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20. Shoham DA, Vupputuri S, Diez Roux AV *et al.* Kidney disease in life-course socioeconomic context: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2007; 49: 217–226
21. Iseki K, Ikemiya Y, Iseki C *et al.* Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 2003; 63: 1468–1474
22. White SL, Polkinghorne KR, Atkins RC *et al.* Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis* 2010; 55: 660–670

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Albuminuria is associated with a higher prevalence of depression in a population-based cohort study: the Maastricht Study

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ABSTRACT

Background. Depression is common in individuals with chronic kidney disease (CKD). However, data on the association of albuminuria, which together with reduced estimated glomerular filtration rate (eGFR) defines CKD, with depression are scarce and conflicting. In addition, it is not clear when in the course from normal kidney function to CKD the association with depression appears.

Methods. We examined the cross-sectional associations of albuminuria and eGFR with depressive symptoms and depressive episodes in 2872 and 3083 40- to 75-year-old individuals, respectively, who completed the baseline survey of an ongoing population-based cohort study conducted in the southern part of The Netherlands between November 2010 and September 2013. Urinary albumin excretion (UAE) was the average UAE in two 24-h urine collections and eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine and cystatin C. Depressive symptoms were assessed with the 9-item Patient Health Questionnaire (PHQ-9) and the presence of a minor or major depressive episode was assessed with the MINI-International Neuropsychiatric Interview.

Results. In total, 5.4% had a minor or major depressive episode. UAE was <15 mg/24 h in 81.2%, 15–<30 mg/24 h in 10.3% and ≥30 mg/24 h in 8.6%. In a multivariable logistic regression analysis adjusted for potential confounders, and with UAE <15 mg/24 h as reference category, the odds ratio for a minor or major depressive episode was 2.13 [95% confidence interval (CI) 1.36–3.36] for UAE 15–<30 mg/24 h and 1.81 (95% CI 1.10–2.98) for UAE ≥30 mg/24 h. The average eGFR was 88.2

± 14.7 mL/min/1.73 m^2. eGFR was not associated with the presence of a minor or major depressive episode. Results were similar when we assessed associations with depressive symptoms or clinically relevant depressive symptoms (PHQ-9 score ≥10).

Conclusions. Albuminuria was associated with depressive symptoms and depressive episodes, even at levels of UAE that do not fulfil the CKD criteria. Future longitudinal studies should examine the direction of this association and whether albuminuria could serve as a biomarker to identify individuals at risk of depression.

Keywords: albuminuria, depression, depressive symptoms, estimated glomerular filtration rate, urinary albumin excretion

INTRODUCTION

Depression is common in individuals with chronic kidney disease (CKD) (prevalence ∼25%) [1], in whom it is associated with increased morbidity [2] and mortality [3]. The frequent occurrence of cerebral small vessel disease (cSVD) in CKD [4] may be one explanation for the high prevalence of depression in CKD. According to the vascular depression hypothesis [5, 6], cSVD may lead to depression through disruption of neuronal circuits involved in mood regulation. Furthermore, neurotoxic effects of the uraemic milieu [7] and the presence of comorbidities [8] such as obesity, type 2 diabetes mellitus (T2DM) and hypertension may be involved.

However, data on the association of albuminuria, which together with reduced estimated glomerular filtration rate (eGFR) defines CKD [9], with depression are scarce and conflicting [10, 11]. Albuminuria may indicate generalized endothelial dysfunction [12, 13], which in the brain may cause cSVD [14]. Therefore, albuminuria may be a biomarker of vascular disease processes involved in depression. Indeed, albuminuria was borderline statistically significantly associated with depressive symptoms in individuals with DM without cardiovascular disease (CVD) [10]. In contrast, it was not associated in individuals with DM with CVD [10] or in a CKD population [11]. However, in both studies, assessment of depressive symptoms instead of a diagnosis of minor or major depressive episode may have led to misclassification of somatic symptoms of (comorbid) disease as depressive symptoms [1].

In addition, it is not clear when in the course from normal kidney function to CKD the associations of eGFR and albuminuria with depression appear. Literature on the associations of eGFR and albuminuria with CVD [15, 16] suggests that both may already be associated with adverse health outcomes at levels that do not fulfil the CKD criteria. In this regard, the results of previous studies suggest that eGFR may not be associated with depression until moderately to severely reduced [11, 17–29], whereas data on this topic are lacking for albuminuria.

In view of the above, we examined whether albuminuria and eGFR were, independent of each other, associated with both self-reported depressive symptoms and an interview-based diagnosis of minor or major depressive episode in a population-based cohort without substantial CKD.

MATERIALS AND METHODS

The Maastricht Study population and design

We used data from the Maastricht Study, an observational prospective population-based cohort study [30]. Eligible for participation were all individuals between 40 and 75 years of age living in the southern part of The Netherlands. Recruitment was stratified according to known T2DM, with an oversampling of individuals with T2DM, for reasons of efficiency. The present report includes cross-sectional data from the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. The study was approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131 088-10 5234-PG) and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Kidney function

To assess urinary albumin excretion (UAE), participants were requested to collect two 24-h urine collections (Supplemental Methods). UAE was based on the average of two (available in 91.5% of the participants) 24-h urine collections. GFR was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation based on the combination of serum creatinine and serum cystatin C ($eGFR_{crcys}$) (Supplemental Methods) [31].

Depressive symptoms

Depressive symptoms were assessed with a validated Dutch version of the 9-item Patient Health Questionnaire (PHQ-9) [32]. 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. It comprises nine items rated on a 4-point scale, ranging from 0 ('not at all') to 3 ('nearly every day'). Response options are used to calculate a continuous total depressive symptom score ranging from 0 (no symptoms) to 27 (all symptoms present nearly every day). When one or two items were missing, the total score was calculated as 9 × (total points/9 − number of missing items) and rounded to the nearest integer. As a continuous variable, scores 0–9 represent no, 10–14 represent moderate, 15–19 represent moderately severe and 20–27 represent severe depression [33]. A predefined cut-off score of ≥10 was considered to indicate clinically relevant depressive symptoms [32].

In addition, we calculated affective (i.e. anhedonia, depressed mood, feeling of worthlessness, thoughts of death) and somatic (i.e. fatigue, appetite changes, sleep difficulties, concentration difficulties, psychomotor agitation/retardation) subscores, based on a confirmatory factor analysis conducted previously [34].

Minor and major depressive episode

The Mini-International Neuropsychiatric Interview (MINI) [35] was used to assess the presence of a minor or major depressive episode in the preceding 2 weeks according to the DSM-IV criteria. A major depressive episode was diagnosed if participants had at least one core symptom (i.e. depressed mood or

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anhedonia) and at least four other symptoms of depression (i.e. significant weight change or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, 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 classified as having a minor depressive episode.

Potential confounders

We assessed glucose metabolism status, body mass index, waist circumference, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, office blood pressure, 24-h average ambulatory blood pressure, medication use, smoking behaviour, alcohol consumption, prevalent CVD, educational level, marital status, medical history, physical activity and cognitive performance, as described previously [30, 36]. Glucose metabolism was classified according to the World Health Organization 2006 criteria [37] into normal glucose metabolism, impaired fasting glucose, impaired glucose tolerance and DM. Participants with DM and participants using glucose-lowering medication were considered as having T2DM if they had no (self-reported) type 1 or other specific type of DM. For this study, impaired fasting glucose and impaired glucose tolerance were combined into prediabetes. Body mass index was calculated by dividing weight by height^2 and classified into normal weight ($<$25 kg/m^2), overweight (25–$<$30 kg/m^2) and obesity ($\geq$30 kg/m^2). The total:HDL cholesterol ratio was calculated by dividing total cholesterol by HDL cholesterol. Hypertension was defined as an office systolic pressure $\geq$140 mmHg, an office diastolic pressure $\geq$90 mmHg and/or the use of antihypertensive medication. Smoking behaviour was classified into never, former and current. Alcohol consumption was classified into no consumption, low consumption ($<$7 glasses per week for women; $<$14 glasses per week for men) and high consumption ($>$7 glasses per week for women; $>$14 glasses per week for men). Prevalent CVD was defined as a self-reported history of myocardial infarction, cerebrovascular infarction or hemorrhage or percutaneous artery angioplasty of or vascular surgery on the coronary, abdominal, peripheral or carotid arteries. Educational level was classified into low (none, primary, or lower vocational education only), intermediate (intermediate general secondary, intermediate vocational or higher general secondary education) and high (higher vocational education or university level of education) [38, 39]. Participants who were married or in a civil partnership or who cohabited were classified as married/living with spouse. Participants were classified as having comorbid disease other than T2DM and CVD if they reported being diagnosed with non-skin cancer, inflammatory bowel disease, inflammatory respiratory disease and/or Parkinson's disease (28 participants with missing data were classified as having no comorbid disease). A modified version of the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire [40] was used to assess weekly total and moderate to vigorous physical activity. The Mini-Mental State Examination (MMSE) was used as a measure of global cognitive performance [41]. In addition, we assessed information processing speed as the standardized composite score of the Stroop Color Word Test Parts I and II [42], the Concept Shifting Test Parts A and B [43] and the Letter-Digit Substitution Test [44], as this cognitive domain has been associated with albuminuria in the present cohort [36].

Statistical analyses

All analyses were performed with SPSS Statistics Version 22.0 (IBM, Armonk, NY, USA) unless stated otherwise. Population characteristics were presented stratified by the presence of clinically relevant depressive symptoms and by the presence of a major depressive episode. Associations of albuminuria and eGFR$_{crcys}$ with depressive symptoms were evaluated with negative binomial regression analyses because of the extremely skewed distribution of PHQ-9 scores [45] (Stata Statistical Software, release 11.2SE; StataCorp, College Station, TX, USA). Albuminuria was entered as a categorical variable [$<$15 mg/24 h (reference category), 15–$<$30 mg/24 h and $\geq$30 mg/24 h] since the associations appeared to be nonlinear [46]. eGFR$_{crcys}$ was entered as a continuous variable and expressed per 10 mL/min/1.73 m^2 lower eGFR$_{crcys}$. The regression coefficients were exponentiated to obtain the ratio of the depressive symptom score per 10 mL/min/1.73 m^2 lower eGFR$_{crcys}$ or when compared with UAE $<$15 mg/24 h.

Associations of albuminuria and eGFR$_{crcys}$ with clinically relevant depressive symptoms, major depressive episode and minor or major depressive episode were evaluated with multivariable logistic regression analyses.

All regression analyses were adjusted for potential confounders as follows: model 1: unadjusted model; model 2: age, sex, educational level, marital status, comorbid disease, glucose metabolism status; model 3: model 2 + waist circumference, total:HDL cholesterol, triglycerides, the use of lipid-modifying medication, smoking behaviour, alcohol consumption; model 4: model 3 + eGFR$_{crcys}$ or UAE; model 5a: model 4 + office systolic pressure, the use of antihypertensive medication, prevalent CVD; model 5b: model 5a but with replacement of office systolic pressure by 24-h average ambulatory systolic pressure. Blood pressure and prevalent CVD were added separately, as these variables may be confounders and/or intermediates in the above associations.

Several additional analyses were performed to explore the robustness of our results. First, we restricted the analyses to participants with UAE $\leq$300 mg/24 h and to the subpopulation with two valid urine collections. Second, we additionally adjusted for total or moderate to vigorous physical activity. Third, we additionally adjusted for cognitive performance, expressed as either the MMSE score or information processing speed. Fourth, we assessed associations of albuminuria and eGFR$_{crcys}$ with affective and somatic subscores of the PHQ-9 to explore whether any associations with the total PHQ-9 score were driven by somatic complaints in individuals with higher UAE or lower eGFR$_{crcys}$. Fifth, we included antidepressant use in our definitions of major depressive episode and minor or major depressive episode.

RESULTS

Characteristics of the study population

Figure 1 presents a flow diagram delineating the derivation of the final study populations. The analyses on the PHQ-9 were

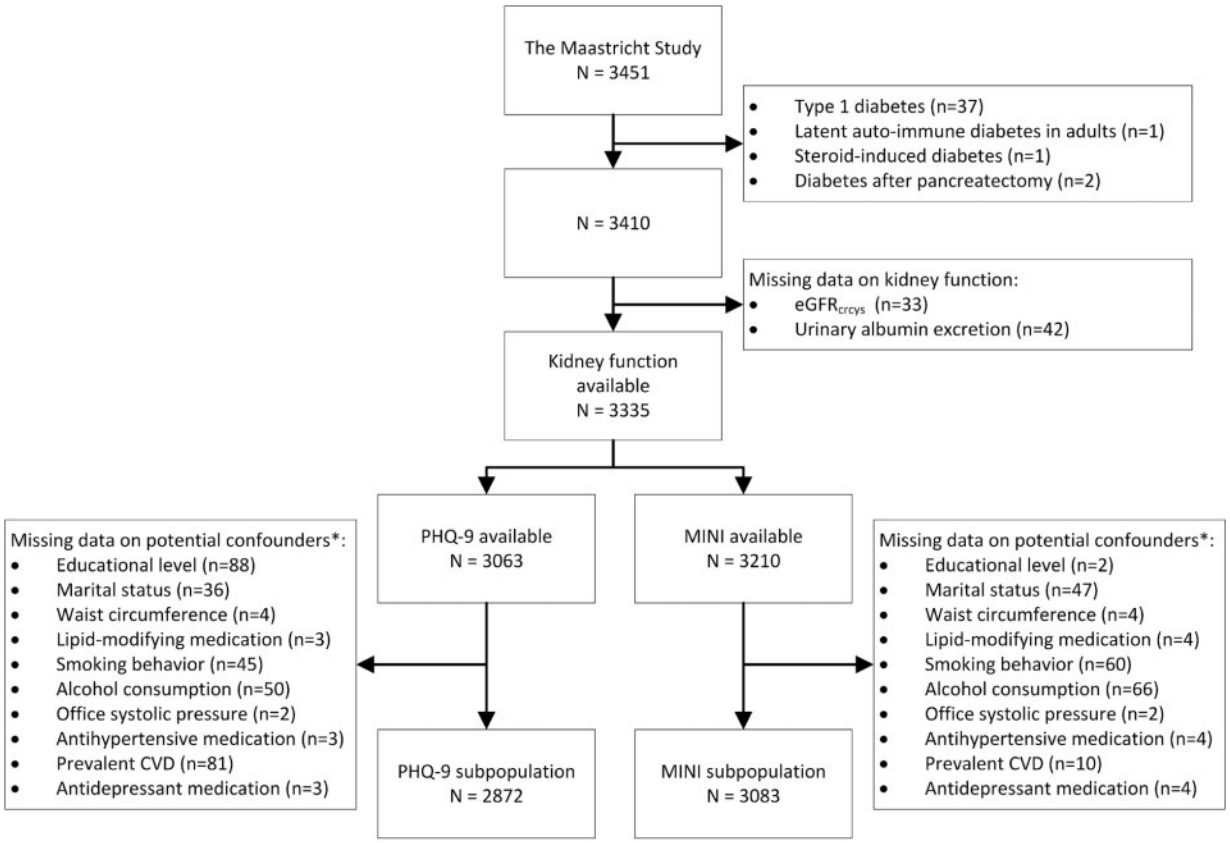

FIGURE 1: Flow diagram delineating the derivation of the final study populations. $eGFR_{crcys}$, estimated glomerular filtration rate based on creatinine and cystatin C; CVD, cardiovascular disease; MINI, MINI-International Neuropsychiatric Interview; PHQ-9, Patient Health Questionnaire-9. *Missing data were not mutually exclusive.

based on 2872 participants (PHQ-9 subpopulation) and the analyses on the MINI on 3083 participants (MINI subpopulation).

Table 1 shows the characteristics of the MINI subpopulation. Due to oversampling, 846 (27.4%) participants had T2DM. In total, 122 (4.3%) participants had clinically relevant depressive symptoms, 112 (3.6%) had a major depressive episode and 54 (1.8%) had a minor depressive episode. Of those with a major or minor depressive episode, 33 (29.5%) and 4 (7.4%) used an antidepressant, respectively. Characteristics of the PHQ-9 subpopulation (Table 1) were similar.

In general, participants with a major depressive episode were slightly younger, slightly more often women, less educated, more often lived alone, more often had T2DM or other comorbid disease, had a worse CVD risk profile and had a lower information processing speed.

Albuminuria, depressive symptoms and depressive episodes

The median UAE was 6.7 [interquartile range (IQR) 4.0–11.9] mg/24 h. UAE was <15 mg/24 h in 2502 (81.2%) participants, 15–<30 mg/24 h in 317 (10.3%) participants and ≥30 mg/24 h in 264 (8.6%) participants (Table 1).

The median depressive symptom score was 2 (IQR 0–4), 2 (IQR 0–5) and 2 (IQR 1–5) in individuals with UAE <15 mg/24 h, 15–<30 mg/24 h and ≥30 mg/24 h, respectively. After adjustment, and when compared with participants with UAE <15 mg/24 h, participants with UAE 15–<30 mg/24 h and ≥30 mg/24 h had a higher depressive symptom score and more often had a depressive episode, regardless of their definitions (Table 2, model 5a). That is, the odds ratio (OR) and for clinically relevant depressive symptoms was 2.28 [95% confidence interval (CI) 1.34–3.89] for UAE 15–<30 mg/24 h and 1.84 (95% CI 1.00–3.35) for UAE ≥30 mg/24 h (Table 2, model 5a). Similarly, the OR for a major depressive episode was 2.49 (95% CI 1.48–4.21) for UAE 15–<30 mg/24 h and 1.76 (95% CI 0.97–3.21) for UAE ≥30 mg/24 h (Table 2, model 5a). In addition, the OR for minor or major depressive episode was 2.13 (95% CI 1.36–3.36) for UAE 15–<30 mg/24 h and 1.81 (95% CI 1.10–2.98) for UAE ≥30 mg/24 h (Table 2, model 5a).

When the above associations were adjusted for 24-h average ambulatory systolic pressure the instead of office systolic pressure, the results were similar (Table 2, model 5b).

eGFR, depressive symptoms and depressive episodes

The average $eGFR_{crcys}$ was 88.2 ± 14.7 mL/min/1.73 m^2 (Table 1). $eGFR_{crcys}$ was ≥90 mL/min/1.73 m^2 in 1497 (48.6%) participants, 60–<90 mL/min/1.73 m^2 in 1461 (47.4%) participants and <60 mL/min/1.73 m^2 in 125 (4.1%) participants.

The median depressive symptom score was 2 (IQR 0–5), 1.5 (IQR 0–4) and 2 (IQR 0–4) for individuals with $eGFR_{crcys}$ <60 mL/min/1.73 m^2, 60–<90 mL/min/1.73 m^2 and ≥90 mL/min/1.73 m^2, respectively.

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

	Study population[a]	Clinically relevant depressive symptoms (PHQ-9)[a]			Major depressive episode (MINI)[a]		
		No ($n = 2749$)	Yes ($n = 123$)	P-value[c]	No ($n = 2971$)	Yes ($n = 112$)	P-value[c]
Demographics							
Age (years)	59.8 ± 8.2	59.8 ± 8.2	55.9 ± 7.8	<0.001	59.8 ± 8.2	58.4 ± 8.4	0.07
Men	1596 (51.8)	1423 (51.8)	50 (40.7)	0.02	1542 (51.9)	54 (48.2)	0.44
Married/living with spouse	2482 (80.5)	2250 (81.8)	77 (62.6)	<0.001	2405 (80.9)	77 (68.8)	0.001
Educational level				<0.001			<0.001
Low	508 (16.5)	406 (14.8)	33 (26.8)		472 (15.9)	36 (32.1)	
Intermediate	1323 (42.9)	1194 (43.4)	57 (46.3)		1271 (42.8)	52 (46.4)	
High	1252 (40.6)	1149 (41.8)	33 (26.8)		1228 (41.3)	24 (21.4)	
Lifestyle variables							
Smoking behaviour				<0.001			<0.001
Never smoker	1078 (35.0)	987 (35.9)	28 (22.8)		1055 (35.5)	23 (20.5)	
Former smoker	1598 (51.8)	1425 (51.8)	58 (47.2)		1541 (51.9)	57 (50.9)	
Current smoker	407 (13.2)	337 (12.3)	37 (30.1)		375 (12.6)	32 (28.6)	
Alcohol consumption				<0.001			<0.001
None	563 (18.3)	462 (16.8)	44 (35.8)		521 (17.5)	42 (37.5)	
Low (women ≤7 glasses/week; men ≤14 glasses/week)	1707 (55.4)	1550 (56.4)	55 (44.7)		1659 (55.8)	48 (42.9)	
High (women >7 glasses/week; men >14 glasses/week)	813 (26.4)	737 (26.8)	24 (19.5)		791 (26.6)	22 (19.6)	
Total physical activity (h/week)[b]	13.0 (8.3–18.5)	13.0 (8.3–18.5)	11.5 (6.0–19.8)	0.08	13.0 (8.3–18.8)	11.0 (6.0–16.9)	0.006
Moderate to vigorous physical activity (h/week)[b]	4.5 (2.3–8.0)	4.5 (2.3–8.0)	3.0 (0.8–6.7)	<0.001	4.5 (2.3–8.0)	3.0 (0.8–5.9)	<0.001
Clinical characteristics							
BMI categories[b]				0.001			<0.001
Normal weight (<25 kg/m^2)	1074 (34.8)	989 (36.0)	29 (23.6)		1051 (35.4)	23 (20.5)	
Overweight (25–30 kg/m^2)	1322 (42.9)	1179 (42.9)	52 (42.3)		1274 (42.9)	48 (42.9)	
Obesity (≥30 kg/m^2)	686 (22.3)	581 (21.1)	42 (34.1)		645 (21.7)	41 (36.6)	
Waist circumference (cm)							
Men	101.4 ± 11.9	100.9 ± 11.5	107.0 ± 15.8	0.01	101.2 ± 11.7	106.8 ± 13.9	
Women	90.0 ± 12.9	89.4 ± 12.5	97.7 ± 18.3	<0.001	89.8 ± 12.7	96.4 ± 16.6	
Office systolic pressure (mmHg)	135.0 ± 18.2	134.9 ± 18.2	134.2 ± 16.6	0.69	135.0 ± 18.2	135.6 ± 18.3	0.71
Office diastolic pressure (mmHg)	76.3 ± 9.9	76.3 ± 9.9	77.5 ± 10.6	0.18	76.2 ± 9.9	77.2 ± 11.2	0.39
24 h average ambulatory systolic pressure (mmHg)[b]	119.1 ± 11.7	118.9 ± 11.8	120.3 ± 12.2	0.22	119.0 ± 11.6	120.9 ± 14.5	0.21
24 h average ambulatory diastolic pressure (mmHg)[b]	73.5 ± 7.2	73.5 ± 7.2	75.4 ± 8.0	0.007	73.5 ± 7.1	75.5 ± 9.0	0.03
Hypertension	1728 (56.0)	1519 (55.3)	75 (61.0)	0.21	1658 (55.8)	70 (62.5)	0.16
Glucose metabolism status				0.001			<0.001
Normal glucose metabolism	1761 (57.1)	1618 (58.9)	56 (45.5)		1715 (57.7)	46 (41.1)	
Impaired fasting glucose	132 (4.3)	118 (4.3)	2 (1.6)		130 (4.4)	2 (1.8)	
Impaired glucose tolerance	344 (11.2)	314 (11.4)	15 (12.2)		333 (11.2)	11 (9.8)	
T2DM	846 (27.4)	699 (25.4)	50 (40.7)		793 (26.7)	53 (47.3)	
Total cholesterol (mmol/l)	5.2 ± 1.2	5.3 ± 1.2	5.2 ± 1.2	0.36	5.2 ± 1.2	5.1 ± 1.1	0.35
HDL cholesterol (mmol/l)							
Men	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	0.14	1.3 ± 0.4	1.2 ± 0.3	
Women	1.7 ± 0.5	1.8 ± 0.5	1.6 ± 0.5	0.006	1.7 ± 0.5	1.5 ± 0.5	
LDL cholesterol (mmol/l)	3.1 ± 1.0	3.1 ± 1.0	3.0 ± 1.1	0.11	3.1 ± 1.0	3.0 ± 1.1	0.54
Triglycerides (mmol/l)	1.21 (0.88–1.72)	1.20 (0.87–1.70)	1.49 (1.05–2.18)	<0.001	1.20 (0.88–1.70)	1.49 (1.02–2.13)	<0.001
Total:HDL cholesterol ratio	3.7 ± 1.2	3.7 ± 1.2	3.9 ± 1.5	0.12	3.7 ± 1.2	4.0 ± 1.4	0.005
Prevalent cardiovascular disease	509 (16.5)	434 (15.8)	28 (22.8)	0.04	482 (16.2)	27 (24.1)	0.03
Comorbidity	488 (15.8)	407 (14.8)	34 (27.6)	<0.001	460 (15.5)	28 (25.0)	0.007
Kidney function							
$eGFR_{crcys}$ (ml/min/1.73 m^2)	88.2 ± 14.7	88.2 ± 14.6	90.2 ± 14.8	0.14	88.2 ± 14.7	87.4 ± 15.6	0.57
$eGFR_{crcys}$ categories				0.17			0.74
≥90 mL/min/1.73 m^2	1497 (48.6)	1335 (48.6)	69 (56.1)		1445 (48.6)	52 (46.4)	
60–<90 mL/min/1.73 m^2	1461 (47.4)	1310 (47.7)	48 (39.0)		1407 (47.4)	54 (48.2)	
<60 mL/min/1.73 m^2	125 (4.1)	104 (3.8)	6 (4.9)		119 (4.0)	6 (5.4)	
Urinary albumin excretion rate (mg/24 h)	6.7 (4.0–11.9)	6.5 (4.0–11.5)	7.8 (4.2–21.6)	0.007	6.6 (4.0–11.6)	8.8 (4.1–21.4)	0.004
Urinary albumin excretion categories				<0.001			<0.001
<15 mg/24 h	2502 (81.2)	2258 (82.1)	81 (65.9)		2432 (81.9)	70 (62.5)	

Continued

Table1. Continued

	Study population[a]	Clinically relevant depressive symptoms (PHQ-9)[a]			Major depressive episode (MINI)[a]		
		No ($n = 2749$)	Yes ($n = 123$)	P-value[c]	No ($n = 2971$)	Yes ($n = 112$)	P-value[c]
15–<30 mg/24 h	317 (10.3)	272 (9.9)	22 (17.9)		294 (9.9)	23 (20.5)	
≥30 mg/24 h	264 (8.6)	219 (8.0)	20 (16.3)		245 (8.2)	19 (17.0)	
Medication							
Antihypertensive medication	1214 (39.4)	1052 (38.3)	60 (48.8)	0.02	1157 (38.9)	57 (50.9)	0.01
Renin–angiotensin system inhibitor	915 (29.7)	790 (28.7)	45 (36.6)	0.06	869 (29.2)	46 (41.1)	0.007
Lipid-modifying medication	1092 (35.4)	940 (34.2)	51 (41.5)	0.10	1044 (35.1)	48 (42.9)	0.09
Antidepressant medication	205 (6.6)	149 (5.4)	35 (28.5)	<0.001	172 (5.8)	33 (29.5)	<0.001
Mental health and cognitive performance							
PHQ-9 score[b]	2 (0–4)	2 (0–4)	12 (11–16)	<0.001	2 (0–4)	10 (7–16)	<0.001
Clinically relevant depressive symptoms (PHQ-9 ≥ 10)[b]	122 (4.3)	–	–	–	75 (2.7)	47 (51.6)	<0.001
Major depressive episode	112 (3.6)	44 (1.6)	47 (38.5)	<0.001	–	–	–
Minor or major depressive episode	166 (5.4)	81 (3.0)	57 (46.7)	<0.001	–	–	–
MMSE score[b]	29 (28–30)	29 (28–30)	29 (28–30)	0.01	29 (28–30)	29 (28–30)	<0.001
Information processing speed[b]	0.00 ± 1.00	0.01 ± 0.98	−0.16 ± 1.20	0.13	0.02 ± 0.99	−0.41 ± 1.19	<0.001

Data are presented as *n* (%), mean ± SD or median (IQR). BMI, body mass index.

[a]The columns 'Study population' and 'Major depressive episode (MINI)' present the characteristics of the MINI subpopulation ($n = 3083$), whereas the column 'Clinically relevant depressive symptoms (PHQ-9)' presents the characteristics of the PHQ-9 subpopulation ($n = 2872$).

[b]For the MINI subpopulation available in $n = 2704$ (total physical activity), $n = 2703$ (moderate to vigorous physical activity), $n = 3082$ participants (BMI categories), $n = 2731$ participants (24 h average ambulatory systolic and diastolic pressure), $n = 2842$ (PHQ-9 score), $n = 2842$ (clinically relevant depressive symptoms (PHQ-9 ≥ 10)), $n = 3081$ (MMSE score) and $n = 3029$ (information processing speed) participants. For the PHQ-9 subpopulation available in $n = 2686$ (total physical activity), $n = 2685$ (moderate to vigorous physical activity), $n = 2871$ (BMI categories), $n = 2559$ (24 h average ambulatory systolic and diastolic pressure), $n = 2842$ (major depressive episode and major or minor depressive episode), $n = 2865$ (MMSE score) and $n = 2818$ (information processing speed) participants.

[c]P-values for the comparison of participants with and without clinically relevant depressive symptoms and of participants with and without a major depressive episode were calculated with the independent Student *t*-test for normally distributed variables, the Mann–Whitney *U* test for non-normally distributed variables and the χ^2 test for categorical variables.

Table 2. Associations of albuminuria with depressive symptoms and depressive episodes

		PHQ-9		Clinically relevant depressive symptoms (PHQ-9 ≥10)		Major depressive episode		Minor or major depressive episode	
Model	UAE	Ratio (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
1	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15–<30 mg/24 h	1.34 (1.16–1.54)	<0.001	2.26 (1.38–3.67)	0.001	2.72 (1.67–4.42)	<0.001	2.32 (1.52–3.54)	<0.001
	≥30 mg/24 h	1.43 (1.23–1.67)	<0.001	2.55 (1.53–4.23)	<0.001	2.69 (1.60–4.55)	<0.001	2.63 (1.70–4.07)	<0.001
2	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15–<30 mg/24 h	1.38 (1.20–1.58)	<0.001	2.45 (1.46–4.12)	0.001	2.64 (1.58–4.40)	<0.001	2.24 (1.44–3.50)	<0.001
	≥30 mg/24 h	1.42 (1.22–1.66)	<0.001	2.36 (1.33–4.17)	0.003	2.11 (1.19–3.73)	0.01	2.11 (1.31–3.40)	0.002
3	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15–<30 mg/24 h	1.33 (1.16–1.52)	<0.001	2.31 (1.35–3.92)	0.002	2.47 (1.47–4.17)	0.001	2.14 (1.36–3.36)	0.001
	≥30 mg/24 h	1.30 (1.12–1.52)	0.001	1.90 (1.05–3.44)	0.04	1.82 (1.01–3.30)	0.05	1.87 (1.14–3.07)	0.01
4	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15–<30 mg/24 h	1.32 (1.15–1.52)	<0.001	2.30 (1.35–3.92)	0.002	2.49 (1.48–4.20)	0.001	2.14 (1.36–3.37)	0.001
	≥30 mg/24 h	1.31 (1.12–1.53)	0.001	1.90 (1.05–3.45)	0.04	1.80 (0.99–3.27)	0.05	1.86 (1.13–3.05)	0.01
5a	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15–<30 mg/24 h	1.32 (1.15–1.51)	<0.001	2.28 (1.34–3.89)	0.003	2.49 (1.48–4.21)	0.001	2.13 (1.36–3.36)	0.001
	≥30 mg/24 h	1.29 (1.10–1.50)	0.02	1.84 (1.00–3.35)	0.05	1.76 (0.97–3.21)	0.06	1.81 (1.10–2.98)	0.02
5b	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15–<30 mg/24 h	1.39 (1.20–1.61)	<0.001	2.45 (1.36–4.39)	0.003	3.24 (1.83–5.72)	<0.001	2.60 (1.61–4.20)	<0.001
	≥30 mg/24 h	1.30 (1.10–1.54)	0.002	1.86 (0.95–3.65)	0.07	1.73 (0.85–3.51)	0.13	1.83 (1.04–3.20)	0.04

Ratios represent the ratio of the depressive symptom score when compared with participants with UAE <15 mg/24 h. ORs represent the odds of having clinically relevant depressive symptoms, a major depressive episode and a minor or major depressive episode, respectively, relative to the odds in participants with UAE <15 mg/24 h. Model 1: unadjusted model; model 2: model 1 + age, sex, educational level, marital status, comorbid disease, glucose metabolism status; model 3: model 2 + waist circumference, total:HDL cholesterol ratio, triglycerides, the use of lipid-modifying medication, smoking behaviour, alcohol consumption; model 4: model 3 + $eGFR_{crcys}$; model 5a: model 4 + office systolic pressure, the use of antihypertensive medication, prevalent cardiovascular disease; model 5b: similar to model 5a but adjusted for ambulatory systolic pressure instead of office systolic pressure (missing in $n = 313$ participants for PHQ-9 and $n = 352$ for major depressive episode and minor or major depressive episode).

After adjustment, $eGFR_{crcys}$ was not associated with the depressive symptom score or the presence of a depressive episode, regardless of their definitions (Table 3, models 5a and 5b).

Additional analyses

Results were not materially altered when the analyses were restricted to individuals with UAE ≤300 mg/24 h or to

Table 3. Associations of $eGFR_{crcys}$ with depressive symptoms and depressive episodes

	PHQ-9 score		Clinically relevant depressive symptoms (PHQ-9 ≥10)		Major depressive episode		Minor or major depressive episode	
Model	Ratio (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
1	0.98 (0.95; 1.01)	0.23	0.91 (0.80; 1.03)	0.14	1.04 (0.91; 1.18)	0.57	1.04 (0.94; 1.15)	0.47
2	1.02 (0.99; 1.05)	0.29	1.06 (0.92; 1.22)	0.44	1.08 (0.94; 1.24)	0.28	1.07 (0.95; 1.20)	0.27
3	0.99 (0.96; 1.03)	0.62	0.99 (0.86; 1.15)	0.90	1.03 (0.89; 1.18)	0.73	1.02 (0.90; 1.15)	0.77
4	0.99 (0.95; 1.02)	0.48	1.00 (0.86; 1.15)	0.95	1.03 (0.89; 1.19)	0.68	1.02 (0.90; 1.15)	0.78
5a	0.98 (0.95; 1.02)	0.29	0.99 (0.86; 1.15)	0.91	1.03 (0.89; 1.18)	0.73	1.01 (0.90; 1.14)	0.85
5b	0.99 (0.95; 1.02)	0.48	1.04 (0.88; 1.21)	0.67	1.05 (0.90; 1.24)	0.52	1.04 (0.91; 1.18)	0.58

Ratios represent the ratio of the depressive symptom score per 10 mL/min/1.73 m^2 lower eGFR. ORs represent the relative difference in the odds of having clinically relevant depressive symptoms, a major depressive episode and a minor or major depressive episode, respectively, per 10 mL/min/1.73 m^2 lower eGFR. Model 1: unadjusted model; model 2: model 1 + age, sex, educational level, marital status, comorbid disease, glucose metabolism status; model 3: model 2 + waist circumference, total:HDL cholesterol ratio, triglycerides, the use of lipid-modifying medication, smoking behavior, alcohol consumption; model 4: model 3 + UAE (categorical); model 5a: model 4 + office systolic pressure, the use of antihypertensive medication, prevalent cardiovascular disease; model 5b: similar to model 5a but adjusted for ambulatory systolic pressure instead of office systolic pressure (missing in $n = 313$ participants for PHQ-9 and $n = 352$ for major depressive episode and minor or major depressive episode).

Table 4. Additional analyses of the associations of albuminuria with depressive symptoms and depressive episodes

	PHQ-9		Clinically relevant depressive symptoms (PHQ-9 ≥ 10)		Major depressive episode		Minor or major depressive episode	
UAE	Ratio (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Model 5a + total physical activity ($n = 2686$ for PHQ-9; $n = 2704$ for major and minor or major depressive episode)								
<15 mg/24 h	Reference		Reference		Reference		Reference	
15–<30 mg/24 h	1.33 (1.16–1.53)	<0.001	2.35 (1.33–4.15)	0.003	3.09 (1.74–5.49)	<0.001	2.71 (1.66–4.42)	<0.001
≥30 mg/24 h	1.30 (1.10–1.53)	0.002	2.10 (1.09–4.02)	0.03	1.32 (0.60–2.90)	0.49	1.69 (0.92–3.11)	0.09
Model 5a + moderate to vigorous physical activity ($n = 2685$ for PHQ-9; $n = 2703$ for major and minor or major depressive episode)								
<15 mg/24 h	Reference		Reference		Reference		Reference	
15–<30 mg/24 h	1.33 (1.16–1.53)	<0.001	2.35 (1.33–4.15)	0.003	3.08 (1.73–5.46)	<0.001	2.70 (1.66–4.40)	<0.001
≥30 mg/24 h	1.30 (1.10–1.53)	0.002	2.09 (1.09–4.01)	0.03	1.32 (0.60–2.88)	0.49	1.68 (0.92–3.08)	0.09
Model 5a + MMSE ($n = 2865$ for PHQ-9; $n = 3081$ for major and minor or major depressive episode)								
<15 mg/24 h	Reference		Reference		Reference		Reference	
15–<30 mg/24 h	1.32 (1.15–1.52)	<0.001	2.33 (1.36–3.98)	0.002	2.51 (1.48–4.23)	0.001	2.15 (1.37–3.39)	0.001
≥30 mg/24 h	1.29 (1.11–1.51)	0.001	1.92 (1.05–3.52)	0.03	1.77 (0.97–3.23)	0.06	1.81 (1.10–3.00)	0.02
Model 5a + information processing speed ($n = 2818$ for PHQ-9; $n = 3029$ for major and minor or major depressive episode)								
<15 mg/24 h	Reference		Reference		Reference		Reference	
15–<30 mg/24 h	1.31 (1.15–1.52)	<0.001	2.41 (1.40–4.13)	0.001	2.55 (1.50–4.33)	0.001	2.16 (1.37–3.42)	0.001
≥30 mg/24 h	1.27 (1.09–1.49)	0.003	2.07 (1.12–3.80)	0.02	1.69 (0.91–3.13)	0.10	1.75 (1.05–2.92)	0.03
Model 5a in subpopulation with UAE ≤ 300 mg/24 h ($n = 2852$ for PHQ-9; $n = 3061$ for major and minor or major depressive episode)								
<15 mg/24 h	Reference		Reference		Reference		Reference	
15–<30 mg/24 h	1.32 (1.15–1.52)	<0.001	2.26 (1.33–3.86)	0.003	2.50 (1.48–4.22)	0.001	2.14 (1.36–3.37)	0.001
≥30 mg/24 h	1.30 (1.11–1.54)	0.001	1.96 (1.06–3.61)	0.03	1.84 (1.00–3.39)	0.05	1.92 (1.16–3.19)	0.01
Model 5a in individuals who collected two 24-h urine collections ($n = 2645$ for PHQ-9; $n = 2821$ for major and minor or major depressive episode)								
<15 mg/24 h	Reference		Reference		Reference		Reference	
15–<30 mg/24 h	1.23 (1.07–1.42)	0.005	2.04 (1.13–3.70)	0.02	1.84 (1.00–3.36)	0.05	1.76 (1.06–2.91)	0.03
≥30 mg/24 h	1.31 (1.11–1.54)	0.001	1.88 (0.98–3.59)	0.06	1.82 (0.97–3.42)	0.06	1.92 (1.14–3.22)	0.01

Ratios represent the ratio of the depressive symptom score when compared with participants with UAE <15 mg/24 h. ORs represent the odds of having clinically relevant depressive symptoms, a major depressive episode, and a minor or major depressive episode, respectively, relative to the odds in participants with UAE <15 mg/24 h. Model 5a: age, sex, educational level, marital status, comorbid disease, glucose metabolism status, waist circumference, total:HDL cholesterol ratio, triglycerides, the use of lipid-modifying medication, smoking behavior, alcohol consumption, $eGFR_{crcys}$, office systolic pressure, the use of antihypertensive medication, prevalent cardiovascular disease.

individuals with two valid urine collections (Table 4) or when results were additionally adjusted for total or moderate to vigorous physical activity, the MMSE score or information processing speed (Tables 4 and 5). Analyses of the associations of albuminuria and $eGFR_{crcys}$ with somatic and affective subscores of the PHQ-9 showed that albuminuria was associated with both a higher affective and somatic symptom score, although the association of UAE ≥30 mg/24 h with affective symptoms was not statistically significant after adjustment for lifestyle factors and CVD risk factors. $eGFR_{crcys}$ was associated with neither subscore (data not shown). When we included antidepressant use in our definition of major depressive episode and minor or major depressive episode, UAE 15–<30 mg/24 h and ≥30 mg/24 h remained associated with both major depressive episode and minor or major depressive episode, although the strength of the associations was attenuated and the association of UAE ≥30 mg/24 h with major depressive episode was no longer statistically significant after adjustment for lifestyle factors and CVD risk factors. $eGFR_{crcys}$ was not associated with the alternative definitions of depressive episode (data not shown).

Table 5. Additional analyses of the associations of $eGFR_{crcys}$ with depressive symptoms and depressive episodes

PHQ-9		Clinically relevant depressive symptoms (PHQ-9 ≥ 10)		Major depressive episode		Minor or major depressive episode	
Ratio (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Model 5a + total physical activity ($n = 2686$ for PHQ-9; $n = 2704$ for major and minor or major depressive episode)							
0.97 (0.94–1.00)	0.08	1.00 (0.86–1.16)	0.98	0.98 (0.82–1.16)	0.79	0.99 (0.86–1.14)	0.90
Model 5a + moderate to vigorous physical activity ($n = 2685$ for PHQ-9; $n = 2703$ for major and minor or major depressive episode)							
0.97 (0.93–1.00)	0.06	0.99 (0.85–1.16)	0.93	0.97 (0.82–1.15)	0.74	0.99 (0.86–1.13)	0.84
Model 5a + MMSE ($n = 2865$ for PHQ-9; $n = 3081$ for major and minor or major depressive episode)							
0.98 (0.95–1.02)	0.31	0.99 (0.85–1.14)	0.85	1.02 (0.89–1.18)	0.78	1.01 (0.89–1.14)	0.91
Model 5a + information processing speed ($n = 2818$ for PHQ-9; $n = 3029$ for major and minor or major depressive episode)							
0.98 (0.95–1.01)	0.24	0.98 (0.84–1.14)	0.77	1.01 (0.87–1.17)	0.93	1.00 (0.89–1.13)	0.99

Ratios represent the ratio of the depressive symptom score per 10 mL/min/1.73 m^2 $eGFR_{crcys}$. ORs represent the relative difference in the odds of having clinically relevant depressive symptoms, a major depressive episode, and a minor or major depressive episode, respectively, per 10 mL/min/1.73 m^2 lower $eGFR_{crcys}$. Model 5a: age, sex, educational level, marital status, comorbid disease, glucose metabolism status, waist circumference, total:HDL cholesterol ratio, triglycerides, the use of lipid-modifying medication, smoking behavior, alcohol consumption, UAE (categorical), office systolic pressure, the use of antihypertensive medication, prevalent cardiovascular disease.

DISCUSSION

To our knowledge, this study is the first to examine whether albuminuria and eGFR are, independent of each other, associated with depression in a population-based setting. It had two main findings. First, albuminuria was associated with both self-reported depressive symptoms and minor or major depressive episode after adjustment for demographic variables, comorbidity, lifestyle factors and CVD risk factors (including eGFR), even at levels of UAE that do not fulfil the CKD criteria. Second, eGFR was neither associated with depressive symptoms nor with minor or major depressive episode in this cohort without substantial CKD.

The results of this study contrast with a study in individuals with CKD [11], which showed no independent association between albuminuria and depressive symptoms. However, its participants were selected for the presence of CKD based on eGFR values [11], whereas most participants in the present population-based study had normal or mildly reduced eGFR. The higher burden of symptoms of CKD and comorbid disease [11] may have reduced the contrast between participants with higher and lower albuminuria levels. In another study, albuminuria was only borderline statistically significantly associated with depressive symptoms in individuals with DM without CVD but not with CVD [10]. However, a large proportion had poor glycaemic control, and its complications may have been classified erroneously as depressive symptoms.

Generalized endothelial dysfunction may explain the association between albuminuria and depression. According to this concept, microvascular endothelial dysfunction in the kidney causes albuminuria [12, 13], whereas in the brain it causes cSVD [14]. According to the vascular depression hypothesis [5, 6], the latter may lead to depression through disruption of neuronal circuits involved in mood regulation in fronto-limbic brain areas [5, 6]. Indeed, albuminuria has been associated with magnetic resonance imaging findings of cSVD [47] and cSVD has been associated with incident depressive symptoms [48, 49]. In addition, studies showing an association of (plasma) biomarkers of endothelial dysfunction with depressive symptoms [50] and minor or major depressive episode [51] indirectly support this view. However, we cannot rule out reverse causation. Indeed, depressive symptoms [52] and major depressive episode [2, 53] have been associated with a higher risk of end-stage renal disease [2, 52, 53]. This may also be true for albuminuria, e.g. through the adoption of an unhealthy lifestyle and poor treatment adherence [54, 55]. However, adiposity, smoking behavior, alcohol consumption and physical activity did not explain the reported associations.

The non-linear association of albuminuria with depression contrasts with the reported linear associations of (plasma) biomarkers of endothelial dysfunction with depressive symptoms [50] and minor or major depressive episode [51]. Selective non-participation of individuals with depression and UAE ≥30 mg/24 h due to a higher comorbid disease burden in these individuals [46, 56] (i.e. incidence–prevalence bias [57]) could account for the non-linearity. Furthermore, the small number of cases with depression limited power and the 95% CIs do not exclude a linear association.

Importantly, the association of albuminuria with depression is not likely due to misclassification of somatic symptoms of comorbid disease, as albuminuria was associated with both self-reported depressive symptoms and an interview-based diagnosis of minor or major depressive episode. Furthermore, we adjusted for comorbid disease and albuminuria was related to affective as well as somatic depressive symptoms.

A lack of power probably explains why the association of UAE ≥30 mg/24 h with major depressive episode was borderline statistically significant, whereas it was statistically significant for minor and major depressive episode combined. Minor and major depressive episodes are part of a continuum of mood disorders, differing only in the number of depressive symptoms [58]. Indeed, lower quality of life, more disability, higher health care consumption and, although not consistently, increased mortality in individuals with a minor depressive episode [58] point to its clinical importance.

In contrast, the inclusion of individuals who only had an early onset major depressive episode may have attenuated the association between albuminuria and depression when antidepressant use was included in our definition of depression. Early

and late-onset depression may have different causes [59] and cerebrovascular disease is more likely involved in late-onset depression [60]. In addition, antidepressants may have been prescribed for indications other than depression, e.g. neuropathic pain, leading to misclassification of depression status.

In this study without substantial CKD, eGFR was not associated with depression. However, this study was underpowered to comment on the association of eGFR <60 mL/min/1.73 m^2 with depression. Nevertheless, when combined with the results of other studies on the association of eGFR with depression [11, 17–29], eGFR seems not to be associated with depression until it is moderately toseverely reduced.

An important strength of this study was the assessment of albuminuria with 24-h urine collections and the assessment of eGFR based on creatinine and cystatin C. Another strength was the evaluation of an interview-based diagnosis of DSM-IV minor or major depressive episode, which reduced the risk of misclassification of symptoms of somatic diseases as depressive symptoms [1]. In addition, the elaborate clinical characterization of the study participants allowed for extensive adjustment for potential confounders, including 24-h average ambulatory blood pressure. However, some limitations of this study should be considered. First, the cross-sectional design limited causal inferences. Second, even though we adjusted for an extensive series of potential confounders, we cannot fully exclude residual confounding. For example, we had no data on polymorphisms of the renin–angiotensin system [60, 61] or activity of the hypothalamic–pituitary–adrenal axis [62, 63]. Third, the exclusion of participants with missing data may have led to an underestimation of the examined associations if those with a higher UAE or reduced eGFR and concomitant (severe) depression were selectively excluded. Fourth, we had no data on the use of non-pharmacological treatments of depression, which may have been applied successfully in some participants and could have led to an underestimation of the association of eGFR and albuminuria with depression. Fifth, the study population was recruited from a single region in The Netherlands and primarily consisted of Caucasian individuals of European descent (98.6%), which may limit generalizability to other ethnic and racial groups.

In conclusion, albuminuria was associated with depressive symptoms and minor or major depressive episode, even at levels of UAE that do not fulfil the CKD criteria. Future longitudinal studies should examine the direction of this association and whether albuminuria could serve as a biomarker to identify individuals at risk of depression.

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CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or in part, except in abstract format.

REFERENCES

1. Palmer S, Vecchio M, Craig JC *et al.* Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. *Kidney Int* 2013; 84: 179–191
2. Hedayati SS, Minhajuddin AT, Afshar M *et al.* Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. *JAMA* 2010; 303: 1946–1953
3. Palmer SC, Vecchio M, Craig JC *et al.* Association between depression and death in people with CKD: a meta-analysis of cohort studies. *Am J Kidney Dis* 2013; 62: 493–505
4. Makin SD, Cook FA, Dennis MS *et al.* Cerebral small vessel disease and renal function: systematic review and meta-analysis. *Cerebrovasc Dis* 2015; 39: 39–52
5. Alexopoulos GS, Meyers BS, Young RC *et al.* 'Vascular depression' hypothesis. *Arch Gen Psychiatry* 1997; 54: 915–922
6. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. *Am J Psychiatry* 1997; 154: 497–501
7. De Deyn PP, Vanholder R, Eloot S *et al.* Guanidino compounds as uremic (neuro)toxins. *Semin Dial* 2009; 22: 340–345
8. Kimmel PL. Depression in patients with chronic renal disease: what we know and what we need to know. *J Psychosom Res* 2002; 53: 951–956
9. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150
10. Katon WJ, Lin EH, Russo J *et al.* Cardiac risk factors in patients with diabetes mellitus and major depression. *J Gen Intern Med* 2004; 19: 1192–1199
11. Fischer MJ, Xie D, Jordan N *et al.* Factors associated with depressive symptoms and use of antidepressant medications among participants in the Chronic Renal Insufficiency Cohort (CRIC) and Hispanic-CRIC Studies. *Am J Kidney Dis* 2012; 60: 27–38

12. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K *et al.* Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 1989; 32: 219–226
13. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. *J Am Soc Nephrol* 2006; 17: 2106–2111
14. Wardlaw JM, Sandercock PA, Dennis MS *et al.* Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? *Stroke* 2003; 34: 806–812
15. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC *et al.* Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; 375: 2073–2081
16. Stam F, van Guldener C, Becker A *et al.* Endothelial dysfunction contributes to renal function-associated cardiovascular mortality in a population with mild renal insufficiency: the Hoorn Study. *J Am Soc Nephrol* 2006; 17: 537–545
17. Shidler NR, Peterson RA, Kimmel PL. Quality of life and psychosocial relationships in patients with chronic renal insufficiency. *Am J Kidney Dis* 1998; 32: 557–566
18. Hedayati SS, Jiang W, O'Connor CM *et al.* The association between depression and chronic kidney disease and mortality among patients hospitalized with congestive heart failure. *Am J Kidney Dis* 2004; 44: 207–215
19. Odden MC, Whooley MA, Shlipak MG. Depression, stress, and quality of life in persons with chronic kidney disease: the Heart and Soul Study. *Nephron Clin Pract* 2006; 103: c1–c7
20. Cohen SD, Patel SS, Khetpal P *et al.* Pain, sleep disturbance, and quality of life in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2007; 2: 919–925
21. Abdel-Kader K, Unruh ML, Weisbord SD. Symptom burden, depression, and quality of life in chronic and end-stage kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1057–1064
22. Fischer MJ, Kimmel PL, Greene T *et al.* Sociodemographic factors contribute to the depressive affect among African Americans with chronic kidney disease. *Kidney Int* 2010; 77: 1010–1019
23. Ricardo AC, Fischer MJ, Peck A *et al.* Depressive symptoms and chronic kidney disease: results from the National Health and Nutrition Examination Survey (NHANES) 2005–2006. *Int Urol Nephrol* 2010; 42: 1063–1068
24. Minev E, Unruh M, Shlipak MG *et al.* Association of cystatin C and depression in healthy elders: the health, aging and body composition study. *Nephron Clin Pract* 2010; 116: c241–c246
25. McClellan WM, Abramson J, Newsome B *et al.* Physical and psychological burden of chronic kidney disease among older adults. *Am J Nephrol* 2010; 31: 309–317
26. Kop WJ, Seliger SL, Fink JC *et al.* Longitudinal association of depressive symptoms with rapid kidney function decline and adverse clinical renal disease outcomes. *Clin J Am Soc Nephrol* 2011; 6: 834–844
27. Campbell KH, Huang ES, Dale W *et al.* Association between estimated GFR, health-related quality of life, and depression among older adults with diabetes: the Diabetes and Aging Study. *Am J Kidney Dis* 2013; 62: 541–548
28. Hedayati SS, Minhajuddin AT, Toto RD *et al.* Prevalence of major depressive episode in CKD. *Am J Kidney Dis* 2009; 54: 424–432
29. Kalender B, Ozdemir AC, Koroglu G. Association of depression with markers of nutrition and inflammation in chronic kidney disease and end-stage renal disease. *Nephron Clin Pract* 2006; 102: c115–c121
30. Schram MT, Sep SJ, van der Kallen CJ *et al.* The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *Eur J Epidemiol* 2014; 29: 439–451
31. Inker LA, Schmid CH, Tighiouart H *et al.* Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; 367: 20–29
32. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16: 606–613
33. Smolderen KG, Spertus JA, Reid KJ *et al.* The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2009; 2: 328–337
34. Janssen EP, Köhler S, Stehouwer CD *et al.* The PHQ-9 as a screening tool for depression in type 2 diabetes mellitus: The Maastricht Study. *J Am Geriatr Soc* 2016; Accepted for publication
35. Sheehan DV, Lecrubier Y, Sheehan KH *et al.* The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59(Suppl 20): 22–33, quiz 34–57
36. Martens RJ, Kooman JP, Stehouwer CD *et al.* Estimated GFR, albuminuria, and cognitive performance: the Maastricht Study. *Am J Kidney Dis* 2016
37. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. 2006. http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf (December 2015, last date accessed)
38. De Bie SE. *Standaardvragen 1987: Voorstellen voor uniformering van vraagstellingen naar achtergrondkenmerken en interviews [Standard questions 1987: Proposal for uniformization of questions regarding background variables and interviews]*. Leiden, The Netherlands: Leiden University Press, 1987
39. Spauwen PJ, van Eupen MG, Kohler S *et al.* Associations of advanced glycation end-products with cognitive functions in individuals with and without type 2 diabetes: the Maastricht Study. *J Clin Endocrinol Metab* 2015; 100: 951–960
40. Stewart AL, Mills KM, King AC *et al.* CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med Sci Sports Exerc* 2001; 33: 1126–1141
41. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–198
42. Van der Elst W, Van Boxtel MP, Van Breukelen GJ *et al.* The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment* 2006; 13: 62–79
43. Van der Elst W, Van Boxtel MP, Van Breukelen GJ *et al.* The Concept Shifting Test: adult normative data. *Psychol Assess* 2006; 18: 424–432
44. van der Elst W, van Boxtel MP, van Breukelen GJ *et al.* The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24–81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex. *J Clin Exp Neuropsychol* 2006; 28: 998–1009
45. Sachdev PS, Parslow RA, Lux O *et al.* Relationship of homocysteine, folic acid and vitamin B12 with depression in a middle-aged community sample. *Psychol Med* 2005; 35: 529–538
46. Hillege HL, Janssen WM, Bak AA *et al.* Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med* 2001; 249: 519–526
47. Wada M, Nagasawa H, Kurita K *et al.* Microalbuminuria is a risk factor for cerebral small vessel disease in community-based elderly subjects. *J Neurol Sci* 2007; 255: 27–34
48. Godin O, Dufouil C, Maillard P *et al.* White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study. *Biol Psychiatry* 2008; 63: 663–669
49. van Sloten TT, Sigurdsson S, van Buchem MA *et al.* Cerebral small vessel disease and association with higher incidence of depressive symptoms in a general elderly population: the AGES-Reykjavik study. *Am J Psychiatry* 2015; 172: 570–578
50. van Sloten TT, Schram MT, Adriaanse MC *et al.* Endothelial dysfunction is associated with a greater depressive symptom score in a general elderly population: the Hoorn Study. *Psychol Med* 2014; 44: 1403–1416
51. Lesperance F, Frasure-Smith N, Theroux P *et al.* The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. *Am J Psychiatry* 2004; 161: 271–277
52. Tsai YC, Chiu YW, Hung CC *et al.* Association of symptoms of depression with progression of CKD. *Am J Kidney Dis* 2012; 60: 54–61
53. Yu MK, Weiss NS, Ding X *et al.* Associations between depressive symptoms and incident ESRD in a diabetic cohort. *Clin J Am Soc Nephrol* 2014; 9: 920–928
54. Ziegelstein RC, Fauerbach JA, Stevens SS *et al.* Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch Intern Med* 2000; 160: 1818–1823
55. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med* 2000; 160: 3278–3285
56. Bello AK, Hemmelgarn B, Lloyd A *et al.* Associations among estimated glomerular filtration rate, proteinuria, and adverse cardiovascular outcomes. *Clin J Am Soc Nephrol* 2011; 6: 1418–1426

57. Delgado-Rodriguez M, Bias Llorca J. Bias. *J Epidemiol Community Health* 2004; 58: 635–641
58. Meeks TW, Vahia IV, Lavretsky H *et al.* A tune in "A minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *J Affect Disord* 2011; 129: 126–142
59. Pedersen CB, Mors O, Bertelsen A *et al.* A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry* 2014; 71: 573–581
60. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry* 2013; 18: 963–974
61. Ruggenenti P, Bettinaglio P, Pinares F *et al.* Angiotensin converting enzyme insertion/deletion polymorphism and renoprotection in diabetic and non-diabetic nephropathies. *Clin J Am Soc Nephrol* 2008; 3: 1511–1525
62. Broadley AJ, Korszun A, Abdelaal E *et al.* Metyrapone improves endothelial dysfunction in patients with treated depression. *J Am Coll Cardiol* 2006; 48: 170–175
63. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med* 2008; 358: 55–68

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ORIGINAL ARTICLE

Nationwide multicentre kidney biopsy study of Japanese patients with type 2 diabetes

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ABSTRACT

Background. The clinical and pathologic manifestations of nephropathy due to type 2 diabetes are diverse, but large-scale pathologic studies with long-term observations are limited.

Methods. Kidney biopsies and clinical data of 600 patients with type 2 diabetes were collected retrospectively from 13 centres across Japan. Thirteen pathologic findings (nine glomerular lesions, two interstitial lesions and two vascular lesions) were clearly defined and scored.