Research Article

Association between Depression and Renal Hyperfiltration in a General Chinese Population

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Keywords

Renal hyperfiltration · Depression · Depressive symptoms · Estimated glomerular filtration rate · Patient Health Questionnaire

Abstract

Background: Depression is prevalent in patients with all stages of CKD and is associated with adverse outcome. Abnormally elevated GFR, or hyperfiltration, may play a crucial role in the initiation and progression of CKD. However, the association between depression and hyperfiltration is not known. The aim of this study is to investigate the relationship between depression and hyperfiltration. **Methods:** This was an observational cross-sectional study. A total of 3,716 volunteers (1,303 males and 2,413 females) aged 40–75 years without CKD from a community in China were included for the study. Depressive symptoms and the presence of a minor or major depressive episode were assessed with the 9-item Patient Health Questionnaire (PHQ-9) and Diagnostic and Statistical Manual of Mental Disorders (4th edition)-based structured interview, respectively. **Results:** The mean age of the participants in the present study was 53.8 ± 9.0 years. 115 participants had clinically relevant depression, and 122 participants had a minor or major depressive episode. In a multivariable logistic regression analysis adjusted for potential confounders, the association between clinically relevant depression and renal hyperfiltration remained significant in men but not in women. As compared with men

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without depression (PHQ <5) or depressive episodes, those with clinically relevant depression (PHQ ≥10) had a significantly higher risk of renal hyperfiltration. The fully adjusted OR (95% CI) was 4.81 (1.62–14.30, $p = 0.005$), those with a major depressive episode had a higher risk of renal hyperfiltration (OR 7.45; 95% CI 2.04–27.21, $p = 0.002$). **Conclusion:** Depressive symptoms and major depressive episodes are associated with renal hyperfiltration in middle-aged and elderly Chinese men without CKD. Future studies are needed to verify and clarify the role of depression in the development of abnormally high eGFR and CKD.

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Introduction

Emerging evidences have shown that depression and chronic kidney disease (CKD) may both affect large proportions of the global population. Depression is more common among patients with CKD than those without CKD. Symptoms including fatigue, anorexia, pain, muscle cramps, sleep disturbance, and sexual dysfunction lead to substantial impairments in the quality of life of CKD patients [1, 2]. It was estimated that as many as 15–30% of patients with CKD may suffer from depression [3, 4], which is longitudinally associated with higher risks of adverse outcomes, including faster estimated glomerular filtration rate (eGFR) decrease, dialysis therapy initiation, death, or hospitalization [5–7]. Moreover, the presence of depression in various comorbidities, such as obesity, and diabetes, cardiovascular diseases, may further predict the poor renal and cardiovascular outcomes [8, 9].

However, data on the association between depression and earlier stages of CKD are scarce and conflicting. Albuminuria was associated with depressive symptoms and depressive episodes, even at levels that do not fulfil the CKD criteria [10]. The association between eGFR and depression remains unclear. Previous studies showed that eGFR may not be associated with depressive symptoms or major depressive episodes until it is moderately to severely reduced [11–13]. Several physiologic factors such as endothelial dysfunction, alterations in platelet reactivity, changes of the autonomic nervous system and hypothalamic pituitary adrenal axis, and dysregulation in immune response and inflammation in the setting of depression may explain the association between depression and albuminuria/decreased eGFR. On the other hand, increased GFR, also known as hyperfiltration, has been considered a predictor of renal function decline in various clinical conditions, including diabetes, hypertension, and obesity [14]. Renal hyperfiltration could be a novel marker of all-cause mortality [15] and be associated with coronary artery calcification [16]. Additionally, many lifestyle factors such as smoking [17], alcohol consumption [18], physical activity [19], and sleep duration [20] may be associated with renal hyperfiltration and predict the progression of albuminuria and CKD.

Currently, the association between depression and renal hyperfiltration in the general population remains unclear. In this study, we evaluated the association between depression and renal hyperfiltration in a large apparently healthy Chinese population.

Methods

Setting and Study Population

A population-based cross-sectional study was performed in Ningde, China, between June 2011 and January 2012. A total of 4,025 participants aged between 40 and 75 years were considered for inclusion in this study. The mean age of the participants in the present study was 53.8 ± 9.0 years. The current work was performed at Fujian Provincial Hospital, Fujian Medical University.

Depressive Symptoms

All participants were required to complete a self-reported structured questionnaire by a trained clinician. Depressive symptoms were assessed with a validated Chinese version of the 9-item Patient Health Questionnaire (PHQ-9) [21, 22]. The PHQ-9 is a self-administered questionnaire based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for a major depressive episode [23]. It comprises 9 items rated on a 4-point scale, ranging from 0 (“not at all”) to 3 (“nearly every day”). As a continuous variable, scores 0–4 represent no or minimal, 5–9 represent mild, 10–14 represent moderate, 15–19 represent moderately severe, and 20–27 represent severe depression. A predefined cutoff score of ≥ 10 was considered to indicate clinically relevant depressive symptoms in the preceding 2 weeks taking into account how well the participants understood the questionnaire [10].

Minor and Major Depressive Episode

The presence of a minor or major depressive episode was assessed by the Mini-International Neuropsychiatric Interview (MINI) according to the DSM-IV criteria [24]. A major depressive episode was diagnosed if participants had at least one core symptom (i.e., loss of interest or pleasure, feeling down or depressed) and at least four other symptoms of depression (i.e., insomnia or hypersomnia, fatigue or loss of energy, change in appetite and significant weight change, guilt or worthlessness, diminished ability to think or concentrate or indecisiveness, and suicidal thoughts or plans). Persons suffering from one core symptom and one to three other symptoms were considered to have a minor depressive episode.

Measurements and Definition

Blood samples were drawn after an overnight fast. Blood pressure was measured using an automated blood pressure measurement device (Omron Healthcare, Kyoto, Japan) after 10 min of rest, and the last two readings were averaged. The diagnosis of diabetes was based on the American Diabetes Association criteria, and hypertension was diagnosed according to the Eighth Joint National Commission recommendation or the use of antihypertensive medications. Serum creatinine was measured using the modified Jaffe reaction with a Beckman Analyzer (Beckman Instruments Inc., Fullerton, CA, USA). The serum creatinine measurement was reduced by 5% as previously proposed. eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation on the basis of serum creatinine. For the present analysis, renal hyperfiltration was defined as eGFR 95th percentile value of the whole population as previously suggested [15].

Statistical Analyses

All analyses were performed using SPSS 17.0 for windows (SPSS Inc., Chicago, IL, USA). $p < 0.05$ (two sided) was considered statistically significant. All normally distributed continuous variables were presented as mean $\pm$ standard deviation, and categorical variables were presented as percentages. Differences between two groups of continuous variables were compared using the t test or the Mann-Whitney U test. Differences between categories were compared with one-way analysis of variance, χ^2 and nonparametric tests as appropriate. Multiple logistic regression models were used to determine the odds ratio (OR) and 95% confidence intervals (CIs) for the presence of clinically relevant depressive symptoms and major depressive episodes associated with renal hyperfiltration compared with the reference group in men and women, respectively. Subgroup analyses were performed for participants without risk factors associated with depression such as diabetes mellitus and hypertension.

Table 1. Characteristics of the study population stratified by the presence of clinically relevant depressive symptoms and by the presence of a depressive episode

Characteristics	Clinically relevant depressive symptoms (PHQ-9)				Depressive episode			
	PHQ <5	5 ≤ PHQ <10	PHQ ≥10	p value ^a	no	minor	major	p value ^a
n	3,218	383	115		3,594	64	58	
Age, years	54.9±9.0	54.9±8.9	54.2±8.5	0.721	54.9±9.0	53.7±8.1	54.7±9.3	0.583
Men, %	36.4	26.6	26.1	<0.001	35.2	32.8	27.6	0.448
BMI	23.8±3.1	23.3±3.1	23.5±3.6	0.012	24.2±3.2	24.1±3.3	23.5±3.5	0.317
<18.5, %	2.7	5	5.2	0.014	3	3.1	6.9	0.149
≥25.0, %	32.3	27.7	24.3		31.7	34.4	19	
Married/living with spouse, %	91.8	88	88.7	0.026	91.4	92.2	86.2	0.371
Educational level, %				<0.001				0.021
Low	51.8	64.8	71.3		53.2	65.6	70.7	
Intermediate	42	29.8	23.5		40.5	31.3	27.6	
High	6.2	5.5	5.2		6.3	3.1	1.7	
Systolic BP, mm Hg	132.2±20.2	129.8±19.3	129.5±20.5	0.036	131.9±20.1	128.4±21.7	130.5±20.0	0.326
Diastolic BP, mm Hg	75.2±10.9	73.6±11.0	74.7±10.9	0.02	75.1±10.9	73.3±12.1	74.3±11.2	0.377
FSG, mmol/L	5.3±1.3	5.3±1.4	5.5±1.5	0.398	5.3±1.3	5.3±1.5	5.4±1.0	0.814
HDL, mmol/L	1.3±0.4	1.2±0.4	1.2±0.4	0.068	1.3±0.4	1.2±0.4	1.2±0.4	0.066
LDL, mmol/L	2.9±0.9	2.8±0.9	2.8±1.0	0.001	2.9±0.9	2.7±1.0	2.6±0.8	0.033
CHOL, mmol/L	5.0±1.3	4.7±1.3	4.8±1.3	<0.001	5.0±1.3	4.6±1.4	4.6±1.2	0.012
TG, mmol/L	1.7±1.2	1.5±0.9	1.5±1.0	0.019	1.4±1.0	1.3±0.7	1.5±1.1	0.325
Serum creatinine, mmol/L	66.0±12.1	62.1±11.1	61.7±10.0	<0.001	65.6±12.0	63.7±10.8	60.6±8.7	0.003
eGFR ^b , mL/min/1.73 m ²	96.4±11.9	98.4±11.2	99.0±11.3	<0.001	96.6±11.9	98.5±9.9	99.9±10.6	0.051
RHF ^c , %	4.5	7.8	9.6	0.001	4.8	4.7	13.8	0.008
Smoking, %				0.274				0.839
Nonsmoker	76.8	81.2	78.3		77.3	78.1	79.3	
Former smoker	7.6	5.2	5.2		7.3	7.8	3.4	
Current smoker	15.6	13.6	16.5		15.4	14.1	17.2	
Alcohol consumption, %				0.207				0.621
None	54.7	52	58.3		54.4	54.7	58.6	
Former drinker	8.7	12	10.4		9	12.5	12.1	
Current drinker	36.6	36	31.3		36.6	32.8	29.3	
Physical activity, %	18.2	15.5	13.5	0.065	18	21.7	12.7	0.285
Diabetes, %	7.1	8.1	7.8	0.76	7.3	9.4	3.4	0.432
Hypertension, %	17.8	23.8	22.6	0.01	18.4	18.8	27.6	0.205
Treatments for comorbid conditions, %								
Diabetes	6.2	7.3	7	0.682	6.3	9.4	3.4	0.405
Hypertension	12.3	14.6	13.9	0.396	12.5	15.6	13.8	0.731
Dyslipidemia	0.6	0.0	0	0.228	0.5	0	0	0.723
Antidepressant medication	0.1	0.0	0.0	0.734	0.1	0	0	0.934

BMI, body mass index; BP, blood pressure; CHOL, cholesterol; eGFR, estimated glomerular filtration rate; FSG, fasting serum glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RHF, renal hyperfiltration; TG, triglyceride. ^a χ^2 tests for discrete variables, Kruskal-Wallis tests for nonparametric variables, and one-way analysis of variance for continuous variables. ^b eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation. ^c eGFR higher than the age-, sex-, BMI-, and the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker-adjusted 95th percentile (details in Methods).

Results

The mean age of the participants in the present study was 53.8 ± 9.0 years. Table 1 shows the general characteristics of the participants according to different categories of PHQ-9 or depressive episodes.

Overall, 115 participants had clinically relevant depressive symptoms. Compared with participants without depression (PHQ <5), participants with clinically relevant depressive symptoms (PHQ ≥10) were more often women, less educated, had a lower level of diastolic

Table 2. Characteristics of individuals with and without RHF

	Without RHF	With RHF	<i>p</i> value ^a
<i>n</i>	3,531	185	
Age, years	54.7±8.5	57.4±8.5	<0.001
Men, %	34.4	48.6	<0.001
BMI	23.7±3.1	23.7±3.7	0.969
<18.5, %	2.8	7	0.003
≥25.0, %	31.5	34.1	
Married/living with spouse, %	91.1	95.1	0.06
Educational level, %			
Low	53.4	77.8	<0.001
Intermediate	41.2	20	
High	6.3	2.2	
Systolic BP, mm Hg	131.9±20.1	130.3±20.1	0.272
Diastolic BP, mm Hg	75.2±10.9	71.7±10.6	<0.001
FSG, mmol/L	5.3±1.3	5.8±1.7	<0.001
HDL, mmol/L	1.3±0.4	0.9±0.3	<0.001
LDL, mmol/L	3.0±0.9	1.8±0.7	<0.001
CHOL, mmol/L	5.0±1.2	3.2±1.1	<0.001
TG, mmol/L	1.4±1.0	0.9±0.6	<0.001
Serum creatinine, mmol/L	66.4±11.4	47.1±6.4	<0.001
eGFR ^b , mL/min/1.73 m ²	95.9±11.5	111.3±8.4	<0.001
Smoking, %			0.072
Nonsmoker	77.6	70.8	
Former smoker	7.2	8.1	
Current smoker	15.2	21.1	
Alcohol consumption, %			0.118
None	54.8	49.2	
Former drinker	8.9	13	
Current drinker	36.3	37.8	
Physical activity, %	18.4	14.7	0.168
Depressive symptoms, %			0.001
PHQ ≥10	2.9	5.9	
5 ≤ PHQ <10	10	16.2	
PHQ <5	87.1	77.8	
Depressive episode, %			0.008
Major	1.4	4.3	
Minor	1.7	1.6	
No	96.9	94.1	
Diabetes, %	7.1	10.8	0.059
Hypertension, %	18.6	18.9	0.923
Treatments for comorbid conditions, %			
Diabetes	6.3	7.6	0.441
Hypertension	12.5	14.6	0.425
Dyslipidemia	0.5	0.5	1
Antidepressant medication	0.1	0	1

BMI, body mass index; BP, blood pressure; CHOL, cholesterol; eGFR, estimated glomerular filtration rate; FSG, fasting serum glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RHF, renal hyperfiltration; TG, triglyceride. ^a χ^2 for discrete variables, Kruskal-Wallis tests for nonparametric variables, and one-way analysis of variance for continuous variables. ^b eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation.

Table 3. Multiple adjusted ORs (95% CI) of renal hyperfiltration across depressive symptoms categories

PHQ-9	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Men (<i>n</i> = 1,303)						
PHQ ≥10	4.72 (1.96–11.36)	0.001	4.34 (1.73–10.88)	0.002	4.81 (1.62–14.30)	0.005
5 ≤ PHQ <10	2.07 (1.08–3.95)	0.028	1.98 (1.00–3.91)	0.049	1.22 (0.56–2.64)	0.614
PHQ <5	ref		ref		ref	
Women (<i>n</i> = 2,413)						
PHQ ≥10	1.34 (0.48–3.74)	0.582	1.13 (0.40–3.23)	0.817	1.07 (0.34–3.33)	0.909
5 ≤ PHQ <10	1.85 (1.09–3.15)	0.023	1.63 (0.94–2.82)	0.081	1.18 (0.63–2.21)	0.603
PHQ <5	ref		ref		ref	

Model 1, unadjusted; Model 2, adjustment for age, BMI, current smoking, alcohol intake, and exercise; Model 3, model 2 + systolic BP, diastolic BP, fasting glucose, LDL cholesterol, HDL cholesterol, triglyceride.

blood pressure and triglyceride, and a higher proportion of renal hyperfiltration and underweight. Characteristics of the subpopulation with a major depressive episode (Table 1) were similar. 58 participants had a major depressive episode, and 64 participants had a minor depressive episode. Compared with those participants without depressive episodes, participants with a major depressive episode were also less educated, more often underweight, had a lower level of low-density lipoprotein and cholesterol, and a higher proportion of renal hyperfiltration. No difference in self-reported medications, particularly antidiabetic agents, antihypertensive agents, lipid-regulating drugs, and antidepressant agents, was observed across all the depressive categories.

Table 2 shows the characteristics of participants with renal hyperfiltration compared with those without renal hyperfiltration. In general, 90 men and 95 women with hyperfiltration had mean eGFRs of 112.1 (range 95.5–140.9) and 110.5.2 (range 94.1–128.33.2) mL/min/1.73 m², respectively, compared with 94.6 (range 60.14–125.32) and 96.7 (range 60.4–123.5) mL/min/1.73 m² for men and women without renal hyperfiltration, respectively. Participants with renal hyperfiltration were older, more often male, had a lower level of triglyceride, cholesterol, high-density lipoprotein, and diastolic blood pressure, had a higher proportion of overweight and underweight, a higher proportion of symptomatic depression and major depressive episodes.

The association between depression and renal hyperfiltration was analyzed using a multivariate logistic regression adjusted for possible confounding variables, such as age, sex, smoking status, alcohol intake, diabetes, hypertension, dyslipidemia, BMI, systolic blood pressure, diastolic blood pressure, fasting glucose, and vigorous physical activities. As shown in Table 3, the association between clinically relevant depression and renal hyperfiltration remained significant in men but not in women after adjustment for all confounders (model 3). As compared with men without depression (PHQ <5), those with renal clinically relevant depression (PHQ ≥10) had a significantly higher risk of renal hyperfiltration. The fully adjusted OR (95% CI) was 4.81(1.62–14.30, *p* = 0.005). Similarly, as shown in Table 4, men with major depressive episodes had a higher risk of renal hyperfiltration than those without a depressive episode. The adjusted OR (95% CI) was 7.45 (2.04–27.21, *p* = 0.002). In addition, renal hyperfiltration was significantly associated with age and diastolic blood pressure for men, and was associated with fasting glucose, age, triglyceride, and BMI for women. The logistic regression models were repeated with a definition of hyperfiltration by defining

Table 4. Multiple adjusted ORs (95% CI) of renal hyperfiltration across depressive episodes categories

Depressive episode	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Men (<i>n</i> = 1,303)						
Major	8.55 (3.03–24.11)	<0.001	9.04 (3.03–27.01)	<0.001	7.45 (2.04–27.21)	0.002
Minor	0.71 (0.09–5.38)	0.742	0.73 (0.09–5.65)	0.76	0.92 (0.11–7.88)	0.94
No	ref		ref		ref	
Women (<i>n</i> = 2,413)						
Major	1.23 (0.29–5.17)	0.778	1.24 (0.29–5.34)	0.772	1.03 (0.22–4.96)	0.968
Minor	1.20 (0.29–5.03)	0.804	1.11 (0.26–4.74)	0.892	0.54 (0.12–2.55)	0.541
No	ref		ref		ref	

Model 1, unadjusted; Model 2, adjustment for age, BMI, current smoking, alcohol intake, and exercise; Model 3, model 2 + systolic BP, diastolic BP, fasting glucose, LDL cholesterol, HDL cholesterol, triglyceride, cholesterol.

Table 5. Multiple adjusted ORs (95% CI) of renal hyperfiltration across different subgroups

Subgroup	PHQ-9	OR (95% CI)	<i>p</i> value	Depressive episode	OR (95% CI)	<i>p</i> value
Without hypertension (<i>n</i> = 1,066)	PHQ ≥10	3.523 (0.930–13.350)	0.064	major	7.467 (1.856–30.045)	0.005
	5 ≤ PHQ <10	0.765 (0.290–2.016)	0.587	minor	0.631 (0.054–7.365)	0.713
	PHQ <5	ref		no	ref	
Without diabetes (<i>n</i> = 1,190)	PHQ ≥10	5.254 (1.623–17.003)	0.006	major	5.143 (1.012–26.152)	0.048
	5 ≤ PHQ <10	1.312 (0.592–2.908)	0.504	minor	0.615 (0.052–7.344)	0.615
	PHQ <5	ref		no	ref	

Adjustment for age, BMI, current smoking, alcohol intake and exercise, educational level, marital status, systolic BP, diastolic BP, fasting glucose, LDL cholesterol, HDL cholesterol, triglyceride, cholesterol and hypertension or diabetes.

those with adjusted absolute GFR >90th percentile as having hyperfiltration (data not shown). These analyses yielded similar findings.

Multivariate logistic analysis was also performed in men without major risk factors for renal hyperfiltration. After adjustment of all the confounders, renal hyperfiltration was associated with clinically relevant depression in participants without diabetes (OR 5.254, 95% CI 1.623–17.003; *p* = 0.006) (Table 5). Symptomatic depression had a trend to be associated with renal hyperfiltration in participants without hypertension, but it did not reach statistical significance. On the other hand, major depressive episodes were associated with renal hyperfiltration in participants without diabetes (OR 7.467, 95% CI 1.856–30.045; *p* = 0.005) and participants without hypertension (OR 5.143, 95% CI 1.012–26.152; *p* = 0.048).

Discussion

In this study, we identified an association between clinically relevant depression and major depressive episodes and the incidence of renal hyperfiltration in an apparently healthy population from a community in China. Self-reported depressive symptoms and major

depressive episodes were associated with renal hyperfiltration in men but not in women. This relationship was valid even after adjustment for a variety of confounding or explanatory variables such as hypertension and diabetes.

It has been well documented that the high prevalence of depression is an independent risk factor of poor outcomes even in patients with CKD before dialysis [5], as well as renal transplantation [25]. The relationships between depression and eGFR have been investigated in a number of previous studies which concentrated on low eGFR. In a cohort without substantial CKD, albuminuria but not eGFR was shown to be associated with depression [10]. Whether depression is also associated with the progression of earlier stages of CKD remains unknown. Recently, in a large prospective cohort study of US veterans with diabetes and $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$, Novak et al. [8] demonstrated that patients with depression at baseline had higher eGFR and more comorbidities. During the follow-up period, the presence of depression was associated with a higher risk of incident CKD and high all-cause mortality, incident cardiac events, and incident stroke [8]. It is unclear whether depression could be independently associated with renal hyperfiltration in the general population. Several cardiometabolic factors such as high blood pressure, left ventricular hypertrophy, microalbuminuria, and coronary artery calcification may explain the high all-cause mortality associated with renal hyperfiltration recently ascertained in a number of recent studies [16, 26]. Renal hyperfiltration might be the missing link between cardiorenal risk factors and CKD or cardiovascular disease. The bidirectional relationships between depression and cardiometabolic disease such as diabetes, metabolic syndrome, and cardiovascular diseases have been proofed in several population-based studies [27–29]. To date, no study has yet reported the association between depression and renal hyperfiltration. To address this issue, we performed a cross-sectional study in a large general Chinese population without CKD.

The results of this study differ from a recent population-based study that have shown no association between depression and eGFR in participants with normal or mildly reduced eGFR. However, that study only concentrated on the risk of depressive symptoms per 10 mL/min/1.73 m² lower eGFR but not in subgroups with renal hyperfiltration [10]. Previous studies that have examined health-related quality of life (HRQoL) and depression in patients with CKD showed that the stronger effect of lower eGFR on depressive symptoms may attribute to the increased cardiovascular disease present at CKD [12]. In this study, patients with a known history of cardiovascular disease were excluded on inclusion. Renal hyperfiltration is a characteristic functional abnormality in comorbid conditions such as diabetes, hypertension, and obesity; depressive symptoms and major depressive episodes are also associated with those comorbidities [30–34]. The association between renal hyperfiltration and depressive symptoms might in part be confounded by the indirect effect of diabetes and hypertension. However, the association remained significant in the subgroup analysis of participants without diabetes or hypertension. Therefore, it is unlikely that diabetes or hypertension mainly contribute to depression in this study.

In this study, eGFR was evaluated on the basis of serum creatinine, it could not be excluded that high eGFR might be a manifestation of decreased muscle mass but not truly high GFR. Previous studies have shown that low body mass and sarcopenia were associated with depression in elderly men [35]. Because participants with a BMI <18.5 had a greater possibility of muscle wasting than those with a BMI ≥ 18.5 [36]. In this study, the association between depression with high GFR did not change after participants with a BMI <18.5 were excluded (data not shown).

Consistent with previous studies that showed a higher prevalence of major depression in women than men, a major depressive episode and symptomatic depression were more common in women than in men in this study [37]. However, depression was found to be

related to renal hyperfiltration in men, but not in women. Similarly, the gender differences in depression as a risk factor for comorbid diseases have been reported in previous studies [38–40]. For example, In the National Health and Nutrition Examination Survey, cardiovascular disease mortality was only related to depression in men, while depression had no effect on cardiovascular disease mortality in women [39]. Increasing inflammation predicted by the depressive symptoms for men, but not for women, may partially explain the gender-related finding.

A potential explanation that connects high eGFR and depression could be low-grade inflammation and endothelial cell dysfunction. A variety of vasoactive mediators including the nitric oxide system, cyclooxygenase 2 (COX2)-derived prostanoids, protein kinase C, and endothelin may contribute to the renal hyperfiltration [41]. Inflammatory cytokines and adipokines were also associated with glomerular hyperfiltration. A number of these inflammatory markers have been consistently associated with endothelial cell dysfunction and depression. Indeed, depressed patients have been found to have high levels of inflammatory markers, such as C-reactive protein, interleukin 1, 2, 6, and tumor necrosis factor, and endothelial chemokines, such as sICAM-1, sE-Selectin [42–44]. In addition, renin-angiotensin system (RAS) activation in glomerular hyperfiltration patients may also play a role in depression. AGTR1, the gene coding for the type 1 angiotensin II receptor (AT1R), has been shown to be associated with a diagnosis of depression [45]. Furthermore, increased sympathetic nerve activity to the kidney and the renal afferent nerve activity to the central nervous system may also contribute to the development of depression.

The major strengths of our study include its large sample size of the general population, detailed epidemiologic profiles, and thorough statistical analyses. However, there are several limitations. First, the results might be biased because GFR was estimated using serum creatinine-based (CKD-EPI) equation rather than direct measurement or CKD-EPI creat-cys calculation. In the current study, renal hyperfiltration was defined after adjustment for age, sex, BMI, and angiotensin-converting-enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB) treatment. Nevertheless, it does not completely avoid overestimating GFR, especially in participants with muscle waste. Second, information on depression relies on self-reports, which could lead to recall bias and misclassification. We also performed an interview to assess minor and major depressive episodes. Consistent with other depression screening scales, the item responses and total scores on the PHQ-9 follow the same characteristic patterns, which may serve as a basis for the estimation of the distribution of depression in a general population [46]. In the current study, 3.1% of participants had clinically relevant depression and 3.3% had major or minor depressive episodes. The result was similar to other studies that were performed in a general population of China [47, 48]. Third, although patients with a known history of CKD including eGFR <60 mL/min/1.73 m², or dipstick proteinuria ≥1+ or ACR (albumin creatinine ratio) ≥30 mg/g had been excluded on inclusion, we could not evaluate the effect of proteinuria at levels that do not fulfil the CKD criteria in this study. Fourth, although we have adjusted for several confounders that could explain the relationship between depression and renal hyperfiltration, it is possible that residual factors not captured in this study could lead to misclassification of depression. Additionally, the cross-sectional design limits causal inference. Follow-up studies are required to examine the long-term effect of depression on proteinuria and incidence of CKD in this population. This study might not represent the general population in China, and we should be cautious in generalizing the results.

In conclusion, our study is novel in demonstrating the associations between depression and renal hyperfiltration in middle-aged and elderly men, and this relationship was independent of diabetes and hypertension. Whether depression could be a modifiable factor in the development of renal hyperfiltration and CKD with cardiometabolic risk factors warrants further investigation.

Acknowledgements

This study was supported by grants from the Chinese Medical Association Foundation and Chinese Endocrine Society (12020240314), National Key New Drug Creation and Manufacturing Program of Ministry of Science and Technology (2012ZX09303006-001), Joint Science and Technology Innovation Fund of Fujian province (No.2016Y9001), and Key Clinical Specialty Discipline Construction Program of Fujian, China.

Statement of Ethics

The study protocol was approved by the Ethics Committee of Fujian Provincial Hospital in accordance with the Declaration of Helsinki, and written informed consent was obtained from each participant.

Disclosure Statement

The authors declare no conflict of interest.

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