RENAL FAILURE
2025, VOL. 47, NO. 1, 2473668
https://doi.org/10.1080/0886022X.2025.2473668

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Association between renal function and memory-related disease: evidence from the China Health and Retirement Longitudinal Study

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ABSTRACT

Background: Previous studies have reported that renal function is associated brain structure and cognitive dysfunction. However, the association between renal function and memory-related disease was not well characterized.

Methods: Altogether, 5,282 individuals were included in this study based on China Longitudinal Study of Health and Retirement. Four estimated glomerular filtration rate indicators (eGFR), including CG, CKD-EPIscr, CKD-EPIscr-cys, and CKD-EPIcys were used to evaluate the association between renal function and memory-related disease.

Results: The multivariable-adjusted HRs (95% CIs) of the memory-related disease in the low eGFR group (eGFR < 90 mL/min/1.73m^2) were 1.56 (1.13–2.16) for CG, 1.56 (1.19–2.06) for CKD-EPIscr, 1.45 (1.06–1.99) for CKD-EPIscr-cys and 1.27 (0.91–1.77) for CKD-EPIcys, respectively. Similarly, each SD increase of eGFR was associated with reduced risk of memory-related disease on continuous analyses. Subgroup analyses further confirmed these associations. Moreover, the addition of eGFR to conventional risk factors improved the predictive power for memory-related disease (net reclassification improvement: 13.90% for CG, 19.83% for CKD-EPIscr and 30.65% for CKD-EPIscr-cys).

Conclusions: In conclusion, impaired renal function was associated with the increasing risk of memory-related disease, indicating that renal function may be a potential indicator for memory-related disease. Further studies from other races and populations are needed to replicate our findings and to clarify the potential mechanisms.

ARTICLE HISTORY
Received 18 November 2024
Revised 21 February 2025
Accepted 22 February 2025

KEYWORDS
Renal function; eGFR; memory-related disease; longitudinal study

Introduction

Due to population aging, the prevalence of dementia increases dramatically worldwide, especially after the age of 65 [1]. According to the 2019 Global Burden of Disease Study analysis, around 55 million people worldwide were living with dementia in 2019, and it is expected to reach 139 million by 2050, with the majority coming from low-income and middle-income countries [2]. The primary causes of dementia are memory-related disorders among older adults, including disease such as Alzheimer's disease (AD), brain atrophy, and Parkinson's disease (PD) [3,4]. In addition, dementia carries a significant medical burden and economic costs. It is estimated that the cost of care for all AD patients in the United States will exceed $500 billion in 2020 and is projected to rise to $1.6 trillion by 2050 [5]. Hence, it is necessary to comprehensively understand the risk factors related to the occurrence of memory-related disorders and strengthen preventive measures.

Chronic kidney disease (CKD) is defined as structural abnormalities and dysfunction of the kidney due to multiple causes [6], and the latest figures show that nearly 10% of adults worldwide have chronic kidney disease [7]. Impaired renal function may lead to structural changes in the brain and cognitive dysfunction [8]. A case-control study of patients with CKD indicated a higher incidence of brain atrophy in patients with CKD compared to the general population [9]. Besides, another observational study based on Copenhagen General Population Study showed that impaired renal function was association with the

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/0886022X.2025.2473668.
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increased risk of dementia [10]. However, there has been less research on the link between renal function and memory-related disease, especially in developing countries, including China. Therefore, based on the China Longitudinal Study of Health and Retirement (CHARLS), we investigated whether renal function is associated with memory-related disease and explored the predictive value of various formulas for calculating renal function in assessing the risk of such diseases. Our aim was to enhance early detection capabilities and tailor interventions accordingly.

Methods

Study design and participants

The CHARLS is an ongoing nationally representative cohort study, that uses a multistage clustering sample method to select participants [11]. A total of 17,708 participants from 10,257 households recruited from 28 provinces within China were included at baseline (2011-2012, Wave 1). CHARLS respondents were followed up every 2 years, using a face-to-face computer-assisted personal interview. Three subsequent follow-ups were carried out in 2013-2014 (Wave 2), in 2015-2016 (Wave 3) and 2017-2018 (Wave 4) among survivors. The details of the CHARLS data are available at its website (http://charls.pku.edu.cn/en).

Of 17,708 participants at baseline, individuals who met all the following criteria were included: aged ≥ 45 years; participants with the levels of fasting blood cystatin, creatinine, and weight at baseline; participants without memory-related disease at baseline; participants with follow-up (Wave 4). Finally, a total of 5,282 individuals were eligible for subsequent analysis (Figure 1).

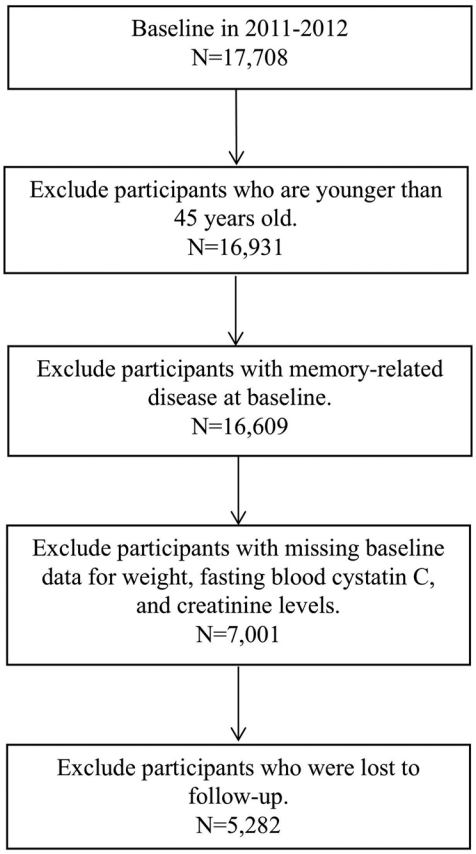

Figure 1. Flowchart of inclusion and exclusion criteria for participants in this study.

Human ethics and consent to participate declarations

All research involving human subjects adheres to the principles enshrined in the Declaration of Helsinki. Ethical approval for all waves of the CHARLS study was obtained from the Institutional Review Board at Peking University (Approval numbers: IRB00001052-11015 and IRB00001052-11014). During fieldwork, each participant provided informed consent prior to their involvement in the survey.

Measurement of renal function

Following four indicators were calculated to reflect estimated glomerular filtration rate (eGFR), which were used to evaluate renal function. The Cockcroft-Gault (CG) equation estimates glomerular filtration rate by estimating creatinine clearance [12]. In addition, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recommended 3 equations to calculate eGFR for clinical applications in 2012: CKD-EPIscr, CKD-EPIcys, and CKD-EPIscr-cys based on serum creatinine (Scr), serum cystatin C (CysC) and the combination of the 2 markers respectively [13]. The calculation formulas of the 4 indicators were provided in the Table S1.

Covariate assessments

Several important covariates from the CHARLS questionnaire were included in this study. These covariates encompassed age, gender, educational attainment, smoking status (yes or no), drinking status (yes or no), the presence or absence of other chronic diseases (hypertension, cancer, kidney disease, liver disease, arthritis, digestive disease, chronic lung disease, asthma, hyperlipidemia, diabetes,) other health conditions were obtained by physical examination and blood tests. These included body mass index (weight in kilograms divided by the square of height in meters, BMI), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), fasting blood glucose, total cholesterol, TC (Total cholesterol), TG (Triglycerides), HDL-C (High density lipoprotein-Cholesterol), LDL-C (Low density lipoprotein-Cholesterol), serum creatinine, cystatin C, Center for Epidemiologic Studies Depression Scale (CESD-10) score at baseline, and average hours for one night sleeping time during the past month at baseline.

Blood pressure was measured with an electronic sphygmomanometer (Omron HEM-7200 Monitor) after 5 min of rest in the sitting position and was defined as the average of three separate measurements. According to the 2010 Chinese Hypertension Guidelines, participants with an average systolic blood pressure of 140 mmHg or higher and/or an average diastolic blood pressure of 90 mmHg or higher were considered hypertensive, and participants who self-reported using

antihypertensive medications within two weeks were similarly considered hypertensive. The definition of diabetes encompasses those with fasting blood glucose levels equal to or greater than 7.0 mmol/L, and participants who were currently receiving hypoglycemic medications were also considered to have diabetes.

Outcome assessments

Memory-related disease was the outcome of the present study. Memory-related disease was assessed from the record of "Have you been diagnosed with Memory-related disease (such as dementia, brain atrophy, and Parkinson's disease) by a doctor?" in the CHARLS data. Participants were divided into two groups based on responses: with memory-related disease or no memory-related disease.

Statistical analysis

All participants were categorized into 2 groups according to whether the eGFR was greater than 90 mL/min/1.73m^2 (normal: high eGFR group, ≥ 90 mL/min/1.73m^2; mildly impaired and moderately to severely impaired: low eGFR group,< 90 mL/min/1.73m^2) [14]. Participants' baseline characteristics were expressed as percentages; the mean ± SD or median (quartile) was used for the continuous variables. Cox proportional hazards regression models were used to examine the association between renal function (including CG, CKD-EPIscr, CKD-EPIcys, and CKD-EPIscr-cys) and the risk of memory-related disease. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated of the group with eGFR < 90 with the reference group (eGFR ≥ 90). Important covariates for memory-related disease including smoking, drinking, level of education, diabetes, hypertension, hyperlipidemia, heart disease, stroke, psychosis disease, blood glucose, BMI, systolic BP, diastolic BP, TC, TG, HDL-C, LDL-C, CESD-10 score, and average hours for one night sleeping time during the past month were selected based on our prior knowledge and were adjusted in multivariate analysis.

Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were 2 indexes to assess improvement in model performance accomplished by adding new markers [15]. We examined the incremental prognostic value of eGFR in patients with memory-related disease by net reclassification improvement (NRI) and integrated discrimination index (IDI). Subgroup analyses were further performed to evaluate the association between renal function and the risk of memory-related disease according to smoking, drinking, hypertension, diabetes, hyperlipidemia, heart disease, stroke, systolic BP, blood glucose subgroups. Statistical significance was determined as a two-sided *P* value less than 0.05. All analyses were conducted using SAS statistical software (version 9.4, Cary, NC).

Results

Baseline characteristics

In this study, a total of 52,82 participants (2,899 male and 2,383 female) were finally included, with a mean (SD) age of participants at the time of enrollment was 53.94 (9.21) years. The median eGFR level calculated by four indicators were 79.15, 94.76, 85.97 and 78.12 mL/min/1.73 m^2 for CG, CKD-EPIscr, CKD-EPIscr-cys and CKD-EPIcys, respectively (interquartile range were 63.50-97.20, 84.10-102.47, 74.47-96.95 and 64.70-92.74 mL/min/1.73 m^2, respectively). Baseline characteristics of all participants are shown in Table 1.

Association of renal function and the risk memory-related disease

Unadjusted Cox regression analyses showed a significant association between lower eGFR (eGFR < 90 mL/min/1.73 m^2, CKD-EPIscr, and CKD-EPIscr-cys) level and the increase risk of memory-related disease (Table 2). The multivariable-adjusted

Table 1. Baseline characteristics of participants.

Characteristics	
Age, years	59.34 ± 9.21
Sex	
Female	2,383 (45.12)
Male	2,899 (54.88)
Smoking	1,997 (37.81)
Alcohol use	2,022 (38.28)
Hypertension	1,374 (26.01)
Diabetes	318 (6.02)
Hyperlipidemia	497 (9.41)
Heart disease	614 (11.62)
Stroke	113 (2.14)
Psychosis disease	63 (1.19)
Body mass index, kg/m^2	23.13 (20.82–25.88)
Weight, kg	57.60 (50.70–65.70)
Systolic BP, mmHg	128.00 (115.33–143.00)
Diastolic BP, mmHg	74.33 (67.33–82.33)
Glucose, mg/dL	102.42 (94.32–113.04)
Total cholesterol, mg/dL	190.98 (167.78–216.11)
Triglyceride, mg/dL	105.32 (75.23–153.11)
Low-density lipoprotein cholesterol, mg/dL	115.21 (93.94–137.63)
High-density lipoprotein cholesterol, mg/dL	49.48 (40.59–59.92)
Education levels	
No formal education illiterate	1,629 (30.84)
Did not finish primary school but capable of reading and/or writing	988 (18.71)
Sishu/home school	15 (0.28)
Elementary school	1,182 (22.38)
Middle school	969 (18.35)
High school	366 (6.93)
Vocational school	90 (1.70)
Two/Three Year College/Associate degree	29 (0.55)
Four Year College/Bachelor's degree	12 (0.23)
Post-graduated (Master/PhD)	2 (0.04)
Center for Epidemiologic Studies Depression Scale	7 (3–12)
Average Hours for One Night Sleeping Time During the Past Month, h	6 (5–8)
Serum creatinine, mg/dL	0.76 (0.64–0.87)
Cystatin C, mg/dL	0.97 (0.86–1.11)
eGFR, mL/min/1.73m^2	
CG	79.15 (63.50–97.20)
CKD-EPIscr	94.76 (84.10–102.47)
CKD-EPIscr-cys	85.97 (74.47–96.95)
CKD-EPIcys	78.12 (64.70–92.74)

Table 2. Hazard ratios and 95% confidence intervals for the risk of memory-related disease according to adverse eGFR in participants.

	Un-adjusted	Multivariable adjusted model
The level of CG		
≥90	Reference	Reference
<90	1.34 (0.99–1.81)	1.56 (1.13–2.16)
P	0.055	0.007
Each SD (0.14) increase in log-(CG)	0.84 (0.75–0.95)	0.78 (0.69–0.89)
The level of CKD-EPIscr		
≥90	Reference	Reference
<90	1.41 (1.09–1.82)	1.56 (1.19–2.06)
P_{trend}	0.009	0.001
*Each SD (0.08) increase in log- (*CKD-EPIscr*)*	0.85 (0.75–0.96)	0.82 (0.72–0.93)
The level of CKD-EPIscr-cys		
≥90	Reference	Reference
<90	1.37 (1.01–1.85)	1.45 (1.06–1.99)
P_{trend}	0.043	0.020
*Each SD (0.09) increase in log- (*CKD-EPIscr-cys*)*	0.88 (0.78–0.99)	0.84 (0.74–0.96)
The level of CKD-EPIcys		
≥90	Reference	Reference
<90	1.23 (0.90–1.69)	1.27 (0.91–1.77)
P_{trend}	0.200	0.165
*Each SD (0.12) increase in log- (*CKD-EPIcys*)*	0.88 (0.78–0.99)	0.87 (0.76–0.99)

*Adjusted for current smoking, alcohol use, level of education, diabetes, hypertension, hyperlipidemia, heart disease, stroke, psychosis disease, blood glucose, body mass index, systolic BP, diastolic BP, total cholesterol, triglycerides, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, Center for Epidemiologic Studies Depression Scale and average hours for one night sleeping time during the past month at baseline.

Table 3. Subgroup analysis of HRs (95% CI) of CG levels for memory-related disease.

	Memory-related disease /Total participations	HR (95%CI)	*P*	$P_{interaction}$
All patients	235/5,282	0.78 (0.69–0.89)		
Smoking				0.638
No	138 (4.20)	0.79 (0.65–0.96)	0.019	
Yes	97 (4.86)	0.85 (0.69–1.07)	0.162	
Alcohol use				0.556
No	131 (4.02)	0.81 (0.69–0.96)	0.015	
Yes	104 (5.14)	0.82 (0.64–1.04)	0.099	
Hypertension				0.595
No	169 (4.32)	0.79 (0.68–0.93)	0.003	
Yes	66 (4.80)	0.84 (0.61–1.14)	0.265	
Diabetes				0.527
No	224 (4.51)	0.80 (0.71–0.92)	0.001	
Yes	11 (3.48)	0.15 (0.01–1.54)	0.110	
Heart disease				0.531
No	198 (4.24)	0.84 (0.73–0.97)	0.015	
Yes	37 (6.02)	0.68 (0.41–1.10)	0.117	
Stroke				0.098
No	222 (4.30)	0.79 (0.69–0.90)	<0.001	
Yes	13 (11.40)	0.53 (0.19–1.51)	0.235	
Systolic BP				0.089
<140 mmHg	157 (4.23)	0.74 (0.62–0.87)	<0.001	
≥140 mmHg	78 (4.98)	0.98 (0.75–1.27)	0.878	
Blood glucose				0.704
<110 mg/dL	157 (4.23)	0.75 (0.63–0.88)	0.001	
≥110 mg/dL	78 (4.93)	0.89 (0.67–1.19)	0.444	

Subgroup analyses of the association between the levels of CKD-EPIscr-cys and memory-related disorders. HR (95% CI) was calculated for each standard deviation (0.09) increase in log-EPIscr-cys after adjustment for current smoking, alcohol use, level of education, diabetes, hypertension, hyperlipidemia, heart disease, stroke, psychosis disease, blood glucose, body mass index, systolic BP, diastolic BP, total cholesterol, triglycerides, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, Center for Epidemiologic Studies Depression Scale and average hours for one night sleeping time during the past month at baseline. CI, confidence interval; HR, hazard ratio.

HRs (95% CIs) of memory-related disease in the group (eGFR < 90) were 1.56 (1.13–2.16) for CG, 1.56 (1.19–2.06) for CKD-EPIscr, 1.45 (1.06–1.99) for CKD-EPIscr-cys and 1.27 (0.91–1.77) for CKD-EPIcys compared with the group with eGFR ≥ 90. Similarly, on continuous analyses, each SD increase of log-transformed eGFR was associated with reduced risk of memory-related disease, with 0.78 (0.69-0.89) for CG, 0.82 (0.72-0.93) for CKD-EPIscr, 0.84 (0.74-0.96) for CKD-EPIscr-cys, and 0.87 (0.76-0.99) for CKD-EPIcys, respectively.

Subgroup analyses on the association between renal function and the risk of memory-related disease

Subgroup analyses were conducted to examine the potential effect modification by smoking, drinking, hypertension, diabetes, heart disease, stroke, systolic blood pressure, and blood glucose on the associations of renal function with memory-related disease. The modest positive associations between high eGFR (GC, CKD-EPIscr, and CKD-EPIscr-cys) level and reduced risk of memory-related disease were observed in all subgroups and reached significant levels in most subgroups. There was no significant interaction between renal function and important covariates on memory-related disease (*P* for interaction >0.05, Tables 3–5).

Incremental prognostic value of renal function in patients with memory-related disease

We examined whether adding eGFR (GC, CKD-EPIscr, and CKD-EPIscr-cys) to the conventional risk factors improved the risk prediction of memory-related disease. As shown in Table 6, adding eGFR to conventional risk factors significantly improved predictive power for memory-related disease (CG: NRI = 13.90%, $p = 0.037$; CKD-EPIscr: NRI = 19.83%, $p = 0.003$; CKD-EPIscr-cys: NRI = 30.65%, $p < 0.001$).

Discussion

Using data from a nationally representative survey in China, a total of 5,282 participants (2,899 male and 2,383 female) were included in the longitudinal study. To our knowledge, this is the first study to analyze the association between renal function and memory-related disease *via* multiple eGFR indicators. We used four eGFR indicators to evaluate renal function and then further examined the association of renal function reflected by the four indicators with memory-related disease. As expected, the lower eGFR level defined by 3 indicators were associated with high risk of memory-related disease. Continuous analysis of the 3 indicators also showed that memory-related disease was associated with reduced

Table 4. Subgroup analysis of HRs (95% CI) of CKD-EPIscr levels for memory-related disease.

	Memory-related disease /Total participations	HR (95%CI)	*P*	$P_{interaction}$
All patients	235/5,282	0.82 (0.72–0.93)		
Smoking				0.745
No	138 (4.20)	0.81 (0.68–0.95)	0.010	
Yes	97 (4.86)	0.93 (0.74–1.18)	0.552	
Alcohol use				0.725
No	131 (4.02)	0.79 (0.66–0.94)	0.007	
Yes	104 (5.14)	0.86 (0.71–1.05)	0.142	
Hypertension				0.507
No	169 (4.32)	0.81 (0.69–0.95)	0.008	
Yes	66 (4.80)	0.86 (0.68–1.09)	0.213	
Diabetes				0.574
No	224 (4.51)	0.84 (0.74–0.96)	0.011	
Yes	11 (3.48)	0.43 (0.10–1.79)	0.243	
Heart disease				0.633
No	198 (4.24)	0.86 (0.75–0.99)	0.039	
Yes	37 (6.02)	0.68 (0.48–0.97)	0.033	
Stroke				0.093
No	222 (4.30)	0.83 (0.72–0.94)	0.004	
Yes	13 (11.40)	0.76 (0.38–1.52)	0.435	
Systolic BP				0.247
<140 mmHg	157 (4.23)	0.78 (0.66–0.92)	0.004	
≥140 mmHg	78 (4.98)	0.96 (0.78–1.18)	0.663	
Blood glucose				0.885
<110 mg/dL	157 (4.23)	0.78 (0.66–0.91)	0.002	
≥110 mg/dL	78 (4.93)	0.91 (0.71–1.17)	0.463	

Subgroup analyses of the association between the levels of CKD-EPIscr-cys and memory-related disorders. HR (95% CI) was calculated for each standard deviation (0.09) increase in log-EPIscr-cys after adjustment for current smoking, alcohol use, level of education, diabetes, hypertension, hyperlipidemia, heart disease, stroke, psychosis disease, blood glucose, body mass index, systolic BP, diastolic BP, total cholesterol, triglycerides, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, Center for Epidemiologic Studies Depression Scale and average hours for one night sleeping time during the past month at baseline. CI, confidence interval; HR, hazard ratio.

Table 5. Subgroup analysis of HRs (95% CI) of CKD-EPIscr-cys levels for memory-related disease.

	Memory-related disease /Total participations	HR (95%CI)	*P*	$P_{interaction}$
All patients	235/5,282	0.84 (0.74–0.96)		
Smoking				0.738
No	138 (4.20)	0.80 (0.68–0.94)	0.007	
Yes	97 (4.86)	0.93 (0.75–1.15)	0.519	
Alcohol use				0.724
No	131 (4.02)	0.82 (0.69–0.98)	0.028	
Yes	104 (5.14)	0.84 (0.69–1.02)	0.078	
Hypertension				0.513
No	169 (4.32)	0.84 (0.72–0.98)	0.024	
Yes	66 (4.80)	0.85 (0.66–1.09)	0.188	
Diabetes				0.569
No	224 (4.51)	0.86 (0.76–0.98)	0.027	
Yes	11 (3.48)	0.48 (0.16–1.48)	0.204	
Heart disease				0.683
No	198 (4.24)	0.85 (0.74–0.97)	0.017	
Yes	37 (6.02)	0.68 (0.46–1.02)	0.064	
Stroke				0.095
No	222 (4.30)	0.85 (0.75–0.97)	0.016	
Yes	13 (11.40)	0.59 (0.26–1.32)	0.198	
Systolic BP				0.229
<140 mmHg	157 (4.23)	0.83 (0.70–0.97)	0.021	
≥140 mmHg	78 (4.98)	0.91 (0.73–1.41)	0.409	
Blood glucose				0.895
<110 mg/dL	157 (4.23)	0.81 (0.69–0.95)	0.009	
≥110 mg/dL	78 (4.93)	0.95 (0.75–1.21)	0.673	

Subgroup analyses of the association between the levels of CKD-EPIscr-cys and memory-related disorders. HR (95% CI) was calculated for each standard deviation (0.09) increase in log-EPIscr-cys after adjustment for current smoking, alcohol use, level of education, diabetes, hypertension, hyperlipidemia, heart disease, stroke, psychosis disease, blood glucose, body mass index, systolic BP, diastolic BP, total cholesterol, triglycerides, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, Center for Epidemiologic Studies Depression Scale and average hours for one night sleeping time during the past month at baseline. CI, confidence interval; HR, hazard ratio.

risk as the eGFR increased, showing highly consistent results. In addition, we performed subgroup analyses of 3 renal function measures to further confirm the robustness of the relationship between renal function and memory-related disease. Finally, adding eGFR to the conventional risk factors substantially improved the risk prediction of memory-related disease, as evidenced by NRI. These results suggest that decreased renal function may be associated with the development of memory-related disease. Given the prevalence of decreased renal function in the older population, memory-related disease in older people is often associated with an increased risk of many adverse outcomes. Therefore, it is of great public health significance to put forward corresponding prevention and control measures.

Renal dysfunction is associated with a variety of diseases, including such as cognitive impairment and memory loss. Results from a cohort study base on Northern Ireland Cohort for the Longitudinal Study of Aging (NICOLA) showed that impaired renal function was associated with an increased risk of cognitive impairment [16]. Another case-control study indicated memory impairment in patients with end-stage renal disease compared with healthy controls [17]. As the objective index to evaluate glomerular filtration capacity, eGFR is the best indicator of renal function. Previous studies on the relationship between eGFR and memory-related disease have been few and controversial, still lacked of longitudinal cohort studies with large sample sizes. A case-control study of 676 patients (n case = 508 and n control = 168) with PD identified eGFR as a biomarker of cognitive impairment in PD, and other renal measures were not associated with cognitive impairment [18]. Results from a secondary analysis of the Framingham Heart Study, which included 2,604 patients, showed that lower eGFR was associated with a higher risk of incident dementia [19]. While Euan N Paterson et.al contacted a cross-sectional cohort study based on a Northern Ireland cohort showed that this study failed to find an association between eGFR and AD in a cross-sectional sample study of elderly white individuals [20].

Herein, we conducted a study to further explore the relationship between renal function and the risk of memory-related disease. This study based on CHARLS, a longitudinal study from 10,257 households recruited from 28 provinces within China in exploring the relationship between renal function and the risk of memory-related disease. We calculated eGFR using four indicators to assess the relationship between renal function and memory-related disease, and suggesting that decreased renal function was independently associated with the risk of memory-related disease. In addition, these findings were further confirmed by subgroup analysis, which showed no statistically significant

Table 6. Reclassification and discrimination statistics for memory-related disease by anthropometric indices among participants.

	NRI (category free)		IDI	
	Estimate (95% CI), %	*P* value	Estimate (95% CI), %	*P* value
Conventional model	Reference		Reference	
Conventional model + the levels of CG	13.90 (1.81–25.98)	0.037	0.12 (−0.41–0.65)	0.667
Conventional model				
Conventional model + the levels of CKD-EPIscr	19.83 (6.80–32.86)	0.003	0.20 (−0.41–0.81)	0.524
Conventional model				
Conventional model + the levels of CKD-EPIscr-cys	30.65 (19.17–42.12)	<0.001	−0.07 (−0.55–0.40)	0.756

*Adjusted for current smoking, alcohol use, level of education, diabetes, hypertension, hyperlipidemia, heart disease, stroke, psychosis disease, blood glucose, body mass index, systolic BP, diastolic BP, total cholesterol, triglycerides, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, Center for Epidemiologic Studies Depression Scale and average hours for one night sleeping time during the past month at baseline.

interaction of important covariates on the memory-related disease. Furthermore, comprehensive information about potential confounders was adjusted in the multivariate models to eliminate the confounding effects, suggesting the robustness and reliability of the results in this study.

The precise mechanisms linking renal function and risk of memory-related disease are not well understood, but a number of hypotheses have been identified. Patients with renal dysfunction are prone to vascular stiffness and vascular calcification, which may cause cerebral vascular endothelial dysfunction and further cause cognitive decline or AD [21]. In addition, accumulation of uremic toxins (such as indoxyl sulfate) caused by renal impairment, which have endothelial toxicity and can damage the cerebral endothelium [22,23]. The breakdown of the blood-brain barrier (BBB) has been implicated multiple neurodegenerations, and BBB disruption appears to be an important mechanism behind cognitive impairment in CKD [24]. Besides, renal dysfunction is closely associated with increased activation of the renin-angiotensin system, which leads to an increase in renin-angiotensin system and may further cause elevated levels of amyloid β-protein, while β-protein has been identified in past studies as the substance most closely associated with the onset of AD [25,26]. Finally, we did not find a significant association between CKD-EPIcys as estimated by serum cystatin C and memory-related diseases in our study. The association between serum cystatin C and memory-related disease has not been fully evaluated in past studise. A study based on the UK Biobank showed a U-shaped relationship between CKD-EPIcys estimated by serum cystatin C and the risk of all-cause dementia and vascular dementia [27]. However, results from a case-control study conducted by Sara F Hansson et al. showed no significant change in plasma cystatin C levels in patients with AD [28]. Future studies are needed to explore the relationship between CKD-EPIcys estimated by cystatin C and memory-related disease.

Our study has several strengths. First, this study was based on the data from the CHARLS study, which is a large nationally representative cohort study with a high response rate, with high quality data. In addition, because of the subjects in this study were drawn from a nationally representative study, our findings can be generalized to the general adult population. Several limitations also exist in this study. First, consistent with other previous studies based on CHARLS [29–31], the reliance on self-reported diagnoses of memory-related diseases, based on physician assessments, introduces the possibility of reporting bias. Although a study had suggested about 75% accuracy in self-reported disease [32]. Second, we did not find that CKD-EPIcys was associated with the memory-related disease. This may be because the EPIscr-cys and CKD-EPIscr equations are superior to the CKD-EPIcys equation in the Chinese population, and the CKD-EPIcys equation may underestimate kidney function [33,34]. Third, our study did not explore the effect of dynamic changes in renal function on memory-related disease, but tentatively revealed the effect of baseline renal function status on memory-related diseases. Further studies are needed to explore the influence of dynamic changes in renal function on memory-related diseases. Besides, due to the lack of data on specific subtypes for different memory-related disease (e.g. dementia, brain atrophy, and Parkinson's disease) and some variables (e.g. antipsychotic drug use), we were unable to make a more definitive analysis of specific subtypes as well as other variables. Finally, the CHARLS study was only conducted in the Chinese population, and our findings may not be generalizable to other populations.

Conclusion

In conclusion, we found that impaired renal function was associated with the increasing risk of memory-related disease, indicating that renal function may be a potential indicator for memory-related disease. Further studies from other races and populations are needed to replicate our findings and to clarify the potential mechanisms.

Author statement

All coauthors contributed to this work, and agreed with the contents of the manuscript.

Acknowledgement

This analysis uses data or information from the Harmonized CHARLS dataset and Codebook, Version C as of April 2018 developed by the Gateway to Global Aging Data. The development of the Harmonized CHARLS was funded by the National Institute on Ageing (R01AG030153, RC2 AG036619,

R03 AG043052). For more information, please refer to www.g2aging.org.

Author contributions

Kaixin Zhang and Xiaowei Zheng contributed to the conception and design of the study; Yu Wang and Qian Zhao contributed to the acquisition and analysis of data; Yu Wang and Qian Zhao contributed to drafting the text or preparing the figures.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was funded by the Science Technology Department of Suzhou (grant number: SKY2022099).

Data availability statement

The data that support the findings of this study are openly available in CHARLS at https://charls.pku.edu.cn/en/.

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