

## Low eGFR is associated with dysexecutive and amnestic mild cognitive impairment

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### Abstract

**Background:** Few studies have explored the association between renal function and major subtypes of mild cognitive impairment (MCI).

**Methods:** The sample was from the Einstein Aging Study. The estimated glomerular filtration rate (eGFR, calculated in mL/min/1.73 m<sup>2</sup> units) was classified into low (<45), moderate (45–59), and high (≥60). Separate binary logistic regression models were run to determine if eGFR is associated with amnestic MCI (aMCI) and dysexecutive MCI (dMCI).

**Results:** Of 622 eligible participants 65 (10.5%) had low eGFR, 43 (7.1%) had aMCI, and 46 (7.6%) had dMCI. Low eGFR was independently associated with dMCI and aMCI in fully adjusted models.

**Conclusion:** At cross-section low eGFR is associated with a higher risk of both dMCI and aMCI. eGFR may contribute to the development of these cognitive states directly. Alternatively, low eGFR may be a marker for risk factors that influence both the kidney and the brain, such as coronary microvascular disease.

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### Keywords:

Amnestic MCI; Dysexecutive MCI; Renal function

### 1. Introduction

Chronic kidney disease (CKD) has a well-established association with impairment on neurocognitive tests, particularly measures of frontal/executive function [1–4]. In a systematically recruited sample of older adults from the Einstein Aging Study we examined three cognitive domains derived from a principal components analysis of 13 neurocognitive tests. The domains included general ability, executive function, and episodic memory. Our results showed an association between low estimated glomerular filtration rate (eGFR) and the executive function composite composed of four tests, including Trail

Making Tests A and B [5], Digit Symbol Coding [6], and Block Design [6] and two of the four individual tests [7].

Although CKD has been associated with cognitive status and decline in older adults it has rarely been investigated in relation to clinically significant cognitive states, such as mild cognitive impairment (MCI) or dementia. MCI is a transitional state between normative cognitive aging and dementia [8]. MCI is often divided into amnestic (aMCI) form, with reduced memory performance and nonamnestic forms (naMCI), with reduced performance in cognitive domains other than memory [8]. Recent work has highlighted the potential importance of a subtype of naMCI with predominant impairment in executive function [9]. This condition, known as dysexecutive MCI has been defined as objective memory impairment in an executive function composite characterized as 1.5 standard deviations lower than that of a normative sample [9].

Studies by Post et al. [10] and Griva et al. [11] have introduced the concept of MCI in CKD and hemodialysis (HD)

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populations. Post et al. used a clinical sample of 51 patients—24 persons with CKD and 27 persons on HD, and found that 39 (76%) had some form of MCI. aMCI occurred in 20% of the CKD group and in 29% of the HD group; non-amnesic MCI occurred in 80% of the CKD group and in 71% of the HD group were classified as naMCI. In Griva et al.'s study on 145 dialysis patients, the authors found that up to 67.5% of participants were cognitively impaired, as defined by performance 1 standard deviation (SD) lower than the mean on two or more of five neuropsychological tests. The authors did not distinguish between aMCI and naMCI, thus participants may have impairments in more than one cognitive domain. Results showed that 49% of participants had executive function impairment (as indicated by Trails B) and 49% had verbal memory impairment (as measured by Rey Auditory Verbal Learning Test).

Many studies of cognitive function and kidney disease are limited by modest sample sizes [10–12] and by the selection of patients based from referral populations with CKD and HD [1,10,11,13,14]. Furthermore, Griva et al. did not distinguish between MCI subtypes; although, studies continually show an association between the executive component of cognitive function and memory [7,10,11]. Thus research on MCI in decreased renal function [10,11,15] usually adopts a patient population diagnosed with CKD or end-stage renal disease (ESRD), or are receiving hemodialysis to investigate dementia or MCI [1,10,11,13,14]. Many individuals with CKD, or decreased eGFR, are community-dwelling elderly; however, there are few studies that investigate eGFR and dementia in community-dwelling samples [16], and there are no studies to our knowledge that have investigated MCI and kidney function in representative community-based samples.

Determining if MCI is present in community-dwelling elderly with decreased eGFR will help in determining if MCI develops before the individual begins treatment at renal clinics. Identifying cognitive impairment early on in the course of any potential CKD developments may result in fewer complications and allow for longer independent living, and subsequently less hospitalizations. It will benefit the individual if practitioners are aware that noncompliance may be due to imminent MCI states rather than negligence.

In this analysis we adopted a cross-sectional design to explore the association between eGFR and MCI, specifically aMCI and a subcomponent of naMCI known as dysexecutive MCI (dMCI) [9,16,17]. dMCI reflects executive dysfunction and is treated as a clinical subtype in many studies [9,18]. Our aims were to determine whether an association exists between low eGFR and aMCI and/or dMCI. Based on our prior work [7], in which an association was found between eGFR and the executive function composite, but not between eGFR and the episodic memory composite, we anticipated an independent association between eGFR and dMCI; however, we did not hypothesize an association between eGFR and aMCI.

## 2. Methods

This analysis was cross-sectional and was conducted within a subset of the Einstein Aging Study (EAS) cohort. EAS enrolls community-dwelling, English-speaking residents of Bronx county in New York who are 70 years or older. Participants were systematically recruited from the Health Care Financing Administration/Centers for Medicaid and Medicare Services rosters for Medicare-eligible persons who were 70 years or older between 1993 and 2004, and from New York City Board of Elections from 2004 onward. Individuals are first mailed introductory letters about the study and research assistants then followed up by phoning to obtain oral consent and administer a brief screening interview. Participants then come in for “Day 1” where the neuropsychological battery, the clinical interview and a physical examination are administered to them. After this they are scheduled for “Day 2”, which takes place within 2 weeks after the first visit; here we collect blood and urine samples of the participants and administer experimental cognitive tests. Thus, the administration of the neuropsychological battery and the blood collection of the participants are done within a 2-week period. In the EAS participants are excluded if they have visual and/or auditory impairments that interfere with neuropsychological testing, psychiatric symptomatology that interferes with test completion, or a nonambulatory status. Written informed consent is obtained on their first clinical visit (Katz et al., 2012). The study protocol was approved by the local institutional review board. Individuals with dementia at baseline status for eGFR were excluded from these analyses. Baseline status here refers to the first wave of data for which participants have eGFR data.

### 2.1. Assessment of estimated glomerular filtration rate

We estimated eGFR in mL/min/1.73 m<sup>2</sup> using the modification of diet in renal disease [19] formula:

$$\text{eGFR} = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \\ \times [1.210 \text{ if Black}] \times [0.742 \text{ if Female}]$$

This eGFR formula has been recommended for older people [20]. We treated eGFR in predefined categories in units of mL/min/1.73 m<sup>2</sup> as low (<45), moderate (45–59), and high (≥60). This is an often used cut-off in studies on renal function and cognition [2,4,21]. Furthermore, older adults with an eGFR lower than 45 mL/min/1.73 m<sup>2</sup> are at increased risk for progression of CKD to ESRD and other adverse outcomes than patients with eGFR more than 60 mL/min/1.73 m<sup>2</sup>.

### 2.2. Diagnosis of aMCI

Participants were diagnosed with aMCI according to updated criteria [22], which required that objective memory impairment in the memory domain be defined as 1.5 SDs

lower than the age-adjusted mean on Logical Memory [23] or a score of 24 or less on the Free and Cued Selective Recall Test [24], subjective memory impairment indicated by self or significant other (self: the Consortium to Establish a Registry for Alzheimer's Disease [CERAD] assessment [25], other: CERAD or IQ CODE [26]), absence of functional decline (based on self or significant other's report or as indicated by the Independent Activities of Daily Living [IADLs] Lawton Brody Scale [27]), and not clinically diagnosed with dementia.

### 2.3. Classification of dMCI

Individuals were classified as dMCI if they were impaired at 1.5 SDs lower than the age-adjusted mean of the sample on at least one of the following four executive function tests: Digit Symbol Coding [6], Block Design [6], Trail Making Test A, and Trail Making Test B [5]. This classification is based on our previous work [7] in which these four tests comprised the executive function composite in a principal components analysis based on a battery of 13 neurocognitive tests administered in the EAS. A similar approach to defining dMCI was also taken in previous studies [9].

aMCI and naMCI are different subtypes of cognitive impairment, one primarily characterized by memory impairment, and the other reflects impairment in domains of language, executive function, attention, and speed. In this article we only explored the dysexecutive component of naMCI, thus aMCI and dMCI remained independent components of MCI. Also when investigating aMCI and dMCI individually, we excluded any cases that may have had comorbid aMCI and dMCI to allow for "pure" subtypes to be studied individually. Thus, the aMCI subtype only consisted of individuals with aMCI but no dMCI, and the dMCI subtype only consisted of individuals with dMCI but no aMCI. In this study we did not explore other subtypes of naMCI. aMCI and dMCI were mutually exclusive. Individuals with aMCI and individuals with dMCI were compared with the rest of the sample, i.e. individuals without any aMCI, dMCI or both, referred to here as no aMCI and no dMCI.

Baseline characteristics were examined according to (1) eGFR category, and (2) aMCI/dMCI/no aMCI and no dMCI.

### 2.4. Descriptive characteristics and covariates

Descriptive characteristics and covariates included information on demographics, vascular conditions, anemia, body mass index (BMI), mood and *APOE*  $\epsilon$ 4, a genetic marker for risk of Alzheimer's disease. Vascular indicators were represented by a cardiovascular disease (CVD) morbidity summary measure composed of the sum of presence of hypertension, diagnosis of diabetes, a history of myocardial infarction, and a history of stroke. Mood variables included the geriatrics depression scale [28] (GDS, range 0–15, with 6 scores or more indicating depression). This information was obtained via the clinical interview which included questions

on medical history, medications, and health behavior [29]. The *APOE*  $\epsilon$ 4 gene, known for its risk for Alzheimer's disease, was obtained from the whole blood, or was isolated from buffy coat that had been stored at  $-70^{\circ}\text{C}$  using the Puregene DNA Purification System (Gentra System, Minneapolis, MN). Genotyping was performed using a Pyrosequencing PSQ HS 96A system (<http://www.pyrosequencing.com>).

### 2.5. Statistical analysis

The mean  $\pm$  SD of continuous variables was compared using analysis of variance for characteristics according to eGFR category, and MCI status. Categorical variables were compared using the  $\chi^2$  and presented in percentages.

We then used binary logistic regression to assess the association between eGFR category and cognitive status separately for aMCI, and for dMCI. In the models we adjusted for descriptive variables that significantly distinguished among participant groups of eGFR and cognitive status.

Analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 22.0, SPSS Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Descriptive characteristics

#### 3.1.1. Characteristics by eGFR

Table 1 summarizes descriptive characteristics by eGFR category for the 622 qualified participants. The mean age of the sample was 79.7 years and 60.6% were female. Overall mean eGFR was 68.4 mL/min/1.73 m<sup>2</sup>. As eGFR increased from low to moderate and high, mean age decreased (82.0 vs. 80.0 and 79.2) as did mean GDS (2.7 vs. 2.2 and 2.0). Years of education increased with eGFR group (13.0 vs. 14.3 and 14.2). There was also a significantly higher frequency of individuals with CVD comorbidity (96.9% and 87.6% and 64.4%) in the low eGFR group than in the moderate or high groups.

#### 3.1.2. Characteristics of aMCI, dMCI vs. no aMCI or dMCI

Table 2 shows the characteristics of the sample divided into participants with aMCI, dMCI, and no aMCI and no dMCI. Of the 622 participants 517 had neither dMCI nor aMCI. There were 43 (7.1%) participants with aMCI but not dMCI and 46 (7.6%) participants with dMCI but not aMCI. There were 16 participants that had both aMCI and dMCI; these were excluded from our main analysis as they met the criteria for dementia with the exception of functional decline.

Results showed that participants with aMCI and dMCI were significantly older than individuals without either disorder (82.6 and 81.4 vs. 79.2 years). Individuals with aMCI scored higher on the GDS than individuals with dMCI and those free of these conditions (3.1 vs. 2.0 and

Table 1

Baseline characteristics of the sample according to renal function category defined by eGFR (standard deviations in brackets unless otherwise stated as % for categorical variables)

	Total n = 622	eGFR, <45 n = 65 (10.5%)	eGFR, 45–59 n = 144 (23.2%)	eGFR, ≥60 n = 413 (66.4%)	P
eGFR mean	68.4 (18.9)	36.4 (7.2)	53.3 (3.7)	78.7 (13.4)	.000
<b>Demographics</b>					
Age	79.7 (5.5)	82.0 (6.2)	80.0 (5.4)	79.2 (5.4)	.001
Females (%)	377 (60.6)	37 (56.9)	101 (70.1)	239 (57.9)	.028
Caucasian	429 (69.0)	43 (66.2)	92 (63.9)	294 (71.2)	.232
Education, yrs	14.1 (3.5)	13.0 (3.4)	14.3 (3.4)	14.2 (3.5)	.022
<b>Vascular variables</b>					
Anemia (%)	85 (13.7)	9 (13.8)	27 (18.8)	49 (11.9)	.117
CVD morbidity (%)	448 (72.0)	63 (96.9)	119 (82.6)	266 (64.4)	.000
Past smokers (%)	331 (53.5)	41 (63.1)	74 (51.4)	216 (52.7)	.517
Smokers (%)	27 (8.2)	3 (7.5)	7 (9.6)	17 (7.8)	.878
BMI	27.3 (4.8)	26.8 (4.6)	28.0 (5.2)	27.2 (4.7)	.128
<b>Mood</b>					
GDS	2.12 (2.04)	2.7 (2.3)	2.2 (2.2)	2.0 (2.0)	.023
<b>Genes</b>					
APOE ε4 (%)	127 (23.6)	17 (13.4)	26 (20.5)	84 (23.4)	.399

Abbreviations: eGFR, estimated glomerular filtration rate; CVD morbidity, cerebrovascular disease morbidity; BMI, body mass index; GDS, Geriatric Depression Scale; APOE ε4, apolipoprotein E allele ε4.

NOTE. Individuals with dementia have been excluded.

NOTE. All percentages are column percentages. This includes history of myocardial infarction, history of stroke, diagnosis of diabetes, and hypertension. The Pearson's chi-square was used for categorical variables.

Table 2

Characteristics of the whole sample divided in according to no aMCI or dMCI, with aMCI, and with dMCI (standard deviations in brackets unless otherwise stated as % for categorical variables)

	No aMCI or dMCI N = 517 (85.3)	aMCI N = 43 (7.1)	dMCI N = 46 (7.6)	P
Age, mean (±SD)	79.2 (5.3)	82.6 (5.9)	81.4 (6.00)	.000
Females (%)	315 (60.9)	15 (32.6)	31 (67.4)	.107
Caucasian (%)	369 (71.4)	29 (63.0)	17 (23.0)	.000
Years in education	14.4 (3.4)	14.0 (3.0)	11.8 (4.2)	.000
eGFR, mean (±SD)	69.7 (18.2)	63.4 (23.2)	59.7 (19.3)	.000
Low eGFR	40 (7.7)	10 (23.3)	13 (28.3)	.000
Moderate eGFR	118 (22.8)	11 (25.6)	10 (21.7)	
High eGFR	359 (69.4)	22 (51.2)	23 (50.0)	
Anemia (%)	73 (14.1)	2 (4.7)	8 (17.4)	.223
CVD morbidity (%)	361 (69.8)	32 (74.4)	42 (91.3)	.008
Past smokers (%)	280 (54.5)	22 (51.2)	21 (45.7)	.801
Current smokers (%)	25 (8.9)	0	2 (9.5)	.340
BMI	27.4 (4.8)	26.8 (5.3)	27.7 (4.8)	.692
GDS	2.0 (2.01)	3.1 (2.4)	2.0 (1.6)	.002
APOE ε4 carriers (%)	100 (22.2)	10 (28.6)	13 (33.3)	.202

Abbreviations: aMCI, amnesic mild cognitive impairment; dMCI, dys-executive MCI; eGFR, estimated glomerular filtration rate; SD, standard deviation; CVD morbidity, cerebrovascular disease morbidity; BMI, body mass index; GDS, Geriatric Depression Scale; APOE ε4, apolipoprotein E allele ε4.

NOTE. Dementia cases have been excluded.

NOTE. All percentages are column percentages. This includes the history of myocardial infarction, history of stroke, diagnosis of diabetes, and hypertension. The Pearson's Chi-square was used for categorical variables.

2.0). A significantly higher percentage of participants with dMCI (28.3%) belonged to the low eGFR group than individuals with aMCI (23.3%) and neither aMCI nor dMCI condition (7.7%).

### 3.2. Probabilistic analysis

Variables that significantly differentiated among the groups included basic demographic characteristics, CVD morbidity, and GDS. We included these as covariates in the binary logistic models. We also included APOE ε4 because of its association with Alzheimer's disease, which is thought to be a precursor of aMCI [30].

#### 3.2.1. eGFR and aMCI

Results from the binary logistic regression for aMCI (Table 3) showed that low eGFR (as opposed to high) was associated with aMCI after adjusting for GDS (odds ratio [OR] = 2.88, 95% confidence interval [CI] = 1.20–6.92,  $P = .018$ ; Model 1), CVD morbidity (OR = 3.19, CI = 1.30–7.82,  $P = .011$ ; Model 2), and APOEε4 (OR = 3.42, CI = 1.34–8.77,  $P = .010$ ; Model 3). eGFR remained significant even after simultaneously adjusting for all three covariates (GDS, CVD comorbidity, and APOEε4) (OR = 3.04, CI = 1.11–8.33,  $P = .031$ ; Model 4). There were no differences between the moderate and the high groups. Furthermore, for every increased year of age the odds of having a classification of aMCI was 1.07 (CI = 1.00–1.14) independent of GDS score, CVD morbidity, and APOE ε4. For every added point on the GDS, the odds of having aMCI was 1.21 (CI = 1.05–1.40), independent of the eGFR and CVD morbidity.



Table 3  
Odds ratios for aMCI diagnosis as defined by eGFR group membership

	aMCI			
	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	1.10* (1.04–1.17)	1.10** (1.04–1.17)	1.07* (1.00–1.14)	1.07 (1.00–1.14)
Sex (M)	1.79 (0.92–3.49)	1.69 (0.88–3.25)	1.98 (0.96–4.06)	2.09* (1.00–4.37)
Education	1.00 (0.91–1.11)	0.99 (0.90–1.09)	0.96 (0.86–1.07)	0.97 (0.87–1.09)
Caucasian	1.16 (0.52–2.60)	1.27 (0.57–2.81)	1.06 (0.46–2.40)	1.02 (0.44–2.35)
eGFR (low)	2.88* (1.20–6.92)	3.19* (1.30–7.82)	3.42** (1.34–8.77)	3.04* (1.1–8.33)
eGFR (moderate)	1.45 (0.66–3.18)	1.57 (0.72–3.45)	1.73 (0.74–4.04)	1.67 (0.69–4.06)
GDS	1.22* (1.07–1.39)	–	–	1.21** (1.05–1.40)
CVD morbidity	–	1.03 (0.48–2.22)	–	1.02 (0.42–2.50)
APOE ε4	–	–	1.61 (0.73–3.58)	1.86 (0.82–4.21)

Abbreviations: aMCI, amnesic mild cognitive impairment; dMCI, dysexecutive MCI; GDS, Geriatric Depression Scale; CVD morbidity, cerebrovascular disease morbidity; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; APOE ε4, apolipoprotein E allele ε4.

NOTE. Low eGFR = <60 mL/min/1.73 m<sup>2</sup>, moderate eGFR = 45–59 mL/min/1.73 m<sup>2</sup>, high eGFR = ≥60 mL/min/1.73 m<sup>2</sup>. This includes history of myocardial infarction, history of stroke, diagnosis of diabetes, and hypertension. Model 1 was adjusted for age, sex, education, race, and GDS. Model 2 was adjusted for age, sex, education, race, and GDS and CVD morbidity. Model 3 was adjusted for age, sex, education, race, GDS, and APOE ε4. Model 4 was adjusted for age, sex, education, race, GDS, CVD morbidity, and APOE ε4. The high eGFR group was the reference group.

\**P* < .05.

\*\**P* < .01.

### 3.2.2. eGFR and dMCI

Table 4 shows the results from the binary logistic regression for dMCI. Low eGFR (as opposed to high) was associated with higher odds of developing dMCI independent of GDS (OR = 4.30, CI = 1.89–9.81, *P* = .001; Model 1); CVD morbidity (OR = 3.21, CI = 1.40–7.35, *P* = .006; Model 2); APOEε4 (OR = 4.88, CI = 2.04–11.71, *P* = .000; Model 3); and GDS, CVD, and APOEε4 together (OR = 4.18, CI = 1.67–10.44, *P* = .002; Model 4). There were no differences between the moderate and the high groups. Increasing age, less years in education, and not being Caucasian were also associated with higher odds of developing dMCI independent of eGFR, GDS, CVD comorbidity, and APOEε4 in all four models. In Model 4, for every added year in life the odds of dMCI were 1.08 (CI = 1.02–1.15); and for every added year of formal education the odds were 0.86 (CI = 0.77–0.95). Last, if the individual is Caucasian, the odds of developing executive dysfunction were 0.26 (CI = 0.51–3.07) independent of GDS, CVD morbidity, and APOEε4.

## 4. Discussion

In this cross-sectional study, we explored aMCI and dMCI in relation to eGFR in a sample of community-dwelling older adults. aMCI is widely considered a pre-Alzheimer's disease state; whereas dMCI is a subcomponent, or a more specific area of naMCI reflecting executive dysfunction, and typically associated with vascular dementia (VaD) [9].

This is the first report of eGFR relating to memory impairment and executive dysfunction in community-dwelling elderly in the absence of dementia. Our results showed independent associations between dMCI and decreased eGFR, and aMCI and eGFR as opposed to high eGFR. These results

yield some discussion. We anticipated and found a strong association between dMCI and decreased eGFR; our results showed an OR of 4.18 (CI = 1.67–10.44). In our previous work [7] we found an association between poor eGFR and poor scores on the executive function composite developed from four neurocognitive tests (Trail Making tests A and B, Digit Symbol, and Block Design). These results were also supported by an earlier study that found high prevalence of naMCI (more than 70%), but not aMCI, in CKD and HD dementia-free patients [10]. Previous research on CKD and cognitive function has also depicted impairment in tests measuring attention and executive function [1,2,14]. Thus, our first results supported our hypothesis of an independent association between dMCI and decreased eGFR.

We did not anticipate an association between aMCI and decreased eGFR. Our previous work and previous research do not consistently show an association between neurocognitive function tests measuring memory, aMCI, or Alzheimer's disease and decreased eGFR or CKD. Although studies report associations between neurocognitive memory measures and decreased eGFR [2,3,31] results vary from study to study. For example, in Yaffe et al. [14] decreased eGFR (defined as <30 mL/min/1.73 m<sup>2</sup>) was associated with delayed memory, but not with category fluency, which is a measure of semantic memory; whereas in Kurella et al. [2] decreased eGFR (also defined as <30 mL/min/1.73 m<sup>2</sup>) was associated with both delayed memory and category fluency. Similarly, in prevalence studies, executive dysfunction, naMCI and VaD seem to be more prevalent in CKD than are memory impairment, aMCI, or Alzheimer's disease, with prevalence rates going up as high as 32% for executive dysfunction vs 24% for memory impairment [12], 80% for naMCI vs. 20% for aMCI [10], and annual declines in eGFR being associated with higher risk of VaD (relative

Table 4  
Odds ratios for dMCI as defined by eGFR group membership

	dMCI			
	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	1.07* (1.01–1.14)	1.08** (1.02–1.15)	1.08* (1.02–1.14)	1.08* (1.02–1.15)
Sex (male)	0.98 (0.49–2.01)	0.95 (0.47–1.94)	1.01 (0.49–2.02)	1.01 (0.47–2.20)
Education	0.83*** (0.75–0.92)	0.84*** (0.76–0.92)	0.83*** (0.76–0.92)	0.86** (0.77–0.95)
Caucasian	0.24*** (0.12–0.48)	0.25*** (0.13–0.50)	0.24*** (0.12–0.47)	0.26*** (0.12–0.54)
eGFR (low)	4.30*** (1.89–9.81)	3.21** (1.40–7.35)	4.88*** (2.04–11.71)	4.18** (1.67–10.44)
eGFR (moderate)	1.25 (0.55–2.85)	1.11 (0.48–2.53)	1.43 (0.59–3.46)	1.26 (0.51–3.07)
GDS	0.96 (0.80–1.13)	–	–	0.99 (0.83–1.18)
CVD morbidity	–	3.05* (1.01–9.22)	–	0.42 (0.14–1.31)
APOE ε4	–	–	1.75 (0.79–0.87)	1.86 (0.83–4.16)

Abbreviations: dMCI, dysexecutive MCI; eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval; GDS, Geriatrics Depression Scale; CVD morbidity, cerebrovascular disease morbidity; APOE ε4, apolipoprotein E allele ε4.

NOTE. Low eGFR = <60 mL/min/1.73 m<sup>2</sup> moderate eGFR = 45–59 mL/min/1.73 m<sup>2</sup> high eGFR = ≥60 mL/min/1.73 m<sup>2</sup>. This includes history of myocardial infarction, history of stroke, diagnosis of diabetes, and hypertension. Model 1 was adjusted for age, sex, education, and race. Model 2 was adjusted for age, sex, education, race, and CVD morbidity. Model 3 was adjusted for age, sex, education, race, and APOE ε4. Model 4 was adjusted for age, sex, education, race, CVD morbidity, and APOE ε4. The high eGFR group was the reference group.

\**P* < .05.

\*\**P* < .01.

\*\*\**P* < .001.

risk [RR] = 5.35, 95% CI = 1.76–16.32, *P* = .003) but not AD (RR = 1.29, 95% CI = 0.68–2.43, *P* = .432) [13,21].

One explanation for our association between decreased eGFR and aMCI could be that decreased eGFR may actually lead to aMCI. For example, poor kidney function may lead to metabolic abnormalities which interfere with brain function. Second, eGFR may be a marker for vascular or other risk factors that are associated with neural dysfunction and poor cognitive performance. Although AD and VaD are distinguished, the conditions often occur together in the same individual. Vascular pathology may unmask AD pathology leading to earlier or more prominent cognitive dysfunction. In addition, vascular disease with its associated hypoperfusion may lead to accelerated accumulation of beta amyloid and ultimately to higher rates of cognitive decline [32,33].

We excluded individuals with both aMCI and dMCI from the primary analysis. eGFR was associated with the co-occurrence of aMCI and dMCI independent of CVD morbidity and APOE ε4; however, the GDS attenuated this association (OR = 2.42, CI = 0.83–7.07) (Supplementary Table 1). This showed that the GDS is associated with both eGFR and comorbid aMCI and dMCI. The attenuated association between low eGFR and aMCI once the GDS is entered into the model may also show that depression is a stronger associate of comorbid aMCI and dMCI than eGFR. However, this association is difficult to interpret and may indicate that aMCI may precede kidney impairment; thus although eGFR may not play a role in the onset of aMCI per se, it may trigger its development, and a quick succession of AD or mixed dementia may follow rapidly.

Our results lend support to two hypotheses: (1) the shared environmental risk factor hypothesis in which an underlying vascular mechanism is affecting both the kidney

and the brain, and (2) the unidirectional casual hypothesis where vascular toxins because of decreased kidney function affect cognition. Both of these hypotheses lead to eventual cognitive decline, which may develop into VaD, AD, or mixed AD. Given that eGFR is a vascular marker affecting bodily function, including the brain, and that cognitive function is a marker of brain integrity and possibly cognitive reserve, it is safe to speculate that both these mechanisms affect each other and are affected by several potential risk factors.

The results of this study are important in several ways: First, our results demonstrate that MCI together with decreased eGFR, possibly without a CKD diagnosis, is present long before individuals are receiving treatment or have received a diagnosis for CKD. Second, our results also show that MCI together with decreased eGFR is not always specifically targeted to executive function but rather seems to extend to memory function as well. Last, correlations do not imply causation, and much speculation may surround the associations found in this study. Decreased eGFR already hints at signs of disease; the possibilities of how eGFR may affect or be affected by cognition are broad, ranging from common underlying mechanisms to eGFR causing or triggering MCI, to even initial poor cognition or MCI leading to poor compliance of medication escalating to poorer prognosis. This knowledge provides further insight into the nature of cognitive impairment in possibly early or pre-CKD development, and attention should be thwarted toward identifying and minimizing risk-factors. It is still the case that a strong association is present between decreased eGFR and MCI in community-dwelling elderly. In the general population, individuals with MCI are also 5 to 10 times more likely to develop dementia (Petersen et al., 2001). Interventions in

the general population to slow the progression of cognitive impairment would have a major impact on public health [34]. Methods that may detect early CVD risk and complications may not only avoid morbidity and disease, but also halt or delay the onset of cognitive impairment. Unrecognized dMCI may result in an inability to address fully activities of daily living such as planning meals, taking care of finances, following any medication regimens, keeping or following up appointments, and following directions. Thus, the importance of developing awareness among practitioners may not only help in targeting these individuals and identify underlying problems but will also help in improving the quality of life of these individuals and may eventually decrease frequency of hospitalizations.

The strengths of the sample include the ethnically diverse group of participants, the wide range of variables available to study the MCIs, medical and psychological variables, and the relatively large sample available to study MCI and potential CKD in community-based individuals. One limitation of the sample is that the eGFR was not measured directly, but rather estimated from serum creatinine. Although these estimations may be unreliable in obese people, we did not have any significant differences between MCI subtypes and those without MCI in BMI measures.

## 5. Conclusion

The results from this study further emphasized the role cognitive impairment plays in potential CKD development. The association between poor eGFR and MCI is suggestive of a pathway to VaD and/or AD; it seems that cognitive impairment that is rooted in vascular pathology is not only a risk factor for VaD but also for AD [35]. The association that we found between decreased eGFR and aMCI and dMCI illustrates how this may be true. Although it still is not clear what links eGFR to MCI, vascular risk factors seem to be playing a role. We urge researchers to further investigate the eGFR-MCI association in relation to both traditional risk factors, such as the roles of diabetes and hypertension, and nontraditional risk factors, such as measuring endothelial function, cerebral hemodynamics, white matter hyperintensities, homocysteine levels, oxidative stress, and inflammatory markers such as fibrinogen and C-reactive protein. If the association is attenuated, we may have some answers as to what links eGFR to cognitive impairment. Longitudinal investigations are also necessary to find out the association between low eGFR/CKD and incident MCI cases; further investigation into potential mediatory mechanisms, such as the mentioned nontraditional risk factors may also provide insight into causality. Although continuous cognitive testing to monitor changes is ideal in the early stages of CKD, identifying risk factors that affect kidney and cognitive function would help lead to preventative strategies of the deterioration of these mechanisms and also enhance intervention plans for those already affected by disease.

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## Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.dadm.2014.12.002>.

## RESEARCH IN CONTEXT

1. Systematic review: For our literature search we started by looking for keywords, such as "cognitive function & CKD" in PubMed, and narrowed down to research articles that specifically looked at kidney function and mild cognitive impairment (MCI). We also identified papers from articles we read.
2. Interpretation: Our results showed that decreased estimated glomerular filtration rate (eGFR) is independently associated with amnesic MCI (aMCI) and dysexecutive MCI (dMCI). Two interpretations seemed viable: (1) renal dysfunction may be causing MCI or (2) renal dysfunction may be a marker of vascular risk factors, such as the metabolic syndrome or small vessel disease.
3. Future directions: We urge researchers to further investigate the association between eGFR and MCI in relation to both traditional and nontraditional risk factors to find out what links eGFR to cognitive impairment. Identifying cognitive impairment early in potential chronic kidney disease development may result in fewer complications and allow for longer independent living, and subsequently less hospitalizations.

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