HHS Public Access

Author manuscript

Alzheimers Dement (Amst). Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Alzheimers Dement (Amst). 2015 June 1; 1(2): 152–159. doi:10.1016/j.dadm.2014.12.002.

Low eGFR is associated with dysexecutive and amnestic mild cognitive impairment

Andrea R. Zammit[1],[2], **Mindy J. Katz**[1],[2], **Molly E. Zimmerman**[1],[2], **Markus Bitzer**[4], and **Richard B. Lipton**[1],[2],[3]

[1]Saul B. Korey Department of Neurology Albert Einstein College of Medicine, NY

[2]Einstein Aging Study Albert Einstein College of Medicine, NY

[3]Department of Epidemiology and Population Health Albert Einstein College of Medicine, NY

[4]Department of Internal Medicine, University of Michigan, MI

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/1.73m2 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 withamnestic MCI (aMCI) and dysexecutive MCI (dMCI).

Results—Out 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.

Keywords

amnestic MCI; dysexecutive MCI; renal function

Andrea R. Zammit, Saul B. Korey Department of Neurology, Albert Einstein College of Medicine 1165 Morris Park Avenue, Rousso Building 338, Bronx, NY 10461; Mindy J. Katz, Saul B. Korey Department of Neurology, Albert Einstein College of Medicine 1165 Morris Park Avenue, Rousso Building 338, Bronx, NY 10461; Molly E. Zimmerman, Saul B. Korey Department of Neurology, Albert Einstein College of Medicine 1165 Morris Park Avenue, Rousso Building 338, Bronx, NY 10461; Markus Bitzer, University of Michigan, Department of Internal Medicine, Nephrology, 1150 W. Medical Center Dr. Ann Arbor, Michigan MI 48109; Richard B. Lipton, Saul B. Korey Department of Neurology, Albert Einstein College of Medicine 1165 Morris Park Avenue, Rousso Building 338, Bronx, NY 10461.

Conflict of Interest: All authors declare that there are no financial, personal, or other potential conflicts of interest.

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 eGFR and the executive function composite (composed of 4 tests, including Trail Making Tests A and B[5], Digit Symbol Coding[6], and Block Design[6] as well as 2 of the 4 individual tests[7].

Though 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 non-amnestic 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 below 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) 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 amnestic MCI occurred in 80% of the CKD group and in71% 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 1SD below the mean on 2 or more of 5 neuropsychological tests. The authors did not distinguish between aMCI and naMCI, thus participants may have impairments in more than one cognitive domainResults showed that 49% ofparticipants 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 e.g. [10, 11, 12] and by the selection of patients based from referral populations with CKD and HD[1, 10, 11, 13, 14]. Further 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[17], 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, 17, 18]. dMCI reflects executive dysfunction and is treated as a clinical subtype in many studies e.g. [9, 19]. 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.

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 onwards. 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 exam are administered to them. After this they are scheduled for "Day 2", which takes place within two 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 two-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.

Assessment of estimated glomerular filtration rate (eGFR)

We estimated eGFR in mL/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD)[20] formula:

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

This eGFR formula has been recommended for older people[21]. We treated eGFR in predefined categories in units of mL/min/1.73m^2 as low (<45), moderate (45-59) and high (≥60). This is an often used cut-off in studies on renal function and cognition[2,4,16]. Further, older adults with an eGFR below 45 mL/min/1.73m^2 are at increased risk for progression of CKD to ESRD and other adverse outcomes than patients with eGFR above 60mL/min/1.73m^2.

Diagnosis of aMCI

Participants were diagnosed with aMCI according to updated criteria[22], which required objective memory impairment in the memory domain defined as 1.5 SDs below the age-adjusted mean on Logical Memory[23] or a score of 24 or less on the Free and Cured Selective Recall Test[24], subjective memory impairment indicated by self or significant other (self: CERAD[25], other: CERAD or IQ CODE[26], absence of functional decline (based on self or significant other's report or as indicated by the IADL Lawton Brody Scale[27], and were not clinically diagnosed with dementia.

Classification of dMCI

Individuals were classified as dMCI if they were impaired at 1.5 standard deviations below 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 (TMTA), and Trail Making Test B (TMTB)[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 paper 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 to 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 i) eGFR category, and ii) aMCI/dMCI/no aMCI and no dMCI.

Descriptive characteristics and covariates

Descriptive characteristics and covariates included information on demographics, vascular conditions, anemia, BMI, mood and APOE e4, a genetic marker for risk of Alzheimer's disease. Vascular indicators were represented by a 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 above indicating depression). This information was obtained via the clinical interview which included questions on medical history, medications and health behavior[29]. The APOEe4 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°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).

Statistical analysis

The mean ±SD of continuous variables were compared using analysis of variance (ANOVA) for characteristics according to eGFR category, and MCI status. Categorical variables were compared using the χ^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 amongst 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).

Results

Descriptive characteristics

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/1.73m^2. 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.

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 or 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 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%).

Probabilistic analysis

Variables that significantly differentiated amongst the groups included basic demographic characteristics, CVD morbidity, and GDS. We included these as covariates in the binary logistic models. We also included APOE e4 because of its association with Alzheimer's disease, which is thought to be a precursor of aMCI[30].

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 APEOe4 (OR = 3.42, CI = 1.34 – 8.77, p = .010; Model 3). eGFR remained significant even after simultaneously adjusting for all 3 covariates (GDS, CVD comorbidity, and APEOe4) (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 e4. 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.

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); APEOe4 (OR = 4.88, CI = 2.04 – 11.71, p = .000; Model 3), and GDS, CVD and APEOe4 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 APEOe4 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). Lastly, 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 APEOe4.

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[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 (over 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 <30mL/min/1.73m^2) 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 <30mL/min/1.73m^2) was associated with both delayed memory and category fluency. Similarly, in prevalence studies, executive dysfunction, naMCI and vascular dementia 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 vascular dementia (relative 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)[13,16].

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 vascular dementia (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 APOEe4; 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 due to decreased kidney function affect cognition. Both of these hypotheses lead to eventual cognitive decline, which may develop into vascular dementia, 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: Firstly, 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. Secondly, 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. Lastly, 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 towards identifying and minimizing risk-factors. It still is 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 regiments, 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 identifying 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 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.

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 vascular dementia and/or AD; it seems that cognitive impairment that is rooted in vascular pathology is not only a risk factor for vascular dementia 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 non-traditional 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 non-traditional 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the EAS research participants. We thank Charlotte Magnotta, Diane Sparracio and April Russo for assistance in participant recruitment; Betty Forro, Alicia Gomez, Wendy Ramratan, and Mary Joan Sebastian for assistance in clinical and neuropsychological assessments; Michael Potenza for assistance in data management.

Funding sources: This research was supported by the Einstein Aging Study (PO1 AG03949) from the National Institutes on Aging program; the National Institutes of Health CTSA (1UL1TR001073) from the National Center for Advancing Translational Sciences (NCATS), the Sylvia and Lenard Marx Foundation, and the Czap Foundation. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

References

1. Kurella M, Chertow GM, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. J Am Ger Soc. 2004; 52:1863–9.
2. Kurella M, Yaffe K, Shlipak MG, Wenger NK, Chertow GM. Chronic kidney disease and cognitive impairment in menopausal women. Am J Kidney Dis. 2005; 45:66–76. [PubMed: 15696445]
3. Thornton WL, Shapiro RJ, Deria S, Gelb S, Hill A. Differential impact of age on verbal memory and executive functioning in chronic kidney disease. JINS. 2007; 13:344–53. [PubMed: 17286891]
4. Slinin Y, Paudel ML, Ishani A, Taylor BC, Yaffe K, Murray AM, Ensrud KE. Kidney function and cognitive performance and decline in older men. J Am Ger Soc. 2008; 56:2082–8.
5. Army Individual Test Battery. Manual of Directions and Scoring. War Department, Adjutant General's Office; Washington, DC: 1944.

6. Wechsler, D. Wechsler Adult Intelligence Scale. Third Edition. The Psychological Corporation; New York: 1997.
7. Zammit AR, Katz MJ, Lai JY, Zimmerman ME, Bitzer M, Lipton RB. Renal function and cognitive composites of function in the Einstein Aging Study: A cross-sectional analysis. J Gerontol Med Sci. in press.
8. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabbins PV, Ritchie K, Rossor M, Thal L, Winblad B. Current concepts in mild cognitive impairment. JAMA. 2001; 58:1985–1992.
9. Huey ED, Manly JJ, Tang MX, Schupf N, Brickman AM, Manoochehri M, Mayeux R. Course and etiology of dysexecutive MCI in a community sample. Alzheimers Dement. 2003; 9(6):632–9. [PubMed: 23452959]
10. Post JB, Jegede AB, Morin K, Spungen AM, Langhoff E, Sano M. Cognitive profile of chronic kidney disease and hemodialysis patients without dementia. Nephron. Clin Prac. 2010; 116(3):c247–55.
11. Griva K, Stygall J, Hankins M, Davenport A, Harrison M, Newman SP. Cognitive impairment and 7-year mortality in dialysis patients. AM J Kidney Dis. 2010; 56(4):693–703. doi:10.1053/j.ajkd.2010.07.003. [PubMed: 20800327]
12. Sánchez-Román S, Ostrosky-Solís F, Morales-Buenrostro LE, Nogués-Vizcaíno MG, Alberú J, McClintock SM. Neurocognitive profile of an adult sample with chronic kidney disease. JINS. 2011; 17(1) (2011).
13. Seliger SL, Siscovick DS, Steham-Breen CO, Gillen DL, Fitzpatrick A, Bleyer A, Kuller LH. Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. J Am Soc Nephrol. 2004; 15:1904–11. [PubMed: 15213280]
14. Yaffe K, Ackerson L, Kurella Tamura M, Le Blanc P, Kusek JW, Sehgal AR, Go AS. Chronic kidney disease and cognitive function in older adults: findings from the chronic renal insufficiency cohort cognitive study. J Am Geriat Soc. 2010; 58:338–45. [PubMed: 20374407]
15. Murray AM, Knopman DS. Cognitive impairment in CKD: no longer an occult burden. Am J Kidney Dis. 2010; 56:615–8. [PubMed: 20851318]
16. Helmer C, Stengel B, Metzger M, Froissart M, Massy Z, Tzourio C, Dartigues J-F. Chronic kidney disease, cognitive decline, and incident dementia: the 3C Study. Neurology. 2011; 77:2043–51. [PubMed: 22116945]
17. Manly JJ, Tang MX, Schupf N, et al. Frequency and course of mild cognitive impairment in a multiethnic community. Ann Neurol. 2008; 63:494–506. [PubMed: 18300306]
18. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. Arch Neurol. 2009; 66:1447–1455. [PubMed: 20008648]
19. Pa J, Boxer A, Chao LL, Gazzaley A, Freeman K, Kramer J, Miller BL, Weiner MW, Neuhaus J, Johnson JK. Clinical-neuroimaging characteristics of dysexecutive mild cognitive impairment. Ann Neurol. 2009; 65:414–423. [PubMed: 19399879]
20. Levey AS, Bosch JP, Breyer Lewis J, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med. 1999; 130:461–470. [PubMed: 10075613]
21. Cirillo M, Anastasio P, De Santo NG. Relationship of gender, age and body mass index to errors in predicting kidney function. Nephrol Dial Transplant. 2005; 20:1791–8. [PubMed: 15998649]
22. Artero S, Petersen R, Touchon J, Ritchie K. Revised criteria for mild cognitive impairment: validation within a longitudinal population study. Dement Geriatr Cogn Disord. 2006; 22:465–70. (2006). [PubMed: 17047325]
23. Wechsler, D. Wechsler Memory Scale—Revised. The Psychological Corporation; San Antonio, Texas: 1987.
24. Buschke H. Cued recall in amnesia. J Clin Neuropsych. 1984; 6:433–440.
25. Morris JC, Heyman A, Mohs RC, et al. The consortium to establish a registry for alzheimer's disease (CERAD). part I. clinical and neuropsychological assessment of alzheimer's disease. Neurology. 1989; 39:1159–1165. [PubMed: 2771064]
26. Jorm AF, Jacomb PA. The informant questionnaire on cognitive decline in the elderly (IQCODE): Socio-demographic correlates, reliability, validity and some norms. Psychol Med. 1989; 19:1015–1022. [PubMed: 2594878]

27. Lawton MP, Brody EM. Assessment of older people: Self-maintianing and instrumental activities of daily living. Gerontologist. 1969; 9:179–186. [PubMed: 5349366]

28. Sheikh JI, Yesavage JA. Geriatric depression scale (GDS); recent evidence and development of a shorter version. Gerontologist. 1986; 5:165–173.

29. Katz MJ, Lipton RB, Hall CB, et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. Alzheimer Dis Assoc Disord. 2012; 26:335–43. [PubMed: 22156756]

30. Sadigh-Eteghad S, Talebi M, Farhoudi M. Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer's disease: A meta-analysis. Neurosciences. 2012; 17:321–326. [PubMed: 23022896]

31. Elias MF, Elias PK, Seliger SL, Narsipur SS, Dore GA, Robbins MA. Chronic kidney disease, creatinine and cognitive functioning. Nephrol Dial Transplant. 2009; 24:2446–52. [PubMed: 19297357]

32. Caroli A, Teast C, Geroldi C, Nobili F, Barnden LR, Guerra U, Bonetti M, Frisoni GB. Cerebral perfusion correlates of conversion to Alzheimer's disease in amnestic mild cognitive impairment. J Neurol. 2007; 254:1698–1707. [PubMed: 17990057]

33. Launer LJ. Demonstrating the case that AD is a vascular disease: epidemiologic evidence. Ageing ResRev. 2002; 1:61–77.

34. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Pub Health. 1998; 88:1337–1342. [PubMed: 9736873]

35. de la Torre JC. Vascular risk factor detection and control may prevent Alzheimer's disease. Ageing Res Rev. 2010; 9:218–25. [PubMed: 20385255]

Research in context

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 MCI. We also identified papers from articles we read.

Interpretation

Our results showed that decreased eGFR is independently associated with aMCI and dMCI. Two interpretations seemed viable: i) renal dysfunction may be causing MCI; or ii) renal dysfunction may be a marker of vascular risk factors, such as the metabolic syndrome or small vessel disease.

Future directions

We urge researchers to further investigate the association between eGFR and MCI in relation to both traditional and non-traditional risk factors to find out what links eGFR to cognitive impairment. Identifying cognitive impairment early in potential CKD development may result in fewer complications and allow for longer independent living, and subsequently less hospitalizations.

Table 1

Baseline characteristics of the sample according to renal function 1 category defined by eGFR (standard deviations in brackets unless otherwise stated as % for categorical variables). Individuals with dementia have been excluded

	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
		Demographics			
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, years	14.1 (3.5)	13.0 (3.4)	14.3 (3.4)	14.2 (3.5)	.022
		Vascular variables			
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
		Mood			
GDS	2.12 (2.04)	2.7 (2.3)	2.2 (2.2)	2.0 (2.0)	.023
		Genes			
APOEe4 (%)	127 (23.6)	17 (13.4)	26 (20.5) 8	4 (23.4)	.399

Note. All percentages are column percentages. eGFR = estimated glomular filtration rate. CVD morbidity = cerebrovascular disease morbidity; this includes history of myocardial infarction, history of stroke, diagnosis of diabetes, and hypertension. BMI = Body Mass Index. GDS = Geriatric Depression Scale. APOEe4 = Apolipoprotein E allele e4. 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). Dementia cases have been excluded.

	No aMCI or dMCI	**aMCI**	**dMCI**	***p***
	N = 517 (85.3)	N = 43 (7.1)	N = 46 (7.6)	
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
APOEe4 carriers (%)	100 (22.2)	10 (28.6)	13 (33.3)	.202

Note. All percentages are column percentages. eGFR = estimated glomerular filtration rate. SD = standard deviation. CVD morbidity = cerebrovascular disease morbidity; this includes history of myocardial infarction, history of stroke, diagnosis of diabetes, and hypertension. BMI = Body Mass Index. GDS = Geriatric Depression Scale. APOEe4 = Apolipoprotein E allele e4. The Pearson's chi square was used for categorical variables.

Table 3

Odds ratios for aMCI diagnosis as defined by eGFR group membership.

	aMCI			
	Model 1	**Model2**	**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* (1.11 – 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)
APOEe4	-	-	1.61 (0.73 – 3.58)	1.86 (0.82 – 4.21)

Note. aMCI = amnestic mild cognitive impairment. OR = odds ratio. CI = confidence interval. eGFR = estimated glomerular filtration rate. Low eGFR = < 60 mL/min/1.73m^2, moderate eGFR = 45 – 59 mL/min/1.73m^2 , high eGFR = ≥ 60 mL/min/1.73m^2. GDS = geriatric depression scale. CVD morbidity = cerebrovascular disease morbidity; this includes history of myocardial infarction, history of stroke, diagnosis of diabetes, and hypertension. APOEe4 = Apolipoprotein E allele e4. Model 1 was adjusted for age, sex, education, race and GDS. Model 2 was adjusted for age, sex, education, race, GDS and CVD morbidity. Model 3 was adjusted for age, sex, education, race, GDS and APOEe4. Model 4 was adjusted for age, sex, education, race, GDS, CVD morbidity, and APOEe4. The high eGFR group was the reference group.

Alzheimers Dement (Amst). Author manuscript; available in PMC 2016 June 01.

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)
APOEe4	-	-	1.75 (0.79 – 3.87)	1.86 (0.83 – 4.16)

Note. OR = odds ratio. CI = confidence interval. eGFR = estimated glomerular filtration rate. Low eGFR = < 60 mL/min/1.73m^2 moderate eGFR = 45 – 59 mL/min/1.73m^2 high eGFR = ≥ 60 mL/min/1.73m^2. GDS = Geriatrics Depression Scale. CVD morbidity = cerebrovascular disease morbidity; this includes history of myocardial infarction, history of stroke, diagnosis of diabetes, and hypertension.. APOEe4 = Apolipoprotein E allele e4. 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 APOEe4. Model 4 was adjusted for age, sex, education, race, CVD morbidity, and APOEe4. The high eGFR group was the reference group.