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Association between chronic kidney disease and depressive symptoms: a cross-sectional and mediation analysis

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ABSTRACT

Chronic kidney disease (CKD) is a clinical syndrome characterised by declining renal function, linked to depressive symptoms, though the mediating role of biochemical markers in this association remains unclear. We downloaded and analyzed data from the National Health and Nutrition Examination Survey (NHANES) spanning from 2005 to 2018. This study employed multivariate logistic regression, restricted cubic spline models, subgroup analyses, and interaction tests to investigate the association between CKD and depressive symptoms. Additionally, mediation analyses assessed the potential role of biochemical markers in the relationship between CKD and depressive symptoms. A total of 2902 CKD participants were included, with 291 presenting depressive symptoms, and estimated glomerular filtration rate (eGFR) was negatively associated with depressive symptoms with full adjustment [odds ratio (OR), 0.98; 95% confidence interval (95% CI), 0.97–1.00]. After converting eGFR to a categorical variable by quartiles (Q1-Q4), compared to Q1, the highest eGFR quartile was linked to a significantly decreased likelihood of depressive symptoms (OR=0.53, 95% CI: 0.30–0.92). Subgroup analysis further revealed a negative relationship between eGFR and depressive symptoms. Mediation analysis indicated that six biochemical markers mediated the association between CKD and depressive symptoms, with the following contributions: 49.72% for blood urea nitrogen, 17.82% for alkaline phosphatase, 17.21% for albumin, 9.78% for globulin, 8.94% for iron, and 6.95% for glucose. In this cross-sectional analysis, lower eGFR was associated with higher presence of depressive symptoms. Blood urea nitrogen, alkaline phosphatase, albumin, globulin, iron, and glucose mediated the association of CKD on depressive symptoms.

1. Introduction

Chronic kidney disease (CKD) is classified based on its underlying cause and further stratified by the estimated glomerular filtration rate (eGFR) and albuminuria levels [1]. As a progressive and irreversible condition, CKD is an increasing global health concern, with an estimated 800 million people (approximately 10% prevalence) affected by any stage of CKD [2]. The Global Burden of Disease Study reports that CKD contributed to 1.2 million deaths and 35.8 million disability-adjusted life years in 2017, with 1.4 million cardiovascular-related deaths attributed to impaired kidney function [3]. The COVID-19 pandemic has exacerbated the disease burden, including increased vulnerability, heightened psychological distress, and rising healthcare demands [4][5]. Despite advances in clinical guidelines and evidence-based treatments, CKD continues to be significantly underdiagnosed and undertreated. By 2024, CKD is projected to become the fifth leading cause of death globally [6][7].

Psychiatric disorders are common among patients with CKD, with depression being particularly prominent [8]. Over 20% of CKD patients suffer from major depressive episodes, a proportion significantly higher

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than the lifetime prevalence (3.0%–5.9%) and point prevalence (1.7%–3.4%) observed in the general population [9][10]. Existing research has primarily focused on the prevalence, mortality, quality of life, and treatment of dialysis patients with depressive symptoms [11]. In patients with renal failure receiving dialysis, major depressive disorder is associated with increased risks of hospitalisation and mortality [12][13]. Furthermore, a 20-year prospective cohort study confirmed a bidirectional association between CKD and depressive symptoms, with both conditions potentially exacerbating each other over time [14]. However, evidence regarding the entire disease course of CKD and the underlying mechanisms linking the two conditions remains relatively limited. Consequently, identifying risk factors and developing targeted treatments are crucial for managing this comorbidity. However, studies exploring the mechanisms underlying the association between CKD and depressive symptoms remain limited.

CKD is typically accompanied by multiple biochemical abnormalities, including electrolyte disturbances, hyperuricemia, and renal anemia [15][16]. As renal function declines, alterations in metabolic and inflammatory markers provide insight into disease progression and potential biological pathways linking CKD to depressive symptoms [17]. Previous studies have reported that peripheral biochemical and cellular markers such as albumin, bilirubin, and white blood cell counts are associated with depressive symptoms [18][19][20]. In addition, depressive symptoms in CKD patients have been linked to serum urea and glucose metabolism abnormalities, reflecting disturbances in neuronal and metabolic functions [21][22]. These biochemical alterations may contribute to depressive symptoms through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, inflammation, and oxidative stress, suggesting possible bidirectional mechanisms. Although a few markers such as C-reactive protein (CRP) have been extensively studied, many biochemical indicators remain underexplored [23]. Therefore, this study aims to examine the association between CKD and depressive symptoms and to further investigate the potential mediating role of biochemical markers among adults in the United States.

2. Methods

2.1 Study design and population

Figure 1 shows the inclusion-exclusion criteria for the study, which utilized data from the 2005-2018 National Health and Nutrition Examination Survey (NHANES) https://www.cdc.gov/nchs/nhanes/index.htm. Initially, we included all adults (⩾ 18 years) with CKD (eGFR<60 ml/min per1.73m2). Additionally, 316 patients lacking complete PHQ-9 questionnaire data were excluded. Finally, 2902 eligible CKD patients with complete PHQ-9 data, aged 18 years or older, were included in this study.

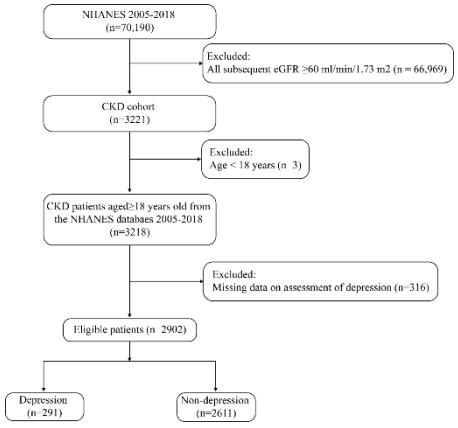

Fig. 1 - Flowchart of participant selection. CKD, Chronic kidney disease; NHANES, National Health and Nutrition Examination Survey.

2.2 Chronic kidney disease

The CKD was defined as having an ALB-to-creatinine ratio (ACR) ⩾ 30 mg/g/d or an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2. In this study, we estimated eGFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

eGFR = 141 ∗ min (Scr / κ ,1) α ∗ max (Scr / κ ,1) −1.209 ∗ 0.993Age ∗ Sex ∗ Race

For females, the following values are used: Sex = 1.018; α = − 0.329; κ = 0.7; For males, the following values are used: Sex = 1; α = − 0.411; κ = 0.9. If black, Race = 1.159, for white or other, Race = 1.

2.3 Depressive symptoms

Depressive symptoms were assessed using the nine-item Patient Health Questionnaire (PHQ-9). This brief instrument is a validated measure for screening and grading depression severity [24]. Scores range from 0 to 27, with higher values indicating greater symptom burden. In this study, a score ⩾10 defined clinically meaningful depressive symptoms, consistent with DSM-IV – aligned conventions [25][26].

2.4 Laboratory measures

Based on prior studies, clinical experience, and the availability of measurements in NHANES 2005–2018, we included the following biochemical markers: hemoglobin; albumin (ALB); alkaline phosphatase (ALP); bicarbonate (HCO_3^-); blood urea nitrogen (BUN); calcium; total cholesterol; glucose; iron; phosphorus; electrolytes (K^+, Cl^-, Na^+); total bilirubin; uric acid; and globulin.

2.5 Covariates

Continuous covariates included age and body-mass index (BMI), calculated as the weight (kg) divided by height squared (m^2). Age groups (<60, ⩾60), ethnicity (white, black, Mexican, other), education level (< high school, completed high school, > high school), marital status (never married, married/living with partner, or divorced/separated/widowed), smoking status (never, former, current), alcohol status (never, former, mild, moderate, heavy) were used as categorical variables.

Alcohol consumption patterns were determined from two 24-hour dietary recalls. Participants reporting alcohol intake in either recall were considered alcohol users. Alcohol use was categorized into five levels: never drinkers (⩽12 drinks in lifetime), former drinkers (>12 drinks in lifetime but no drinking in the past year), mild drinkers (⩽1 drink/day for women or ⩽2 drinks/day for men), moderate drinkers (>2 drinks/day for women or >3 drinks/day for men, or binge drinking on more than two occasions per month), and heavy drinkers (>3 drinks/day for women or >4 drinks/day for men, or binge drinking on more than five occasions per month). Smoking status was assessed as never smoked (smoked < 100 cigarettes), former smoker (not currently smoking but smoked ⩾ 100 cigarettes), or current smoker (⩾ 100 cigarettes and currently smoking every day or on some days).

2.6 Statistical analysis

DecisionLinnc 1.0 software was used for data analysis [27]. DecisionLinnc 1.0 is a platform that integrates multiple programming language environments and enables data processing, data analysis, and machine learning through a visual interface.

Continuous variables were summarized as mean ± SD or median (IQR), categorical variables as counts (%). Group differences were tested using χ^2 for categorical data, ANOVA for normally distributed continuous data, and Mann–Whitney U test otherwise. A two-sided $p<0.05$ indicated significance.

Associations between CKD and depressive symptoms were examined with logistic regression. Restricted cubic splines assessed nonlinear effects; subgroup and interaction analyses tested heterogeneity. Biochemical markers were log-transformed. Pearson's correlation was applied for linear associations. Mediation analyses (1,000 bootstrap samples) estimated indirect effects, proportion mediated, and p-values.

Table 1 - Descriptive statistics of the manifest variables (n=2902).

Variables	Total	Depressive symptoms (n = 291)	Non-depressive symptoms (n = 2611)	p
Male, n (%)	1415 (48.76)	118 (40.55)	1297 (49.67)	0.003
BMI, kg/m2, mean (SD)	29.93 (6.71)	32.22 (8.24)	29.67 (6.47)	<0.001
Age groups				<0.001
<60	322 (11.10)	58 (19.93)	264 (10.11)	
≥60	2580 (88.90)	233 (80.07)	2347 (89.89)	
Ethnicity, n (%)				0.002
White	1748 (60.23)	150 (51.55)	1598 (61.20)	
Black	600 (20.68)	64 (21.99)	536 (20.53)	
Mexican	222 (7.65)	34 (11.68)	188 (7.20)	
Other	332 (11.44)	43 (14.78)	289 (11.07)	
Educational level, n (%)				<0.001
<High school	726 (25.02)	112 (38.49)	614 (23.52)	
Completed high school	622 (21.43)	56 (19.24)	566 (21.68)	
>High school	1084 (37.35)	85 (29.21)	999 (38.26)	
Marital status, n (%)				0.002
Never married	192 (6.62)	30 (10.31)	162 (6.20)	
Married/living with partner	53 (1.83)	6 (2.06)	47 (1.80)	
Divorced/Separated/Widowed	349 (12.03)	53 (18.21)	296 (11.34)	
Smoking status, n (%)				0.466
Never	929 (56.37)	85 (60.71)	844 (55.97)	
Former	369 (22.39)	26 (18.57)	343 (22.75)	
Current	350 (21.24)	29 (20.71)	321 (21.29)	
Alcohol use status, n (%)				0.846
Never	220 (15.71)	21 (17.36)	199 (15.56)	
Former	226 (16.14)	21 (17.36)	205 (16.03)	
Mild	458 (32.71)	34 (28.10)	424 (33.15)	
Moderate	218 (15.57)	19 (15.70)	199 (15.56)	
Heavy	278 (19.86)	26 (21.49)	252 (19.70)	
PHQ-9 score, mean (SD)	3.60 (5.21)	15.08 (8.05)	2.32 (2.57)	<0.001
eGFR, mL/min/1.73 m², M (Q)	49.68 (39.84-55.65)	46.35 (36.65-54.81)	49.74 (40.37-55.65)	0.002
Hemoglobin, g/dL, M (Q)	13.4 (12.3-14.5)	13 (12-14.3)	13.4 (12.3-14.5)	0.004
ALB,g/dL, M (Q)	4.1 (3.9-4.3)	4 (3.8-4.3)	4.1 (3.9-4.3)	0.001
ALP, U/L, M (Q)	71 (57-89)	76 (62-96)	70 (57-88)	<0.001
BUN, mg/dL, M (Q)	22 (17-28)	21 (17-28)	22 (17-28)	0.978
Calcium, mg/dL, M (Q)	9.4 (9.1-9.7)	9.4 (9.1-9.7)	9.4 (9.2-9.7)	0.128
Cholesterol, mg/dL, M (Q)	181 (152-213)	179 (146-217)	181 (153-213)	0.606
HCO3-, mmol/L, M (Q)	25 (23-27)	25 (23-27)	25 (23-27)	0.035

Variables	Total	Depressive symptoms (n = 291)	Non-depressive symptoms (n = 2611)	p
Glucose, mg/dL, M (Q)	101 (91-124)	105 (92-141)	101 (90-123)	0.008
Iron, ug/dL, M (Q)	75 (58-94)	70 (52-91)	75 (58-94)	0.009
Phosphorus, mg/dL, M (Q)	3.8 (3.4-4.1)	3.8 (3.5-4.2)	3.8 (3.4-4.1)	0.024
Total bilirubin, mg/dL, M (Q)	142 (98-205)	156 (104.5-221.5)	140 (98-203.25)	0.003
Uric acid, mg/dL, M (Q)	6.5 (5.5-7.6)	6.5 (5.5-7.6)	6.5 (5.5-7.6)	0.682
Na+, mmol/L, M (Q)	140 (138-141)	139 (138-141)	140 (138-141)	0.043
K+, mmol/L, M (Q)	4.2 (3.9-4.5)	4.2 (3.9-4.5)	4.2 (3.9-4.5)	0.667
Cl-, mmol/L, M (Q)	103 (101-106)	103 (100-105)	103 (101-106)	0.116
Globulin, g/dL, M (Q)	2.9 (2.6-3.3)	3 (2.7-3.4)	2.9 (2.6-3.3)	0.014

Abbreviations: SD, standard deviation; BMI, body mass index; PHQ-9, Patient Health Questionnaire-9; eGFR, estimated Glomerular Filtration Rate; ALB, Albumin; ALP, Alkaline phosphatase; BUN, Blood urea nitrogen.

3. Results

3.1 Baseline characteristics

The baseline demographic characteristics of the eligible subjects are shown in Table 1. The study included a total of 2902 adult patients with CKD, among whom 291 (10.03%) suffered from depressive symptoms. The median eGFR concentration for all subjects was 49.68 mL/min/1.73 m^2 (Q1=39.84, Q3=55.65). The median BMI of the participants was 29.93 kg/m2, with 1415 (48.76%) males and 1487 (51.24%) females. The majority of participants were ⩾60 years old (2580, 88.90%) and white (1748, 60.23%). There were statistical differences between the groups with and without depressive symptoms on variables of gender, BMI, age, ethnicity, education level, marital status, PHQ-9 score, eGFR, hemoglobin, ALB, ALP, HCO3-, glucose, iron, phosphorus, total bilirubin, sodium and globulin (all $P < 0.05$).

3.2 Relationships between the CKD and depressive symptoms

Table 2 displays the findings of the multiple logistic regression of the association of CKD and depressive symptoms. A significant negative correlation was found between the incidence of depressive symptoms and the eGFR in the unadjusted crude models (OR=0.98, 95% CI: 0.97–0.99), partially adjusted (OR=0.98, 95% CI: 0.98–0.99), and the fully adjusted models (OR=0.98, 95% CI: 0.97–1.00). This finding indicates a 2% reduction in the risk of depressive symptoms for each unit increase in eGFR. To facilitate further research, the current study converted eGFR from a continuous variable to a categorical variable (quartiles). Compared to participants in the Q1 group with the lowest eGFR, those in the Q4 group with the highest eGFR had a decreased risk of depressive symptoms (OR=0.53, 95% CI: 0.30–0.92). The effect sizes between the eGFR quartiles were not uniform in the fully adjusted model (Q1: OR=1; Q2: OR=0.83; Q3: OR=0.56; Q4: OR=0.53). However, the subsequent restricted cubic spline (RCS) analysis indicated that there was no significant non-linear relationship between CKD and depressive symptoms (non-linear P>0.05), but rather a nearly linear negative correlation (Figure 2).

Table 2. Association between CKD and depressive symptoms in different models.

	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
eGFR	0.98 (0.97,0.99)	<0.001	0.98(0.98,0.99)	<0.001	0.98(0.97,1.00)	0.008
Q1	reference		reference		reference	
Q2	0.64(0.46,0.88)	0.007	0.69(0.49,0.95)	0.026	0.83(0.50,1.38)	0.481
Q3	0.55(0.39,0.78)	0.001	0.59(0.42,0.83)	0.003	0.56(0.32,0.97)	0.043
Q4	0.61(0.44,0.85)	0.004	0.63(0.45,0.87)	0.006	0.53(0.30,0.92)	0.025
p for trend	0.002		0.003		0.010	

95% CI: 95% confidence interval; Model 1: no covariates were adjusted; Model 2: adjusted for sex, age groups, BMI; Model 3: adjusted for sex, age groups, BMI, ethnicity, educational level, marital status, smoking status, alcohol use status

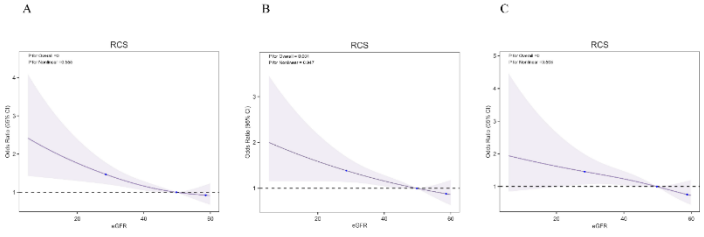

Fig. 2 - Association between CKD and depressive symptoms. (A) adjusted for none; (B) adjusted for sex, age groups, BMI; (C) adjusted for sex, age groups, BMI, ethnicity, educational level, marital status, smoking status, alcohol use status.

Subgroup analyses were performed to investigate the association between CKD and depressive symptoms (Figure 3). The results showed that the eGFR had a significant negative association with depressive symptoms in several subgroups. The prevalence of depressive symptoms in gender, <60 years, black, >high school, married/living with partner, moderate drinkers, heavy drinkers and former smokers was significantly associated with the CKD. A one-unit decrease in eGFR accounted for an increment of 4% in the prevalence of depressive symptoms in <60 years participants (OR=0.96, 95% CI: 0.93–0.98), 5% in former smokers (OR=0.95, 95% CI: 0.93–0.98), 3% in >high school participants (OR=0.97, 95% CI: 0.95–0.99), and 3% in black participants (OR=0.97, 95% CI: 0.95–0.99). The log-likelihood ratio test showed a significant interaction between CKD and depressive symptoms among the age groups (p=0.009). However, there were no significant differences among the other groups (all p for interaction >0.05).

Variable	Count	Percent	OR	low	high	P value	P for interaction
Overall	1358	100	0.98	0.97	0.99	0.002	
Gender							0.830
Male	645	47.5	0.98	0.96	1	0.029	
Female	713	52.5	0.98	0.96	1	0.035	
Age_groups							0.009
<60	133	9.8	0.96	0.93	0.98	<0.001	
≥60	1225	90.2	0.99	0.98	1.01	0.425	
Ethnicity							0.511
White	866	63.8	0.99	0.97	1.01	0.257	
Black	284	20.9	0.97	0.95	0.99	0.007	
Mexican	94	6.9	1	0.96	1.05	0.951	
Other	114	8.4	0.98	0.94	1.01	0.184	
Educational_level							0.428
<High school	440	32.4	0.99	0.97	1.01	0.234	
Completed high school	347	25.6	0.99	0.96	1.02	0.393	
>High school	571	42	0.97	0.95	0.99	0.006	
Marital_status							0.539
Never mreeied	92	6.8	0.97	0.93	1.01	0.124	
Married/Living with partner	735	54.1	0.97	0.96	0.99	0.007	
Divorced/Separated/Widowed	531	39.1	0.99	0.97	1.01	0.323	
Alcohol_use_status							0.589
Never	215	15.8	1	0.96	1.04	0.890	
Former drinkers	222	16.3	0.99	0.96	1.02	0.457	
Mild drinkers	445	32.8	0.98	0.95	1	0.061	

Fig. 3 - Subgroup analysis of the association between CKD and depressive symptoms

3.3 Association between biochemical markers and depressive symptoms

The results of RCS analysis suggested a nonlinear association between ALB (p-overall: <0.001, p-nonlinear: 0.036), calcium (p-overall: <0.001, p-nonlinear: 0.017), cholesterol (p-overall: <0.001, p-nonlinear: 0.039) and depressive symptoms. However, no nonlinear associations were found between other biochemical markers and depressive symptoms, as detailed in Figure 4.

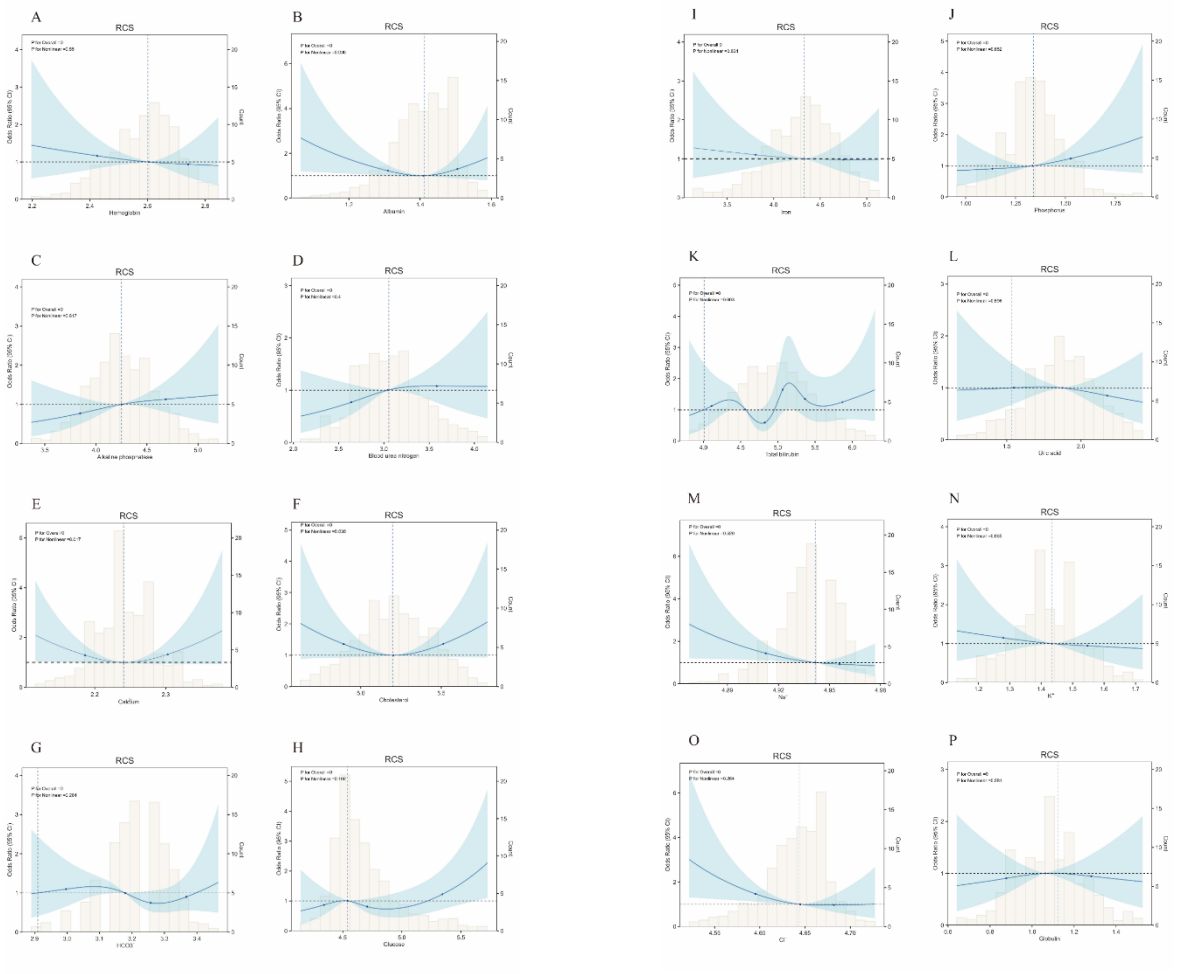

Fig. 4 - Restricted cubic spline (RCS) analyses of the associations between biochemical markers and depressive symptoms. Odds ratios (solid lines) with 95% confidence intervals (shaded areas) are shown, with histograms representing the distributions of each marker. Panel A: hemoglobin; B: albumin; C: alkaline phosphatase; D: blood urea nitrogen; E: calcium; F: cholesterol; G: bicarbonate; H: glucose; I: iron; J: phosphorus; K: total bilirubin; L: uric acid; M: sodium (Na^+); N: potassium (K^+); O: chloride (Cl^-); P: globulin.

3.4 Mediating effect of biochemical markers

Figure 5 shows the biochemical markers that played a significant role in mediating the relationship between CKD and depressive symptoms. The results of the study showed that six common biochemical markers (ALB, ALP, BUN, glucose, iron, globulin) modestly mediated the relationship

between CKD and depressive symptoms. Among them, BUN mediated the largest proportion of 49.72%, while glucose mediated the smallest proportion of 6.95% (all P<0.05).

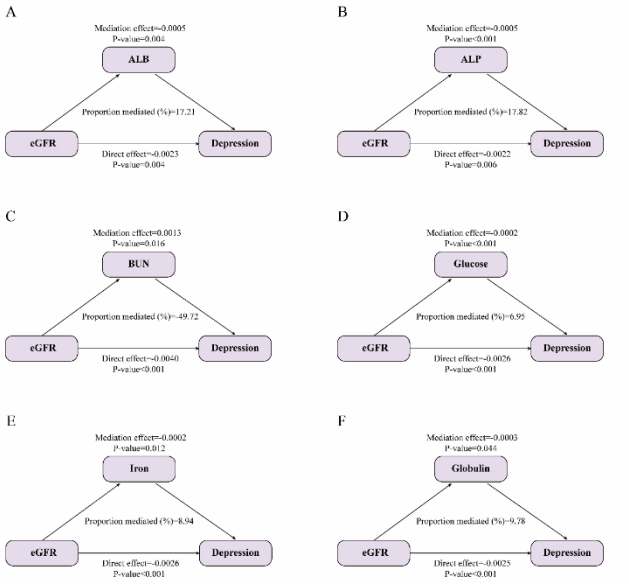

Fig. 5 - Mediation effects of biochemical markers on the association between CKD and depressive symptoms. Proportion mediated (PM) = βindirect/βtotal. Abbreviations: ALB, Albumin; ALP, Alkaline phosphatase; BUN, Blood urea nitrogen.

4. Discussion

In this study involving 2902 participants, we identified a significant cross-sectional association between eGFR and the presence of depressive symptoms. Furthermore, mediation analyses showed that biochemical markers mediated the relationship of CKD and depressive symptoms, suggesting that metabolic disturbance may be an underlying biological mechanism.

The chronic nature of CKD, combined with management challenges such as dietary restrictions and dialysis, as well as financial burdens, increases patients' vulnerability to depressive symptoms [11]. Zhang et al. reported that, among individuals with normal kidney function, severe depressive symptoms were significantly associated with an elevated risk of rapid renal function decline [28]. Furthermore, CKD induces oxidative stress and chronic inflammation, disrupting neurotransmitter metabolism, neuroendocrine regulation, and neural plasticity [29][30]. These factors are critical in the pathophysiology of depressive symptoms. Elevated levels of pro-inflammatory cytokines in CKD patients may impair serotonin metabolism and activate the hypothalamic-pituitary-adrenal (HPA) axis, thereby exacerbating depressive symptoms [31]. Conversely, depressive symptoms can stimulate the HPA axis through the release of corticotrophin-releasing hormone, leading to heightened inflammation, impaired renal microcirculation, and accelerated CKD progression [32][33][34][35]. Notably, Patients with severe depressive symptoms are more likely to exhibit poor treatment adherence and engage in unhealthy behaviors, such as obesity, smoking, and physical inactivity, all of which increase CKD risk [36][37][38][39]. These shared risk factors may partially explain the bidirectional relationship between CKD and depressive symptoms.

Our findings suggest that six biochemical markers (e.g., ALB, ALP, BUN, glucose, iron, and globulin) play a modest role in mediating the relationship between CKD and depressive symptoms in adults. Notably, BUN accounted for 49.72% of the mediated effect, implicating uremic burden as a major pathway linking CKD to depressive symptoms. This positions BUN as a biomarker for risk stratification and early detection of depressive symptoms in CKD, and as a priority target for mechanistic studies on uremic metabolite–brain interactions [40][41][42]. Wang et al. demonstrated that urea accumulation in the brain can independently lead to depressive symptoms, irrespective of psychosocial stress [43]. Mechanistically, urea disrupts synaptic plasticity in the medial prefrontal cortex by inhibiting mTORC1-S6K-dependent dendritic protein synthesis through carbamoylation of mTOR, ultimately contributing to depressive symptoms [43]. Moreover, urea transporter B (UT-B), a key mediator of urea transport in the brain, particularly in the hippocampus, plays a critical role in this process. Studies in UT-B knockout mice revealed that hippocampal urea accumulation disrupts the nitric oxide synthase/nitric oxide (NOS/NO) system, resulting in depressive symptoms-like behaviors [44].

ALP is a hydrolytic enzyme implicated in various diseases, including liver dysfunction, bone disorders, diabetes, and kidney disease [45]. Our findings revealed that ALP accounted for 17.82% of the mediating effect, which is closely associated with abnormal bone metabolism in CKD patients. CKD is characterized by disruptions in mineral metabolism, contributing to CKD-mineral and bone disorder (CKD-MBD), with elevated ALP levels serving as a key biomarker [46]. Furthermore, chronic pain experienced by CKD patients is associated with disturbances in bone metabolism. Zhang et al. demonstrated that inhibiting the 5-HTDRN → SOMCeA pathway induces depressive symptoms-like behaviors in male mice with chronic pain [47]. Elevated ALP levels may also disrupt calcium and phosphorus metabolism, potentially affecting brain signaling pathways, such as the Wnt/β-catenin pathway, which is critical for regulating neuronal function [48].

The mediating effects of ALB and globulin were 17.21% and 9.78%, respectively. A recent cross-sectional study using NHANES data (2005–2018) found that ALB concentration is significantly associated with a protective effect against depressive symptoms [49]. CKD patients with depressive symptoms had significantly lower ALB levels compared to those without depressive symptoms [50]. Studies also indicate that depressive symptoms in CKD patients is significantly and independently linked to lower serum ALB levels [51]. IIn Japanese CKD patients, a secondary analysis of a prospective cohort revealed a negative, non-linear association between ALB levels and both renal function decline and prognosis. ALB levels below 4.1 g/dL were closely associated with poor renal outcomes [52]. Additionally, Lang et al. reported that lower serum ALB levels were strongly correlated with eGFR decline, an indicator of kidney function. This association was independent of traditional risk factors, including urine ALB, inflammatory markers, and known clinical risks for kidney disease [53]. A 12-year community-based prospective study identified a low serum ALB-to-globulin (AG) ratio as an independent predictor of CKD development, with a stronger predictive value than inflammatory markers [54]. Reduced ALB levels may also contribute to oxidative stress dysregulation, as elevated free radical levels and oxidative damage are commonly observed in patients with depressive symptoms [55][56]. ALB plays a role in the inflammatory system, decreasing with increased inflammation, which may trigger depressive symptoms via the acute phase response instead of the immune response [49]. Furthermore, reduced ALB availability limits tryptophan, an essential amino acid necessary for producing 5-hydroxytryptophan, a critical neurotransmitter linked to depressive symptoms [57][58].

Iron accounted for 8.94% of the mediation effect, indicating that iron metabolism plays an important mediating role between CKD and depressive symptoms. Anemia is a common complication in CKD and iron deficiency is one of its main causes [59]. Even without anemia, iron deficiency can contribute to depressive symptoms, especially through disrupted neurotransmission [60]. Iron is essential for neurotransmitter synthesis (serotonin, dopamine, and noradrenaline), and its deficiency can disrupt the balance of these neurotransmitters, potentially leading to depressive symptoms [60]. In addition, studies have shown that iron supplementation significantly reduces the risk of mental disorders [61]. However, inflammation affects iron metabolism, leading to an increase in serum ferritin and a concomitant decrease in serum iron. Higher iron status has been associated with an increased risk of depressive symptoms and psychiatric disorders [62]. Both iron deficiency and iron overload may influence the risk of developing psychiatric disorders; thus, it is essential to consider the iron status of patients when treating refractory depressive symptoms.

The mediating effect of glucose is only 6.95%, but its role should not be ignored. CKD patients are often accompanied by insulin resistance and abnormal glucose metabolism, and hyperglycaemic state may affect the central nervous system through oxidative stress and impaired blood-brain barrier function [63][64]. Notably, hyperglycemia increases the production of advanced glycation end products (AGEs), and the elevated expression of receptors for AGEs (RAGE) activates MAPK (JNK and p38K)-dependent cell death pathways, promoting neuroinflammation, apoptosis, and neuronal damage [65][66]. Lee et al. found that glucose dysregulation could serve as a prognostic biomarker for depression [67]. Elevated glucose levels are linked to dysthymia and higher HbA1c is observed in recurrent or psychotic depression [68]. A large cross-sectional study reported that glucose dysregulation correlates with a higher risk of suicidal ideation and suicidal behavior in patients with depression [69].

Taken together, our findings suggest that six biochemical markers mediate the relationship between CKD and depressive symptoms through distinct biological pathways, with BUN showing the most prominent effect. The high mediating effect of BUN highlights the neurotoxic impact of uremic toxin accumulation. ALB and ALP contribute to the development of depressive symptoms through mechanisms related to malnutrition, inflammation, and disordered bone metabolism. Although the mediating effects of glucose, iron, and globulin are relatively smaller, their critical roles in glucose metabolism, iron regulation, and immune system modulation should not be overlooked. These insights provide potential targets for future interventions and underscore the importance of early monitoring and management of these biochemical markers in CKD patients.

5. Limitations

This study has several limitations that should be acknowledged. First, as NHANES is a cross-sectional study, causality or long-term implications cannot be inferred. Additional cohort studies are needed to determine if a longitudinal relationship exists between blood biomarkers and depressive symptoms. Second, our study relied on peripheral blood biomarkers, which may not fully reflect central nervous system alterations due to the restriction of the blood–brain barrier. Future studies incorporating cerebrospinal fluid (CSF) markers are needed to better elucidate the biological mechanisms underlying depression. Third, the lack of sample weighting may limit the generalizability of the findings to the entire United States population. Future studies with sample weighting and more representative datasets are needed to confirm these results. Fourth, despite adjusting for known confounders, there is a possibility of unmeasured confounding. Finally, the use of self-reported measures for depressive symptoms may introduce recall bias.

6. Conclusion

In conclusion, this study indicates that biochemical markers (blood urea nitrogen, alkaline phosphatase, albumin, globulin, iron, and glucose) mediate the association between CKD and depressive symptoms, highlighting the potential role of metabolic dysregulation in CKD-related depressive symptoms. However, the cross-sectional study design limits causal inferences, prospective longitudinal studies are required to confirm whether CKD patients are susceptible to metabolically driven depression. Furthermore, mechanistic investigations should delve into specific metabolic pathways to elucidate the biological basis of this association. This study underscores the importance of integrating mental health screening with biochemical marker assessment into CKD management protocols.

Declaration

A.1. Data availability

This study used data from the National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/nchs/nhanes/index.htm).

A.2. Author contributions

All authors contributed to the study conception and design. Wei Zhang: Writing – review & editing, Supervision, Project administration. Wei Zhou: Writing – review & editing. Hongxia Tao: Formal analysis, Writing – original draft.

A.3. Competing interests

The authors declare no competing interests.

A.4. Ethics approval and consent to participate

The National Health and Nutrition Examination Survey involving human participants was reviewed and approved by the National Center for Health Statistics Ethics Review Board. The patients/participants provided their written informed consent. This study involved secondary data analysis of the National Health and Nutrition Examination Survey, and this study we conducted was exempt from institutional review for this reason.

A.5. Funding statement

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