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Renal function affects hippocampal volume and cognition: The role of vascular burden and amyloid deposition

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Aim: We determined if differences in renal function, even within normal levels, influenced hippocampal volume (HCV) and cognition.

Methods: Cognitively normal (CN) and mild cognitive impairment (MCI) subjects with eGFR ≥ 60 ml/min/1.73m^2 were selected from the ADNI database (N = 1,269) and divided into three groups (eGFR 60–75, 75–90 and ≥90). Associations between eGFR, HCV and cognition scores were examined using regression methods, and random-coefficient models. The relationship between various factors, such as vascular burden and brain amyloid deposition, were investigated using path analysis.

Results: Higher eGFR was associated with larger HCVs and better cognition in all subjects at baseline. In MCI subjects, hippocampal atrophy in the eGFR ≥ 90 group progressed at just half the rate of the eGFR 75–90 group (P = .006), and was also somewhat slower than the eGFR 60–75 group (P = .08). A comprehensive path model linking eGFR, HCV and cognition, and integrating vascular burden and amyloid deposition, is proposed.

Conclusions: Higher renal function was associated with slower hippocampal atrophy and cognitive decline even within normal levels of renal function. This relationship was mediated mainly through cardiovascular risk burden and amyloid deposition. Further studies examining neuroinflammation are needed. **Geriatr Gerontol Int 2017; 17: 1899–1906.**

Keywords: dementia, glomerular filtration rate, hippocampus, kidney, vascular burden.

Introduction

Alzheimer's disease (AD) currently affects more than five million people in the U.S.[1] It is a major cause of cognitive decline, and features include hippocampal atrophy and brain amyloid deposition.[2]

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Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data, but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Poor renal function has been associated with AD, or cognitive impairment. A recent study showed that chronic kidney disease (CKD) was a risk factor for AD,[3] and another found that lower renal function was associated with lower cognitive function.[4] However, most previous studies were focused on subjects with clinically significant renal impairment (e.g. eGFR < 60 ml/min/1.73m^2), which comprises only about 20 % of older adults,[5] thus limiting their applicability.

Also, reports of renal function and brain atrophy have been scarce. A literature search yielded only one cross-sectional study,[6] and no reports on longitudinal data.

An increasing number of reports have implicated vascular injury as a major player in the pathogenesis of AD.[7,8] As renal function is closely related to vascular injury,[9] investigations into the relationship between renal function and AD could provide valuable insight into the pathophysiology of AD.

Candidate mediators linking renal function and AD have been proposed. Hypotheses focused on anatomical

similarities have suggested vascular injury and endothelial dysfunction.[10] The kidney and brain are both end-organs with low resistance, and high-volume blood flow,[11] thus, making them highly vulnerable to vascular damage. This damage, influenced by vascular burden, may result in white matter lesions, silent brain infarcts, or microbleeds, and ultimately cause AD. On the other hand, chronic inflammation, possibly due to reduced clearance and subsequent build-up of toxic chemicals, has also been proposed.[10] The role of clearance in the pathophysiology of AD has been highlighted,[12] showing that reduced clearance of amyloid-β or uremic toxins may increase their concentration and cause chronic inflammation, resulting in neurodegeneration. Although there have been numerous reports concerning each factor, we were unable to find any studies comparing each from a broader perspective.

In this study, we determined if differences in renal function, even within normal levels, influenced hippocampal atrophy and cognitive decline. Furthermore, the relationship of renal function, hippocampal atrophy and cognitive decline, along with vascular burden and amyloid deposition, was explored using path analysis.

Methods

Data used for this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) in April, 2015. The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a $60 million, 5-year public-private partnership. For up-to-date information, see www.adni-info.org.[13]

Participants

The inclusion and exclusion criteria for ADNI subjects have been published elsewhere.[14] Briefly, subjects from 55 to 90 years of age, were screened, and categorized as Cognitively Normal (CN), Mild cognitive Impairment (MCI), or AD. AD was diagnosed based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Collection of demographic data, and a full medical work-up was conducted at baseline. Afterwards, annual, biannual, or biennial visits that included neuropsychological test batteries, MRI or PET and cerebrospinal fluid (CSF) collection were repeated.

Subjects categorized as CN or MCI at baseline (N = 1,269) were obtained. eGFR was used as a proxy of renal function. It was calculated from baseline creatinine levels, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[15] This, rather than the Modification of Diet in Renal Disease (MDRD) equation, was used, as it is more accurate in subjects with eGFR ≥60 ml/min/1.73m^2.[15] The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) defines normal GFR as 60 ml/min/1.73m^2 or higher[16]; thus subjects with eGFR < 60 ml/min/1.73m^2 were excluded (N = 314). Subjects without apolipoprotein E (APOE) genotype data were also excluded (N = 9). The remaining subjects (N = 946) were first divided by cognitive function (CN, N = 292; MCI, N = 654), and then further by renal function into three subgroups; the low normal group (60 ≤ eGFR < 75; CN, N = 144; MCI, N = 335), middle normal group (75 ≤ eGFR < 90; CN, N = 120; MCI, N = 246), and high normal group (eGFR ≥ 90; CN, N = 28; MCI, N = 73). As CN subjects and MCI subjects would have different characteristics, each were analyzed separately, using similar methods and models. AD subjects were not included, due to the small number of subjects with eGFR ≥ 90 (N = 16).

MRI and PET biomarker data acquisition and analysis

Among MRI measurements, hippocampal volume, intracranial volume, and Arterial Spin Label (ASL) imaging measurements from the University of California, San Francisco, and white matter hyperintensity (WMH) volume measurements from the University of California, Davis were used in analysis. Florbetapir amyloid PET standardized uptake value ratio (SUVR) measurements from the University of California, Berkeley were also used. The analysis protocols of each lab are available at the ADNI website.[17–20]

Neuropsychological and functional assessments

Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) scores were used to reflect cognitive function. Combined scores range from 0 to 70 and higher scores indicate worse cognitive function.[21]

Cardiovascular burden assessment

Framingham score was used as an indicator of cardiovascular disease burden, or vascular burden.[22] The office-based prediction model that includes age, body mass index (BMI), systolic blood pressure, smoking history, and diabetes history was used. Higher scores indicate increased risk of cardiovascular events.

Statistical analysis

Baseline characteristics were compared using Chi-square tests and one-way analysis of variance (ANOVA) with Bonferroni correction and Tukey's test.

Linear and poisson regression models were constructed, with baseline HCV or ADAS-Cog score as the dependent variable. These models incorporated age, gender, years of education, race, apolipoprotein E4 (APOE4) genotype, Framingham score, amyloid

PET SUVR, and WMH volume. HCV was included in models with ADAS-Cog score as the dependent variable. Two-way interactions, as well as three-way interactions that included eGFR, were also included in a stepwise fashion.

Random-coefficients models with random intercepts and slopes were used to investigate the longitudinal effect of eGFR on cognition and HCV. Age, gender, years of education, race, apolipoprotein E4 (APOE4) genotype, Framingham score, amyloid PET SUVR, and WMH volume, as well as two-way interactions of various variables with eGFR, were included in analysis. Non-significant interaction terms were eliminated in the final models. Only measurements from baseline up to the 5-year follow-up visit were included in analysis, as the number of subjects with visits after that was very small.

Lastly, path analysis was used to comprehensively compare the role of various factors mediating the effects of renal function on brain atrophy and cognition. All subjects were included. The model incorporated baseline amyloid PET SUVR, Framingham score, WMH volume, and hippocampal ASL value, and eGFR, HCV and ADAS-Cog score. ASL was included in this analysis only. eGFR was included as a nominal variable in the regression and random-coefficients models, and as a continuous variable in the path analysis model. Statistical Package for the Social Sciences (SPSS) ver. 21 (IBM Inc., Chicago, IL), R statistics ver. 3.1.2 (www.r-project.org), and AMOS ver. 23 (IBM Inc., Chicago, IL) was used in analysis.

Results

Baseline clinical and demographic characteristics

The high normal eGFR group was significantly younger [$F(2,651) = 34.6$, $P < .001$], and had larger hippocampal volumes [$F(2,555) = 6.99$, $P = .001$] compared to the other two groups.(Table 1).

Association of renal function with baseline hippocampal volume and cognition

In MCI subjects, mean hippocampal volumes were smaller in the middle normal and low normal eGFR groups, compared to the high normal eGFR group. (Table 2). Results were similar for CN subjects. Lower renal function was also associated with higher ADAS-Cog scores, but in MCI subjects only. In CN subjects, the direction of this association was negative, possibly due to the presence of several outliers in the high eGFR group. Several two-way and three-way interactions were also significant in subjects with MCI. Two-way interactions of eGFR with almost all factors were significant, as were three-way interactions that included age, APOE4 status and WMH volume.

Table 1 Baseline Clinical and Demographic Characteristics of Subjects by Cognitive Level and Renal Function

Variable	Mild Cognitive Impairment				Cognitively Normal			
	eGFR ≥90 ($N = 73$)	eGFR 75–90 ($N = 246$)	eGFR 60–75 ($N = 335$)	p	eGFR ≥90 ($N = 28$)	eGFR 75–90 ($N = 120$)	eGFR 60–75 ($N = 144$)	p
Age (years)	**65.5 ± 6.7**	**71.7 ± 7.1**	**72.9 ± 6.7**	**<.001**[a]	**70.3 ± 3.43**	**74.0 ± 5.80**	**75.6 ± 5.37**	**<.001**[a]
Female, *n* (% eGFR group)	37 (50.7)	93 (37.8)	133 (39.7)	.14	18 (64.3)	62 (50.8)	74 (51.0)	.40
APOE4 carrier, *n* (% eGFR group)	39 (53.4)	129 (52.4)	175 (52.2)	.98	11 (39.3)	35 (29.2)	38 (26.4)	.38
Education (years)	16.3 ± 2.7	16.0 ± 2.9	15.9 ± 2.9	.60	15.5 ± 3.02	16.3 ± 2.67	15.9 ± 2.60	.28
ADAS-Cog (points)	9.04 ± 5.1	10.1 ± 4.4	10.4 ± 4.7	.07	6.49 ± 2.86	5.80 ± 3.22	6.19 ± 3.00	.44
HCV (% of ICV)	**0.48 ± 0.08**	**0.45 ± 0.08**	**0.44 ± 0.08**	**.001**[a]	**0.53 ± 0.05**	**0.49 ± 0.07**	**0.49 ± 0.06**	**.005**[a]
Amyloid PET SUVR	1.17 ± 0.23	1.23 ± 0.22	1.23 ± 0.23	.28	1.05 ± 0.11	1.11 ± 0.18	1.14 ± 0.17	.27

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; APOE, Apolipoprotein E; eGFR, estimated glomerular filtration rate; FAQ, Functional Activities Questionnaire; HCV, Hippocampal volume; ICV, intracranial volume; PET SUVR, Positron Emission Tomography Standardized Uptake Value Ratio; SD, standard deviation, Significant findings ($P < .05$) are indicated in bold. [a]Significant difference on post-hoc analysis between eGFR ≥90 group and other groups.

Table 2 Association of eGFR with Baseline Hippocampal Volume and Cognitive Function

Variables	Mild Cognitive Impairment		Cognitively Normal	
	HCV	ADAS-Cog	HCV	ADAS-Cog
eGFR 60–75	**-3.89 (1.53)***	**2.17 (0.81)****	**-0.41 (0.18)***	**-19.1 (9.02)***
75–90	**-4.53 (1.59)****	**1.68 (0.83)***	-0.26 (0.18)	**-18.5 (9.03)***
≥ 90	Reference	Reference	Reference	Reference

HCV, hippocampal volume (as % of intracranial volume); ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive subscale; eGFR, estimated glomerular filtration rate, Linear regression was used to examine the association of eGFR with baseline hippocampal volume and cognitive function. Both models included age, gender, years of education, race, APOE4 carrier status, Framingham score, Amyloid PET SUVR and WMH volume. Hippocampal volume was included when appropriate. Data are presented as ß (SE). Significant findings (*$p < .05$; **$p < .01$) are indicated in bold.

Longitudinal influence of renal function on hippocampal volume and cognition

In MCI subjects, the high normal eGFR group lost about 1 % of their hippocampal volume every year, which was half that of the middle normal eGFR group, which lost about 2 % per year (Model 3, −0.0040 vs. -0.0082, $P = .006$).(Table 3 and Fig. 1). In the low normal eGFR group, hippocampal atrophy progressed at a rate of about 1.5 % volume reduction per year (Model 3, −0.0040 vs. -0.0065, $P = .083$). Slope differences of ADAS-Cog scores bordered on significance (Model 2 and 3, $P = .08$) in a number of models. The number of subjects in model 4 was much smaller than the other models, due to the comparatively small number of subjects with WMH and amyloid PET SUVR measurements.

Table 3 Longitudinal Effect of eGFR on Hippocampal Volume and Cognition

		Mild Cognitive Impairment		Cognitively Normal	
		HCV	ADAS-Cog	HCV	ADAS-Cog
Model 1($N = 619$)	Time (per year)	**-0.007 (0.001)****	**0.91 (0.41)***	-0.006 (0.002)	-0.10 (0.20)
	eGFR 60–75 x time	-0.0023 (0.002)	0.64 (0.46)	-0.0002 (0.002)	0.25 (0.22)
	eGFR 75–90 x time	**-0.0043 (0.002)****	0.97 (0.47)	-0.0009 (0.002)	0.28 (0.22)
	eGFR ≥90 x time	reference	reference	reference	reference
Model 2($N = 618$)	Time (per year)	**-0.004 (0.001)****	0.21 (0.43)	-0.004 (0.002)	-0.091 (0.20)
	eGFR 60–75 x time	-0.0025 (0.002)	0.71 (0.45)	-0.0010 (0.002)	0.23 (0.22)
	eGFR 75–90 x time	**-0.0042 (0.002)****	1.03 (0.46)	-0.0011 (0.002)	0.25 (0.22)
	eGFR ≥90 x time	reference	Reference	reference	reference
Model 3($N = 616$)	Time (per year)	**-0.004 (0.001)****	0.21 (0.43)	-0.004 (0.002)	-0.09 (0.20)
	eGFR 60–75 x time	-0.0025 (0.002)	0.71 (0.46)	-0.0010 (0.002)	0.23 (0.22)
	eGFR 75–90 x time	**-0.0042 (0.002)****	1.03 (0.46)	-0.0011 (0.002)	0.25 (0.22)
	eGFR ≥90 x time	reference	reference	reference	Reference
Model 4($N = 335$)	Time (per year)	**0.014 (0.005)****	**-4.03 (0.79)****	-0.009 (0.005)	-0.47 (0.69)
	eGFR 60–75 x time	-0.0019 (0.002)	0.27 (0.39)	0.0047 (0.006)	0.05 (0.73)
	eGFR 75–90 x time	-0.0026 (0.002)	0.26 (0.41)	0.0022 (0.006)	0.56 (0.76)
	eGFR ≥90 x time	reference	reference	reference	reference

ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive subscale; eGFR, estimated glomerular filtration rate; HCV, hippocampal volume (as % of intracranial volume), Values indicate annual change (SE) of hippocampal volume (as % of intracranial volume). Significant findings (*$p < .05$; **$p < .01$) are indicated in bold. Random coefficient effect models were used to examine the longitudinal effect of eGFR on hippocampal volume and cognition. Model 1: unadjusted model Model 2: Adjusted for baseline HCV or ADAS-Cog values, age, gender, education, race, and presence of apolipoprotein E4(APOE4) genotype. Models in the right column also included HCV. Model 3: Adjusted for all variables of model 2 and Framingham score. Model 4: Adjusted for all variables of model 3 and white matter hyperintensity volume and amyloid positron emission tomography (PET) standardized uptake value ratios (SUVR).

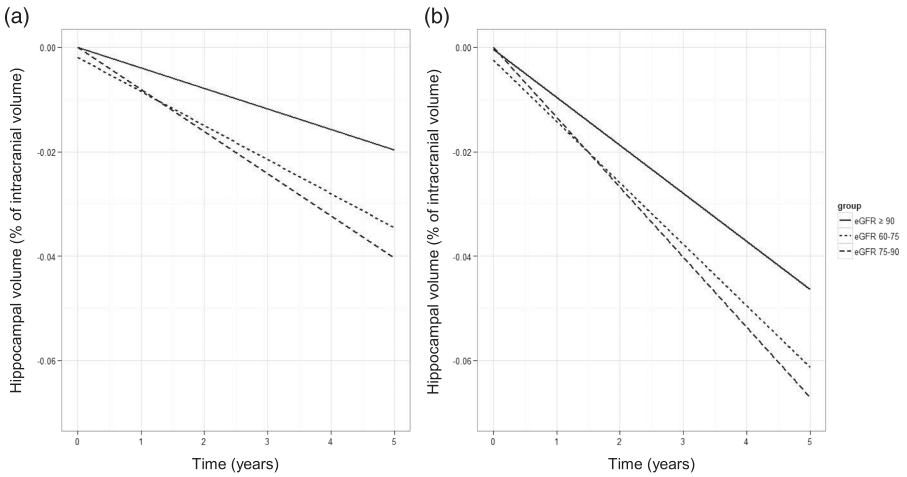

Figure 1 Slopes of hippocampal volume change by estimated glomerular filtration rate (eGFR) in APOE4 non-carriers (a) and carriers (b) with mild cognitive impairment. The rate of hippocampal atrophy in the high normal eGFR group (eGFR >90, solid line) was significantly slower than the middle normal eGFR group (75 ≤ eGFR <90, short dashes) (P = .006), and somewhat slower than the low normal eGFR group (60 ≤ eGFR <75, long dashes) (P = .083), after controlling for baseline hippocampal volume, age, gender, education, race, APOE4 genotype and Framingham score (Table 3, Model 3).

Factors mediating the relationship between renal function, cognition and hippocampal volume

Our path analysis model is presented in Figure 2. ASL measurements of both hippocampi, amyloid PET SUVR and Framingham scores were entered as indicators of hippocampal perfusion, brain amyloid deposition, and vascular burden, respectively. These factors and WMH volume were arranged as mediators between eGFR, ADAS-Cog score and HCV. All factors were entered as continuous variables.

eGFR had both direct (P = .014) and indirect effects on HCV. The indirect effects were mediated mainly by vascular burden (eGFR → vascular burden, $P < .001$; vascular burden → hippocampal volume, $P < .001$) and also by brain amyloid deposition (vascular burden → brain amyloid deposition, $P < .001$; brain amyloid deposition → hippocampal volume, $P < .001$). Notably, amyloid deposition did not

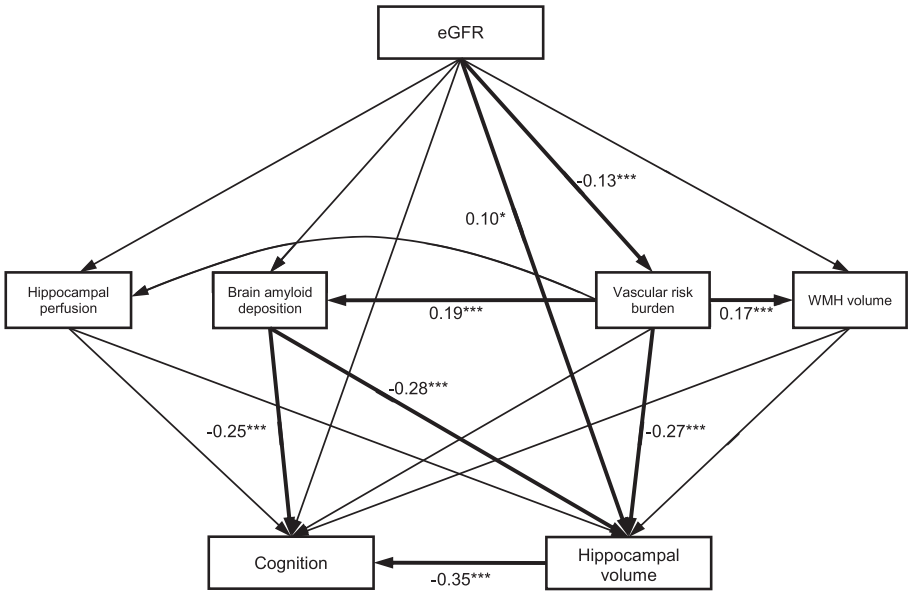

Figure 2 Path analysis model of estimated glomerular filtration rate (eGFR), hippocampal volume, and cognition. Baseline arterial spin labeling measurements of both hippocampi, amyloid PET standardized uptake value ratios (SUVR), Framingham scores and white matter hyperintensity(WMH) volume measurements were entered as indicators of hippocampal perfusion, brain amyloid deposition, vascular burden and WMH volume, respectively. All factors were entered as continuous variables. Bold arrows indicate significant associations, and numbers correspond to standardized regression weights.*$P < .05$, ***$P < .001$.

have a direct association with renal function, but was a mediator of vascular burden, and the effect of vascular burden on brain volume was mediated through brain amyloid deposition, and not through WMH volume or hippocampal perfusion. In the case of ADAS-Cog score, the direct effect of eGFR was not significant (P = .379). However, it did have an indirect effect through several mediators, which included vascular burden, brain amyloid deposition, and HCV (brain amyloid deposition → cognition, $P < .001$; hippocampal volume → cognition, $P < .001$). Model fit indexes indicated a good fit [χ^2=4.258, df = 3, P = .235, root mean square error of approximation (RMSEA) = .025, 90 % confidence interval of RMSEA: .000–.075, comparative fit index (CFI) = .995].

Discussion

To our knowledge, this is the first longitudinal study investigating the association of renal function with brain atrophy. Our results show that even within normal levels, higher renal function was associated with reduced progression rates of hippocampal atrophy in MCI subjects. By path analysis, we were able to demonstrate that the relationship between renal function, hippocampal atrophy and cognition is mediated mainly through vascular burden and amyloid deposition.

Our results shed light on the mechanisms connecting renal function with hippocampal atrophy. Reports concerning the 'kidney-brain axis' have suggested several candidates that include vascular injury and chronic inflammation.[10,11] Our path analysis model shows that within normal levels of renal function, vascular burden does indeed play a major role, even when it is not severe enough to cause white matter lesions, or reduce perfusion. Rather, vascular burden was associated with amyloid deposition, strongly suggesting that the two contrasting pathologies are linked. A plausible explanation is endothelial injury and neuroinflammation. Mildly reduced renal function and increased vascular burden may cause endothelial injury, increasing the production of reactive oxygen species (ROS) and oxidative stress.[23] As amyloid-β is not abundant in the hippocampus during the MCI stage, this mechanism would be able to explain the association between amyloid deposition and HCV found in our analysis. Furthermore, vascular burden had a direct effect on HCV. This effect may also include some forms of inflammation or oxidative stress. The direct effect of eGFR on HCV was also comparatively strong, and was not associated with amyloid deposition or vascular burden. We suspect that this effect may also be mediated through neuroinflammation. Future studies will be needed to verify these speculations.

Our results add weight to the theories suggesting that vascular pathology is a major causative mechanism of AD.[7,24] In this study, baseline Framingham score was associated with HCV in MCI subjects but not with cognition. However, path analysis revealed that vascular burden may impact cognition through hippocampal atrophy and brain amyloid deposition.

A notable finding of from our path analysis model was the association between HCV and ADAS-Cog; HCV is mainly associated with memory, whereas ADAS-Cog includes a much wider range of cognitive functions. The association suggests that memory may be a major factor of the ADAS-Cog. This reflects the results of a previous cohort study which found that the rates of hippocampal volume loss are correlated with rates of ADAS-Cog decline.[25]

A noteworthy difference of our study is that all subjects had clinically normal eGFR levels. Thus, our results, may be applicable to a larger population.

There are several limitations to this study. First, due to characteristics of the study sample, such as the high proportion of Caucasians, the applicability of our results may be limited, as previous studies have reported.[26] Second, compared to the chronic course of AD, the five-year duration of our longitudinal analysis may seem somewhat short. However, this was sufficient to reveal differences in the progression of HCV, and to compensate for this possible shortcoming, analysis of baseline data was also carried out. Third, the number of subjects with all visits was not large. However, a substantial number had been followed for at least five years. Fourth, we used an estimate of renal function that was calculated from blood creatinine levels, rather than a direct measurement. But, such estimations are widely used in clinical practice. Furthermore, among the currently used equations (MDRD, CKD-EPI), the NIDDK has acknowledged that the CKD-EPI equation is more accurate for eGFR ≥60 ml/min/1.73m^2 (http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx). Thus, it was best possible option for our subjects. Fifth, comparatively poorer overall medical condition or medical comorbidities may have influenced hippocampal volume and cognition. However, subjects with serious medical conditions were excluded from the study following the ADNI protocol, and Framingham scores were included to control for vascular burden; thus we think the influence of medical comorbidity was mostly eliminated, or controlled for. Nonetheless, history of hyperlipidemia is not included in the Framingham score, and future studies examining this are needed. Sixth, age is an important modifying factor of HCV and eGFR, and our analyses may not have been able to fully account for its affects. However, eGFR was calculated using the CKD-EPI equation, which incorporates the effects of age, and age was further included as a covariate in our models. Therefore, a substantial portion of the effects of age were probably accounted for. Seventh, the sensitivity of the cognitive measurement used (ADAS-Cog score) may have been insufficient for subjects with normal or near normal

levels of cognition. Although examination of other ADNI measurements did not result in significant findings, future studies with more sensitive instruments may yield different results. Eighth, path analysis was based on baseline data only. This was done to reduce the complexity of our results, as longitudinal models tend to be complex and difficult to interpret. Ninth, the path analysis model included measurements of amyloid deposition and HCV, although tau proteins, and not amyloid-β build-up in the hippocampus during the MCI stage. As tau-PET has been added to the ADNI protocol, future studies will be able to examine whether the effects of eGFR on HCV are mediated through neuroinflammation, or tau deposition.

In conclusion, we report that differences in renal function, even within normal levels, are associated with reduced hippocampal atrophy and cognition decline. Furthermore, we provide a larger picture of the various factors linking renal function and AD. Further studies including measures of chronic inflammation will be able to shed more light on this relationship.

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Disclosure statement

The authors declare no conflict of interest.

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