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Cystatin C and risk of new-onset depressive symptoms among individuals with a normal creatinine-based estimated glomerular filtration rate: A prospective cohort study

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ABSTRACT

The association between cystatin C and depressive symptoms in the general population has not been thoroughly elucidated to date. We investigated the association of cystatin C with new-onset depressive symptoms among individuals with normal creatinine-based estimated glomerular filtration rates (eGFR). In the China Health and Retirement Longitudinal Study, 5111 participants without depressive symptoms or renal dysfunction (eGFR < 60 ml/min/1.73 m^2) were included. The outcome was new-onset depressive symptoms over 4 years, defined as a score of ≥12 on the 10-item Center for Epidemiologic Studies Depressive Symptoms Scale. The incidence risk ratio (IRR) and 95% confidence interval (CI) were calculated using modified Poisson regression models. During a 4-year follow-up period, 1746 (34.16%) incidents of depressive symptoms occurred. In a multivariable-adjusted model, the risk of incident depressive symptoms was 1.07 (95% CI 1.02–1.11) per-SD change in cystatin C. A greater cystatin C level was associated with a higher risk of new-onset depressive symptoms among subjects with relatively normal renal function.

1. Introduction

Chronic kidney disease (CKD) or reduced renal function with advanced age is highly prevalent in the elderly (Hill et al., 2016). There is growing evidence that impaired renal function is associated with cardiovascular diseases (Ix et al., 2007; Matsushita et al., 2012), all-cause mortality (Shlipak et al., 2005) and cognitive decline (Buchman et al., 2009) in the elderly. Generally, the glomerular filtration rate (GFR) estimated from the serum creatinine is considered the best overall index of renal function in the clinical practice (Traynor et al., 2006). However, serum creatinine levels are influenced by age, gender, body weight and muscle mass (Stevens et al., 2006). Consequently, cystatin C has been identified as a novel alternative endogenous marker of renal function and is more sensitive than creatinine (Rule et al., 2013; Shardlow et al., 2017). Previous studies suggest that the cystatin C level has a stronger association with cardiovascular disease and mortality than do serum creatinine and GFR in the elderly (Shlipak et al., 2005). Blood urea nitrogen (BUN) is a serum byproduct of protein metabolism and is used to evaluate renal function (Macedo, 2011). The BUN concentration rises as renal function decreases; however, BUN may vary independently of the GFR (Lopez-Giacoman and Madero, 2015).

Depressive symptoms are a major global public health problem. Depression is also highly common among the elderly and is linked to a wide range of adverse health outcomes including cardiovascular disease and mortality (Ye et al., 2013). It is estimated that approximately 26.5% of individuals with CKD experience depressive symptoms, and this number rises to 40% for the subset of individuals who require dialysis treatment (Palmer et al., 2013). Participants with kidney impairment suffer severe psychological distress (Tong et al., 2009), and they have a 3-fold higher risk of depressive symptoms than individuals without kidney impairment (Palmer et al., 2013). Additionally, depressive symptoms increase the risk of end-stage renal disease by 66%

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(Tsai et al., 2012). The majority of previous studies have focused on the impact of depressive symptoms on the risk of CKD or death (Ix et al., 2007; Shlipak et al., 2005; Tsai et al., 2012; Wu et al., 2010); however, research on the relationship between renal function and depressive symptoms in the general population are scarce and conflicting. For example, Odden et al. conducted a cross-sectional study of 967 patients with cardiovascular disease who were enrolled in the Heart and Soul Study; this study showed that impaired renal function, as indicated by creatinine clearance, was not associated with depressive symptoms (Odden et al., 2006). In the Maastricht Study, high albuminuria levels were cross-sectionally associated with depressive symptoms (Martens et al., 2016). In addition, in the Health, Aging and Body Composition Study of 3075 subjects aged 70–79 years over 6 years of follow up, Minev et al. found that a high cystatin C (>1.25 mg/l) was associated with a 2-fold increased risk of depressive symptoms (Minev et al., 2010). However, this association has not been adequately evaluated among older adults with normal renal function.

To the best of our knowledge, no study has compared the effects of various renal function measurements on the risk of depressive symptoms in a middle-aged adult with normal renal function. Therefore, we aimed to examine the associations of cystatin C, BUN and the estimated GFR with the risk of depressive symptoms in a population-based cohort study of middle-aged Chinese adults. We hypothesized that cystatin C would be a stronger and linear predictor of the risk of depressive symptoms among subjects with normal function than the BUN or GFR.

2. Methods

2.1. Study participants

The China Health and Retirement Longitudinal Study (CHARLS) is a community-based, national representative longitudinal study that was initiated in 2011–2012 (Zhao et al., 2014). The main objective of CHARLS is to evaluate the main health and economic issues associated with rapid population aging in China. Briefly, 17,708 individuals aged 45 years or older were randomly recruited from 150 counties or districts from 28 provinces using a four-stage, stratified, and cluster sampling method. Among those participants, 11,847 individuals provided fasting blood samples. A description of the study design, quality control procedures, laboratory methods, and procedures for physical examination can be found on the CHARLS website (http://charls.pku.edu.cn/en). The ethical committees of Peking University approved the study protocol, and all participants provided written informed consent. For this analysis, 5111 participants without depressive symptoms, whose serum was available for the measurement of cystatin C, and who had a normal renal function (GFR ≥ 60 ml/min/1.73 m^2) were included. The cohort selection of flowchart is included in the Supplementary Materials (Fig. S1).

2.2. Measurements of renal function

Serum from fasting blood samples was stored at −70 °C until analysis at the Center for Clinical Laboratory of Capital Medical University. Cystatin C was measured using a particle-enhanced turbidimetric assay (Voskoboev et al., 2012). The intra-individual coefficient of variation (CV) was <5%, and the between-individual CV was <5%. The detection range of the assay was 0.5–8.0 mg/l. The serum creatinine level was measured using a rate-blanked and compensated Jaffe creatinine method. The intra-individual CV was <1.6%, and the between-individual CV was <2.1%. The detection range of the assay was 0.1–25 mg/dL. We estimated the GFR using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation (Levey et al., 2009). The BUN was measured using an enzymatic UV method with urease. The intra-individual CV was <4.4%, and the between-individual CV was <4.1%. The range of detection of the assay was 5–100 mg/dL.

2.3. Ascertainment of depressive symptoms

Depressive symptoms were evaluated at baseline and every two years at follow-up using the 10-item Center for Epidemiologic Studies Depressive Symptoms Scale (CES-D) short form (Andresen et al., 1994). To clarify frequency of the mood and behavioral symptoms, participants were asked to rate how often they experienced then symptoms during the previous week: (1) I was bothered by things that do not usually bother me; (2) I had trouble keeping my mind on what I was doing; (3) I felt depressed; (4) I felt everything I did was an effort; (5) I felt hopeful about the future; (6) I felt fearful; (7) My sleep was restless; (8) I was happy; (9) I felt lonely; (10) I could not get "going". Each item was scored on a 4-point Likert scale ranging from 0 ("not at all") to 3 ("nearly every day"). Items 5 and 8 were reversely scored before analysis. In the current analysis, individuals missing three or more responses on the CES-D were excluded. Therefore, the total CES-D scores ranged from 0 to 30, with a higher score representing a greater level of depressive symptoms. The 10-item CES-D has been widely validated among older Chinese adults and shows satisfactory psychometric properties (Boey, 1999; Chen and Mui, 2014; Cheng and Chan, 2005). A recent validation study conducted in a subsample of 742 CHARLS participants aged ≥60 years showed that the two-factor model was the best fit, and the completely standardized factor loadings were ≥0.30 (Chen and Mui, 2014). Following the validation study, the binary depressive symptoms were defined as total CES-D scores of 12 or higher in the current study (Chen and Mui, 2014). We excluded those individuals who had depressive symptoms at baseline.

2.3. Assessment of covariates

Baseline demographic and risk factors were collected by trained personnel according to standard procedures. Sociodemographic factors, including age, sex, residential area (urban, rural), education level (no formal education, primary school, middle school or above), marital status (unmarried, married) and retirement status (retired, nonretired) were self-reported. Health behaviors including smoking (never, former, current), alcohol use (never, <1 times/month, ≥1 times/month) were assessed using a questionnaire. Self-reported health was recoded into three categories (very good/good, fair, poor/very poor). Life satisfaction was recoded into three categories (completely/very satisfied, somewhat satisfied, not very/not at all satisfied). Family-based social support was assessed by evaluating the family-based network size measured by the number of core family members, whether the respondent had received help and whether the respondent had provided help (Shen and Yeatts, 2013). Social participation was assessed by respondent participation in the following social activities: (1) interacted with a friend; (2) played mahjong, or went to a sport, social or other kind of club; (3) took part in a community-related organization; (4) took part in a community-related organization; (5) took part in voluntary or charity work; (6) attended an educational or training course (Tu et al., 2018). The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Sitting blood pressure was measured three times after a 5-min rest period in quiet space using an Omron™ HEM-7200 Monitor, and an average of three values was obtained for the systolic blood pressure (SBP) and diastolic blood pressure (DBP). The self-reported prior history of physician-diagnosed diseases included hypertension, diabetes mellitus, dyslipidemia, coronary artery heart disease, stroke, and obstructive pulmonary disease. Using plasma samples, the total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), fasting blood glucose (FBG), and C-reactive protein (CRP) levels were measured using standard assays (Yang et al., 2016).

2.4. Statistical analysis

All statistical analyses were performed using Stata/MP, version 14.1, and 2-sided *P* values <0.05 were considered statistically significant. In the cohorts, the data were 80% complete in relation to potential confounders. We first used multiple imputation with multivariable chained equations to impute missing data for continuous variables (BMI, SBP, DBP, HDL-C, LDL-C, and FBG) and categorical variables (retirement status, receiving help, providing help, self-reported health and life satisfaction) (Harel and Zhou, 2007). Because family-network size, TG and CRP values were not normally distributed, log transformation was used. Participants were divided into five groups based on the quintiles of cystatin C levels based on values for the entire cohort (<0.82 mg/l, 0.83–0.93 mg/l, 0.94–1.02 mg/l, 1.03–1.16 mg/l, and ≥ 1.17 mg/l). The *P* value for linear trend across the quintiles was calculated from the logistic regression for categorical variables and linear regression for continuous variables.

To evaluate the association of each renal function measurement with depressive symptoms, we initially created quintiles of the study population according to the cystatin C, BUN and estimated GFR levels. We used a modified Poisson regression with robust error variance (McNutt et al., 2003) to evaluate the likelihood of developing depressive symptoms (yes or no) at follow-up for each index of renal function among participants who were free of depressive symptoms at baseline. Incidence risk ratio (IRR) and the corresponding 95% confidence interval (CI) were reported. The main analysis was based on the combined the results obtained by running each model in 10 independent imputed data sets. Potential confounding variables for statistical adjustment were chosen a priori according to known associations with depressive symptoms and renal function. The analysis was adjusted for age, sex, education, marital status, living area, alcohol use, smoking status, retirement status, social participation, family-based social support, self-reported health, life satisfaction, history of hypertension, diabetes, dyslipidemia, coronary artery heart disease, stroke, and chronic obstructive pulmonary disorder, SBP, BMI, TC, LDL-C, HDL-C, baseline CES-D score and log-transformed TG, and log-transformed CRP level. For tests of linear trend, we applied linear terms using the median of each renal function measurement quintile. The association of cystatin C, BUN or the estimated GFR with depressive symptoms was also assessed as a continuous scale (per 1-SD change).

Furthermore, the association between incident depressive symptoms and cystatin C levels on a continuous scale was examined using restricted cubic splines with 3 knots located at the 10th, 50th, and 90th percentiles (Harrell, 2010) of cystatin C incorporated in a modified Poisson regression. A cystatin C concentration of 1 mg/l was used as the reference value for this analysis because it approximated the median value. Sensitivity analysis using complete data ($n = 4128$) was conducted to examine the association between measurements of renal function and depressive symptoms.

3. Results

3.1. Study participants

Among the 5111 individuals included in this analysis, the overall mean (± SD) serum cystatin C was 0.99 ± 0.21 mg/l (1st–99th percentile range, 0.55–1.58 mg/l). The baseline characteristics of the participants are shown in Table 1. The participants with the highest cystatin C levels were more likely to be older, male, and current smokers and drinkers, compared with participants with lower cystatin C levels (Table 1). Nearly all of the coexisting conditions were more prevalent among those with elevated levels of cystatin C (Table 1).

3.2. Incidence rate of depressive symptoms

During 4 years of follow-up, 1746 (34.16%) individuals developed new-onset depressive symptoms. The crude incidence rate of depressive symptoms across each quintile of cystatin C, BUN, and estimated GFR are shown in Fig. 1.

3.3. Renal function with depressive symptoms

Table 2 shows the IRR and 95% CI of depressive symptoms according to measures of renal function. After multivariate adjustment, compared to those with the lowest level of cystatin C (Quintile 1), individuals with the highest level of cystatin C (Quintile 5) had an adjusted IRR of 1.18 (95% CI: 1.03–1.35) for depressive symptoms. Individuals with an intermediate BUN level (Quintile 3) were at lower risk of depressive symptoms (IRR: 0.86, 95% CI: 0.76–0.97). Individuals with lower estimated GFR values were showed an at increased depressive symptoms risk (IRR: 1.15, 95% CI: 1.01–1.31). The association remained robust when analysis limited to complete data (Table S1).

3.4. Dose-response analysis

The restricted cubic spline analysis suggested a linear relationship between cystatin C and depressive symptoms (Fig. 2). The multivariate-adjusted IRR using serum cystatin C levels on a continuous scale was 1.13 (95% CI: 1.08–1.19) per 1-SD change (Fig. 3). The association between the BUN and estimated GFR on a continuous scale and depressive symptoms were not statistically significantly (Fig. 3).

4. Discussion

Our results demonstrate that the cystatin C concentration is linearly and independently associated with new-onset depressive symptoms in a general population with a creatinine-based estimated GFR of 60 mL/min/1.73 m^2 or greater. In contrast, the BUN level and estimated GFR on a continuous scale had no statistically significant association with depressive symptoms in the fully adjusted model.

4.1. Association between renal function and depressive symptoms

Depressive symptoms are a major contributor to the global disease burden and are highly prevalent in patients with chronic kidney disease or end-stage renal disease. A recent meta-analysis reported that the prevalence of depressive symptoms was as high as 40% among CKD patients (Palmer et al., 2013). Several previous studies suggested that impaired renal function measured by estimated GFR may be associated with depressive symptoms (Abdel-Kader et al., 2009; Fischer et al., 2012; Liu et al., 2018), whereas other studies did not find this association (Campbell et al., 2013; Fischer et al., 2010; Martens et al., 2016). For example, in the Chronic Renal Insufficiency Cohort (CRIC) Study, Fischer et al. found that there were an 8% increased odds of depressive symptoms for every 10 ml/min/1.73 m^2 decrease in GFR in the fully adjusted model (Fischer et al., 2012). This association was also observed in an older Chinese cross-sectional study (Liu et al., 2018). Furthermore, a recent meta-analysis conducted by Lee et al. demonstrated that self-management programs for the estimated GFR improved depressive symptoms in CKD patients (Lee et al., 2016). Additionally, in the Diabetes Study of Northern California survey, older adults in the lowest estimated GFR category (≤ 29 mL/min/1.73 m^2) were cross-sectionally demonstrated to have twice the probability of depressive symptoms compared with these with the normal estimated GFR category (≥ 90 mL/min/1.73 m^2) (Campbell et al., 2013). However, this association was no longer statistically significant adjustment for the hemoglobin level (Campbell et al., 2013). In the current analysis, we did not find a perspective significantly association between the estimated GFR and depressive symptoms. Our finding was consistent with previous studies (Campbell et al., 2013; Martens et al., 2016).

Previous studies on the association of cystatin C with depressive symptoms are lacking. One study conducted by Minev et al. reported

Table 1
Baseline characteristics of middle-aged participants in the China health and retirement longitudinal study, according to quintiles of cystatin C.

Characteristic	Quintile 1 (≤0.82)	Quintile 2 (0.83–0.92)	Quintile 3 (0.93–1.01)	Quintile 4 (1.02–1.14)	Quintile 5 (≥1.15)	*P* for trend
No. of participants	1047	1022	1020	1018	1004	
Age—years	54.4 ± 7.6	56.2 ± 7.9	58.1 ± 8.1	60.9 ± 8.7	66.0 ± 9.2	<0.001
Median (min–max)	53 (45–82)	55 (45–82)	57 (45–83)	60 (45–88)	67 (45–93)	
Male sex—no. (%)	352 (33.6)	437 (42.8)	541 (53.0)	586 (57.6)	675 (67.2)	<0.001
Area urban—no. (%)	451 (43.1)	395 (38.6)	401 (39.3)	393 (38.6)	389 (38.7)	0.068
Education—no. (%)						<0.001
No formal education	392 (37.4)	421 (41.2)	428 (42.0)	451 (44.3)	477 (47.5)	
Primary school	211 (20.2)	203 (19.9)	237 (23.2)	233 (22.9)	264 (26.3)	
Middle school or above	444 (42.4)	398 (38.9)	355 (34.8)	334 (32.8)	263 (26.2)	
Smoking status—no. (%)						<0.001
Never	762 (72.8)	683 (66.8)	582 (57.1)	519 (51.0)	475 (47.3)	
Former	66 (6.3)	69 (6.8)	91 (8.9)	107 (10.5)	112 (11.2)	
Current	219 (20.9)	270 (26.4)	347 (34.0)	392 (38.5)	417 (41.5)	
Alcohol use—no. (%)						<0.001
Never	742 (70.9)	686 (67.1)	631 (61.9)	627 (61.6)	638 (63.5)	
< 1 times/month	72 (6.9)	71 (6.9)	84 (8.2)	84 (8.3)	82 (8.2)	
≥ 1 times/month	233 (22.3)	265 (25.9)	305 (29.9)	307 (30.2)	284 (28.3)	
Married—no. (%)	978 (93.4)	936 (91.6)	933 (91.5)	910 (89.4)	840 (83.7)	<0.001
Retired—no. (%)*	221 (21.2)	211 (20.7)	226 (22.2)	291 (28.6)	371 (37.0)	<0.001
Social participation—no. (%)	573 (54.7)	507 (49.6)	496 (48.6)	471 (46.3)	501 (49.9)	0.008
Family-based social support						
Network size—log	1.2 ± 0.5	1.2 ± 0.5	1.2 ± 0.5	1.1 ± 0.5	1.1 ± 0.6	<0.001
Receiving help—no. (%)*	328 (31.3)	367 (35.9)	363 (35.6)	416 (40.9)	488 (48.6)	<0.001
Providing help—no. (%)*	474 (45.3)	418 (40.9)	404 (39.6)	370 (36.3)	319 (31.8)	<0.001
Self-reported health—no. (%)*						0.002
Very good/good	323 (30.9)	297 (29.1)	283 (27.7)	276 (27.1)	230 (22.9)	
Fair	556 (53.1)	536 (52.4)	536 (52.5)	554 (54.4)	550 (54.8)	
Poor/very poor	168 (16.0)	189 (18.5)	201 (19.7)	188 (18.5)	223 (22.2)	
Life satisfaction—no. (%)*						0.493
Completely/very satisfied	246 (25.0)	235 (24.9)	248 (26.6)	258 (27.6)	234 (26.1)	
Somewhat satisfied	649 (66.0)	616 (65.3)	596 (64.0)	592 (63.4)	575 (64.2)	
Not very/not at all satisfied	88 (9.0)	93 (9.9)	87 (9.3)	84 (9.0)	87 (9.7)	
History of hypertension—no. (%)	214 (20.4)	212 (20.7)	234 (22.9)	249 (24.5)	287 (28.6)	<0.001
History of diabetes—no. (%)	72 (6.9)	49 (4.8)	57 (5.6)	39 (3.8)	50 (5.0)	0.029
History of dyslipidemia—no. (%)	98 (9.4)	94 (9.2)	103 (10.1)	78 (7.7)	71 (7.1)	0.029
History of CHD—no. (%)	51 (4.9)	74 (7.2)	90 (8.8)	100 (9.8)	115 (11.5)	<0.001
History of stroke—no. (%)	13 (1.2)	10 (1.0)	16 (1.6)	13 (1.3)	25 (2.5)	0.022
History of COPD—no. (%)	90 (8.6)	82 (8.0)	107 (10.5)	121 (11.9)	136 (13.5)	<0.001
Body mass index—kg/m^2*	24.4 ± 3.9	23.8 ± 3.6	23.6 ± 3.7	23.5 ± 4.1	22.9 ± 4.0	<0.001
Systolic blood pressure—mm Hg*	127.4 ± 19.5	128.9 ± 20.5	130.0 ± 21.0	132.5 ± 22.1	134.1 ± 23.0	<0.001
Diastolic blood pressure—mm Hg*	75.9 ± 11.4	75.9 ± 11.8	75.8 ± 12.0	76.5 ± 12.4	74.9 ± 12.5	0.289
Total cholesterol— mg/dl	199.7 ± 40.7	192.2 ± 36.3	192.4 ± 37.8	191.2 ± 37.6	188.0 ± 39.0	<0.001
LDL cholesterol— mg/dl*	116.3 ± 35.7	117.4 ± 33.0	116.8 ± 35.5	116.3 ± 34.7	114.2 ± 35.3	0.130
HDL cholesterol—mg/dl*	48.4 ± 14.3	51.5 ± 14.6	51.1 ± 15.4	51.0 ± 15.1	51.6 ± 15.7	<0.001
Triglycerides—log	4.9 ± 0.6	4.7 ± 0.5	4.7 ± 0.6	4.7 ± 0.5	4.6 ± 0.5	<0.001
Fasting blood glucose—mg/dl*	116.3 ± 49.0	109.0 ± 32.8	108.3 ± 29.9	107.6 ± 26.7	106.3 ± 25.4	<0.001
C-reactive protein—log	0.0 ± 1.0	0.0 ± 1.0	0.1 ± 0.9	0.2 ± 1.1	0.4 ± 1.1	<0.001
Cystatin C—mg/l	0.7 ± 0.1	0.9 ± 0.0	1.0 ± 0.0	1.1 ± 0.0	1.3 ± 0.2	<0.001
Creatinine—mg/dl	0.7 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.2	<0.001
BUN—mg/dl	14.5 ± 4.0	14.9 ± 3.8	15.6 ± 4.0	16.3 ± 4.5	17.1 ± 4.8	<0.001
Estimated GFR—ml/min/1.73 m^2	100.7 ± 11.5	97.5 ± 10.6	94.8 ± 10.9	90.0 ± 11.3	82.6 ± 12.5	<0.001
Baseline CES-D score	5.1 ± 3.2	5.4 ± 3.4	5.2 ± 3.4	5.3 ± 3.3	5.3 ± 3.3	0.262

Data are given as mean ± SD value or number (percentage) of participants.
CHD denotes coronary artery heart disease, COPD denotes chronic obstructive pulmonary disease, LDL denotes low-density lipoprotein, HDL denotes high-density lipoprotein, BUN denotes blood urea nitrogen, GFR denotes glomerular filtration rate, and CES-D denotes Center for Epidemiologic Studies Depression Scale. C-reactive protein was measured in mg/l.

* Missing data: retired (n = 1), receiving help (n = 1), providing help (n = 1), life satisfaction (n = 407), body-mass index (n = 581), systolic blood pressure (n = 583), diastolic blood pressure (n = 582), LDL cholesterol (n = 1), HDL cholesterol (n = 1), fasting glucose (n = 1).

that a high level of cystatin C (>1.25 mg/l) increased the risk of depressive symptoms 2-fold during a 6-year follow-up in the American healthy elders (Minev et al., 2010). In addition, the Confucius Hometown Aging Project showed that a high serum cystatin C level and impaired kidney function were longitudinally associated with incident geriatric depressive symptoms among Chinese older adults (Wu et al., 2018). However, that study did not compare the relative association of cystatin C, BUN and the estimated GFR with the risk of new-onset depressive symptoms. Our results were robust to statistical adjustment of a series of confounders. Our results provide the new evidence that cystatin C increases the risk of depressive symptoms in a middle-aged population. Further research is needed to validate our findings regarding the association between renal function and depressive symptoms; this relationship has not been thoroughly explored among the elderly.

Cystatin C as a measure of renal function overcomes the limitations of using the creatinine level because C concentration is not influenced by age, sex, or body mass (Fliser and Ritz, 2001). We also used restricted cubic splines to estimate the trend in the risk for depressive symptoms. The cystatin C concentration was confirmed to have a linear relationship with the risk of depressive symptoms. These findings were in alignment with prior studies that reported a linear relationship

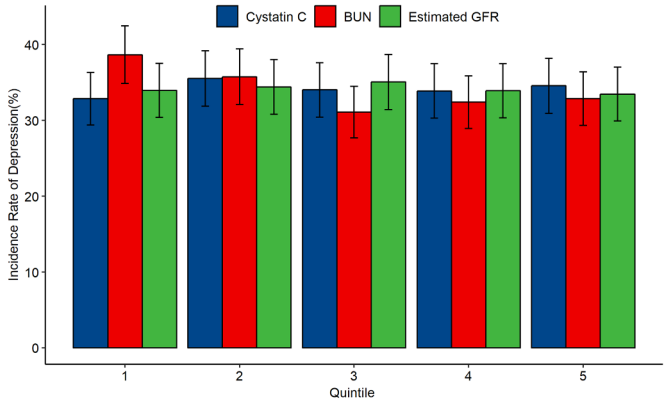

Fig. 1. Crude incidence rate of depressive symptoms according to quintile of measures of renal function. GFR denotes estimated glomerular filtration rate, and BUN means blood urea nitrogen.

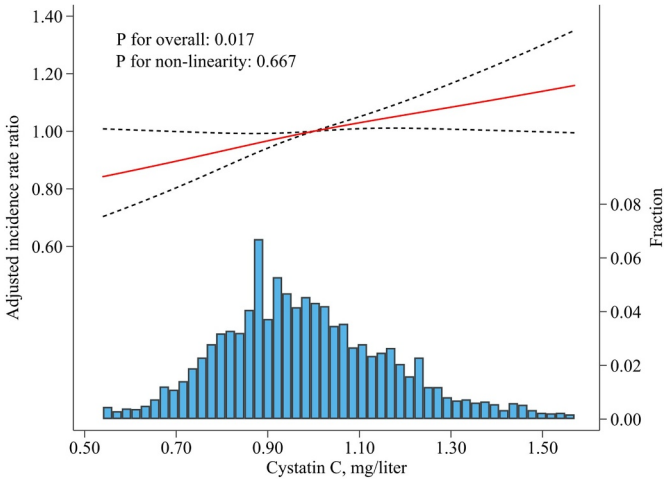

Fig. 2. Multivariable adjusted incidence risk ratio of new-onset depressive symptoms according to cystatin C levels. Solid-red lines are multivariable-adjusted incidence risk ratio, and dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression with five knots chosen by Akaike information criterion. Cystatin C of 1.00 mg/l was used as the reference because it approximated the median value. The graphs are truncated at the 1st and 99th percentiles. The modified Poisson regression with robust error variance adjusted for age, sex, education, marital status, living area, alcohol use, smoking status, retirement status, social participation, family-based social support, self-reported health, life satisfaction, history of hypertension, diabetes, dyslipidemia, coronary artery heart disease, stroke, and chronic obstructive pulmonary disorder, systolic blood pressure, body-mass index, total, low-density, high-density lipoprotein cholesterol levels, log-transformed triglyceride level, log-transformed C-reactive protein level and baseline CES-D score.

between cystatin C and an increased the risk of heart failure (Sarnak et al., 2005), hypertension (Kestenbaum et al., 2008), cardiovascular disease and mortality (Shlipak et al., 2005).

Several potential mechanisms may explain the association between cystatin C and depressive symptoms. First, cystatin C was used as an index of cerebral small vessel disease (Wada et al., 2010), which has been associated with incident depressive symptoms (van Sloten et al., 2015); this relationship is termed the "vascular depressive symptoms hypothesis (Alexopoulos, 2006)." In addition, physiological factors such as endothelial dysfunction and inflammation, have both linked to cystatin C (Balta et al., 2013; Zhang et al., 2016) and depressive symptoms (Al Shweiki et al., 2017; Bouzinova et al., 2014; Miller and Raison, 2016).

4.2. Limitations

There were several limitations. First, depressive symptoms measured by CES-D are not equivalent to a clinical diagnosis of major depressive symptoms. Second, depressive symptoms tend to fluctuate over time (White et al., 2016), and we did not assess the variability in depressive symptoms. Additionally, owing to the observational nature of our investigation, unmeasured potential confounding factors such as physical activity may still be present. Several important strengths of this study were the prospective design, and the large sample size and the use of the validated CES-D to assess depressive symptoms in 28 provinces in China. An additional strength is the complete assessment of renal function, which included cystatin C, BUN, and estimated GFR.

Table 2
Risk of depression according to measures of renal function among middle-aged participants in the China health and retirement longitudinal study.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Cystatin C – mg/liter					
Range of values	≤0.82	0.83–0.92	0.93–1.01	1.02–1.14	≥1.15
No. at risk	1047	1022	1020	1018	1004
No. of depression	344	363	347	345	347
Incidence rate ratio (95% CI)					
Unadjusted	1.00	1.08 (0.96–1.22)	1.04 (0.92–1.17)	1.03 (0.91–1.17)	1.05 (0.93–1.19)
Full adjusted[a]	1.00	1.08 (0.96–1.22)	1.09 (0.96–1.23)	1.11 (0.97–1.26)	1.18 (1.03–1.35)
Blood urea nitrogen (BUB) – mg/dl					
Range of values	≤12.0	12.1–14.12	14.13–16.16	16.17–19.1	≥19.2
No. at risk	1032	1015	1023	1031	1010
No. of depression	399	363	318	334	332
Incidence rate ratio (95% CI)					
Unadjusted	1.00	0.93 (0.83–1.04)	0.80 (0.71–0.91)	0.84 (0.75–0.94)	0.85 (0.76–0.96)
Full adjusted[a]	1.00	0.96 (0.86–1.08)	0.86 (0.76–0.97)	0.91 (0.81–1.03)	0.92 (0.82–1.04)
Estimated GFR - ml/min/1.73 m^2					
Range of values	≥104.43	98.36–104.42	91.58–98.35	82.72–91.57	≤82.71
No. at risk	1025	1020	1024	1020	1022
No. of depression	348	351	359	346	342
Incidence rate ratio (95% CI)					
Unadjusted	1.01 (0.90–1.15)	1.03 (0.91–1.16)	1.05 (0.93–1.18)	1.01 (0.90–1.14)	1.00
Full adjusted[a]	1.10 (0.96–1.26)	1.15 (1.01–1.31)	1.13 (0.99–1.28)	1.03 (0.91–1.16)	1.00

[a] Adjusted for age, sex, education, marital status, living area, alcohol use, smoking status, retirement status, social participation, family-based social support, self-reported health, life satisfaction, history of hypertension, diabetes, dyslipidemia, coronary artery heart disease, stroke, and chronic obstructive pulmonary disorder, systolic blood pressure, body-mass index, total, low-density, high-density lipoprotein cholesterol levels, log-transformed triglyceride level, log-transformed C-reactive protein level and baseline CES-D score.

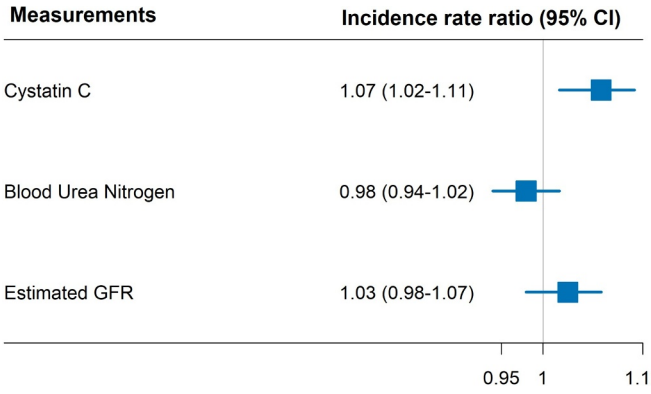

Fig. 3. . Association of renal function with new-onset depressive symptoms on a continuous scale. The incidence risk ratio (IRR) have been adjusted for age, sex, education, marital status, living area, alcohol use, smoking status, retirement status, social participation, family-based social support, self-reported health, life satisfaction, history of hypertension, diabetes, dyslipidemia, coronary artery heart disease, stroke, and chronic obstructive pulmonary disorder, systolic blood pressure, body-mass index, total, low-density, high-density lipoprotein cholesterol levels, log-transformed triglyceride level, log-transformed C-reactive protein level and baseline CES-D score.

To the best of our knowledge, this study is first to explore the association between cystatin C and depressive symptoms in a large cohort with normal renal function.

4.3. Conclusions

Our study demonstrated that cystatin C, a sensitive measure of renal function, is significantly associated with future depressive symptoms in the general population with relatively normal renal function. It is clinically important for individuals with normal renal function but high cystatin C to treat depressive symptoms and improve the quality of life.

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Declarations

The authors declare that there is no duality of interest associated with this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.01.009.

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