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A new approach for cognitive impairment pattern in chronic kidney disease

Hélène Levassort[1,2,3], Julie Boucquemont[1], Natalia Alencar de Pinho[1], Oriane Lambert[1], Catherine Helmer[4], Marie Metzger[2], Laurent Teillet[1,2], Luc Frimat[5,6], Christian Combe[7], Denis Fouque[8], Maurice Laville[9], Christian Jacquelinet[1,10], Sophie Liabeuf[11,12], Bénédicte Stengel[1], Ziad A. Massy[1,3,†], Marion Pépin[1,2,†] and on behalf of the CKD-REIN Study Collaborators

[1]Center for Research in Epidemiology and Population Health (CESP), Clinical Epidemiology Team, Paris-Saclay University, Versailles Saint-Quentin-en-Yvelines University, Inserm, Villejuif, France
[2]Department of Geriatric Medicine, Ambroise Paré Hospital, Boulogne-Billancourt, France
[3]Department of Nephrology, Ambroise Paré Hospital, Boulogne-Billancourt, France
[4]University of Bordeaux, INSERM, Bordeaux Population Health Research Center, Bordeaux, France
[5]Department of Nephrology, CHRU-Nancy, Lorraine University, Vandoeuvre, France
[6]EA 4360, INSERM CIC-EC CIE6, Medicine Faculty, Lorraine University, Apemac, France
[7]Department of Nephrology, Bordeaux University Hospital, INSERM, Univ. Bordeaux, Bordeaux, France
[8]Department of Nephrology, LyonSud hospital – Hospices Civils de Lyon, Claude Bernard Lyon1 University, Pierre Benite, France
[9]Carmen INSERM U1060, Claude Bernard Lyon 1 University, Pierre-Bénite, France
[10]Medical and Scientific Department, Agence de la biomédecine, Saint-Denis la Plaine, France
[11]Pharmacology Department, Amiens University Medical Center, Amiens, France
[12]MP3CV Laboratory, EA7517, University of Picardie Jules Verne, Amiens, France
Correspondence to: Hélène Levassort; E-mail: helene.levassort@aphp.fr; Marion Pépin; E-mail: marion.pepin@aphp.fr; Ziad A. Massy; E-mail: ziad.massy@aphp.fr
[†]These authors contributed equally.

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ABSTRACT

Background. Chronic kidney disease (CKD) is associated with an elevated risk of neurocognitive disorders (NCDs). It remains unclear whether CKD-related NCDs have a specific cognitive pattern or are earlier-onset phenotypes of the main NCDs (vascular NCDs and Alzheimer's disease).

Methods. We used the Mini Mental State Examination score (MMSE) to assess cognitive patterns in 3003 CKD patients (stage 3–4) followed up over 5 years in the Chronic Kidney Disease–Renal Epidemiology and Information Network (CKD-REIN) cohort. After normalizing MMSE scores to a 0-to-100 scale, the associations between the baseline estimated glomerular filtration rate (eGFR, using the Chronic Kidney Disease Epidemiology Collaboration creatinine formula) and changes in each MMSE domain score were assessed in linear mixed models.

Results. Patients (age: 67 ± 13 years old; males: 65%, mean eGFR: 33± 12 mL/min/1.73 m^2) had a good baseline cognitive functions: the mean MMSE score was 26.9/30 ± 2.9. After adjustment for age, sex, educational level, depression (past or present), cardiovascular risk factors and cerebrovascular disease, a lower baseline eGFR (per 10 mL/min/1.73 m^2) was associated with a 0.53-point decrement [$P < .001$; 95% confidence interval (CI) (–0.98, –0.08)] for orientation, a 1.04-point decrement [$P = .03$; 95% CI (–1.96, –0.13)] for attention and calculation, a 0.78-point decrement [$P = .003$; 95% CI (–1.30, –0.27)] for language, and a 0.94-point decrement [$P = .02$; 95% CI (–1.75, –0.13)] for praxis. Baseline eGFR was not, however, associated with significant changes over time in MMSE domain scores.

Conclusion. A lower eGFR in CKD patients was associated with early impairments in certain cognitive domains: praxis, language and attention domains before an obvious cognitive decline. Early detection of NCD in CKD patients must be performed before clinically cognitive decline using preferably tests assessing executive, attentional functions and language, rather than memory tests. This early cognitive screening could lead to a better management of cognitive impairment and their consequences on CKD management.

Keywords: chronic kidney disease, cognition, Mini Mental State Examination, psychometric

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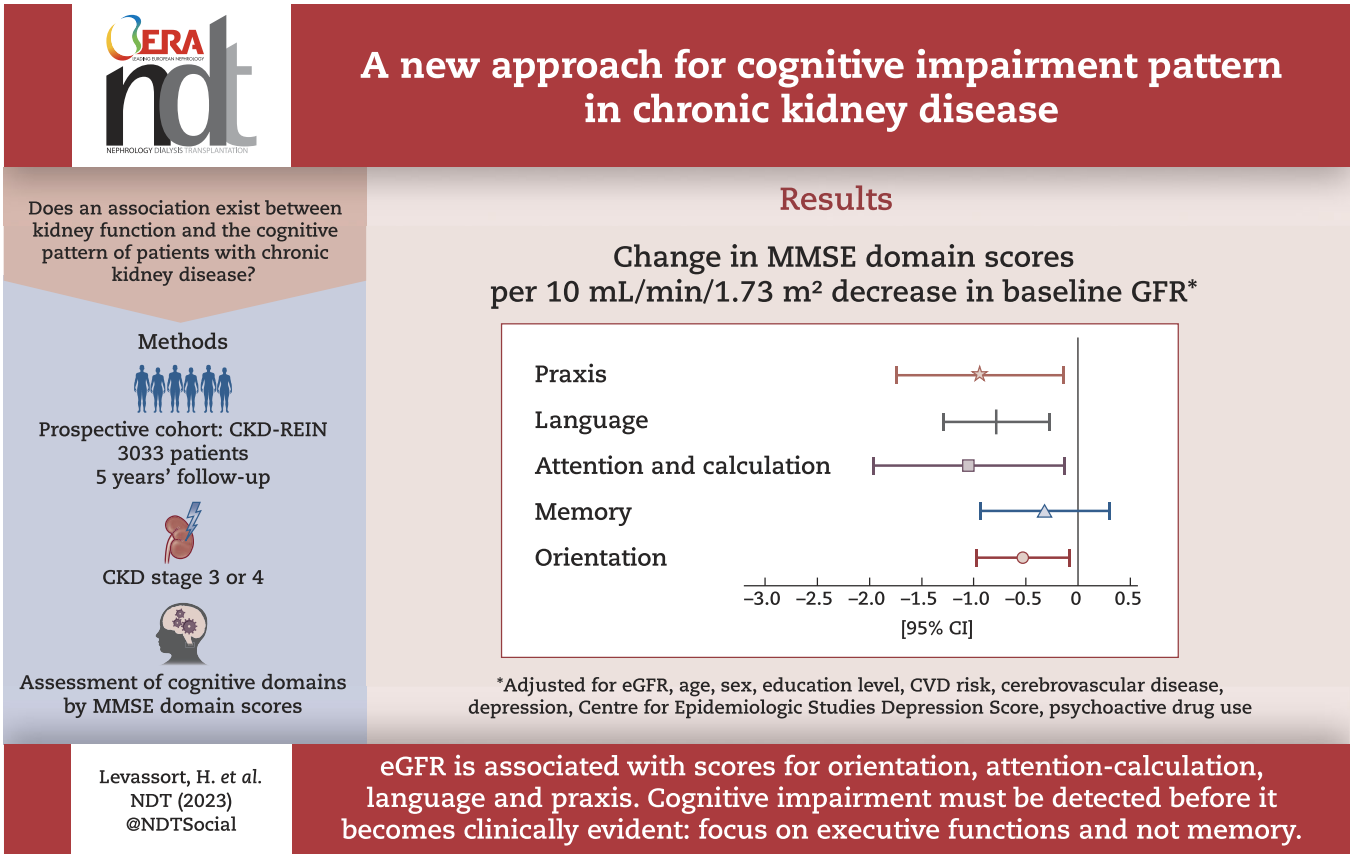
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Chronic kidney disease (CKD) is associated with poor cognitive performance. Cognitive patterns have have been documented extensively in patients with CKD who have initiated kidney replacement therapy (kidney transplant or dialysis), but less so in patients who have not.

This study adds:

- In 3003 stage 3 or 4 CKD and non-dialysis-dependent patients, with good cognitive performances at baseline, kidney function was associated with impairments in specific cognitive domains (orientation, language, attention and praxis) even after adjustment for confounding factors (sociodemographic variables, cardiovascular disease and depression).

Potential impact:

- Patients with CKD should be screened before the onset of clinically obvious cognitive impairment.
- Focus on executive function, language and attention (rather than memory) might facilitate the screening and management of neurological disorders in CKD and the consequences of NCD on CKD, such as compliance with care or decision-making.

INTRODUCTION

The prevalence of chronic kidney disease (CKD) and neurocognitive disorder (NCD) both increase with age. Cognitive impairment can occur early in CKD, i.e. when the estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m^2 or sometimes even earlier [1–4]. Regardless of the stage, CKD patients have a higher risk of NCD than patients without CKD; the prevalence of NCD can be as high as 40%, depending on the definition of cognitive impairment [5–7]. Subtle changes in cognition may impact healthcare engagement, comprehension, decision-making and treatment compliance [8].

In a previous study, we showed that a lower eGFR was associated with worse cognitive performance and incident cognitive events, independently of demographics, cardiovascular risk factors and depression [4]. However, it remains unclear which cognitive functions are most frequently impaired in patients with CKD. Indeed, NCD can affect one or more of the following domains: attention, memory, executive functions (organization, orientation, planning, abstraction, judgment, self-control and flexibility),

instrumental functions (language, gnosis, praxis) and visuospatial functions. These functions are governed by various brain structures. Therefore, cognition is complex and involves several interconnected areas of the brain. NCD can appear in very different forms, depending on the mechanisms and structures affected and the person's medical-social context. The patient's cognitive pattern can help the clinician to determine the cause of the NCD (e.g. Alzheimer's disease, frontotemporal degeneration, etc.).

The links between CKD and NCD are underpinned by a vascular hypothesis and a neurodegenerative hypothesis [5, 9, 10]. The prevalence of NCD increases with the CKD stage even after adjustment for cofounding factors, such as cardiovascular damage; hence, CKD has a specific role [2, 4]. In CKD, NCD might be at least partially related to the accumulation of uremic toxins or the presence of chronic inflammation.

Few studies have reported on cognitive pattern in CKD patients not requiring kidney replacement therapy (KRT) [11]. Indeed, most studies have been conducted in patients on dialysis and/or who have received a kidney transplant [12–14]. A meta-analysis of non-KRT patients found the same cognitive impairments (mainly executive, attentional and psychomotor dysfunctions) as in patients on KRT [15, 16]. However, the studies differed markedly with regard to the sample size, CKD stage and/or the cognitive tests administered. Understanding NCD in patients with CKD is essential for (i) identifying early symptoms of cognitive decline in this population, (ii) managing these impairments promptly through rehabilitation, (iii) predicting the disorder's progression (in order to plan care provision), and (iv) mitigating difficulties in self-management and decision-making [17].

The objectives of the present study of a large cohort of non-dialyzed CKD patients were to evaluate the associations between kidney function and cognitive pattern and to study the changes in associations over time.

MATERIALS AND METHODS

We worked on the French, prospective Chronic Kidney Disease–Renal Epidemiology and Information Network (CKD-REIN) cohort of patients with CKD (ClinicalTrials.gov identifier: NCT 03381950) [18].

Population

The CKD-REIN cohort collected data from 3033 stage 3–4 CKD patients recruited at 40 randomly selected nephrology facilities in mainland France between July 2013 and April 2016 [18, 19]. The eligibility criteria included an eGFR below 60 mL/min/1.73 m^2 (measured twice at least 1 month apart) and the absence of long-term KRT. Patients also had to be over the age of 18 years and able to give their written, informed consent during a routine visit to their nephrologist. According to the CKD-REIN protocol, patients were followed up for 5 years or for up to 6 months after the initiation of KRT. Each year, clinical research assistants collected information from patient interviews, medical records and patient self-questionnaires. The CKD-REIN protocol was approved by the institutional review board at the Institut National de la Santé et de la Recherche Médicale (INSERM, Paris, France; reference: IRB 00003888).

Cognitive evaluation

The Mini Mental State Examination (MMSE) is a 30-item questionnaire assessing five domains: orientation, memory, attention and calculation, language, and praxis [20]. Each question scores one point: 10 points for temporospatial orientation, 6 points for memory, 5 points for attention and calculation, 8 points for language and 1 point for praxis (Supplementary data, Fig. S1). This test is frequently used to screen for NCD before further in-depth explorations.

We used the MMSE to evaluation the CKD-REIN participants at baseline and at 5 years. For logistic reasons, only the first 1200 patients were tested with the MMSE at their 2-year follow-up visit. The present study was performed (in part) during the COVID-19 pandemic; hence, a number of patients were invited to complete the 5-year interview by telephone, and the MMSE could not be administered.

Data

Data (including patient-level and provider-level questionnaires) were collected extensively at baseline and then annually by trained clinical research associates from medical records and prescriptions (including the CKD history, comorbidities and medication use) [18]. For the purposes of the present study baseline data were used, with the exception of longitudinal MMSE data.

The eGFR was estimated from the serum creatinine value using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) including the ethnic factor [21, 22].

The other relevant information collected at baseline included sociodemographic data [age, sex, educational level, living alone or not, autonomy by activities of daily living (ADL) scale and instrumental ADL (IADL) scale, sedentarity status by the Global Physical Activity Questionnaire (GPAQ)]; history of depression, depressive symptoms by the Center for Epidemiologic Studies Depression Scale (CES-D-10); medication (polymedication, psychoactive, antidepressant and anxiolytics drugs intake); cardiovascular risk factor and cardiovascular comorbidities (hypertension, diabetes mellitus, dyslipidemia, smoking status, cerebrovascular disease, atrial fibrillation, heart failure); and biological data [urine albumin-to-creatinine ratio (uACR), serum level of phosphate, urea, 25-OH vitamin D, albumin, calcium and parathyroid hormone]. These baseline characteristics have been reported elsewhere [4]. Definitions of operational variables are reported in Supplementary data, Table S1.

Statistical analysis

First, we compared the patients' baseline characteristics as a function of the eGFR class (<30, 30–44, and ≥45 mL/min/1.73 m^2). Some of the MMSE's metrological properties (ceiling/floor effects, curvilinearity, lack of normality and a variable sensitivity to change) make it difficult to apply standard statistical methods. We therefore normalized the MMSE subscores to a 0-to-100 scale, in order to better analyze and compare changes in the various MMSE domains [23]. This method is derived from a latent process mixed model and has been validated in several cohorts. We then performed longitudinal analyses using linear mixed models. They account for measurement correlations when the outcome (here the MMSE score) is repeatedly measured and can be applied even when some data are missing. Thus, even though some of the patients lacked follow-up data for the MMSE, all those with an MMSE score at baseline could be included in the mixed model. For this analysis, we included a random intercept in the models. A random slope could not be introduced into the model because of convergence concerns. To assess the association between the baseline eGFR level and changes over time in the MMSE subscores, we tested the interaction between baseline eGFR and time.

For each cognitive domain, we performed separate univariate regressions for all covariates. These models took account for the follow-up time as a continuous variable and an indicator of the

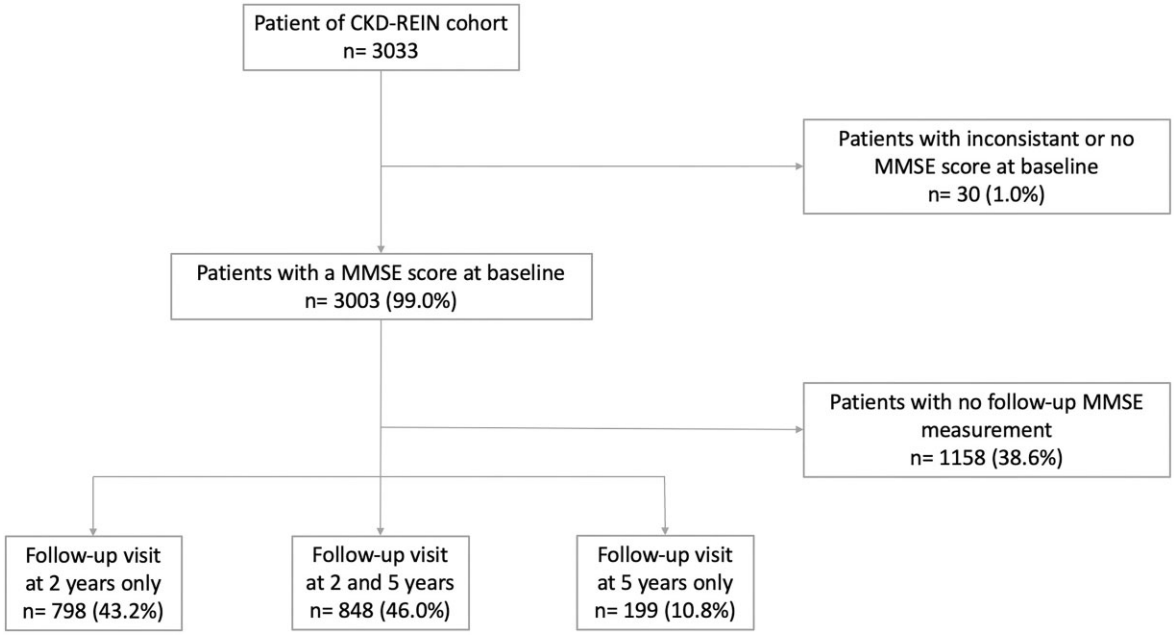


Figure 1: Flow chart of the study.

"learning effect" to handle this phenomenon [24]. Next, multivariate models were built with several confounders at baseline [associated ($P < .2$) with cognitive domains in a univariate analysis]. eGFR was analyzed as a continuous variable, and results were presented for a 10 mL/min/1.73 m^2 decrement in baseline eGFR. Model 1 was adjusted for age, sex and educational level (known to influence the MMSE score) [25]. Models 2 and 3, respectively, evaluated the contributions of cardiovascular variables (hypertension, diabetes mellitus, dyslipidemia, obesity, smoking and cerebrovascular disease) and psychological variables (the CES-D-10 score, psychoactive drug intake and a history of depression) known to affect cognitive performance in CKD patients [5, 26]. In a sensitivity analysis, we built a supplementary model including uACR. Variables such as the ADL, IADL and GPAQ scores (reflecting the consequences of NCD, rather than its causes) were not included in the linear mixed models. Similarly, polymedication and serum levels of urea, phosphate, calcium, PTH and hemoglobin (known to be collinearly associated with a lower eGFR) were not included in the models.

We performed multiple imputations of missing data, using chained equations [27]. Thirty datasets were created with 30 iterations. All variables presented in the linear mixed model were included in the imputation procedure.

The results of the regressions are reported with their 95% confidence interval (CI), and the threshold for statistical significance was set to $P < .05$. Statistical analyses were performed with R software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) [28]. Linear mixed models were built with the lmer function in the lme4 package in R.

RESULTS

Baseline characteristics of the study population

Of the 3033 patients in the CKD-REIN cohort, 3003 had a full MMSE dataset at baseline (Fig. 1). We analyzed data from the 3003 patients who had a complete MMSE dataset at baseline [4]. The mean age was 67 years [standard deviation (SD) 13], 65% of the patients were men and the mean eGFR was 33 mL/min/1.73 m^2 (SD 12.2) (Table 1). Patients with more advanced CKD had greater prevalence of polymedication ($P < .001$), dependency in IADL ($P < .001$), depressive symptoms ($P = .003$) or heart failure history ($P < .001$).

Description of MMSE and cognitive domains scores at baseline

The mean MMSE score at baseline was 26.9/30 (SD 2.9). With regard to the various domains, we found a mean score of 9.6/10 (SD 0.8) for orientation, 5.4/6 (SD 0.88) for immediate and working memory, 3.7/5 (SD 1.7) for attention and calculation, 7.3/8 (SD 0.80) for language, and 0.9/1 (SD 0.3) for praxis (Table 1, Fig. 2). At baseline, patients with advanced CKD had a lower overall MMSE score ($P < .001$) and lower domain subscores ($P = .001$ for orientation, $P = .003$ for attention and calculation, $P < .001$ for language, $P = .004$ for praxis) except for the memory domain ($P = .08$) (Table 1).

Factors associated with MMSE and cognitive domains scores

In the unadjusted linear mixed model, age, sex, lower educational level, depressive symptoms, psychoactive drug intake, cardiovascular risk factors, cerebrovascular disease and a history of depression were all associated with the mean normalized MMSE domain scores (Supplementary data, Table S3). After adjustment for all confounding factors (Models 1, 2 and 3), the baseline eGFR was associated with the normalized scores for the orientation, attention and calculation, language, and praxis domains, but not with memory domain. In Model 3, a lower baseline eGFR (per 10 mL/min/1.73 m^2) was associated with a decrement of 0.53 points for orientation ($P = .02$), 1.04 points for attention and calculation ($P = .03$), 0.78 points for language ($P = .003$) and 0.94 points for praxis ($P = .02$) (Fig. 3A, Table 2).

Regarding the analysis by CKD stages, an eGFR <30 mL/min/1.73 m^2 was associated with a lower mean

Table 1: Baseline characteristics of the study participants (including the MMSE domain scores) by CKD stage ($n = 3003$).

	NA (%)	Overall, $n = 3003$	eGFR ≥45 mL/min, $n = 534$ (17.8%)	eGFR 30–44 mL/min, $n = 1114$ (37.2%)	eGFR <30 mL/min, $n = 1355$ (45.1%)	P^*
Overall MMSE score (/30), mean (SD)	0	26.88 (2.94)	27.36 (2.60)	26.97 (2.88)	26.61 (3.08)	**<.001**
Orientation (/10), mean (SD)	0	9.63 (0.81)	9.72 (0.73)	9.65 (0.75)	9.57 (0.88)	**.001**
Memory (learning and recall) (/6), mean (SD)	0	5.35 (0.88)	5.42 (0.83)	5.37 (0.89)	5.32 (0.88)	.08
Attention and calculation (/5), mean (SD)	0	3.67 (1.72)	3.84 (1.63)	3.72 (1.71)	3.56 (1.75)	**.003**
Language (/8), mean (SD)	0	7.34 (0.80)	7.46 (0.76)	7.35 (0.78)	7.29 (0.82)	**<.001**
Praxis (/1), mean (SD)	0	0.88 (0.32)	0.93 (0.26)	0.88 (0.32)	0.87 (0.34)	**.004**
Age, years, mean (SD)	0	66.78 (12.90)	63.61 (12.46)	67.30 (12.03)	67.62 (13.56)	**<.001**
Male sex, *n* (%)	0	1961 (65.3)	372 (69.7)	731 (65.6)	858 (63.3)	**.03**
Educational level ≥12 years, *n* (%)	1.1	1077 (35.9)	226 (42.3)	404 (36.3)	447 (33.0)	**<.001**
Living alone, *n* (%)	14.8	581 (19.3)	87 (16.3)	216 (19.4)	278 (20.5)	.2
CES-D-10 score (/30), mean (SD)	13.0	7.58 (5.15)	7.24 (5.06)	7.27 (5.02)	7.96 (5.27)	**.003**
ADL score (/5), mean (SD)	11.8	4.92 (0.43)	4.91 (0.50)	4.91 (0.48)	4.93 (0.35)	.6
IADL score (/8), mean (SD)	12.1	7.20 (1.27)	7.46 (1.01)	7.28 (1.20)	7.05 (1.39)	**<.001**
Sedentary (GPAQ, class 3), *n* (%)	16.7	1197 (39.9)	181 (33.9)	435 (39.0)	581 (42.9)	**<.001**
Polymedication (≥5/day), *n* (%)	0.3	2410 (80.3)	375 (70.2)	861 (77.3)	1174 (86.6)	**<.001**
Psychoactive drugs[a], *n* (%)	0.3	590 (19.6)	93 (17.4)	216 (19.4)	281 (20.7)	.3
Antidepressant, *n* (%)	0.3	226 (7.50)	35 (6.6)	85 (7.6)	106 (7.8)	.6
Anxiolytics, *n* (%)	0.3	312 (10.4)	52 (9.7)	118 (10.6)	142 (10.5)	.7
Cardiovascular risk factors[b] and comorbidities						
Hypertension, *n* (%)	0.2	2718 (90.5)	455 (85.2)	1015 (91.1)	1248 (92.1)	**<.001**
Diabetes mellitus, *n* (%)	0.2	1292 (43.0)	209 (39.1)	490 (44.0)	593 (43.8)	.2
Dyslipidemia, *n* (%)	0.4	2199 (73.2)	372 (69.7)	825 (74.1)	1002 (73.9)	.2
Obesity, *n* (%)	2.0	1044 (34.8)	153 (28.7)	402 (36.1)	489 (36.1)	**.02**
Smoking[c], *n* (%)	0.6	358 (11.9)	70 (13.1)	125 (11.2)	163 (12.0)	.7
Cerebrovascular disease[d], *n* (%)	2.3	346 (11.5)	53 (9.9)	120 (10.8)	173 (12.8)	.4
Atrial fibrillation, *n* (%)	0.2	342 (11.4)	43 (8.1)	137 (12.3)	162 (12.0)	**.04**
Heart failure[e], *n* (%)	0.2	388 (12.9)	43 (8.1)	146 (13.1)	199 (14.7)	**.001**
History or current depression, *n* (%)	2.5	223 (7.4)	42 (7.9)	87 (7.8)	94 (6.9)	.9
Laboratory parameters						
Serum hemoglobin level (g/dL), mean (SD)	0.7	13.0 (1.65)	13.79 (1.53)	13.25 (1.61)	12.49 (1.56)	**<.001**
Serum phosphate level (mmol/L), mean (SD)	4.0	1.16 (0.23)	1.06 (0.18)	1.11 (0.19)	1.24 (0.24)	**<.001**
Serum urea level (mmol/L), mean (SD)	4.1	14.0 (6.51)	8.71 (2.97)	11.55 (3.96)	18.00 (6.72)	**<.001**
Serum 25-OH vitamin D level (ng/mL), mean (SD)	12.0	29.35 (13.91)	28.57 (13.57)	29.19 (13.69)	29.78 (14.21)	.3
Serum albumin level (g/L), mean (SD)	16.1	40.10 (4.34)	40.65 (4.03)	40.46 (4.37)	39.62 (4.38)	**<.001**
uACR, *n* (%)	9.0					**<.001**
Normal: <3 mg/mmol		759 (25.3)	213 (39.9)	347 (31.1)	199 (14.7)	
Moderate elevation: 3–30 mg/mmol		853 (28.4)	152 (28.5)	331 (29.7)	370 (27.3)	
Severe elevation: >30 mg/mmol		1122 (37.4)	131 (24.5)	325 (29.2)	666 (49.2)	
Serum calcium level (mmol/L), mean (SD)	2.7	2.35 (0.13)	2.36 (0.11)	2.36 (0.12)	2.34 (0.14)	**<.001**
Serum parathyroid hormone level (ng/mL), median (IQR)	14.4	79.20 (49.15, 132.93)	49.10 (34.05, 70.46)	69.58 (45.62, 102.0)	114.1 (70.0, 174.4)	**<.001**

*ANOVA test or Mann–Whitney test for continuous variables, Chi^2 test for categorical variables.
The three CKD stages were defined according to the eGFR: eGFR ≥45 mL/min/1.73 m^2 (stage G3a), eGFR between 30 and 44 mL/min/1.73 m^2 (stage G3b) and eGFR <30 mL/min/1.73 m^2 (stage G4) [22].
[a]Psychoactive drugs were defined as antidepressants, anxiolytics or antipsychotics.
[b]Hypertension was defined as a history of hypertension or the use of blood pressure–lowering medication. Diabetes mellitus was defined as a history of diabetes, antidiabetic medication use, a glycosylated hemoglobin level ≥6.5%, a fasting glycemia value ≥7 mmol/L or a non-fasting glycemia value ≥11 mmol/L. Dyslipidemia was defined as a history of dyslipidemia or the use of lipid-lowering medication. Obesity was defined as a body mass index ≥30 kg/m^2. Current smoking was defined as at least one cigarette per day.
[c]Smoking at least 1 cigarette per day or detoxed less than a year ago.
[d]Cerebrovascular disease was defined as a history of stroke, transient ischemic attack or cerebral hemorrhage.
[e]History of heart failure or pulmonary edema.
IQR, interquartile range; SD, standard deviation.

normalized score in the orientation ($P = .02$), attention ($P = .03$), language ($P < .001$) and praxis domains ($P = .03$). For the eGFR stage between 30 and 45 mL/min/1.73 m^2 the normalized scores for language and praxis were significantly lower (by 1.94 points ($P = .03$) and 3.03 points ($P = .03$), respectively) than in patients with an eGFR ≥45 mL/min/1.73 m^2 (Supplementary data, Table S4).

In contrast, the uACR was not associated with any of the normalized MMSE domain scores in unadjusted and adjusted models (Table 2, Supplementary data, Table S3) Adjustment for uACR did not change the associations describe above.

Changes in MMSE and cognitive domain scores during follow-up

The mean total follow-up time of the cohort was 4.56 years (SD 1.56). During the 5-year follow-up period, 38.6% of the patients had a single MMSE measurement (the baseline measurement), 33.2% had two MMSE measurements and 28.2% had three MMSE

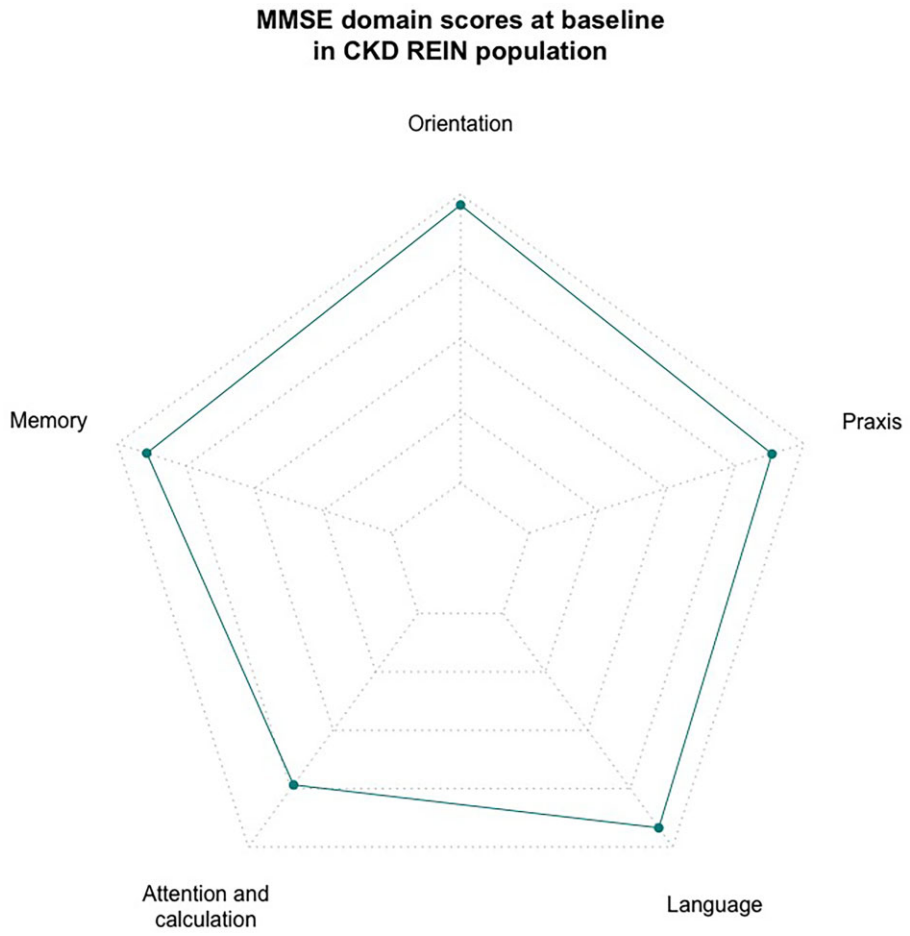


Figure 2: Mean score (in points, standardized out of 10) at baseline in the various MMSE domains (n = 3003).

measurements. Altogether, 1845 patients had at least one additional MMSE assessment during the follow-up [4]. Patients who did not have an MMSE assessment during the follow-up period had a lower MMSE score at baseline ($P < .001$), had more comorbidities, were more dependent and more likely to start KRT or die ($P < .001$) (Supplementary data, Table S2).

Before and after adjustment for confounders (Model 3), only the normalized scores for orientation, language and praxis declined significantly over the 5-year follow-up period: 0.70 points ($P < .001$) for orientation, 0.74 points ($P = .001$) for language and 1.45 points ($P < .001$) for praxis (Fig. 3B, Table 2).

The interaction between baseline eGFR and time in Model 3 was not statistically significant for orientation ($P = .6$), memory ($P = .4$), attention and calculation ($P = .4$), language ($P = .5$), or praxis ($P = .9$); this reflected a lack of association between baseline eGFR and subsequent cognitive decline over the 5-year follow-up period.

DISCUSSION

In the present study assessing cognitive pattern in CKD patients, we observed that eGFR was associated with changes in orientation, attention and calculation, language and praxis domain scores, but not with the memory domain. Secondly, we found that orientation, language and praxis decreased during the 5-year follow-up period.

Despite the absence of a clinically obvious cognitive impairment (i.e. with mean and median MMSE total scores >26/30, when the threshold of 24/30 detect cognitive impairment with the greatest accuracy), eGFR appears to be associated with orientation, attention, language and praxis disorders—even after adjustment for confounders known to promote cognitive decline [25]. These results are consistent with literature reports in which some cognitive functions appear to be affected in CKD before the onset of clinical impairment. These domains include orientation, attention, language, concept formation and reasoning, memory, and executive and global cognitive functions [9, 11, 15, 26, 29, 30]. Furthermore, studies of pediatric cohorts have also detected neurocognitive disorders (particular executive function, memory and attention disorders) in children with CKD [31]. In our study, early impairment of executive functions, language and attention underline the importance of not focusing only on memory disorders, while physicians often look for this domain to screen for NCD [17, 32, 33]. Our results and the literature data suggest that pediatric populations with CKD would also benefit from the early detection of NCDs (i.e. before clinically evident symptoms are reported).

Furthermore, we found an association between eGFR and the language and praxis domain score from CKD stage 4, while orientation and attention where affected at stage 5. These literature data and our present results support the hypothesis whereby cognitive domains are affected by "domino effect" in which

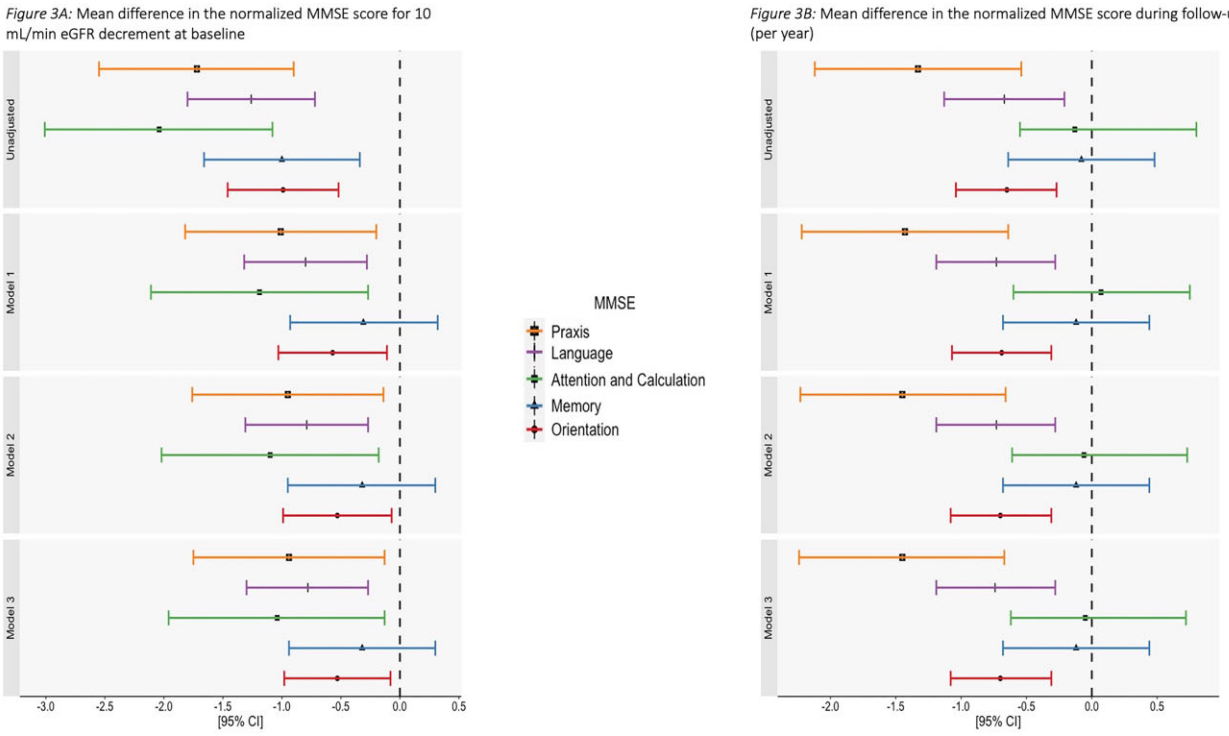


Figure 3: Mean difference in the normalized MMSE score for a 10 mL/min eGFR decrement at baseline and during follow-up (per year) in an adjusted, mixed linear regression ($n = 3003$).

impairments in some cognitive functions lead to impairments in the others [14, 34]. Even though we observed decreased performance in orientation, language and praxis domain scores, we did not evidence an impact of the baseline eGFR level on cognitive decline over time. We hypothesize that baseline eGFR is indeed linked to changes over time in cognitive domains but that our short follow-up period and the loss of information on patients who did not have a follow-up MMSE measurement prevented our study from highlighting the association. Preferential impairment of executive functions have also been observed in patients on hemodialysis or peritoneal dialysis [6, 12]. Moreover, several studies have shown that executive function impairment is more frequent in patients with cardiovascular disease [35]. Other mechanisms directly or indirectly related to CKD might increase executive disorders: the serum level of cystatin C (which colocalizes with beta-amyloid in the brain, areas involved in Alzheimer's disease), the serum urea level (which is associated with cardiovascular disease), vascular damage, anemia (by reducing cerebral oxygen level), depression and sleep disorders [10, 17, 30, 36].

After matching by age and educational level, the median MMSE score in the French PAQUID control cohort of subjects with normal kidney function (29 out of 30) was slightly higher than that found here (28 out of 30) [37]. Furthermore, the results of the 3C study showed that in a population with better kidney function (98% of the individuals had a GFR >45 mL/min/1.73 m^2), the GFR at baseline was not associated with the MMSE score during the 7 years of follow-up [38]. These results highlight the influence of advanced CKD on cognition. Moreover, the fact that we observed an association between kidney function and the presence of NCDs after adjustment for many confounding factors suggests that CKD has a specific influence on cognition.

A few clinical studies have shown an association between cognitive impairment (in executive functions, specifically) and higher serum levels of uremic toxins (such as indoxyl sulfate) in patients with CKD but not in patients without CKD [39]. Likewise, elevated levels of guanidine (another uremic toxin) interfere with the balance between glutamatergic and GABA systems which is particularly involved in anxiety and depressive symptoms, which in turn are linked to cognitive functions [40–45]. These data suggest that uremic toxins influence neurotransmission. Such an effect would explain the occurrence of cognitive impairment in CKD independently of confounders in general and vascular diseases in particular.

Our study had many strengths. Unlike the majority of studies of this subject, we assessed a large cohort of CKD patients who did not initiate KRT [18]. We assessed a broad panel of variables and adjusted for a large number of confounding factors. Cognitive function was evaluated via the MMSE by trained clinical research associates, and the test results were recorded and checked at baseline for 3003 of the 3033 patients in the cohort. Moreover, the mixed-model design allowed us to take account of MMSE data for the 3003 patients and not only those who were administered the MMSE several times during follow-up. Lastly, we transformed the MMSE score so that we could increase the models' validity.

Conversely, our study has some limitations. The main limitation was our use of the MMSE as the only cognitive assessment (the only cognitive assessment incorporated into the primary CKD-REIN study). MMSE remains an overall cognitive screening test, and is not very sensitive for the detection of executive dysfunction [in contrast to the Montreal Cognitive Assessment (MoCA)] which is particularly affected in CKD patients [15, 17, 32, 34]. Moreover, given that praxis is only assessed by a single point

Table 2: Risk factors associated with mean normalized MMSE domains scores during follow-up (considered as a continuous variable) in an adjusted linear mixed regression ($n = 3003$).

	Orientation		Memory		Attention and calculation		Language		Praxis	
	Effect (95% CI)	*P*	Effect (95% CI)	*P*	Effect (95% CI)	*P*	Effect (95% CI)	*P*	Effect (95% CI)	*P*
Model 1										
Time (year)	−0.69 (−1.07, −0.31)	**<.001**	−0.12 (−0.68, 0.44)	.7	0.07 (−0.60, 0.75)	.8	−0.73 (−1.19, −0.28)	**.002**	−1.43 (−2.22, −0.64)	**<.001**
eGFR (−10 mL/min/1.73 m^2)	−0.57 (−1.03, −0.11)	**.01**	−0.31 (−0.93, 0.32)	.3	−1.19 (−2.11, −0.27)	**.01**	−0.80 (−1.32, −0.28)	**.002**	−1.01 (−1.82, −0.20)	**.01**
Model 2										
Time (year)	−0.70 (−1.08, −0.31)	**<.001**	−0.12 (−0.68, 0.44)	.7	0.06 (−0.61, 0.73)	.9	−0.73 (−1.19, −0.28)	**.002**	−1.45 (−2.23, −0.66)	**<.001**
eGFR (−10 mL/min/1.73 m^2)	−0.53 (−0.99, −0.07)	**.02**	−0.32 (−0.95, 0.30)	.3	−1.10(−2.02, −0.18)	**.02**	−0.79 (−1.31, −0.27)	**.003**	−0.95 (−1.76, −0.14)	**.02**
Model 3										
Time (year)	−0.70 (−1.08, −0.31)	**<.001**	−0.12 (−0.68, 0.44)	.7	0.05 (−0.62, 0.72)	.9	−0.74 (−1.19, −0.28)	**.001**	−1.45 (−2.24, −0.67)	**<.001**
eGFR (−10 mL/min/1.73 m^2)	−0.53 (−0.98, −0.08)	**.02**	−0.32 (−0.94, 0.30)	.3	−1.04 (−1.96, −0.13)	**.03**	−0.78 (−1.30, −0.27)	**.003**	−0.94 (−1.75, −0.13)	**.02**
Age (10 years)	−1.26 (−1.73, −0.80)	**<.001**	−4.52 (−5.16, −3.88)	**<.001**	−0.72 (−1.66, 0.22)	.1	−1.23 (−1.76, −0.69)	**<.001**	−2.68 (−3.51, −1.84)	**<.001**
Male sex	2.09 (0.89, 3.28)	**<.001**	−3.86 (−5.50, −2.22)	**<.001**	9.64 (7.21, 12.07)	**<.001**	−0.30 (−1.66, 1.07)	.7	4.64 (2.51, 6.76)	**<.001**
Educational level ≥12 years	5.51 (4.34, 6.68)	**<.001**	6.79 (5.19, 8.40)	**<.001**	16.16 (13.78, 18.54)	**<.001**	8.80 (7.46, 10.14)	**<.001**	7.08 (4.99, 9.17)	**<.001**
CES-D-10 score	−0.14 (−0.27, −0.02)	**.02**	−0.24 (−0.40, −0.08)	**.003**	−0.59 (−0.83, −0.35)	**<.001**	−0.23 (−0.37, −0.09)	**<.001**	−0.15 (−0.36, 0.06)	.2
Psychoactive drug[a]	−2.33 (−3.82, −0.84)	**.02**	−1.19 (−3.23, 0.84)	.3	−2.85 (−5.86, 0.16)	.06	−0.81 (−2.51, −0.90)	.4	−1.49 (−4.14, 1.17)	.3
Cardiovascular risk factors[b] and comorbidities										
Hypertension	0.25 (−1.71, 2.21)	.8	0.76 (−1.92, 3.44)	.6	−1.49 (−5.46, 2.49)	.5	2.73 (0.49, 4.97)	**.02**	−0.96 (−4.45, 2.52)	.6
Diabetes mellitus	−1.56 (−2.77, −0.35)	**.01**	−0.93 (−2.57, 0.71)	.3	−1.92 (−4.36, 0.52)	.1	−2.68 (−4.05, −1.32)	**<.001**	−3.83 (−5.95, −1.70)	**<.001**
Dyslipidaemia	−0.52 (−1.83, 0.79)	.4	2.11 (0.32, 3.90)	**.02**	0.04 (−2.62, 2.70)	1.0	−1.99 (−3.48, −0.49)	**.009**	−0.18 (−2.51, 2.15)	.9
Obesity	−0.96 (−2.21, 0.28)	.1	−0.54 (−2.52, 1.18)	.5	−1.92 (−4.45, 0.62)	.1	−2.44 (−3.85, −1.03)	**<.001**	−2.00 (−4.18, 0.18)	.07
Smoking[c]	−0.33 (−2.04, 1.39)	.7	3.02 (0.67, 5.37)	**.01**	−0.56 (−4.02, 2.90)	.8	1.13 (−0.83, 3.09)	.3	0.52 (−2.52, 3.56)	.7
Cerebrovascular disease[d]	−4.05 (−5.83, −2.27)	**<.001**	−1.68 (−4.09, 0.73)	.2	−4.60 (−8.17, −1.04)	**.01**	−1.59 (−3.61, 0.42)	.2	−4.25 (−7.36, −1.13)	**.008**
History or current depression	−1.98 (−4.20, 0.25)	.08	−2.71 (−5.75, 0.33)	.08	0.49 (−4.02, 5.00)	.8	−1.82 (−4.37, 0.73)	.2	0.96 (−2.98, 4.90)	.6

[a] Psychoactive drugs were defined as antidepressants, anxiolytics or antipsychotics.
[b] Hypertension was defined as a history of hypertension or the use of blood pressure–lowering medication. Diabetes mellitus was defined as a history of diabetes, antidiabetic medication use, a glycosylated hemoglobin level ≥6.5%, a fasting glycemia value ≥7 mmol/L or a non-fasting glycemia value ≥11 mmol/L. Dyslipidemia was defined as a history of dyslipidemia or the use of lipid-lowering medication. Obesity was defined as a body mass index ≥30 kg/m^2. Current smoking was defined as at least one cigarette per day.
[c] Smoking at least 1 cigarette per day or detoxed less than a year ago.
[d] Cerebrovascular disease was defined as a history of stroke, transient ischemic attack or cerebral hemorrhage.
All models were adjusted for the MMSE follow-up time and a putative "learning effect" of the MMSE test. Model 1 was adjusted for eGFR (per 10 mL/min/1.73 m^2 decrement), age, sex and educational level. Multiple imputation by chained equations was applied to the dataset. Model 2 was adjusted for eGFR (per 10 mL/min/1.73 m^2 decrement), age, sex, educational level, hypertension, diabetes mellitus, dyslipidemia, obesity, smoking and cerebrovascular disease. Multiple imputation by chained equations was applied to the dataset. Model 3 was adjusted for eGFR (per 10 mL/min/1.73 m^2 decrement), age, sex, educational level, hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, cerebrovascular disease, CES-D-10 score, psychoactive drug intake and history of depression. Multiple imputation by chained equations was applied to the dataset.

in the MMSE, other cognitive tests would be needed to confirm the presence of an impairment in this specific domain. Thus, the MoCA might be more relevant as a screening test for neurocognitive disorders in the CKD population, especially in view of its sensitivity. Other tests that assess executive functions could also be administered routinely: the Frontal Assessment Battery for example, which also assesses language to some extent.

Unlike other studies that took account of the connections between memory and other cognitive functions (such as language or orientation), we chose to consider the MMSE questions related to memory separately and thus screen for a specific impairment of this domain [46]. The lack of an observed association between eGFR and the memory domain in our study might be due to this methodological choice.

Our study was subject to the selection bias inherent in all cohort studies because cognitively impaired patients are less compliant with follow-up procedures. Only patients able to give their written informed consent participated in the study. We were also exposed to selection bias because patients who did not have MMSE measurement had more severe CKD at baseline and started KRT or died more frequently. They were therefore likely to have more NCD. These selection biases might have reduced the effect size for the association between eGFR and cognitive function, and conceal a probable effect of eGFR level at baseline on the evolution of cognitive domains over time. Moreover, the annual change in the GFR was relatively small (1.5 mL/min/1.73 m^2 per year) in this population with good nephrological follow-up. This relatively small rate of change might account for the small change over time in the MMSE score and the small (albeit statistically significant) effect of the eGFR on the MMSE score. Mixed models did not enable us to study the influence of the change over time in the GFR (as a continuous variable) on the MMSE score over the 5 years of follow-up. We would not have been able to determine whether the decrease in the GFR influenced the MMSE score or, in contrast, whether the change in the MMSE score led to worsening of the CKD. To study the GFR's effect over time on cognition, we would have had to create a cognitive event from the MMSE score. We considered that this approach would not be reliable, given the absence of a clear definition of cognitive decline on the basis of the score in the MMSE, which remains a screening test.

Furthermore, the small effect found here (when expressed as a point decrease per year) might be explained by this selection bias and by the slow onset of NCD (i.e. an onset that cannot always be detected by monitoring over 5 years or by applying a test not specifically designed for the measurement of executive functions). In contrast to previous studies, we did not find a statistically significant association between albuminuria and cognitive performance [47, 48]. The great majority of studies evaluating the impact of albuminuria on cognition focused on the general population or on stage 1 or 2 CKD; the majority of these participants had little or no albuminuria, whereas the majority of the patients in our study had high albuminuria values [47, 49, 50]. We hypothesize that the association between albuminuria and cognitive function in patients, those with advanced CKD or with more comorbidities is difficult to demonstrate because all these factors lead to similar types of white matter damage [51–53]. The COVID-19 pandemic had a strong impact on our collection of data and a large number of patients were not able to have their cognitive assessment at 5 years. The small number of follow-up MMSE datasets enabled us to use a random slope in our mixed models because of convergence problems.

CONCLUSION

Despite good overall cognitive performance at baseline and the absence of obvious clinical NCDs, a lower eGFR in CKD patients was associated with early impairments in some cognitive domains. An initial focus on executive function, language and attention (rather than memory) might facilitate the early detection and management of neurological disorders in CKD (e.g. specific cognitive therapy) and thus result in better recognition and management of the consequences of NCD on CKD, such as compliance with care or decision-making. Closer collaboration between nephrologists and geriatricians/neurologists might help to improve the detection and management of NCDs in patients with CKD.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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Steering committee and study coordination: Natalia Alencar de Pinho, Carole Ayav, Christian Combe, Denis Fouque, Luc Frimat, Christian Jacquelinet, Maurice Laville, Sophie Liabeuf, Ziad A Massy, Christophe Pascal, Bruce M Robinson, Roberto Pecoits-Filho, Bénédicte Stengel, Céline Lange, Marie Metzger, Elodie Speyer.

CKD-REIN site investigators: Alsace: Profs T. Hannedouche and B. Moulin (CHU, Strasbourg), Dr A. Klein (CH Colmar); Aquitaine: Prof. C. Combe (CHU, Bordeaux), Dr J.P. Bourdenx (Clinique St Augustin, Bordeaux), Dr A. Keller, Dr C. Delclaux (CH, Libourne), Dr B. Vendrely (Clinique St Martin, Pessac), Dr B. Deroure (Clinique Delay, Bayonne), Dr A. Lacraz (CH, Bayonne); Basse Normandie: Dr T. Lobbedez (CHU, Caen), Dr I. Landru (CH, Lisieux); Ile de France: Prof. Z. Massy (CHU, Boulogne—Billancourt), Prof. P. Lang (CHU, Créteil), Dr X. Belenfant (CH, Montreuil), Prof. E. Thervet (CHU, Paris), Dr P. Urena (Clinique du Landy, St Ouen), Dr M. Delahousse (Hôpital Foch, Suresnes); Languedoc—Roussillon: Dr C. Vela (CH, Perpignan); Limousin: Prof. M. Essig, Dr D. Clément (CHU, Limoges); Lorraine: Dr H. Sekhri, Dr M. Smati (CH, Epinal), Dr M. Jamali, Dr B. Hacq (Clinique Louis Pasteur, Essey-les-Nancy), Dr V. Panescu, Dr M. Bellou (Polyclinique de Gentilly, Nancy), Prof. Luc Frimat (CHU, Vandœuvre-les-Nancy); Midi-Pyrénées: Prof. N. Kamar (CHU, Toulouse); Nord-Pas-de-Calais: Profs C. Noël and F. Glowacki (CHU, Lille), Dr N. Maisonneuve (CH, Valenciennes), Dr R. Azar (CH, Dunkerque), Dr M. Hoffmann (Hôpital privé La Louvière, Lille); Pays-de-la Loire: Prof. M. Hourmant (CHU, Nantes), Dr A. Testa (Centre de dialyse, Rezé), Dr D. Besnier (CH, St Nazaire); Picardie: Prof. G. Choukroun (CHU, Amiens), Dr G. Lambrey (CH, Beauvais); Provence-Alpes—Côte d'Azur: Prof. S. Burtey (CHU, Marseille), Dr G. Lebrun (CH, Aix-en-Provence), Dr E. Magnant (Polyclinique du Parc Rambot, Aix-en-Provence); Rhône-Alpes: Prof. M. Laville, Prof. D. Fouque (CHU, Lyon-Sud) and L. Juillard (CHU Edouard Herriot, Lyon), Dr C. Chazot (Centre de rein artificiel Tassin Charcot, Ste Foy-les-Lyon), Prof. P. Zaoui (CHU, Grenoble), Dr F. Kuentz (Centre de santé rénale, Grenoble).

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AUTHORS' CONTRIBUTIONS

Research idea and study design: H.L., M.P. and J.B.; Z.A.M. designed the present study, and C.C., L.F., M.L., C.J., D.F., S.L., Z.A.M. and B.S. designed the CKD-REIN cohort; data acquisition: C.C., D.F., L.F., C.J., M.L., Z.A.M., S.L. and B.S.; data analysis/interpretation: H.L., M.P., J.B., N.A.P., C.H., M.M., O.L., L.T. and Z.A.M.; statistical analysis: H.L., M.P., J.B., N.A.P., M.M. and O.L.; final manuscript: H.L., M.P., J.B., B.S., C.H., N.A.P., O.L. and Z.A.M.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available, due to privacy or ethical restrictions.

CONFLICT OF INTEREST STATEMENT

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