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Chronic kidney disease and cognitive decline in patients with type 2 diabetes at elevated cardiovascular risk

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ABSTRACT

Aims: We addressed the question whether chronic kidney disease (CKD) may contribute to cognitive decline in type 2 diabetes.

Methods: Participants with type 2 diabetes with elevated cardiovascular risk or CKD from cognition substudies of two large trials were studied prospectively (CARMELINA: $n = 2666$, mean ± SD age 68.1 ± 8.7 years, CAROLINA: $n = 4296$; 64.7 ± 9.4 years). Estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) at baseline were related to cognitive performance (Mini-Mental State Examination (MMSE) and attention and executive functioning score (A&E)) in linear regression analyses, adjusted for demographics, cardiovascular risk factors and treatment, at baseline and follow-up.

Results: CKD at baseline was more common in CARMELINA than CAROLINA (eGFR<60 in 72.6 % and 19.6 %, macroalbuminuria in 35.0 % and 4.1 %, respectively). Baseline eGFR was related to A&E in CARMELINA ($b = 0.02$ per 10 ml/min/1.73m^2, 95%CI [0.01,0.03]). Baseline UACR was related to A&E in CAROLINA ($b = -0.01$ per doubling of UACR mg/g, 95%CI [−0.02,−0.002]). Baseline UACR predicted decline in A&E in CAROLINA (median 6.1 years follow-up; $b = -0.01$, 95%CI [−0.03,−0.0001] per doubling of UACR mg/g).

Conclusions: eGFR and UACR were associated with A&E in two cohorts with type 2 diabetes, enriched for CKD and cardiovascular disease. The small effect size estimates indicate limited impact of kidney dysfunction on cognition in this setting.

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1. Introduction

Type 2 diabetes is associated with chronic kidney disease (CKD) as well as cognitive impairment,[1,2] possibly with shared underlying processes, such as microvascular damage.[2] It is also possible that CKD contributes to cognitive impairment in type 2 diabetes, but few studies have addressed this.[3,4]

In people without diabetes, CKD is associated with brain changes and

Abbreviations: A&E, Attention and executive functioning; ANCOVA, Analysis of Covariance; BMI, Body Mass Index; CARMELINA, Population of CARMELINA cognition substudy; CARMELINA-COG, CARMELINA cognition substudy; CAROLINA, Population of CAROLINA cognition substudy; CAROLINA-COGNITION, CAROLINA cognition substudy; CKD, Chronic kidney disease; CV, Cardiovascular; eGFR, Estimated glomerular filtration rate; HDL, High-density-lipoprotein; HbA1c, Hemoglobin A1c; LDL, Low-density-lipoprotein; MDRD, Modification of Diet in Renal Disease; MMSE, Mini-Mental State Examination; NCT, National Clinical Trial number; SD, Standard deviation; TMT, Trail Making Test; UACR, Urine albumin-to-creatinine ratio; VFT, Verbal Fluency Test.

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cognitive impairment.[5–11] Although no causal relations can be inferred from these observational studies, it is known that severe CKD, particularly kidney failure, can negatively impact the brain via various mechanisms, including the accumulation of uremic toxins, which may induce oxidative stress and vascular dysfunction.[3,4] However, whether CKD in stages that more commonly occur in people with type 2 diabetes is also associated with worse cognition needs further investigation.

We assessed the relationship between kidney parameters (i.e. estimated glomerular filtration rate and urine albumin-to-creatinine ratio) and cognitive performance, cross-sectionally and prospectively, in two trial populations of people with type 2 diabetes at elevated cardiovascular (CV) risk, with CKD, or both.

2. Materials and methods

2.1. Subjects

The present study included 2666 patients with type 2 diabetes from the CARMELINA cognition substudy (CARMELINA-COG) and 4296 from the CAROLINA cognition substudy (CAROLINA-COGNITION). CARMELINA-COG was an integral part of the CARMELINA trial: a multicenter, international, randomized, double-blind study in patients with long-standing type 2 diabetes at high cardiorenal risk (NCT 01897532). CAROLINA-COGNITION was part of the CAROLINA trial and included patients with relatively early type 2 diabetes at elevated CV risk (NCT 01243424). Both cognition substudies investigated the effect of linagliptin versus comparators on the incidence of accelerated cognitive decline at end of study. Detailed inclusion criteria can be found in Table A1 in Supplementary Material. Participants were eligible for the cognition substudies when they were from countries using the Latin alphabet. They were included in the analyses when they were literate, their years of education were recorded and they had a valid cognitive assessment at baseline. By study design, a valid follow-up cognitive assessment within seven days after the last drug intake was required for the longitudinal analyses. Participants with scores below 24 on the Mini-Mental State Examination (MMSE) at baseline (i.e. indicating cognitive impairment) were not included for follow-up cognitive analyses.[12,13] For the current study, the availability of measures of kidney function (glomerular filtration rates) and kidney damage (urine albumin-to-creatinine ratio) were required.

The CARMELINA and CAROLINA cognition substudies found neutral results for the effect of linagliptin on accelerated cognitive decline when compared with placebo or glimepiride, respectively.[14,15] Hence, the treatment arms of the studies were combined in the present analyses.

2.2. Measurements

2.2.1. Kidney function and damage

Two commonly used kidney parameters were investigated at baseline. Estimated glomerular filtration rate in ml/min/1.73m^2 (eGFR), a marker for kidney function, was calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation (Levey et al. 1999). Serum creatinine was measured using the Jaffe method (Jaffe, 1886). Urine albumin-to-creatinine ratio (UACR) in mg/g (i.e. albuminuria), a marker for kidney damage, was assessed on a first morning void specimen wherever possible. The calculation was performed at the central laboratory. Continuous values of baseline eGFR and baseline UACR were used for the primary analyses on cognitive outcomes at baseline and follow-up. Lower eGFR values represent worse kidney function, higher UACR values represent more kidney damage. For the baseline table and figures and secondary analyses, eGFR and UACR were also categorized (eGFR $\geq$90 (normal kidney function), $\geq$ 60 to $<$90 (mildly decreased kidney function), $\geq$ 30 to $<$60 (moderately decreased kidney function), $\geq$ 15 to $<$30 (severely decreased kidney function), $<$ 15 (kidney failure); UACR $<$30 (no to mildly increased kidney damage; normoalbuminuria), $\geq$ 30 to $\leq$300 (moderately increased kidney damage; microalbuminuria), $>$ 300 (severely increased kidney damage; macroalbuminuria)).[16]

2.2.2. Cognitive performance

The following neuropsychological tests were used to assess cognition in both trials:

1. The MMSE is a widely-used screening test for dementia that globally assesses certain aspects of cognitive functioning. It is used in both primary and specialized care and clinical research settings.[17,18] It briefly assesses orientation in time and place, verbal registration, attention, short term verbal memory, language and visuoconstruction up to a maximum score of 30. A score below 24 indicates cognitive impairment. This test was used to for our baseline selection.
2. The Trail Making Test (TMT) is a timed test consisting of two parts.[19,20] Part A measures psychomotor speed, scanning ability and number sequencing. Part B measures divided attention, working memory and task shifting or mental flexibility.[19] The TMT ratio ((TMT-B – TMT-A) / TMT-A) reflects the time needed to complete part B, corrected for the time needed to complete part A, which is a measure for executive functioning. Since processing speed and executive functioning are both sensitive measures to the cognitive consequences of white matter injury due to microvascular disease, the TMT is able to pick up subtle cognitive decline and cognitive decrements known to occur in people with type 2 diabetes.
3. The Verbal Fluency Test (VFT) is a timed test that measures fluency of speech. It depends on vocabulary size, access of lexical speed, strategy finding, updating and inhibition ability.[20,21] Participants are instructed to verbalize as many words from a particular category (i.e. animals) or with the same initial letter (i.e. F-A-S) within 60 s. Category-driven search provides more structure in search strategy compared to word generation according to an initial letter[19]; the latter relies more heavily upon executive function abilities. In both the CARMELINA and CAROLINA cognition substudies fluency scores were adjusted for language to correct for language-specific differences in word frequencies.

We used a standardized algorithm to identify invalid cognitive tests (while being blinded to treatment arm), using notes from the test-administrators and by defining implausible values. A composite score combining both the z-scores on Trail Making Test (TMT) and Verbal Fluency Test (VFT) was used to assess attention and executive functioning altogether in one robust score (A&E z-score). Details on the derivation were described previously.[13]

2.3. Statistical analyses

In baseline analyses, the relation between kidney parameters (eGFR, UACR; independent variables) and cognitive measures (MMSE and A&E z-score; outcome variables) was investigated in four different models using linear regression analyses: Model 1: unadjusted; Model 2: adjusted for age, sex, race (White, Black, Asian or other) and level of formal education (in years); Model 3: additionally adjusted for glycemic control (Hba1c (mmol/mol (%)), diabetes duration and CV risk factors (i.e. BMI (kg/m^2), systolic and diastolic blood pressure (mmHg), history of smoking and cholesterol ratio (total cholesterol/HDL)); Model 4: model 3 additionally adjusted for CV treatment (statins and anti-hypertensive drugs) and treatment arm (linagliptin versus comparator). We used this stepwise approach to provide insight in the data and potential confounding, but considered model 4 as the final model to answer our primary research question.

In longitudinal analyses, baseline eGFR and UACR were related to the change in cognitive performance at follow-up. Again, we used linear regression analyses using the same four models as described before, however, baseline cognitive performance and follow-up duration were

also added as covariates to each model. The results of models 1 to 3, both at baseline and follow-up, were used to gain insight into the relationship between eGFR and UACR and cognition. UACR was non-normally distributed and was therefore log-transformed.

In secondary analyses, we compared MMSE and A&E z-scores of subgroups with normal kidney function (eGFR ≥90) to those with mildly (eGFR ≥60 to <90), moderately (eGFR ≥30 to <60), and severely decreased kidney function (eGFR <30) and those with normoalbuminuria (UACR <30) to those with microalbuminuria (UACR ≥ 30 to ≤300), and macroalbuminuria (UACR >300) (Table A4 in Supplementary Material). We used ANCOVA analyses with covariates for age, sex, years of formal education and race to calculate least squares means differences for both MMSE and A&E z-score at baseline and at follow-up (i.e. mean cognitive change from baseline). For analyses at follow-up covariates for baseline cognitive performance and follow-up duration were also included. Bonferroni correction was used to correct for multiple-comparison testing.

Data are expressed as mean ± standard deviation or as number (percentage). Follow-up duration is expressed as mean (min, max). Least squares means (LSM) are expressed as mean (min, max). Results from linear regression analyses are shown in unstandardized regression coefficient (95 % confidence interval). Unstandardized regression coefficients for eGFR are shown per 10 units. For UACR these are shown per doubling because of log transformation.

All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

Out of 2694 participants from the CARMELINA and 4529 participants from the CAROLINA cognition substudies, a total of 2666 and 4296, respectively, were eligible for the baseline analyses in the current study (Fig. A1, Supplementary Material).

In CARMELINA, 36.2 % of the participants were female and 89.7 % were white. Mean ± standard deviation age was 68.1 ± 8.7 years, mean years of formal education 11.5 ± 4.0, and mean duration of diabetes 15.5 ± 9.6 years. At baseline, 338/2666 participants (12.7 %) had an MMSE <24. Of the 2328 participants eligible for follow-up (i.e. those with an available baseline MMSE ≥24 at baseline), 783 (33.6 %) had no valid follow-up cognitive assessment. Of this group, 233 participants had died, 308 had missing or implausible cognitive values at follow-up or prematurely discontinued the study. A further 252 did not meet the pre-specified trial requirement that follow-up assessment should be performed within seven days after the last drug intake. This resulted in a follow-up population of 1545 participants. After a median follow-up duration of 2.5 (min 0.1, max 4,2) years, mean cognitive change from baseline (adjusted for age, sex, education, race, follow-up duration and baseline cognitive performance) was −0.5 ± 0.3 on the MMSE and -0.1 ± 0.1 for the A&E z-score (details per test Table A2, Supplementary Material).

In CAROLINA, 39.5 % of the participants were female and most were white (82.7 %). Mean age was 64.7 ± 9.4, years of formal education was 10.6 ± 3.6 and mean duration of diabetes was 7.8 ± 6.2 years. At baseline, a smaller proportion of participants than in CARMELINA had an MMSE <24 (or missing) (279/4296 (6.8 %)), rendering 4017 participants eligible for follow-up. Of those, 855 (21.3 %) had no valid

Table 1
Baseline characteristics for CARMELINA-COG and CAROLINA-COGNITION.

	CARMELINA	CAROLINA
	(*n* = 2666)	(*n* = 4296)
Age [years]	68.1 ± 8.7	64.7 ± 9.4
Female *n,* (%)	964 (36.2%)	1695 (39.5%)
Years of formal education	11.5 ± 4.0	10.6 ± 3.6
Mini-mental state examination	27.2 ± 3.1	28.0 ± 2.5
Race *n,* (%)		
White	2392 (89.7%)	3552 (82.7%)
Black	193 (7.2%)	312 (7.3%)
Asian	61 (2.3%)	234 (5.5%)
Other	20 (0.8%)	198 (4.6%)
Diabetes-specific characteristics		
Time since diagnosis of diabetes [years]	15.5 ± 9.6	7.8 ± 6.2
eGFR [ml/min/1.73 m^2]	49.5 ± 22.1	75.8 ± 19.2
≥90 (normal)	173 (6.5%)	908 (21.1%)
≥60 to <90 (mild)	559 (21.0%)	2547 (59.3%)
≥30 to <60 (moderate)	1501 (56.3%)	820 (19.1%)
≥15 to <30 (severe)	426 (16.0%)	18 (0.4%)
<15 (end-stage)	7 (0.3%)	2 (0.1%)
UACR [mg/g]	573.5 ± 1113.1	69.4 ± 327.7
<30 (normoalbuminuria)	615 (23.1%)	3245 (75.5%)
≥30 to ≤300 (microalbuminuria)	1117 (41.9%)	877 (20.4%)
>300 (macroalbuminuria)	933 (35.0%)	174 (4.1%)
Hba1c [mmol/mol (%)]	62.2 ± 10.4 (7.8 ± 1.0)	54.6 ± 6.2 (7.1 ± 0.6)
Systolic blood pressure [mmHg]	141.2 ± 17.6	136.2 ± 16.4
Diastolic blood pressure [mmHg]	76.7 ± 10.5	78.7 ± 9.5
Cholesterol ratio[a]	4.0 ± 1.5	3.8 ± 1.3
BMI [kg/m^3]	32.7 ± 5.3	30.7 ± 5.1
Currently smokes (%)	321 (12.1%)	789 (18.4%)
Ex-smoker (%)	1035 (38.9%)	1597 (37.2%)
Medication use		
Statins (%)	2118 (79.4%)	2949 (68.7%)
Anti-hypertensiva (%)	2585 (97.0%)	3814 (88.8%)

Results shown in means and standard derivation (M ± SD) or number and percentage (n (%)) for baseline populations (see flowchart/Fig. A1 in Supplementary Material).

[a] Cholesterol ratio = total cholesterol/HDL, eGFR = estimated glomerular filtration rate in ml/min/1.73 m^2 using the MDRD-formula, UACR = urine albumin-to-creatinine ratio in mg/g.

Table 2
Relationships between eGFR and UACR and cognitive tests at baseline and follow-up.

		Model 1: Unadjusted	Model 2: Adj. for age, sex, race and years of formal education	Model 3: + Adj. for diabetes-related and CV risk factors	Model 4: + Adj. for treatment
Cognitive performance in relation to eGFR (per 10 points).					
Baseline					
CARMELINA	MMSE ($n = 2649$)	**0.10, (0.05, 0.16)****	−0.003, (−0.06, 0.05)	0.005, (−0.05, 0.06)	−0.01, (−0.07, 0.04)
	A&E ($n = 2348$)	**0.03, (0.02, 0.04)****	**0.02, (0.004, 0.03)***	**0.02, (0.005, 0.03)***	**0.02, (0.01, 0.03)***
CAROLINA	MMSE ($n = 4261$)	**0.06, (0.02, 0.10)***	0.01, (−0.03, 0.04)	0.003, (−0.04, 0.04)	0.01, (−0.03, 0.06)
	A&E ($n = 3925$)	**0.02, (0.004, 0.03)***	0.01, (−0.01, 0.02)	0.01, (−0.01, 0.02)	0.005, (−0.01, 0.02)
Change over time‡					
CARMELINA	MMSE ($n = 1541$)	0.02, (−0.02, 0.07)	−0.03, (−0.09, 0.02)	−0.03, (−0.09, 0.02)	−0.04, (−0.09, 0.02)
	A&E ($n = 1453$)	**0.02, (0.004, 0.03)***	0.01, (−0.003, 0.02)	0.01, (−0.01, 0.02)	0.01, (−0.005, 0.02)
CAROLINA	MMSE ($n = 3014$)	**0.06, (0.01, 0.11)***	−0.01, (−0.06, 0.04)	−0.02, (−0.07, 0.03)	−0.02, (−0.07, 0.03)
	A&E ($n = 2911$)	0.01, (−0.01, 0.02)	−0.01, (−0.02, 0.01)	−0.01, (−0.02, 0.01)	−0.01, (−0.02, 0.01)
Cognitive performance in relation to UACR (per doubling).					
Baseline					
CARMELINA	MMSE ($n = 2648$)	**0.05, (0.01, 0.09)***	0.001, (−0.04, 0.04)	−0.0003, (−0.04, 0.04)	0.01, (−0.04, 0.05)
	A&E ($n = 2647$)	0.01, (−0.004, 0.02)	−0.003, (−0.01, 0.01)	−0.0002, (−0.01, 0.01)	−0.001, (−0.01, 0.01)
CAROLINA	MMSE ($n = 4257$)	**−0.08, (−0.12, −0.05)****	−0.02, (−0.05, 0.01)	−0.02, (−0.06, 0.01)	−0.03, (−0.07, 0.01)
	A&E ($n = 3921$)	**−0.03, (−0.04, −0.02)****	**−0.01, (−0.02, −0.004)***	**−0.01, (−0.02, −0.003)***	**−0.01, (−0.02, −0.002)***
Change over time‡					
CARMELINA	MMSE (n = 1541)	0.01, (−0.03, 0.06)	−0.01, (−0.06, 0.03)	−0.02, (−0.06, 0.03)	−0.02, (−0.06, 0.03)
	A&E (n = 1453)	0.0001, (−0.01, 0.01)	−0.005, (−0.02, 0.01)	−0.0004, (−0.01, 0.01)	−0.001, (−0.01, 0.01)
CAROLINA	MMSE ($n = 3010$)	**−0.08, (−0.13, −0.04)****	**−0.05, (−0.09, −0.005)***	−0.04, (−0.08, 0.01)	−0.04, (−0.08, 0.005)
	A&E ($n = 2907$)	**−0.03, (−0.04, −0,01)****	**−0.02, (−0.03, −0.004)***	**−0.01, (−0.03, −0.001)***	**−0.01, (−0.03, −0.001)***

This table shows unstandardized regression coefficients (*b)* and 95 % confidence intervals in parentheses for the relationship between baseline eGFR (per 10 units) and UACR (per doubling) and cognitive tests at baseline and follow-up (i.e. change from baseline), using linear regression analyses. Unadjusted (model 1), adjusted for age, sex, years of formal education and race (model 2), additionally adjusted for diabetes-related and CV risk factors (BMI, history of smoking, systolic- and diastolic blood pressure, Hba1c, cholesterol ratio and diabetes duration) (model 3) and treatment (statins, anti-hypertensive drugs and treatment arm) (model 4). For change over time, follow-up duration and baseline performance were included as additional covariates in all analyses. Significant relationships are presented in bold face.
eGFR = estimated glomerular filtration rate in ml/min/1.73 m2, UACR = Urine Albumin-to-creatinine ratio in mg/g, CV = cardiovascular, MMSE = Mini-Mental state examination, A&E = attention and executive functioning.
** $p < .001$.
* $p < .05$.

follow-up assessment. This resulted in a follow-up population of 3162 participants (161 participants died, 405 prematurely discontinued the study, and 289 did not meet the pre-specified trial requirement that follow-up assessment should be performed within seven days after last drug intake) (Fig. A1, Supplementary Material). After a median follow-up of 6.1 (0.0, 7.4) years, the adjusted mean cognitive change from baseline was −0.5 ± 0.2 on the MMSE, and − 0.1 ± 0.1 for the A&E z-score (details per test Table A2, Supplementary Material).

Participants in CAROLINA had higher levels of eGFR (75.8 ± 19.2 ml/min/1.73m^2) and lower levels of UACR (69 ± 328 mg/g) at baseline than those in CARMELINA (eGFR: 50 ± 22 ml/min/1.73m^2, UACR: 574 ± 1113 mg/g) (Table 1). Overall, participants in CARMELINA and CAROLINA without follow-up assessment, compared to those with a follow-up assessment, had a slightly lower MMSE score, longer diabetes duration, and more CKD (Table A3, Supplementary Material).

In the baseline analysis of CARMELINA, there was an association between eGFR and A&E z-score after adjusting for demographics, diabetes-related and CV risk factors and treatment ($b = 0.02$ per 10 eGFR points, 95 % CI [0.01, 0.03]) $p = .004$) (model 4). This relation was not observed in CAROLINA (Table 2, Fig. 1). However, in CAROLINA, there was a significant inverse association of UACR with A&E z-score ($b = -0.01$ per UACR doubling 95 % CI [−0.02,−0.002], $p = .02$), a result not found in CARMELINA. There were no significant associations between eGFR or log UACR and baseline MMSE.

In the longitudinal analyses in CAROLINA, but not CARMELINA, log UACR at baseline was significantly and inversely associated with change in cognitive performance for A&E z-score ($b = -0.01$ per doubling, 95 % CI [−0.03,−0.0001], $p = .04$) (model 4). Baseline eGFR was not associated with change in A&E z-score in either CAROLINA or CARMELINA. There were no associations between eGFR or log UACR at baseline and change in MMSE (Table 2, Fig. 1b).

The secondary analyses comparing subgroups based on UACR and eGFR categories were largely consistent with the primary analyses, although categorization did affect power to detect small effects (Fig. 1,

Table A4-A6 in Supplementary Material). Only in CAROLINA the small subgroup with eGFR <30 (n = 20) scored 1.5 MMSE points lower compared to the reference group with eGFR ≥90. This was not replicated in the larger sample of patients with eGFR <30 (n = 431) in CARMELINA.

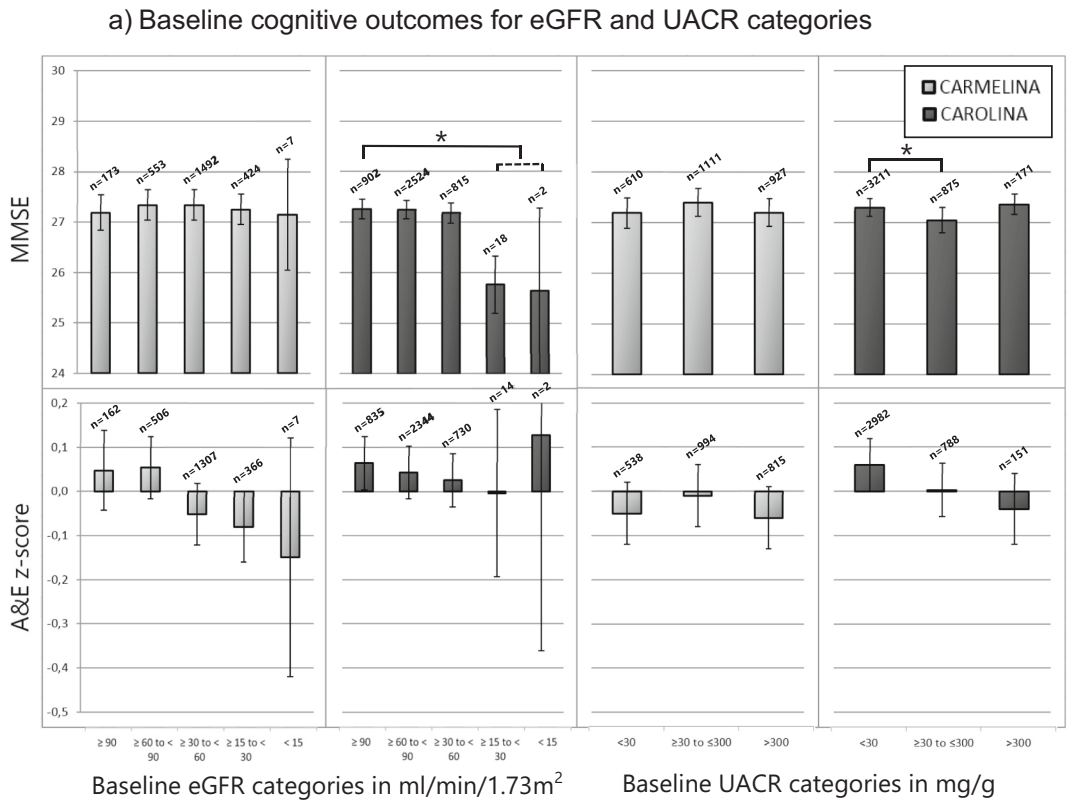

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Fig. 1. (a) Baseline cognitive outcomes for eGFR and UACR categories
Vertical bars represent least squares means and their standard error for MMSE and A&E z-score adjusted for age, sex, years of education and race for each eGFR- and UACR category. Bar charts are for visualization of the data, statistical analyses are presented in Table 2 and Table A4-A6 in Supplementary Material. * Significant differences between subgroups. The subgroups eGFR ≥15 to <30 and eGFR <15 are taken together due to small sample sizes. eGFR = Estimated Glomerular Filtration Rate in ml/min/1.73m^2 using the MDRD-formula, UACR = Urine Albumin-to-creatinine ratio in mg/g, MMSE = Mini-Mental state examination, A&E = attention and executive functioning. (b) Change in cognitive performance at follow-up for baseline eGFR and UACR categories.
Vertical bars represent least squares means and their standard error for change from baseline in MMSE and A&E z-score adjusted for age, sex, years of education, race, follow-up duration and baseline performance for each eGFR and UACR category. Change from baseline is presented for those with MMSE ≥24 at baseline and an available follow-up assessment (see flowchart/Fig. A1). Bar charts are for visualization of the data, statistical analyses are presented in Table 2 and Table A4-A6 in Supplementary Material. eGFR = Estimated Glomerular Filtration Rate in ml/min/1.73m^2 using the MDRD-formula, UACR = Urine Albumin-to-creatinine ratio in mg/g, MMSE = Mini-Mental state examination, A&E = attention and executive functioning.

4. Discussion

In two large cohorts of people with type 2 diabetes at elevated cardiorenal risk, lower eGFR or higher UACR were related with worse attention and executive functioning at baseline. Higher baseline UACR was also related to a significant decline in attention and executive functioning over time in one of the cohorts. However, the effect sizes of these associations were small.

Only a few studies have explored the relationship between CKD and cognition in older people with type 2 diabetes. In a cross-sectional analysis of ACCORD-MIND, to our knowledge the largest study on this topic thus far, the relationship between eGFR, UACR and cystatin C with cognition was investigated in participants with type 2 diabetes at high risk for CV disease ($n = 6457$).[22] Participants with albuminuria (UACR ≥30 mg/mg) were more likely to fall in the lowest tertile of cognitive performance for verbal memory (OR: 1.30 [95 % CI 1.09–1.55]) and processing speed (OR: 1.47 [95%CI 1.20–1.80]), compared to those without albuminuria. Other cross-sectional studies with relatively small sample sizes showed conflicting results on the association between eGFR or UACR and cognitive impairment in people with type 2 diabetes.[23–25] Longitudinal analyses in ACCORD-MIND in people with type 2 diabetes with persistent albuminuria over time, showed that albuminuria was related to a larger decline in processing speed (% change from baseline for those with albuminuria: −5.8 % [95 % CI -7.3, −4.2] versus no albuminuria: −2.6 % [95 % CI -3.4, −1.9]), $p = .001$, $n = 2977$). The same was not seen in verbal memory ($p = .11$).[26] Of note, there was no relationship between albuminuria and performance on the MMSE or an executive functioning test in ACCORD-MIND, similar to our study. Further, eGFR (and cystatin C) was not related to cognitive performance.[22] A recently published paper on the GRADE study cohort ($n = 4998$) explored cross-sectional associations between kidney parameters and cognitive performance in middle-aged adults with short duration of diabetes (mean: 4.0 ± 2.8 years), low CV burden and moderate to advanced kidney disease (15.8 % with albuminuria, 2.5 % with eGFR <60). Significant associations between eGFR or UACR and cognitive performance were primarily observed in unadjusted models and were attenuated when demographics and vascular risk factors were considered.[27] All in all, these previous studies are in line with our results. Statistical significant associations were only observed for a subset of kidney parameters, generally with small to modest effect sizes. There were some differences in associations of kidney parameters and cognition between CAROLINA and CARMELINA, likely reflecting differences in population and different stages of diabetes (CAROLINA: relatively early type 2 diabetes; CARMELINA: later stages of diabetes, higher burden of cardiovascular comorbidities and CKD).[28,29] In addition, these associations seem to be primarily captured by sensitive cognitive tests and not by the MMSE, which is too crude a test to detect milder cognitive decline in these populations. While previous research predominantly included participants with normal eGFR values and relatively few patients with macroalbuminuria (UACR >300),[26] our study population covered a comprehensive range of CKD (from no CKD to severe CKD). >1000 of the participants in our study had macroalbuminuria and almost 40 % had an eGFR <60. Hence, even in a population enriched for CKD, eGFR and UACR were not, or only modestly, related to cognitive performance.

Because of the observational nature of our study, a causal relationship between CKD and cognition cannot be established. Nevertheless, even if there would be a causal relationship, the finding of such minor or absent effects indicates that CKD in the stages present in our populations is probably not an essential player in type 2 diabetes associated cognitive decline. These observations should not be extrapolated to more severe forms of kidney failure, such as end-stage renal disease, which is known to have an impact on cognition.[30]

Strengths of our study include our longitudinal analyses with a median follow-up duration of 2.5 and 6.1 years. The large sample sizes of the two cohorts provide precise effect size estimates with narrow confidence intervals. Also, complementary to the widely-used measure for global cognition (MMSE), we used an attention and executive composite measure sensitive for capturing small effects and subtle cognitive decline that is seen in type 2 diabetes.[31] Our findings should be interpreted in context. We studied two selected CV outcome trial populations with type 2 diabetes at elevated CV risk.[12,32] CARMELINA had a relatively short median follow-up duration of 2.5 years, which might explain why no change in cognitive function has been found. The kidney parameters that were used (UACR and eGFR) can be under-or overestimated in some patients because of reasons such as reduced muscle mass, a small body surface area, unstable creatinine concentrations (e.g. due to strenuous exercise) or medication intake that blocks the tubular secretion of creatinine (e.g. kinase inhibitors, cimetidine and antibiotics).[33–36] Also, repeated measurements over time could have further increased the reliability of our kidney parameters. Since our dataset only included kidney parameters at baseline, we could not include different rates of progression of CKD over time in our analyses. Including variations in CKD progression could be of additional value in future research. Further, although our cognitive outcome is sensitive to diabetes-related cognitive decline, we cannot generalize our results regarding (non-existing) associations of CKD with cognitive decline to other cognitive domains that might be affected. Finally, no cognitive follow-up was obtained from a relatively large proportion of participants; 33.6 % in CARMELINA and 21.3 % in CAROLINA. Participants without follow-up assessment had relatively more kidney disease (Table A3, Supplementary Material). Competing mortality risk or survival bias might have influenced our results. Yet, since the cross-sectional results point in the same direction as the longitudinal results (i.e. only small effects), we believe competing mortality risk or survival bias has not essentially changed our outcome.

5. Conclusions

In conclusion, in two large type 2 diabetes cohorts that covered a wide range of kidney disease and included a substantial number of patients with advanced CKD, we observed modest associations between albuminuria or eGFR and attention and executive functioning. The large sample sizes provide precise effect size estimates; these were small. Therefore, it appears that CKD has a limited impact on cognition and further cognitive decline in this setting.

Data availability

The sponsor of the CARMELINA and CAROLINA trial (Boehringer

Ingelheim) is generally committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries via the Vivli website (https://vivli.org/).

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CRediT authorship contribution statement

CV: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Visualization, **JJ:** Methodology, Writing - Review & Editing, **CM:** Conceptualization, Methodology, Writing – Review & Editing, **EvdB:** Writing – Review & Editing **CW:** Conceptualization, Methodology, Writing – Review & Editing, **AP:** Methodology, Software, Formal analysis, Writing – Review & Editing **OEJ**: Resources, Writing - Review & Editing, Funding acquisition, **GJB:** Conceptualization, Methodology, Writing - Review & Editing, Supervision, Funding acquisition. **GJB** is taking responsibility for the contents of this article.

Prior presentation

Parts of this study (baseline analysis) were presented in a poster presentation at the 5th Cardiovascular Outcome Trial (CVOT) Summit in München, 25th of October 2019

Declaration of competing interest

The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work. OEJ was previously employed by Boehringer Ingelheim. The UMC Utrecht has received research support from Boehringer Ingelheim for GJBs projects. CW has received grant support, fees for advisory services and lecturing from Boehringer Ingelheim.

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Appendix A. Supplementary data.

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