Published in final edited form as:

J Am Geriatr Soc. 2012 December ; 60(12): 2215–2222. doi:10.1111/j.1532-5415.2012.04238.x.

Relationship Between Longitudinal Measures of Renal Function and Onset of Dementia Among a Community Cohort of Older Adults

Ann M. O'Hare, MD^{1,2,3}, Rod Walker, MS¹, Sebastian Haneuse, PhD⁴, Paul K. Crane, MD^{1,3}, Wayne C. McCormick, MD³, James D. Bowen, MD⁵, and Eric B. Larson, MD, MPH^{1,3}

¹Group Health Research Institute, Group Health, Seattle, WA

²Department of Medicine, VA Puget Sound Healthcare System, Seattle, WA

³Department of Medicine, University of Washington, Seattle, WA

⁴School of Public Health, Harvard University, Boston

⁵Swedish Neuroscience Institute, Seattle, WA

Abstract

Background—Prior studies have described a higher incidence of dementia or worsening cognitive function in patients with lower levels of kidney function at a single point in time.

Objectives—To evaluate the association between dynamic measures of renal function ascertained over time with onset of dementia.

Design—prospective community cohort study.

Setting and Participants—2,968 adults aged 65 and older followed for the development of dementia over a median of 6.0 years (interquartile range 3.1–10.1 years).

Measurements—Time varying measures of renal function were constructed based on a total of 49,340 serum creatinine measurements and included: the average level of estimated glomerular filtration rate (eGFR), eGFR trajectory and variability in eGFR around this trajectory over 5-year exposure windows. The association between these three eGFR exposure measures and risk of dementia was estimated using a Cox regression model adjusted for other patient characteristics. In sensitivity analyses, we also adjusted for time-varying measures of urine protein by dipstick.

Results—Patients with lower levels of eGFR had a higher incidence of dementia but this did not reach statistical significance in adjusted analyses (omnibus p value=0.14). There were trends toward a higher adjusted incidence of dementia in patients with positive eGFR trajectories (omnibus p value=0.07) and greater variability in eGFR (omnibus p value=0.04) over time. The

Corresponding Author: Ann M. O'Hare, MA, MD, Associate Professor of Medicine and Staff Physician, VA Puget Sound Healthcare System, 1160 South Columbian Way, Seattle, WA 98119, PHONE: (206) 277-3192, FAX: (206) 764-2022, Ann.OHare@va.gov.

Author Contributions:

Ann O'Hare: study concept and design, analysis and interpretation of data, preparation of manuscript

Rod Walker: analysis and interpretation of data, critical manuscript revision

Sebastian Haneuse: analysis and interpretation of data, critical manuscript revision

Paul Crane: study concept and design, analysis and interpretation of data, critical manuscript revision, acquisition of subjects and data

Wayne McCormick: critical manuscript revision, acquisition of subjects and data.

James Bowen: critical manuscript revision, acquisition of subjects and data.

Eric Larson: study concept and design, analysis and interpretation of data, critical manuscript revision, acquisition of subjects and data

results of sensitivity analyses, including those in which we included time-varying measures of proteinuria, were consistent with those of the primary analysis.

Conclusion—Among a community cohort of older adults followed for a median of 6 years, we did not find strong associations between measures of kidney disease severity and progression and incident dementia.

Keywords

dementia; renal function; eGFR; variability; trajectory

INTRODUCTION

There is growing evidence for a connection between brain and kidney function. Epidemiologic studies evaluating the relationship between renal and cognitive function have described a higher prevalence of cognitive insufficiency,^{1–7} more rapid loss of cognitive function over time^{8,9} and a higher incidence of dementia¹⁰ in patients with lower levels of kidney function. Similar relationships have been described for urinary albumin excretion, with several studies demonstrating greater loss of cognitive function in patients with higher levels of albuminuria, even after accounting for baseline level of kidney function.^{11–16} Collectively, the results of these studies suggest that measures of kidney disease severity are associated with greater dementia risk.^{17, 18}

Prior studies evaluating the relationship between level of renal function and cognitive outcomes have relied almost exclusively on static measures of renal function assessed at a single point in time, usually at study entry. However, renal function is a complex measure that is variable over both shorter and longer periods of time, and may not be well captured by measures ascertained at a single arbitrary point in time. We designed a study to characterize the relationship between renal function and incident dementia using time-varying measures of renal function in a community cohort of older adults that underwent serial evaluation for incident dementia.

METHODS

Study participants

The Adult Changes in Thought (ACT) study is a population-based prospective study of risk factors for incident dementia and Alzheimer's disease (AD) in which study participants, who are at least 65 years of age and dementia free at enrollment, are followed and evaluated every 2 years to identify cases of incident dementia.¹⁹ The study population includes randomly selected members of Group Health (GH), an integrated healthcare system based in Seattle, Washington. An original ACT cohort of 2,581 participants was enrolled between 1994 and 1996; an expansion cohort of 811 was enrolled from 2000–2002; and, at the time of these analyses, an additional 620 participants had been enrolled to replace participants who had died or exited the study since 2003 (total n=4,012). The age-adjusted incidence of dementia among members of ACT is similar to that for other epidemiologic studies,¹⁹ and the socio-demographic characteristics of Group Health enrollees are comparable to those of residents in the Seattle-Tacoma-Bremerton area.²⁰ Because our current analyses investigated the association between renal function and risk of incident dementia, we restricted the study population to the 2,978 individuals (74.2% of those ever enrolled) with at least 1 follow-up study visit (to allow the opportunity for a dementia evaluation), at least 5 years of continuous enrollment in GH prior to ACT study entry (to allow availability of renal related lab measures taken as part of clinical care at GH), and at least one measure of creatinine taken during that 5 year period. Of the 841 excluded ACT participants, 661 were excluded

because they did not have a follow-up study visit (with the majority of these people having only recently been enrolled in ACT). We further excluded 3 individuals who were missing race information and 7 individuals who were on chronic dialysis or had an estimated glomerular filtration rate <15 mL/min/1.73 m² at time of study entry. The final study sample consisted of 2,968 ACT participants. The research protocols for this study were approved by institutional review boards at both GH and the University of Washington.

Outcome ascertainment

The outcome of interest was incident dementia. At each ACT study visit (including baseline), participants underwent cognitive evaluation using the Cognitive Abilities Screening Instrument (CASI).^{19, 21} Individuals scoring below 86 on this screening tool were referred for a standardized dementia diagnostic workup, which included a battery of neuropsychological tests and clinical evaluations. Diagnoses of incident dementia were then assigned at consensus diagnostic conferences according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Participants determined to have onset of dementia then underwent at least one annual follow-up examination to verify dementia status. By convention, the date of dementia onset was defined as the midpoint between the ACT study visit that triggered the incident dementia diagnosis and the preceding study visit. As a secondary outcome, we also evaluated probable or possible cases of AD identified using the NINCDS-ADRDA criteria.²²

Exposure measures

Because ACT participants were members of GH, we had access to all electronic outpatient laboratory measures obtained while they were enrolled in GH from 1988 onward. Outpatient serum creatinine measures obtained as part of outpatient clinical care for cohort members were converted to an estimated glomerular filtration rate (in mL/min/1.73 m²) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on age, race, and gender.²³ Urinary protein was assessed by dipstick.

We defined three exposure constructs to capture dynamic changes in estimated glomerular filtration rate (eGFR) over time: the level of eGFR, eGFR trajectory, and short-term variability of eGFR. These exposures were constructed as time varying measures (updated for each risk set) described as follows. We used age as the time axis. Each dementia case occurred at a particular age and all ACT participants on-study and at risk for dementia at that age were part of that case's risk set. Using the five years preceding that age, we fitted ordinary least squares regression lines to all eGFR measures obtained from each individual during the five year period, with separate lines being fit for each individual. We then used each person's fitted regression line to derive the person's average eGFR level two years preceding the dementia outcome, their eGFR trajectory over this time period, and their short-term variability in eGFR around this trajectory, defined as the standard error of the regression (i.e. square root of the estimated residual variance). An individual was considered to have missing exposure if the person lacked sufficient eGFR measures to fit a least-squares line (in this analysis, sufficient was defined as having at least 3 eGFR values spanning at least two of the five years corresponding to the risk set).

We also constructed time-varying exposure measures based on urine protein measurements. In each five year window, we recorded each individual's highest level of urinary protein excretion categorized as "negative", "trace", and "positive".

Other covariates

Demographic characteristics and measured or self-reported health information were collected from individuals at ACT study baseline and during each of the biennial follow-up

visits. Information included age, sex, race, level of education, frequency of exercise, self-rated health, smoking status, blood pressure, depression level, and whether a doctor had ever told them they had a history of cerebrovascular disease, diabetes, hypertension, kidney disease, congestive heart failure, or other heart disease. Any self-report of exercise activity for at least 15 minutes 3 times per week was defined as 'regular exercise'.²⁴ Depression level was measured using the Center for Epidemiologic Studies Depression Scale.²¹ Cerebrovascular disease was defined as a self-reported history of stroke, carotid endarterectomy, or transient ischemic attack. Other heart disease included self-reported myocardial infarction, angina, coronary artery bypass graft, or angioplasty.

Statistical analysis

For our primary analysis we used a Cox regression model, with age as the time scale, to evaluate the association between our 3 time-varying eGFR-based exposure measures (level, trajectory, and variability) and risk of incident dementia. The 3 exposure measures were included in the model simultaneously and are thus adjusted for each other. Further, we modeled these continuous exposure measures using natural cubic splines to allow for the possibility of a nonlinear relationship between the measures and the log hazard ratio (HR). We chose adjustment variables *a priori* based on review of the literature or on hypothesized associations between eGFR and risk of dementia. These included: current age (implicitly via the time scale), study cohort and age at enrollment, gender, race, depression status, diabetes, hypertension, congestive heart failure or other heart disease, cerebrovascular disease, and self-rated health.

Because some participants were missing exposure information due to insufficient eGFR measures in one or more risk sets, we further adjusted the model to account for potential bias stemming from missing exposure information on these individuals. This adjustment was accomplished using inverse probability weighting, with weights estimated from a marginal logistic regression selection model fit across all risk sets in the analysis and based on factors thought potentially to be related to the general or renal health of subjects and thus to influence their utilization of clinical care. Variables included in the selection model were: age, diabetes, hypertension, heart problems, kidney disease, cerebrovascular disease, and self-rated health.

Based on our fitted, fully adjusted Cox model, we generated plots showing the estimated adjusted HRs of dementia (with pointwise 95% confidence intervals based on robust standard errors) for each of the 3 renal function exposure measures.²⁵ Curves in these plots show how dementia risk increases or decreases across values of the exposure measures (relative to an arbitrary reference value for each exposure). Additionally, we provided tables showing a few select points along these curves to aid with interpretation of results.

We also evaluated the association between urinary protein excretion and risk of dementia. We performed this analysis on the subset of individuals who had at least one urine dipstick data point available within the five years prior to ACT enrollment (n=2,577). We used the same Cox regression model as described for the eGFR exposures with the addition of time-varying indicator variables to the model to denote each individual's highest level of urinary protein excretion during the prior five years. Individuals without a measure in a given five year period were considered at the lowest possible level (negative) for that time.

We obtained p-values for each of the exposures of interest from omnibus Wald tests, which jointly test the significance of the eGFR exposure related spline parameters (from our primary model) and the significance of the urinary protein exposure variables (from our additional analysis), and thus assess any overall association between each exposure and

dementia risk. We repeated all of the above analyses for the outcome of probable or possible AD.

We performed a variety of sensitivity analyses to assess the robustness of our findings for all-cause dementia as follows: 1) We adjusted for additional covariates including education level, smoking status, regular exercise, and self-reported insulin use (among diabetics); 2) We varied the selection model to include more potential predictors of missing data (education, race, and gender); 3) We used linear terms rather than splines; 4) We adjusted for the number of eGFR measures within each five year window; and 5) We increased the window of exposure to eight years. A P value of 0.05 was used to define statistical significance. We performed all analyses using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC), and R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

When stratified by their most recent eGFR prior to study enrollment, participants with the lowest levels of eGFR tended to be older, smaller proportions had a college education, and a higher percentage had comorbid health conditions compared with participants with normal eGFR values (< 60 mL/min/1.73 m²) (Table 1). The prevalence of self-reported hypertension, diabetes, and heart disease was highest in those with lower levels of eGFR at baseline. The 2,968 participants were followed for a median of 6.0 years (interquartile range, 3.1–10.1) and a total of 49,340 creatinine/eGFR measures (average of 17 measurements per participant) were available for analysis, which allowed for construction of 335,441 analytic exposure measures (five year windows of values from which we computed eGFR level trajectory and variability) across all analysis risk sets (Table 2). Higher mean eGFR and steeper eGFR trajectories (in either a positive or negative direction) tended to be associated with greater variability, while lower mean eGFR and trajectories close to 0 tended to be associated with lower variability. Patients with more creatinine measures tended to have greater variability in eGFR. A total of 25,293 urinary protein measures were available for analysis (average of 9 measurements per participant) including 15% positive, 8% trace, and 77% negative results.

The curves in Figure 1 present the estimated relationships between the 3 eGFR-based exposure measures (level, trajectory, and variability) and risk of all-cause dementia and AD, as measured by HRs. All-cause dementia risk tended to be higher for participants with low average levels of eGFR (upper left panel), as evidenced by the increasing HR with eGFR levels less than 60 mL/min/1.73 m²; whereas, risk did not tend to vary quite as much across eGFR levels between 60 and 80 mL/min/1.73 m² as evidenced by the relatively flatter HR curve over that range. Looking at the trajectory exposure measure (upper middle panel), participants with increasing levels of eGFR over time (i.e., mean changes of 0 to 6 mL/min/1.73 m² per year) tended to have greater risk of dementia than those with declining levels of eGFR (i.e., those with mean changes of 0 to –6 mL/min/1.73 m² per year). For the variability exposure measure (upper right panel), participants with greater variability in eGFR tended to have greater risk of dementia as shown by the overall increasing HR with increasing values of the exposure measure. Significance tests of these 3 associations (level, trajectory, and variability), yielded p values of 0.14, 0.07, and 0.04, respectively. Estimated relationships between the 3 eGFR exposure constructs and risk of AD were similar (lower panels) to that of all-cause dementia, though p-values for the associations were all >0.05 .

In a secondary analysis that incorporated time-varying urinary protein measures, we found no statistically significant association between proteinuria and all-cause dementia risk ($p=0.26$), though the point estimates were in the direction of elevated dementia risk for

patients with proteinuria. The adjusted HRs (and 95% confidence intervals) for positive or trace proteinuria were 1.15 (95% CI: 0.91–1.45) and 1.25 (95% CI: 0.92–1.69), respectively. Incorporating the urinary protein measures in the model had little effect on the magnitude of the point estimates of eGFR exposure constructs; though the precision of those estimates diminished ($p=0.36$, 0.13, 0.08, for level, trajectory, and variability, respectively), likely due to the smaller effective sample size for this secondary analysis (included 2,577 participants rather than 2,968). Repeating this secondary analysis with AD as the outcome yielded no association between proteinuria and AD risk ($p=0.69$); the adjusted HRs for positive or trace proteinuria were 1.01 (95% CI: 0.77–1.32) and 1.17 (95% CI: 0.82–1.66), respectively. The direction of point estimates for the association between eGFR-based exposure measures and risk of all-cause dementia were consistent across these analyses, although there were differences in level of statistical significance (Appendix Figure 1)

DISCUSSION

Among a cohort of community dwelling older adults followed prospectively over a median of six years for onset of dementia, traditional measures of kidney disease severity and progression were not statistically significantly associated with an increased dementia risk.

Prior studies have reported an association between lower levels of eGFR and worsening cognitive function over time.^{1–10,11–16} However, most prior studies did not prospectively ascertain dementia as an outcome, relying instead on cognitive function test scores.^{8, 9, 16, 26–28} Only two prior studies have described the relationship between baseline level of renal function and incident dementia.^{10,15, 29} While conducted in community based samples of older adults, the design of both studies differed substantially from that of the ACT study. Participants in the Cardiovascular Health Cognition Study underwent assessment for prevalent and incident dementia at two different time points approximately seven years apart.^{10, 15} At all but one study site, follow-up cognitive testing was performed only among those at high risk for dementia. Among participants in this sub-study, an elevated serum creatinine (1.3 mg/dL for women and 1.5 mg/dL for men) was associated with an increased odds of developing dementia (odds ratio (OR) 1.37, 95% confidence interval (CI) 1.06 to 1.78).¹⁰ However, this association was selectively present only among participants with good or excellent self-reported health, and not among those with fair or poor self-reported health. A modest association between albuminuria and incident dementia was reported in a separate analysis among members of this cohort (OR for a doubling of urine albumin-to-creatinine ratio (ACR) 1.12, 95% CI 1.03 to 1.22), although albuminuria defined as an ACR ≥ 30 mg/g was not statistically significantly associated with dementia (OR 1.07, 95% CI 0.74 to 1.54).¹⁵ The Osaki-Tariji project was conducted among Japanese adults aged 65 and older. Among 455 participants in this study without dementia at baseline who underwent MRI testing and were assessed for the development of dementia at a single point in time five years later, 28 had developed dementia, and an eGFR <60 ml/min/1.73 m² was associated with this outcome (OR 5.3, 95% CI 1.7 to 16.2).²⁹ Unlike these studies, the ACT study was expressly designed to ascertain incident dementia in older adults, and study procedures included prospective biennial assessment for this outcome.

While prior studies have used a single baseline measure of serum creatinine or eGFR, we used serial measures of eGFR ascertained over time. Any potential relationship between renal function and dementia risk is likely complex. Our time-varying approach allowed us to characterize different facets of a person's changing renal function and to test whether any of these features might be associated with dementia onset. Two prior studies did evaluate the relationship between time-varying measures of albuminuria with cognitive function, but neither study included dementia as an outcome.^{16, 30} Barzilay and colleagues described an association between incident and worsening albuminuria and worsening cognitive function

based on urinary albumin assessments collected prospectively at two points in time among a high risk clinical trial population with diabetes.¹⁶ Joosten and colleagues described an association between higher baseline levels of albuminuria and worsening albuminuria over time (also systematically ascertained at two different time points) with worsening cognitive function in a community based epidemiologic study. This association was present in younger but not in older participants.³⁰

While we did not observe statistically significant associations between measures of kidney disease severity and progression (i.e., lower levels of eGFR and declining eGFR) and incident dementia, patients with greater variability in eGFR were more likely to develop dementia over time. Most likely, variability in eGFR is a complex marker that reflects both unmeasured intercurrent health events and resilience of renal function in the face of these events. To our knowledge, only one prior study has evaluated clinical outcomes associated with variability in eGFR.³¹ This study reported an increased risk of mortality in patients with greater variability in eGFR. Similar to the previously observed association of acute illness with loss of cognitive function among members of ACT,³² we suspect that a higher incidence of dementia among participants with greater variability in eGFR reflects the greater medical complexity and more limited reserve across a range of organ systems of patients who go on to develop late life dementia. It is possible that such associations may not be causal but instead reflect multisystem processes (e.g., microvascular disease) or shared features of a dementia prodrome.

Our study has the following limitations. First, in contrast to many of the aforementioned studies that have examined the association of renal function with dementia and cognitive outcomes, measures of renal function were not collected systematically as part of the ACT study design. Because these measures were collected as part of clinical care, there are differences in the spacing and frequency of measurements across individuals and patients with greater variability in eGFR had a greater number of eGFR measurements. We attempted to address potential concern about confounding by adjusting our estimates using weights from a selection model. Unadjusted and adjusted results were quite similar and were robust to changes in the selection model, although the association with variability did not reach statistical significance when adjusted for number of serum creatinine measures. Second, inpatient serum creatinine measures were not available, precluding an analysis of how changes in renal function in the context of acute illness might relate to dementia risk. Third, eGFR based on serum creatinine measurements is an imperfect measure of renal function, and may reflect changes in muscle mass as well as kidney function. The borderline statistically significant association between more positive eGFR trajectory and dementia risk in particular might reflect greater loss of muscle mass in patients at risk for dementia. Finally, while approximately half of cohort members had an eGFR < 60 ml/min/1.73 m², relatively few cohort members had severe reductions in eGFR, thus we had limited ability to examine the relationship of incident dementia with advanced kidney disease.

In conclusion, among community dwelling older adults followed prospectively for the development of clinical dementia over a median of 6 years, measures of kidney disease severity and progression were not strongly associated with dementia risk.

Acknowledgments

This work was supported by NIH grants U01 AG006781 (PI: Larson) and 1K23AG28980 (PI: O'Hare).

Sponsor's Role: The sponsor had no role in the design, methods, subject recruitment, data collections, analysis and preparation of paper.

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Figure 1. Risk of dementia outcomes associated with estimated glomerular filtration rate (eGFR) based exposure constructs

The plots demonstrate the estimated relationship between all-cause dementia risk (top panels) or Alzheimer's disease (AD) risk (bottom panels) and each of the three eGFR-based renal function exposure measures (Level, Trajectory, and Variability - the left, middle, and right panels, respectively). The solid curves illustrate how risk (as measured by a hazard ratio (HR)) increases or decreases across values of each of the three exposure measures relative to a reference value. Reference values used for comparison are: 60 mL/min/1.73m² for Level; 0 mL/min/1.73m² per year for Trajectory; 6 mL/min/1.73m² for Variability. Dotted curves represent pointwise 95% confidence intervals for the HR estimates. The tables below the plots show a few select points (HRs) along these curves for each of the estimated exposure/outcome associations, as well as p-values from omnibus significance tests of the overall associations estimated in each of the plots.

Sensitivity analysis 1: Repeat primary analysis but with additional adjustment variables: education level, smoking status, regular exercise, and self-reported insulin use (among diabetics).

Sensitivity analysis 2: Repeat primary analysis but with different selection model: age, diabetes, hypertension, heart problems, kidney disease, cerebrovascular disease, self-rated health, education, race, and gender.

Sensitivity analysis 3: Repeat primary analysis but using only linear terms, rather than splines, for the exposures.

Appendix Figure 1. Results of sensitivity analyses to assess robustness of associations between risk of all-cause dementia and estimated glomerular filtration rate (eGFR) based exposure constructs

Sensitivity analysis 1: Repeat primary analysis but with additional adjustment variables: education level, smoking status, regular exercise, and self-reported insulin use (among diabetics).

Sensitivity analysis 2: Repeat primary analysis but with different selection model: age, diabetes, hypertension, heart problems, kidney disease, cerebrovascular disease, self-rated health, education, race, and gender.

Sensitivity analysis 3: Repeat primary analysis but using only linear terms, rather than splines, for the exposures.

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Table 1

Participant characteristics at time of ACT enrollment.

	All participants		Baseline eGFR (mL/min/1.73 m ²)					
			<45		45–60		>60	
	N	% ^a	N	% ^a	N	% ^a	N	% ^a
Total	2,968		332		894		1,742	
Cohort								
Original	2,100	70.8	250	75.3	697	78.0	1,153	66.2
Expansion	632	21.3	56	16.9	147	16.4	429	24.6
Replacement	236	8.0	26	7.8	50	5.6	160	9.2
Age in years, median (IQR)	74 (70–80)		80 (75–84)		76 (71–81)		73 (69–77)	
Female	1,780	60.0	237	71.4	582	65.1	961	55.2
At least some college	1,837	61.9	182	54.8	517	57.8	1,138	65.3
Non-white	268	9.0	30	9.0	65	7.3	173	9.9
Kidney disease	164	5.5	27	8.1	50	5.6	87	5.0
Diabetes	313	10.6	61	18.4	100	11.2	152	8.7
Hypertension	1,224	41.5	210	64.0	383	43.0	631	36.4
Average systolic BP, median (IQR)	139 (126–155)		145 (130–161)		140 (127–158)		137 (125–151)	
Average diastolic BP, median (IQR)	75 (69–82)		72 (67–80)		74 (68–82)		75 (69–82)	
CHF or other heart disease	659	22.3	112	34.0	216	24.3	331	19.1
Cerebrovascular disease	305	10.4	61	18.5	108	12.2	136	7.9
Regular exercise	2,110	71.2	215	64.8	624	69.9	1,271	73.1
Depression (CESD score 10+)	327	11.1	51	15.5	98	11.0	178	10.3
Low self-rated health	509	17.2	9	27.4	165	18.5	253	14.5
All-cause dementia (at end of follow-up)	594	20.0	92	27.7	189	21.1	313	18.0
AD dementia ^b (at end of follow-up)	452	15.2	62	18.7	144	16.1	246	14.1
Urinary protein excretion								
Negative	2,187	84.9	237	78.0	645	82.6	1,305	87.5
Trace	177	6.9	23	7.6	69	8.8	85	5.7
Positive	213	8.3	44	14.5	67	8.6	102	6.8
Missing	391	13.2	28	8.4	113	12.6	250	14.4

eGFR exposure constructs, median (IQR)	Baseline eGFR (mL/min/1.73 m ²)					
	All participants		<45		45–60	
	N	% ^a	N	% ^a	N	% ^a
Level						
Trajectory	63 (53 – 73)		42 (38 – 47)		55 (50 – 59)	70 (64 – 78)
Variability	0 (–2 – 2)		–1 (–4 – 0)		0 (–3 – 1)	1 (–1 – 3)
Missing	6 (4 – 9)		5 (4 – 7)		6 (4 – 8)	7 (4 – 9)
	686	23.1	30	9.0	177	19.8
					479	27.5

^aPercentages based on non-missing data (<2% missing for each of the variables unless explicitly shown).

^bPossible/probable Alzheimer's disease (NINCDS-ADRDA criteria).

^cExposure constructs based on least-squares regression line fit to each person's eGFR measures in five year windows.

Level = person's estimated mean eGFR in prior two years. Trajectory (i.e. slope) = the estimated change in person's mean eGFR per year. Variability = person's short-term variability in eGFR, defined by the standard error of the regression (i.e. square root of the estimated eGFR residual variance).

Table 2

Renal function measurements and exposure constructs.

	N	Percentiles							
		1st	5th	25th	50th	75th	95th	99th	
Creatinine (mg/dL)	49,340	0.8	0.9	1.1	1.3	1.6	2.4	3.9	
eGFR (mL/min/1.73 m ²)	49,340	16.2	28.2	46.7	59.1	71.5	87.4	94.3	
Exposure constructs ^a									
Level	335,441	27.0	36.3	50.9	60.5	70.7	83.2	88.8	
Trajectory	335,441	-9.6	-5.9	-2.4	-0.5	1.2	4.4	7.1	
Variability	335,441	0.1	1.5	4.0	5.9	8.1	12.6	16.8	

^aExposure constructs based on least-squares regression line fit to each person's eGFR measures in five year windows corresponding to risk sets.

Level = person's estimated mean eGFR in prior two years. Trajectory (i.e. slope) = the estimated change in person's mean eGFR per year. Variability = person's short-term variability in eGFR, defined by the standard error of the regression (i.e. square root of the estimated eGFR residual variance).