositories. The names of the repository and the accession number(s) can be found at the following link: http://charls.pku.edu.cn/en.

Declarations

Consent for publication

Not Applicable.

Human ethics and consent to participate

The protocol received approval from the Ethical Review Committee of Peking University (approval numbers: IRB00001052-11015 for the main household survey and IRB00001052-11014 for biomarker collection). The study was conducted in compliance with the Declaration of Helsinki principles. All participants signed the informed consent and repository consent that permitted their data to be shared after a detailed presentation of the risks and benefits related to study participation.

Competing interests

Authors state no conflict of interest.

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