

Original Article

Chronic kidney disease is associated with incident cognitive impairment in the elderly: the INVADE study

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Abstract

Background. Limited data exist regarding the relationship between decreased renal function and cognitive impairment.

Methods. A total of 3679 participants of the Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg (INVADE) composed the community-based cohort study. Measures of renal function were estimated using the Cockcroft–Gault equation and divided into normal, mild and moderate-to-severe impaired renal function (creatinine clearance ≥ 60 , 45–59 and < 45 mL/min/1.73 m², respectively). The main outcome measures were cognitive impairment at baseline and new cognitive impairment after a 2-year follow-up. Cognitive function was measured using the 6-Item Cognitive Impairment Test (6CIT). Multiple logistic regression analysis was used to assess the association between renal function and cognitive impairment.

Results. At baseline, 396 participants (10.8%) had cognitive impairment. After the 2-year follow-up, 194 participants (6.2%) developed new cognitive impairment. The incidence of cognitive impairment across the groups with normal renal function, mild and moderate-to-severe kidney disease at baseline were 5.8, 9.9 and 21.5%, respectively. Multiple logistic regression analysis after adjustment for possible confounders including traditional cardiovascular risk factors showed a significant association for participants with moderate-to-severe kidney disease at baseline to develop new cognitive impairment after the 2-year follow-up [odds ratio: 2.14 (95% confidence interval: 1.18–3.87), $P = 0.01$].

Conclusions. In summary, moderate-to-severe impaired renal function is associated with incident cognitive impairment after 2 years in a large cohort of elderly subjects.

Keywords: chronic kidney disease; cognitive impairment; elderly

Introduction

Chronic diseases affecting the elderly are gaining more importance. Among those, chronic kidney disease (CKD) and cognitive impairment are growing worldwide public health problems [1,2]. Both conditions are associated with traditional cardiovascular disease risk factors including older age, diabetes, hypertension and dyslipidaemia [3–5].

A high prevalence of cognitive impairment and dementia in patients requiring chronic dialysis is well established. Recent data have suggested that early stages of kidney disease are also an independent risk factor for cognitive impairment [6–11]. However, the existing literature is limited by the variability in testing for cognitive function [6], the lack of follow-up data on renal function and its relationship with newly developed cognitive impairment [6,8–10], or the population studied has been mainly restricted to menopausal women with established coronary artery disease [10] or older men [11]. Furthermore, none of these studies have been performed among non-U.S. cohorts.

Using data of the INVADE (Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg, Bavaria) study [12], the present longitudinal analysis was undertaken to test the hypothesis that renal function is independently and prospectively associated with newly diagnosed impairment of cognitive function using the 6-Item Cognitive Impairment Test (6CIT). This is a simple and brief test of cognition that correlates well with the Mini-Mental State Exam [13], performs better in mild dementia and is thus a useful tool for cognitive screening in primary care [14].

Subjects and methods

Subjects

The INVADE study is a prospective and population-based cohort study [12,15,16]. All inhabitants of the district of Ebersberg, Germany, born

before 1946, and being members of the health insurance company AOK ('Allgemeine Ortskrankenkasse') were identified in the AOK database and then invited to participate ($n = 10\,325$). In the area of Ebersberg, >40% of all inhabitants aged over 55 years were AOK members. During the baseline period of 2001–03, 3908 subjects followed up the invitation, of which 3679 subjects could be included in the present study. The remaining subjects were excluded due to incomplete data for calculation of renal function ($n = 227$) or missing baseline 6CIT ($n = 2$).

Evaluations

The baseline investigation was done by primary care physicians of the district of Ebersberg ($n = 65$) and included a standardized questionnaire, medical history, an evaluation of several risk factors, a physical examination, a 12-lead electrocardiogram (ECG) and an overnight fasting venous blood sample for analysis in a central laboratory. All data were entered in a central database after plausibility checks for further evaluation. After the initial baseline investigation, the primary care physician performed a physical examination of the participants every 3 months. Complete evaluations were scheduled after the 2-year follow-up. The local institutional review board approved this study. All patients provided written informed consent before entering the study. Details of the study design have recently been published in detail [12].

Cardiovascular disease status and risk factors

Information on current health status, medical history, lifestyle, cognitive status, mood disorders, drug use and former cardiovascular risk factors was obtained by a highly structured questionnaire at baseline. The determined risk factors included the following: BMI (kg/m^2), smoking status (never, former or current), alcohol consumption (<7 drinks/week or \geq), physical activity (exercise < 3 times/week or \geq), depression [Geriatric Depression Score (GDS) ≥ 6] [17], arterial hypertension (treatment with antihypertensive medication or documented blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic measured in a standardized fashion) [18], diabetes mellitus [treatment with anti-diabetic drugs or overnight fasting serum glucose levels ≥ 126 mg/dL (7.0 mmol/L)], hyperlipidaemia (treatment with lipid-lowering medication or cholesterol ≥ 200 mg/dL or triglycerides ≥ 150 mg/dL) [19], prevalent history of ischaemic heart disease (documented by previous myocardial infarction or angina pectoris, bypass surgery or > 50% angiographic stenosis of more than one major coronary artery) and prevalent history of stroke (neurological deficit that persisted longer than 24 h, evaluated by a neurologist). Myocardial infarction (MI) and stroke were diagnosed according to recent recommendations [20,21].

Definition of kidney function

Because a number of factors such as age, sex and weight can influence serum creatinine concentrations, the level of kidney function was calculated as clearance of creatinine (Ccr) using the Cockcroft–Gault (CG) equation [22], which includes measures of age, weight and sex, and was standardized for body surface area (BSA):

$$\begin{aligned} \text{Creatinine clearance}(\text{mL}/\text{min}/1.73\text{m}^2) = & \{[(140 - \text{Age}) \\ & \times (\text{weight}) \times (0.85 \text{ if female})]/(72) \\ & \times (\text{serum creatinine})\} \times 1.73\text{m}^2\text{BSA}, \end{aligned}$$

where serum creatinine is in mg/dL, age is in years, weight is in kilograms and BSA is body surface area, estimated using the Dubois formula [23]:

$$\text{BSA}(\text{m}^2) = 0.20247 \times (\text{height})^{0.725} \times (\text{weight})^{0.425}$$

where height is in metres and weight in kilograms. This prediction equation has been used in other analyses of the INVADE study [15,16] and has been validated in older European adults [24,25]. For the purpose of this analysis, we defined mild CKD as Ccr between 45 and 59 mL/min/1.73 m² and moderate-to-severe CKD as Ccr <45 mL/min/1.73 m² [8,11,26]. These categories were chosen since Ccr < 45 mL/min/1.73 m² is considered a more advanced state of kidney disease and only 40 subjects (1.1%) had Ccr < 30 mL/min/1.73 m². We also performed a sensitivity analysis using serum creatinine as a measure of kidney function instead of Ccr measured by the CG formula. Additional analyses were performed using the above definitions of kidney disease progression measured by using the four-variable Modification of Diet in Renal Disease (MDRD) formula [27].

Laboratory examinations

Overnight fasting blood samples were drawn from each subject and were transferred on ice to a central laboratory that performed all analyses including fasting serum glucose, cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides. Serum creatinine was assessed by a kinetic alkaline picrate (Jaffe) method [28].

Cognitive screening

Screening for cognitive function was performed by using the 6CIT. The 6CIT is an abbreviation of the Blessed Information Memory Concentration Scale [29] and consists of six questions (asking for year, month and time; counting backwards from 20 to 1; saying the months of the year in reverse; remembering an address with five components; see the Appendix) [14]. Levels between 0 and 7 points are considered normal levels and scores >7 are consistent with cognitive impairment [13,14]. The 6CIT is a brief and simple test of cognition that correlates well with the Mini-Mental State Examination [13]. It also performs better in mild dementia, and time needed to perform the test is ~3–4 min that makes the 6CIT a useful tool for cognitive screening in primary care [14]. The test itself was applied by the primary care physicians who were all trained in the use of the 6CIT prior to study begin.

Statistical analysis

All values are given as mean and standard deviation (SD) or 95% confidence intervals (CI) or as counts and percentages. We used chi-square tests, independent *t*-tests, Mann–Whitney *U*-tests and Pearson's correlation for univariate analysis, as appropriate. The study population was divided according to baseline renal function (Ccr ≥ 60 , 45–59 and <45 mL/min/1.73 m², respectively). Multiple logistic regression analysis was used to analyse the association of cognitive impairment with a function of Ccr or serum creatinine. Candidate covariates included age, sex, smoking, prevalent history of ischaemic heart disease and/or stroke, hypertension, diabetes, body mass index, hyperlipidaemia, alcohol consumption, physical activity and depression at baseline. Unadjusted analysis examined the association between Ccr status or serum creatinine and all candidate covariates. Adjustment of all multiple regression models included all covariates found to be significant in unadjusted analysis and the biologically plausible covariates. Regression analysis for new cognitive impairment at follow-up included also adjustment for the baseline 6CIT score. For all calculations, SPSS version 16.0.1 for Windows (SPSS Inc., Chicago, IL, USA) was used. *P*-values <0.05 were considered to be statistically significant.

Results

Baseline characteristics

We included 3679 subjects in the analysis. The baseline characteristics for participants by Ccr are summarized in Table 1. Compared with participants with Ccr ≥ 60 mL/min/1.73 m², participants with Ccr <60 mL/min/1.73 m² were older and more likely to be women. Participants with CKD of any degree had a greater prevalence of hypertension and ischaemic heart disease. No differences were observed in total cholesterol. Of note, a lower prevalence for smoking and obesity was observed in subjects with Ccr <60 mL/min/1.73 m². At baseline, 396 participants (10.8%) had cognitive impairment. The prevalences of cognitive impairment by the Ccr group among participants with normal or near normal renal function, mild and moderate-to-severe CKD at baseline were 9.3, 15.4 and 22.2%, respectively.

Cross-sectional association between kidney function and baseline cognitive impairment

The unadjusted analysis showed a significant association between cognitive impairment at baseline and the following confounders: age ($P < 0.001$), sex ($P = 0.033$), diabetes

Table 1. Baseline characteristics of participants by creatinine clearance

	Ccr \geq 60 mL/min/1.73 m ² (n = 3031)	Ccr 45–59 mL/min/1.73 m ² (n = 441)	Ccr < 45 mL/min/1.73 m ² (n = 207)	P-value
Age (years)	66.1 \pm 6.5	73.7 \pm 8.0	79.2 \pm 7.9	<0.0001
Sex (male)	1394 (46.0%)	85 (19.3%)	29 (14.0%)	<0.0001
History of stroke	96 (3.2%)	20 (4.6%)	10 (4.9%)	0.171
History of ischaemic heart disease	317 (10.7%)	81 (19.1%)	56 (27.7%)	<0.0001
Diabetes mellitus	340 (11.2%)	51 (11.6%)	33 (15.9%)	0.120
Hypertension	2224 (73.4%)	344 (78.2%)	181 (87.4%)	<0.0001
Hyperlipidaemia	2413 (79.6%)	368 (83.6%)	169 (81.6%)	0.122
Antihypertensive drugs	1675 (55.3%)	280 (63.5%)	156 (75.4%)	<0.0001
Lipid-lowering drugs	608 (20.1%)	97 (22.0%)	21 (10.0%)	0.039
6CIT > 7	282 (9.3%)	68 (15.4%)	46 (22.2%)	<0.0001
6CIT (absolute score)	2.5 \pm 3.5	3.5 \pm 4.8	4.5 \pm 5.2	<0.0001
Depression (GDS \geq 6)	263 (8.7%)	48 (10.9%)	43 (20.8%)	<0.0001
Physical activity (\geq 3 times/week)	1476 (48.7%)	167 (37.9%)	61 (29.5%)	<0.0001
Current smoking	336 (11.1%)	24 (5.4%)	13 (6.3%)	<0.0001
Alcohol (\geq 7 drinks/week)	700 (23.1%)	45 (10.2%)	12 (5.8%)	<0.0001
Body mass index (kg/m ²)	28.4 \pm 4.4	25.1 \pm 3.4	24.4 \pm 3.9	<0.0001
Fasting glucose (mg/dL)	96.1 \pm 30.7	94.5 \pm 31.6	100.0 \pm 34.4	0.109
Cholesterol (mg/dL)	219 \pm 39	220 \pm 41	225 \pm 42	0.06
HDL cholesterol (mg/dL)	57 \pm 15	63 \pm 18	63 \pm 18	<0.0001
LDL cholesterol (mg/dL)	133 \pm 35	132 \pm 34	134 \pm 39	0.674
Triglyceride (mg/dL)	147 \pm 86	132 \pm 67	133 \pm 77	<0.0001
Systolic blood pressure (mmHg)	140 \pm 18	140 \pm 20	142 \pm 20	0.228
Diastolic blood pressure (mmHg)	83 \pm 10	81 \pm 9	79 \pm 11	<0.0001
Baseline creatinine (mg/dL)	0.84 \pm 0.19	0.96 \pm 0.25	1.31 \pm 0.94	<0.0001
Baseline Ccr (mL/min/1.73 m ²)	101.0 \pm 33.9	53.3 \pm 4.2	35.8 \pm 7.5	<0.0001

Categorical variables are expressed as percentages with *P*-values calculated by the chi-square test and continuous variables are given as mean (standard deviation) with *P*-values calculated by ANOVA.

Ccr: clearance of creatinine; CIT: Cognitive Impairment Test; GDS: Geriatric Depression Score; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table 2. Association between renal function and cognitive function impairment (6CIT >7) at baseline

Model	Ccr \geq 60 mL/min/1.73 m ²	Model		Ccr < 45 mL/min/1.73 m ²	
		OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Unadjusted	1.00	1.78 (1.34–2.37)	<0.001	2.79 (1.96–3.95)	<0.001
Adjusted for age and sex	1.00	1.20 (0.87–1.65)	0.269	1.38 (0.92–2.09)	0.124
Fully adjusted ^a	1.00	1.16 (0.82–1.63)	0.400	1.28 (0.83–1.98)	0.263

OR: odds ratio; CI: confidence interval; 6CIT: 6-Item Cognitive Impairment Test.

^aAdjusted for age, sex, depression, physical activity, alcohol, diabetes, history of ischaemic heart disease and/or stroke, hyperlipidaemia, hypertension and smoking.

(*P* = 0.001), prevalent history of ischaemic heart disease (*P* < 0.001) and stroke (*P* < 0.001), physical activity (*P* < 0.001), alcohol consumption (*P* = 0.015) and depression (*P* < 0.001). In unadjusted analysis, moderate-to-severe CKD disease showed a stronger relationship with baseline cognitive impairment than mild CKD. However, the fully adjusted model for age, sex, depression, physical activity, alcohol, diabetes, history of ischaemic heart disease and/or stroke, hyperlipidaemia, hypertension and smoking did not reach statistical significance (Table 2). Additional fully adjusted analysis using the MDRD prediction equation (OR: 1.51; 95% CI: 0.88–2.60; *P* = 0.133) or serum creatinine (OR: 1.08; 95% CI: 0.80–1.46; *P* = 0.606) as a measure of renal function was also non-significant.

Follow-up characteristics

The mean time of follow-up was 784 \pm 72 days. Data on cognitive function could be obtained in 3154 subjects. Data

were not available in 525 (14.2%) participants because of death (*n* = 106), change of health insurance company (*n* = 25) or incomplete data (*n* = 394). Compared with the remaining 3154 participants, the 525 participants lost to follow-up showed the following significant differences in the baseline characteristics: older (69.1 \pm 9.3 versus 67.5 \pm 7.5 years; *P* < 0.001), higher diastolic blood pressure (83 \pm 10 versus 82 \pm 10 mmHg; *P* = 0.022), higher 6CIT score (3.5 \pm 5.0 versus 2.6 \pm 3.6; *P* < 0.001), higher GDS (3.1 \pm 2.9 versus 2.3 \pm 2.4; *P* < 0.001) and higher serum creatinine (0.92 \pm 0.40 versus 0.88 \pm 0.29 mg/dL; *P* = 0.001). Prevalent stroke (5.9% versus 3.0%; *P* = 0.001) and ischaemic heart disease (17.9% versus 11.4%; *P* < 0.001) were increased, but hyperlipidaemia (77.0% versus 80.7%; *P* = 0.043) and alcohol consumption (16.8% versus 21.2%; *P* = 0.019) were less common in the participants lost to follow-up. After excluding participants with cognitive impairment at baseline, 194 participants (6.1%) developed new cognitive impairment at the end of the follow-up period. The

Table 3. Characteristics of 194 participants with new cognitive impairment by creatinine clearance at baseline

	Ccr ≥ 60 mL/min/1.73 m ² (n = 136)	Ccr 45 to 59 mL/min/1.73 m ² (n = 32)	Ccr < 45 mL/min/1.73 m ² (n = 26)	P-value
Age (years)	68.2 \pm 6.7	78.3 \pm 8.0	81.5 \pm 7.7	<0.0001
Sex (male)	69 (50.7%)	12 (37.5%)	3 (11.5%)	<0.0001
History of stroke	6 (4.4%)	0	2 (7.7%)	0.329
History of ischaemic heart disease	20 (14.7%)	8 (25.0%)	8 (30.8%)	0.116
Diabetes mellitus	1 (0.7%)	1 (3.1%)	3 (11.5%)	0.003
Hypertension	109 (80.1%)	27 (84.4%)	24 (92.3%)	0.316
Hyperlipidaemia	110 (80.9%)	25 (78.1%)	20 (76.9%)	0.868
Baseline 6CIT	3.0 \pm 2.3	3.6 \pm 2.4	3.0 \pm 2.4	0.414
Follow-up 6CIT	9.5 \pm 2.8	10.1 \pm 2.6	10.7 \pm 4.7	0.156
Depression (GDS ≥ 6)	22 (16.2%)	5 (15.6%)	3 (11.5%)	0.858
Physical activity (≥ 3 times/week)	56 (41.2%)	21 (65.6%)	5 (19.2%)	0.093
Current smoking	17 (12.5%)	3 (9.4%)	2 (7.7%)	0.107
Alcohol (≥ 7 drinks/week)	28 (20.6%)	4 (12.5%)	3 (11.5%)	0.371
Body mass index (kg/m ²)	28.7 \pm 4.3	25.6 \pm 3.3	24.1 \pm 4.3	<0.0001
Fasting glucose (mg/dL)	99.8 \pm 35.7	95.6 \pm 33.6	109.2 \pm 42.0	0.347
Cholesterol (mg/dL)	217 \pm 38	222 \pm 44	223 \pm 41	0.703
HDL cholesterol (mg/dL)	58 \pm 16	59 \pm 14	68 \pm 22	0.022
LDL cholesterol (mg/dL)	131 \pm 35	136 \pm 36	130 \pm 37	0.794
Triglyceride (mg/dL)	145 \pm 84	140 \pm 75	152 \pm 138	0.881
Systolic blood pressure (mmHg)	142 \pm 17	137 \pm 16	138 \pm 19	0.157
Diastolic blood pressure (mmHg)	82 \pm 10	79 \pm 9	77 \pm 9	0.010
Baseline creatinine (mg/dL)	0.84 \pm 0.18	0.98 \pm 0.26	1.38 \pm 1.20	<0.0001
Follow-up creatinine (mg/dL)	0.92 \pm 0.20	1.13 \pm 0.39	1.59 \pm 1.26	<0.0001
Baseline Ccr (mL/min/1.73 m ²)	99.7 \pm 38.7	52.1 \pm 5.0	33.3 \pm 7.7	<0.0001
Follow-up Ccr (mL/min/1.73 m ²)	87.4 \pm 28.2	44.2 \pm 12.0	29.2 \pm 14.3	<0.0001

Categorical variables are expressed as percentages with *P*-values calculated by the chi-square test, and continuous variables are given as mean (standard deviation) with *P*-values calculated by ANOVA.

Ccr: clearance of creatinine; CIT: Cognitive Impairment Test; GDS: Geriatric Depression Score; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

characteristics of those participants with new cognitive impairment are shown in Table 3. The incidence of cognitive impairment among participants with normal or near normal renal function, mild and moderate-to-severe CKD at baseline was 5.8, 9.9 and 21.5%, respectively.

The mean Ccr at follow-up among participants with normal or near normal renal function, mild and moderate-to-severe CKD at baseline were 89.3 \pm 31.0, 50.1 \pm 11.5 and 34.7 \pm 12.7 mL/min/1.73 m², respectively. The correlation between Ccr at baseline and at follow-up was high ($r = 0.86$).

Longitudinal association between renal function and cognitive impairment at follow-up

Unadjusted analysis yielded a strong relationship between baseline renal function and the development of new cognitive function impairment in participants with moderate-to-severe CKD when compared to participants with normal or near normal kidney function. After adjustment for age, sex, diabetes, baseline cognitive function, prevalent history of ischaemic heart disease and/or stroke, there remained a significant association with new cognitive function impairment in moderate-to-severe CKD when compared to those with Ccr ≥ 60 mL/min/1.73 m² (Table 4). The inclusion in the multivariate models of covariates that have a biological plausibility for developing cognitive impairment but were not significant in univariate analysis (i.e. hypertension, hyperlipidaemia and smoking) did not alter

the results, as the odds ratio for developing new cognitive function impairment in moderate-to-severe CKD remained 2.14 (95% CI: 1.18–3.87; $P = 0.012$). The fully adjusted analysis with serum creatinine as a measure of renal function revealed similar results (OR: 1.67; 95% CI: 1.04–2.7; $P = 0.035$). The same fully adjusted analysis was repeated using the MDRD prediction equation; however, an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m² was not significantly associated with new cognitive impairment (OR: 1.43; 95% CI: 0.61–3.32; $P = 0.411$).

After excluding all participants with CKD at baseline, newly developed CKD (i.e. Ccr < 60 mL/min/1.73 m²) was found to be independently associated with developing new cognitive impairment when compared to participants with normal or near normal renal function during the 2-year follow-up (OR: 1.73; 95% CI: 1.26–2.43; $P < 0.001$).

Discussion

This population-based prospective study of a large cohort of elderly subjects found that moderate-to-severe impaired renal function, defined as Ccr <45 mL/min/1.73 m², yielded a significant association with newly diagnosed cognitive impairment after 2 years. This result remained significant even after adjustment of important potential confounders as age, sex, baseline cognitive status and cardiovascular risk factors.

Table 4. Association between renal function and new cognitive impairment (6CIT >7) at follow-up

Model	Ccr \geq 60 mL/min/1.73 m ²	Ccr 45–59 mL/min/1.73 m ²		Ccr < 45 mL/min/1.73 m ²	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Unadjusted	1.00	1.82 (1.22–2.73)	0.004	4.55 (2.85–7.25)	<0.001
Adjusted for age and sex	1.00	1.20 (0.76–1.87)	0.43	2.06 (1.18–3.61)	0.01
Adjusted for age, sex and baseline 6CIT	1.00	1.15 (0.72–1.83)	0.56	2.15 (1.21–3.82)	0.009
Adjusted for age, sex, baseline 6CIT, diabetes, history of ischaemic heart disease and/or stroke	1.00	1.13 (0.70–1.81)	0.625	2.11 (1.17–3.79)	0.013
Fully adjusted ^a	1.00	1.12 (0.69–1.82)	0.651	2.14 (1.18–3.87)	0.012

OR: odds ratio; CI: confidence interval; 6CIT: 6-Item Cognitive Impairment Test.

^aAdjusted for age, sex, baseline 6CIT, depression, physical activity, alcohol, diabetes, history of ischaemic heart disease and/or stroke, hyperlipidaemia, hypertension and smoking.

Our results are in line with other studies that have found an association between renal function and cognitive function decline. Some landmark cross-sectional studies have reported a relationship between prevalent renal disease and cognitive function impairment. In a study of 1015 women with established coronary artery disease (Heart Estrogen/Progestin Replacement Study), women with an eGFR <30 mL/min/1.73 m² had a 5-fold greater odds of cognitive impairment compared with those with an eGFR \geq 60 mL/min/1.73 m², independent of age, race and other potential confounders [10]. A major limitation was the assessment of women with established coronary artery disease. Hailpern and colleagues using data from the Third National Health and Nutrition Examination Survey studied the relationship between renal function and cognitive performance among young adults (aged 20–59 years) using at least one of three computerized tests including visual-motor reaction time, visual attention and learning/concentration in 4849 participants. Moderate CKD defined as an eGFR 30–59 mL/min/1.73 m² was significantly associated with poorer learning/concentration (OR: 2.41; 95% CI: 1.30–5.63; $P = 0.04$) and impairment in visual attention (OR: 2.74; 95% CI: 1.01–7.40; $P = 0.05$) [6]. The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study also assessed in a cross-sectional design the association between renal function and cognitive impairment in 23 405 participants using the 6-Item Screener which is a short version of the Mini-Mental Status Examination including recall and temporal orientation. Impaired kidney function was associated with an increased prevalence of cognitive impairment independent of confounding factors (OR: 1.23; 95% CI: 1.06–1.43) [9]. The performance of cognitive testing by a telephone interview was one major limitation of this study.

Other studies have examined the longitudinal association between renal function and cognitive impairment, but the results have been conflicting. The Cardiovascular Health Cognition Study, Seliger *et al.* reported in 3349 participants an elevated risk for incident dementia confirmed through neurological testing in elderly individuals with CKD. After adjustment for potential confounders, moderate renal impairment (defined as a serum creatinine \geq 1.3 mg/dL for women and \geq 1.5 mg/dL for men) was found to be associated with a 37% increased risk of dementia (95% CI: 1.06–1.78) [7]. One limitation of this study was the assessment

of renal function with serum creatinine [30]. Similarly, the Health, Aging, and Body Composition Study analysed cognitive function using the modified Mini-Mental State Exam at baseline and after 2–4 years of follow-up among 3034 elderly people with CKD. These investigators noted an increased risk for cognitive impairment in CKD participants (OR: 1.32; 1.03–1.69 for eGFR 45–59 mL/min/1.73 m² and OR 2.43; 1.38–4.29 for eGFR <45 mL/min/1.73 m²) [8]. Contrary to previous reports, the Osteoporotic Fractures in Men Study (MrOS) assessed cognitive function using the modified Mini-Mental State Examination and Trail Making Test B at baseline and after 5 years of follow-up in 5529 men aged 65 and older. In this study, no association was established between CKD defined as eGFR <60 mL/min/1.73 m² and global cognitive impairment or risk of a cognitive decline [11].

Of note, when using the MDRD equation, an eGFR <45 mL/min/1.73 m² was not significantly associated with new cognitive impairment. In a recent review of how to assess kidney function best, Stevens *et al.* clearly stated that in some studies, the MDRD study equation has been reported to be more accurate than the CG equation, whereas other studies have found that the CG outperforms the MDRD prediction equation [31]. For example, in a landmark study [32], the predictive performance of eight prediction equations, including the CG and the MDRD formula, in patients with CKD and serum creatinine levels in the normal range was compared to standard iohexol GFR values. The results of this study revealed that the most accurate renal function estimates were derived by using the CG prediction equation [32]. A likely explanation of the discrepancy of our results using the CG formula and the MDRD equation is that most participants with CKD in the INVADE cohort had serum creatinine values in the normal range similar to the cohort reported in the publication by Bostom *et al.*

This study cannot explain the mechanism behind the observed association between incident cognitive impairment and moderate impaired renal function. Patients with CKD have a higher prevalence of subclinical cerebrovascular and traditional vascular risk factors including hypertension, diabetes mellitus and dyslipidaemia than the general population [33]. Non-traditional vascular risk factors including haemostatic abnormalities, hypercoagulable states, inflammation and oxidative stress may also be associated with cognitive impairment [34]. The association

of cognitive impairment or dementia and CKD may reflect long-term vascular disease burden manifested in two end organs, kidney and brain. This hypothesis is supported by two new cross-sectional studies demonstrating that albuminuria is associated with worse cognitive performance as well as increased white matter hyperintensity volume [35,36]. Furthermore, there is a broad spectrum of nonvascular risk factors that may have a role in the development of cognitive decline like anaemia in CKD that has been associated strongly with cognitive impairment [37]. In addition, neurophysiological testing has shown improvement with the treatment of anaemia in CKD [38]. Other potential risk factors for cognitive function decline in CKD patients include side effects and interaction of medications as well as sleep disturbances that result in an impaired concentration, excessive daytime fatigue and possibly cognitive dysfunction [39].

Amyloid metabolism may also explain the link between CKD and cognitive impairment. Changes in the solubility of amyloid- β proteins play a key role in the pathophysiology of cognitive decline [40]. As the major clearance of amyloid- β proteins is probably through the kidneys [41], the clearance of amyloid- β proteins in the central nervous system to peripheral blood and excretion by the kidney could be a determinant of amyloid deposition and plaques in the brain [42].

The strengths of our study are the large number of patients, the complete nature of the dataset, the longitudinal assessment of renal function and cognitive performance and the regular examination by general practitioners. Another advantage includes the ability to adjust for multiple vascular risk factors that may affect cognitive function. Despite the comprehensive nature of the dataset, this study also has several limitations. First, the definition of renal disease was based on two measurements of renal function (i.e. creatinine and Ccr) rather than more precise measures of kidney function, like iothalamate clearance. Second, the follow-up period for cognitive decline of 2 years is relatively short. Third, the assessment of cognitive function was based only on the use of the 6CIT. However, it has been shown that the 6CIT is equivalent to the Mini-Mental State Exam in identifying dementia [43], and current data suggest a better performance of the 6CIT when compared to other testing in patients with mild dementia favouring its use as a screening tool for cognitive function in primary care [14]. Fourth, data on albuminuria and brain imaging were lacking. This additional information might have added some light on pathogenesis [35,36]. Last, we cannot fully exclude the bias by the observational nature of this study design as, for example, participants with cognitive impairment at beginning could be less likely to get involved or those participants who were lost to follow-up had a higher risk of death.

In summary, the present study found that in a general elderly population, moderate-to-severe impaired renal function is independently associated with new cognitive impairment after the 2-year follow-up. Further studies focussing on the long-term natural history of moderately impaired renal function and assessing preventive and therapeutic strategies for cognitive function decline in CKD patients are recommended.

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Conflict of interest statement. None declared.

Supplementary data

Supplementary data is available online at <http://ndt.oxfordjournals.org>

Appendix

6-Item Cognitive Impairment Test (6CIT)

Question	Resulting score	
	Correct	Incorrect
1. What year is it?	0	4
2. What month is it?	0	3
3a. Give the patient an address phrase to remember with five components, e.g. John, Smith, 42, High Street, Bedford		
4. About what time is it (within 1 h)?	0	3
5. Count backwards from 20 to 1.	0	1 error = 2 > 1 error = 4
6. Say the months of the year in reverse.	0	1 error = 2 > 1 error = 4
3b. Repeat address phrase.	0	1 error = 2 2 errors = 4 3 errors = 6 4 errors = 8 5 errors = 10

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