Albuminuria and Cognitive Decline in People with Diabetes and Normal Renal Function

Joshua I. Barzilay, James F. Lovato, Anne M. Murray, Jeff Williamson, Faramaz Ismail-Beigi, Diane Karl, Vasilios Papademetriou, and Lenore J. Launer

Summary

Background and objectives Diabetes mellitus is associated with increased risk of cognitive impairment. This study examines whether microvascular disease, as measured by albuminuria and decline in estimated GFR (eGFR), is associated with cognitive decline during 3.3 years of follow-up in individuals with diabetes with a normal baseline eGFR (approximately 90 ml/min per 1.73 m^2).

Design, setting, participants, & measurements Participants were from the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes study (N=2977; mean age 62.5±5.8 years; recruitment from August 2003 to December 2005, followed through June 2009), which examined the association of intensive versus standard glucose control on cognitive function. Participants underwent three neuropsychologic tests at baseline, 20 months, and 40 months. Tests included information processing speed, verbal memory, and executive function. Mixed-effects models were used to assess the association of albuminuria and eGFR on the percentage decline in each test.

Results Participants with albuminuria at baseline and follow-up (persistent albuminuria) (−5.8% [95% confidence interval (CI), −7.3 to −4.2]) and participants with albuminuria at follow-up but none at baseline (progressive albuminuria) (−4.1% [95% CI, −5.6 to −2.7]) had greater percentage declines on information processing speed than participants without albuminuria at baseline and at follow-up (no albuminuria) (−2.6% [95% CI, −3.4 to −1.9]) (P=0.001 and P=0.10, respectively). There were borderline percentage changes in the test of verbal memory (4.8% [95% CI, 2.4 to 7.1] and 4.7% [95% CI, 2.5 to 7.0] versus 7.1% [95% CI, 6.0 to 8.3]; P=0.11 and P=0.08, respectively). On logistic regression analysis, persistent albuminuria (odds ratio, 1.37 [95% CI, 1.09 to 1.72]) and progressive albuminuria (odds ratio, 1.25 [95% CI, 1.02 to 1.56]) were associated with a ≥5% decline in information processing speed scores but not with verbal memory or executive function performance. A 1 ml/min per 1.73 m^2 per year eGFR decline had a borderline association with decline in tests of cognitive function.

Conclusions Persistent albuminuria and progressive albuminuria are associated with a decline in cognitive function in relatively young individuals with diabetes with unimpaired eGFR. These findings do not rule out the possibility of other processes causing cognitive decline.

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Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence:
Dr. Joshua Barzilay, Kaiser Permanente of Georgia, 3650 Steve Reynolds Boulevard, Duluth, GA 30096. Email: joshua.barzilay@kp.org

Introduction

Individuals with type 2 diabetes (DM) are at a 50%–60% increased risk of cognitive impairment compared with people without DM (1). They also develop cognitive decline more rapidly and at an earlier age (2). Identifying markers for very early cognitive decline in people with DM before the onset of evident impairment is therefore of interest and importance.

Moderate CKD (estimated GFR [eGFR] <60 ml/min per 1.73 m^2) and end stage renal failure are associated with an increased risk of cognitive impairment (3,4). Davey *et al.* (5) recently examined cognitive function in people with mild CKD (eGFR of approximately 78 ml/min per 1.73 m^2). Those with a rapid decline in eGFR of ≥3 ml/min per 1.73 m^2 per year over 5 years had a greater risk of cognitive impairment than those without such a decline. This finding not only expanded the range of renal function associated with cognitive impairment, but also suggested that dynamic markers of renal function, such as a decline in eGFR, and not only levels of attained eGFR, are important in determining cognitive decline.

Albuminuria is another marker of renal microvascular disease. Its prevalence has increased over the past 2 decades, owing to the increasing prevalence of hypertension, diabetes, and obesity (6). In people with DM, its prevalence reaches 37.6% by age 60–69 years (7). We have shown that albuminuria, based on a single measurement, is associated with an increased prevalence and risk of cognitive impairment in people with and without DM (8–10).

Recently, our understanding of the natural history of albuminuria has changed. Unlike the paradigm of the 1980s, which posited that albuminuria was a first

step in a committed process that inexorably leads to renal failure, it is now known that albuminuria can be dynamic. It can be stable, intermittent, progressive, or remitting (hereafter called *albuminuria status*) (11,12). How albuminuria status is associated with cognitive change has not been studied.

In this study, we examine the association between albuminuria status with performance on three tests of cognitive function in a cohort of adults with DM whose baseline eGFR level was approximately 90 ml/min per 1.73 m^2. We further test whether decline in eGFR during follow-up was an independent risk factor for cognitive impairment. Participants for this analysis were from the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes (ACCORD MIND) study. It examined whether intensive lowering of hemoglobin A1c (HbA1c) levels prevents decline in cognitive function compared with standard treatment of blood glucose levels. The study reported no differences in cognitive outcomes between the two groups (13).

Materials and Methods

ACCORD was a randomized, multicenter, 2×2 factorial design trial of 10,251 participants with DM at risk for cardiovascular disease (CVD) events (14). All participants were enrolled in the glycemia trial, which compared a therapeutic strategy targeted to a glycated HbA1c level of <6.0% with a strategy that targeted an HbA1c level of 7.0%–7.9%. The primary study outcome was the time to the first occurrence of a major cardiovascular event, the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. The lipid trial (54% of the cohort) compared the masked administration of placebo or fenofibrate to persons taking simvastatin, whose LDL was <100 mg/dl. This substudy tested the hypothesis that lowering triglycerides and raising HDL cholesterol on the background of the LDL level <100 mg/dl lowers CVD outcomes. The BP trial included the other 46% of participants and compared a therapeutic strategy targeted to a systolic BP (SBP) of <120 mmHg to one targeting <140 mmHg for CVD outcomes. The glycemia and lipid studies reported no benefit for intensive interventions (13,15). The BP study reported no benefit either, except for the prevention of stroke (16). All participants signed informed consent upon entry into the main ACCORD trial and all study sites obtained institutional review board permission for study participation. The study was conducted in accordance with the Declaration of Helsinki (ClinicalTrials.gov NCT00182910).

ACCORD MIND was an ancillary study to ACCORD (17). It consisted of 2977 ACCORD participants, recruited from August 2003 through December 2005 and followed through June 2009. Its primary objective was to determine whether intensive versus standard glucose therapy slowed deterioration of cognitive function (specifically the Digit Symbol Substitution Test [DSST]) over 40 months of follow-up. Secondary outcomes were to determine whether intensive BP control and lowering of triglycerides and raising HDL cholesterol slowed the rate of DSST decline compared with standard treatment. To achieve these aims, there were at least 350 participants in each of the eight cells of the ACCORD randomization scheme (glucose intensive versus standard subgrouped by BP and lipid assignment groups). To account for a 15% loss to follow-up, >350 participants were recruited for each cell. Power calculations for arriving at these estimates were previously published (17,18).

Cognition was assessed at baseline (within 45 days of randomization), 20 months, and 40 months after randomization using a 30-minute battery that included standardized tests sensitive to changes in memory, information processing speed, and executive function, and that had been validated in older persons and was available in a Spanish version. The test selection was based on tests used previously as part of a large multicenter magnetic resonance imaging study of vascular determinants of brain lesions (19). Quality of testing was ensured through training, certification, and monitoring. Inclusion criteria were willingness to participate in a 5-year study, age ≥55 years, and English or Spanish as a primary language. Exclusion criteria were preexisting conditions that could interfere with participation (*e.g.*, dementia, substance abuse, recent stroke) or nonskin cancer within the past 5 years. Participants had to have a creatinine level <1.5 mg/dl at entry into the ACCORD study and the MIND substudy.

The DSST is a measure of psychomotor speed and performance (20,21). It is calculated as the total number of test items correctly coded in 90 seconds, with a maximum possible score of 90. Other cognitive outcomes were verbal memory and executive function. Verbal memory was measured with the Rey Auditory Verbal Learning Test (RAVLT) (22), and is reported as the average number of words recalled (0–15) over the immediate, short, and delayed recall trials. Executive function was measured with the modified Stroop test (23) and is reported as the interference score; a higher score is indicative of worse function. A baseline DSST was obtained for 2957 participants (99%); 94% had at least one (20- or 40-month) follow-up and were included in the final analysis. Completion rates for the RAVLT (baseline of 2977; 2744 with at least one follow-up test [93.2%]) and Stroop (baseline of 2941; 2732 with at least one follow-up examination [92.9%]) tests were similar. The Mini Mental State Examination (MMSE) (24), a screening test for dementia, was also administered to compare our cohort with other cohorts in terms of baseline cognition. It was not considered a study outcome.

Albuminuria was defined as ≥30 mg albumin per gram creatinine in a spot urine sample. Owing to the small number of participants with macroalbuminuria, albuminuria was not dichotomized into microalbuminuria and macroalbuminuria. Participants were categorized by the presence or absence of albuminuria at baseline and on at least one test at follow-up. Participants with albuminuria at baseline and on all three follow-up urine tests had persistent albuminuria. Those with no albuminuria at baseline and on the three follow-up urine tests had no albuminuria. Participants with no albuminuria at baseline who had albuminuria on at least one follow-up test were progressors. Those with albuminuria at baseline but none on follow-up were remitters. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (25).

Baseline covariates were age, race/ethnicity, sex, level of highest attained education, body mass index (BMI), duration of DM, smoking status, number of alcoholic drinks consumed

per day, lipid levels, BP, and prior CVD events. Depression was assessed using the Patient Health Questionnaire. A value of ≥10 is consistent with depression. The number of severe hypoglycemic episodes (in which the participant reported receiving medical care or assistance from another individual and either a documented blood glucose <50 mg/dl [2.8 mmol/L] or recovery with carbohydrate treatment) was recorded.

Participant characteristics are summarized as means ± SDs and percentages. To test the association of the albuminuria status with cognitive function, mixed-effects models were used that incorporated information from baseline and from the 20-month and 40-month outcome measures (26). This approach uses all available outcome data to adjust for possible bias resulting from missing data at the 40-month examination in the estimation of the 40-month difference. Contrasts were used to test the hypothesis of no difference between albuminuria status groups. Model 1 adjusts for baseline cognitive measure, a visit effect, albuminuria status, and an albuminuria status by visit interaction. Model 2 further adjusts for age, sex, race, and education. Model 3 adds secondary prevention status, hypertension status, systolic BP, smoking status, BMI, eGFR, and a term for the randomized intervention groups as covariates. Mean baseline values of covariates were used. Model 4 adds baseline eGFR and change in eGFR over 40 months.

Logistic regression models were done to examine the associations of albuminuria status and change in eGFR with tests of cognition. Modeling was done in the following steps: model 1, unadjusted; model 2, age, race, sex, alcohol, education; model 3, variables in model 2 plus BMI, baseline SBP, and LDL cholesterol and history of CVD; and model 4, variables in model 3 plus baseline eGFR and change in eGFR over 40 months.

In sensitivity analyses, an indicator variable for having had a hypoglycemic event requiring assistance during the trial period was added to model 4 to see to what extent a hypoglycemic event affected the relationship between albuminuria status and change in DSST or RAVLT scores.

Analyses were conducted with SAS 9.2 software (SAS Institute, Cary, NC).

Results

Baseline and Follow-Up Characteristics

Compared with participants with no albuminuria (57.1% of the cohort), those with persistent albuminuria (15.9%) were older, were more likely to be male and African American, and were more likely to have higher SBP, BMI, longer duration of DM, and more CVD (Table 1). Characteristics of the remitters (12.5%) and progressors (14.5%) varied somewhat from those with persistent albuminuria. Remitters were more likely than the other three albuminuria group to be in the intensive BP arm of the ACCORD Blood Pressure Study. All four groups had on average preserved renal function (eGFR approximately 90 ml/min per 1.73 m^2). After adjustment for age, depression, and education status, participants with persistent albuminuria had the poorest performance on tests of cognition at baseline, whereas those with no albuminuria had the best levels.

Participants without albuminuria had greater decreases in mean and median eGFR over follow-up compared with the other albuminuria groups. The mean eGFR decline was <1 ml/min per 1.73 m^2 per year in all albuminuria groups. Participants with no albuminuria had fewer hypoglycemic events than the other three albuminuria groups.

Longitudinal Change in Cognition by Albuminuria Status

Participants with persistent albuminuria had a statistically significant percentage decline in DSST scores over 40 months compared with those with no albuminuria (−5.8% [95% confidence interval (CI), −7.3 to −4.2] versus −2.6% [95% CI, −3.4 to −1.9]; P=0.001) (Table 2 and Supplemental Table 1). Participants with progressive albuminuria had a decline in DSST score (−4.1% [95% CI, −5.6 to −2.7]) approaching statistical significance compared with those without any albuminuria (P=0.10). Both of these albuminuria groups had trends toward a decline in RAVLT scores (P=0.11 and P=0.08, respectively), but little change in Stroop scores. Remitters had cognition scores similar to participants without albuminuria.

Factors Independently Associated with ≥5% Decline in DSST Score

On unadjusted analysis, persistent albuminuria and progressive albuminuria were each significantly associated with a ≥5% decline in DSST score, with odds ratios (ORs) of 1.47 (95% CI, 1.20 to 1.86) and 1.31 (95% CI, 1.05 to 1.62), respectively (Table 3; full model in Supplemental Table 2). Successive adjustment for demographic, cardiovascular, and renal factors mildly attenuated these estimates (OR, 1.37 [95% CI, 1.09 to 1.72]; OR, 1.26 [95% CI, 1.002 to 1.56], respectively) but they remained statistically significant. A 1 ml/min per 1.73 m^2 per year decline in eGFR (approximately twice the median annual decrease during the trial) had a marginal association with DSST decline (OR, 1.02 [95% CI, 0.99 to 1.04]). The association of persistent albuminuria on DSST decline relative to 1 year of aging was approximately 7.2 years (ratio of log [OR persistent albuminuria] to log [OR per year of age]), *i.e.*, persistent albuminuria was equivalent to 7.2 years of aging in terms of DSST decline. The association of progressive albuminuria was equivalent to approximately 3.2 years.

When a hypoglycemic event requiring assistance was added to model 4 in a sensitivity analysis, ORs and 95% CIs were similar (persistent albuminuria versus no albuminuria: OR, 1.48 [95% CI, 1.17 to 1.89]; remitters versus no albuminuria: OR, 1.01 [95% CI, 0.84 to 1.36]; and progressors versus no albuminuria: OR, 1.27 [95% CI, 1.01 to 1.58]).

Factors Independently Associated with ≥5% Decline in RAVLT Score

None of the albuminuria categories was significantly related to a >5% decline in verbal memory (Supplemental Table 3). A 1 ml/min per 1.73 m^2 per year decline in eGFR was also not significantly related to RAVLT decline (OR, 1.02 [95% CI, 0.99 to 1.04]; P=0.18). A sensitivity analysis showed that adding hypoglycemic episodes requiring assistance to model 4 did not change the nonsignificant associations of albuminuria status with a change in RAVLT score.

Table 1. Baseline and follow-up results of ACCORD MIND participants categorized by albuminuria status

Characteristic	No Albuminuria	Albuminuria	Remitters	Progressors	Overall	*P* Value
Participants	1689 (57.1)	469 (15.9)	370 (12.5)	429 (14.5)	2957	
Age (yr)	62.1±5.8	63.2±6.0	62.6±5.8	63.0±5.8	62.5±5.8	0.002
Female sex	851 (50.4)	170 (36.2)	156 (42.2)	200 (46.6)	1377 (46.6)	<0.001
Education						0.12
Less than high school graduate	200 (11.8)	77 (16.4)	55 (14.9)	54 (12.6)	386 (13.1)	
High school graduate/GED	428 (25.3)	118 (25.2)	93 (25.1)	126 (29.4)	765 (25.9)	
Some college/technical training	590 (34.9)	167 (35.6)	123 (33.2)	144 (33.6)	1024 (34.6)	
College graduate or more	471 (27.9)	107 (22.8)	99 (26.8)	105 (24.5)	782 (26.4)	
Race/ethnicity						0.02
African American	247 (14.6)	92 (19.6)	76 (20.5)	64 (14.9)	479 (16.2)	
White	1207 (71.5)	304 (64.8)	252 (68.1)	299 (69.7)	2062 (69.7)	
Hispanic	108 (6.4)	41 (8.7)	24 (6.5)	36 (8.4)	209 (7.1)	
Other	127 (7.5)	32 (6.8)	18 (4.9)	30 (7.0)	207 (7.0)	
Alcohol consumption (drinks per week)						0.71
0	78.0	77.0	74.6	79.7	77.7	
1–2	12.7	13.4	14.3	12.4	13.0	
3–7	6.6	5.8	6.8	5.4	6.3	
≥8	2.8	3.8	4.3	2.6	3.1	
Systolic BP (mmHg)	133.0±16.5	141.9±18.9	141.0±18.6	133.6±17.7	135.5±17.8	<0.001
Duration of diabetes (yr)	9.5±7.1	12.5±7.5	11.8±8.1	10.3±6.9	10.4±7.4	<0.001
Total cholesterol (mg/dl)	183.3±40.7	185.4±45.5	184.4±44.2	181.1±40.2	183.4±41.9	0.59
LDL (mg/dl)	104.1±33.5	103.1±34.7	102.8±33.2	102.4±33.2	103.5±33.6	0.31
HDL, women (mg/dl)	47.5±12.1	46.3±11.8	46.6±11.8	46.2±12.8	47.1±12.1	0.11
HDL, men (mg/dl)	38.9±9.0	38.4±10.8	38.5±9.4	37.7±8.4	38.6±9.3	0.08
eGFR (MDRD formula)	91.2 (86.3–96.2)	88.6 (83.0–94.4)	90.0 (84.0–95.2)	88.9 (83.7–94.2)	90.4 (85.0–95.6)	<0.001
BMI (kg/m^2)	32.8±5.3	33.0±5.4	33.8±5.5	33.1±5.3	33.0±5.4	0.03
History of CVD	404 (23.9)	173 (36.9)	135 (36.5)	151 (35.2)	863 (29.2)	<0.001
Intensive lipid participant (%)	51.6	48.0	58.0	46.2	50.9	0.09
Intensive BP participant (%)	53.2	45.1	57.7	46.6	51.8	0.02
Intensive glucose participant (%)	50.4	45.8	53.2	47.1	49.5	0.11
Depression (PHQ >10)	245 (14.5)	73 (15.6)	61 (16.5)	60 (14.0)	439 (14.8)	0.71
Baseline cognition test levels (age, education, and depression adjusted)						
DSST	54.3±15.6	48.1±15.9	50.6±15.6	52.4±15.8	52.6±15.9	<0.001
Stroop test	30.9±15.5	33.8±17.5	33.3±19.1	33.2±17.7	32.0±16.7	0.001
RAVLT	7.7±2.5	7.0±2.5	7.2±2.6	7.6±2.5	7.5±2.5	0.04
MMSE	27.5±2.5	27.2±2.6	27.3±2.5	27.4±2.5	27.4±2.5	0.33
Follow-up renal function						
ΔeGFR per year	−0.60 (−0.77, −0.01)	−0.58 (−0.72, 0.25)	−0.54 (−0.75, 0.21)	−0.59 (−0.76, 0.14)	−0.59 (−0.76, 0.05)	0.003
ΔeGFR per year	−0.38±0.93	−0.20±1.19	−0.27±1.13	−0.28±1.15	−0.32±1.04	<0.001

Table 1. (Continued)

Characteristic	No Albuminuria	Albuminuria	Remitters	Progressors	Overall	*P* Value
Hypoglycemic episodes requiring any assistance during the trial period	98 (6.6)	40 (10.7)	33 (9.5)	41 (9.9)	212 (8.1)	0.01

Data are presented as *n* (%), mean ± SD, or median (interquartile range), unless otherwise specified. GED, General Education Development, equivalent of high school diploma; eGFR, estimated GFR; MDRD, Modification of Diet in Renal Disease study equation; BMI, body mass index; CVD, cardiovascular disease; PHQ, Patient Health Questionnaire; DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; MMSE, Mini Mental State Examination.

Discussion

In this study of middle-aged adults with diabetes with preserved baseline eGFR (approximately 90 ml/min per 1.73 m^2), the DSST declined in participants with persistent and progressive albuminuria compared with participants without albuminuria. Decline was greater in participants with persistent albuminuria compared with those with progressive albuminuria, suggestive of a dose effect. The findings were independent of baseline eGFR and declining eGFR, which were only mildly diminished (0.54–0.60 ml/min per 1.73 m^2 per year) at the end of follow-up, leaving most participants with normal to near normal renal function. These findings extend prior studies of the association of renal disease and cognitive decline to an even earlier stage of renal disease than previously reported.

Diabetes and albuminuria are vascular risk factors. The cognitive findings described here may therefore be vascular in origin. Several mechanisms by which albuminuria and cognitive impairment are related can be offered. One possibility is that the two microcirculatory systems share common pathomechanisms: both are low resistance beds exposed to high circulatory flow (27). Impaired autoregulation from small vessel endothelial dysfunction can increase pressure in both circulatory systems, leading to organ damage. For example, with impaired renal function, nitric oxide inhibitor levels increase. Nitric oxide regulates the microcirculation and the blood–brain barrier, which are implicated in brain white matter disease (28). Alternatively, complications associated with albuminuria, such as anemia, acidosis, hyperparathyroidism, and hypertension, can affect cognitive function (29).

Our findings should be put into context. Participants had on average normal baseline cognitive function (MMSE score >26), and were generally well educated, a factor that protects against cognitive decline (30). The changes in the DSST were modest and on an individual level would not likely be clinically significant. However, the average age of the cohort was 10–15 years younger than the age at which cognitive impairment is usually recognized (31). If the rate of information processing speed decline persisted, evident cognitive impairment would likely develop with aging. Participants with persistent and progressive albuminuria had the equivalent of 7.2 and 3.2 years of cognitive aging relative to 1 year of calendar aging, respectively. On a population level, these findings could have large effects.

Our findings are consistent with studies that have shown that the DSST detects small cognitive changes in people with high levels of cognition (32) and in people with DM (1,33). The Stroop test, which measures executive function, did not show change in association with albuminuria status. However, previous studies using other measures of executive function have found (34–36) associations of albuminuria with decline in executive function.

In our study, albuminuria progressors were more likely to experience DSST decline. This is similar to a study in which progressors had increased odds of cognitive decline as measured by the MMSE (8). In that study, like ours, albuminuria remitters were similar in terms of cognitive change to participants without any albuminuria. Another study with longitudinal data reported poorer cognitive function in participants with progressive albuminuria compared with those with stable albuminuria (37). These

Table 2. Percentage change in cognitive tests at 40 months compared with baseline adjusted for baseline score, age, sex, race, and level of education

Model	No Albuminuria	Albuminuria	Remitters	Progressors
Participants (*n*)	1689	469	370	429
DSST	−2.6 (−3.4, −1.9)	−5.8 (−7.3, −4.2)	−2.8 (−4.3, −1.2)	−4.1 (−5.6, −2.7)
Stroop	−1.3 (−3.4, 0.8)	1.4 (−2.9, 5.6)	−1.0 (−5.4, 3.3)	−0.7 (−4.7, 3.2)
RAVLT	7.1 (6.0, 8.3)	4.8 (2.4, 7.1)	6.7 (4.3, 9.1)	4.7 (2.5, 7.0)
MMSE	−1.2 (−1.6, −0.08)	−1.6 (−2.4, −0.08)	−0.05 (−1.4, 0.03)	−1.2 (−2.0, −0.05)

See the Supplemental Material for raw data. *P* values are as follows: No albuminuria versus albuminuria: 0.001 for DSST, 0.28 for Stroop, 0.11 for RAVLT, and 0.46 for MMSE; no albuminuria versus remitters: 0.82 for DSST, 0.75 for Stroop, 0.80 for RAVLT, and 0.19 for MMSE; and no albuminuria versus progressors: 0.10 for DSST, 0.88 for Stroop, 0.08 for RAVLT, and 0.86 for MMSE. DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; MMSE, Mini Mental State Examination.

Table 3. Abbreviated Cox proportional hazards model of factors significantly associated with a ≥5% DSST decline in the ACCORD MIND study

	Model 1	Model 2	Model 3	Model 4
No albuminuria	1.00	1.00	1.00	1.00
Persistent albuminuria	1.47 (1.20 to 1.86)[a]	1.44 (1.56 to 1.80)[a]	1.41 (1.12 to 1.76)[a]	1.37 (1.09 to 1.72)[a]
Remitters	1.15 (0.92 to 1.45)	1.12 (0.89 to 1.42)	1.08 (0.85 to 1.37)	1.07 (0.84 to 1.36)
Progressors	1.31 (1.05 to 1.62)[a]	1.26 (1.02 to 1.57)[a]	1.26 (1.02 to 1.57)[a]	1.25 (1.002 to 1.56)[a]
Baseline eGFR (ml/min per 1.73 m^2)				0.99 (0.98 to 1.01)
Δ eGFR (1 ml/min per 1.73 m^2 per year)				1.02 (0.995 to 1.04)
Age (per year)		1.02 (1.00 to 1.03)[a]	1.02 (1.01 to 1.03)[a]	1.02 (1.00 to 1.03)[a]

The full model appears in the Supplemental Material. Model 1, unadjusted; model 2, adjusted for age, sex, race (white, black, Hispanic, other), education (less than high school, high school, some college, college or higher), and alcohol consumption (1–2, 3–7, ≥8 drinks per week); model 3, variables in model 2 plus body mass index, systolic BP, secondary cardiovascular disease prevention (yes versus no), and LDL; model 4, variables in model 3 plus baseline eGFR and 1 ml/min per 1.73 m^2 per year decrease in eGFR. DSST, Digit Symbol Substitution Test; ACCORD MIND, Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes; eGFR, estimated GFR.
[a]Statistically significant.

findings emphasize that dynamic characteristics of albuminuria are important determinants of cognitive decline.

Several studies have shown that moderate CKD can be associated with impaired cognition (38–41). There are few studies, however, that have longitudinally examined the effect of eGFR decline on cognition. In the Cardiovascular Health Study (3), an increase in serum creatinine from 1.0 to 2.0 mg/dl was associated with a 26% increased risk (95% CI, 1.02 to 1.60) of dementia. That study did not have measures of eGFR. In our study, there was a trend for a 1 ml/min per 1.73 m^2 per year eGFR decline (approximately double the median annual eGFR decline) to be associated with lower DSST scores in the cohort. Two population-based studies with unimpaired renal function and a low prevalence of diabetes reported that only an eGFR decline of >3–4 ml/min per 1.73 m^2 per year was significantly associated with cognitive decline (5,42).

Our results suggest that in an exclusively diabetic population, small declines in eGFR may have a stronger negative association with cognitive decline than in populations without DM.

Our findings are characterized by prospective data collection, repeated measures of cognitive testing, near complete data capture, characterization of albuminuria over time, and a large number of participants. Risk factors for cognitive decline were captured, permitting for adjustment. We recognize that the follow-up was short and may not be predictive of subsequent cognitive decline. A follow-up study, entitled ACCORDION, will add 3–5 years of follow-up.

In summary, we identify adults with diabetes, whose eGFR at baseline was approximately 90 ml/min per 1.73 m^2, with persistent or progressive albuminuria as a group at risk for cognitive decline. Such observations offer a possible new avenue for understanding subsequent cognitive impairment in persons with diabetes and offer an opportunity for intervention.

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Disclosures

None.

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