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Associations between uric acid and depressive symptoms, and the mediating role of immunoinflammatory: Findings from rural older adults

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ABSTRACTS

Background: In the low-resource rural areas, older adults may experience prolonged and severe depressive symptoms. This study aimed to investigate the relationship between uric acid, depressive symptoms and immunoinflammatory among rural older adults.

Method: This case-control study was conducted in 17 rural villages in Hunan Province, China, between January 2023 and April 2024. This study included 180 participants: (1) Rural Older Adults with Depressive Symptoms group:90 patients with first-time diagnosed with depressive symptoms (Geriatric Depression Scale-15, GDS-15 $\geq$ 5 scores); (2) Control group: 90 individually matched (age and sex) healthy subjects (GDS-15 $<$ 5 scores) who were aged $\geq$60 years.

Results: Both males and females, depressive symptoms were associated with higher uric acid levels and C-reactive protein levels (All $P < 0.05$). Whereas in females, depressive symptoms were also linked to higher procalcitonin ($P = 0.005$) and serum amyloid A ($P = 0.008$) levels. In addition, C-reactive protein plays a significant mediating role between uric acid and depressive symptoms in males.

Conclusion: Further investigation is necessary to clarify the underlying mechanisms, examine gender-specific disparities, and assess potential therapeutic interventions targeting uric acid and inflammation levels to mitigate mental disorders risk.

1. Introduction

Depression in older adults a common psychiatric disorder tends to have serious psychosocial and biological consequences("Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990–2019," 2020; Psychiatry, 2024; Wilkinson et al., 2018). Globally, more than 350 million people worldwide suffer from depression (COVID-19 Mental Disorders Collaborators, 2021). In particular, 35–40% of older adults reported significant depressive symptoms in China, and rural areas are significantly higher than urban areas(John et al., 2019; Tang et al., 2022; Zhou et al., 2021). Depressive symptoms severely affect rural older adults, including worsened physical illness and functional impairment(White et al., 2016; Zeng et al., 2017), increased healthcare utilization and costs(X. Chen et al., 2022; Lundberg et al., 2023), as well as elevated risk of suicide and all-cause mortality (Chesney et al., 2014; Miloyan and Fried, 2017). Despite the need for appropriate psychotherapy and management, rural older adults are less likely to actively visit community health services due to financial concerns, poor mobility, social stigma, or limited use of transportation(X. Chen et al., 2022). In addition, challenges such as limited medical resources and inadequate sanitation in rural areas often exacerbate the deterioration in the mental health of older adults(Lu et al., 2021).

Uric acid, as the final metabolism product of purine, is widely present in intracellular fluids and body fluids, holding significant pathological value. Hyperuricemia (abnormally increased uric acid) has been identified as a significant global public health concern with a rising morbidity rate, which can seriously affect patients' quality of life(Dehlin et al., 2020; Niu et al., 2024). Previous studies suggested that the

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prevalence of hyperuricemia was 15.1 % (21.2 % for males and 8.5 % for females) in the China, affecting about one-fifth of Chinese older adults (Piao et al., 2022). Both elevated uric acid and hyperuricemia were reported as the pathogenesis of gout and contributed to cardiovascular diseases(Feng et al., 2022; Major et al., 2018), and some studies have suggested that uric acid may also lead to mental disorders, including depressive symptoms(J. Chen et al., 2024; Kim et al., 2023). Uric acid as a strong antioxidant and is constantly consumed to counterattack the oxidative stress. The possible pathophysiological mechanism of uric acid leading to depressive symptoms is mainly a series of adverse consequences caused by oxidative stress, such as increased oxidative damage and lower levels of antioxidants, resulting in the deregulation of brain functions and abnormalities in neuronal signaling, which affect the occurrence of depressive symptoms(Bhatt et al., 2020; X et al., 2020). Several studies have explored the link between uric acid and depressive symptoms, but the findings of these studies are inconsistent. A cross-sectional study of 10,522 Chinese middle-aged and older adults showed that a negative correlation between uric acid levels and depressive symptoms, but only among men(Li et al., 2019). Interestingly, a national study in Korea found the opposite result that uric acid was associated with depressive symptoms in older women, but not in men(Feng et al., 2022). In addition, a cross-sectional study indicated that participants with depressive symptoms have higher uric acid levels than controls(Li et al., 2019).However, another longitudinal study showed that the relationship between uric acid and depressive symptoms was not significant in pre-menopause women. These differing results may be mainly due to differences in study methods, study populations, and the diagnostic criteria for uric acid and depressive symptoms. Therefore, further studies are needed to provide more precise research evidence on the association between uric acid and depressive symptoms.

Generally, an abnormal increase in uric acid can destroy the oxidation-reduction balance system of the body in various ways, leading to the state of oxidative stress. Then, oxidative stress can activate the immune inflammatory reaction, resulting in immune cell dysregulation and elevated levels of pro-inflammatory markers. Some studies revealed that subjects with abnormally increased uric acid are strongly associated with immune-inflammatory markers, as manifested by increased counts of white blood cell (WBC) count, C-reactive protein (CRP), and interleukin-6 (IL-6)(Liu et al., 2019; Ruggiero et al., 2006). Immune-inflammatory markers have been linked to not only with abnormal increase of uric acid, but also with depressive symptoms and other mental health disorders. Increased WBC counts, IL-6, serum amyloid A (SAA), and higher concentrations of CRP have been reported to be associated with more severe depressive symptoms(Bryleva et al., 2017; Eswarappa et al., 2019). In addition, immunoglobulin A(IgA) and Procalcitonin (PCT) are two emerging immune-inflammatory markers of potential diagnostic value. Unfortunately, there is little evidence on whether IgA and PCT levels are associated with depressive symptoms among rural older adults in China. With the development of precision medicine, a variety of neuro-immune drugs have been used to treat mental disorders with remarkable results(Drevets et al., 2022; Miller and Raison, 2016). Although the pathophysiologic mechanisms of depressive symptoms remain unclear, some studies have shown that immunoinflammatory plays a role in the occurrence and development of depressive symptoms(Bai et al., 2024; Chiang et al., 2021). Thus, we speculated that immunoinflammatory may partially mediate the relationship between uric acid and depressive symptoms.

This study aimed to explore the association between uric acid, depressive symptoms, and immune-inflammatory, as well as the potential mediating role of immune-inflammatory markers in the association between uric acid and depressive symptoms based on older adults in rural areas of China.

2. Methods

2.1. Study design and population

This case-control study investigated immune-inflammatory markers, blood uric acid, and psycho-social outcomes among rural older adults, and was conducted in 17 rural villages in Hunan Province, China, between January 2023 and April 2024. This study included 180 participants: (1) Rural Older Adults with Depressive Symptoms (ROADS) group:90 patients with first-time diagnosed with depressive symptoms (Geriatric Depression Scale-15, GDS-15 $\geq$ 5 scores); (2) Control group: 90 individually matched (age and sex) healthy subjects (GDS-15 $<$ 5 scores) who were aged $\geq$60 years. Exclusion criteria included serious physical illness, tobacco use, excessive drinking, and persistent systemic immune system diseases such as systemic lupus erythematosus. Individuals who fulfilled the diagnostic criteria for schizophrenia, bipolar illness, and organic mental disorder (DSM-5) and who also satisfied the Wechsler Adult Intelligence Scale (WAIS) criteria for intellectual disability were also excluded. In addition, patients using anti-inflammatory and immunosuppressive drugs were not allowed to participate. The study was approved by the ethics committee of the Third Xiangya Hospital, Central South University. Written informed consent was obtained before participation from the participants. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed.

2.2. Measures

2.2.1. Depressive symptoms

Depressive symptoms were assessed with the Geriatric Depression Scale-15 (GDS-15) (Sheikh J, Yesavage JA, n.d.),which measures self-reported personality traits of emotional status and life satisfaction and has been validated in a Chinese-speaking population(B. Chen et al., 2023; Xu et al., 2019). This questionnaire has good internal consistency and acceptable test-retest reliability, and has been applied in various patient samples. Participants rate the accuracy of 15 statements. Higher GDS-15 scores indicate a more severe degree of depressive symptoms. Considering that part of rural older adults are less educated, they may not be able to understand Mandarin. We translated the content of the questionnaire into dialect and collected the questionnaire after homogenization training to ensure that all participants could understand the content.

2.2.2. Clinical blood evaluations

Participants were tested for clinical blood evaluations after an overnight fast. Serum uric acid levels were measured by a colorimetric method whereby uric acid was oxidized to allantoin and hydrogen peroxide by uricase. Values were reported in milligrams per deciliter. To investigate the mediating role of immunoinflammatory in the association between rural older adults' depressive symptoms and uric acid levels, we chose immune and inflammatory markers that are reported to be involved in different inflammatory processes, including C-reactive protein (CRP, mg/L), immunoglobulin A(IgA, g/L), interleukin-6 (IL-6, pg/mL), procalcitonin (PCT, ng/mL), serum amyloid A (SAA, ng/mL), and white blood cell (WBC,10^3/μL) count. All blood samples were obtained in the local rural clinics and stored at 4 °C for 10 min and separated. Subsequently, the samples were stored at −80 °C for future use. Internal controls were used for all ELISA plates, and samples from all participants were assayed in the same batch. For quality control, multiple plasma aliquots from a single donor were prepared, and one aliquot was analyzed with the batch of samples. Frozen aliquots were stored for repetitive testing if necessary. For statistical analysis, all cytokine data were transformed with the natural logarithm to reach the normality of data distribution.

2.2.3. Covariates

The sociodemographic factors collected included age, sex, living status, marital status, education level, and economic condition. The above information was obtained through the electronic medical records and personal confirmation by the participants. Height and weight were measured to calculate body mass index (BMI), according to the standard formula (kg/m^2).

2.3. Statistical analysis

Before conducting the statistical analyses, a base-10 logarithmic transformation was performed on the inflammatory cytokine data because of its non-normal distribution. We assessed the differences between ROADS group and control group regarding the basic sociodemographic and clinical blood characteristics using Mann-Whitney U tests and chi-square tests. Moreover, considering the differences in the prevalence of depressive symptoms among different sex groups, we also stratified the analyses by sex.

Linear regression analysis was used to further assess group differences (ROADS group vs Control group) concerning uric acid level and immunoinflammatory markers. For consistency, analyses were adjusted for age, sex, living status, marital status, education level, BMI, and economic condition. In addition, we used variance inflation factor (VIF) values to test for multicollinearity and performed Levene's homoscedasticity test. Multicollinearity becomes a problem when VIF is > 10. However, in this study, all VIF scores (range = 1.106–1.846) fell within an acceptable range.

A mediational model was employed to investigate the relationship between uric acid and depressive symptoms, with immunoinflammatory markers serving as the mediator. This involved the application of bootstrapping procedures using the PROCESS version 4.1 Model 4. To estimate the 95 % confidence interval (CI), we employed the percentile bootstrap method, as well as the bias-corrected percentile bootstrap method, utilizing a total of 5000 bootstrap samples. The mediating impact was significant if the 95 % CI for the indirect effect (path a*b) did not contain 0. Each of models incorporated control variables such as age, living status, marital status, education level, BMI, and economic condition. All analyses were performed using SPSS (version 26.0) and R (version 4.2.3), with $P < 0.05$ defined as statistically significant.

3. Results

3.1. Population characteristics

Table 1 shows the demographic variables and clinical blood characteristics of ROADS group and control group. ROADS group did not significantly differ from the control group in demographic variables, such as age, sex, living status, marital status, education level, BMI, and economic condition (All $P > 0.05$). ROADS group exhibited significantly higher levels of uric acid than control group (ROADS: 351.00 [289.50, 422.75] umol/l; Controls: 298.00 [260.00, 353.00] umol/l; $p < 0.001$). Compared with controls, ROADS group had significantly higher levels of CRP (ROADS log-transformed: 0.51[0.36, 0.76] mg/l; Controls log-transformed: 0.38[0.30, 0.57)] mg/l; $P < 0.001$), IgA (ROADS log-transformed: 0.45[0.33, 0.57] g/l; Controls log-transformed: 0.38 [0.29, 0.48] g/l; $P = 0.036$), PCT (ROADS log-transformed: −1.18 [−1.28, −1.01] ng/ml; Controls log-transformed: −1.22[−1.32, −1.14] ng/ml; P = 0.013), SAA (ROADS log-transformed: 2.9[2.38, 3.66] ng/ml; Controls log-transformed: 2.64[2.17, 3.10]ng/ml; P = 0.004) (Fig. 1).The IL-6 and WBC levels were not statistically significant between the two groups.

Considering the differences in the prevalence of depressive symptoms among different sex groups, we further stratified the analyses by sex. Both males and females, depressive symptoms were associated with higher uric acid levels and C-reactive protein levels (All $P < 0.05$). Whereas in females, depressive symptoms were also linked to higher PCT ($P = 0.005$) and SAA ($P = 0.008$) levels (See Table 2).

Table 1
Demographic and clinical characteristics stratified by group.

Population characteristics	ROADS group (n = 90)	Control group (n = 90)	*P* value
Demographic characteristics			
Sex, No. (%)			.134[a]
Male	54(60.00)	44(51.11)	
Female	36(40.00)	46(48.89)	
Age, mean (SD), y	72.23(6.22)	72.12(5.93)	.902[a]
BMI, mean (SD), kg/m^2	24.37(4.27)	23.88(3.58)	.403[b]
Economic condition			.742[a]
Annuity	63 (70.00)	65 (72.22)	
Support from others	25 (27.78)	27 (30.00)	
Marital status			.083[a]
Married	54 (60.00)	65 (72.22)	
Divorce/Widowed	36 (40.00)	25 (27.78)	
living alone			.594[a]
Yes	22 (24.44)	19 (21.11)	
No	68 (75.56)	71 (78.89)	
Education level			.058[a]
Illiteracy	39 (43.33)	25 (27.78)	
Primary school	38 (42.22)	43 (47.78)	
Junior high school and above	13 (14.44)	22 (24.44)	
Clinical characteristics			
CRP, median (IQR)	0.51 (0.36, 0.76)	0.38 (0.30, 0.57)	**<.001**[b]
Ig A, median (IQR)	0.45 (0.33, 0.57)	0.38 (0.29, 0.48)	**.036**[b]
PCT, median (IQR)	−1.18 (−1.28, −1.01)	−1.22 (−1.32, −1.14)	**.013**[b]
IL-6, median (IQR)	0.73 (0.59, 0.95)	0.78 (0.62, 0.95)	.548[b]
SAA, median (IQR)	2.97 (2.38, 3.66)	2.64 (2.17, 3.10)	**.004**[b]
WBC, median (IQR)	0.80 (0.71, 0.90)	0.78 (0.72, 0.84)	.277[b]
Uric acid	351.00 (289.50, 422.75)	298.00 (260.00, 353.00)	**<.001**[b]

Abbreviations: CRP, C-reactive protein; IgA, Immunoglobulin A; PCT, Procalcitonin; IL-6, Interleukin-6; SAA, Serum amyloid A; WBC, White blood cell. ROADS, rural older adults with depressive symptoms.
[a] Two-sampled $\chi 2$ test.
[b] Two-sampled; two-sided Mann-Whitney *U* test.

3.2. Association between uric acid, depressive symptoms, and immunoinflammatory markers

To control for the influence of relevant confounders on the outcomes, we used a multiple linear regression model. Table 3 displays the linear correlations between uric acid, immunoinflammatory markers, and depressive symptoms. There was a significant difference in uric acid (β, 0.01 [95% CI, 0.01 to 0.02]; adjusted $P = 0.014$), CRP (β, 2.87 [95% CI, 0.66 to 5.09]; adjusted $P = 0.012$), PCT (β, 4.18 [95% CI, 056 to 7.80]; adjusted $P = 0.025$) between participants who have depressive symptoms compared with those who did not.

3.3. The mediating role of uric acid on depressive symptoms via immunoinflammatory markers in males

Based on the above-mentioned statistical findings, we used PROCESS version 4.1 Model 4 to investigate if immunoinflammatory markers (M) mediated the association between uric acid (X) and depressive symptoms (Y). The study found correlations among uric acid, CRP and depressive symptoms, and CRP plays a significant mediating role between uric acid and depressive symptoms in males. Fig. 2 and Table 4 display the results of the mediation analyses, indicating that the total effect (path c) of uric acid on depressive symptoms was significant in males (B = 0.017, 95% CI: 0.008, 0.028). The coefficient values for path a (uric acid→ CRP: B = 0.002, 95% CI: 0.001, 0.002) and path b (CRP → depressive symptoms: B = 3.084, 95% CI: 0.784, 5.384) indicated positive associations of uric acid on CRP in males, as well as CRP on depressive symptoms in males. In addition, the point estimate of the

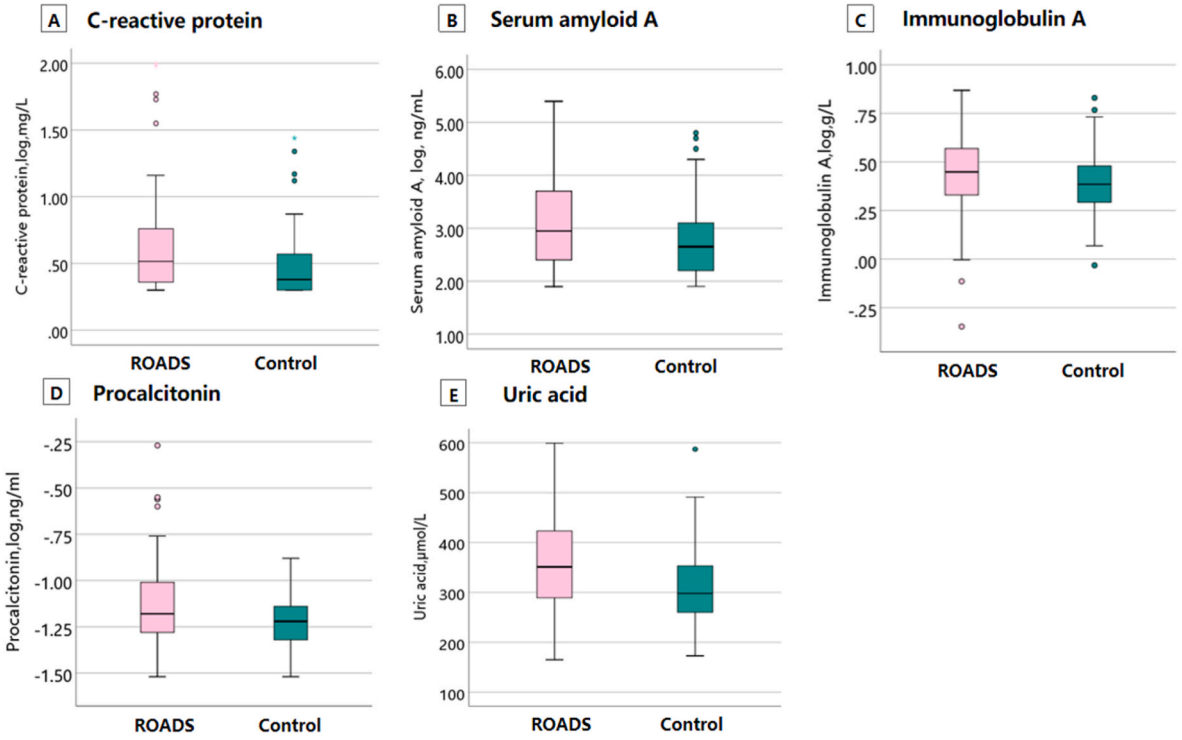

Fig. 1. Group Comparisons for Uric Acid Levels and Immunoinflammatory Markers
The lower and upper borders of the box represent the first and third quartiles. The line within the box corresponds to the median. Outliers are represented by circles. ROADS indicates rural older adults with depressive symptoms.

Table 2
Uric Acid and Immunoinflammatory Markers in Subjects with and without Depressive Symptoms were Compared by Sex Stratification.

Variables	Male (N = 82)		Z	*P* value	Female (N = 98)		Z	*P* value
	With DS (N = 46)	No DS (N = 36)			With DS (N = 54)	No DS (N = 44)		
CRP, median (IQR)	0.54 (0.36, 1.01)	0.38 (0.30, 0.54)	−2.65	**.008**	0.51 (0.36, 0.63)	0.36(0.30–0.59)	−2.81	**.005**
IgA, median (IQR)	0.44 (0.32, 0.60)	0.40 (0.30, 0.50)	−1.07	0.283	0.46 (0.35, 0.56)	0.37 (0.27, 0.44)	−1.94	0.052
PCT, median (IQR)	−1.06 (−1.24, −0.96)	−1.15 (−1.27, −1.06)	−1.50	0.134	−1.19 (−1.31, −1.07)	−1.31 (−1.36, −1.20)	−2.80	**.005**
IL-6, median (IQR)	0.83 (0.70, 0.98)	0.79 (0.71, 0.95)	−0.40	0.691	0.70 (0.54, 0.91)	0.74 (0.57, 0.94)	−0.74	0.458
SAA, median (IQR)	2.63 (2.28, 4.16)	2.53 (2.18, 3.12)	−1.08	0.278	3.11 (2.63, 3.64)	2.74 (2.15, 3.02)	−2.63	**.008**
WBC, median (IQR)	0.81 (0.74, 0.89)	0.80 (0.75, 0.85)	−0.65	0.513	0.76 (0.71, 0.90)	0.76 (0.70, 0.83)	−1.15	0.248
Uric acid, median (IQR)	362.50 (291.25, 434.50)	296.00 (261.00, 326.50)	−3.21	**.001**	346.50 (287.25, 390.75)	303.50 (260.00, 376.50)	−3.81	**<.001**

Abbreviations: CRP, C-reactive protein; IgA, Immunoglobulin A; PCT, Procalcitonin; IL-6, Interleukin-6; SAA, Serum amyloid A; WBC, White blood cell. DS, depressive symptoms.

Table 3
Linear correlations between uric acid and immunoinflammatory markers in subjects with and without depressive symptoms.

Variables	b	SE	t	*P*	β (95%CI)
Intercept	12.05	4.96	2.43	**.016**	12.05 (2.33–21.78)
Uric acid	0.01	0.00	2.48	**.014**	0.01 (0.01–0.02)
Log CRP	2.87	1.13	2.54	**.012**	2.87 (0.66–5.09)
Log PCT	4.18	1.85	2.26	**.025**	4.18 (0.56–7.80)

Abbreviations: CRP, C-reactive protein; PCT, Procalcitonin.Controlling for age, sex, living status, body mass index, marital status, education level, and economic condition.

indirect effect (path a*b) between uric acid and depressive symptoms through CRP was 0.004 (SE = 0.002), and the 95 % CI was 0.001–0.009, which indicated that the indirect effect of uric acid and depressive symptoms was statistically significant in males.

4. Discussion

This study first systematically demonstrated the relationship between uric acid, depressive symptoms, and immune-inflammatory markers among rural older adults in China. Compared with healthy controls, we found that ROADS group exhibited significantly higher levels of uric acid, CRP, IgA, PCT, and SAA. Due to the differences in the prevalence of depressive symptoms among different sex groups, we further stratified by sex. We found that both males and females, depressive symptoms were associated with higher uric acid levels and C-reactive protein levels. Whereas in females, depressive symptoms were also linked to higher PCT and SAA levels. In addition, we found that CRP plays a significant mediating role between uric acid and depressive symptoms. However, this mediation effect was only observed among males. To our knowledge, the relationship between uric acid and depressive symptoms was not consistent in previous studies(Rhee et al., 2021). In our study, uric acid was significantly positively associated with depressive symptoms among rural older adults, contrary to the findings of a Korean study(Kim et al., 2023). The difference in the results between the two studies may be explained by the different statistical

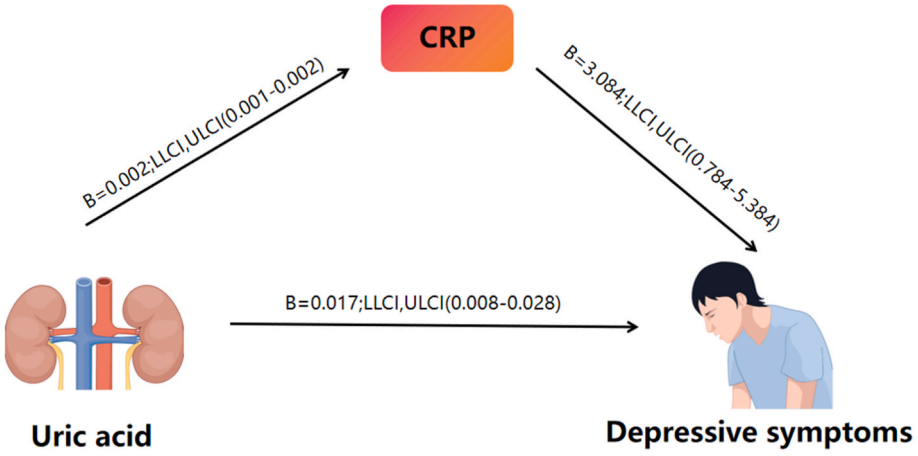

Fig. 2. Path diagram of the mediating effect of CRP on the association between Uric Acid Levels and Depressive Symptoms in Males
Abbreviations: unstandardized coefficient, B; lower limits of the 95% confidence intervals, LLCI; upper limits of the 95% confidence intervals, ULCI; CRP, C-reactive protein.
Controlling for age, sex, living status, body mass index, marital status, education level, and economic condition.

Table 4
CRP as a mediator of uric acid and depressive symptoms in males.

Variable	Uric acid (X)				CRP (M)			
	Effect	SE	LLCI	ULCI	B	SE	LLCI	ULCI
Path a (X→M)					0.002	0.001	0.001	0.002
Path b (M→Y)					3.084	1.154	0.784	5.384
Path c (total effect)	0.017	0.005	0.008	0.028				
Path c' (direct effect)	0.013	0.005	0.003	0.023				
Path a*b (indirect effect)					0.004	0.002	0.001	0.009

Abbreviations: standard error, SE; lower limits of the 95% confidence intervals, LLCI; upper limits of the 95% confidence intervals, ULCI; CRP, C-reactive protein.
Controlling for age, sex, living status, body mass index, marital status, education level, and economic condition.

analysis methods, characteristics of participants, and measuring of depressive symptoms. Therefore, more studies are needed to verify the association between depressive symptoms and uric acid among rural older adults.

Notably, accumulating evidence implicates the immune system in the pathogenesis of depression. Low-grade inflammation, as indicated by higher CRP levels, is present in about one-quarter of patients with major depression and longitudinally predicts the occurrence of depressive symptoms(Kappelmann et al., 2021). A cohort study indicated that CRP was a significant predictor of depressive symptoms at 5-year follow-up among older adults, which underlines the importance of targeting inflammation pathways in the treatment of mental disorders(Zalli et al., 2016). Our study found that depressive symptoms were associated with higher CRP and PCT levels in rural older adults and remained so after correction for all socio-demographic, possibly because pro-inflammatory markers can modulate the tryptophan/kynurenine pathway and decrease tryptophan availability for serotonin synthesis, further increasing the risk of depressive symptoms(Sakurai et al., 2020; Wang et al., 2015). It is worth mentioning that as an inflammatory marker with emerging potential diagnostic value, PCT expression level is not affected by non-infectious factors, which is a highly sensitive and specific indicator(Varun et al., 2018). However, PCT has not been well studied in the context of mental disorders. It deserves further exploration in future studies.

Secondly, the results showed that depressive symptoms were associated with higher uric acid levels and C-reactive protein levels in both males and females, whereas in females, depressive symptoms were also linked to higher PCT and SAA levels. The social signal transduction theory of depression viewed depressive symptoms as a biopsychosocial disease state, and inflammation was known to induce depression-like behavior in many human and animal studies(Slavich and Sacher, 2019). Particularly pro-inflammatory markers can also promote depressive symptoms and increase the risk for the types of physical health problems that frequently co-occur with depressive symptoms (Kelly et al., 2021). Therefore, a focus on inflammatory markers is essential for developing a more comprehensive understanding of psychiatric disorders and their clinical symptoms. Previous studies have suggested that disparities in inflammatory activity between the genders may partly attributed to variations in reproductive hormones(de Vries et al., 2022; Mauvais-Jarvis et al., 2020). Females appear to exhibit a relatively greater risk for inflammation-related depressive symptoms compared to males, especially for those already at heightened risk for mental disorders(Slavich and Sacher, 2019). The sex differences in inflammation-related mental health may be caused by genetic cues, or environmental and preprogrammed hormonal, and from the complex interplay of environmental influences mediated by epigenetic regulation driving gene expression for males and females(Derry et al., 2015). In sum, additional longitudinal studies are needed to examine sex differences in depressive symptoms and the associated neuroimmune responses, and the negative effects of these processes on mood and behavior.

Our results demonstrate that the relationship between uric acid and depressive symptoms in males is partially mediated by inflammatory markers. Inflammation is one of the causal factors that may be the link between uric acid with mental disorders. Clinical studies have shown that uric acid is a strong pro-inflammatory factor. In a large representative sample of older community patients, abnormally high uric acid levels were associated with high levels of several inflammatory markers, such as WBC and CRP.[25] Furthermore, baseline uric acid levels and uric acid changes significantly predicted CRP levels after three years in a population-based cohort study(Ruggiero et al., 2007),which is consistent with previous epidemiological study results(Tanaka et al., 2017).

Furthermore, a growing body of evidence that higher levels of the inflammatory markers, such as CRP, IL-6, and TNF-α are related to more severe depressive symptoms(Vermeulen et al., 2018). The CRP is easily measured because of its high sensitivity and its used primarily as a biomarker of chronic low-grade inflammation in clinical practice. A large body of research supports immune dysfunction in the form of low-grade inflammation as a characteristic of depressive symptoms, and meta-analyses research has established higher circulating levels of pro-inflammatory markers CRP in patients than those without depressive symptoms(Bell et al., 2017). Reasonable pathways exist for the depressogenic effects of inflammation, including chronically heightened stress responses, the creation of neurotoxic metabolites, and mood-enhancing neurotransmitters(Carvalho et al., 2014; Nusslock and Miller, 2016). In sum, our findings provide a better understanding of the relationship between uric acid, depressive symptoms, and immunoinflammatory among rural older adults and its mechanisms of action.

5. Limitations

The limitations of our study need to be considered. First, this study focused only on the psychological status of rural older adults and not on those in urban areas. This is due to the fact that the psychological condition of the rural older adults is more serious and more likely to be neglected. Second, different dietary habits and lifestyle factors may exist among the rural elderly groups, which might partially alter the relationship between uric acid and depressive symptoms. Thus, we will further focus on the influence of dietary patterns and lifestyle on it. In addition, although a variety of potential confounders were controlled during the analysis, the existence of other possible influences cannot be ruled out due to the limitations of observational studies. Finally, this study design makes inferences about causality and effect challenging. Further investigation through longitudinal studies is necessary to study the causal nature of these relationships.

6. Conclusion

This case-control study is the first, to our knowledge, to provide evidence that rural older adults with depressive symptoms showed higher uric acid levels and immunoinflammatory markers than controls. The intermediary analysis indicates that inflammatory markers, particularly CRP levels, plays a significant mediating role between uric acid and depressive symptoms in males. Further investigation is necessary to clarify the underlying mechanisms, examine gender-specific disparities, and assess potential therapeutic interventions targeting uric acid and inflammation levels to mitigate mental disorders risk.

CRediT authorship contribution statement

Yating Luo: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sha Wang:** Supervision, Software, Formal analysis, Conceptualization. **Qinqin Cheng:** Writing – review & editing, Validation, Supervision, Conceptualization. **Jing Li:** Methodology, Investigation. **Huiyi Zhang:** Methodology, Investigation. **Jingying Wang:** Methodology, Investigation. **Juan Luo:** Methodology, Investigation. **Chen Pan:** Writing – review & editing, Validation, Software. **Qiuxiang Zhang:** Writing – review & editing, Validation, Supervision, Project administration. **Jianfei Xie:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Andy S.K. Cheng:** Writing – review & editing, Validation, Supervision, Conceptualization.

Conflict of interest Disclosures

The authors have no funding or conflicts of interest to disclose.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jianfei Xie reports financial support was provided by China Medical Board. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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