



# Mild to moderate decrease in eGFR and cognitive decline in older adults

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## ABSTRACT

**Background.** Whether mild to moderately low estimated glomerular filtration rate (eGFR) is associated with cognitive decline in older adults is not clear. We evaluated changes in cognition in relation to baseline eGFR in older adults participating in the Alzheimer's Disease Neuroimaging Initiative (ADNI).

**Methods.** This is a longitudinal secondary analysis of an established observational cohort. We used data from the ADNI, an National Institutes of Health-funded, multicenter longitudinal observational study that includes participants with and without cognitive impairment who were administered a comprehensive battery of neuropsychological tests every 6 months. We related the Chronic Kidney Disease Epidemiology Collaboration eGFR with previously validated cognition composite scores for memory (ADNI-Mem) and executive function (ADNI-EF) in multivariable linear regression analysis adjusted for age, sex, race and level of education.

**Results.** A total of 1127 ADNI participants (mean age  $74 \pm 7$  years, 57% men, 97% Caucasian, mean follow-up  $6 \pm 2.6$  years) were included in the analysis. The mean baseline eGFR was  $76 \pm 19$  mL/min/1.73 m<sup>2</sup>, with 6% with eGFR <45, 22% with eGFR 45–<60, 51% with eGFR 60–90 and 21% with eGFR >90 mL/min/1.73 m<sup>2</sup> at baseline. Both ADNI-Mem and ADNI-EF scores declined over time. In the multivariable linear regression model, older age ( $\beta = -0.117$ ,  $P = 0.01$ ), female sex ( $\beta = 0.312$ ,  $P < 0.001$ ) and lower education ( $\beta = 0.079$ ,  $P < 0.001$ ) were associated with a decline in ADNI-Mem scores, whereas baseline eGFR (each 10 mL/min/1.73 m<sup>2</sup> change) was not [ $\beta = -0.03$  [confidence interval (CI)  $-0.06$ – $0.001$ ],  $P = 0.11$ ]. Similarly, older age ( $\beta = -0.278$ ,  $P < 0.001$ ) and lower education ( $\beta = 0.099$ ,  $P < 0.001$ ) were associated with a decline in ADNI-EF scores, whereas baseline eGFR was not [ $\beta = 0.004$  (95% CI  $-0.04$ – $0.04$ ),  $P = 0.84$ ].

**Conclusions.** In this cohort from the ADNI study, there was no association between baseline eGFR and cognitive decline in older adults with mild to moderately low eGFR.

**Keywords:** CKD, cognition, eGFR, kidney function, older adults

## INTRODUCTION

Approximately one-half of adults >70 years of age have an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m<sup>2</sup>, the current diagnostic threshold for chronic kidney disease (CKD) [1]. Like CKD, dementia is an age-related disease that negatively affects individuals, society and the healthcare system [2–4]. With increasing life expectancy, the prevalence of both dementia and CKD is expected to increase further [1, 5, 6]. Cognitive impairment is common in CKD with or without kidney transplant [7, 8]. While there is some indication that CKD is a risk factor for cognitive impairment and dementia [8–10], there is also evidence that this association between CKD and cognition may be lost in older adults with mild to moderate CKD [10–16]. Accurate determination of whether it is the lower eGFR or accompanying comorbidities and systemic inflammation [17] that are risk factors for cognitive decline in older adults is important for risk prediction and efforts at prevention of dementia.

Kidney disease is associated with changes in the brain [18]. Moderate to severe CKD has been associated with cognitive impairment in cross-sectional studies [8] and cognitive decline in longitudinal studies [9, 10]. A meta-analysis of six published studies showed an association between lower eGFR and cognitive decline [19]. However, another meta-analysis [20] found no association and attributed the difference in results to inadequate adjustment for confounding variables in the previous meta-analysis. Indeed, these studies differ in participant

demographics and adjustment for confounders. Both meta-analyses reported high levels of heterogeneity, as the included studies varied in the population included, confounding variables and methods used for assessment of kidney function and cognition. It is possible that adjustment for comorbidities attenuates the association between eGFR and cognition [16]. Moreover, it has been long debated that reduced eGFR in older adults may not reflect a true kidney disease. GFR declines with age [21–25], and the prognostic implications of lower GFR in older adults are different from those in younger adults [26–30]. The effect of a decline in eGFR in older adults on adverse outcomes and mortality is lower than a decline in eGFR from a kidney disease [21, 24, 25, 31]. A decline in GFR with age is less likely to progress to end-stage renal disease (ESRD), and most older people die with CKD rather than from it [26–28]. Similar to the lower risk for ESRD and cardiovascular outcomes with a decline in eGFR with aging, the risk for cognitive decline with a lower eGFR may also be different in older adults. Thus, for a clinician seeing an older patient with mild to moderately low eGFR, it remains unclear whether these patients are at risk of cognitive decline.

To help clinicians with better risk prediction, we analyzed data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort. The ADNI is an ongoing, National Institutes of Health (NIH)-supported, multicenter, longitudinal, prospective, observational study of cognitive aging that was launched in 2004. The ADNI cohort includes both males and females of varying races and education levels from 57 locations in the USA and Canada and excludes those with serious illnesses other than dementia [32]. The ADNI has the advantage of having older participants (mean age 74 years), measurement of kidney function (often lacking in dementia studies), exclusion of participants with severe comorbidities, multiple follow-up visits with extensive neuropsychological assessments and confirmation of stages of cognitive impairment. We previously showed that a mild to moderate decrease in eGFR was not associated with cognition in cross-sectional analysis [15]. We now present the longitudinal follow-up analysis of the ADNI study.

## MATERIALS AND METHODS

### Participants

We obtained data from the ADNI (<http://adni.loni.usc.edu/>). The ADNI is a longitudinal, observational cohort of participants with ages ranging from 55 to 90 years and is aimed at understanding the progression of dementia. The ADNI includes participants with general good health with normal cognition, mild cognitive impairment (MCI) and dementia. For our analysis, we considered participants with MCI and dementia together as the group with cognitive impairment. Per the ADNI criteria, participants with normal cognition had a Clinical Dementia Rating (CDR) of 0 with a Memory Box Score of 0 [33], a normal education-adjusted Logical Memory II score from the Wechsler Memory Scale, a Mini-Mental State Exam (MMSE) score  $\geq 24$  and a lack of subjective memory concerns. The other participants with cognitive impairment had a CDR  $\geq 0.5$ , an abnormal education-adjusted score on the Logical Memory II subscale

and a subjective memory concern reported by a participant, study partner or clinician that was confirmed by a study partner. Participants with significant neurological diseases other than possible Alzheimer’s disease were excluded. Other exclusion criteria included significant systemic illness or unstable medical condition, major depression, bipolar disorder, alcohol or substance abuse or residence in a skilled nursing facility that could interfere with the study. For this analysis, we included all ADNI participants with baseline serum creatinine measurements and at least one follow-up visit. Participant recruitment for the ADNI occurred in several phases. We used data from three phases of the ADNI (ADNI-1, ADNI-GO and ADNI-2) and excluded participants from ADNI-3, as they lacked serum creatinine measurements (Figure 1).

### Clinical and demographic variables

We obtained baseline demographic information from the ADNI database. This included age, sex, race, ethnicity, education, marital status, body mass index (BMI), Functional Activities Questionnaire (FAQ) score, handedness, family history of dementia, cognitive status, systolic and diastolic blood pressure (BP), seated heart rate, smoking history, Hachinski Ischemic Score (HIS; a clinical tool for differentiating major types of dementia and identifying those with vascular dementia) [34] and CDR [35].

### Measurement of kidney function

Kidney function was measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate eGFR [36]. We chose the CKD-EPI equation over the Modification of Diet in Renal Disease equation because it is more accurate in older persons and at higher levels of kidney function [37] and better predicts the risk for mortality, cardiovascular events and ESRD [38].

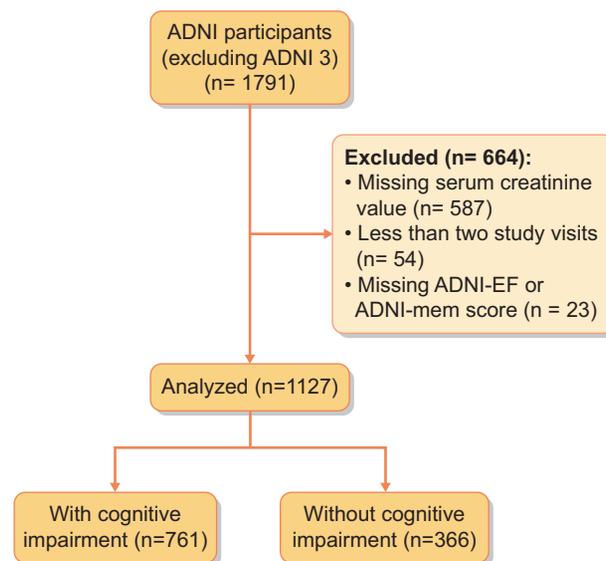


FIGURE 1: Consort diagram.

## Measurement of cognition

Cognition was measured via previously validated composite scores for memory (ADNI-Mem) and executive function (ADNI-EF) based on the ADNI's battery of neuropsychological testing [39, 40]. Both these scores are interval-type data, with means of 0 and standard deviations (SDs) of 1 and are strongly associated with brain imaging findings [39, 40]. Specific tests included in ADNI-Mem are the Rey Auditory Verbal Learning Test (two versions), AD Assessment Schedule–Cognition (three versions), MMSE and Logical Memory data. Tests included in the ADNI-EF are the revised Wechsler Adult Intelligence Scale (WAIS-R) Digit Symbol Substitution, Digit Span Backwards, Trails A and B, Category Fluency and Clock Drawing [39, 40].

## Statistical analysis

We divided participants into four categories of baseline eGFR (<45, 45–60, 61–90 and >90 mL/min/1.73 m<sup>2</sup>) and compared the baseline clinical and demographic variables with linear trend tests (for continuous variables) and chi-square tests (for categorical variables). To determine the association between the change in ADNI-Mem and ADNI-EF scores over time (outcome variables) and eGFR (exposure variable) after adjusting for age, sex, race and education (covariates), we used multivariable repeated measures linear regression models using proc glimmix. We used this model to assess the interaction of time and eGFR in predicting the ADNI-Mem and ADNI-EF scores. We also did a subgroup analysis on participants with and without cognitive impairment. In an additional adjusted multivariable linear regression we assessed the relationship between eGFR and CDR. We further represented the change in ADNI-Mem and ADNI-EF scores over time by eGFR categories. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). P-values ≤0.05 indicated statistical significance.

## RESULTS

There were 1127 ADNI participants with a baseline serum creatinine measurement, at least two study visits and ADNI-EF and ADNI-Mem scores, making them eligible for our analysis (Figure 1). Table 1 shows their baseline characteristics. Cognitive impairment (MCI or dementia) was present in 761 (68%) participants. When participants were grouped by eGFR, 6% had eGFR <45, 22% had eGFR 45–60, 51% had eGFR <60–90 and 21% had eGFR >90 mL/min/1.73 m<sup>2</sup>. Age, ethnicity, education, BMI, FAQ score, handedness, BP, heart rate, smoking history, HIS, CDR and ADNI-EF score did not differ between the eGFR categories. Participants in the higher eGFR groups were more likely to be male and less likely to be Caucasian or widowed. Additionally, ADNI-Mem scores were lower in the higher eGFR groups.

In unadjusted analysis, both ADNI-EF (Figure 2A) and ADNI-Mem (Figure 2B) (P < 0.001 for both) declined over time in all eGFR categories. The decline in ADNI-Mem differed by eGFR group (P < 0.001) with participants with an eGFR of 45–60 mL/min/1.73 m<sup>2</sup> showing the least decline. There was a similar trend in the decline of ADNI-EF by eGFR group

(P = 0.07). There was no difference in the decline of ADNI-EF or ADNI-Mem scores in the other eGFR categories.

In the multivariable linear regression model, ADNI-Mem and ADNI-EF decreased progressively over time. Baseline eGFR did not predict a change in ADNI-EF or ADNI-Mem scores in the entire cohort in the subgroups with and without cognitive impairment (Table 2). Older age and lower levels of education were associated with a decline in both ADNI-EF and ADNI-Mem scores. Male sex was associated with a faster decline in ADNI-Mem but not ADNI-EF score. There was no interaction between baseline eGFR and time for both ADNI-EF (P = 0.56) and ADNI-Mem (P = 0.32).

In the subgroup analysis separating participants with MCI and dementia (Supplementary data, Table S1a and b), baseline eGFR did not predict a change in ADNI-EF or ADNI-Mem scores in participants with dementia. Higher eGFR was associated with a better ADNI-EF score, but not ADNI-Mem score, in participants with MCI. Baseline eGFR did not predict a change in CDR in the entire cohort or in subgroup analysis by baseline cognition status (Supplementary data, Table S2).

## DISCUSSION

Our results add to data on the association between CKD and cognition in older adults. We found that both ADNI-Mem and ADNI-EF scores decrease over time across all eGFR categories. However, the decline in either ADNI-Mem or ADNI-EF score was not associated with baseline eGFR. To further assess if these results were confounded due to the presence of cognitive impairment in some of the participants, we performed a subgroup analysis of participants with and without cognitive impairment at baseline and found that there was no change in results in either subgroup—there was no association between baseline eGFR and cognitive decline in either subgroup. Further subgroup analysis after dividing participants with cognitive impairment into MCI and dementia showed that baseline eGFR was not predictive of ADNI-Mem scores in the MCI or dementia groups. However, baseline eGFR was predictive of ADNI-EF scores in MCI but not in dementia. It is possible that the rate of decline was easier to measure in participants with MCI compared with those with dementia.

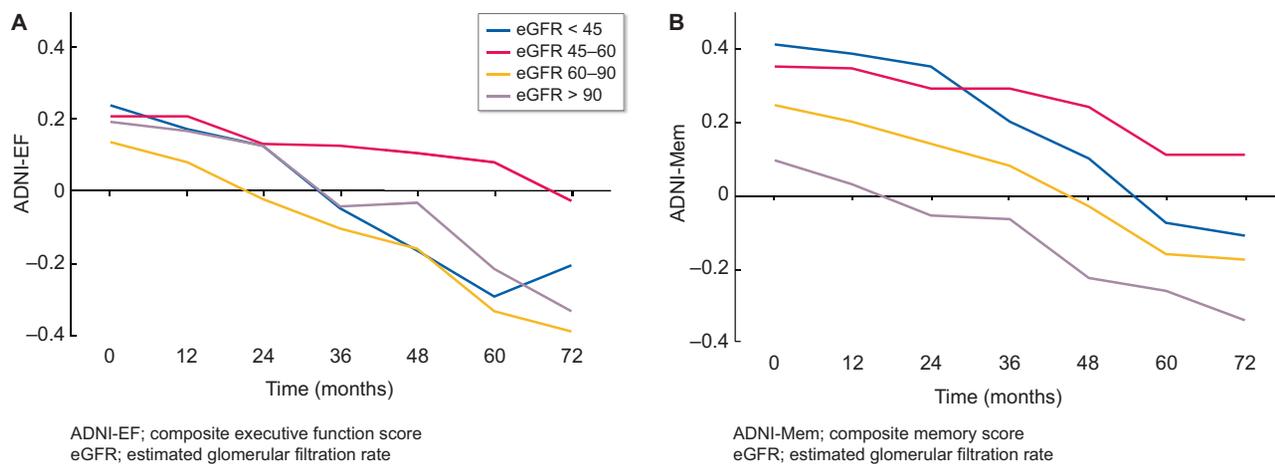
We used composite scores, ADNI-Mem and ADNI-EF for evaluation of cognitive function. Both ADNI-Mem and ADNI-EF have been validated for detecting a change in cognitive function over time in MCI and dementia and both performed equal to or better than individual neuropsychological tests in predicting conversion to dementia [39, 40]. Compared with the CKD prevalence of almost 50% in persons >70 years of age in the general population [1], only 28% of the participants in our study had an eGFR <60 mL/min/1.73 m<sup>2</sup> (Table 1). The ADNI excluded participants with severe health conditions other than dementia. Since CKD is associated with other comorbidities, the ADNI cohort had a lower proportion of participants with CKD. While this may limit generalizability, this exclusion criterion also reduced confounding in the assessment of association between eGFR and cognition [16].

We observed that participants with eGFR 45–60 mL/min/1.73 m<sup>2</sup> had the least decline in ADNI-Mem and ADNI-EF

**Table 1. ADNI participant demographic characteristics grouped by eGFR**

| Characteristics                          | Total<br>sample<br>(N = 1127) | eGFR (mL/min/1.73 m <sup>2</sup> ) |                    |                    |                  | P-value |
|------------------------------------------|-------------------------------|------------------------------------|--------------------|--------------------|------------------|---------|
|                                          |                               | <45<br>(n = 66)                    | 45–60<br>(n = 251) | 60–90<br>(n = 571) | >90<br>(n = 239) |         |
| Age (years), mean ± SD                   | 74 ± 7                        | 73 ± 7                             | 74 ± 7             | 74 ± 7             | 74 ± 8           | 0.59    |
| Number of follow-up visits, mean ± SD    | 6.0 ± 2.6                     | 6.1 ± 2.2                          | 5.8 ± 2.5          | 6.0 ± 2.7          | 6.1 ± 2.7        | 0.87    |
| Male, n (%)                              | 643 (57)                      | 15 (23)                            | 68 (27)            | 357 (63)           | 203 (85)         | <0.001  |
| Ethnicity, n (%)                         |                               |                                    |                    |                    |                  |         |
| Not Hispanic/Latino                      | 1098 (97)                     | 65 (99)                            | 240 (96)           | 558 (98)           | 235 (98)         | 0.21    |
| Hispanic/Latino                          | 23 (2)                        | 1 (2)                              | 7 (3)              | 11 (2)             | 4 (2)            |         |
| Unknown                                  | 6 (0.5)                       | 0 (0)                              | 4 (2)              | 2 (0.4)            | 0 (0)            |         |
| Race, n (%)                              |                               |                                    |                    |                    |                  |         |
| Caucasian                                | 1051 (93)                     | 64 (97)                            | 239 (95)           | 536 (94)           | 212 (89)         | 0.003   |
| African American                         | 42 (4)                        | 1 (2)                              | 4 (2)              | 16 (3)             | 21 (9)           |         |
| American Indian/Alaskan Native           | 3 (0.3)                       | 0 (0)                              | 2 (0.8)            | 1 (0.2)            | 0 (0)            |         |
| Asian                                    | 20 (2)                        | 0 (0)                              | 2 (0.8)            | 13 (2)             | 5 (2)            |         |
| Native Hawaiian/Other Pacific Islander   | 1 (0.1)                       | 0 (0)                              | 1 (0.4)            | 0 (0)              | 0 (0)            |         |
| More than one race                       | 10 (0.9)                      | 1 (2)                              | 3 (1)              | 5 (0.9)            | 1 (0.4)          |         |
| Marital status, n (%)                    |                               |                                    |                    |                    |                  |         |
| Married                                  | 861 (76)                      | 45 (68)                            | 176 (70)           | 449 (79)           | 191 (80)         | 0.01    |
| Widowed                                  | 139 (12)                      | 16 (24)                            | 38 (15)            | 63 (11)            | 22 (9)           |         |
| Divorced                                 | 92 (8)                        | 4 (6)                              | 25 (10)            | 45 (8)             | 18 (8)           |         |
| Never married                            | 33 (3)                        | 1 (2)                              | 12 (5)             | 14 (3)             | 6 (3)            |         |
| Unknown                                  | 2 (0.2)                       | 0 (0)                              | 0 (0)              | 0 (0)              | 2 (0.8)          |         |
| Education (years), mean ± SD             | 15.9 ± 2.9                    | 15.6 ± 2.9                         | 15.8 ± 2.8         | 16.0 ± 2.9         | 16.1 ± 2.9       | 0.18    |
| Retired, n (%)                           |                               |                                    |                    |                    |                  |         |
| No                                       | 200 (18)                      | 20 (30)                            | 52 (21)            | 86 (15)            | 42 (18)          | <0.001  |
| Yes                                      | 916 (81)                      | 46 (70)                            | 192 (77)           | 481 (84)           | 197 (82)         |         |
| Not available                            | 11 (1)                        | 0 (0)                              | 7 (3)              | 4 (0.7)            | 0 (0)            |         |
| BMI, mean ± SD                           | 27 ± 4                        | 28 ± 6                             | 26 ± 5             | 26 ± 4             | 27 ± 4           | 0.47    |
| Family history of dementia, n (%)        | 1030 (91)                     | 61 (92)                            | 229 (91)           | 523 (92)           | 217 (91)         | 0.97    |
| FAQ score, mean ± SD                     | 4.7 ± 7.0                     | 6.1 ± 8.7                          | 4.9 ± 7.5          | 4.4 ± 6.9          | 4.6 ± 6.2        | 0.09    |
| Right-handed, n (%)                      | 1034 (92)                     | 61 (92)                            | 234 (93)           | 522 (91)           | 217 (91)         | 0.77    |
| Systolic BP (mmHg), mean ± SD            | 134 ± 19                      | 132 ± 17                           | 134 ± 21           | 134 ± 19           | 132 ± 16         | 0.91    |
| Diastolic BP (mmHg), mean ± SD           | 74 ± 11                       | 75 ± 11                            | 75 ± 11            | 73 ± 11            | 75 ± 9           | 0.86    |
| Heart rate (beats per minute), mean ± SD | 65 ± 11                       | 64 ± 11                            | 65 ± 12            | 65 ± 11            | 65 ± 11          | 0.46    |
| History of smoking, n (%)                | 410 (39)                      | 23 (37)                            | 89 (38)            | 215 (40)           | 83 (37)          | 0.83    |
| Hachinski ischemic score, n (%)          |                               |                                    |                    |                    |                  |         |
| 0                                        | 521 (50)                      | 32 (51)                            | 114 (49)           | 269 (51)           | 106 (48)         | 0.91    |
| 1                                        | 457 (44)                      | 27 (43)                            | 100 (43)           | 223 (42)           | 107 (48.0)       |         |
| 2                                        | 37 (4)                        | 2 (3)                              | 11 (5)             | 20 (4)             | 4 (2)            |         |
| 3                                        | 30 (3)                        | 2 (3)                              | 8 (3)              | 16 (3)             | 4 (2)            |         |
| 4                                        | 3 (0.3)                       | 0 (0)                              | 0 (0)              | 2 (0.4)            | 1 (0.4)          |         |
| 5                                        | 2 (0.2)                       | 0 (0)                              | 1 (0.4)            | 0 (0)              | 1 (0.4)          |         |
| 7                                        | 1 (0.1)                       | 0 (0)                              | 0 (0)              | 1 (0.2)            | 0 (0.0)          |         |
| Not available                            | 76                            | 3                                  | 17                 | 40                 | 16               |         |
| Cognitive impairment, n (%)              | 761 (68)                      | 40 (61)                            | 161 (64)           | 375 (66)           | 185 (77)         | 0.002   |
| MCI, n (%)                               | 575 (51)                      | 32 (48)                            | 123 (49)           | 278 (49)           | 142 (59)         |         |
| Dementia, n (%)                          | 186 (17)                      | 8 (12)                             | 38 (15)            | 97 (17)            | 43 (18)          |         |
| ADNI-Mem score, mean ± SD                | 0.248 ± 0.875                 | 0.414 ± 0.909                      | 0.351 ± 0.934      | 0.248 ± 0.884      | 0.094 ± 0.752    | 0.004   |
| ADNI-EF score, mean ± SD                 | 0.172 ± 1.021                 | 0.239 ± 1.054                      | 0.208 ± 0.983      | 0.140 ± 1.053      | 0.193 ± 0.977    | 0.64    |
| Clinical dementia rating, n (%)          |                               |                                    |                    |                    |                  |         |
| 0                                        | 359 (32)                      | 24 (36)                            | 72 (29)            | 195 (34)           | 68 (29)          | 0.55    |
| 0.5                                      | 630 (56)                      | 33 (50)                            | 148 (59)           | 304 (54)           | 145 (61)         |         |
| 1                                        | 115 (10)                      | 8 (12)                             | 25 (10)            | 62 (11)            | 20 (8)           |         |
| 2                                        | 15 (1)                        | 1 (2)                              | 5 (2)              | 5 (1)              | 4 (2)            |         |
| 3                                        | 1 (0.1)                       | 0 (0)                              | 0 (0)              | 0 (0)              | 1 (0.4)          |         |
| Serum creatinine (mg/dL), mean ± SD      | 1.0 ± 0.2                     | 1.6 ± 0.3                          | 1.2 ± 0.2          | 1.0 ± 0.1          | 0.7 ± 0.1        | <0.001  |
| eGFR (CKD-EPI), mean ± SD                | 76 ± 20                       | 41 ± 7                             | 59 ± 9             | 78 ± 12            | 102 ± 8          | <0.001  |
| eGFR (MDRD), mean ± SD                   | 69 ± 17                       | 36 ± 5                             | 51 ± 5             | 72 ± 9             | 91 ± 7           | <0.001  |

Smoking history was missing in 62 participants.



**FIGURE 2:** Change in (A) ADNI-EF and (B) ADNI-Mem scores over time with participants grouped by eGFR at baseline. Blue: baseline eGFR <45 mL/min/1.73 m<sup>2</sup>, red: baseline eGFR 45–60 mL/min/1.73 m<sup>2</sup>, yellow: baseline eGFR 60–90 mL/min/1.73 m<sup>2</sup>, purple: baseline eGFR > 90 mL/min/1.73 m<sup>2</sup>.

**Table 2. Multivariable linear regression analyses predicting ADNI-Mem score and ADNI-EF score**

|                                                     | $\beta$ estimate for<br>ADNI-Mem score | 95% CI           | P-value | $\beta$ estimate for<br>ADNI-EF score | 95% CI           | P-value |
|-----------------------------------------------------|----------------------------------------|------------------|---------|---------------------------------------|------------------|---------|
| <i>In the entire cohort</i>                         |                                        |                  |         |                                       |                  |         |
| Age (+10)                                           | -0.117                                 | -0.199 to -0.034 | 0.01    | -0.278                                | -0.368 to -0.189 | <0.001  |
| Female sex                                          | 0.312                                  | 0.179–0.444      | <0.001  | 0.136                                 | -0.008–0.28      | 0.07    |
| Caucasian race                                      | -0.124                                 | -0.355–0.107     | 0.29    | 0.149                                 | -0.102–0.4       | 0.24    |
| Years of education (+1)                             | 0.079                                  | 0.059–0.100      | <0.001  | 0.099                                 | 0.077–0.121      | <0.001  |
| eGFR (+10)                                          | -0.029                                 | -0.063–0.006     | 0.11    | 0.004                                 | -0.034–0.041     | 0.84    |
| <i>In participants with cognitive impairment</i>    |                                        |                  |         |                                       |                  |         |
| Age (+10)                                           | -0.191                                 | -0.276 to -0.107 | <0.001  | -0.298                                | -0.399 to -0.197 | <0.001  |
| Female sex                                          | 0.197                                  | 0.048–0.345      | 0.01    | 0.079                                 | -0.099–0.258     | 0.38    |
| Caucasian race                                      | -0.087                                 | -0.353–0.179     | 0.52    | 0.097                                 | -0.222–0.417     | 0.55    |
| Years of education (+1)                             | 0.058                                  | 0.036–0.080      | <0.001  | 0.077                                 | 0.050–0.103      | <0.001  |
| eGFR (+10)                                          | 0.001                                  | -0.037–0.040     | 0.94    | 0.041                                 | -0.005–0.088     | 0.08    |
| <i>In participants without cognitive impairment</i> |                                        |                  |         |                                       |                  |         |
| Age (+10)                                           | -0.233                                 | -0.329 to -0.136 | <0.001  | -0.29                                 | -0.387 to -0.192 | <0.001  |
| Female sex                                          | 0.328                                  | 0.206–0.449      | <0.001  | 0.066                                 | -0.107–0.239     | 0.46    |
| Caucasian race                                      | 0.064                                  | -0.135–0.263     | 0.53    | 0.107                                 | -0.194–0.408     | 0.49    |
| Years of education (+1)                             | 0.054                                  | 0.034–0.074      | <0.001  | 0.078                                 | 0.052–0.104      | <0.001  |
| eGFR (+10)                                          | -0.009                                 | -0.041–0.023     | 0.58    | 0.035                                 | -0.010–0.080     | 0.13    |

scores when compared with other eGFR groups. As eGFR varies with muscle mass, a higher muscle mass could result in a lower eGFR. Since a higher muscle mass reflects potentially healthier participants, this could explain the lower decline in cognition. Conversely, the subgroup with eGFR <45 mL/min/1.73 m<sup>2</sup> likely had kidney disease, since it is rare for the eGFR to be <45 mL/min/1.73 m<sup>2</sup> due to differences in muscle mass or an age-associated decline in eGFR.

Our results are consistent with the results from the BRain IN Kidney disease study, where eGFR >30 mL/min/1.73 m<sup>2</sup> was not associated with cognitive impairment in older adults [11]. This study, although smaller than our cohort, used detailed assessment of cognition with several neuropsychological tests to assess memory and executive function similar to the ADNI. In

another study in older men [12], the association of lower eGFR with cognition was lost after adjusting for differences in age, race and education. Moreover, lower eGFR was not associated with cognitive decline over time. Similarly, the 3C study did not show an increased risk of cognitive decline or dementia with low baseline eGFR [13]. The Adult Changes in Thought study did not find the average eGFR or the trajectory of eGFR to be associated with dementia in older adults [41]. The HUNT [42] and Hisayama [43] studies also did not find an association between lower eGFR and increased incidence of dementia. Additionally, the Sydney Memory and Aging Study [44] found kidney disease to be protective against a decline in memory. This may be due to a change in muscle mass increasing eGFR in those with cognitive impairment. Our study adds to this

growing literature that demonstrates that the association between eGFR and cognition may be different in older adults with a mild to moderate decrease in eGFR.

Our results differ from some other studies that have suggested an association between low eGFR and cognition. This difference in results may be explained by the difference in participants' ages. The ADNI comprises older participants. Results from population-based studies in younger participants thus may not be applicable to older adults for risk estimation of cognitive decline and clinical decisions targeted at prevention of dementia. For example, although the Health ABC study concluded that lower baseline eGFR is an independent predictor of an increased risk of cognitive decline, the subgroup analysis of the Health ABC study [10] showed that in participants >73 years of age, eGFR 45–60 mL/min/1.73 m<sup>2</sup> was not associated with an increased cognitive decline when compared with participants with an eGFR >60 mL/min/1.73 m<sup>2</sup>. This differed from participants <73 years of age, where both eGFR 45–60 and <45 mL/min/1.73 m<sup>2</sup> were associated with cognitive decline when compared with those with an eGFR >60 mL/min/1.73 m<sup>2</sup>. Thus a mild to moderate decrease in eGFR in older adults could be age-associated and may not impact cognition in the same way as in younger adults.

We also observed a paradoxical relationship with a steeper decline in cognition in the group with an eGFR >60 mL/min/1.73 m<sup>2</sup> compared with the group with eGFR 45–60 mL/min/1.73 m<sup>2</sup>. The ADNI-Mem score was also lower in the group with an eGFR >90 mL/min/1.73 m<sup>2</sup> at baseline. Dementia is associated with a lower muscle mass (despite similar BMI) [45] that can result in a higher eGFR. Thus we suspect that this group had lower muscle mass and cognitive impairment at baseline. The lower muscle mass resulted in a higher eGFR. The current standard methods for measuring kidney function and classification of CKD use creatinine-based equations that can overestimate eGFR in the presence of sarcopenia and, conversely, underestimate GFR with more muscle mass [31, 46]. The use of a creatinine-based equation to estimate GFR can explain some of our observations. We have previously shown that the associations between low eGFR, dementia and brain atrophy change after accounting for lean body mass in the eGFR equation [47]. Indeed, methods to incorporate lean body mass [48, 49] or cystatin C [50] for calculation of eGFR may need consideration in older adults [50] for dementia risk estimation and clinical care. Unfortunately we did not have a measure of lean body mass in this study. The Cardiovascular Health Study [51] showed a different association between cognition and kidney function with cystatin C-based versus creatinine-based eGFR. Being unaffected by age or muscle mass, cystatin C may be able to measure kidney function more accurately in older adults [52]. However, cystatin C represents more than kidney function; it is an inflammatory marker and a predictor for cardiovascular disease, dementia and mortality [52, 53]. Thus the association of cystatin C and cognitive decline may be independent of kidney function.

Another limitation of our study was a lack of follow-up serum creatinine values or measurement of proteinuria. Also, with the ADNI study population being predominantly

Caucasian, the generalizability of these results may be limited. Strengths of our study include the use of extensive neuropsychological tests to assess memory and executive function compiled in validated composite scores and a relatively healthy cohort minimizing bias due to comorbidities.

Incorporating measured GFR or body composition and proteinuria in future studies will be helpful to clarify the association between kidney function and the risk for cognitive decline. The addition of biomarkers for kidney function such as serum creatinine and urine protein:creatinine ratio in established dementia registries and population-based studies should be considered.

In conclusion, we did not find an association between mild to moderately low eGFR and cognitive decline in the ADNI cohort. Mild to moderately low eGFR may not be a predictor for future dementia in older patients. However, while lower eGFR may not be an independent predictor of cognitive impairment in older patients, kidney and brain health may be linked due to indirect complex associations and pathological processes common to both organs, such as systemic inflammation and endothelial dysfunction. Additional studies with matching of baseline characteristics of patients with and without CKD are needed to understand the true impact of eGFR and cognition.

## SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfab226/6325032).

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## CONFLICT OF INTEREST STATEMENT

The authors do not have any conflicts of interest relevant to this publication.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the ADNI at <http://adni.loni.usc.edu/>.

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