Lipids in Health and Disease

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Association between cardiorenal syndrome and depressive symptoms among the US population: a mediation analysis via lipid indices

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Abstract

Background Cardiovascular diseases (CVD), chronic kidney disease (CKD), and lipids are positively correlated with the presence of depressive symptoms. However, investigation into the complex link that exists between cardiorenal syndrome (CRS) and lipid indices and depression remains scarce.

Methods This study analyzed data from 11, 729 adults in the National Health and Nutritional Examination Surveys from 2005 to 2018. Weighted regression analysis was employed to examine the relationships between CRS and depression, CRS and the Patient Health Questionnaire-9 score, and lipid indices with depression. The restricted cubic spline analysis was used to determine whether there is a linear association between lipid indices and depression. Smooth curve fitting was employed to illustrate the relationship between lipids, depression, and cardiorenal diseases. Subgroup and sensitivity analyses were also conducted to enhance the stability of the results. Finally, we applied mediation analysis to explore whether the Atherogenic Index of Plasma (AIP), triglyceride glucose (TyG) index, and remnant cholesterol (RC) mediate the association between CRS and depression.

Results After applying propensity score matching (PSM), 1,509 adults remained in the study. After PSM, more remarkable results were rendered that CRS was associated with depression compared with non-CRS (OR: 1. 240, 95% CI: 1. 237 ~ 1. 243), only-CVD (OR: 0. 646, 95% CI: 0. 644 ~ 0. 649), and only-CKD (OR: 1.432, 95% CI: 1.428 ~ 1.437) in a fully corrected model. Smooth curve fitting shows that the intersection point of the lines of CRS and non-CRS occurs at a higher value on the horizontal axis than the intersection point of the lines representing CVD and non-CVD. In the fully corrected model, AIP, TyG, and RC did not independently mediate the association between CRS and depression.

Conclusion There was a significant association between CRS and depression and a linear relationship between AIP, TyG, and RC and depression. However, the above lipid indicators did not mediate the association between CRS and depression.

Keywords Cardiorenal syndrome, Depression, Lipids, Mediation analysis, NHANES

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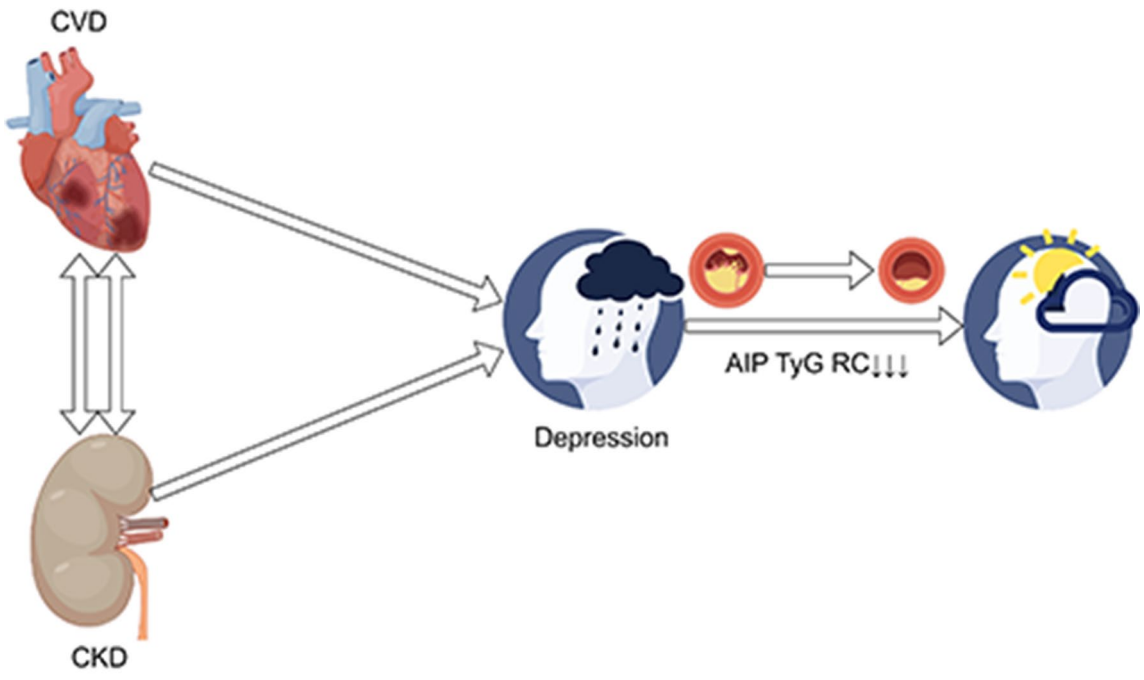
Graphical Abstract



A visualization of the study of the link between cardiorenal syndrome and depression by Figdraw.

Introduction

Cardiovascular disease (CVD) is a common disease with high morbidity, disability, and mortality in the world. Due to the activation of the sympathetic-renin-angiotensin-aldosterone system, it can be observed in clinical practice that patients with CVD tend to have a higher incidence of chronic kidney disease (CKD) and vice versa. The co-existence of both diseases often predicts a poor prognosis and careful administration of medication. In Framingham Offspring Study participants without CVD, participants with even mildly reduced kidney function experienced approximately 1.4 times the incidence of CVD [1]. Data from the Global Burden of Disease, CKD and its effect on CVD resulted in 2.6 million (95% UI: 2.4–2.8) deaths in 2017 and CKD has risen from 19th to 11th in rank among leading causes of death between 1990 and 2019 due to aging and an increasing burden of risk factors for CKD [2]. Decreased renal function induced by acute or chronic cardiovascular function decline, heart failure (HF) caused by acute or chronic renal function deterioration, or organ failure secondary to other physical conditions is defined as cardiorenal syndrome (CRS) by The Acute Dialysis Quality Initiative [3]. There is an urgent need to impede the progression of CRS, reduce the risk of disease, improve the quality of life of patients, and increase the disability-free survival rate of patients.

Dyslipidemia is commonly seen in individuals with CVD and is widely acknowledged as a risk factor for CVD. Several novel lipid indices demonstrate better results than traditional single indicators in studies related to cardiovascular metabolism disease incidence and mortality rates [4–7]. The Atherogenic Index of Plasma (AIP), a reliable marker of plasma atherogenicity, was independently associated with an increased risk of major adverse cardiovascular and cerebrovascular events in patients with acute coronary syndrome undergoing percutaneous coronary intervention with low-density lipoprotein-cholesterol below 1.8mmol/L [8]. The triglyceride glucose (TyG) index, which represents insulin resistance, is even associated with an increased probability of cardiac arrest in the general population [9]. In an observational study and Mendelian randomization analysis, serum remnant cholesterol (RC) was significantly associated with higher risks of cardiometabolic multimorbidity, particularly the multimorbidity of ischemic heart disease and type 2 diabetes [10].

Depression is a mood disorder or affective disorder characterized by a predominantly depressed mood, and its main clinical manifestations are downheartedness, slowed thinking, diminished voluntary activity, and impaired cognitive functioning. Depressed patients are at increased risk for CVD through various mechanisms such as increased sympathetic excitability and decreased

adherence to disease treatment. So, in recent years there have been some studies on the links between CVD, CKD, lipids, and depression [11–15]. However, investigation into the complex link that exists between CRS and lipid indices and depression remains scarce.

Hence, in this study, we firstly examined the association between CRS and depression, secondly studied the relationship between lipids indices and depression in different disease states, and finally explored the mediating role of lipid indicators using the publicly available database.

Methods

Data source and study participants

The National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention aims to evaluate the health and nutritional status of individuals in the United States. Participation in NHANES is voluntary and confidential, and follows a complex, multistage, probability cluster design. Therefore, our study did not necessitate ethical review and additional signed informed consent from the participants. The NHANES study set 2 years as a cycle and included about 10, 000 participants every cycle since 1999. The NHANES database started to use the Patient Health Questionnaire-9 (PHQ-9) to determine depression from 2005 to now, so we extracted 2005–2018 participants data for our current cross-sectional study.

For our study, we included 70,190 participants from the NHANES 2005–2018 cohort, excluding those with missing PHQ-9 data (n=33,931), incomplete responses (n=155), or missing covariates data (n=22,930). We also excluded pregnant women (n=226) and individuals with cancer (n=1,219) who have a tendency to be depressed themselves, which could easily affect the results of the study [16, 17]. Ultimately, we included 11,729 eligible participants, of which 454 had CRS and 11,275 did not, ensuring a refined study group for our analysis. After applying propensity score matching (PSM), the sample was refined to 395 CRS and 1,114 non-CRS subjects. Detailed inclusion and exclusion criteria are in Fig. 1.

Ascertainment of CRS, non-CRS, only-CVD, and only-CKD

The concept of CRS was defined based on previous studies reporting [18]. On the one hand, the presence of a positive self-report of cardiovascular diseases (congestive heart failure, angina pectoris, coronary artery disease, heart attack, and stroke) from the medical condition questionnaire in the NHANES study was defined as CVD patients. On the other hand, we used creatinine as the core indicator to calculate the estimated glomerular filtration rate (eGFR) by the CKD-EPI formula, and we defined subjects as CKD patients if they had an eGFR<60 ml/min/1.73m^2 [19]. Alternatively, we also reckoned the urinary albumin-to-creatinine ratio (UACR); participants with UACR>30 mg/g were regarded as CKD patients. If the diagnostic criteria were met in both categories, we ascertained subjects as CRS patients. The only-CVD was defined as subjects with a positive report of CVD and a negative report of CKD, while the only-CKD also had its homologous definition.

Ascertainment of depression

PHQ-9 was used to measure the severity of depressive symptoms most often in primary care settings, and its validity and performance have been validated in heart disease or renal insufficiency patients [20, 21]. The PHQ-9 comprises nine items on depressive symptoms (lack of interest, depressed mood, trouble sleeping, fatigue, appetite problems, worthlessness, lack of concentration, psychomotor agitation or retardation, and suicidal thoughts). Each item is scored on a scale ranging from 0 (not at all) to 3 (nearly every day), added to an overall score ranging from 0 to 27, with higher PHQ-9 scores indicating more severe depressive symptoms. Individuals with an overall score≥10 points were considered to be suffering from major depression; the sensitivity of this threshold was 88% and the specificity was 88% [22].

Ascertainment of the lipid indices

AIP, TyG index, and RC were derived from the routine biochemistry profile of laboratory assay and involved with total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting plasma glucose (FPG). Subjects were collected blood samples in a fasting state at the mobile examination center. The NHANES Laboratory/Medical Technologies Procedures Manual contains detailed instructions for specimen collection and processing [23]. The computational formula was as follows: AIP=$\log_{10}$(TG/HDL-C), TyG index=Ln (TG [mg/dl] × FPG [mg/dl]/2), and RC=TC- HDL- LDL.

Covariates

Depending on previous studies [15, 18, 20, 23], covariates associated with CRS and depression were selected. These covariates were related to sociodemographic characteristics, personal habits, disease history, laboratory indicators, and prescription drug use. Sociodemographic characteristics embodied age, gender, race, education level, marital status, and poverty income ratio (PIR). Personal habits included body mass index (BMI), waist circumference (WC), physical activity (PA), drinking status, and smoking status. Disease history contained diabetes, hypertension, HF, coronary heart disease, angina pectoris, myocardial infarction, stroke, and CKD. Laboratory indicators incorporated TC, TG, HDL, LDL, FPG, hemoglobin A1c (HbA1c), uric acid (UA), eGFR, blood urea nitrogen (BUN), and UACR. There were five main

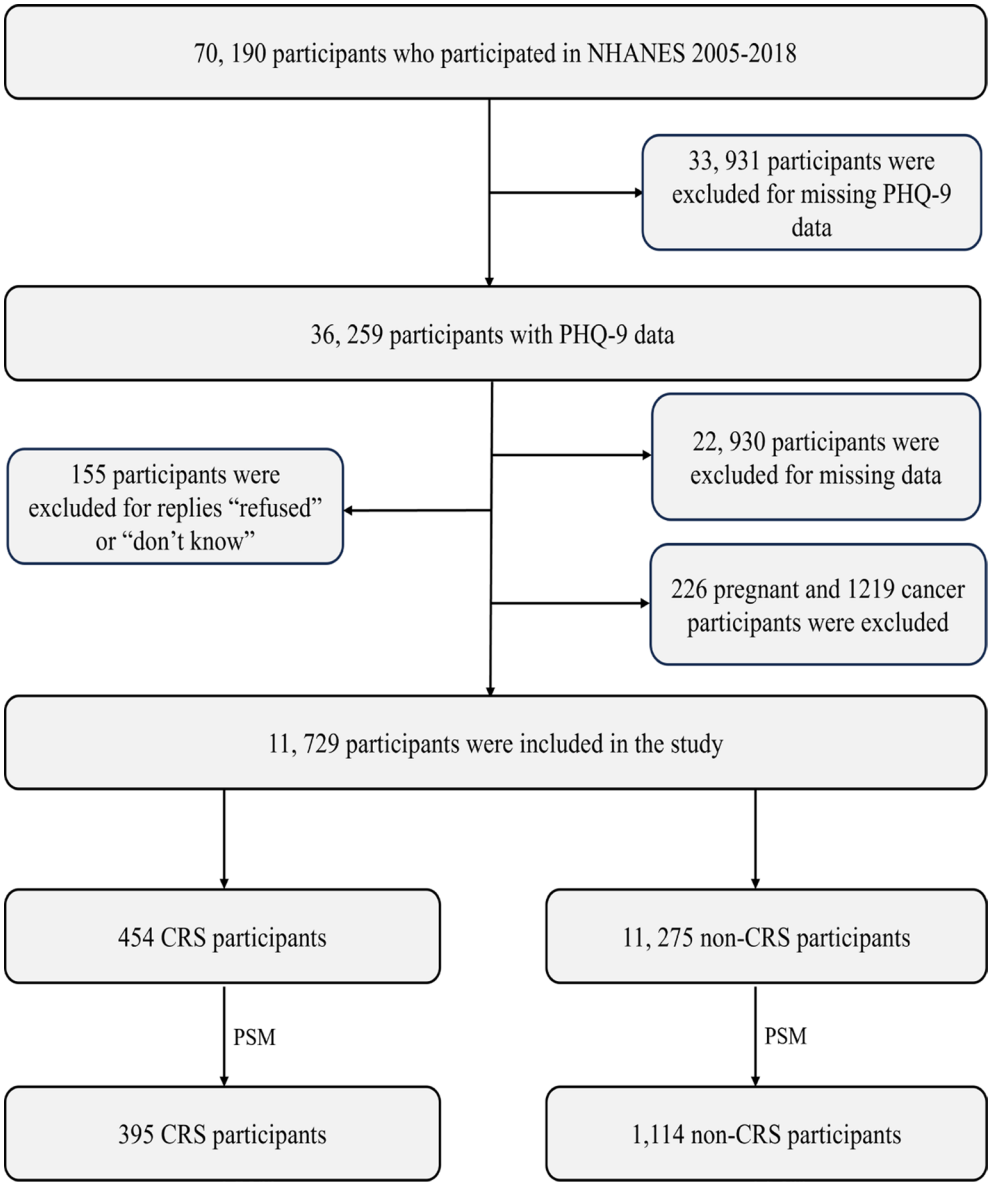


Fig. 1 Flowchart for selecting the study population

categories of prescription drugs: antihyperglycemic drugs, antihypertensive drugs, antithrombotic drugs, lipid-lowering drugs, and antidepressant drugs. PA was defined as having performed moderate to heavy physical activity in the past 30 days and a detailed description can be found in the questionnaire section of the NHANES website [24, 25]. Smoking status was defined as participants who smoked at least 100 cigarettes in their entire life [26, 27]. Smokers were categorized into 'current' and 'former' based on their current smoking status. We assess that this method may not be the most objective and relevant, but nothing is better. Drinking status was defined as participants who drank more than 12 times every year. Alcohol consumers were classified as 'moderate' or 'heavy' drinkers according to their consumption levels: moderate drinkers were defined as those consuming less than one drink per day for women and less than two drinks per day for men, while heavy drinkers were defined as those having one or more drinks per day for women and two or more drinks per day for men [26, 28]. Hypertension was defined as self-reported physician-diagnosed hypertension or using antihypertensive agents. The definition of diabetes included self-reported diagnosis, use of insulin or oral hypoglycemic agents, fasting glucose≥7 mmol/L, or HbA1c≥6.5%.

Statistical analyses

Tables 1 and Table S1 included baseline characteristics of participants according to different grouping methods. Continuous variables were expressed as mean±standard

Table 1 Baseline characteristics of CRS and non-CRS populations before and after PSM abbreviations: PIR, poverty income ratio; BMI, body mass index; WC, waist circumference; PA, physical activity; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TyG, triglyceride-glucose index; RC, remnant cholesterol; AIP, atherogenic index of plasma; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; UA, uric acid; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; UACR, urine albumin-creatinine ratio

Characteristics	Before PSM			After PSM		
	non-CRS	CRS	*P*-value	non-CRS	CRS	*P*-value
Age (years)	47.15 ± 16.73	69.48 ± 11.04	< 0.001	67.59 ± 11.52	68.85 ± 11.33	0.111
Gender, n (%)			0.024			0.546
Male	5651 (50.12)	252 (55.51)		598 (53.68)	219 (55.44)	
Female	5624 (49.88)	202 (44.49)		516 (46.32)	176 (44.56)	
Race, n (%)			< 0.001			0.976
Mexican American	1830 (16.23)	39 (8.59)		92 (8.26)	34 (8.61)	
Other Hispanic	1100 (9.76)	36 (7.93)		88 (7.90)	32 (8.10)	
Non-Hispanic White	4773 (42.33)	251 (55.29)		618 (55.48)	217 (54.94)	
Non-Hispanic Black	2337 (20.73)	103 (22.69)		257 (23.07)	88 (22.28)	
Other races	1235 (10.95)	25 (5.51)		59 (5.30)	24 (6.08)	
Education level, n (%)			< 0.001			0.705
Less Than 9th Grade	1009 (8.95)	62 (13.66)		134 (12.03)	53 (13.42)	
9-11th Grade	1600 (14.19)	81 (17.84)		185 (16.61)	72 (18.23)	
High School Graduate	2565 (22.75)	123 (27.09)		291 (26.12)	107 (27.09)	
Some College or AA degree	3356 (29.76)	121 (26.65)		323 (28.99)	102 (25.82)	
College Graduate or above	2745 (24.35)	67 (14.76)		181 (16.25)	61 (15.44)	
Marital status, n (%)			0.169			0.391
Yes	5835 (51.75)	220 (48.46)		561 (50.36)	189 (47.85)	
No	5440 (48.25)	234 (51.54)		553 (49.64)	206 (52.15)	
PIR	2.55 ± 1.63	2.15 ± 1.44	< 0.001	2.25 ± 1.45	2.18 ± 1.48	0.461
BMI (kg/m^2)	29.01 ± 6.82	30.94 ± 7.41	< 0.001	30.55 ± 7.08	30.55 ± 7.08	0.589
WC (cm)	98.71 ± 16.32	107.48 ± 16.60	< 0.001	106.44 ± 16.10	106.44 ± 16.10	0.731
PA, n (%)			< 0.001			0.300
Yes	5240 (46.47)	136 (29.96)		373 (33.48)	121 (30.63)	
No	6035 (53.53)	318 (70.04)		741 (66.52)	274 (69.37)	
Drinking, n (%)			< 0.001			0.359
Never drinkers	3351 (29.72)	186 (40.97)		446 (40.04)	158 (40.00)	
Moderate drinkers	1874 (16.62)	146 (32.16)		319 (28.64)	126 (31.90)	
Heavy drinkers	6050 (53.66)	122 (26.87)				
Smoking, n (%)			< 0.001			0.885
Never smokers	6236 (55.31)	191 (42.07)		472 (42.37)	162 (41.01)	
Former smokers	2640 (23.41)	177 (38.99)		418 (37.52)	153 (38.73)	
Current smokers	2399 (21.28)	86 (18.94)				
Diabetics, n (%)			< 0.001			0.111
Yes	1768 (15.68)	231 (50.88)		473 (42.46)	186 (47.09)	
No	9507 (84.32)	223 (49.12)		641 (57.54)	209 (52.91)	
Hypertension, n (%)			< 0.001			0.324
Yes	3785 (33.57)	383 (84.36)		900 (80.79)	328 (83.04)	
No	7490 (66.43)	71 (15.64)		214 (19.21)	67 (16.96)	
Depression, n (%)			< 0.001			0.002
Yes	894 (7.93)	57 (12.56)		43 (8.02)	75 (13.99)	
No	10,381 (92.07)	397 (87.44)		493 (91.98)	461 (86.01)	
TC (mg/dL)	191.99 ± 40.06	175.61 ± 43.50	< 0.001	177.88 ± 44.77	177.88 ± 44.77	0.214
HDL-C (mg/dL)	54.17 ± 15.74	51.12 ± 15.35	< 0.001	51.53 ± 15.14	51.53 ± 15.14	0.243
LDL-C (mg/dL)	114.52 ± 35.20	97.43 ± 36.81	< 0.001	99.67 ± 37.75	99.67 ± 37.75	0.371
TG (mg/dL)	116.48 ± 65.67	135.24 ± 71.90	< 0.001	133.31 ± 71.68	133.31 ± 71.68	0.842
TyG	8.57 ± 0.63	8.90 ± 0.68	< 0.001	8.88 ± 0.62	8.84 ± 0.65	0.326

Table 1 (continued)

Characteristics	Before PSM			After PSM		
	non-CRS	CRS	*P*-value	non-CRS	CRS	*P*-value
RC	23.30 ± 13.14	27.05 ± 14.39	< 0.001	26.83 ± 14.02	26.67 ± 14.35	0.840
AIP	-0.07 ± 0.31	0.02 ± 0.31	< 0.001	0.01 ± 0.30	0.01 ± 0.30	0.824
FPG (mmol/L)	5.97 ± 1.84	7.25 ± 2.97	< 0.001	7.07 ± 2.82	7.07 ± 2.82	0.400
HbA1c (%)	5.70 ± 1.05	6.48 ± 1.49	< 0.001	6.36 ± 1.41	6.36 ± 1.41	0.471
UA (mg/dL)	5.46 ± 1.38	6.54 ± 1.74	< 0.001	6.38 ± 1.58	6.38 ± 1.58	0.007
eGFR (ml/min/1.73m^2)	96.36 ± 20.99	58.23 ± 23.03	< 0.001	61.06 ± 22.67	61.06 ± 22.67	< 0.001
BUN (mmol/L)	4.62 ± 1.73	7.78 ± 4.00	< 0.001	7.24 ± 3.31	7.24 ± 3.31	< 0.001
UACR (mg/g)	34.44 ± 283.63	254.84 ± 712.09	< 0.001	196.17 ± 485.85	196.17 ± 485.85	0.291
Antihyperglycemic drugs, n (%)			< 0.001			0.135
Yes	1047 (9.29)	174 (38.33)		341 (30.61)	341 (30.61)	
No	10,228 (90.71)	280 (61.67)		773 (69.39)	773 (69.39)	
Antihypertensive drugs, n (%)			< 0.001			0.036
Yes	1384 (12.27)	239 (52.64)		496 (44.52)	200 (50.63)	
No	9891 (87.73)	215 (47.36)		618 (55.48)	195 (49.37)	
Antithrombotic drugs, n (%)			< 0.001			< 0.001
Yes	337 (2.99)	155 (34.14)		224 (20.11)	114 (28.86)	
No	10,938 (97.01)	299 (65.86)		890 (79.89)	281 (71.14)	
Lipid-lowering drugs, n (%)			< 0.001			0.096
Yes	1797 (15.94)	293 (64.54)		626 (56.19)	241 (61.01)	
No	9478 (84.06)	161 (35.46)		488 (43.81)	154 (38.99)	
Antidepressant drugs, n (%)			< 0.001			0.804
Yes	1089 (9.66)	90 (19.82)		208 (18.67)	76 (19.24)	
No	10,186 (90.34)	364 (80.18)		906 (81.33)	319 (80.76)	

deviation and categorical variables were presented as number (percentage). Continuous or categorical variables were compared separately using t-tests for continuous variables and chi-square tests for categorical variables. Furthermore, Table 1 includes data about the CRS and non-CRS subjects both before and after being matched 1:4 using PSM. We utilized covariates with a p-value of less than 0.05, which demonstrated variances between the CRS and non-CRS groups, to generate the propensity scores. When performing PSM, we chose the 'nearest neighbor' method with a caliper value set at 0.2.

The variance inflation factor (VIF) for each covariate was computed to eliminate the severe co-linearity among the variables. VIF was calculated as $VIF = 1/(1\text{-}R^2)$, where R^2 was the value of R-squared from a linear regression equation. If the VIF of a variable is 5 or higher, that variable will be removed. Then, the VIF of the remaining variables will be recalculated. This process would be repeated until the VIF of all variables in the equation is less than 5. To more thoroughly analyze the relationship between CRS and depression, we performed weighted logistic regression using odds ratio (OR) and 95% confidence interval (95%CI) on CRS and depression with non-CRS, only-CVD, and only-CKD as references, respectively. We set different references to enhance the robustness of the results and indirectly verify which of the heart and kidney is more closely related to depression. Weighted linear regression analyses were also performed with the PHQ-9 score replaced as the dependent variable. A fully corrected model adjusted for age, gender, race, education level, marital status, PIR, drinking, smoking, diabetes, hypertension, BMI, PA, HDL-C, LDL-C, TG, FPG, HbA1c, UA, BUN, eGFR, UACR, antithrombotic drugs, antihyperglycemic drugs, antihypertensive drugs, antidepressant drugs, and lipid-lowering drugs was applied. Weighted logistic regression was also used to assess the association of lipid indices and depression and the trend tests were also applied. Restricted cubic spline (RCS) analysis with 4 knots (5th, 35th, 65th, and 95th) was conducted to determine whether the association between lipid indices and depression is linear. To better visualize the link between CRS, lipid indices, and depression, smooth curve fitting using the generalized additive model was employed to explore differences in the relationship between lipid indices and depression across disease states.

Subgroup and sensitivity analyses were also performed. CRS and non-CRS subjects based on age, gender, race, BMI, PA, drinking, smoking, diabetes, and hypertension were divided into subgroups to examine the relationship between CRS and depression between and after PSM and tested for interaction in the fully corrected model. In the sensitivity analyses, we excluded one CVD individually to detect the association between CRS and depression to

Table 2 Comparison of depression in patients with CRS versus other references before and after PSM

	non-CRS[a]	only-CVD[a]	only-CKD[a]
Before PSM	1.152 (1.150, 1.155) ***	0.800 (0.798, 0.803) ***	1.605 (1.600, 1.609) ***
After PSM	1.240 (1.237, 1.243) ***	0.646 (0.644, 0.649) ***	1.432 (1.428, 1.437) ***

The model adjusted for age, gender, race, education level, marital status, PIR, drinking, smoking, diabetes, hypertension, BMI, PA, HDL-C, LDL-C, TG, FPG, HbA1c, UA, BUN, eGFR, UACR, antihyperglycemic drugs, antihypertensive drug, antithrombotic drugs, lipid-lowering drugs, and antidepressant drugs

Notes: The statistics presented above are OR (95%CI). *** $P<0.001$. [a] OR = 1.000

Table 3 Comparison of the PHQ-9 score in patients with CRS versus others before and after PSM

	non-CRS[a]	only-CVD[a]	only-CKD[a]
Before PSM	0.504 (0.502, 0.506) ***	-0.121 (-0.125, -0.118) ***	0.518 (0.516, 0.521) ***
After PSM	0.497 (0.494, 0.499) ***	-0.216 (-0.220, -0.211) ***	0.506 (0.502, 0.509) ***

The model adjusted for age, gender, race, education level, marital status, PIR, drinking, smoking, diabetes, hypertension, BMI, PA, HDL-C, LDL-C, TG, FPG, HbA1c, UA, BUN, eGFR, UACR, antihyperglycemic drugs, antihypertensive drug, antithrombotic drugs, lipid-lowering drugs, and antidepressant drugs

Notes: The statistics presented above are β (95%CI). *** $P<0.001$. [a] β = 1.000

prevent bias caused by a strong association of a particular CVD with depression. Finally, CRS was an independent variable, lipid indices served as a mediator, and depression was a dependent variable for mediation analysis in the fully corrected model. The parameter for the applied Bootstrap method is set to 1000. Direct and indirect effects and proportions mediated by mediators were presented in the study.

A two-sided p-value of less than 0.05 was taken as statistically significant while the statistical analysis involved multiple comparisons the threshold for the corrected p-value using the Bonferroni correction method was 0.017 [29]. All the statistical analyses were performed using R version 4.3.3 software.

Results

Description of baseline profiles

Most covariates between the two CRS and non-CRS groups were not statistically different after PSM. Figure S1 illustrates the standardized mean difference in covariates before and after PSM. A smaller value indicates better equalization of covariates between the groups post-matching. As shown in Table 1, the mean age of CRS patients is 69.48 years and 55.51% are male. The percentage of depressed patients in the CRS group was 12.56% more than 7.93% in the non-CRS group ($P<0.05$). As displayed in Table S1, the average age of patients with depressive symptoms is 47.92 years and 37.33% are male. A greater proportion of history of diabetics, hypertension, CVD, CKD, and CRS disease was demonstrated in the depressed patient group ($P<0.05$). Participants in the PHQ-9 ≥ 10 group showed higher values in these biochemical markers TG, TyG, RC, AIP, FPG, HbA1c, UA, and UACR ($P<0.05$). Subjects with depressive symptoms also showed more recurrent use of drugs ($P<0.05$).

Association of CRS and depression

The covariates WC and TC are excluded due to co-linearity and a detailed elimination process is described in Table S2. The results presented in Table 2 show that the association between CRS and depression was statistically significant across different references. The OR between CRS and depression was greater than 1 in the comparisons with non-CRS and only-CKD, but any OR was smaller than 1 when only-CVD was used as the comparison. Before PSM, CRS was associated with depression compared with non-CRS (OR: 1.152, 95% CI: 1.150 ~ 1.155), only-CVD (OR: 0.800, 95% CI: 0.798 ~ 0.803), and only-CKD (OR: 1.605, 95% CI: 1.600 ~ 1.609) in the fully corrected model. After PSM, equal remarkable results were rendered that CRS was associated with depression compared with non-CRS (OR: 1.240, 95% CI: 1.237 ~ 1.243), only-CVD (OR: 0.646, 95% CI: 0.644 ~ 0.649), and only-CKD (OR: 1.432, 95% CI: 1.428 ~ 1.437).

Similar results can be seen in Table 3 with the PHQ-9 score as the dependent variable using the weighted linear regression model. CRS was associated with depression compared with non-CRS (β: 0.504, 95% CI: 0.502 ~ 0.506), only-CVD (β: -0.121, 95% CI: -0.125~-0.118), and only-CKD (β: 0.518, 95% CI: 0.516 ~ 0.521) in the fully corrected model before PSM. After PSM, CRS was positively correlated with depression compared with non-CRS (β: 0.497, 95% CI: 0.494 ~ 0.499), only-CVD (β: -0.216, 95% CI: -0.220~-0.211), and only-CKD (β: 0.506, 95% CI: 0.502 ~ 0.509).

Association of lipids indices and depression

Table 4 illustrates the statistically significant positive correlation between lipid indices and depression. For each unit increase in AIP, TyG, and RC, there was a 31.3% (OR = 1.313, 95%CI: 1.311 ~ 1.314), 18.2% (OR = 1.182, 95%CI: 1.182 ~ 1.183), and 0.7% (OR = 1.007, 95%CI: 1.007 ~ 1.007) increase in depression risk, respectively. When transforming a continuous variable into a categorical one, OR and 95% CI from lowest to highest AIP quartile were 1.000 (reference), 0.920 (0.919 ~ 0.921), 0.971 (0.969 ~ 0.972), and 1.221 (1.220 ~ 1.223), respectively (p for trend < 0.001); OR and 95% CI from lowest to highest TyG quartile were 1.000 (reference), 0.973 (0.972 ~ 0.974), 0.907 (0.906 ~ 0.908), and 1.342 (1.340 ~ 1.343), respectively (p for trend < 0.001); OR and 95% CI from lowest to highest RC quartile were 1.000 (reference), 0.945 (0.944 ~ 0.946), 0.859 (0.858 ~ 0.860), and 1.245 (1.243 ~ 1.246), respectively (p for trend < 0.001). The RCS

Table 4 Associations between lipid indices and depression

Variables	AIP		TyG		RC	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Continuous	1.313 (1.311 ~ 1.314)	**< 0.001**	1.182 (1.182 ~ 1.183)	**< 0.001**	1.007 (1.007 ~ 1.007)	**< 0.001**
Q1	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
Q2	0.920 (0.919 ~ 0.921)	**< 0.001**	0.973 (0.972 ~ 0.974)	**< 0.001**	0.945 (0.944 ~ 0.946)	**< 0.001**
Q3	0.971 (0.969 ~ 0.972)	**< 0.001**	0.907 (0.906 ~ 0.908)	**< 0.001**	0.859 (0.858 ~ 0.860)	**< 0.001**
Q4	1.221 (1.220 ~ 1.223)	**< 0.001**	1.342 (1.340 ~ 1.343)	**< 0.001**	1.245 (1.243 ~ 1.246)	**< 0.001**
P for trend	**< 0.001**		**< 0.001**		**< 0.001**	

OR: Odds Ratio, CI: Confidence Interval, Q: Quartile

The model adjusted for age, gender, race, education level, marital status, PIR, CVD, CKD, drinking, smoking, diabetes, FBG, HbA1c, hypertension, BMI, UA, GFR, BUN, PA, UACR, antihyperglycemic drugs, antihypertensive drug, antithrombotic drugs, lipid-lowering drugs, and antidepressant drugs

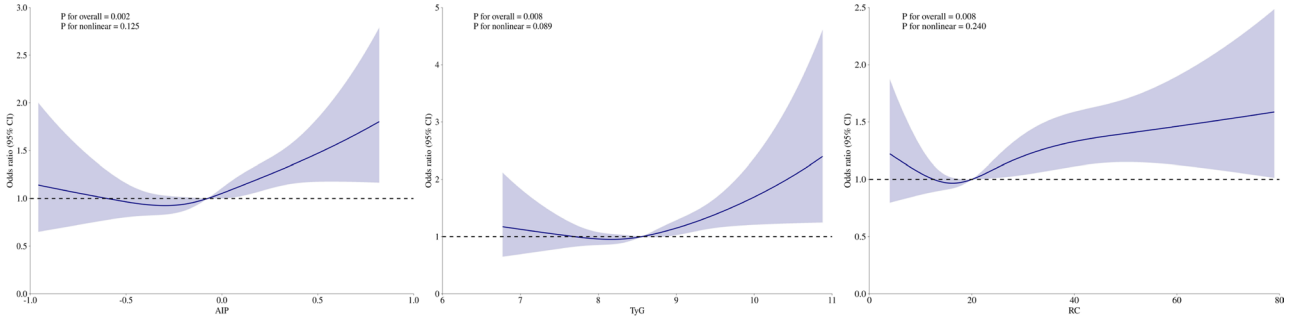


Fig. 2 Restricted cubic spline plots on the relationship between AIP, TyG, and RC and depression
Caption: The navy-blue line in the figure represents OR, and the gray line represents the 95% CI

analysis of Fig. 2 depicts a linear association between AIP, TyG, RC, and depression, with no evident threshold or saturation effects.

As depicted in Fig. 3, further analyses by smooth curve fitting reveal that irrespective of the RC value, subjects with cardiorenal diseases exhibited a higher risk of depression compared to their non-diseased counterparts, and this risk gap widened as the RC values increased. The majority of the curves in the graph demonstrated that subjects with cardiorenal diseases had a higher risk of depression compared to those without cardiorenal diseases. CVD subjects had a higher risk of depression than non-CVD subjects, regardless of changes in AIP, TyG, and RC. However, when we reduced the values of AIP and TyG to lower levels, the risk of depression in patients with CRS could be lower than in patients with non-CRS, suggesting that lipid-lowering therapy has a significant role in preventing depression in patients with CRS.

Subgroup analysis and sensitive analysis

Figure 4 presents subgroup analyses before and after PSM, showing that the relationship between CRS and depression remained positively associated. The interaction tests were positive in age, PA, and hypertension subgroups before PSM, and only PA was positive after PSM ($P=0.023$). Table S3 shows the sensitivity analysis is similar to the previous one, with no single CVD influencing the relationship between CRS and depression.

Analysis of mediation between CRS and depression

In the fully corrected model, AIP, TyG, and RC did not significantly mediate the association between CRS and depression. Detailed data are presented in Fig. 5.

Discussion

Through this comprehensive and well-characterized analysis of cardiorenal disease, lipids, and depression, we came up with the following several major results: First of all, CRS showed a positive and statistically significant association with depression when using non-CRS and only-CKD as references. In contrast, when using only-CVD as a reference, the association between CRS and depression did not show a positive statistically significant association in the fully corrected model regardless of pre-PSM and post-PSM. Secondly, forward linear relationships between AIP, TyG, RC, and depression were observed. Thirdly, lowering AIP and TyG in CRS patients significantly reduces the risk of depression even lower than in non-CRS patients. Fourthly, after correcting for multiple confounders, AIP, TyG, and CR did not mediate the link between CRS and depression.

A community-based matched cohort study based on the UK Biobank indicated that patients hospitalized for

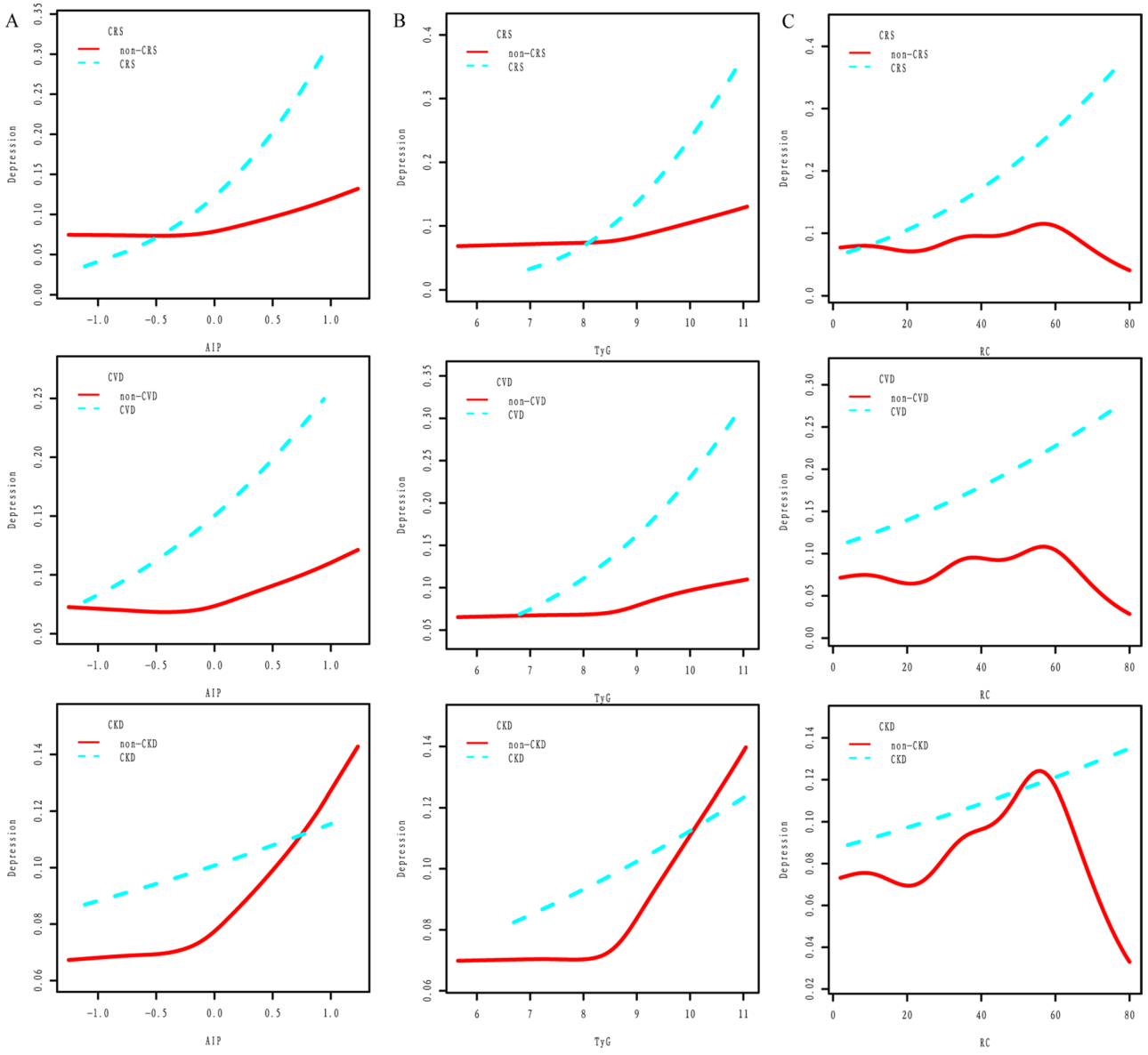


Fig. 3 Smoothed curve fitting of the relationship between lipid indices and depression across various disease states
Caption: **A** The link between AIP and depression is between CRS and non-CRS, CVD and non-CVD, and CKD and non-CKD.; **B** The link between TyG and depression is between CRS and non-CRS, CVD and non-CVD, and CKD and non-CKD; **C** The link between RC and depression is between CRS and non-CRS, CVD and non-CVD, and CKD and non-CKD

CVD were at increased subsequent risk of multiple types of psychiatric disorders and suicide attempts, especially in the first year after hospitalization, irrespective of their genetic susceptibilities to studied psychiatric conditions [30]. Life's Essential 8, a proxy indicator of cardiovascular health, negatively correlates with depression in both overall and subunit scores [31]. Even more, a study has shown that at the time of admission for acute myocardial infarction, women (39%) experienced a higher percentage of depressive symptoms than men (22%) ($P<0.0001$; adjusted OR: 1.64; 95% CI: 1.36, 1.98) [32]. In a prospective cohort of young and middle-aged adults, depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale and the authors demonstrate a bidirectional causal association between depression and CKD [33]. Among patients with nondialysis-dependent CKD stages 3–5, new-onset depression is linked to a negative outlook, such as increased hospitalizations, CKD advancement, major adverse cardiovascular events, and overall mortality [34]. However, studies on the link between CRS and depression are sparse. The present study findings showed a positive association when CRS was compared with non-CRS, only-CKD, but not when compared with only-CVD. This may be due

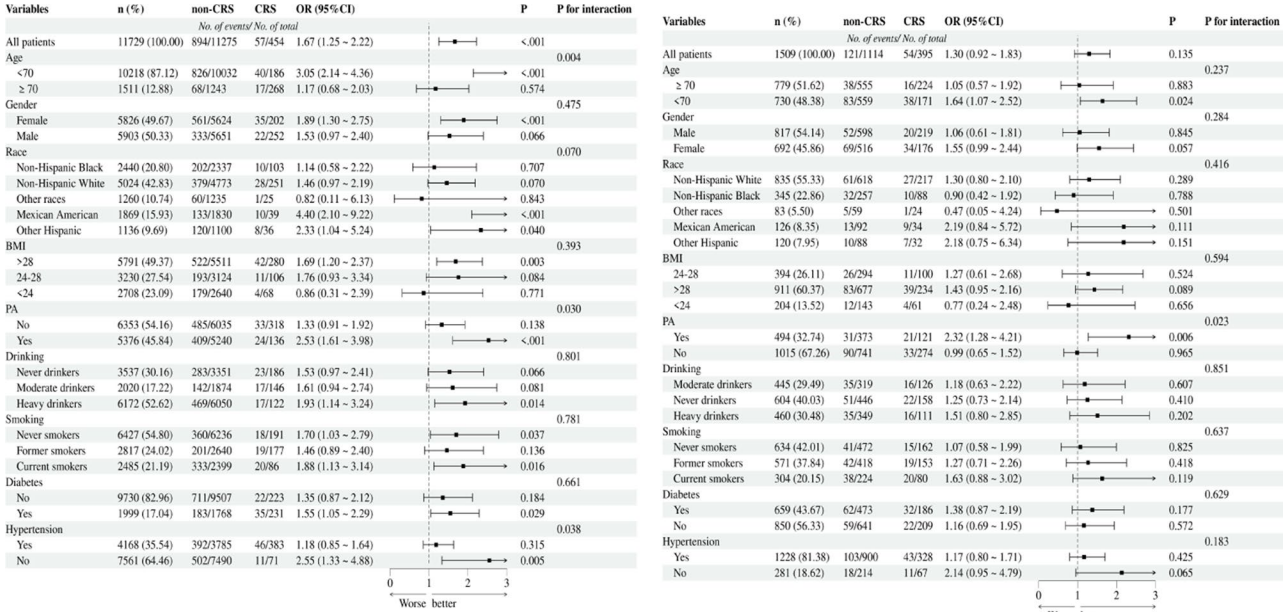


Fig. 4 Subgroup analysis of the association between CRS and depression before and after PSM

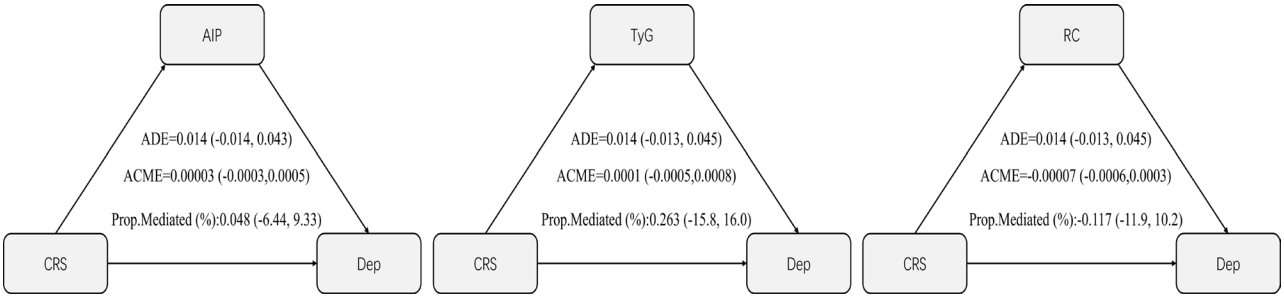


Fig. 5 Mediation effects of AIP, TyG, and RC in the association of CRS with depression
Caption: ACME, average causal mediation effects (indirect effect); ADE, average direct effects; Dep: depression. * $P<0.05$, ** $P<0.01$, and *** $P<0.001$. The model adjusted for age, gender, race, education level, marital status, PIR, drinking, smoking, diabetes, hypertension, BMI, PA, HDL-C, LDL-C, TG, FPG, HbA1c, UA, BUN, eGFR, UACR, antihyperglycemic drugs, antihypertensive drug, antithrombotic drugs, lipid-lowering drugs, and antidepressant drugs

to the high incidence of CVD or unknown associations with depression, which require further exploration. On the one hand, this phenomenon may come from a more strongly bidirectional causality and this relationship has been validated in several studies [35–38]. On the other hand, some behavioral and lifestyle factors contributing to the risks of CVD also promote and aggravate depressive symptoms, such as non-adherence to prescribed medication, physical inactivity, cigarette smoking, alcohol consumption, poor social support, and income [35], instead, CKD is often caused by inadequate effective circulating blood volume, medications, toxins, genetic factors, infections, and immune factors.

The mechanism of CRS is still not fully understood at this time [39]. Elevation of central venous pressure (CVP) due to secondary systemic congestion, pulmonary arterial hypertension, and right ventricular dysfunction is considered the main factor contributing to renal dysfunction [40]. Elevated CVP can be directly transmitted to the renal veins, and under the condition of constant renal blood flow, the intrarenal arteriovenous gradient decreases, leading to a reduction in renal perfusion pressure [41]. Renal venous congestion causes an increase in renal interstitial pressure. When the renal interstitial pressure exceeds the intraluminal pressure, it results in vascular and tubular compression or occlusion. The renal parenchyma becomes hypoxic, causing renal tubular dysfunction and decreased filtration efficiency [42]. Besides, insufficient effective circulating blood volume caused by CVD or other factors can activate the sympathetic nervous system and the renin-angiotensin-aldosterone system. That not only exacerbates systemic congestion and increases cardiac burden but also leads to inflammation occurrence and oxidative stress damage. Based on previous literature, we presume that pro-inflammatory cytokines such as tumor necrosis factor-α

(TNF-α) and TNF-α related weak inducers of apoptosis, members of the interleukin-1 (IL-1) family, and interleukin-6 (IL-6) probably are associated with CRS [43]. There may be some potential connections between the two. Firstly, hypertension promotes CVD such as HF, coronary artery disease, cerebral hemorrhage, and aortic coarctation, and hypertension itself interacts with CKD. Adamis et al. found that the incidence of hypertension increased in patients with depression and the depressive mood was associated with increased blood pressure levels [44]. Secondly, a bidirectional causal association between anemia and CVD has been demonstrated [45, 46]. When CKD is present, decreased production of erythropoietin, low intake of folic acid, protein, and iron due to poor appetite, and bone marrow suppression by toxins combine to cause anemia. Anemia makes a person less tolerant of low oxygen, making it easier for the body to provide insufficient oxygen and energy to the brain, leading to impaired cognitive performance and susceptibility to depressive symptoms [47]. Thirdly, anxiety and life stress activate the sympathetic nervous system exacerbating the vicious cycle between the heart and kidneys, sodium and water retention, and increased cardiac load leading to ventricular hypertrophy, and anxiety and stress go hand in hand with depression [48]. Based on previous studies [39, 41, 43, 48], inflammation, oxidative stress, hypercoagulability, and platelet activation are also potential mechanisms linking CRS to depression and require further in-depth research.

There have been many studies analyzing the relationship between AIP, TyG, and RC and depression. Ye et al. constructed a generalized additive model utilizing spline functions and found a positive link between AIP and depressive symptoms (PHQ-9 score), but this study did not analyze whether there was a linear association between the two [49]. In a cross-sectional study by Zhang et al., it was found that there is an L-shaped pattern in the relationship between depression and AIP. The study showed an inflection point at -0.289, and beyond this inflection point, individuals with elevated AIP levels were associated with higher odds of depression (OR=2.25; 95% CI: 1.49–3.39) [50]. Liu et al. found that Triglyceride-Glucose-BMI, Triglyceride-Glucose-Waist Circumference, and Triglyceride-Glucose-Waist-to-Height Ratio exhibited a positive and linear relationship with depressive symptoms rather than TyG in premenopausal women [14]. However, our study demonstrated a linear positive relationship between AIP and TyG with depression. This discrepancy may arise from different inclusion and exclusion criteria and the heterogeneity of the populations across studies. Wang et al. demonstrated that even after adjusting for multiple confounding factors, RC still showed a significant correlation with depression [15]. Still, the study did not investigate the existence of a linear association or a saturation threshold effect. Therefore, the linear association of RC and depression from our study specifically fills this void in the existing literature. Inflammation is an important mechanism by which lipids are associated with depression. A recent mouse experiment showed that depression-like behaviors, impaired 5-hydroxytryptamine neurotransmission, and disordered lipid metabolism were observed upon high-fat diet consumption, and levels of interleukin-1β, IL-6, TNF-α, and inflammation-related metabolites were increased in high-fat diet mice [51]. Lipids contribute to atherosclerosis, the clogging of blood vessel lumens, which may also be associated with depression. Population-based data indicates that increased carotid artery stiffness is linked to a higher risk of depressive symptoms [52]. Additionally, the increase in lipids leads to the formation of more foam cells. Foam cells express IL-6 and circulating IL-6 stimulates disruption of the hypothalamic-pituitary-adrenal axis [53]. The hypothalamic-pituitary-adrenal axis is strongly associated with impaired authentication function and depression [54]. It is conceivable that increased levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, may contribute to the observed inflammation. However, it is important to note that these cytokines were not measured in the current study and, therefore, this assertion remains speculative. The absence of direct measurement of these cytokines is a limitation of our study, primarily due to the constraints of the study design and available resources. Future research with comprehensive cytokine profiling will be necessary to confirm this hypothesis.

The generation of the relationship in people with CRS between some lipid complex indicators and depression may be caused by other risk factors such as age, diabetes mellitus, hypertension, smoking, and alcohol consumption, so the mediation analysis did not show a significant result.

As shown in Fig. 3, even patients with CVD who have very low lipid indices still have a higher risk of developing depression than patients with non-CVD, and CVD may be an independent risk factor for the onset of depression, independently of the cardiovascular risk factors. So, we should not ignore patients with CVD who have good disease indices. The fact that the three plots related to TyG tend to have intersections and are all located at larger horizontal coordinates compared to AIP and RC implies that TyG may be a more appropriate indicator of intervention and that lowering it to a reduced level can have a lower risk of morbidity than unaffected population. This phenomenon can be explained by TyG reflecting lipid profile and representing insulin resistance. It is also associated with CVD, CKD, diabetes, non-alcoholic fatty liver disease, and obstructive sleep apnea, and lower TyG is more pronounced in patients with multiple comorbidities

[9, 55–58]. In describing the relationship between lipids and depression in the curve of CRS and non-CRS, there are greater lipid index intersections, indicating that the intervention of AIP, TyG, and RC in patients with CRS can better reduce the risk of the development of depression than only-CVD and only-CKD, which may require further future research.

Strengths and limitations

Our study has several strengths. To our knowledge, this is the first study in the American population to examine the correlation between CRS and depression and explore the mediating role of lipids in this relationship. Secondly, we employed the PSM method to better control for confounding factors, carry out subgroup analysis and sensitive analysis, and utilized NHANES weights to enhance the robustness of our results. Thirdly, we established different references, speculating that in the relationship between CRS and depression, CVD may play a more significant role. Fourthly, the smooth curve fitting shows that reducing AIP and TyG can reduce the risk of depression in CRS patients to even lower than that of non-CRS patients. CVD may be an independent risk factor for depression, separate from lipids.

However, certain limitations need to be discussed. Firstly, due to database limitations, our definition of CRS is general, limited to chronic kidney disease only, and does not specify the subtypes. Secondly, the data on CVD comes from self-reported questionnaires, which may be subject to recall bias. Thirdly, there may be an introduction of selection bias because of the exclusion of some samples with missing variables. Fourthly, some unknown confounding factors in the study cannot be completely excluded. Fifthly, the nature of this study is cross-sectional, hence it does not permit the inference of causal associations between CRS and depression. The presence of a bidirectional causal relationship between the two is uncertain and necessitates further exploration through future multicenter randomized controlled trials. Sixthly, the relationship between lipids, depression, and cardiorenal diseases as shown in Fig. 3 may have a certain degree of randomness and may not be generalizable to other studies. It necessitates further validation through other large-sample datasets in future research. Seventhly, people in different countries or regions often have large genetic differences, varying living environments, different medical conditions, and diverse cultural personalities, which can affect the results of the same study in different populations. The study population is American and the findings may not apply to populations from other countries. Eighthly, missing information on some covariates, such as the amount of alcohol consumed, the mode of physical activity, and the duration of medication taken may have affected the study.

Conclusion

There was a significant association between CRS and depression and a linear relationship between AIP, TyG, and RC and depression. Reducing AIP, TyG, and RC can significantly reduce the risk of depression especially in CRS patients. However, the above lipid indicators did not mediate the association between CRS and depression.

Abbreviations

CVD	Cardiovascular disease
CKD	Chronic kidney disease
HF	Heart failure
CRS	Cardiorenal syndrome
AIP	Atherogenic Index of Plasma
TyG index	Triglyceride glucose index
RC	Remnant cholesterol
NHANES	National Health and Nutrition Examination Survey
PHQ-9	Patient Health Questionnaire-9
PSM	Propensity score matching
eGFR	Estimated glomerular filtration rate
UACR	Urinary albumin-to-creatinine ratio
TC	Total cholesterol
TG	Triglycerides
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
FPG	Fasting plasma glucose
PIR	Poverty income ratio
WC	Waist circumference
BMI	Body mass index
PA	Physical activity
HbA1c	Hemoglobin A1c
UA	Uric acid
BUN	Blood urea nitrogen
VIF	Variance inflation factor
OR	Odds ratio
CI	Confidence interval
RCS	Restricted cubic spline
CVP	Central venous pressure
TNF-α	Tumor necrosis factor-α
IL-1	Interleukin-1
IL-6	Interleukin-6

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02356-x.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

Conception and design: Guangzan Yu; Acquisition, statistical analysis or interpretation of the data: Guangzan Yu, Lulu Liu, Qian Ma; Drafting manuscript: Guangzan Yu, Hua He, Supervision of work: Hua He.

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Data availability

Data can be found at https://wwwn.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors have reviewed and approved the final version of the manuscript.

Competing interests
The authors declare no competing interests.

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References

1. Ataklte F, Song RJ, Upadhyay A, Musa Yola I, Vasan RS, Xanthakis V. Association of mildly reduced kidney function with Cardiovascular Disease: the Framingham Heart Study. J Am Heart Assoc. 2021;10(16):e020301.
2. KDIGO. 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2024, 105(4s):S117-s314.
3. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J* 2010, 31(6):703–711.
4. Quispe R, Martin SS, Michos ED, Lamba I, Blumenthal RS, Saeed A, Lima J, Puri R, Nomura S, Tsai M, et al. Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: a primary prevention study. Eur Heart J. 2021;42(42):4324–32.
5. Castañer O, Pintó X, Subirana I, Amor AJ, Ros E, Hernáez Á, Martínez-González M, Corella D, Salas-Salvadó J, Estruch R, et al. Remnant cholesterol, not LDL cholesterol, is Associated With Incident Cardiovascular Disease. J Am Coll Cardiol. 2020;76(23):2712–24.
6. Navarro-González D, Sánchez-Íñigo L, Pastrana-Delgado J, Fernández-Montero A, Martinez JA. Triglyceride-glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: the vascular-metabolic CUN cohort. Prev Med. 2016;86:99–105.
7. Xie F, Zhou H, Wang Y. Atherogenic index of plasma is a novel and strong predictor associated with fatty liver: a cross-sectional study in the Chinese Han population. Lipids Health Dis. 2019;18(1):170.
8. Wang Y, Wang S, Sun S, Li F, Zhao W, Yang H, Wu X. The predictive value of atherogenic index of plasma for cardiovascular outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention with LDL-C below 1.8mmol/L. Cardiovasc Diabetol. 2023;22(1):150.
9. Zhang S, Liu W, Xu B, Wang S, Du Z, Cheng W. Association of triglyceride glucose index and triglyceride glucose-body mass index with sudden cardiac arrest in the general population. Cardiovasc Diabetol. 2024;23(1):173.
10. Zhao Y, Zhuang Z, Li Y, Xiao W, Song Z, Huang N, Wang W, Dong X, Jia J, Clarke R et al. Elevated blood remnant cholesterol and triglycerides are causally related to the risks of cardiometabolic multimorbidity. Nat Commun 2024, 15(1).
11. Lu D, Valdimarsdóttir UA, Wei D, Chen Y, Andreassen OA, Fang F, László KD, Bränn E. Perinatal depression and risk of maternal cardiovascular disease: a Swedish nationwide study. Eur Heart J 2024.
12. Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, Pellegrini F, Saglimbene V, Logroscino G, Fishbane S, et al. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int. 2013;84(1):179–91.
13. Zhang G, Zhang H, Fu J, Zhao Y. Atherogenic Index of Plasma as a Mediator in the association between body roundness index and depression: insights from NHANES 2005–2018. Lipids Health Dis. 2024;23(1):183.
14. Liu X, Li J, He D, Zhang D, Liu X. Association between different triglyceride glucose index-related indicators and depression in premenopausal and postmenopausal women: NHANES, 2013–2016. J Affect Disord. 2024;360:297–304.
15. Wang Y, Shen R. Association of remnant cholesterol with depression among US adults. BMC Psychiatry. 2023;23(1):259.
16. Bortolato B, Hyphantis TN, Valpione S, Perini G, Maes M, Morris G, Kubera M, Köhler CA, Fernandes BS, Stubbs B, et al. Depression in cancer: the many biobehavioral pathways driving tumor progression. Cancer Treat Rev. 2017;52:58–70.
17. Becker M, Weinberger T, Chandy A, Schmukler S. Depression during pregnancy and Postpartum. Curr Psychiatry Rep. 2016;18(3):32.
18. Lin J, Li Z, Xu J, Pan M, Yin T, Wang J, Sun Q, Zheng W, Chen R. Independent and joint associations of monocyte to high-density lipoprotein-cholesterol ratio and body mass index with cardiorenal syndrome: insights from NHANES 2003–2020. Lipids Health Dis. 2024;23(1):153.
19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
20. Zhang Z, Jackson SL, Gillespie C, Merritt R, Yang Q. Depressive symptoms and mortality among US adults. JAMA Netw Open. 2023;6(10):e2337011.
21. Zhou T, Zhao J, Ma Y, He L, Ren Z, Yang K, Tang J, Liu J, Luo J, Zhang H. Association of cognitive impairment with the interaction between chronic kidney disease and depression: findings from NHANES 2011–2014. BMC Psychiatry. 2024;24(1):312.
22. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13.
23. He X, Zou R, Du X, Li K, Sha D. Association of remnant cholesterol with decreased kidney function or albuminuria: a population-based study in the U.S. Lipids Health Dis. 2024;23(1):2.
24. Yang D, Yang M, Bai J, Ma Y, Yu C. Association between Physical Activity Intensity and the risk for depression among adults from the National Health and Nutrition Examination Survey 2007–2018. Front Aging Neurosci. 2022;14:844414.
25. You FF, Gao J, Gao YN, Li ZH, Shen D, Zhong WF, Yang J, Wang XM, Song WQ, Yan H, et al. Association between atherogenic index of plasma and all-cause mortality and specific-mortality: a nationwide population–based cohort study. Cardiovasc Diabetol. 2024;23(1):276.
26. Chen F, Du M, Blumberg JB, Ho Chui KK, Ruan M, Rogers G, Shan Z, Zeng L, Zhang FF. Association among Dietary Supplement Use, Nutrient Intake, and Mortality among U.S. adults: a Cohort Study. Ann Intern Med. 2019;170(9):604–13.
27. Zhang YB, Chen C, Pan XF, Guo J, Li Y, Franco OH, Liu G, Pan A. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. BMJ. 2021;373:n604.
28. Chen C, Ye Y, Zhang Y, Pan XF, Pan A. Weight change across adulthood in relation to all cause and cause specific mortality: prospective cohort study. BMJ. 2019;367:l5584.
29. Zhao L, Sun M, Yin Z, Cui J, Wang R, Ji L, Geng G, Chen J, Cai D, Liu Q et al. Long-Term effects of Individualized acupuncture for chronic Neck Pain: a Randomized Controlled Trial. Ann Intern Med 2024.
30. Yang J, Zeng Y, Yang H, Qu Y, Han X, Chen W, Sun Y, Hu Y, Ying Z, Liu D et al. Cardiovascular Disease, genetic susceptibility, and risk of Psychiatric disorders and suicide attempt: a community-based Matched Cohort Study based on the UK Biobank. J Am Heart Assoc 2024:e031280.
31. Zhao S, Tang Y, Li Y, Shen H, Liu A. Associations between Life's essential 8 and depression among US adults. Psychiatry Res. 2024;338:115986.
32. Smolderen KG, Strait KM, Dreyer RP, D'Onofrio G, Zhou S, Lichtman JH, Geda M, Bueno H, Beltrame J, Safdar B et al. Depressive symptoms in younger women and men with acute myocardial infarction: insights from the VIRGO study. J Am Heart Assoc 2015, 4(4).
33. Liu M, Zhang Y, Yang S, Wu Q, Ye Z, Zhou C, He P, Zhang Y, Hou FF, Qin X. Bidirectional relations between depression symptoms and chronic kidney disease. J Affect Disord. 2022;311:224–30.
34. Zhu N, Virtanen S, Xu H, Carrero JJ, Chang Z. Association between incident depression and clinical outcomes in patients with chronic kidney disease. Clin Kidney J. 2023;16(11):2243–53.
35. Banerjee P, Chau K, Kotla S, Davis EL, Turcios EB, Li S, Pengzhi Z, Wang G, Kolluru GK, Jain A, et al. A potential role for MAGI-1 in the bi-directional relationship between Major Depressive Disorder and Cardiovascular Disease. Curr Atheroscler Rep. 2024;26(9):463–83.
36. Wium-Andersen MK, Wium-Andersen IK, Prescott EIB, Overvad K, Jørgensen MB, Osler M. An attempt to explain the bidirectional association between ischaemic heart disease, stroke and depression: a cohort and meta-analytic approach. Br J Psychiatry. 2020;217(2):434–41.

37. Li GH, Cheung CL, Chung AK, Cheung BM, Wong IC, Fok MLY, Au PC, Sham PC. Evaluation of bi-directional causal association between depression and cardiovascular diseases: a mendelian randomization study. Psychol Med. 2022;52(9):1765–76.
38. Ziwei Z, Hua Y, Liu A. Bidirectional association between depressive symptoms and cardiovascular disease in the middle-aged and elderly Chinese: a 5-year longitudinal study. BMJ Open. 2023;13(7):e071175.
39. Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, Coresh J, Baker-Smith CM, Carnethon MR, Després JP, et al. A synopsis of the evidence for the Science and Clinical Management of Cardiovascular-kidney-metabolic (CKM) Syndrome: A Scientific Statement from the American Heart Association. Circulation. 2023;148(20):1636–64.
40. Husain-Syed F, Gröne HJ, Assmus B, Bauer P, Gall H, Seeger W, Ghofrani A, Ronco C, Birk HW. Congestive nephropathy: a neglected entity? Proposal for diagnostic criteria and future perspectives. ESC Heart Fail. 2021;8(1):183–203.
41. Tabucanon T, Tang WHW. Right heart failure and Cardiorenal Syndrome. Cardiol Clin. 2020;38(2):185–202.
42. Ananthram MG, Gottlieb SS. Renal dysfunction and heart failure with preserved ejection fraction. Heart Fail Clin. 2021;17(3):357–67.
43. Kumar U, Wettersten N, Garimella PS. Cardiorenal Syndrome: pathophysiology. Cardiol Clin. 2019;37(3):251–65.
44. Adamis D, Ball C. Physical morbidity in elderly psychiatric inpatients: prevalence and possible relations between the major mental disorders and physical illness. Int J Geriatr Psychiatry. 2000;15(3):248–53.
45. Gan T, Hu J, Liu W, Li C, Xu Q, Wang Y, Lu S, Aledan AKO, Wang Y, Wang Z. Causal Association between Anemia and Cardiovascular Disease: a 2-Sample bidirectional mendelian randomization study. J Am Heart Assoc. 2023;12(12):e029689.
46. Savarese G, von Haehling S, Butler J, Cleland JGF, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. Eur Heart J. 2023;44(1):14–27.
47. Palazzuoli A, Antonelli G, Nuti R. Anemia in Cardio-Renal syndrome: clinical impact and pathophysiologic mechanisms. Heart Fail Rev. 2011;16(6):603–7.
48. Joynt KE, Whellan DJ, O'Connor CM. Depression and cardiovascular disease: mechanisms of interaction. Biol Psychiatry. 2003;54(3):248–61.
49. Ye Z, Huang W, Li J, Tang Y, Shao K, Xiong Y. Association between atherogenic index of plasma and depressive symptoms in US adults: results from the National Health and Nutrition Examination Survey 2005 to 2018. J Affect Disord. 2024;356:239–47.
50. Zhang H, Zhang G, Fu J. Exploring the L-shaped relationship between Atherogenic Index of plasma and depression: results from NHANES 2005–2018. J Affect Disord. 2024;359:133–9.
51. Yu H, Yu B, Qin X, Shan W. A unique inflammation-related mechanism by which high-fat diets induce depression-like behaviors in mice. J Affect Disord. 2023;339:180–93.
52. van Sloten TT, Boutouyrie P, Tafflet M, Offredo L, Thomas F, Guibout C, Climie RE, Lemogne C, Pannier B, Laurent S, et al. Carotid artery stiffness and incident depressive symptoms: the Paris prospective study III. Biol Psychiatry. 2019;85(6):498–505.
53. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 2000, 148(2):209–14.
54. Keller J, Gomez R, Williams G, Lembke A, Lazzeroni L, Murphy GM Jr., Schatzberg AF. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. Mol Psychiatry. 2017;22(4):527–36.
55. Hou XZ, Lv YF, Li YS, Wu Q, Lv QY, Yang YT, Li LL, Ye XJ, Yang CY, Wang MS, et al. Association between different insulin resistance surrogates and all-cause mortality in patients with coronary heart disease and hypertension: NHANES longitudinal cohort study. Cardiovasc Diabetol. 2024;23(1):86.
56. Ye Z, An S, Gao Y, Xie E, Zhao X, Guo Z, Li Y, Shen N, Zheng J. Association between the triglyceride glucose index and in-hospital and 1-year mortality in patients with chronic kidney disease and coronary artery disease in the intensive care unit. Cardiovasc Diabetol. 2023;22(1):110.
57. Guo W, Lu J, Qin P, Li X, Zhu W, Wu J, Xu N, Zhang Q. The triglyceride-glucose index is associated with the severity of hepatic steatosis and the presence of liver fibrosis in non-alcoholic fatty liver disease: a cross-sectional study in Chinese adults. Lipids Health Dis. 2020;19(1):218.
58. Wang C, Shi M, Lin C, Wang J, Xie L, Li Y. Association between the triglyceride glucose index and obstructive sleep apnea and its symptoms: results from the NHANES. Lipids Health Dis. 2024;23(1):133.

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