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Association between changes in depressive symptoms and risk of anemia: from the China Health and Retirement longitudinal study

Yucong Bi[1,2], Liping Zheng[1], Leping Zhang[1], Longyang Han[4], Yang Liu[3], Xiaowei Zheng[4*] and Chongke Zhong[1*]

Abstract

Background Previous studies have reported that anemia was associated with depression, but the association between changes in depressive symptoms and the risk of anemia was unclear. This study aimed to explore whether changes in depressive symptoms were associated with anemia among the middle-aged and elderly adults.

Methods A total of 6112 patients aged 45 years and older from the China Health and Retirement Longitudinal Study (CHARLS) were included in this analysis. Elevated Depression Symptoms (EDS) was defined as the Center for Epidemiological Studies Depression Scale-10 score ≥ 10. Depression status was defined as no depressive symptom [no EDS at Wave 1 (2011–2012) and Wave 2 (2013–2014)], decreasing depressive symptoms (EDS at Wave 1, no EDS at Wave 2), increasing depressive symptoms (no EDS at Wave 1, EDS at Wave 2), persistent depressive symptoms (EDS at Wave 1 and Wave 2). Multivariable logistic regression analyses were conducted to estimate the relationships between depressive symptoms and the changes and risk of anemia.

Results During the follow-up of Wave 1 and Wave 3 (2015–2016), 906 participants (14.82%) developed anemia, the multivariable-adjusted odds ratio for the depressive symptom compared with the no depressive symptom was 1.24 (95% CI, 1.12–1.58) for anemia. From Wave 2 to Wave 3, there were 828 participants (14.62%) diagnosed with anemia. Compared to participants with no depressive symptom, those with persistent depressive symptoms during Wave 1 and Wave 2 had the significantly elevated risk of anemia (odds ratio 1.44, 95% CI 1.21–1.84).

Conclusions The present study demonstrated that baseline depressive symptoms and changes in depressive symptoms were associated with increased risks of anemia.

Keywords Depressive symptoms, Anemia, Dynamic changes, Middle-aged and older Chinese adults

*Correspondence:
Xiaowei Zheng
zxw19921212@163.com
Chongke Zhong
ckzhong@suda.edu.cn
[1]Department of Epidemiology, School of Public Health, Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, MOE Key Laboratory of Geriatric Diseases and Immunology, Suzhou Medical College of Soochow University, 199 Renai Road, Industrial Park District, Suzhou, Jiangsu Province 215123, China
[2]The First Hospital of Jiaxing, Jiaxing, China
[3]Department of Cardiology, First Affiliated Hospital of Soochow University, Suzhou, China
[4]Public Health Research Center, Department of Public Health and Preventive Medicine, Wuxi School of Medicine, Jiangnan University, 1800 Lihu Road, Binhu District, Wuxi, Jiangsu Province 214122, China

Text box 1. Contributions to the literature

Depressive symptoms were associated with a 24% increased risk of anemia.

Depressive symptoms changes were associated with the risk of anemia.

Participants with persistent depressive symptoms had a 44% increased risk of anemia.

Introduction

Depressive symptom, a common illness, has become one of the most severe psychiatric disorders all over the world. The prevalence of depression is high in China, especially in middle-aged and elderly Chinese adults [1, 2]. The depressive disorders are common across the life course and are present in up to a third of older adults [3]. Numerous epidemiological studies have shown that depression is associated with an increased risk of cardiovascular disease and all-cause mortality [4–7]. Depressive symptom limits psychosocial functioning and diminishes quality of life, and is one of the leading causes of disease burden worldwide [8, 9].

People with depression may suffer from poor health behaviors, such as excessive alcohol consumption or malnutrition caused by an unhealthy diet, which may trigger a drop in hemoglobin levels [10]. Anemia is manifested by a decrease in hemoglobin levels that is more common in the elderly [11]. Previous studies have reported that anemia affects individual's quality of life and physical function [12, 13]. Currently, most studies have assessed the relationship between anemia and risk of depression [14–17], only a few studies have evaluated whether depressive symptoms would increase the risk of subsequent anemia or decreased hemoglobin levels [10, 18–21]. The InCHIANTI study indicated that the risk of anemia progressively and significantly increased with increasing depression severity [18]. A recent cohort study suggested that depression symptoms seemed related to anemia in the middle-aged and elderly in China [22]. However, the Netherlands Study of Depression and Anxiety showed that there was no independent association between depressive disorders and hemoglobin levels or anemia status [21]. Up to now, evidence of longitudinal association of depression with risk of anemia or decreased hemoglobin levels is still lacking.

Furthermore, depressive symptoms were only measured at baseline in most studies, which could not capture within-person and inter-person variation over time. Therefore, single time assessment of depressive symptoms may be insufficient to reveal the complex predictive effects of depressive fluctuations. Since depressive disorders may vary considerably over the course of a lifetime [23, 24], it is needed to assess the dynamic changes of depressive symptoms and risk of anemia.

This study aimed to explore the relationships between changes in depressive symptoms and risk of anemia among middle-aged and older Chinese adults, using data from the China Longitudinal Study of Health and Retirement (CHARLS).

Methods

Study sample

This study was derived from the CHARLS, which used a multistage clustering sample method to select participants in China [25]. A total of 17,708 participants from 10,257 households recruited from 28 provinces within China were included at baseline (2011–2012, Wave 1). CHARLS respondents are followed every 2 years, using a face-to-face computer-assisted personal interview. Three subsequent follow-ups were carried out in 2013–2014 (Wave 2) and 2015–2016 (Wave 3). The design details and main results have been described previously [26]. The inclusion criteria were as follows: (1) aged ≥ 45 years; (2) reported 2 complete measurements (Wave 1, Wave 2) about depressive symptoms evaluated by the Center for Epidemiological Studies Depression Scale-10 (CESD-10); (3) reported 2 complete measurements (Wave1, Wave 3) about hemoglobin level. Participants without data about study outcome (anemia, Wave 3) were excluded. Finally, a total of 6112 participants were included in this analysis (Fig. 1).

The CHARLS study was approved by the institutional review board of Peking University. Written informed consent was obtained from all participants.

Measurements of depressive symptoms

Data was collected through face-to-face interviews by trained personnel at each wave including depressive symptoms. The CESD-10 was administrated to measure depressive symptoms at baseline and each follow-up visit of the CHARLS [27], which has been proved to be a reliable and valid approach to detect depression in Chinese adults [28, 29]. The CESD-10 scale consists of 10 items, including depression and positive affected parts. The total score ranges from 0 to 30, depressive symptom was defined as a CESD score of ≥ 10 [30]. Among those with CESD score ≥ 10, the higher the score, the higher the degree of depressive symptoms. In this study, all participants were classified into 4 groups according to the first and second wave of depression. Depression status was defined as No depressive symptom [no Elevated Depression Symptoms (EDS) at Wave 1 and Wave 2], Decreasing depressive symptoms (EDS at Wave 1, no EDS at Wave 2), Increasing depressive symptoms (no EDS at Wave 1, EDS at Wave 2), Persistent depressive symptoms (EDS at Wave 1 and Wave 2).

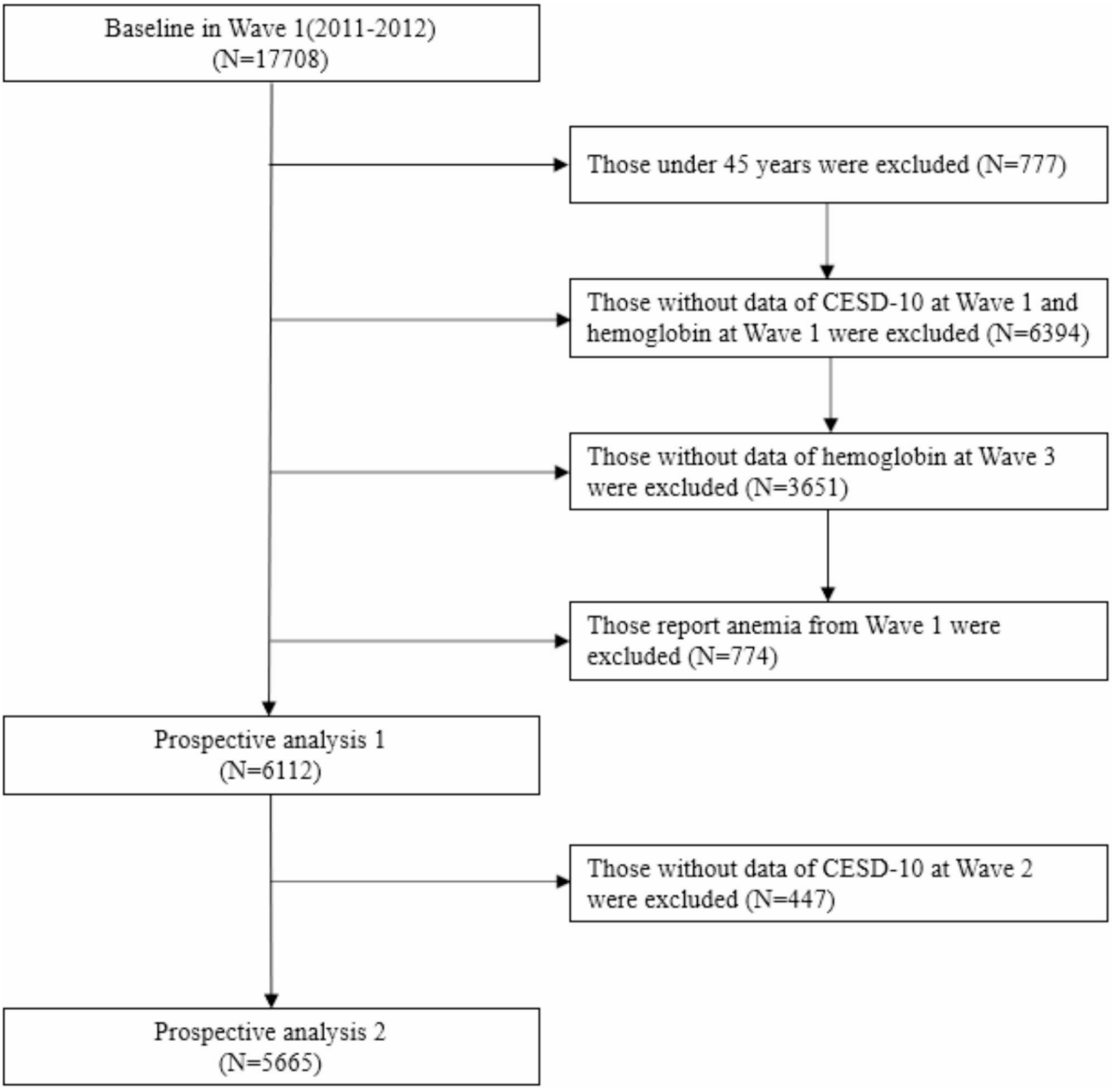

Fig. 1 Flow chart of sample selection and exclusion criteria. Prospective analysis 1: The association between depressive symptoms at Wave 1 (2011–2012) and anemia at Wave 3 (2015–2016). Prospective analysis 2: The association between changes in depressive symptoms between Wave 1 (2011–2012) and Wave 2 (2013–2014) and anemia at Wave 3 (2015–2016)

Covariates assessments

At baseline, trained interviewers used a structured questionnaire to collect information on socio-demographic status and health-related factors. Sociodemographic variables included age, sex, educational level (Illiteracy, Primary school, Middle school or above), living place (rural or urban). Health-related factors included smoking status (ever smoking vs. never smoking), drinking status (ever drinking or never drinking), and 8 common co-morbidities (hypertension, dyslipidemia, diabetes mellitus, heart disease, stroke, psychiatric disease, liver disease, and asthma). Body mass index was defined as weight in kilograms divided by the square of height in meters. "Ever smoking" means that the respondent reported smoking at some point, and "never smoking" means that the respondent reported never having smoked. "Ever drinking" means that the respondent reports having had an alcoholic beverage in the past, and "never drinking" means that the respondent reported not having any alcoholic beverage in the past. Common co-morbidities were

measured with the following question: "Have you been diagnosed with conditions listed below by a doctor?" The conditions included hypertension, dyslipidemia, diabetes mellitus, heart disease, stroke, psychiatric disease, liver disease, and asthma. Each condition was assessed by trained investigators separately.

Outcome assessments

The details on blood sampling and determination of biological parameters have been described previously [31]. Anemia was defined according to the World Health Organization (WHO) criteria as a hemoglobin (Hb) concentration < 12 g/dl (7.5 mmol/l) in women and < 13 g/dl (8.1 mmol/l) in men (Fig. 2).

Statistical analysis

The baseline characteristics among the four groups were compared. Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as frequency (percentage). Generalized linear regression models were applied for trends across depression status for continuous variables, and chi-square trend tests were used for categorical variables. Binary logistic regression model was conducted to estimate the relationships between baseline depressive symptoms and changes in depressive symptoms with anemia, with the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Multivariable logistic regression models adjusted for age, sex, living place, education level, smoking, drinking, body mass index, systolic blood pressure, antidepressant, Mini-Mental State Examination score, and medical history (hypertension, dyslipidemia, diabetes mellitus, heart disease, stroke, psychiatric disease, liver disease, and asthma).

Due to some demographic characteristics and medical histories may affect the association between changes in depressive symptoms and anemia, we further conducted subgroup analyses to assess whether the relationships were potentially modified by age, sex, educational level, living place, smoking, drinking, history of hypertension and diabetes. Twelve is another cut point for CESD score, to examine the robustness of the findings, we conducted a sensitivity analysis by defining depressive symptom as a CESD score ≥ 12 [32].Multiple imputation for missing covariate values was performed using the Markov chain Monte Carlo method. All *P* values were 2-tailed, and a significance level of 0.05 was used. Data analyses were performed using SAS, version 9.4 (SAS Institute Inc; Cary, North Carolina, USA).

Results

Baseline characteristics

A total of 6112 participants (2856 men and 3256 women) were included in the current study, and the mean age of participants was 58.47 ± 8.52 years. Baseline

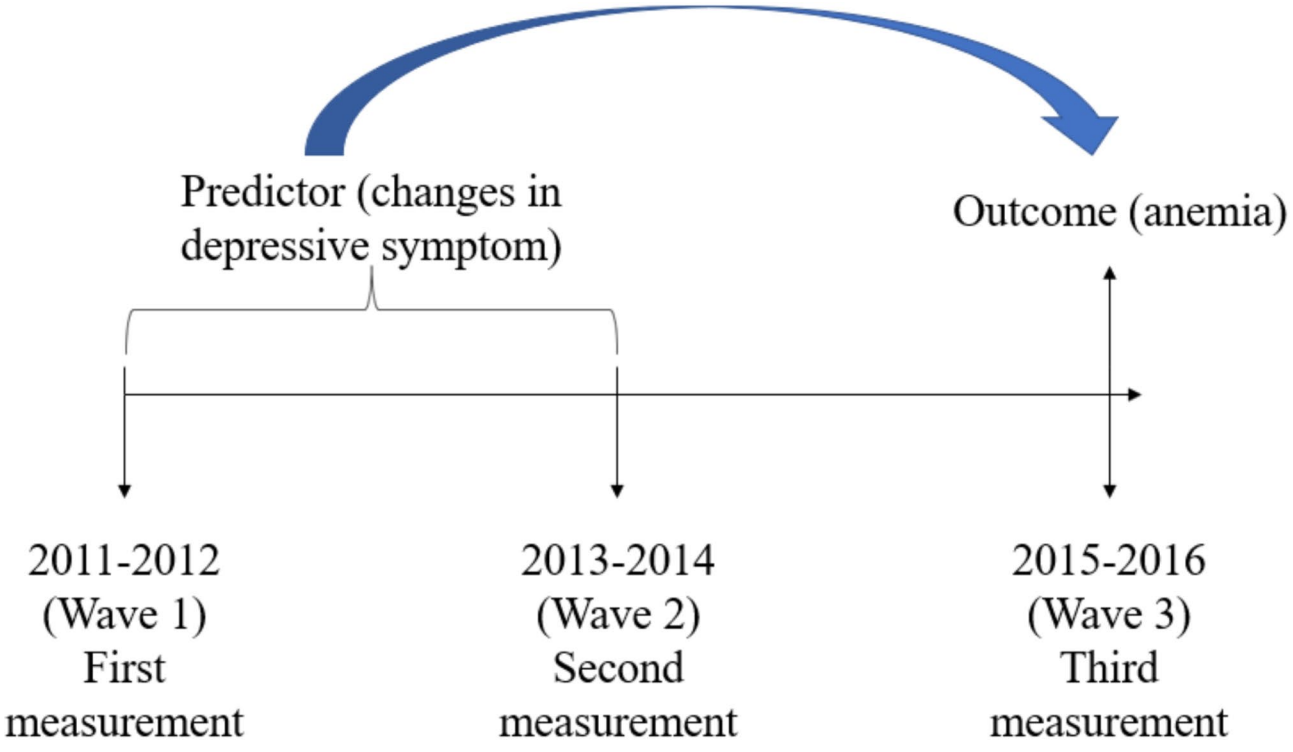

Fig. 2 Timeline of exposure and follow-up assessment

characteristics of participants according to changes in depressive symptoms are presented in Table 1. The baseline characteristics such as sex, living place, education level, history of hypertension, history of dyslipidemia, history of heart problems, history of stroke, history of psychosis, history of liver disease, history of asthma, smoking, drinking, body mass index and antidepressant medication were significantly different among the four groups (Table 1).

Prospective associations of changes in depressive symptoms with anemia

During the follow-up of Wave 1 and Wave 3, 906 participants patients (14.82%) developed anemia. In age- and sex-adjusted model, participants with depressive symptoms at Wave 1 had a higher risk of anemia at Wave 3, compared with those with no depressive symptom. After additional adjustment for living place, education level, smoking, drinking, body mass index, systolic blood pressure, antidepressant and medical history, the OR for participants with depressive symptoms was 1.24 (95% CI 1.12–1.58) for the risk of anemia.

From Wave 2 to Wave 3, there were 828 participants (14.62%) diagnosed with anemia (Table 2). Compared to those with no depressive symptom, multivariable logistic regression models showed that participants with persistent depressive symptoms during Wave 1 and Wave 2 had the significantly elevated risk of anemia (OR 1.44, 95% CI 1.21–1.84). In addition, the subgroup analyses revealed that age, sex, educational level, living place, smoking, drinking, history of hypertension and diabetes did not modify the relationship between depressive symptoms and anemia (*P* for interaction > 0.05; Table 3). Persistent depressive symptoms were associated with increased risk of anemia in most strata.

Furthermore, in our sensitivity analysis, when depressive symptom was defined as a CESD score ≥ 12, multivariable logistic regression models showed that participants with persistent depressive symptoms had

Table 1 Characteristics of participants according to changes in depressive symptoms from Wave 1 (2011–2012) to Wave 2 (2013–2014)

Characteristics	No depressive symptom	Decreasing depressive symptoms	Increasing depressive symptoms	Persistent depressive symptoms	*P* trend
No. of subjects	2865	980	674	1146	
Age, years	58.10 ± 8.40	59.60 ± 8.50	57.51 ± 8.22	58.54 ± 8.16	0.444
Sex, n (%)					< 0.0001
Male	1581 (55.18)	402 (41.02)	288 (42.73)	373 (32.55)	
Female	1284 (44.82)	578 (58.98)	386 (57.27)	773 (67.45)	
Living place, n (%)					< 0.0001
Urban	1744 (60.87)	700 (71.43)	466 (69.14)	825 (71.99)	
Rural	1121 (39.13)	280 (28.57)	208 (30.86)	321 (28.01)	
Education, n (%)					
Illiteracy	703 (44.24)	323 (20.33)	195 (12.27)	368 (23.16)	< 0.0001
Primary school	1306 (55.11)	415 (17.51)	261 (11.01)	388 (16.37)	< 0.0001
Middle school or above	1180 (69.17)	185 (10.84)	164 (9.61)	177 (10.38)	< 0.0001
Medical history					
Hypertension, n (%)	728 (25.41)	290 (29.59)	188 (27.89)	385 (33.60)	< 0.0001
Dyslipidemia, n (%)	288 (10.05)	107 (10.92)	81 (12.02)	167 (14.57)	0.0007
Diabetes mellitus, n (%)	164 (5.72)	61 (6.22)	56 (8.31)	89 (7.77)	0.023
Heart disease, n (%)	277 (9.67)	135 (13.78)	93 (13.80)	227 (19.81)	< 0.0001
Stroke, n (%)	47 (1.64)	31 (3.16)	17 (2.52)	38 (3.32)	0.003
Psychiatric disease, n (%)	15 (0.52)	12 (1.22)	9 (1.34)	23 (2.01)	0.0003
Liver disease, n (%)	81 (2.83)	40 (4.08)	19 (2.82)	61 (5.32)	0.0008
Asthma, n (%)	88 (3.07)	53 (5.41)	33 (4.90)	109 (9.51)	< 0.0001
MMSE score	24 (22–26)	24 (21–26)	24 (22–26)	23 (21–26)	< 0.0001
Antidepressant medication, n (%)	12 (33.33)	8 (22.22)	4 (11.11)	12 (33.33)	0.003
Smoking, n (%)	1255 (43.80)	371 (37.86)	258 (38.28)	375 (32.72)	< 0.0001
Drinking, n (%)	1239 (43.25)	387 (39.49)	239 (35.46)	376 (32.81)	< 0.0001
BMI (kg/m^2)	24.13 (21.70-25.79)	23.78 (21.16–25.60)	24.34 (21.62-26.00)	23.55 (21.11–25.43)	0.004
SBP, mmHg	131.53 ± 24.20	131.31 ± 24.45	131.75 ± 20.92	130.24 ± 24.63	0.198

Abbreviations MMSE: Mini-Mental State Examination score; BMI: body mass index; SBP: systolic blood pressure

Continuous variables are expressed as mean ± standard deviation or median (interquartile range)

Categorical variables are expressed as frequency (percentage)

Table 2 Prospective analyses of depressive symptoms and anemia

	Anemia (Wave 3, 2015–2016)		
	Case (%)	Model 1	Model 2
Depressive symptoms at Wave 1 (2011–2012)			
No depressive symptom	500 (13.15)	1.00 (ref)	1.00 (ref)
Depressive symptoms	406 (17.58)	1.31 (1.13–1.51)	1.24 (1.12–1.58)
Changes in depressive symptoms between Wave 1 (2011–2012) and Wave 2 (2013–2014)			
No depressive symptom	377 (13.16)	1.00 (ref)	1.00 (ref)
Decreasing depressive symptoms	145 (14.80)	1.06 (0.83–1.31)	1.04 (0.72–1.29)
Increasing depressive symptoms	85 (12.61)	0.94 (0.73–1.21)	0.97 (0.84–1.24)
Persistent depressive symptoms	221 (19.28)	1.46 (1.21–1.76)	1.44 (1.21–1.84)
P value for trend		0.0006	0.0016

Model 1: adjusted for age, sex

Model 2: adjusted for age, sex, living place, education level, smoking, drinking, body mass index, systolic blood pressure, antidepressant, Mini-Mental State Examination score, medical history (hypertension, dyslipidemia, diabetes mellitus, heart disease, stroke, liver disease, psychiatric disease, asthma)

Table 4 Sensitivity analysis of changes in depressive symptoms (from Wave 1 to Wave 2) and anemia

	No depressive symptom	Decreasing depressive symptoms	Increasing depressive symptoms	Persistent depressive symptoms	*P* trend
Case, n (%)	457 (13.03)	140 (14.61)	88 (15.94)	143 (18.77)	
Age and sex-adjusted	1.00(ref)	1.23 (1.00-1.52)	1.23 (0.96–1.58)	1.42 (1.15–1.75)	0.0006
Multivariable-adjusted	1.00(ref)	1.18 (0.93–1.40)	1.21 (0.97–1.63)	1.39 (1.14–1.72)	0.0011

Depressive symptom was defined as a CESD score ≥ 12

Multivariable adjusted model included age, sex, living place, education level, smoking, drinking, body mass index, systolic blood pressure, antidepressant, Mini-Mental State Examination score, medical history (hypertension, dyslipidemia, diabetes mellitus, heart disease, stroke, liver disease, psychiatric disease, asthma)

the significantly elevated risk of anemia (OR 1.39, 95% CI 1.14–1.72, Table 4).

Table 3 Subgroup analyses of the association between changes in depressive symptoms (from Wave 1 to Wave 2) and anemia

Characteristics	No depressive symptom	Decreasing depressive symptoms	Increasing depressive symptoms	Persistent depressive symptoms	*P* trend	*P* interaction
Sex						0.984
Male	1.00(Ref)	0.74 (0.36–0.94)	1.06 (0.73–1.51)	1.43 (0.99–1.91)	0.124	
Female	1.00(Ref)	1.34 (1.09–1.76)	0.93 (0.66–1.34)	1.52 (1.27–1.91)	0.013	
Age, years						0.267
< 60	1.00(Ref)	1.12 (0.82–1.51)	0.96 (0.79–1.51)	1.65 (1.26–2.13)	0.004	
≥ 60	1.00(Ref)	1.03 (0.75–1.33)	0.89 (0.62–1.31)	1.23 (0.94–1.63)	0.243	
Education						0.143
Illiteracy	1.00(Ref)	1.33 (0.95–1.86)	0.78 (0.42–1.37)	1.12 (0.78–1.69)	0.862	
Primary school	1.00(Ref)	0.86 (0.61–1.23)	1.40 (0.92–2.01)	1.43 (1.02–2.06)	0.034	
Middle school or above	1.00(Ref)	1.47 (0.89–2.51)	1.91 (1.11–3.23)	1.55 (0.89–2.87)	0.011	
Living place						0.968
Urban	1.00(Ref)	1.04 (0.81–1.33)	0.86 (0.66–1.17)	1.35 (1.12–1.81)	0.036	
Rural	1.00(Ref)	1.03 (0.65–1.56)	1.15 (0.75–1.83)	1.63 (1.16–2.33)	0.020	
Smoking						0.726
No	1.00(Ref)	1.24 (0.95–1.63)	1.02 (0.73–1.38)	1.45 (1.19–1.87)	0.006	
Yes	1.00(Ref)	0.69 (0.47–1.36)	0.95 (0.49–1.52)	1.40 (1.01–2.15)	0.239	
Drinking						0.719
No	1.00(Ref)	1.06 (0.78–1.37)	1.06 (0.76–1.39)	1.46 (1.19–1.88)	0.003	
Yes	1.00(Ref)	1.05 (0.73–1.43)	0.79 (0.43–1.27)	1.32 (0.96–1.86)	0.293	
Hypertension						0.946
No	1.00(Ref)	1.05 (0.82–1.33)	0.86 (0.64–1.16)	1.37 (1.15–1.77)	0.022	
Yes	1.00(Ref)	1.07 (0.72–1.69)	1.27 (0.79–2.12)	1.47 (1.04–2.19)	0.036	
Diabetes mellitus						0.086
No	1.00(Ref)	1.09 (0.88–1.35)	0.91 (0.69–1.16)	1.37 (1.17–1.69)	0.012	
Yes	1.00(Ref)	0.67 (0.20–1.87)	1.90 (0.75–4.65)	2.60 (1.29–5.72)	0.006	

Odds ratios were calculated after adjustment for the same variables as multivariable-adjusted model in Table 3, except for the stratified variable

Discussion

This study explored the relationship between changes in depressive symptoms and anemia based on CHARLS. First, baseline depressive symptoms were associated with an increased risk of anemia. Specifically, there was a 27% elevated risk of anemia in patients with depressive symptoms at Wave 1 (2011–2012). In addition, participants with persistent depressive symptoms during Wave 1 (2011–2012) and Wave 2 (2013–2014) had a 43% increased risk of incident anemia, compared with no depressive symptoms after adjusting for known potential confounders. These findings were consistent across different subgroups, and were further confirmed in the sensitivity analysis using different definition of depressive symptoms. Our study suggested that participants with depressive symptoms, especially for those with long-term depression had a higher risk of anemia in Chinese middle-aged and elderly adults.

Depressive symptoms are common in the elderly, depressed patients often have unhealthy diet and lifestyle, leading to nutritional deficiencies that increase the risk of anemia. Furthermore, it has been shown that depression shares some similar pathological characteristics with anemia, but previous studies have shown inconsistent results of the relationships between depressive symptoms and decreased hemoglobin levels or anemia [14, 20, 21]. For example, the Netherlands Study of Depression and Anxiety recruiting 2920 participants reported that there was no clear evidence for an association between depressive disorders and hemoglobin levels or anemia status [21]. However, a large scale cross-sectional study including 44,137 participants showed that depressed participants were significantly more likely to have anemia compared to non-depressed participants after adjustment for sociodemographic and health-related variables (OR 1.36, 95% CI 1.18–1.57) [20]. Additionally, in a prospective population-based study of participants with a mean age of 75 years found that depressive symptoms are associated with an increased risk of anemia [18]. Our study validated these findings that depressive symptoms were associated with increased risk of incidence of anemia.

Previous studies on depressive symptoms and anemia only measured depressive symptoms once at baseline, failing to take into account the effects of depressive symptoms change [18, 20]. It is reported that the course of depressive symptoms varies across individuals, with some may experience remission or relapse of depression, while others may have long-term chronic depression. Different patterns of depressive symptoms changes may have different risk of anemia. Our study investigated the relationship between changes in depressive symptoms and the risk of anemia, and the results showed that participants with persistent depressive symptoms during Wave 1 and Wave 2 had the 1.43-fold risk of anemia compared with those in the no depressive symptom.

The potential mechanism underlying the association between depressive symptoms and risk of anemia remains to be fully elucidated, while several potential biological mechanisms have been proposed. First, patients with depressed mood often have unhealthy eating practices that can lead to deficiencies in vitamins (such as vitamin B12, folic acid) and minerals (such as iron and zinc), unhealthy dietary intake may also cause or increase activation of inflammatory response systems, such as the inflammatory marker C-reactive protein or interleukin-6, which can lead to anemia [33]. In addition, depressed patients may have increased sympathetic tone, which can affect erythrocyte and bone marrow production by catecholamine modulation [34]. Furthermore, anemia and depressive symptoms are associated with many chronic conditions, and underlying chronic conditions such as cancer, heart failure and diabetes may modulate the observed relationships [35, 36]. However, the association of changes in depressive symptoms and anemia remained significant after adjusting for heart disease and diabetes, further studies are still needed to clarify the potential mechanisms.

In this study, we investigated the prospective associations of baseline depressive symptoms, as well as the changes in depressive symptoms with the risk of anemia, which may provide more predictive evidence of depressive symptoms on anemia. Furthermore, our study was based on a large nationally representative cohort study with a high response rate cohort of CHARLS, potential confounders were collected and controlled in the multivariable models. Nevertheless, there are also some limitations. First, this study obtained the information of the study subject through a self-report questionnaire, which would cause information bias. Second, the CHARLS study was exclusively a Chinese population, and the findings from our study might not be generalizable to other populations. Third, data about the types of anemia was not collected in this study, which limited us to examine the effects of changes in depressive symptoms on different types of anemia. Although we controlled for a range of covariates in our analyses, the influence of unknown factors cannot be ruled out in this study. Finally, CESD-10 score was divided into categorical variables and a lot of information may lost in these analyses. Some of the CESD-10 data in this study were unavoidably missing, and a potential underestimation of the association between depressive symptoms and anemia may exist due to the exclusion of missing data.

Conclusion

This nationally representative longitudinal study provided evidence of the association between depressive symptoms and anemia, and further demonstrated that changes in depressive symptoms were associated with increased risks of anemia among the middle-aged and older Chinese adults. Further experimental and clinical research are needed to verify our findings and clarify the potential mechanisms.

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Author contributions
CKZ and XWZ contributed to the conception and design of the study; YCB LPZ, LPZ and LYH, contributed to the acquisition of data; YCB, LPZ, LYH, YL and CKZ contributed to the analysis of data, preparation of the figures and the drafting of the text. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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