Research Square

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Depressive symptoms and subsequent decline in kidney function in a large community-based prospective cohort study

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Abstract

Background

Depressive symptoms are associated with adverse health outcomes; however, their association with subsequent decline in kidney function in individuals without CKD remains unclear. We aimed to examine this association in a prospective cohort study of a community-based Japanese population without CKD at baseline.

Methods

We analyzed the data from the Miyagi Cohort of the Tohoku Medical Megabank Community-Based Cohort Study and included 20,584 participants with an estimated glomerular filtration rate (eGFR) of 60–119 mL/min/1.73 m² and a urinary albumin level < 30 mg/gCr at baseline. The exposure of interest was depressive symptoms at baseline. The primary outcome was incident eGFR < 60 mL/min/1.73 m² at the second survey (incident eGFR < 60). Odds ratios and 95% confidence intervals were estimated. As a secondary analysis, the association between depressive symptoms and longitudinal change in eGFR was examined using generalized estimating equations.

Results

Among the 20,584 participants, 4,997 had depressive symptoms. Compared with the non-depressive group, participants with depressive symptoms were younger and more likely to be female. Over a median follow-up period of approximately 4.0 years, incident eGFR < 60 was observed in 1,152 (5.6%) participants, including 288 (5.8%) participants in the depressive symptoms group and 864 (5.5%) participants in the non-depressive group. Depressive symptoms were significantly associated with incident eGFR < 60 after multivariable adjustment (fully adjusted OR 1.26, 95% CI, 1.08–1.47; P = 0.003). In the secondary analysis, depressive symptoms were also associated with longitudinal change in eGFR (fully adjusted β = −0.08 mL/min/1.73 m² per year; 95% CI, − 0.15 to − 0.01; *P* = 0.02), although the effect size was small.

Conclusions

Depressive symptoms were associated with incident eGFR < 60 mL/min/1.73 m^2 and a modest longitudinal decline in eGFR in individuals without CKD at baseline in a Japanese community-based population. These findings suggest that depressive symptoms may serve as a risk marker for future kidney function decline.

Background

CKD is a major public health concern and is highly prevalent worldwide. The prevalence of CKD is 14.2% worldwide and 15.6% in Japan.[1] CKD is associated with an increased risk of cardiovascular diseases (CVDs) and mortality.[1,2] In particular, progression to end-stage kidney disease imposes substantial

healthcare and economic burdens.[3] Therefore, identifying risk factors associated with kidney function decline and preventing CKD onset are important public health priorities. Established risk factors, including hypertension, diabetes mellitus, and obesity, are the primary targets of current prevention strategies.[1,4]

Depressive symptoms are a common comorbidity in patients with CKD. Approximately one-quarter of patients with CKD experience depression or depressive symptoms.[5,6] The prevalence of depressive symptoms also increases with declining kidney function.[7] Moreover, depressive symptoms in patients with CKD are associated with adverse clinical outcomes, including dialysis initiation, hospitalization, all-cause mortality, and CKD progression.[8–10]

Several behavioral and biological mechanisms have been proposed to explain this association. Behavioral pathways include less engagement in health-promoting behaviors and poorer treatment adherence, whereas biological pathways involve inflammation, hypothalamic–pituitary–adrenal axis dysregulation, and autonomic nervous system dysfunction.[11–16] These mechanisms suggest that depressive symptoms may contribute to kidney function decline. However, most previous studies have focused on patients with established CKD, making the temporal association between depressive symptoms and CKD progression difficult to determine.

Evidence regarding the association between depressive symptoms and subsequent kidney function decline in individuals without CKD remains limited. Although studies, including analyses of the China Health and Retirement Longitudinal Study (CHARLS), have reported associations between depressive symptoms and kidney function decline in community-based populations with normal kidney function,[17,18] prospective evidence is limited, particularly outside Chinese populations.

Given the high prevalence of depressive symptoms in the general population, clarifying the association between depressive symptoms and kidney function decline is important. If depressive symptoms are associated with subsequent kidney function decline, they may serve as an early risk marker for identifying individuals at high risk of CKD. We therefore investigated whether baseline depressive symptoms are associated with incident estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 in a Japanese community-based population without CKD at baseline. We hypothesized that depressive symptoms would be associated with an increased risk of incident eGFR < 60 mL/min/1.73 m^2 independent of demographic, socioeconomic, lifestyle, and clinical factors. We also examined longitudinal eGFR change as a secondary outcome.

Methods

Study population

This observational cohort study used data from the Miyagi Cohort of the Tohoku Medical Megabank Project Community-Based Cohort Study, which enrolled residents of Miyagi Prefecture, northeastern

Japan. The baseline survey was conducted between May 2013 and March 2016 in individuals aged ≥ 20 years.[19,20] A total of 51,850 participants were enrolled in the baseline survey, of whom 50,923 had baseline data available for these analyses.

Participants were recruited using two main approaches. Type 1 surveys were conducted at annual municipal health checkup sites, whereas type 2 surveys were conducted at seven Community Support Centers established by the Tohoku Medical Megabank Organization of Tohoku University across Miyagi Prefecture. In both survey types, participants underwent basic assessments, including blood and urine tests and self-administered questionnaires on psychological status, socioeconomic conditions, lifestyle factors, and medical history, as previously described in the TMM CommCohort study.[20]

A second detailed follow-up survey was conducted at the Community Support Centers between June 2017 and March 2021. A total of 29,383 participants completed the second survey, and 29,347 participants had follow-up data available for these analyses.[21] This study included participants with both baseline and follow-up data who met the predefined eligibility criteria.

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki and was approved by the Institutional Review Board of the Tohoku Medical Megabank Organization (first approval No. 2012-4-617; latest approval No. 2026-4-065). All participants provided written informed consent before their participation in this study. The reporting followed the STROBE guidelines.

Exclusion criteria

We excluded participants with missing serum creatinine or urinary albumin data at baseline and those with incomplete responses to the Center for Epidemiologic Studies Depression Scale (CES-D).

To restrict the analysis to individuals without evidence of CKD at baseline, participants with an eGFR < 60 mL/min/1.73 m² or urinary albumin level ≥ 30 mg/gCr were excluded in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

We further excluded participants with a history of dialysis, those with unknown dialysis status, and those with extremely high eGFR values (≥ 120 mL/min/1.73 m²). Additionally, participants with missing serum creatinine data at the second survey were excluded.

Assessment of depressive symptoms

Depressive symptoms were assessed at baseline using the self-administered CES-D. The CES-D consists of 20 items, each scored from 0 to 3, yielding a total score ranging from 0 to 60. A total score of ≥ 16 indicated clinically relevant depressive symptoms.[22] The CES-D has demonstrated validity and reliability in general and Japanese populations.[23]

Outcome assessment

The primary outcome was incident eGFR < 60 mL/min/1.73 m² at the second survey (incident eGFR < 60). An eGFR < 60 mL/min/1.73 m² is used as a threshold for kidney dysfunction consistent with CKD in the KDIGO guidelines. eGFR was calculated from serum creatinine levels using a Japanese-specific equation.[24]

For the secondary outcome, longitudinal eGFR change was assessed using eGFR measurements obtained at baseline and the second survey.

Covariates

Prespecified covariates included baseline demographic characteristics, socioeconomic factors, lifestyle factors, and established risk factors for CKD.

Sex was defined as biological sex. It was obtained from the questionnaire (self-reported) and confirmed using official municipal records. Both sources showed complete agreement.

Covariates included sex, age (< 30, 30–39, 40–49, 50–59, 60–69, ≥ 70 years), baseline eGFR (continuous), marital status (married, never married, divorced, widowed, unknown), living alone (no, yes, unknown), employment status (employed, not employed, unknown), educational attainment (junior college or higher, high school or vocational school, junior high school or less, unknown), smoking status (never, former, current, unknown), alcohol consumption (never, former, current, unknown), leisure-time physical activity (< 1 time/month, ≥ 1 time/month but not daily, daily, unknown), hypertension, diabetes mellitus, dyslipidemia, CVD, hypothyroidism, and periodontal disease (each present/absent), body mass index (BMI) (< 18.5, 18.5–24.9, ≥ 25.0 kg/m², unknown), and hemoglobin (Hb) (low, intermediate, high, unknown).

Leisure-time physical activity was assessed based on self-reported frequency of light physical activities, such as walking.

Histories of hypertension, diabetes mellitus, and dyslipidemia were determined from questionnaire responses indicating whether participants had previously been informed of these conditions and their subsequent management status. Histories of CVD, hypothyroidism, periodontal disease, and depression were based on self-administered questionnaires and considered self-reported medical histories.

Hb levels were categorized into sex-specific tertiles as low, intermediate, and high based on their distributions in the study population, with missing values classified as unknown.

Missing information was present for hypertension (11%), diabetes (18%), and dyslipidemia (14%), whereas missingness for CVD, hypothyroidism, and periodontal disease was < 0.5%. For all comorbidity variables, participants with missing comorbidity data were categorized as not having the condition.

Statistical analyses

Continuous variables were presented as means (standard deviations) or medians (interquartile ranges), whereas categorical variables were presented as numbers (percentages).

In the primary analysis, the association between depressive symptoms at baseline and incident eGFR < 60 was assessed using multivariable logistic regression models. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

We constructed four models. The crude model was unadjusted. Model 1 was adjusted for age, sex, and baseline eGFR. Model 2 was further adjusted for socioeconomic factors (marital status, living alone, employment status, and educational attainment). Model 3 additionally included lifestyle factors (smoking status, alcohol consumption, and leisure-time physical activity). Model 4 was further adjusted for comorbidities and clinical factors (hypertension, diabetes mellitus, dyslipidemia, CVD, hypothyroidism, periodontal disease, BMI, and Hb level).

For the secondary analysis, generalized estimating equations (GEEs) with an exchangeable correlation structure were used to assess the association between baseline depressive symptoms and longitudinal eGFR change. eGFR measurements obtained at baseline and the second survey were analyzed as repeated measures, with follow-up time (years since baseline) modeled as a time variable. An interaction term between depressive symptoms and time was included in the model. The coefficient for the interaction term represented the difference in the annual rate of eGFR change by depressive symptom status. The covariates included in Models 1–4 corresponded to those used in the primary analysis, except for baseline eGFR.

We performed additional analyses to assess the robustness and consistency of the findings.

Stratified analyses according to baseline eGFR categories (60–69, 70–79, 80–89, and ≥ 90 mL/min/1.73 m^2) were performed to evaluate heterogeneity across baseline kidney function levels.

Sensitivity analyses were performed with alternative outcome definitions and populations. First, among participants with available eGFR and urinary albumin measurements at the second survey, incident CKD was operationally defined as eGFR < 60 mL/min/1.73 m^2 and/or urinary albumin level ≥ 30 mg/gCr at the second survey. Second, analyses excluding participants with a history of depression at baseline were performed to evaluate whether the observed association was influenced by pre-existing depression or its treatment.

Exploratory stratified analyses were also performed by hypertension and diabetes mellitus status, defined using treatment status and objective clinical measurements. Hypertension was defined as self-reported treatment for hypertension and/or systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus was defined as self-reported treatment for diabetes mellitus and/or hemoglobin A1c ≥ 6.5%. Because hypertension and diabetes mellitus are major risk factors for

kidney function decline, and the primary analyses adjusted for self-reported hypertension and diabetes mellitus, these analyses were performed to evaluate whether the observed association remained consistent when these conditions are defined using treatment status and objective clinical measurements. In these stratified analyses, self-reported hypertension and diabetes mellitus were excluded from the covariates in the fully adjusted model. Interaction terms were tested to assess effect modification.

Sex-stratified analyses were also performed to examine potential sex differences in depressive symptoms and kidney function decline. Interaction terms were tested to assess effect modification.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All analyses were two-sided, and *P* values < 0.05 were considered statistically significant.

Use of generative artificial intelligence

ChatGPT (OpenAI) was used to assist with language refinement and manuscript organization. All AI-assisted content was reviewed and verified by the authors, who take full responsibility for the final content. ChatGPT was not used for data analysis.

Results

Study participants

Of the 50,923 baseline participants, 29,347 had data from both the baseline and second surveys. Participants with missing serum creatinine, urinary albumin, or CES-D data at baseline were excluded. We further excluded those with baseline eGFR < 60 or ≥ 120 mL/min/1.73 m², urinary albumin level ≥ 30 mg/gCr, a history of dialysis, or an unknown dialysis history. In addition, participants with missing serum creatinine data at the second survey were excluded. Ultimately, 20,584 participants were included in the analysis (Fig. 1).

Flowchart showing participant inclusion and exclusion from the Tohoku Medical Megabank Community-Based Cohort. TMM, Tohoku Medical Megabank; CES-D, Center for Epidemiologic Studies Depression Scale; eGFR, estimated glomerular filtration rate. After the eligibility criteria were applied, 20,584 participants were included in the final analysis.

Among the 20,584 participants, 15,587 had no depressive symptoms (CES-D score < 16) and 4,997 had depressive symptoms (CES-D score ≥ 16).

The median follow-up interval between baseline and the second survey was 4.0 (interquartile range, 3.4–4.5) years.

Baseline characteristics

Baseline characteristics are shown in Table 1. Compared with participants without depressive symptoms, those with depressive symptoms were younger (55.8 vs. 59.1 years) and more likely to be female (76.8% vs. 65.8%). Participants with depressive symptoms were more often current smokers and less often former smokers. They were also less often current drinkers and were more often abstainers. For leisure-time physical activity, they more often reported no or infrequent activity and less often reported almost-daily activity.

Table 1
Baseline characteristics of participants according to the presence or absence of depressive symptoms

Characteristic	Total (n = 20 584)	Depressive symptoms (CES-D)	
		(-) (n = 15 587)	(+) (n = 4 997)
Mean age, years, mean ± SD	58.3 ± 12.0	59.1 ± 11.6	55.8 ± 12.7
Female, n (%)	14 094 (68.5)	10 255 (65.8)	3 839 (76.8)
BMI			
< 18.5 kg/m², n (%)	1 300 (6.3)	930 (6.0)	370 (7.4)
≥ 18.5 and < 25 kg/m², n (%)	14 646 (71.2)	11 219 (72.0)	3 427 (68.8)
≥ 25 kg/m², n (%)	4 571 (22.2)	3 388 (21.7)	1 183 (23.7)
Unknown, n (%)	67 (0.3)	50 (0.3)	17 (0.3)
Smoking status			
Current, n (%)	2 186 (10.6)	1 572 (10.1)	614 (12.3)
Past, n (%)	5 033 (24.5)	3 996 (25.6)	1 037 (20.8)
Never, n (%)	13 216 (64.2)	9 917 (63.6)	3 299 (66.0)
Unknown, n (%)	149 (0.7)	102 (0.7)	47 (0.9)
Alcohol consumption			
Current, n (%)	11 191 (54.4)	8 733 (56.0)	2 458 (49.2)
Past, n (%)	469 (2.3)	308 (2.0)	161 (3.2)
Never, n (%)	8 882 (43.2)	6 517 (41.8)	2 365 (47.3)
Unknown, n (%)	42 (0.2)	29 (0.2)	13 (0.3)
Leisure-time physical activity			
< 1 time/month, n (%)	8 666 (42.1)	6 432 (41.3)	2 234 (44.7)
≥ 1 time/month but not daily, n (%)	7 947 (38.6)	5 984 (38.4)	1 963 (39.3)

Depressive symptoms (+) was defined as a CES-D score ≥ 16. Depressive symptoms (-) was defined as a CES-D score < 16. Values are presented as mean ± SD, median (interquartile range), or n (%). Comorbidities were assessed by self-report at baseline.

eGFR was calculated using a creatinine-based equation. Hemoglobin tertiles were defined separately for men and women based on their distributions. The cutoff values (g/dL) were as follows: men, T1 < 14.5, T2 14.5–15.4, T3 ≥ 15.4; women, T1 < 12.9, T2 12.9–13.7, T3 ≥ 13.7. Missing values were minimal for most variables (< 1%), except for hypertension (11%), diabetes mellitus (18%), and dyslipidemia (14%). BMI, body mass index; BUN, blood urea nitrogen; CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c: hemoglobin A1c.

Characteristic	Total (n = 20 584)	Depressive symptoms (CES-D)	
		(-) (n = 15 587)	(+) (n = 4 997)
Daily, n (%)	3 088 (15.0)	2 456 (15.8)	632 (12.7)
Unknown, n (%)	883 (4.3)	715 (4.6)	168 (3.4)
Marital status			
Married, n (%)	16 583 (80.6)	12 923 (82.9)	3 660 (73.2)
Never married, n (%)	1 496 (7.3)	919 (5.9)	577 (11.6)
Divorced, n (%)	983 (4.8)	667 (4.3)	316 (6.3)
Widowed, n (%)	1 355 (6.6)	955 (6.2)	400 (8.0)
Unknown, n (%)	167 (0.8)	123 (0.8)	44 (0.9)
Living alone, n (%)	1 417 (6.9)	972 (6.2)	445 (8.9)
Unknown, n (%)	303 (1.5)	209 (1.3)	94 (1.9)
Employment status, not employed, n (%)	9 657 (46.9)	7 365 (47.3)	2 292 (45.9)
Unknown, n (%)	244 (1.2)	176 (1.1)	68 (1.4)
Educational attainment			
Junior high school or less, n (%)	1 723 (8.4)	1 248 (8.0)	475 (9.5)
High school or vocational school, n (%)	13 888 (67.5)	10 463 (67.1)	3 425 (68.5)
Junior college or higher, n (%)	4 779 (23.2)	3 725 (23.9)	1 054 (21.1)
Unknown, n (%)	194 (0.9)	151 (1.0)	43 (0.9)
History of hypertension, n (%)	6 009 (29.2)	4 600 (29.5)	1 409 (28.2)
History of diabetes mellitus, n (%)	2 710 (13.2)	2 048 (13.1)	662 (13.3)
History of dyslipidemia, n (%)	5 446 (26.5)	4 136 (26.5)	1 310 (26.2)
History of CVD, n (%)	479 (2.3)	366 (2.4)	113 (2.3)

Depressive symptoms (+) was defined as a CES-D score ≥ 16. Depressive symptoms (-) was defined as a CES-D score < 16. Values are presented as mean ± SD, median (interquartile range), or n (%). Comorbidities were assessed by self-report at baseline.

eGFR was calculated using a creatinine-based equation. Hemoglobin tertiles were defined separately for men and women based on their distributions. The cutoff values (g/dL) were as follows: men, T1 < 14.5, T2 14.5–15.4, T3 ≥ 15.4; women, T1 < 12.9, T2 12.9–13.7, T3 ≥ 13.7. Missing values were minimal for most variables (< 1%), except for hypertension (11%), diabetes mellitus (18%), and dyslipidemia (14%). BMI, body mass index; BUN, blood urea nitrogen; CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c: hemoglobin A1c.

Characteristic	Total (n = 20 584)	Depressive symptoms (CES-D)	
		(-) (n = 15 587)	(+) (n = 4 997)
History of hypothyroidism, n (%)	392 (1.9)	259 (1.7)	133 (2.7)
History of periodontal disease, n (%)	5 012 (24.3)	3 738 (24.0)	1 274 (25.5)
History of depression, n (%)	672 (3.3)	306 (2.0)	366 (7.3)
History of kidney disease, n (%)	100 (0.5)	74 (0.5)	26 (0.5)
Systolic blood pressure, mmHg, mean ± SD	126.3 ± 17.6	127.0 ± 17.6	124.3 ± 17.3
Diastolic blood pressure, mmHg, mean ± SD	76.3 ± 10.7	76.6 ± 10.7	75.4 ± 10.8
Serum creatinine, mg/dL, mean ± SD	0.67 ± 0.12	0.68 ± 0.12	0.65 ± 0.11
eGFR, mL/min/1.73 m², mean ± SD	78.9 ± 12.0	78.5 ± 11.8	80.3 ± 12.5
Hemoglobin (tertiles)			
T1 (low), n (%)	6 920 (33.7)	5 207 (33.4)	1 713 (34.3)
T2 (intermediate), n (%)	6 939 (33.6)	5 233 (33.6)	1 706 (34.1)
T3 (high), n (%)	6 712 (32.6)	5 139 (33.0)	1 573 (31.5)
Unknown, n (%)	13 (0.1)	8 (0.1)	5 (0.1)
HbA1c, %, mean ± SD	5.5 ± 0.47	5.5 ± 0.47	5.5 ± 0.49
Triglycerides, mg/dL, mean ± SD	103.7 ± 68.7	103.6 ± 68.1	103.9 ± 70.6
Uric acid, mg/dL, mean ± SD	4.9 ± 1.2	4.9 ± 1.2	4.8 ± 1.2
BUN, mg/dL, mean ± SD	14.2 ± 3.5	14.4 ± 3.5	13.7 ± 3.5

Depressive symptoms (+) was defined as a CES-D score ≥ 16. Depressive symptoms (-) was defined as a CES-D score < 16. Values are presented as mean ± SD, median (interquartile range), or n (%). Comorbidities were assessed by self-report at baseline.

eGFR was calculated using a creatinine-based equation. Hemoglobin tertiles were defined separately for men and women based on their distributions. The cutoff values (g/dL) were as follows: men, T1 < 14.5, T2 14.5–15.4, T3 ≥ 15.4; women, T1 < 12.9, T2 12.9–13.7, T3 ≥ 13.7. Missing values were minimal for most variables (< 1%), except for hypertension (11%), diabetes mellitus (18%), and dyslipidemia (14%). BMI, body mass index; BUN, blood urea nitrogen; CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c: hemoglobin A1c.

[Table 1 near here]

Participants with depressive symptoms were less often married and more often never married.

Participants with depressive symptoms also more often reported a history of depression at baseline. They had a slightly higher baseline eGFR (80.3 vs. 78.5 mL/min/1.73 m²), whereas other comorbidities and laboratory measures were generally similar between the two groups (Table 1).

Primary analysis

The association between depressive symptoms at baseline and incident eGFR < 60 at the second survey was assessed using multivariable logistic regression models.

At the second survey, incident eGFR < 60 occurred in 1,152 (5.6%) participants, including 288 (5.8%) participants in the depressive symptoms group and 864 (5.5%) participants in the non-depressive group. In the crude model, no significant association was observed (OR, 1.04; 95% CI, 0.91–1.20; P = 0.56). However, after adjustment for age, sex, and baseline eGFR (Model 1), depressive symptoms were significantly associated with incident eGFR < 60 (OR, 1.32; 95% CI, 1.13–1.53; P < 0.001). This association remained significant after further adjustment for socioeconomic factors (Model 2), lifestyle factors (Model 3), and comorbidities and clinical factors (Model 4: OR, 1.26; 95% CI, 1.08–1.47; P = 0.003) (Table 2).
Model 1: Adjusted for age, sex, and baseline eGFR. Model 2: Model 1 + socioeconomic factors (marital status, living alone, employment status, and educational attainment). Model 3: Model 2 + lifestyle factors (smoking status, alcohol consumption, and leisure-time physical activity). Model 4: Model 3 + comorbidities and clinical factors (hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, hypothyroidism, periodontal disease, body mass index, and hemoglobin). CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

Secondary analysis

In the secondary analysis, GEEs were used to evaluate the association between depressive symptoms and longitudinal eGFR change. The interaction between depressive symptoms and time indicated a significantly faster eGFR decline (fully adjusted β = −0.08 mL/min/1.73 m² per year; 95% CI, − 0.15 to − 0.01; P = 0.02), and estimates were similar across all models (Table 3).

Table 3
Association between depressive symptoms and longitudinal eGFR change using generalized estimating equation models

Model	β (95% CI)	*P*-value
Crude	−0.08 (− 0.15 to − 0.01)	0.02
Model 1	−0.08 (− 0.15 to − 0.01)	0.03
Model 2	−0.08 (− 0.15 to − 0.01)	0.02
Model 3	−0.08 (− 0.15 to − 0.01)	0.02
Model 4	−0.08 (− 0.15 to − 0.01)	0.02

Model 1: Adjusted for age, sex, and baseline eGFR. Model 2: Model 1 + socioeconomic factors (marital status, living alone, employment status, and educational attainment). Model 3: Model 2 + lifestyle factors (smoking status, alcohol consumption, and leisure-time physical activity). Model 4: Model 3 + comorbidities and clinical factors (hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, hypothyroidism, periodontal disease, body mass index, and hemoglobin). Depressive symptoms (-) was used as the reference group. The covariates included in Models 1–4 corresponded to those used in the primary analysis, except for baseline eGFR. CI, confidence interval; eGFR, estimated glomerular filtration rate.

Stratified analyses by baseline kidney function

Stratified analyses by baseline eGFR category showed that point estimates were > 1.0 across all strata, although the strength and precision varied across categories. The association was most evident in participants with a baseline eGFR of 60–69 mL/min/1.73 m2 (Additional file 2, Supplementary Table S1).

Sensitivity analyses

We performed several sensitivity analyses to assess the robustness of the primary findings.

First, among participants with available urinary albumin measurements at the second survey, defining incident CKD as eGFR < 60 mL/min/1.73 m² and/or urinary albumin level ≥ 30 mg/gCr produced results consistent with the primary analysis (Additional file 2, Supplementary Table S2).

Second, excluding participants with a history of depression at baseline did not materially change the results (Additional file 2, Supplementary Table S3).

Hypertension- and diabetes-stratified analyses

Exploratory analyses using objectively defined hypertension and diabetes mellitus included 18,959 participants with available treatment status and clinical measurements. Similar effect estimates were observed in participants without hypertension or diabetes mellitus (adjusted OR, 1.28; 95% CI, 0.997–1.65) and those with hypertension and/or diabetes mellitus (adjusted OR, 1.26; 95% CI, 1.02–1.56), with no significant interaction by hypertension or diabetes mellitus status (P for interaction = 0.72) (Additional file 2, Supplementary Table S4).

Analyses stratified by sex

Sex-stratified analyses were performed. Among men, incident eGFR < 60 occurred in 363 (6.8%) participants in the non-depressive group and 80 (6.9%) participants in the depressive symptoms group. Although the point estimates exceeded 1.0 across adjusted models, the association was not statistically significant in the fully adjusted model (OR, 1.19; 95% CI, 0.90–1.57; P = 0.23).

Among women, incident eGFR < 60 occurred in 501 (4.9%) participants in the non-depressive group and 208 (5.4%) participants in the depressive symptoms group. Depressive symptoms were significantly associated with incident eGFR < 60 in the fully adjusted model (OR, 1.31; 95% CI, 1.09–1.58; P = 0.004).

However, the interaction by sex was not significant (P for interaction = 0.71) (Additional file 2, Supplementary Table S5).

Discussion

In this prospective cohort study in a community-based Japanese population without CKD at baseline, depressive symptoms at baseline were significantly associated with incident eGFR < 60 after adjustment for demographic, socioeconomic, lifestyle, and clinical factors (fully adjusted OR, 1.26; 95% CI, 1.08–1.47).

Our findings are consistent with the CHARLS results, which also reported an association between depressive symptoms and subsequent kidney function decline among adults without CKD despite differences in outcome definitions.[17] Our study extends previous findings by examining a substantially larger Japanese community-based cohort, including a broader age range, evaluating both incident eGFR < 60 mL/min/1.73 m² and longitudinal eGFR change, and confirming the robustness of the findings using an incident CKD definition incorporating reduced eGFR and albuminuria. These results extend previous evidence from East Asian community-based populations and provide additional support for an association between depressive symptoms and subsequent kidney function decline.

Although the crude incidence was similar between groups, adjustment for age, sex, and baseline eGFR strengthened the association. This may reflect negative confounding, because, compared with participants without depressive symptoms, participants with depressive symptoms were younger, more often women, and had slightly higher baseline eGFR, characteristics generally associated with a lower likelihood of incident eGFR < 60 during follow-up. Furthermore, the association persisted after adjustment for established CKD risk factors, suggesting that depressive symptoms may be associated with kidney function decline beyond these measured factors.

In the secondary analysis, depressive symptoms were also associated with longitudinal eGFR change. However, the effect size was small, indicating a modest average difference at the population level. The clinical significance of this finding remains unclear. Studies with repeated measurements are needed.

In the stratified analyses by baseline eGFR, the direction of the association was generally consistent across strata, with point estimates > 1.0 in all baseline eGFR categories. However, CIs were wider in participants with higher baseline eGFR, and the association was most evident in participants with a baseline eGFR of 60–69 mL/min/1.73 m².

Sensitivity analyses yielded similar results with alternative CKD definitions and after excluding participants with a history of depression, supporting the robustness of the findings. Sex-stratified analyses suggested a slightly stronger association among women, although the interaction by sex was not significant.

Several mechanisms may explain the observed association. Depressive symptoms are associated with poorer treatment adherence and other adverse health behaviors.[25,26] Such behavioral changes may

contribute to suboptimal management of CKD risk factors over time. In this study, we adjusted for several lifestyle-related factors, including smoking and physical activity. However, these factors may also lie on the causal pathway between depressive symptoms and kidney function decline. Thus, adjustment for these variables may have attenuated the observed association and resulted in underestimation of the total effect of depressive symptoms.

In exploratory analyses using objectively defined hypertension and diabetes mellitus, similar effect estimates were observed regardless of hypertension or diabetes mellitus status. These findings suggest that the observed association may not be explained solely by pathways related to the management of hypertension or diabetes mellitus and that other mechanisms may also contribute. However, because these analyses were exploratory, this interpretation is hypothesis-generating.

Biological pathways may also contribute to the observed association. Depressive symptoms are associated with increased inflammation,[12–14] dysregulation of the hypothalamic–pituitary–adrenal axis,[15] and autonomic nervous system dysfunction, including sympathetic overactivity.[16] These alterations may contribute to kidney function decline through endothelial dysfunction and hemodynamic changes. These mechanisms have also been implicated in cardiovascular events in the general population[27] and microvascular complications in patients with diabetes.[28] Previous studies have reported associations between inflammatory markers and CKD incidence and progression,[29,30] providing further support for these proposed mechanisms. However, these mechanisms were not directly examined in this study.

Our findings may have public health implications. CKD imposes a major population burden, and depressive symptoms are common and can be assessed in primary care and community health settings. Therefore, even a modest increase in CKD risk associated with depressive symptoms may have a meaningful impact at the population level. Because depressive symptoms are potentially modifiable, integrating mental health assessment into CKD prevention and early detection strategies may offer a practical and scalable approach. Additionally, the community-based nature of our cohort enhances the generalizability of these findings to the broader population.

This study has some limitations. First, kidney function was assessed at only two time points, which may not adequately capture individual trajectories or gradual decline. Second, eGFR is an estimated measure and may be influenced by factors such as muscle mass and nutritional status. Third, the study population included only individuals who participated in the second survey, and selection bias from loss to follow-up cannot be ruled out. For example, if individuals with more severe depressive symptoms were less likely to complete follow-up, the observed association may have been underestimated. Additionally, participants in community-based cohort studies may be more health-conscious than the general population, which could have influenced both exposure and outcome distributions. Fourth, incident eGFR < 60 was determined at a single follow-up survey and was not confirmed by repeated measurements over at least 3 months. Therefore, the outcome does not necessarily represent confirmed CKD according to guideline-based definitions.

Conclusions

Depressive symptoms were associated with incident eGFR < 60 mL/min/1.73 m² and a slightly faster longitudinal decline in eGFR in a community-based Japanese population without CKD at baseline. Depressive symptoms may serve as an early risk marker, although the observed effect size was small. Further studies with repeated measurements and mediation analyses are warranted to clarify the relative contributions of behavioral and biological pathways underlying this association.

Abbreviations

BMI
Body mass index
CES-D
Center for Epidemiologic Studies Depression Scale
CHARLS
China Health and Retirement Longitudinal Study
CI
Confidence interval
CKD
Chronic kidney disease
CVD
Cardiovascular disease
eGFR
Estimated glomerular filtration rate
GEE
Generalized estimating equation
Hb
Hemoglobin
KDIGO
Kidney Disease:Improving Global Outcomes
OR
Odds ratio

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki and was approved by the Institutional Review Board of the Tohoku Medical Megabank Organization (first approval No. 2012-4-617; latest approval No. 2026-4-065). All participants provided written informed consent before participation in the study.

Consent for publication

Not applicable.

Availability of data and materials

The TMM data sharing policy is publicly available at http://www.megabank.tohoku.ac.jp/english/sample/. A request for the use of TMM biobank data for research purposes should be made to the ToMMo headquarters. All requests are subject to approval from the Sample and Data Access Committees. Details are available upon request from dist@megabank.tohoku.ac.jp.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study planning: MS, KN, TH, NS, JT, NN.

Conceptualization: MS, KN, TH, NS, JT, NN, AH.

Data sampling: KN, IC, MK, RH, MT, ST, NN, AH.

Formal analysis: MS, KN, NN.

Writing – Original Draft: MS, KN, IC, TH, NS, JT, NN.

Writing – Review & Editing: all authors.

Supervision: AH.

All authors read and approved the final manuscript.

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https:// www.megabank.tohoku.ac.jp/english/a220901/ for ToMMo

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Table 2

Table 2 is available in the Supplementary Files section.

Figures

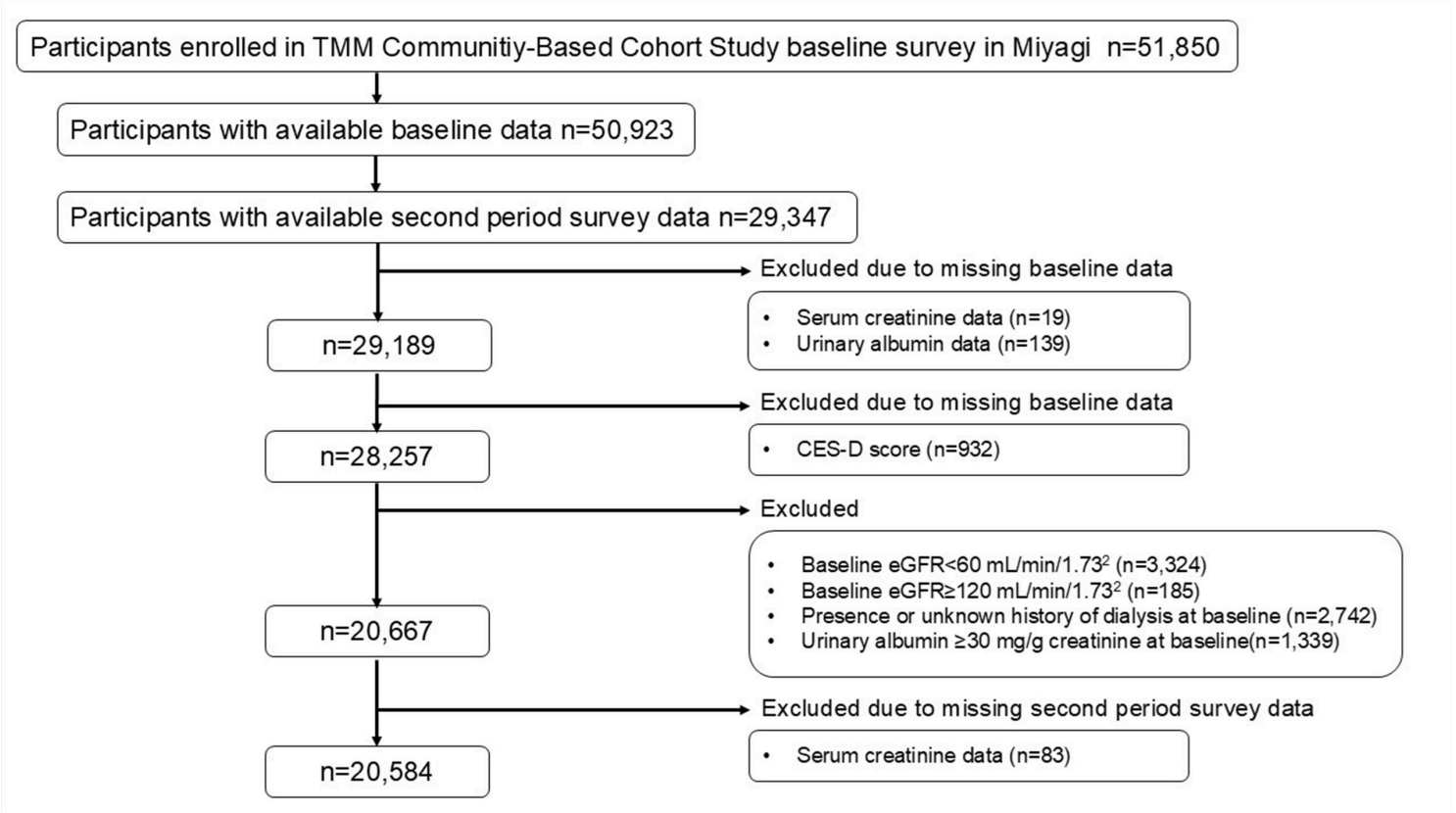


Figure 1

Flowchart of participant selection

Supplementary Files

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