Postprint: Association Between Cumulative C-Reactive Protein Elevations and Somatic Versus Non-somatic Depressive Symptoms in Chinese Middle-aged and Older Adults

Authors: Zhao Ningxuan, Jiang Lin, Hu Meijing, Yao Qiang, Mao Yineng, Zhu Cairong, Zhu Cairong

Date: 2024-02-20T00:00:00+00:00

Abstract

Background The inconsistent conclusions in previous studies on the association between CRP and depressive symptoms among middle-aged and elderly adults may be attributable to whether the cumulative effect of elevated C-reactive protein (CRP) was considered and whether different dimensions of depressive symptoms were distinguished. Currently, research in China on CRP and depressive symptoms lacks exploration of the impact of cumulative times of CRP elevation on different dimensions of depressive symptoms. Objective To explore the longitudinal association between cumulative times of CRP elevation in two consecutive measurements and depressive symptoms, including somatic and non-somatic symptoms, among middle-aged and elderly Chinese adults. Methods This study utilized publicly available data from the China Health and Retirement Longitudinal Study (CHARLS) from 2011 to 2018, including 3868 participants. Based on cumulative times of CRP elevation (CRP>3 mg/L) in two consecutive measurements (2011 and 2015), participants were categorized into a group with 0 elevations (n=2918), a group with 1 elevation (n=763), and a group with 2 elevations (n=187). Depressive symptoms were assessed using the 10-item Center for Epidemiological Studies Depression Scale (CESD-10) in 2011, 2015, and 2018, which was divided into somatic and non-somatic depressive symptoms. Multiple linear regression models were employed to analyze the longitudinal association between cumulative times of CRP elevation in two consecutive measurements and total depressive symptom score, somatic depressive symptom score, and non-somatic depressive symptom score in 2018. Logistic regression models were used to analyze the association between cumulative times of CRP elevation in two consecutive measurements and the prevalence of depressive symptoms (yes/no) in 2018. Results Multiple linear regression analysis

showed that, after adjusting for all covariates, having 2 elevations of CRP in two consecutive measurements compared to 0 elevations was significantly associated with higher scores for total depressive symptoms (β=1.22, P<0.05), somatic depressive symptoms (β=0.51, P<0.05), and non-somatic symptoms (β=0.71, P<0.05). Logistic regression analysis showed that, after adjusting for all covariates, having 2 elevations of CRP in two consecutive measurements compared to 0 elevations was associated with a higher risk of depressive symptoms (OR=1.64, 95%CI=1.18~2.29). Conclusion There is a positive association between cumulative times of CRP elevation and depressive symptoms, including somatic and non-somatic symptoms, among middle-aged and elderly Chinese adults. Timely treatment of potential chronic inflammatory diseases and avoidance of long-term chronic inflammatory states may reduce the risk of depression.

Full Text

Association between Cumulative Episodes of C-reactive Protein Elevations and Somatic/Non-somatic Depressive Symptoms among Chinese Middle-aged and Older Adults

ZHAO Ningxuan[1], JIANG Lin[1], HU Meijing[1], YAO Qiang[1], MAO Yineng[2], ZHU Cairong[1]*

[1]Department of Epidemiology and Health Statistics, West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu 610041, China
[2]School of Public Health, North Sichuan Medical College, Nanchong 637199, Sichuan Province, China

Corresponding author: ZHU Cairong, Professor/Doctoral supervisor; E-mail: cairong.zhu@hotmail.com

---

Abstract

Background
Whether considering the cumulative effect of sustained C-reactive protein (CRP) and distinguishing different aspects of depressive symptoms may explain the inconsistent conclusions of previous studies on the association between CRP and depressive symptoms among middle-aged and older adults. Current research in China has not examined how cumulative episodes of CRP elevations affect different dimensions of depressive symptoms.

Objective
This study aims to examine the longitudinal association between cumulative episodes of CRP elevations over two successive determinations and depressive symptoms, including somatic and non-somatic components, among Chinese middle-aged and older adults.

Methods
Using public data from the 2011–2018 Chinese Health and Retirement Longitudinal Study (CHARLS), we included 3,868 subjects. Participants were categorized based on the frequency of CRP elevations (>3 mg/L) over two consecutive measurements (2011, 2015) as: elevated on zero occasions (n=2,918), elevated on one occasion (n=763), and elevated on two occasions (n=187). Depressive symptoms were assessed in 2011, 2015, and 2018 using the 10-item Center for Epidemiological Studies Depression Scale (CESD-10), which measures both somatic and non-somatic depressive symptoms. Multiple linear regression was used to analyze the longitudinal associations between cumulative CRP elevations and 2018 depressive symptom scores (total, somatic, and non-somatic). Logistic regression examined the association between cumulative CRP elevations and the presence of depressive symptoms in 2018 (yes/no).

Results
Multiple linear regression showed that after adjusting for all covariates, elevations on two occasions versus zero occasions was associated with higher total depressive symptom scores (β=1.22, P<0.05), somatic depressive symptom scores (β=0.51, P<0.05), and non-somatic symptom scores (β=0.71, P<0.05). Logistic regression revealed that after full adjustment, participants with elevations on two occasions had higher odds of depressive symptoms compared to those with zero elevations (OR=1.64, 95%CI=1.18–2.29).

Conclusion
Among Chinese middle-aged and older adults, cumulative episodes of CRP elevations are positively associated with depressive symptoms, encompassing both somatic and non-somatic dimensions. Prompt treatment of chronic inflammatory conditions to avoid sustained chronic inflammatory states may reduce depression risk.

Keywords: Depression; C-reactive protein; Cumulative effect; Chronic inflammation; Somatic retardation; Middle-aged and older adults; Prospective cohort study

Introduction

Depression among middle-aged and older adults represents a major global public health concern [1]. In China, the prevalence of depression among older adults has been increasing [2-3]. Studies show that in 2020, the overall prevalence of depressive symptoms among Chinese older adults reached 20%, creating a substantial disease burden [4-6]. The "inflammation hypothesis" of geriatric depression, based on psycho-neuro-immune dysfunction, has recently gained considerable attention [7-9]. C-reactive protein (CRP) is a commonly used inflammatory biomarker [10], yet longitudinal studies examining the association between CRP and depressive symptoms have yielded inconsistent findings [11-13]. Two studies using the English Longitudinal Study of Ageing (ELSA) database produced

contradictory results: AU et al. [14] used a single CRP measurement, while BELL et al. [15] focused on the cumulative effect of sustained CRP elevations across two consecutive measurements, suggesting that considering cumulative episodes of CRP elevations and distinguishing depressive symptom dimensions may be crucial for understanding these relationships.

Depressive symptoms can be divided into two dimensions: somatic symptoms (fatigue, anorexia, physical disorders) and non-somatic symptoms (cognitive changes, anxiety, irritability) [16]. Clinical research indicates that somatic symptoms may respond to anti-inflammatory treatments, whereas non-somatic symptoms show less response, suggesting different pathophysiological mechanisms [17]. Additionally, based on sickness behavior theory, inflammation may more likely cause somatic depressive symptoms such as fatigue, sleep problems, and psychomotor slowing [18]. Therefore, examining associations between inflammation and different depressive symptom dimensions is essential.

Previous Chinese research on the longitudinal association between CRP and somatic/non-somatic depressive symptoms [19] used only single CRP measurements and did not explore cumulative effects of sustained elevations. Using the China Health and Retirement Longitudinal Study (CHARLS) database, this study investigates the longitudinal association between cumulative episodes of CRP elevations across two consecutive measurements and depressive symptoms, including both somatic and non-somatic components, to provide scientific evidence for depression prevention in middle-aged and older Chinese adults.

Methods

Study Population

Data were obtained from the publicly available CHARLS database (2011-2018). The study was approved by the Peking University Ethics Committee (IRB00001052-11015), and all participants provided written informed consent. CHARLS is a prospective survey of Chinese adults aged 45 years and older, with participants from 150 districts in 28 provinces across 450 villages/communities. Baseline data were collected through computer-assisted personal interviews in 2011, with follow-up surveys completed in 2013, 2015, and 2018. Blood samples were collected at baseline (2011) and again in 2015 [20].

Among 11,847 participants who completed baseline blood tests in 2011, we applied the following exclusion criteria: (1) age <45 years; (2) missing baseline, 2015, or 2018 depressive symptom data, or history of mental/memory disorders; (3) missing baseline or 2015 CRP data, or CRP values >10 mg/L or <0.1 mg/L (CRP>10 mg/L indicates acute infection [21]; the assay' s lower detection limit is <0.1 mg/L); (4) missing baseline covariate data. These exclusions yielded a final sample of 3,868 participants (Figure 1 [Figure 1: see original paper]). Since no established thresholds exist for somatic versus non-somatic depressive symptoms, we retained participants with depressive symptoms at baseline (2011

and 2015) to maximize sample size, adjusting for baseline depressive symptom scores in subsequent analyses.

Study Variables and Definitions

Cumulative Episodes of CRP Elevations Over Two Successive Measurements CRP levels in blood samples were measured using immunoturbidimetry with a detection range of 0.1–20 mg/L and a coefficient of variation of 5.7% [20]. CRP >3 mg/L was used as the threshold for chronic low-grade inflammation [22]. Cumulative episodes were calculated based on measurements from 2011 and 2015 (range: 0–2). Elevations on two occasions indicated chronic low-grade inflammation at both time points.

Depressive Symptoms Depressive symptoms were assessed using the 10-item Center for Epidemiological Studies Depression Scale (CESD-10), reflecting symptoms over the past week. The scale comprises "somatic depressive symptoms" (items 2, 4, 7, 10) and "non-somatic depressive symptoms" (items 1, 3, 5, 6, 8, 9), demonstrating good reliability and validity [23]. Each item is scored from 0 ("rarely or none of the time") to 3 ("most of the time"), with total scores ranging from 0–30. Scores $ $10 indicate clinically significant depressive symptoms [24-25].

Covariates Covariates included baseline demographic characteristics (age, sex, education, marital status), health behaviors (smoking, alcohol consumption, social activities), metabolic indicators (BMI, high-density lipoprotein, triglycerides), and health status (hypertension, diabetes, cancer, heart disease, arthritis, stroke, and lung disease). Education was categorized as below primary school, primary school, middle school, and high school or above. Marital status was defined as married, divorced, widowed, or never married. Smoking and drinking status were classified as never, current, or former. Social activity scores were calculated by summing frequencies of 10 activities in the previous month and categorized as 0, 1–2, or $ $3 points. BMI was calculated from height and weight. Blood samples were assayed for HDL and triglycerides using enzymatic colorimetric methods. Hypertension was defined as systolic blood pressure $ $140 mmHg (1 mmHg=0.133 kPa) and/or diastolic $ $90 mmHg, or use of antihypertensive medication, or self-reported hypertension. Diabetes was defined as fasting glucose $ $126 mg/dL (7.0 mmol/L) and/or HbA1c $ $6.2 mmol/L, or use of glucose-lowering treatment, or self-reported diabetes. Self-reported health conditions included cancer or malignant tumor (excluding minor skin cancers), heart disease (including myocardial infarction, coronary heart disease, angina, stroke, and other cardiac problems), arthritis or rheumatoid arthritis, stroke, and lung disease.

Statistical Analysis

Data were analyzed using SAS 9.4 and Stata 16.0, with statistical significance set at α=0.05. Baseline characteristics were described by CRP elevation categories. Continuous variables with normal distributions were presented as means ± standard deviations, and categorical variables as frequencies and percentages. Group differences were tested using ANOVA for continuous variables and ^{2} tests or Fisher' s exact test for categorical variables.

Multiple linear regression models examined longitudinal associations between cumulative CRP elevations (2011, 2015) and 2018 depressive symptom scores (total, somatic, non-somatic), with regression coefficients and confidence intervals calculated. Logistic regression models examined associations between cumulative CRP elevations and the presence of depressive symptoms in 2018 (yes/no), calculating odds ratios and confidence intervals. Based on previous research and univariate analyses [14,26-27], we constructed five regression models: Model 1 adjusted for baseline depressive symptom scores; subsequent models sequentially added sociodemographic factors, health behaviors, metabolic indicators, and health status. Statistical significance was defined as P<0.05.

Results

Participant Characteristics

Among 3,868 participants included in the analysis, 2,918 had zero CRP elevations, 763 had one elevation, and 187 had two elevations. The mean age was $57.2\$\pm7.8 years; 1,812(46.85\pm4.0 kg/m\hat{}\{2\}, and baseline mean CESD - 10 score was 7.99\pm\$6.08$. No significant differences were observed across CRP elevation groups in age, sex, marital status, education, smoking, social activity scores, cancer, heart disease, HDL, triglycerides, or baseline CESD-10 scores (P>0.05). However, significant differences were found in BMI, alcohol consumption, hypertension, diabetes, arthritis, lung disease, and stroke (P<0.05) (Table 1).

Longitudinal Association Between Cumulative CRP Elevations and Depressive Symptom Scores

Multiple linear regression with 2018 depressive symptom scores as the outcome showed that after adjusting for baseline depressive symptoms, elevations on two occasions versus zero occasions was positively associated with 2018 depressive symptom scores (β=1.20, P<0.05). This association remained significant after adjusting for all covariates (β=1.22, P<0.05). No significant association was found for elevations on one occasion versus zero occasions across all models (P>0.05) (Table 2).

Longitudinal Association Between Cumulative CRP Elevations and Somatic/Non-somatic Symptom Scores

In analyses examining somatic depressive symptoms as the outcome, elevations on two occasions versus zero occasions was positively associated with somatic symptom scores after full adjustment (β=0.51, P<0.05). Similarly, for non-somatic depressive symptoms, elevations on two occasions versus zero occasions showed a positive association (β=0.71, P<0.05). No significant associations were found for elevations on one occasion versus zero occasions for either symptom dimension (P>0.05) (Table 3 , Table 4).

Longitudinal Association Between Cumulative CRP Elevations and Depressive Symptom Prevalence

Depressive symptoms were defined as CESD-10 scores $ $10 in 2018. Logistic regression showed that after adjusting for baseline depressive symptoms, participants with elevations on two occasions versus zero occasions had higher odds of depressive symptoms (OR=1.58, 95%CI=1.15-2.18). This association remained significant after full adjustment (OR=1.64, 95%CI=1.18-2.29) (Table 5).

We further analyzed individual CESD-10 items, defining "rarely or none of the time" responses as absence of that symptom. Logistic regression (Model 5) showed that compared to zero elevations, elevations on two occasions was a risk factor for the somatic item "I felt that everything I did was an effort" (item 4) (OR=1.54, 95%CI=1.11-2.13) and the non-somatic item "I felt unhappy" (item 8, reverse-scored) (OR=1.54, 95%CI=1.12-2.13) (Table 6 , Table 7).

Discussion

This study used a nationally representative longitudinal database of Chinese middle-aged and older adults to examine associations between cumulative episodes of CRP elevations across two measurements and depressive symptoms, including somatic and non-somatic dimensions. Results indicate that elevations on two occasions versus zero occasions were associated with higher risks of total depressive symptoms (β=1.22, P<0.05), somatic depressive symptoms (β=0.51, P<0.05), and non-somatic symptoms (β=0.71, P<0.05).

The cumulative effect of sustained CRP elevations may be an important factor in depressive symptom development among Chinese middle-aged and older adults. Previous Chinese studies examining CRP and depressive symptoms used only single CRP measurements and found no association between inflammation and depressive symptoms [19,28]. Research on cumulative CRP effects has focused primarily on Western populations; our study provides evidence from a Chinese population, with consistent findings across ethnic groups [15,22]. In epidemiological studies of inflammation and chronic disease, considering the chronicity and persistence of inflammatory responses is crucial [29]. Single measurements cannot distinguish sustained exposure and may lead to misclassification.

We found a positive association between sustained CRP elevations and somatic depressive symptoms among Chinese middle-aged and older adults, consistent with a Dutch multicenter cohort study linking somatic depressive symptoms to inflammatory markers [30]. Pathophysiological mechanisms suggest that lipid markers including insulin, fasting glucose, triglycerides, LDL, and HDL may influence somatic depressive symptoms by reducing cellular metabolic function and exacerbating inflammatory responses [18,31]. Additionally, elevated pro-inflammatory proteins like CRP may perpetuate "sickness behavior" (fatigue, reduced activity) and negatively affect brain regions involved in mood regulation, leading to somatic depressive symptoms [32-33].

Cumulative CRP elevations also represent a risk factor for non-somatic depressive symptoms. Failure to consider cumulative effects across multiple measurements may explain inconsistent findings in previous research on CRP and non-somatic symptoms [34-35]. A Chinese study using CHARLS data [19] found no association between single CRP measurements and non-somatic depressive symptoms. A UK study analyzing individual depression scale items found that elevations on two occasions versus zero occasions was positively associated with certain non-somatic symptom items [15], consistent with our findings. The mechanisms linking inflammation to non-somatic depressive symptoms remain unclear and require further biological research.

This study has several limitations. First, limited measurement points in CHARLS required analysis based on the number of times CRP exceeded threshold values. Future longitudinal studies with multiple measurement points should employ trajectory analysis to better capture dynamic CRP changes [36]. Second, depressive symptom assessment relied on the CESD-10 self-report scale rather than clinical diagnosis by healthcare professionals.

Long-term exposure to chronic inflammation represents a risk factor not only for overall depressive symptoms but also for both somatic and non-somatic depressive symptom dimensions among Chinese middle-aged and older adults. Prompt treatment of chronic inflammatory conditions to avoid sustained inflammatory states is recommended to reduce depression risk in this population.

Author Contributions: ZHAO Ningxuan conceptualized the study, performed data curation and statistical analysis, and wrote the manuscript. JIANG Lin curated data, provided statistical design input, and assisted with editing. HU Meijing curated data and analyzed feasibility. YAO Qiang curated data and contributed to statistical design. MAO Yineng curated data. ZHU Cairong supervised the project, provided conceptual guidance, and reviewed and edited the manuscript.

Conflict of Interest: The authors declare no conflicts of interest.

ORCID: ZHU Cairong: https://orcid.org/0000-0001-6795-582X

References

[1] TAYLOR W D. Clinical practice. Depression in the elderly[J]. N Engl J Med, 2014, 371(13): 1228-1236. DOI: 10.1056/NEJMcp1402180.

[2] WANG Y, ZHOU C C. Promoting social engagement of the elderly to cope with aging of the Chinese population[J]. Biosci Trends, 2020, 14(4): 310-313. DOI: 10.5582/bst.2020.03305.

[3] RONG J, GE Y H, MENG N N, et al. Meta-analysis of the prevalence of depression among Chinese elderly from 2010 to 2019[J]. Chin J Evid Based Med, 2020, 20(1): 26-31. DOI: 10.7507/1672-2531.201908088.

[4] TANG T, JIANG J L, TANG X F. Prevalence of depressive symptoms among older adults in mainland China: a systematic review and meta-analysis[J]. J Affect Disord, 2021, 293: 379-390. DOI: 10.1016/j.jad.2021.06.050.

[5] SCHOEVERS R A, GEERLINGS M I, BEEKMAN A T, et al. Association of depression and gender with mortality in old age. Results from the Amsterdam Study of the Elderly (AMSTEL)[J]. Br J Psychiatry, 2000, 177: 336-342. DOI: 10.1192/bjp.177.4.336.

[6] SIVERSTEN H, BJØRKØF G H, ENGEDAL K, et al. Depression and quality of life in older persons: a review[J]. Dement Geriatr Cogn Disord, 2015, 40(5/6): 311-339. DOI: 10.1159/000437299.

[7] FELGER J C. The role of dopamine in inflammation-associated depression: mechanisms and therapeutic implications[J]. 10.1007/7854_{{{2016}}_{{13}}}.

[8] MORIMOTO S S, ALEXOPOULOS G S. Immunity, aging, and geriatric depression[J]. Psychiatr Clin North Am, 2011, 34(2): 437-449, ix. DOI: 10.1016/j.psc.2011.02.006.

[9] KRISHNADAS R, CAVANAGH J. Depression: an inflammatory illness?[J]. J Neurol Neurosurg Psychiatry, 2012, 83(5): 495-502. DOI: 10.1136/jnnp-2011-301779.

[10] WINDGASSEN E B, FUNTOWICZ L, LUNSFORD T N, et al. C-reactive protein and high-sensitivity C-reactive protein: an update for clinicians[J]. Postgrad Med, 2011, 123(1): 114-119. DOI: 10.3810/pgm.2011.01.2252.

[11] OSIMO E F, STOCHL J, ZAMMIT S, et al. Longitudinal population subgroups of CRP and risk of depression in the ALSPAC birth cohort[J]. Compr Psychiatry, 2020, 96: 152143. DOI: 10.1016/j.comppsych.2019.152143.

[12] ZALLI A, JOVANOVA O, HOOGENDIJK W J G, et al. Low-grade inflammation predicts persistence of depressive symptoms[J]. Psychopharmacology, 2016, 233(9): 1669-1678. DOI: 10.1007/s00213-015-3919-9.

[13] HILES S A, BAKER A L, MALMANCHE T D, et al. Unhealthy lifestyle may increase later depression via inflammation in older women but not men[J]. J Psychiatr Res, 2015, 63: 65-74. DOI: 10.1016/j.jpsychires.2015.02.010.

[14] AU B, SMITH K J, GARIÉPY G, et al. The longitudinal associations between C-reactive protein and depressive symptoms: evidence from the English Longitudinal Study of Ageing (ELSA)[J]. Int J Geriatr Psychiatry, 2015, 30(9): 976-984. DOI: 10.1002/gps.4250.

[15] BELL J A, KIVIMÄKI M, BULLMORE E T, et al. Repeated exposure to systemic inflammation and risk of new depressive symptoms among older adults[J]. Transl Psychiatry, 2017, 7(8): e1208. DOI: 10.1038/tp.2017.155.

[16] CAPURON L, GUMNICK J F, MUSSELMAN D L, et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions[J]. Neuropsychopharmacology, 2002, 26(5): 643-652. DOI: 10.1016/S0893-133X(01)00407-9.

[17] VANCASSEL S, CAPURON L, CASTANON N. Brain kynurenine and BH4 pathways: relevance to the pathophysiology and treatment of inflammation-driven depressive symptoms[J]. Front Neurosci, 2018, 12: 499. DOI: 10.3389/fnins.2018.00499.

[18] DANTZER R, O' CONNOR J C, FREUND G G, et al. From inflammation to sickness and depression: when the immune system subjugates the brain[J]. Nat Rev Neurosci, 2008, 9(1): 46-56. DOI: 10.1038/nrn2297.

[19] QIN T T, LIU W H, YIN M H, et al. Body mass index moderates the relationship between C-reactive protein and depressive symptoms: evidence from the China Health and Retirement Longitudinal Study[J]. Sci Rep, 2017, 7: 39940. DOI: 10.1038/srep39940.

[20] ZHAO Y H, HU Y S, SMITH J P, et al. Cohort profile: the China health and retirement longitudinal study (CHARLS)[J]. Int J Epidemiol, 2014, 43(1): 61-68. DOI: 10.1093/ije/dys203.

[21] PEARSON T A, MENSAH G A, ALEXANDER R W, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association[J]. Circulation, 2003, 107(3): 499-511. DOI: 10.1161/01.cir.0000052939.59093.45.

[22] SONSIN-DIAZ N, GOTTESMAN R F, FRACICA E, et al. Chronic systemic inflammation is associated with symptoms of late-life depression: the ARIC study[J]. Am J Geriatr Psychiatry, 2020, 28(1): 87-98. DOI: 10.1016/j.jagp.2019.05.011.

[23] ANDRESEN E M, MALMGREN J A, CARTER W B, et al. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale)[J]. Am J Prev Med, 1994, 10(2): 77-84.

[24] BOEY K W. Cross-validation of a short form of the CES-D in Chinese elderly[J]. Int J Geriatr Psychiatry, 1999, 14(8): 608-617. DOI: 10.1002/(sici)1099-1166(199908)14:8<608::aid-gps991>3.0.co;2-z.

[25] CHENG H G, CHEN S N, MCBRIDE O, et al. Prospective relationship of depressive symptoms, drinking, and tobacco smoking among middle-aged and elderly community-dwelling adults: results from the China Health and Retirement Longitudinal Study (CHARLS)[J]. J Affect Disord, 2016, 195: 136-143. DOI: 10.1016/j.jad.2016.02.023.

[26] MATTHEWS K A, SCHOTT L L, BROMBERGER J T, et al. Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women?[J]. Brain Behav Immun, 2010, 24(1): 96-101. DOI: 10.1016/j.bbi.2009.08.005.

[27] NILES A N, SMIRNOVA M, LIN J, et al. Gender differences in longitudinal relationships between depression and anxiety symptoms and inflammation in the health and retirement study[J]. Psychoneuroendocrinology, 2018, 95: 149-157. DOI: 10.1016/j.psyneuen.2018.05.035.

[28] LI X H, NIE Y, CHANG B R. Lack of bidirectional association between C-reactive protein and depressive symptoms in middle-aged and older adults: results from a nationally representative prospective cohort study[J]. Front Psychol, 2023, 14: 1095150. DOI: 10.3389/fpsyg.2023.1095150.

[29] LIU Y, TANG Y H, ZHAI J X, et al. Progress in research on chronic low-grade inflammation and sleep disorders[J]. Chin J Contemp Neurol Neurosurg, 2023, 23(8): 674-677.

[30] DUIVIS H E, VOGELZANGS N, KUPPER N, et al. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from the Netherlands Study of Depression and Anxiety (NESDA)[J]. Psychoneuroendocrinology, 2013, 38(9): 1573-1585. DOI: 10.1016/j.psyneuen.2013.01.002.

[31] PENNINX B W J H. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms[J]. Neurosci Biobehav Rev, 2017, 74(Pt B): 277-286. DOI: 10.1016/j.neubiorev.2016.07.003.

[32] FELGER J C, LI Z, HAROON E, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression[J]. Mol Psychiatry, 2016, 21(10): 1358-1365. DOI: 10.1038/mp.2015.168.

[33] TORRES-PLATAS S G, CRUCEANU C, CHEN G G, et al. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides[J]. Brain Behav Immun, 2014, 42: 50-59. DOI: 10.1016/j.bbi.2014.05.007.

[34] ELOVAINIO M, AALTO A M, KIVIMÄKI M, et al. Depression and C-reactive protein: population-based health 2000 study[J]. Psychosom Med, 2009, 71(4): 423-430. DOI: 10.1097/psy.0b013e31819e333a.

[35] SCHMIDT F M, SCHRÖDER T, KIRKBY K C, et al. Pro- and anti-inflammatory cytokines, but not CRP, are inversely correlated with severity

and symptoms of major depression[J]. Psychiatry Res, 2016, 239: 85-91. DOI: 10.1016/j.psychres.2016.02.052.

[36] NAGIN D S, ODGERS C L. Group-based trajectory modeling in clinical research[J]. Annu Rev Clin Psychol, 2010, 6: 109-138. DOI: 10.1146/annurev.clinpsy.121208.131413.

Received: December 10, 2023; Revised: January 28, 2024
Edited by JIA Mengmeng

Note: Figure translations are in progress. See original paper for figures.