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Biomarkers of Kidney Function and Cognitive Performance in Middle-aged and Older Adults

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requirements for the degree Doctor of Philosophy

in

Public Health (Epidemiology)

by

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2020

DEDICATION

This dissertation is dedicated to my loving parents, Judy and Don and my wonderful children, Megan and Jonah.

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LIST OF ABBREVIATIONS

95% CI	95% confidence interval
ACR	Albumin-creatinine ratio
BDI	Beck Depression Inventory scale
BMI	Body Mass Index
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
eGFRcre	Creatinine-based estimated glomerular filtration rate
eGFRcys	Cystatin-based estimated glomerular filtration rate
GWAS	Genome-Wide Association Study
HR	Hazard Ratio
LDL-c	LDL-cholesterol
MMSE	Mini-Mental State Examination;
MR	Mendelian Randomization
OR	Odds Ratio
PRS	Polygenic risk score
RBS	Rancho Bernardo Study
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SNP	Single nucleotide polymorphism

SUA	Serum uric acid
T2DM	Type II diabetes
Trails B	Trail-Making Test B
UKBB	UK Biobank

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ABSTRACT OF THE DISSERTATION

Biomarkers of Kidney Function and Cognitive Performance in Middle-aged and Older Adults

by

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University of California San Diego, 2020
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Background: As a consequence of an aging world population, cognitive impairment and dementia are growing public health concerns. Previous studies suggest that kidney dysfunction is associated with cognitive decline. Most studies were limited to one marker of kidney function, and the extent to which associations are modified by genetics has received little consideration. Moreover, whether these associations are causal is not clear.

Methods: This dissertation is composed of three studies. Study one was a longitudinal study conducted among 1,634 participants from the Rancho Bernardo Study of Healthy Aging (RBS), who had repeated measures of kidney function and cognitive follow-up of up to 24 years.

Study two was a cross-sectional study using data from up to 341,208 participants from the UK Biobank (UKBB) with three different measures of kidney function, genetic data, and cognitive function data from the baseline assessment. Study three used data from 357,590 UKBB participants to assess causal associations between biomarkers of kidney function and cognitive performance using a Mendelian Randomization (MR) approach.

Results: In study one, men with albuminuria (urine albumin-to-creatinine ratio [ACR] ≥25 mg/g for men and ACR ≥30 mg/g for women) had faster cognitive decline across multiple domains. High serum uric acid (SUA) was related to lower baseline global cognitive function scores in men. There was no association between kidney function and cognitive performance in women. In study two, albuminuria, creatinine-based estimated glomerular filtration rate (GFRcre) <60ml/min, and cystatin C-based estimated glomerular filtration rate (eGFRcys) <60ml/min were associated with worse cognitive performance, and associations were more robust with eGFRcys versus eGFRcre. The association between albuminuria and reaction time was modified by a polygenic score for cognitive function. In the third study, genetically increased ACR was associated with reaction time, but there was no evidence to support causal effects of SUA, eGFRcre or eGFRcys on cognitive ability.

Conclusions: Multiple markers of kidney function were associated with worse cognitive performance in individuals of European descent. Furthermore, these associations may be modified by sex and genetics. Albuminuria may directly influence cognition, however SUA, eGFRcre and eGFRcys levels do not appear to be causally associated with cognitive performance.

CHAPTER 1: INTRODUCTION

Globally, nearly 50 million people are living with dementia, and unless effective interventions are implemented this number is predicted to triple by 2050 [1]. Dementia represents a huge burden for the affected individual, their caregivers and healthcare systems. Substantial efforts to develop disease-modifying drugs have yet to be successful. Therefore, identifying and addressing risk factors that could prevent or delay the onset of dementia are important public health priorities. Observational studies have demonstrated a connection between chronic medical conditions and cognitive decline suggesting that treatment and control of these risk factors could help preserve cognitive health [2]. Among these chronic health conditions, chronic kidney disease (CKD) has been considered as a potential independent risk factor for dementia and cognitive impairment [4,5].

Chronic kidney disease

According to recent estimates, chronic kidney disease (CKD) affects up to 15% of the US adult population, and almost half of those with severely reduced kidney function are unaware of their disease [3]. This is particularly alarming as CKD is associated with cardiovascular disease, stroke and increased risk of mortality [4]. Moreover, individuals with CKD are at increased risk of cognitive impairment with a prevalence rate of as high as 70% in those with end-stage kidney disease [5]. CKD is generally defined by the presence of reduced estimated glomerular filtration rate (eGFR) or by markers of kidney damage, primarily elevated albuminuria in urine. Disease severity is primarily staged by level of eGFR and is often further stratified by albuminuria status [6]. Although eGFR and albuminuria are closely related they have independent associations with several outcomes including cardiovascular disease and mortality [7].

Estimated glomerular filtration rate

Glomerular filtration rate (GFR) represents the flow rate of filtered fluid through the nephrons in the process of urine formation. Direct measurement of GFR is invasive and expensive and therefore rarely done in practice [8]. Most commonly, an estimated glomerular filtration rate (eGFRcre) is calculated based on serum concentrations of creatinine, a waste product of muscle breakdown [9]. However, serum creatinine can be affected by age, sex, ethnicity, diet, and lean muscle mass and may have poor sensitivity for early kidney disease [10]. eGFR (eGFRcys) based on serum concentrations of cystatin c may offer a superior, albeit more costly, alternative. Cystatin C is a small protein that is ubiquitously distributed in human tissue and therefore is less dependent on muscle mass than creatinine. Indeed, eGFRcys has been shown to outperform eGFRcre as a predictor of incident cardiovascular disease and CKD progression [11].

The majority of studies that have examined the association between kidney function and cognitive ability were limited to eGFRcre only as a marker of renal dysfunction [12]. Several cross-sectional and longitudinal studies have demonstrated that CKD defined as eGFRcre <60 ml/min is associated with cognitive decline [12–14], however some more recent prospective studies found null associations [15,16]. A 2012 meta-analysis by Etgen et al. found a 39% increase in the odds of cognitive impairment in individuals with eGFR<60 ml/min, however this analysis included both crude and adjusted data in estimating the overall effect [12]. In contrast, Deckers et al. found no significant association between eGFRcre and cognitive impairment in a meta-analysis including fully adjusted estimates only, suggesting that prior significant associations may have been affected by residual confounding [15]. Results have also been mixed when cognitive tests score are treated as continuous variables [16–19]. The few studies that have

examined association between eGFRcys and cognitive function suggest that this marker may be more robustly associated with cognitive performance [20,21]. For example, a recent study among participants the Atherosclerosis Risk in Communities study found a significantly increased risk of incident dementia for every 24.3mL/min (interquartile range of eGFRcys) decrement in eGFRcys (Odds ratio (95% confidence interval)=1.30 (1.12-1.52), but no significant association was found with eGFRcre [21].

Albuminuria

Albuminuria, or excessive leakage of albumin into the urine, is the result of endothelial damage in the kidney occurring as a consequence of microvascular dysfunction [22]. It is most often quantified using the urine albumin-to-creatinine ratio (ACR) which corrects for urine dilution. In general, an ACR>30 mg/g is known as moderately increased albuminuria [formerly called microalbuminuria (MA)] and an ACR>300 mg/g is known as severely increased albuminuria (formerly macroalbuminuria) [23]. However, sex specific cutoffs are often used to account for differences in urine creatinine concentrations [24]. Albuminuria has shown consistent associations with increased cardiovascular events and mortality [25,26]. Prior studies suggest that albuminuria may also be a risk factor for cognitive impairment and dementia [15,21]. When assessing cognitive ability as a continuous outcome, Georgakis et al. found that associations between albuminuria and performance varied by cognitive domain such that albuminuria was associated with global cognitive function, processing speed and executive function but not with tests of working memory or visuo-spatial ability [27]. Further study is needed to fully characterize these differences as they may reflect specific pathologies [28].

Serum uric acid

Uric acid, the end product of purine metabolism, is excreted by the proximal tubules of the kidney into the urine [29]. Serum uric acid (SUA) can be elevated in those with CKD and is associated with an increased risk of CKD progression [30] and cardiovascular disease (CVD). However, the literature describing the relationship between SUA and cognitive function has been mixed. Somewhat counterintuitively, lower SUA levels have been observed in cases with dementia versus controls [31,32]. This suggests a potential protective role of SUA that is thought to be a result of its potent anti-oxidant activity [33]. However, the results of longitudinal studies have been conflicting [34,35]. For example, Euser et al. found that higher SUA was associated with a decreased risk of dementia after adjusting for CVD risk factors (Hazard Ratio (HR) 95%CI= 0.89, 0.80 to 0.99 per standard deviation increase in SUA) [34], but a more recent prospective study demonstrated a significant increased risk of vascular or mixed dementia (HR, 95% CI=3.66, 1.29 to 10.41), p=0.015) and marginally significant increased risk of Alzheimer's disease (HR, 95% CI=1.55, 0.92 to 2.61) for those in the highest quartile of SUA vs. the lowest [35].

Repeated measures of kidney function

With few exceptions [18,36,37], the existing body of literature consists primarily of studies that have examined kidney function at one time point only. In a study by Helmer et al. there was no significant difference in cognitive decline according to baseline eGFRcre, however a decrease in eGFRcre over a seven-year follow-up was associated with significant decline in global cognition [36]. This suggests that repeated measures of kidney function may be necessary to fully characterize this association as the rate of renal decline may provide a better indicator of risk than one static measure. To our knowledge, only one previous study has used more than one measure of ACR to assess the association between albuminuria and cognitive function [38].

Barzilay et al. found that individuals who progressed from normal albumin levels to albuminuria had significant decreases in global cognitive function compared to those with no progression [38]. Associations between cognitive function and differences in ACR treated continuously were not reported.

Polygenic score by environment interaction

The heritability estimates of mild cognitive impairment (MCI) and Alzheimer's disease (AD) range between 40–48% and 58-79%, respectively [39,40]. However, variants identified from genome-wide association studies (GWAS) only account for around half of this phenotypic variation (24-33% for AD) [41,42]. It is thought that much of the missing heritability in complex traits may be due to effects of rare SNPs, or gene-gene and gene-environment interactions (GxE) [43,44]. For example, gene variants with little or no marginal effects have been shown to have significant effects in those with obesity or diabetes [45–47]. Similarly, some of the variation in cognitive ability among those with CKD could be explained by genetics. For example, genetic factors may confer a degree of resistance to the effects of kidney disease on the brain. Several approaches have been used to explore GxE interactions, each with distinct advantages and limitations. Candidate gene studies are intuitively easy to understand and require little in terms of resources, however they are dependent on assumptions about biological processes and are not easily replicated. GxE interactions can also be explored by GWAS but this approach may have limited power due to multiple comparisons. An alternative approach to GWAS, is to consider the use of polygenic scores (PRS). By leveraging results from prior GWAS, polygenic scores can be used to predict a phenotype of interest based on an individual's genotype. To our knowledge, there has only been one previous study that addressed gene by environment interactions in the context of kidney function and cognitive performance [48]. Using the candidate gene approach,

Shin et al. found that albuminuria was more strongly associated with poor cognitive performance in *APOE* e4 carriers vs. noncarriers. The potential modification of the kidney function- cognitive ability association by a polygenic score for cognitive function has not been investigated previously.

Mendelian randomization

Higher SUA levels are correlated with diabetes, cardiovascular and kidney disease [49]. Somewhat paradoxically, case-control and cross-sectional studies have reported lower levels of SUA in individuals with Alzheimer's disease compared to those with normal cognition [50–52]. However, the degree to which this association is influenced by unmeasured confounding or the problem of reverse causation remains unknown. Likewise, associations between eGFR and albuminuria could be confounded by the presence of shared risk factors including diabetes, socioeconomic status or other lifestyle factors [53–55]. Mendelian randomization (MR) is an instrumental variable approach that can address some limitations of observational studies such as confounding or reverse causation to make causal inferences [56]. Given certain assumptions, the principal tenet of MR is that if genetic variants that are associated with the exposure of interest are also associated with the outcome one can infer a causality between exposure and outcome. Analogous to randomization in clinical trials, the random assortment of alleles during meiosis allows confounders to be distributed evenly across genotypes. Furthermore, as genotype precedes phenotype the association is not affected by reverse causation. In this sense, genetic variants can serve as an "instrumental variable" for the exposure of interest. The directed acyclic graph shown in **figure 1.1** shows how this approach is used to assess associations between genetically determined SUA and cognitive function. A polygenic score for SUA is used as a genetic instrument in this case.

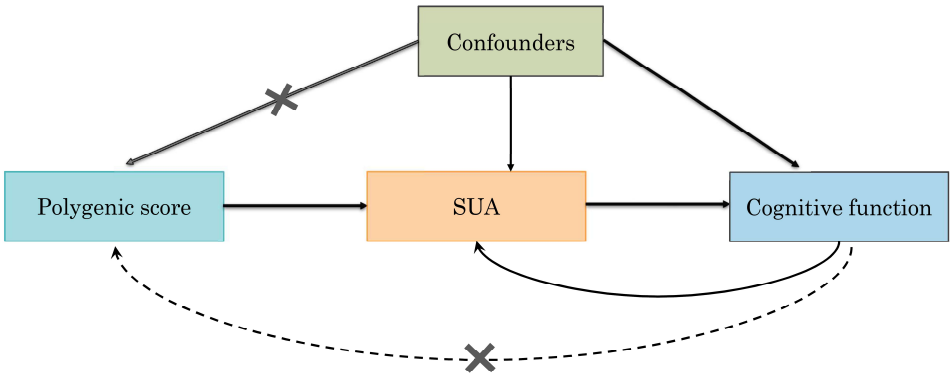

Figure 1.1. Directed acyclic graph (DAG) illustrating the MR approach to assess the association between SUA and cognitive function

There are three primary assumptions underlying the MR approach: (1) the genetic instrument is associated with the exposure (i.e. SUA), (2) the genetic instrument is not associated with confounders of the exposure-outcome association and (3) the genotype-outcome association is explained only through the effect of the biomarker exposure. Many genes influence more than one trait, a phenomenon known as pleiotropy [57] This can be particularly problematic in MR as the second and third assumptions can be violated in instances of pleiotropy, and this may lead to biased estimates and type I error [58]. However, analytical strategies, such as weighted-median and MR-Egger regression [59], have been established so that valid estimates can be obtained in the presence of pleiotropy.

Chapter Summary

The existing body of literature suggests an association between kidney function and cognitive function, but significant gaps exist. The following three chapters will build upon prior research by using a diverse set of approaches to further characterize the associations between different biomarkers of kidney function and multiple domains of cognitive ability. In chapter 2

of this manuscript we used data from 1,634 community-dwelling adult (mean age=71.7 years) participants of the Rancho Bernardo Study of Healthy Aging to assess the association between three biomarkers of kidney function (eGFRcre, albuminuria and high SUA) and decline across multiple domains of cognitive function with the longest cognitive follow-up to date (up to 24 years). Furthermore, this is the first study to use repeated measures of eGFRcre and ACR to relate kidney function trajectories to cognitive performance over time. Chapters 3 and 4 use data from participants of the UK Biobank (UKBB), a large prospective study that enrolled 502,617 participants aged 40-73 years from across the United Kingdom between 2006 and 2010. In chapter 3, we explore the cross-sectional associations between multiple markers of kidney function (eGFRcre, eGFRcys and albuminuria) and cognitive performance in the largest study sample to date. We also explore gene-by-environment interactions by assessing effect modification by a polygenic score for general cognitive function. The fourth chapter employs the MR approach to investigate potentially causal associations between biomarkers of kidney function and cognitive test performance using genetic data from the UKBB to create instrumental variables.

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CHAPTER 2. MARKERS OF KIDNEY FUNCTION AND LONGITUDINAL COGNITIVE ABILITY AMONG OLDER COMMUNITY-DWELLING ADULTS: THE RANCHO BERNARDO STUDY

Abstract

Background: Reduced kidney function has been associated with greater cognitive decline. Most studies have examined a single marker of kidney function and have limited follow-up. This study evaluated the associations between several measures of kidney function (urine albumin, estimated glomerular filtration rate (eGFR), and hyperuricemia) with cognitive performance over time.

Methods: This is a longitudinal study of 1,634 community-dwelling adults (mean age=71.7 years, 60% women), who had kidney function markers and cognitive ability measured at baseline (1992-1996) and at up to five additional time points over 24 years of follow-up. Associations between multiple measures of kidney function and cognitive performance were assessed using linear mixed effects models. Testing for interaction by sex was also conducted.

Results: In fully adjusted models, albuminuria (urine albumin-to-creatinine ratio [ACR] ≥ 25 mg/g for men and ACR ≥ 30 mg/g for women) was associated with steeper annual declines in global cognitive function (MMSE, β=-0.10, p = .003), executive function (Trails B, β=3.87, p < .0001) and episodic memory (Buschke total recall, β=-0.63, p = .02) scores in men. Results were similar when cognitive test scores were regressed on latent trajectory classes of ACR. In men, hyperuricemia (serum uric acid [SUA] ≥ 6.8 mg/dl for men and SUA ≥ 6.0 mg/dl for women) was associated with baseline lower MMSE (β=-0.70, p = .009) scores but not with MMSE change over time. No such associations were detected in women. There were no significant associations between eGFR and cognitive performance for either sex.

Conclusions: In older men, urine albumin is an independent predictor of subsequent cognitive decline. More investigations are needed to explain the observed sex differences and the potential relationship between hyperuricemia and poorer global cognition.

Keywords: Albuminuria, uric acid, glomerular filtration rate, dementia, cognitive aging

1. Introduction

In the face of an aging global population, the burden of dementia continues to increase and is projected to affect over 135 million people worldwide by 2050 [1]. Given the lack of effective interventions and or therapies, it remains a public health imperative to identify and control potential risk factors for the development of Alzheimer's disease and other dementias. One such factor is chronic kidney disease (CKD). CKD, or reduced kidney function defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2 and/ or a urine albumin-to-creatinine (ACR) ≥ 30 mg/g currently affects an estimated 15% of US adults [2], and this prevalence expected to rise as the population ages [3]. This is particularly alarming, as CKD is associated with cardiovascular disease, stroke and increased risk of mortality [4]. Moreover, individuals with CKD are at increased risk of cognitive impairment with the prevalence rate ranging from 30-70% in those with stage 5 CKD [5]. Evidence from population-based studies suggest that mild-to-moderate loss of kidney function may also be associated with worse cognitive function [6,7].

Estimated glomerular filtration rate (eGFR), a widely used measure of kidney function, has previously been associated with cognitive impairment and dementia [6–8]. Similar associations have also been observed between albuminuria, a marker of kidney damage, and cognitive decline [9,10]. However, despite adequate sample sizes, some longitudinal studies have failed to detect significant associations between kidney function and subsequent changes in cognition [11,12]. It should also be noted that the majority of these studies only examined a single measure of kidney function. Repeated measures may be necessary to fully characterize this association as the rate of renal decline may provide a better indicator of risk than one static measure. Furthermore, the majority of these studies have limited follow-up, and few have

information on multiple domains of cognitive function [10,12,13]. Counterintuitively, serum uric acid (SUA), which is elevated in individuals with CKD, has been positively associated with cognitive function in prior case-control and cross-sectional studies [14,15], although results are not entirely consistent. In addition, the degree to which this association is influenced by unmeasured confounding or the problem of reverse causation remains unknown.

This study investigates associations between three measures of kidney function and longitudinal cognitive performance using data from the Rancho Bernardo Study of Healthy Aging [16]. In contrast to prior studies, we were able to examine kidney function at multiple time points in participants with repeated cognitive assessments over an extended follow-up of up to 24 years.

2. Methods

2.1. Study Participants

The Rancho Bernardo Study (RBS) of Healthy Aging is a longitudinal cohort study established in 1972–1974 when 82% (n = 6, 339) of residents aged 30 and older, from the San Diego, CA suburb of Rancho Bernardo, were enrolled in a study of heart disease risk factors [16]. Participants were predominantly white (99.4%), well educated, and middle to upper-middle class adults. In 1992–1996, 1,781 RBS men and women participated in a follow-up clinic visit in which kidney function biomarkers were measured and cognitive function was assessed. Participants were excluded if they were less than 50 years of age at the 1992–1996 visit (n = 49), had missing kidney function biomarker measures (n= 30), no available cognitive function scores

(n = 50) or lacked information about educational attainment (n = 18), yielding a final sample size of 1,634 participants. This study was conducted in compliance with the Declaration of Helsinki and approved by the University of California San Diego Institutional Review Board. All participants provided written informed consent prior to participation at each visit.

2.2. Exposure Measures

Measurements of serum creatinine, urine albumin and urine creatinine were collected at the baseline 1992-96 visit and at three subsequent visits until 2003-2006. SUA was measured in 98% of the participants at baseline and, in a subset of participants (n=515), at the 1997-1999 clinic visit. A timeline of the data collection for the kidney function biomarkers and cognitive tests used in this study is shown in **Figure 2.S1**. At each clinic visit, blood samples were collected after a requested overnight fast, and a single, clean-catch, untimed morning urine sample was collected. Urine albumin and creatinine were measured at the National Institutes of Health laboratory of Dr. Peter Bennett. (Phoenix, Arizona). Urine albumin was measured using the Behring Nephelometer BNA (Dade Behring GmbH, Marburg, Germany). The lower limit of detection of the assay was 6.8 mg/L; values <6.8 mg/L were assigned a value of 6.7 mg/L. The interassay coefficient of variance was 4.5%. Urine creatinine was measured by the kinetic alkaline picrate method using the Ciba-Corning Express (Corning, Medfield, Massachusetts). SUA and serum creatinine were measured by SmithKline Beecham Clinical Laboratories (King of Prussia, Pennsylvania). Serum creatinine was determined by the Jaffe reaction method, and SUA was measured using the phosphotungstate method. Serum creatinine was indirectly calibrated to the Cleveland Clinic Laboratory by using RBS and NHANES III data [17] and

performing a linear regression of data combining the two studies adjusting for age and sex. The visit specific parameter estimates for the RBS versus NHANES III study were then subtracted from the raw serum creatinine values. eGFR was calculated using the CKD-EPI method using calibrated serum creatinine, age, race and sex [18]. Urine albumin to creatinine ratio (ACR) was calculated as follows: ACR (mg/g) = urine albumin (mg/dL)/ urine creatinine (g/dL). Albuminuria was defined as ACR ≥ 25 mg/g for men and ACR ≥ 30 mg/g for women (to reflect a higher urine creatinine excretion in men than in women). Hyperuricemia was defined as SUA ≥ 6.8 mg/dl for men and SUA ≥ 6.0 mg/dl for women.

2.3. Cognitive Function

Cognitive function was assessed at the 1992–1996 research clinic visit and at five subsequent visits at approximate four-year intervals thereafter, with the most recent cognitive assessment occurring between 2014–2016. A battery of standardized neuropsychological tests assessing global cognitive function (the Mini Mental State Exam, MMSE [19], executive function and psychomotor processing speed (the Trail-Making Test Part B ("Trails B") of the Halsted Reitan Battery [20], and verbal semantic fluency [21] (category fluency, assessed by number of unique animals named in one minute) were administered at each of these visits. A measure of verbal episodic memory, the total recall score from the Buschke Selective Reminding Task ("Buschke total recall") [22] was administered at 5 visits; it was not given at the 1992–1996 baseline visit or the 2007–2009 research visits due to time constraints. We created a retest effect variable defined as zero on the participant's first cognitive assessment and one on all following assessments [23].

2.4. Covariate Assessment

Lifestyle variables including smoking, alcohol consumption, and exercise (≥3 times/week), were acquired through standard questionnaires at the 1992–1996 baseline visit. Height and weight were measured using a regularly calibrated stadiometer and balance-beam scale with participants in light clothing and no shoes. Body mass index (BMI) was calculated as: weight (kg)/(height $(m)^2$). Blood pressure was recorded by a trained nurse according to the Hypertension Detection and Follow-up Program protocol [24] as the mean of two readings obtained five minutes apart while the participant was in a rested, seated position. Current use of antihypertensive, antihyperuricemic or antidiabetic medications was obtained by questionnaire. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medications. Diabetes status was based on the following criteria: Fasting plasma glucose > 126 mg/dL, 2-h post-challenge plasma glucose > 200mg/dL, use of diabetes medications, or self-reported physician diagnosis. Total lean body mass (kg) was obtained using dual-energy x-ray absorptiometry (DXA) of the total body.

2.5. Statistical Analysis

Descriptive statistics were calculated for baseline variables including the frequency and percent for categorical variables and the mean and standard deviation (SD) or median and interquartile range (IQR) for normally or non-normally distributed continuous variables, respectively. Differences in covariates by measures of renal function were assessed by chi-square analysis and ANOVAs as appropriate. To account for correlations between renal function and aging, reported p-values have been adjusted for baseline age.

Group-based trajectory analyses using latent class mixture models are utilized to identify distinct groups within the population representing different patterns of change of a measurement over time [25]. Individuals are classified to a group using the estimated posterior probabilities of membership. This method allows for missing data, irregular spacing of measurements and can incorporate both time-stable and time-dependent predictors. In addition, different functional forms of the trajectories (linear, quadratic, etc.) can be modeled. eGFR and log transformed ACR trajectories over 10 years were modeled as a function of time, and the model with the lowest Bayesian Information Criterion (BIC) was used to determine the number of distinct groups. This analysis was limited to individuals with at least two serum creatinine or ACR measurements (n= 1,227 and n=1,246; respectively). eGFR and ACR were adjusted for age by performing a linear regression of each kidney function biomarker on age at the time of measurement and adding the residuals to the biomarker mean prior to trajectory estimation. As SUA was measured only twice in a limited number of individuals, SUA trajectories were not estimated.

Linear mixed effects models were used to assess the associations of baseline eGFR, ACR and SUA and biomarker trajectories on longitudinal changes in test scores for the various cognitive domains. This statistical approach accommodates missing data, inconsistent measurement intervals and accounts for within-subject correlation between repeated measures. Models include random intercept and time (years since baseline) effects, which allows individual subject baseline levels and slopes to vary randomly about the mean trajectory defined by the fixed effects. A time by exposure interaction term was included to assess the influence of kidney function biomarkers on cognitive change over time. To account for potential retest effects, we regressed each cognitive test on the respective retest effect variable and added the residuals to the test mean before subsequent analyses.

Beta estimates and 95% confidence intervals were estimated adjusting for factors that have been previously related to both the kidney biomarkers and cognitive function [26–29] in (1) a minimally adjusted model including time, time squared, baseline age (years), sex, and education (some college; yes/no); (2) a fully adjusted model adding potential confounding lifestyle behaviors including smoking (never/current/former), exercise (≥3 times/week; yes/no) and alcohol consumption (daily alcohol intake; yes/no) and health-related factors including BMI, hypertension (yes/no), diabetes (yes/no), history of stroke (yes/no), history of heart attack (yes/no), antihyperuricemic medication use (yes/no) and lipid-lowering medication use (yes/no). A time by kidney function biomarker interaction term was included in all models to assess the influence of each marker on changes in cognitive function over time. Sex interactions were assessed by testing a two-way sex by biomarker term and a three-way sex by biomarker by time term in the models. Interactions with a likelihood-ratio-test p-value < .05 were considered significant. Due to the presence of significant sex by biomarker interactions analyses were carried out and reported stratified by sex.

To account for multiple testing, we used the PROC MULTTEST procedure in SAS to calculate *q*-values, which are adjusted *p*-values controlling for the false discovery rate [30]. A *q*-value < 0.05 was considered statistically significant. All analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

2.6 Sensitivity analyses

Individuals with decreased renal function may be at higher risk of death or dropout due to poor health (e.g. end-stage renal disease or cardiovascular disease) precluding the event of interest. Assuming these individuals were at increased risk of cognitive impairment, death and dropout would be competing events, which could lead to biased risk estimates. Sensitivity

analyses were performed via a joint model framework that incorporates informative dropout and death into a mixed model using the %SPM SAS macro [31]. The influence of diabetes and stroke on our results was examined by repeating analysis after excluding individuals with diabetes or a history of stroke at baseline. To address the potential confounding effects of muscle mass on serum creatinine, the full models were also repeated with additional adjustment for total lean body mass in the subset of individuals with this measure (n=1515).

3. Results

3.1. Participant Characteristics

Study participants had a mean age of 71.7 years (SD = 10.6) at the baseline (1992-1996) visit and an average follow-up of 8.1 (SD = 6.6) years (maximum 23.4 years). Participant characteristics are presented by sex (**Table 2.S1**), by albuminuria (**Table 2.1**), by hyperuricemia (**Table 2.S2**) and by eGFR<60 (**Table 2.S3**). Albuminuria was evident in 12% (n=201) of participants. Almost 20% of the study population had an eGFR<60 ml/min, however only 4.8% of participants had an eGFR < 45 (n=7) and no participants had an eGFR <15. Mean serum uric acid levels were higher in men compared to women (mean +/- SD = 5.45 +/- 1.32 mg/dl and 4.36 +/- 1.37 mg/dl respectively; p < .001); whereas eGFR levels were similar between women and men (mean, +/-SD = 73.83 +/- 16.94 mg/dl and 74.35 +/- 15.86 mg/dl, respectively; p = 0.59) (Table 2.S1). Women had a higher median ACR compared to men (median, interquartile range (IQR)= 13.40, 13.55 mg/g versus 8.93, 12.14 mg/g; p = 0.001), however albuminuria (elevated ACR) was more frequent in men versus women (16.1% vs 11.8%; p = .02) (Table 2.S1). Participants with albuminuria, hyperuricemia and eGFR<60 ml/min tended to be older and more

likely to have hypertension (*p-values* ≤ .001) with the exception that there was little difference in age in men with or without hyperuricemia (p = .12). Albuminuria was associated with a higher likelihood of being diabetic (p < .01) as was hyperuricemia, but only in women (p = .003).

3.2 Albuminuria and cognitive function

Sex-specific beta-estimates and standard deviations (SD) for the main and slope effects from the longitudinal mixed-effects analyses of baseline albuminuria and cognitive function are shown in **Table 2.2**. No albuminuria is the reference level for all analyses. The main effects indicate baseline differences according to albuminuria status, and the albuminuria by time interaction estimates the slope of cognitive change over time by albuminuria status. We detected a significant interaction between albuminuria and sex for cognitive trajectories in Trails B (p = .04)), such that associations with albuminuria were evident in men, but not women. In sex-specific analyses, there were no significant main or interaction effects of albuminuria on cognitive test performance in women (p-values ≥ 0.14). The modeled trajectories of each cognitive test over time as a function of albuminuria status in men is shown in **Figure 2.1**. As demonstrated by beta estimates of the time by albuminuria interaction terms in minimally adjusted models, albuminuria was significantly associated with larger declines in performance on the MMSE, Trails B and Buschke total recall tests in men only (p = 0.005; p < .0001; p = .03, respectively). The magnitude and significance of these declines were similar after additional adjustment for lifestyle and health related variables. After controlling for the false discovery rate the association between albuminuria and decline in Buschke total recall score in men was significant in fully adjusted models only (p = .02; q=0.04). Men with albuminuria had larger estimated declines in the category fluency test, but these associations were not statistically significant (p = .06, q=0.08) in fully adjusted models.

In our latent class mixture model analysis of repeated log ACR measurements, the best fit to data was obtained with two latent classes in both men and women (**Figures 2.S2 and 2.S3**). Class 1 was considered the low ACR group (median, IQR=5.08, 5.55 in women; 4.69, 5.56 in men), and class 2 was considered the high ACR group (median, IQR=30.60, 63.65 in women; 66.58, 129.74 in men). Results of the mixed model analyses with log ACR latent classes were consistent with those using clinical cut points for albuminuria showing larger declines in cognitive performance for men in the high vs low ACR class and no significant differences among women (**Table 2.S4**).

3.3. Hyperuricemia and Cognitive Function

There were no significant associations between hyperuricemia and longitudinal performance on any cognitive tests (p-values ≥ .11; **Table 2.3**) in either sex. We detected a significant interaction between the main effect of hyperuricemia and sex (p = .002 in fully adjusted models). In men only, hyperuricemia was associated with lower baseline MMSE scores in minimally and fully adjusted models (β=-0.70, p = .009 and β=-0.83, p = .002, respectively). Modeled trajectories of MMSE score according to hyperuricemia status in men are shown in **Figure 2.3.** Hyperuricemia was not associated with baseline scores of Trails B, category fluency or Buschke total recall (p-values ≥ 0.11) in either sex.

3.4. eGFR and Cognitive Function

We found no significant main or time interactive effects of eGFR < 60 status and cognitive performance on any tests (p's ≥ 0.13; **Table 2.S5)** for either sex. Analysis using latent class mixture models in the subsets of men and women with two or more eGFR measurements,

revealed three latent classes within the data. (**Figures 2.S4 and 2.S5**). Class 1 was considered the low eGFR group (mean, SD=57.43, 13.35 in women; 61.12, 13.60 in men), class 2 the intermediate eGFR group (mean, SD=71.55, 11.91 in women; 75.68, 11.58 in men) and class 3 the high eGFR group (mean, SD=86.86, 11.22 in women; 87.82, 11.22 in men). We found no significant differences in cognitive performance on any tests according to eGFR trajectory patterns (**Table 2.S6**).

3.5. Sensitivity Analyses

The results were consistent in joint models that accounted for informative death or dropout (**Tables 2.S7-2.S9**). Parameter estimates were essentially unchanged when individuals with diabetes were not included in the analyses (data not shown). However, when those with a history of stroke were excluded the association between hyperuricemia and overall MMSE score in men was attenuated but remained significant (β=-0.53, p = .03). The addition of lean muscle mass to the models did not substantially change results. Among women, results were similar after controlling for the current use of estrogen replacement therapy (data not shown).

4. Discussion

In this study, albuminuria, an early predictor of kidney disease, was associated with faster cognitive decline across multiple domains among men in a community-dwelling cohort followed up to 24 years. Similar results were found in these men when a latent class trajectory approach was used to characterize change in albumin-creatinine ratios over time. These results build upon an earlier analysis of this cohort that related albuminuria to a greater decline in global cognitive function, executive function, and verbal fluency tests over a single 7 year period in men only [9].

The current study describes this association over an expanded follow-up period and extends this association to a measure of episodic memory. In men only, hyperuricemia was related to poor overall performance in global cognitive function but was not significantly associated with longitudinal decline in cognitive performance on any test. These associations persisted after accounting for health and lifestyle factors. We found no significant associations between eGFR level and cognitive performance over time. No significant associations between kidney function markers and cognitive performance were observed in women.

Our results are in agreement with prior prospective studies suggesting increased albuminuria is associated with poor cognitive performance [32–34]. Prior studies were limited to one or two cognitive assessments. To our knowledge, this study has the longest continued cognitive follow-up to date with up to 6 assessments. In addition, our work benefits from a comprehensive panel of cognitive function tests which allowed us to examine differences across several cognitive domains.

Albuminuria has been linked with cerebral small vessel disease, which is a major contributor to both vascular and mixed-type dementia and may also be a risk factor for Alzheimer's disease [35]. Imaging studies suggest patients with albuminuria have higher frequency of lacunar infarcts, white matter hyperintensities, microbleeds and enlarged perivascular spaces, independent of a history of hypertension, diabetes or known stroke [35–38]. Although stroke and heart attack history and cardiovascular risk factors at baseline were accounted for in our analysis, unmeasured subclinical microvascular dysfunction may have also played a role. It remains unclear whether albuminuria directly impacts brain function or if this association solely reflects a shared risk factor model through which vascular dysfunction affects

the kidney and the brain independently. Further study is necessary to evaluate the potential causal relationship of albuminuria and cognitive decline.

eGFR level was not related to any measure of cognitive function in this study. The association between eGFR and cognitive ability in prospective studies is mixed with the majority of studies reporting a negative [6,8,39] or null association [32,40,41]. In the present study, the prevalence of CKD disease (stages 3b, 4, or 5) at baseline was somewhat modest at less than 4.8%. This may have precluded our ability to detect cognitive declines associated with more severe loss of kidney function. Furthermore, given both the strong correlation between eGFR and age and the steep acceleration of cognitive function at advanced ages, mild or moderate kidney impairment may be a less informative predictor of cognitive ability in older individuals. It is also possible that creatinine based eGFR was confounded by muscle mass. However, results were essentially unchanged after controlling for lean muscle mass.

Our study is one of few that have examined the association of repeated measures of renal function and cognitive performance [39,42]. While we did not find significant differences in cognitive ability by eGFR trajectory, we did observe steeper declines in cognitive function in men with higher baseline log ACR values over time. However, the ACR trajectories did not explain more variation in longitudinal cognitive performance than the baseline measure of albuminuria alone. Nonetheless, it should be noted that we were able to identify individuals at increased risk of cognitive decline independently of a priori clinical cut points suggesting that latent trajectory modelling is an effective method of identifying groups of individuals with different risk profiles. We did not detect groups with a dynamic increase in ACR in the present analysis which may be a consequence of the relatively older mean age of the study sample. A recent study employed similar methodology to explore 20-year trajectories of ACR from young

adulthood and myocardial structure using data from the CARDIA cohort study [43]. The CARDIA study results suggest that ACR trajectories may diverge earlier in the life course, within an age range that was not captured in the current sample.

The biological basis of the observed sex differences is unknown. The sex difference may be related to variation in the specific etiologies of cognitive impairment unique to men and women. Indeed, men have been shown to have higher rates of vascular dementia compared to women [44,45]. It may be possible that in the presence of albuminuria, men have a higher underlying susceptibility to accelerated microvascular dysfunction than women. In support of this, a study of patients with type II diabetes revealed that men with albuminuria were more likely than women to have evidence of ischemic heart disease [46]. In addition, progression of micro to macroalbuminuria is more likely to occur in men than women [47], suggesting that microalbuminuria may impose a greater sustained risk of downstream microvascular damage in men. It is unlikely that differences in exercise habits and muscle mass account for the apparent sex differences, since controlling for both did not change our results.

The literature describing the association between serum uric acid and cognitive function has likewise been inconsistent. Our finding that men with hyperuricemia have worse baseline global cognitive function than men with normal serum uric acid levels is consistent with several previous studies that linked higher serum uric acid levels to decreased cognitive ability [48–50]. In a longitudinal study of older community-dwelling adults, Latourte et al. found a significant association between increased SUA level and the risk of incident dementia [49]. Interestingly, after adjustment for stroke the association with vascular or mixed-type dementia disappeared. In our study, the association between hyperuricemia and MMSE was substantially attenuated after participants with a history of stoke were excluded. Taken together these results suggest a

possible mediating association of cerebrovascular disease in the causal pathway. This is further supported by studies that reported a higher risk of cerebrovascular disease with levels of SUA [50,51]. It is unclear why this association was observed only in men. However, these results are consistent with a small study carried out by Lin et al. that detected lower cognitive test performance and spontaneous brain activity with pre-hyperuricemia and hyperuricemia in men only [52]. In contrast to our results, several observational studies have reported an inverse association between SUA levels and cognitive impairment or Alzheimer's disease [53,54]. Recently, two mendelian randomization studies found no clinically relevant evidence for a causal association between serum uric acid levels and Alzheimer's disease or cognition [55,56] suggesting that the observed associations may be a result of residual confounding or reverse causation.

There are several limitations to this work. The characteristics of the RBS cohort, which is predominantly white, middle class and well educated, may restrict generalizability to other populations. However, the relative homogeneity of participants may help preserve the internal validity of our results by avoiding potential confounding effects of socioeconomic status, education and health care access. Furthermore, the baseline age of the study sample (mean=71.7 years) limited our ability to detect changes in markers of kidney function occurring at an earlier age. There are also several strengths to our study. The comprehensive data collected on the RBS cohort allowed for the adjustment of several potential lifestyle and health-related confounders. In addition, this study leverages one of the longest cognitive follow-up periods (24 years) to date and includes assessments of multiple cognitive domains.

In conclusion, we found significant associations between albuminuria and decline in multiple cognitive domains in men but not women. Men with high serum uric acid also

performed more poorly on a test of global cognitive function. Kidney function as measured by eGFR was not associated with cognitive ability in this study. Given the results of the current and prior studies, it seems albuminuria may serve as a clinically relevant, noninvasive marker of microvascular dysfunction in both the kidney and the brain, particularly among men.

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Table 2.1. Baseline (1992-1996) characteristics of participants according to urine albumin-creatinine ratio; the Rancho Bernardo Study (n=1,634)

	Women (n=993)			**Men (n=641)**		
	ACR<30mg/g (n=876)	**ACR≥30mg/g (n=117)**	**p-value**	**ACR<25mg/g (n=538)**	**ACR≥25mg/g (n=103)**	**p-value**
Age (years)	70.92 (10.66)	78.49 (9.96)	**<.001**	70.72 (10.30)	76.12 (8.89)	**<.001**
Some College	577 (65.9)	81 (69.2)	.29	464 (86.2)	82 (79.6)	.19
Exercise (≥3 times/week)	618 (70.5)	59 (50.4)	**<.001**	408 (75.8)	76 (73.8)	.75
Smoking Status			.75			.28
Never	423 (48.3)	68 (58.1)		189 (35.1)	27 (26.2)	
Past	388 (44.3)	37 (31.6)		320 (59.5)	71 (68.9)	
Current	65 (7.4)	12 (10.3)		29 (5.4)	5 (4.9)	
Daily Alcohol Drinking	256 (29.2)	27 (23.1)	.10	223 (41.4)	41 (39.8)	.42
History of MI	38 (4.3)	10 (8.5)	.49	53 (9.9)	15 (14.6)	.49
History of Stroke	21 (2.4)	9 (7.7)	**.02**	16 (3.0)	8 (7.8)	.08
Diabetes	96 (11.0)	29 (24.8)	**.003**	82 (15.2)	28 (27.2)	**.01**
Hypertension	503 (57.4)	99 (84.6)	**<.001**	306 (56.9)	83 (80.6)	**<.001**
History of Kidney Disease	8 (0.9)	5 (4.3)	**.01**	5 (0.9)	3 (2.9)	.08
Lipid Lowering Drug	81 (9.2)	10 (8.5)	.66	61 (11.3)	5 (4.9)	.14
Antihypertensive Drug	308 (35.2)	72 (61.5)	**<.001**	201 (37.4)	67 (65.0)	**<.001**
Antihyperuricemic Drug	7 (0.8)	0 (0.0)	.26	13 (2.4)	12 (11.7)	**<.001**
Estrogen Use	404 (46)	43 (37)	0.74	NA	NA	
BMI (kg/m^2)	24.78 (4.12)	24.04 (4.82)	.41	26.26 (3.60)	26.25 (4.01)	.24
SBP (mmHg)	136.29 (22.10)	148.72 (25.39)	**.003**	133.30 (19.46)	147.78 (22.89)	**<.001**
DBP (mmHg)	74.49 (9.14)	75.01 (11.35)	.08	77.13 (9.14)	79.47 (9.51)	**.001**
HDL-C (mg/dl)	64.32 (16.61)	63.97 (18.34)	.79	48.86 (13.16)	47.64 (15.17)	.08
LDL-C (mg/dl)	128.23 (33.54)	124.34 (34.82)	.42	124.91 (29.63)	125.55 (37.27)	.35
Hyperuricemia	95 (10.8)	29 (24.8)	**.002**	77 (14.3)	22 (21.4)	.12
CKD (eGFR < 60 ml/min)	152 (17.4)	50 (42.7)	**<.001**	81 (15.1)	42 (40.8)	**<.001**
eGFR (mL/min)	74.86 (16.41)	66.10 (18.76)	**.03**	76.12 (14.32)	65.09 (19.90)	**<.001**
ACR (mg/g)[a]	11.96 (10.09)	55.46 (85.37)	**.001**	8.10 (6.76)	56.22 (104.53)	**<.001**
SUA (mg/dl)	4.27 (1.31)	5.00 (1.65)	**<.001**	5.38 (1.29)	5.85 (1.41)	**.02**

Abbreviations: ACR, albumin-creatinine ratio; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; SBP, systolic blood pressure; SUA, serum uric acid
Values are shown as n (%) for categorical variables and mean (SD) for continuous variables.
[a]Median and interquartile rang

Table 2.2 Results of the longitudinal mixed-effects analyses of baseline albuminuria with cognitive function; the Rancho Bernardo Study(n=1,634)

		Women		Men		P for sex
		β (S.E)	p-value	β (S.E)	p-value	interaction
MMSE						
Albuminuria	Min	-0.24 (0.19)	.22	0.27 (0.39)	.29	.65
Time × albuminuria	Min	-0.02 (0.03)	.65	-0.10 (0.03)	**.005** [b]	.09
Albuminuria[a]	Full	-0.14 (0.19)	.35	0.36 (0.26)	.17	.55
Time × albuminuria[a]	Full	-0.02 (0.03)	.56	-0.10 (0.03)	**.003** [b]	.10
Trails B						
Albuminuria	Min	8.77 (5.94)	.14	-0.37 (6.0)	.95	.28
Time × albuminuria	Min	0.79 (1.06)	.46	3.75 (0.85)	**<.0001**[b]	**.04**
Albuminuria[a]	Full	5.88 (6.01)	.33	-1.25 (5.69)	.82	.38
Time × albuminuria[a]	Full	0.91 (1.07)	.40	3.87 (0.86)	**<.0001**[b]	**.04**
Category fluency						
Albuminuria	Min	-0.47 (0.47)	.30	-0.39 (0.55)	.48	.46
Time × albuminuria	Min	0.01 (0.07)	.87	-0.14 (0.07)	.06	.09
Albuminuria[a]	Full	-0.27 (0.47)	.31	0.14 (0.08)	.79	.52
Time × albuminuria[a]	Full	0.01 (0.07)	.64	-0.14 (0.07)	.06	.11
Buschke total recall						
Albuminuria	Min	-2.15 (1.97)	.26	0.89 (1.90)	.64	.34
Time × albuminuria	Min	0.24 (0.28)	.43	-0.59 (0.26)	**.03**	.06
Albuminuria[a]	Full	-1.76 (1.98)	.38	1.85 (1.94)	.34	.19
Time × albuminuria[a]	Full	0.18 (0.28)	.66	-0.63 (0.26)	**.02** [b]	.06

Abbreviations: MMSE, Mini-Mental State Examination; Trails B, Trail-Making Test B

All models Adjusted for baseline age and education (some college)

[a] Additional adjustment for BMI, smoking, daily alcohol intake, exercise 3 or more times per week, estimated glomerular filtration rate, hypertension, diabetes, stroke, antihyperuricemic medication use, and lipid-lowering medication use.

[b] q-value < 0.05

Table 2.3. Results of the longitudinal mixed-effects analyses of baseline hyperuricemia status with cognitive function; the Rancho Bernardo Study(n=1,634)

		Women		Men		P for sex
		β (S.E)	p-value	β (S.E)	p-value	interaction
MMSE						
Hyperuricemia	Min	0.23 (0.19)	.24	-0.70 (0.27)	**.009** [b]	**.001**
Time × Hyperuricemia	Min	-0.01 (0.03)	.74	0.06 (0.04)	.16	.07
Hyperuricemia [a]	Full	0.12 (0.19)	.54	-0.83 (0.27)	**.002** [b]	**.002**
Time × Hyperuricemia [a]	Full	-0.02 (0.03)	.63	0.05 (0.04)	.18	.07
Trails B						
Hyperuricemia	Min	5.97 (5.54)	.28	2.38 (6.15)	.70	.59
Time × Hyperuricemia	Min	-0.02 (0.92)	.98	0.81 (0.79)	.30	.43
Hyperuricemia [a]	Full	3.72 (5.68)	.51	6.23 (6.15)	.31	.85
Time × Hyperuricemia [a]	Full	0.13 (0.92)	.88	0.85 (0.79)	.28	.48
Category fluency						
Hyperuricemia	Min	-0.38 (0.42)	.38	-0.35 (0.59)	.55	.89
Time × Hyperuricemia	Min	0.03 (0.06)	.60	0.10 (0.07)	.14	.42
Hyperuricemia [a]	Full	-0.17 (0.44)	.71	-0.49 (0.60)	.42	.98
Time × Hyperuricemia [a]	Full	0.03 (0.06)	.65	0.10 (0.07)	.13	.41
Buschke total recall						
Hyperuricemia	Min	2.57 (1.60)	.09	1.80 (1.83)	.33	.79
Time × Hyperuricemia	Min	-0.28 (0.18)	.12	-0.33 (0.21)	.12	.94
Hyperuricemia [a]	Full	2.58 (1.62)	.11	1.48 (1.85)	.43	.85
Time × Hyperuricemia [a]	Full	-0.28 (0.18)	.12	-0.33 (0.20)	.11	.88

Abbreviations: MMSE, Mini-Mental State Examination; Trails B, Trail-Making Test B
All models Adjusted for baseline age and education (some college)
[a] Additional adjustment for BMI, smoking, daily alcohol intake, exercise 3 or more times per week, estimated glomerular filtration rate, hypertension, diabetes,stroke, antihyperuricemic medication use, and lipid-lowering medication use.
[b] q-value < 0.05

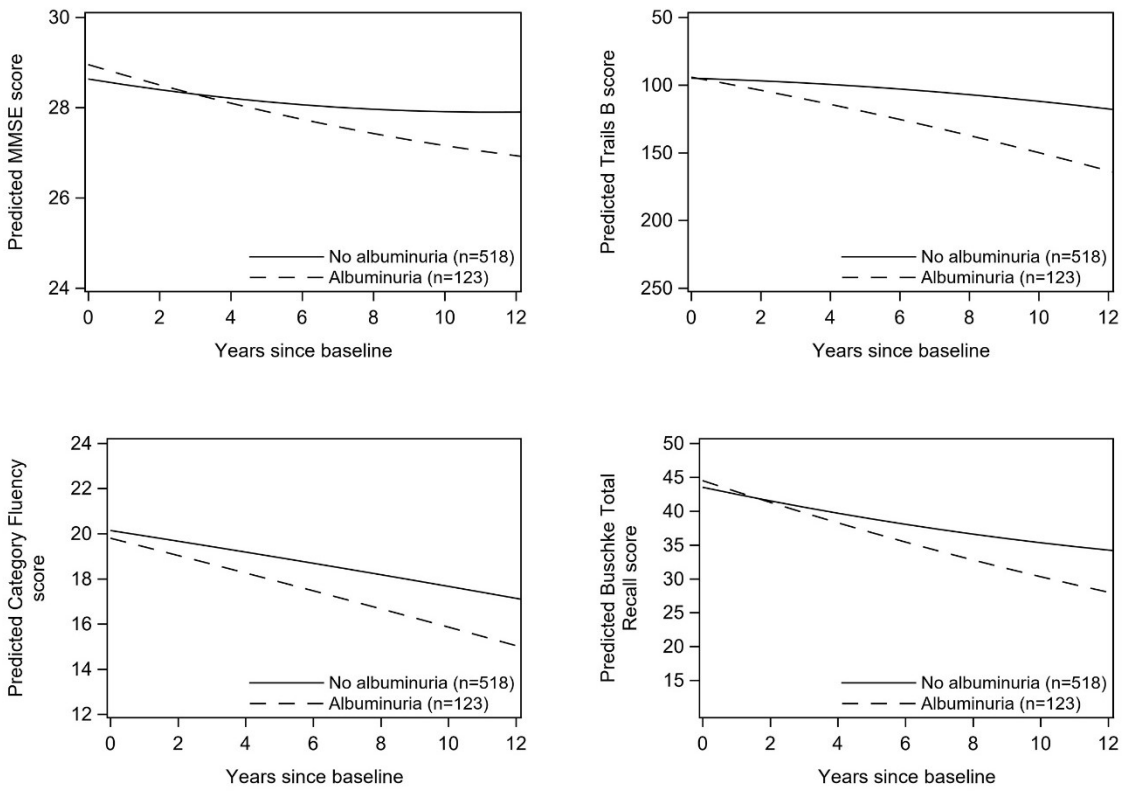

Figure 2.1. Modeled trajectories of cognitive test performance over time as a function of albuminuria status in men. Plots are based on model coefficients using group-specific mean values for covariates: ageand education (some college). The axis for Trails B is reversed so that downward sloping lines show decreasing performance.

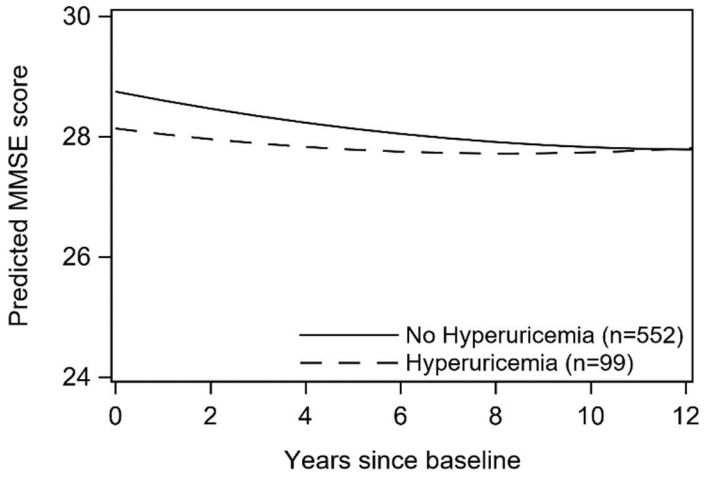

Figure 2.2. Modeled trajectories of MMSE performance over time as a function of hyperuricemia status in men. Plots are based on model coefficients using group-specific mean values for covariates: age and education (some college).

Table 2.S1. Baseline (1992-1996) characteristics of participants according to sex; The Rancho Bernardo Study (n=1,634)

	All participants	Women	Men	p-value[a]
	n=1634	n=993	n=641	
Age (years)	71.72 (10.63)	71.81 (10.86)	71.59 (10.27)	.67
Some College	1204 (73.7)	658 (66.3)	546 (85.2)	**.01**
Exercise (≥3 times/week)	1161 (71.1)	677 (68.2)	484 (75.5)	**.002**
Smoking Status				**<.001**
Never	707 (43.3)	491 (49.4)	216 (33.7)	
Past	816 (49.9)	425 (42.8)	391 (61.0)	
Current	111 (6.8)	77 (7.8)	34 (5.3)	
Daily Alcohol Drinking	547 (33.5)	283 (28.5)	264 (41.2)	**<.001**
History of MI	116 (7.1)	48 (4.8)	68 (10.6)	**<.001**
History of Stroke	54 (3.3)	30 (3.0)	24 (3.7)	.43
History of Kidney Disease	21 (1.3)	13 (1.3)	8 (1.2)	.93
Diabetes	235 (14.4)	125 (12.6)	110 (17.2)	**.01**
Hypertension	997 (61.0)	602 (60.6)	389 (60.7)	.80
Lipid Lowering Drug	157 (9.6)	91 (9.2)	66 (10.3)	.48
Antihypertensive Drug	648 (39.7)	380 (38.3)	268 (41.8)	.16
Antihyperuricemic Drug	32 (2.0)	7 (0.7)	25 (3.9)	**<.001**
Estrogen Use	NA	447 (45)	NA	
BMI (kg/m^2)	25.30 (4.08)	24.69 (4.21)	26.26 (3.67)	**<.001**
SBP (mmHg)	136.91 (22.05)	137.74 (22.84)	135.63 (20.73)	.06
DBP (mmHg)	75.71 (9.45)	74.55 (9.42)	77.51 (9.23)	**<.001**
HDL-C (mg/dl)	58.17 (17.36)	64.28 (16.82)	48.66 (13.50)	**<.001**
LDL-C (mg/dl)	126.69 (32.67)	127.78 (33.70)	125.02 (30.96)	.10
BDI	5.32 (4.41)	5.80 (4.64)	4.60 (3.93)	**<.001**
Albuminuria	201 (12.3)	117 (11.8)	103 (16.1)	**.02**
Hyperuricemia	223 (13.6)	124 (12.5)	99 (15.4)	.08
CKD (eGFR < 60 ml/min)	325 (19.9)	202 (20.3)	123 (19.2)	.61
eGFR (mL/min)	74.03 (16.52)	73.83 (16.94)	74.35 (15.86)	.59
ACR (mg/g)[b]	11.55 (13.77)	13.40 (13.55)	8.93 (12.14)	**.001**
SUA (mg/dl)	4.79 (1.45)	4.36 (1.37)	5.45 (1.32)	**<.001**

Abbreviations: ACR, albumin-creatinine ratio; BDI, Beck Depression Inventory scale; BMI, Body Mass Index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; SBP, systolic blood pressure; SUA, serum uric acid

Values are shown as n (%) for categorical variables and mean (SD) for continuous variables.

[a]P-value adjusted for baseline age.

[b]Median and interquartile range.

Table 2.S2. Baseline (1992-1996) characteristics of participants according to hyperuricemia status; The Rancho Bernardo Study (n=1,634)

	Women (n=993)			Men (n=641)		
	No hyperuricemia (n=869)	**Hyperuricemia (n=124)**	**p-value**	**No hyperuricemia (n=542)**	**Hyperuricemia (n=99)**	**p-value**
Age (years)	71.05 (10.77)	77.10 (9.97)	**<.001**	71.31 (10.19)	73.07 (10.65)	.12
Some College	581 (66.9)	77 (62.1)	.39	460 (84.9)	86 (86.9)	.48
Exercise (≥3 times/week)	608 (70.0)	69 (55.6)	**.008**	415 (76.6)	69 (69.7)	.15
Smoking Status			.38			.29
Never	431 (49.6)	60 (48.4)		182 (33.6)	34 (34.3)	
Past	370 (42.6)	55 (44.4)		327 (60.3)	64 (64.6)	
Current	68 (7.8)	9 (7.3)		33 (6.1)	1 (1.0)	
Daily Alcohol Drinking	247 (28.4)	36 (29.0)	.95	211 (38.9)	53 (53.5)	**.01**
History of MI	29 (3.3)	19 (15.3)	**<.001**	58 (10.7)	10 (10.1)	.67
History of Stroke	23 (2.6)	7 (5.6)	.32	18 (3.3)	6 (6.1)	.26
History of Kidney Disease	9 (1.0)	4 (3.2)	.10	5 (0.9)	3 (3.0)	.08
Diabetes	97 (11.2)	28 (22.6)	**.003**	93 (17.2)	17 (17.2)	.88
Hypertension	498 (57.3)	104 (83.9)	**<.001**	312 (57.6)	77 (77.8)	**<.001**
Lipid Lowering Drug	74 (8.5)	17 (13.7)	.10	54 (10.0)	12 (12.1)	.40
Antihypertensive Drug	295 (33.9)	85 (68.5)	**<.001**	210 (38.7)	58 (58.6)	**<.001**
Antihyperuricemic Drug	5 (0.6)	2 (1.6)	.22	24 (4.4)	1 (1.0)	.08
Estrogen Use	399 (46)	48 (40)	0.54	NA	NA	NA
BMI (kg/m^2)	24.47 (4.03)	26.20 (5.12)	**<.001**	26.00 (3.54)	27.66 (4.06)	**<.001**
SBP (mmHg)	136.93 (22.75)	143.37 (22.75)	.49	135.18 (20.80)	138.08 (20.28)	.47
DBP (mmHg)	74.66 (9.28)	73.80 (10.35)	.86	77.31 (9.20)	78.57 (9.39)	.12
HDL-C (mg/dl)	65.32 (16.45)	57.01 (17.58)	**<.001**	49.25 (13.53)	45.46 (12.97)	**.01**
LDL-C (mg/dl)	127.84 (33.36)	127.29 (36.09)	.86	124.07 (30.59)	130.18 (32.58)	.07
BDI	5.58 (4.54)	7.26 (5.04)	**.007**	4.62 (4.03)	4.46 (3.34)	.35
Albuminuria	88 (10.1)	29 (23.4)	**.002**	66 (12.2)	18 (18.2)	.12
CKD (eGFR < 60 ml/min)	128 (14.7)	74 (59.7)	**<.001**	89 (16.4)	34 (34.3)	**<.001**
eGFR (mL/min)	76.25 (15.51)	56.84 (16.85)	**<.001**	75.86 (15.28)	66.06 (16.54)	**<.001**
ACR (mg/g)[a]	13.20 (13.23)	12.99 (24.22)	.19	8.93 (10.51)	9.30 (18.01)	.12
SUA (mg/dl)	3.99 (0.98)	6.94 (0.84)	**<.001**	5.05 (0.96)	7.64 (0.79)	**<.001**

Abbreviations: ACR, albumin-creatinine ratio; BDI, Beck Depression Inventory scale; BMI, Body Mass Index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; SBP, systolic blood pressure, SUA, serum uric acid

Values are shown as n (%) for categorical variables and mean (SD) for continuous variables.

[a]Median and interquartile range.

Table 2.S3. Baseline (1992-1996) characteristics of participants according to eGFR level; The Rancho Bernardo Study (n=1,634)

	Women (n=993)			Men (n=641)		
	eGFR ≥ 60 (n=791)	**eGFR < 60 (n=202)**	**p-value**	**eGFR ≥ 60 (n=518)**	**eGFR < 60 (n=123)**	**p-value**
Age (years)	69.90 (10.46)	79.28 (9.01)	**<.001**	69.75 (10.05)	79.31 (7.11)	**<.001**
Some College	526 (66.5)	132 (65.3)	.93	447 (86.3)	99 (80.5)	.44
Exercise (≥3 times/week)	543 (68.6)	134 (66.3)	.49	393 (75.9)	91 (74.0)	.79
Smoking Status			.45			.10
Never	393 (49.7)	98 (48.5)		173 (33.4)	43 (35.0)	
Past	330 (41.7)	95 (47.0)		314 (60.6)	77 (62.6)	
Current	68 (8.6)	9 (4.5)		31 (6.0)	3 (2.4)	
Daily Alcohol Drinking	226 (28.6)	57 (28.2)	.63	212 (40.9)	52 (42.3)	.51
History of MI	25 (3.2)	23 (11.4)	**.004**	52 (10.0)	16 (13.0)	.58
History of Stroke	17 (2.1)	13 (6.4)	.09	19 (3.7)	5 (4.1)	.25
History of Kidney Disease	6 (0.8)	7 (3.5)	**.01**	5 (1.0)	3 (2.4)	.38
Diabetes	86 (10.9)	39 (19.3)	**.02**	80 (15.4)	30 (24.4)	.11
Hypertension	442 (55.9)	160 (79.2)	**<.001**	291 (56.2)	98 (79.7)	**<.001**
Lipid Lowering Drug	71 (9.0)	20 (9.9)	.96	58 (11.2)	8 (6.5)	.57
Antihypertensive Drug	263 (33.2)	117 (57.9)	**<.001**	193 (37.3)	75 (61.0)	**<.001**
Antihyperuricemic Drug	4 (0.5)	3 (1.5)	.17	14 (2.7)	11 (8.9)	**.006**
Estrogen Use	385 (48)	62 (31)	0.29	NA	NA	NA
BMI (kg/m^2)	24.72 (4.26)	24.56 (4.04)	.37	26.42 (3.73)	25.56 (3.33)	.89
SBP (mmHg)	135.91 (22.45)	144.91 (22.99)	.51	133.87 (19.95)	143.02 (22.35)	.44
DBP (mmHg)	74.77 (8.99)	73.72 (10.91)	.39	77.84 (8.81)	76.09 (10.75)	.90
HDL-C (mg/dl)	64.70 (16.40)	62.62 (18.31)	.15	48.66 (12.95)	48.66 (15.67)	.08
LDL-C (mg/dl)	127.91 (33.17)	127.27 (35.77)	.81	125.23 (29.81)	124.13 (35.51)	.29
BDI	5.47 (4.52)	7.09 (4.90)	.07	4.28 (3.85)	5.93 (4.00)	.18
Albuminuria	67 (8.5)	50 (24.8)	**<.001**	50 (9.7)	34 (27.6)	**<.001**
Hyperuricemia	50 (6.3)	74 (36.6)	**<.001**	65 (12.5)	34 (27.6)	**<.001**
eGFR (mL/min)	80.11 (12.11)	49.24 (8.73)	**<.001**	79.96 (11.39)	50.71 (8.58)	**<.001**
ACR (mg/g)[a]	13.07 (12.77)	15.37 (23.69)	**.01**	8.48 (9.05)	14.89 (28.42)	**<.001**
SUA (mg/dl)	4.08 (1.17)	5.44 (1.57)	**<.001**	5.30 (1.25)	6.08 (1.42)	**<.001**

Abbreviations: ACR, albumin-creatinine ratio; BDI, Beck Depression Inventory scale; BMI, Body Mass Index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; SBP, systolic blood pressure, SUA, serum uric acid

Values are shown as n (%) for categorical variables and mean (SD) for continuous variables.

[a]Median and interquartile range.

Table 2.S4. Association of ACR trajectory group with cognitive function trajectory; The Rancho Bernardo Study (n=1246)

		Women		Men		P for sex
	Model	**β (S.E)**	**p-value**	**β (S.E)**	**p-value**	**interaction**
MMSE						
High ACR group	Min	-0.30 (0.19)	.13	0.32 (0.24)	.19	.08
Time × High ACR group	Min	0.04 (0.03)	.25	-0.12 (0.04)	**.005** [b]	**.007**
High ACR group [a]	Full	-0.24 (0.19)	.20	0.46 (0.26)	.07	.03
Time × High ACR group [a]	Full	0.03 (0.03)	.28	-0.11 (0.04)	**.006** [b]	**.007**
Trails B						
High ACR group	Min	9.86 (5.88)	.09	-1.74 (7.89)	.82	.25
Time × High ACR group	Min	-0.65 (1.00)	.52	3.73 (1.06)	**.0005** [b]	**.004**
High ACR group [a]	Full	8.03 (5.98)	.18	-1/92 (7.90)	.81	.27
Time × High ACR group [a]	Full	-0.69 (1.01)	.49	3.74 (1.06)	**.0005** [b]	**.004**
Category fluency						
High ACR group	Min	-0.36 (0.52)	.49	0.39 (0.83)	.61	.34
Time × High ACR group	Min	0.02 (0.06)	.81	-0.20 (0.09)	**.04**	**.04**
High ACR group [a]	Full	-0.17 (0.53)	.75	0.65 (0.85)	.39	.32
Time × High ACR group [a]	Full	0.01 (0.06)	.87	-0.21 (0.09)	**.03** [b]	**.04**
Buschke total recall						
High ACR group	Min	-3.12 (1.94)	.11	1.16 (2.49)	.64	.19
Time × High ACR group	Min	0.51 (0.28)	.06	-0.53 (0.34)	.12	**.02**
High ACR group [a]	Full	-3.08 (1.97)	.12	2.07 (2.52)	.26	.12
Time × High ACR group [a]	Full	0.50 (0.27)	.06	-0.60 (0.34)	.08	**.02**

Abbreviations: ACR, albumin-creatinine ratio; MMSE, Mini-Mental State Examination;
Trails B, Trail-Making test B
All models Adjusted for baseline age and education (some college)
Low ACR group serves as reference category for all models.
Minimal Model (Min): Adjusted for baseline age and education (some college)
Full Model: Adds adjustment for BMI, smoking, daily alcohol intake, exercise ≥3 times/ week, hypertension, diabetes, stroke, antihyperuricemic medication use, and lipid-lowering medication use.
[b] q-value < 0.05

Table 2.S5. Results of the longitudinal mixed-effects analyses of eGFR<60 status with cognitive function; The Rancho Bernardo Study (n=1,634)

		Women		Men		P for sex
		β **(S.E)**	**p-value**	***β*** **(S.E)**	**p-value**	**interaction**
MMSE						
eGFR < 60ml/min	Min	0.06 (0.16)	.71	0.27 (0.24)	.26	.76
Time × eGFR < 60ml/min	Min	-0.03 (0.02)	.23	-0.004 (0.03)	.89	.46
eGFR < 60ml/min[a]	Full	0.03 (0.16)	.87	0.22 (0.24)	.38	.59
Time × eGFR < 60ml/min[a]	Full	-0.04 (0.02)	.11	-0.003 (0.03)	.91	.33
Trails B						
eGFR < 60ml/min	Min	1.40 (4.77)	.76	7.07 (13.3)	.59	.02
Time × eGFR < 60ml/min	Min	0.34 (0.77)	.66	-2.29 (1.67)	.17	.46
eGFR < 60ml/min[a]	Full	1.32 (4.76)	.95	7.10 (16.8)	.67	.06
Time × eGFR < 60ml/min[a]	Full	0.43 (0.78)	.57	-2.74 (2.86)	.34	.54
Category fluency						
eGFR < 60ml/min	Min	-0.41 (0.36)	.26	1.44 (1.49)	.32	**.002**
Time × eGFR < 60ml/min	Min	0.04 (0.04)	.44	-0.12 (0.24)	.63	.19
eGFR < 60ml/min[a]	Full	-0.33 (0.34)	.31	1.42 (1.68)	.41	**.003**
Time × eGFR < 60ml/min[a]	Full	-0.01 (0.04)	.85	-0.09 (0.18)	.56	.26
Buschke total recall						
eGFR < 60ml/min	Min	1.22 (1.31)	.35	1.47 (1.67)	.38	.87
Time × eGFR < 60ml/min	Min	-0.22 (0.15)	.15	-0.11 (0.21)	.61	.44
eGFR < 60ml/min[a]	Full	-0.16 (3.95)	.97	1.52 (1.65)	.36	.75
Time × eGFR < 60ml/min[a]	Full	-0.05 (0.41)	.91	-0.12 (0.21)	.59	.45

Abbreviations: ACR, albumin/creatinine ratio; MMSE, Mini-Mental State Examination; Trails B, Trail-Making Test B

All models Adjusted for baseline age and education (some college)

eGFR ≥ 60ml/min serves as reference category for all models

[a] Additional adjustment for BMI, smoking, daily alcohol intake, exercise ≥3 times/ week, hypertension, diabetes, stroke, Antihyperuricemic medication use, and lipid-lowering medication use.

Table 2.S6. Results of the longitudinal mixed-effects analyses of eGFR trajectory with cognitive function; The Rancho Bernardo Study (n=1227)

		Women		Men		P for sex
		β (S.E)	p-value	β (S.E)	p-value	interaction
MMSE						
Low eGFR group	Min	0.19 (0.19)	.31	-0.11 (0.19)	.58	.27
Intermediate eGFR group	Min	0.02 (0.13)	.88	0.19 (0.15)	.18	.91
Time × Low eGFR group	Min	-0.008 (0.03)	.75	-0.004 (0.03)	.90	.92
Time × Intermediate eGFR group	Min	-0.01 (0.02)	.58	-0.012 (0.59)	.59	.87
Low eGFR group	Full	0.09 (0.18)	.61	-0.09 (0.19)	.64	.49
Intermediate eGFR group	Full	-0.03 (0.13)	.80	0.25 (0.15)	.10	.20
Time × Low eGFR group	Full	-0.008 (0.02)	.75	-0.006 (0.03)	.85	.95
Time × Intermediate eGFR group	Full	-0.01 (0.02)	.58	-0.01 (0.02)	.56	.88
Trails B						
Low eGFR group	Min	5.28 (5.69)	.35	-3.84 (6.33)	.54	.49
Intermediate eGFR group	Min	-0.003 (4.11)	.99	3.25 (4.94)	.51	.20
Time × Low eGFR group	Min	-0.70 (0.85)	.41	-0.019 (0.80)	.98	.27
Time × Intermediate eGFR group	Min	-0.80 (0.61)	.19	-0.72 (0.59)	.22	.67
Low eGFR group	Full	6.55 (5.64)	.25	-6.25 (6.34)	.32	.16
Intermediate eGFR group	Full	0.78 (3.99)	.84	3.58 (4.86)	.46	.74
Time × Low eGFR group	Full	-0.69 (0.85)	.42	-0.02 (0.80)	.97	.49
Time × Intermediate eGFR group	Full	-0.81 (0.62)	.19	-0.76 (0.59)	.20	.91
Category fluency						
Low eGFR group	Min	0.36 (0.49)	.45	-0.015 (0.66)	.98	.71
Intermediate eGFR group	Min	0.17 (0.35)	.62	0.51 (0.52)	.32	.58
Time × Low eGFR group	Min	-0.006 (0.05)	.46	0.004 (0.07)	.95	.95
Time × Intermediate eGFR group	Min	0.01 (0.04)	.69	0.03 (0.06)	.53	.85
Low eGFR group	Full	0.38 (0.49)	.44	0.33 (0.68)	.63	.81
Intermediate eGFR group	Full	0.19 (0.36)	.59	0.65 (0.52)	.21	.50
Time × Low eGFR group	Full	-0.006 (0.05)	.90	-0.007 (0.07)	.92	.95
Time × Intermediate eGFR group	Full	0.02 (0.04)	.68	0.03 (0.05)	.59	.86

Table 2.S6 continued

		Women		Men		P for sex
		β (S.E)	**p-value**	**β (S.E)**	**p-value**	**interaction**
Buschke total recall						
Low eGFR group	Min	1.89 (1.43)	.18	1.17 (1.75)	.50	.81
Intermediate eGFR group	Min	-0.56 (1.03)	.59	0.13 (1.38)	.92	.50
Time × Low eGFR group	Min	-0.14 (0.15)	.35	-0.07 (0.19)	.66	.99
Time × Intermediate eGFR group	Min	0.03 (0.10)	.72	0.12 (0.15)	.44	.88
Low eGFR group	Full	1.57 (1.44)	.28	1.56 (1.76)	.38	.78
Intermediate eGFR group	Full	-0.56 (1.02)	.58	0.20 (1.37)	.88	.65
Time × Low eGFR group	Full	-0.14 (0.15)	.35	-0.12 (0.19)	.56	.75
Time × Intermediate eGFR group	Full	0.03 (0.10)	.74	0.11 (0.15)	.46	.71

Abbreviations: ACR, albumin/creatinine ratio; MMSE, Mini-Mental State Examination; Trails B, Trail-Making Test B

All models Adjusted for baseline age and education (some college)

High eGFR group serves as reference category for all models.

[a] Additional adjustment for BMI, smoking, daily alcohol intake, exercise ≥3 times/ week, hypertension, diabetes, stroke, Antihyperuricemic medication use, and lipid-lowering medication use

Table 2.S7. Results of the longitudinal joint model analyses of baseline albuminuria with cognitive function accounting for death and dropout; The Rancho Bernardo Study (n=1,634)

	Women		**Men**	
	***β* (S.E)**	**p-value**	***β* (S.E)**	**p-value**
MMSE				
Albuminuria	-0.52 (0.14)	.21	0.26 (0.25)	.31
Time × albuminuria	-0.04 (0.04)	.58	-0.11 (0.04)	**.004**
Trails B				
Albuminuria	8.78 (5.95)	.14	-0.37 (5.8)	.94
Time × albuminuria	0.80 (1.07)	.46	3.80 (0.85)	**<.001**
Category fluency				
Albuminuria	-0.52 (0.45)	.28	-0.39 (0.55)	.48
Time × albuminuria	0.01 (0.07)	.91	-0.15 (0.07)	**.046**
Buschke total recall				
Albuminuria	-1.74 (1.96)	.35	0.85 (1.90)	.66
Time × albuminuria	0.17 (0.27)	.65	-0.56 (0.27)	**.04**

Abbreviations: MMSE, Mini-Mental State Examination; Trails B, Trail-Making Test B
All models Adjusted for baseline age and education (some college)

Table 2.S8. Results of the longitudinal joint model analyses of baseline hyperuricemia with cognitive function accounting for death and dropout; The Rancho Bernardo Study (n=1,634)

	Women		**Men**	
	β (S.E)	**p-value**	**β (S.E)**	**p-value**
MMSE				
Hyperuricemia	0.22 (0.19)	.25	-0.70 (0.27)	**.009**
Time × Hyperuricemia	-0.01 (0.03)	.69	0.06 (0.04)	.16
Trails B				
Hyperuricemia	5.97 (5.55)	.28	2.37 (6.16)	.70
Time × Hyperuricemia	0.14 (0.92)	.87	0.81 (0.79)	.30
Category fluency				
Hyperuricemia	-0.35 (0.42)	.40	-0.31 (0.59)	.59
Time × Hyperuricemia	0.02 (0.05)	.71	0.10 (0.07)	.13
Buschke total recall				
Hyperuricemia	2.82 (1.61)	.07	1.91 (1.84)	.28
Time × Hyperuricemia	-0.32 (0.18)	.08	-0.35 (0.21)	.09

Abbreviations: MMSE, Mini-Mental State Examination; Trails B, Trail-Making Test B
All models Adjusted for baseline age and education (some college)

Table 2.S9. Results of the longitudinal joint model analyses of baseline eGFR level with cognitive function accounting for death and dropout; The Rancho Bernardo Study (n=1,634)

	Women		**Men**	
	β (S.E)	**p-value**	**β (S.E)**	**p-value**
MMSE				
eGFR < 60ml/min	0.06 (0.16)	.71	0.28 (0.24)	.25
Time × eGFR < 60ml/min	-0.03 (0.02)	.21	-0.004 (0.03)	.89
Trails B				
eGFR < 60ml/min	1.40 (4.78)	.76	7.97 (15.2)	.53
Time × eGFR < 60ml/min	0.49 (0.77)	.52	-2.64 (1.93)	.20
Category fluency				
eGFR < 60ml/min	-0.39 (0.36)	.29	1.42 (1.51)	.34
Time × eGFR < 60ml/min	0.03 (0.05)	.57	-0.10 (0.24)	.69
Buschke total recall				
eGFR < 60ml/min	1.26 (1.32)	.34	1.47 (1.67)	.38
Time × eGFR < 60ml/min	-0.22 (0.16)	.16	-0.04 (0.21)	.83

Abbreviations: MMSE, Mini-Mental State Examination; Trails B, Trail-Making Test B
All models Adjusted for baseline age and education (some college)
eGFR ≥ 60ml/min serves as reference category for all models

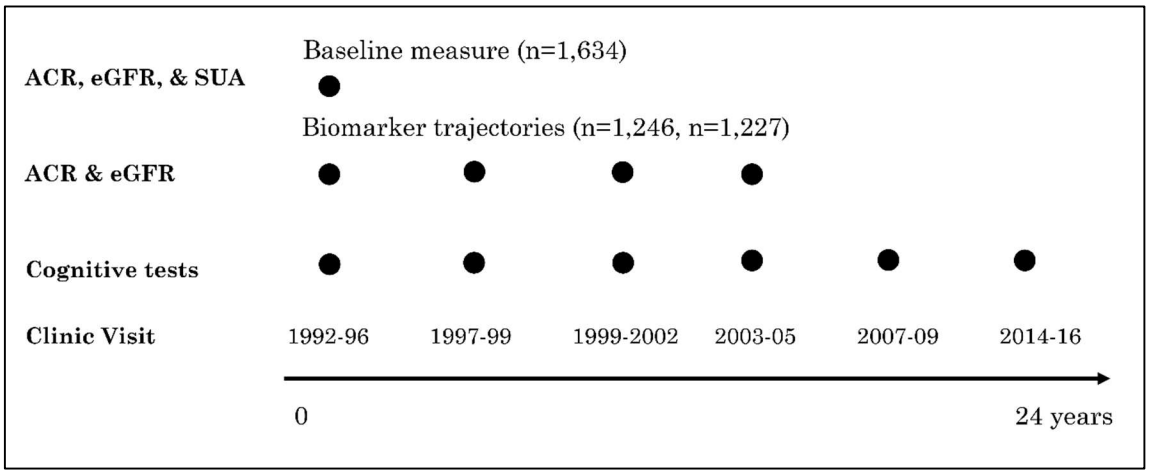

Figure 2.S1. Timeline of kidney function biomarker and cognitive performance measurements used in baseline measure only and group-based biomarker trajectory analyses. Abbreviations: ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; SUA, serum uric acid

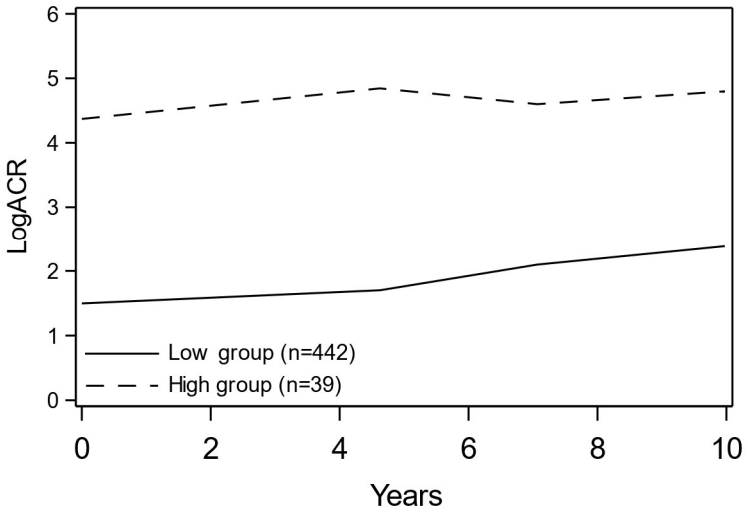

Figure 2.S2. Trajectory groups for logACR over time in men. Results of latent class mixture model analysis of repeated log ACR measurements are shown. The best fit to data was obtained with two trajectory groups. Abbreviations: ACR, albumin-creatinine ratio.

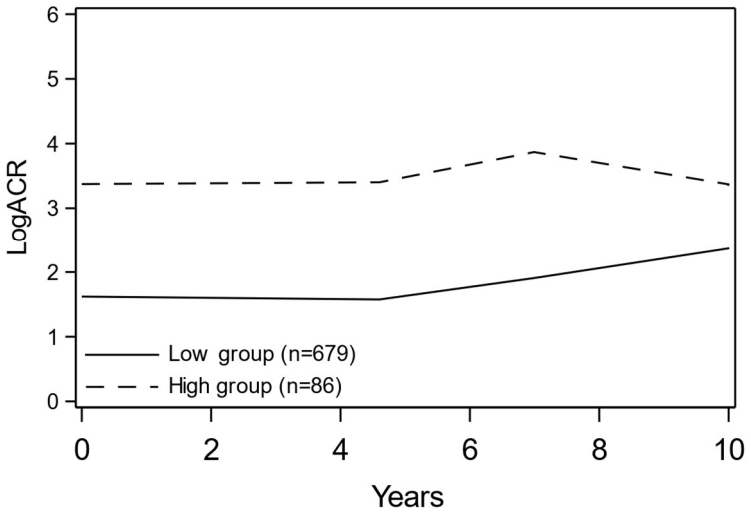

Figure 2.S3. Trajectory groups for logACR over time in women. Results of latent class mixture model analysis of repeated log ACR measurements are shown. The best fit to the data was obtained with two trajectory groups. Abbreviations: ACR, albumin-creatinine ratio.

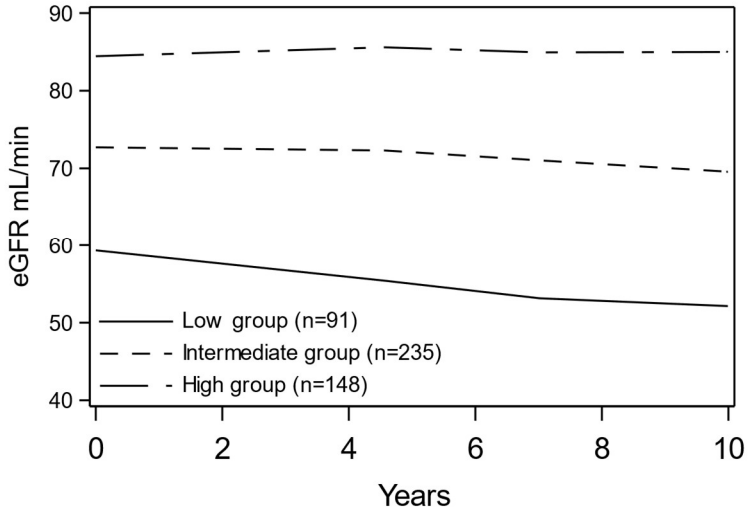

Figure 2.S4. Trajectory groups for eGFR over time in men. Results of latent class mixture model analysis of repeated eGFR measurements are shown. The best fit to the data was obtained with three trajectory groups. Abbreviations: eGFR, estimated glomerular filtration rate.

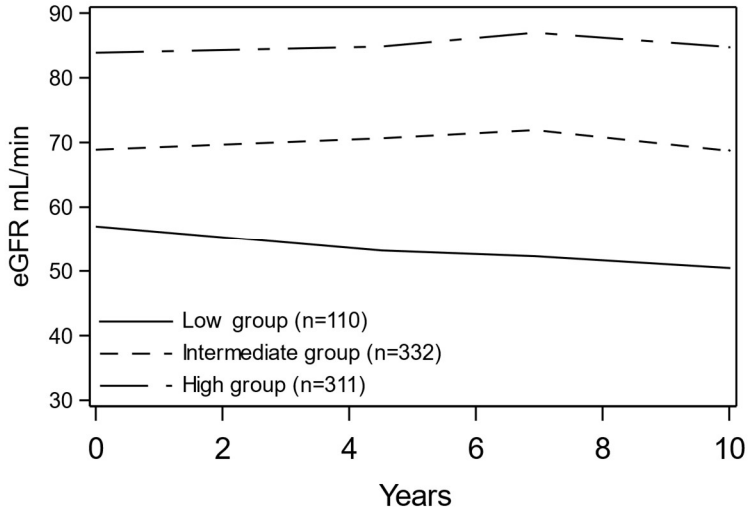

Figure 2.S5. Trajectory groups for eGFR over time in women. Results of latent class mixture model analysis of repeated eGFR measurements are shown. The best fit to the data was obtained with three trajectory groups. Abbreviations: eGFR, estimated glomerular filtration rate.

CHAPTER 3: MARKERS OF KIDNEY FUNCTION, GENETIC VARIATION AND COGNITIVE PERFORMANCE IN THE UK BIOBANK

Abstract

Background: Chronic kidney disease has been linked to worse cognition. However, this association may be dependent on the marker of kidney function used, and studies assessing modification by genetics are lacking. This study examined associations between multiple measures of kidney function and assessed effect modification by a polygenic score for cognitive ability.

Methods: In this cross-sectional study of up to 341,208 European ancestry participants from the UK Biobank study, we examined associations between albuminuria and estimated glomerular filtration rate based on creatinine (eGFRcre) or cystatin C (eGFRcys) with cognitive performance on tests of verbal-numeric reasoning, reaction time and visual memory. Interaction between kidney function markers and a polygenic risk score for general cognitive function was also assessed. Adjustment for confounding factors was performed using multivariate regression and propensity-score matching.

Results: Albuminuria was associated with worse performance on tasks of verbal-numeric reasoning (β=-0.09, $p<0.001$), reaction time (β=7.06, $p<0.001$) and visual memory (β=0.013, $p=0.01$). A polygenic score for cognitive function modified the association between albuminuria and reaction time with significantly slower reaction times in those with albuminuria and a lower polygenic score ($p<0.001$). Compared to participants with GFR≥60ml/min, those with eGFR<60ml/min had lower verbal-numeric reasoning scores and slower mean reaction times (verbal numeric reasoning β=--.11, $p<0.001$ and reaction time β=6.08, $p<0.001$ for eGFRcys<60 vs eGFRcys≥60). Associations were strongerusing cystatin C-based eGFR than creatinine-based eGFR (verbal numeric reasoning β=-0.21, $p<0.001$ and reaction time β=11.21, $p<0.001$ for eGFRcys<60 vs eGFRcys≥60).

Conclusions: Increased urine albumin is associated with worse cognition, but this may depend on low genetic risk. Cystatin C-based eGFR may serve as a better marker of cognitive performance than creatinine-based estimates.

INTRODUCTION

According to the United Nations, older individuals (ages 65 and above) comprise the fastest growing segment of the global population [1]. Older age is a significant risk factor for cognitive decline [2] and the global burden of dementia and cognitive impairment is expected to rise exponentially as a result. While cognitive decline is a natural consequence of aging, there is considerable variability in cognitive function decline with age [3]. Along with increasing age, cognition is also influenced by genetics [4,5], lifestyle factors [6,7] and chronic health conditions such as diabetes, hypertension, and kidney disease [8,9].

Chronic kidney disease (CKD) is also increasing in prevalence. The global all-age prevalence of CKD has increased by almost 30% over the past few decades [10]. Impaired kidney function is typically detected by decreased estimated glomerular filtration rate (eGFR) or by albuminuria (presence of albumin protein in the urine indicative of glomerular damage). There is a growing body of evidence supporting an association between albuminuria and decreased cognitive ability [11,12], but the relationship between eGFR and cognition has been mixed [13–15]. Of the latter studies, the majority use eGFR based serum creatinine concentrations (eGFRcre) which is highly dependent on sex, age, and muscle mass [16]. Cystatin C based eGFR (eGFRcys) has received considerably less attention in epidemiological studies, likely due to the increased cost relative to that of creatinine. However, being a ubiquitous small protein, cystatin C is less influenced by muscle mass and has been shown to be a better predictor of end-stage renal disease (ESRD) and cardiovascular events compared to creatinine [17–19]. Likewise, some studies suggest eGFRcys may be a relevant prognostic factor for worse cognition [20] and incident dementia [21], but studies that consider all three measures of kidney function

are still lacking. Moreover, the extent to which these associations are modified by genetic predictors of cognitive functions has not been sufficiently studied.

Heritability estimates of global cognitive ability range between 20–50% [5]. However, common variants identified though genome wide association analysis (GWAS) only account for a fraction of this phenotypic variation [22,23]. Some of this missing heritability may be due to effects of unmeasured gene-environment interactions. Likewise, individual cognitive differences in those with kidney disease may be influenced by the genetic propensity for cognitive impairment. We hypothesized that genetics and impaired kidney function may jointly influence susceptibility to poor cognitive performance. Here we leveraged UK Biobank data to investigate the associations between eGFRcre, eGFRcys and albuminuria with cognitive performance and evaluated potential modification by a polygenic score for global cognitive function.

METHODS

Study population

The UK Biobank (UKBB) is a National Health Service (NHS) funded prospective cohort that enrolled 502,617 participants aged 40-73 years from across the United Kingdom between 2006 and 2010. UKBB was designed and conducted with data sharing in mind, providing researchers access to genotypic and phenotypic data [24]. Details of enrollment procedures have been previously described [25]. Participants completed a detailed, computerized questionnaire at baseline that included a wide range of information pertaining to lifestyle and health characteristics. A series of cognitive function tests was administered via touchscreen at this time. Biospecimen samples were collected for the full cohort and stored for biochemical tests and genotyping. In addition, study data was linked to participants' national health records for

longitudinal follow-up. Ethical approval for UKBB data collection was received from the North-West Multi-centre Research Ethics Committee and the research was carried out in accordance with the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained for all participants. This analysis of UKBB data was conducted in compliance with the University of California San Diego Institutional Review Board.

Genotyping

The UKBB study was genotyped on the Affymetrix (now part of ThermoFisher Scientific) UK BiLEVE Axiom array (n=49,950 participants) or the similar UKBB Axiom array (n=438,427). To facilitate use of the UKBB resource by the research community, genotyping, quality control (QC) and genotype imputation were performed centrally by the primary UKBB investigators [26]. Genotype imputation is a statistical technique that leverages directly genotyped variants and a reference panel to infer ungenotyped variants. Prior to imputation, genetic data from two arrays were combined and a QC procedure performed. Post quality control, genetic data is available for 488,377 subjects on 805,426 genetic markers and 92,693,895 imputed variants. We carried out the following additional quality control and filtering steps. Individuals with the following characteristics were excluded: extreme heterozygosity or missingness (n=968), individuals with sex chromosome aneuploidy (n=651), individuals whose reported sex did not match genetically inferred sex (n=186), and individuals with high levels of cryptic relatedness (n=73). Principal components were then calculated for the remaining 486,387 participants using 1000 Genomes as the reference population [27]. We used the "aberrant" clustering package in R [28] with a lambda parameter of 8.2 to determine the European ancestry cluster. Subjects with self-report of non-British or non-European ancestry included in European ancestry cluster were excluded, resulting in, 454,488 participants with

European ancestry. To avoid inflation in test statistics due to inclusion of related individuals, we used a custom script that implements a greedy algorithm to determine the unrelated subset. Relatedness was first determined by UKBB using identity by State (IBS). The algorithm sequentially breaks related pairs to retain only unrelated individuals while preferentially maximizing the number of individuals with a user defined characteristic. In this study we chose to maximize those with available verbal-numeric reasoning scores. We excluded those with approximately second degree or closer relatedness (pi-hat =0.0625, n= 69,378 removed). After additionally excluding those who had withdrawn consent at the time of this study, pregnant women (n=119), individuals with probable type 1 diabetes (n=1670) and participants missing data on kidney function exposures or covariates included in multivariate models there remained 118,146, 340,887 and 341,208 participants for analyses with verbal-numerical reasoning, reaction time, and visual memory scores, respectively.

Kidney function markers

Blood and spot urine samples were collected and analyzed at the initial assessment (2006-2010) at a centralized laboratory. Sampling, handling, and quality control of biochemical measures have been described in detail previously [29]. Briefly, serum creatinine, urine creatinine and urine albumin were measured on a Beckman Coulter AU5800 instrument. An enzymatic, IDMS-traceable method was used to measure serum and urine creatinine. Urine albumin was quantified using an immune-turbidimetric method (Randox laboratories) with a lower limit of detection of 6.7 mg/L. Individuals with urine albumin concentrations below this limit were considered normoalbuminuric. Albuminuria was defined as a urine albumin to creatinine ratio (ACR) ≥2.5 mg/mmol for men and ACR ≥3.5 mg/mmol for women. Serum cystatin C was measured on a Siemens ADVIA 1800 instrument using an Immuno-turbidimetric

assay. Estimated GFR was calculated using creatinine (eGFRcre) or cystatin C (eGFRcys) by the CKD-EPI equation [30,31]. Individuals with ESRD (n=405) were not excluded from this analysis.

Cognitive function

Cognitive function was assessed using a battery of self-administered, computerized tests that were specifically designed for the UKBB [32]. The verbal-numeric memory, reaction time and visual memory tests were used in this analysis and are described briefly below:

Verbal-numeric reasoning: This test, labelled the 'fluid intelligence' test, was added part-way through the initial assessment period and therefore was administered to a subset (33%) of those who participated in the baseline visit (Field ID 20016). This test included 13 logic/reasoning-type questions. The score was the number of questions answered correctly within a two-minute time limit. The Cronbach alpha coefficient for this test has been reported as 0.62 [33].

Reaction time: Similar to the card game "Snap", participants were shown a series of card pairs with symbols on them and were instructed to press a large button as quickly as possible when the cards matched (Field ID 20023). The score was the mean time, in milliseconds, to press the button across all trials with a matching pair.

Visual memory: The "pairs-matching" test was used to assess episodic visual memory in the UKBB (Field ID 100030). Participants were briefly shown the positions of six card pairs and were then asked to match them from memory in as few attempts as possible. The score on this test was the number of errors made. Pairs match scores were log(+1) transformed for analyses.

Covariates

Coronary heart disease (CHD), heart failure, and stroke were determined by self-report from a nurse-administered verbal interview or by the presence of relevant inpatient diagnostic or procedural codes from the patients electronic health record prior to the time of enrollment (**table 3.S1**). Menopausal status, cancer history, hyper- and hypothyroidism were self-reported by verbal interview. Type 2 diabetes mellitus (T2DM) was based on a combination of self-report, diabetic medication use and lab values. Type 1 and type 2 diabetes were first differentiated according to an algorithm developed by Eastwood et al. [34]. Individuals identified by this algorithm and those with a random plasma glucose of 11.1mmol/l or higher or an HbA1c of 48 mmol/mol or higher were considered as having T2DM. ESRD was determined by a predefined algorithm [35]. Participants self-reported use of hormone replacement therapy, cholesterol lowering drugs or antihypertensive medications. Smoking (never, previous, current) and alcohol consumption (never, previous, current) were also determined by self-report. Body mass index was measured by trained research staff and calculated as: weight (kg)/(height $(m)^2$). Low density lipoprotein cholesterol (LDL-c) was measured using a direct homogeneous Beckman assay. Townsend socioeconomic deprivation scores were based on postcode of residence with higher scores equating to higher levels of deprivation [36]. We used years of education as a continuous variable by mapping each of the educational qualifications reported by UKBB participants to categories defined in the 1997 International Standard Classification of Education (ISCED) and imputing the number of years of schooling as described by Okbay et al. [37].

Polygenic score calculation

We derived a polygenic score for cognitive function (PRS_{COG}) based on summary statistics from a meta-analysis of GWAS for a general cognitive ability phenotype [5]. Independent SNPs (n=79) associated with cognitive ability at the p=1 x 10e-5 in the original

meta-analysis were used to construct the $PRS_{COG.}$ For each participant, PRS_{COG} was calculated as a weighted sum of the number of effect alleles multiplied by the β coefficient associated with each individual SNP using a custom script in R. Higher values indicate higher cognitive ability.

Statistical analysis

We used multivariate linear regression to assess associations between measures of renal function and cognitive test scores. Potential effect modification by the polygenic score, sex and age were assessed by adding two-way interaction terms with each of these variables and the kidney function exposure (albuminuria, eGFRcr <60, eGFRcys <60) to the model. A three-way kidney function exposure by polygenic score by sex interaction was also evaluated. Interactions with a likelihood ratio test p-value <0.05 were considered significant. Age and PRS_{COG} were treated as continuous variables in the interaction analysis. However, to illustrate potential effect modification, we divided the PRS_{COG} into low (lowest quintile), medium (quintiles 2-4) and high (highest quintile) groups. All models were adjusted for age, sex, education, physical activity, hypertension, T2DM status, BMI, antihypertensive and cholesterol lowering medications, the Townsend Deprivation Index, smoking, alcohol drinking, country of birth (UK or non-UK). To examine the effects of comorbid cardiovascular disease on these associations, we repeated these analyses with additional adjustment for coronary artery disease, stroke history and heart failure. In models testing for interaction with PRS_{COG}, we additionally adjusted for the first 10 ancestry principal components to account for subtle population structure.

As an additional approach to covariate adjustment, we carried out analyses after matching on propensity scores for each kidney function exposure. Logistic regression was used to estimate

the propensity for each kidney function exposure based on age, sex, education, physical activity, hypertension, T2DM status, BMI, antihypertensive and cholesterol lowering medications, the Townsend Deprivation Index, smoking, alcohol drinking, and country of birth (UK or non-UK). We matched exposed to unexposed individuals at a 1:2 ratio using a greedy nearest neighbor method with the MATCHIT package in R [38]. The overall quality of the matched sample was assessed by comparing the standardized mean differences of all covariates and by graphically inspecting propensity scores between groups.

Sensitivity analyses

We repeated multivariate analyses under the following conditions: 1. restricted to post-menopausal women adjusting for use of hormone replacement therapy, 2. excluding individuals with a history of stroke, 3. excluding individuals with T2DM, 4. adjusted for other measures of kidney function (i.e. associations between eGFRcys and cognitive performance were adjusted for albuminuria) 5. adjusted for triglycerides and LDL-c, and 6. models with eGFRcys were additionally adjusted for self-reported history of cancer, hyperthyroidism or hypothyroidism as these conditions can influence cystatin-C concentrations. All analyses were carried out using R in Version 3.6.1.

RESULTS

Summary characteristics of participants according to sex are displayed in **Table 3.1**. The population was 54% female and the mean age was 56.7 years. According to the criteria described in the methods, there were 17,006 (5%) individuals with albuminuria, 7,605 (2.2%) with eGFRcre<60ml/min, and 14,986 (4.4%) with eGFRcys<60ml/min. On average, participants had

a mean verbal-numeric reasoning score of 6.17 (standard deviation (SD)=2.10), a mean reaction time of 555ms (SD=113ms) , and a median of 4.11 (IQR=3.26) incorrect answers on the visual memory task. Participant characteristics by each kidney function exposure are shown in supplementary **Tables 3.S2-3.S4.** The proportion of individuals with eGFRcre<60, eGFRcys<60 and albuminuria according to the age tertile of the full study population is shown in **Figure 3.S1.**

Albuminuria and cognitive function

Beta estimates and 95% confidence intervals for the association between kidney function biomarkers and cognitive test performance among all available subjects and propensity score matched subsets are reported in F**igure 3.1**. In multivariate analyses using all available data, albuminuria was significantly associated with lower verbal reasoning scores (β= -0.09, 95% CI: -0.14 to -0.04), slower reaction time (β= 7.06, 95% CI: 5.42 to 8.69) and more visual memory errors (β= 0.013, 95% CI: 0.003 to 0.023). Regression analysis in matched subsets revealed similar results, though the magnitude of the association between albuminuria and visual memory was slightly larger (β= 0.018, 95% CI: 0.006 to 0.029). Results of multivariate analysis in all available subjects overall and stratified by sex are shown in **supplementary Table 3.S5.** We found no significant interactions with sex or age. Beta estimates for verbal-numeric reasoning and visual memory were essentially unchanged after adjustment for cardiovascular disease factors **(Table 3.S6).** However, the association between albuminuria and reaction time was slightly attenuated (β= 5.54, 95% CI: 3.03 to 8.05).

eGFRcre and cognitive function

In the multivariate analyses using all available subjects, we found significant associations between eGFRcre category and both verbal-numeric reasoning and reaction time scores (**Figure 3.1, Table 3.S5**). However, there was no significant difference in verbal-numeric reasoning score

according to eGFRcre category in matched analysis. We detected a significant sex interaction whereby eGFRcre was associated with verbal-numeric memory in men (β(95%CI)= -0.18(-0.29 to -0.07)) but not in women (β(95%CI)= -0.05 (-0.15 to 0.05), p for interaction=0.01). Associations were slightly attenuated but remained significant after adjustment for cardiovascular disease factors (**Table 3.S6**). There was no significant association between eGFRcre<60 and visual memory score. Associations were not modified by age.

eGFRcys and cognitive function

Participants with eGFRcys<60 performed significantly worse on verbal-numeric reasoning and reaction time tests in analyses including all available subjects (β(95%CI)= -0.21(-0.27 to -0.16) and 11.21 (9.44 to 12.99), respectively, **Figure 3.1; Table 3.S5**). Matched analyses revealed similar results. There was a significant interaction between eGFRcys category and age for reaction time (p for interaction = 0.004). To illustrate this interaction, participants were categorized as younger than the median age of 58 years or as 58 years or older. As shown in **Figure 3.S2**, reaction time was significantly slower with eGFRcys <60 in both older and younger age groups, however the association was strongest in younger individuals (β(95%CI)= -8.01(-12.7 to -3.35) for those < 58 years vs ≥58years). The association between eGFRcys<60 and verbal-numeric memory was slightly stronger in men (β(95%CI)= -0.25(-0.33 to -0.16) in men vs β(95%CI)= -0.18 (-0.25 to 0.11) in women, p for interaction=0.09).

Kidney function by PRS_{COG} interaction

PRS_{COG} was significantly associated with verbal-numeric reasoning (β (95%CI) for highest vs lowest quintile of PRS_{COG}=0.18(1.14 to 0.21), p-value <0.001), reaction time (β(95%CI)= -2.17(-3.22 to -1.02), p-value<0.001) and visual memory (β(95%CI)=-0.007 (-0.013

to -0.001), p-value=0.02). Significant interaction effects were observed between albuminuria and PRS_{COG} for reaction time (p-value<0.001). Associations between albuminuria and reaction time were stronger among individuals with a lower polygenic risk score for cognitive function (**Figure 3.2**). This association was not modified by sex or age. We did not detect any modification by PRS_{COG} for other associations between kidney function exposures and cognitive test performance. Findings were not modified by age or sex.

Sensitivity analysis

After excluding individuals with diabetes or past stroke, effect estimates for associations between all kidney function measures and reaction time were slightly attenuated but remained significant (**Tables 3.S7 and 3.S8**). In contrast, the association between albuminuria and visual memory were attenuated to the null. Results were consistent after adjustment for orthogonal measures of kidney function, LDL-c and triglycerides. Regression estimates for associations in women were similar with and without restriction to postmenopausal status and after adjustment for hormone replacement therapy. Associations between eGFRcys and cognitive ability were essentially unchanged after adjustment for self-reported history of cancer, hyperthyroidism or hypothyroidism.

DISCUSSION

In this study including between 118,146 and 341,208 participants of the UKBB, markers of poor kidney function were associated with worse performance across multiple domains of cognitive function. Individuals with albuminuria scored worse on all tested measures cognitive function including verbal-numeric reasoning, reaction time and visual memory. We observed a potential PRS by environment interaction where participants with both albuminuria and a low polygenic score for cognitive function had the slowest reaction times. Performance on the

reaction time test was worse in male participants with eGFRcre<60, as was performance on the verbal-numeric reasoning test. eGFRcys was more strongly associated with cognitive ability than eGFRcre based on serum creatinine.

Our finding that albuminuria is associated with reduced cognitive performance is in agreement with prior studies [11,12,39,40]. While the mechanism of this association is unclear, it may be related to increased vascular burden affecting both the kidney and the brain. Albuminuria is an early marker of generalized microvascular dysfunction [41] and has a linear relationship with cardiovascular disease risk [42]. In addition, albuminuria is associated with vascular dementia [43], stroke and subclinical cerebrovascular disease including white matter hyperintensities, microbleeds and enlarged perivascular spaces [43,44]. We observed persistent significant associations between albuminuria and cognitive function after adjustment for cardiovascular disease, suggesting that pathological mechanisms may be independent of overt cardiovascular disease. While these results support the hypothesis that this association is the result of concurrent microvascular pathology in the kidney and the brain, further research is needed to clarify the relationship between the kidney damage marked by albuminuria and risk of cognitive decline.

Chronic kidney disease defined by creatinine-based eGFR has been linked with decreased cognitive ability, but the association has not been consistent [39,45–48]. In this study, we found significant differences between eGFRcre category and cognitive performance. However, prior studies with smaller sample sizes may have had limited power to detect statistically significant associations despite comparable effect estimates. The reason for the observed sex difference with regards to eGFRcre and verbal-numeric reasoning is unclear. In cross-sectional analysis, Cornelis et al. found greater age-related decreases in verbal numerical reasoning scores in men

compared to women after covariate adjustment and attributed this to cohort effects [49]. This may obscure an association in older women who would be more likely to have lower eGFRcre but may have smaller age-related decreases in cognitive function compared to men in the same age group.

Cystatin C has received considerably less attention than creatinine in regard to cognitive health [13]. This study supports past research which suggests that serum cystatin C and eGFRcys may be more strongly associated with cognitive performance compared to creatinine-based measurements [20,50]. Cystatin C-based GFR has also been shown to be a stronger predictor of cardiovascular disease outcomes [17,18,51] which may mediate this association. Associations were essentially unchanged after controlling for existing cardiovascular disease in this study. This does not preclude a potential role of subclinical cardiovascular disease. On the other hand, reduced kidney function may also have direct neurodegenerative effects through inflammatory processes and accumulation of uremic toxins [52,53]. This may be particularly relevant here as cystatin C has been related to systemic inflammation [54].

Interestingly, associations between eGFRcys category and reaction time were somewhat attenuated in older individulas. Similar age effects have been seen in observational studies examining associations between eGFRcre and mortality and ESRD [55,56]. In older participants, the moderate-to-mild declines in kidney function observed here may have a proportionately smaller influence on cognitive function relative to other age-related comorbidities. It should also be noted that this observation may in part be due to a selection bias in which healthier older adults chose to participate in the UKBB study.

To our knowledge, there has only been one previous study that explored gene by environment interaction in the context of kidney function and cognitive performance [57]. Shin

et al. found significant interaction between microalbuminuria and the *APOE* e4 allele in a Korean population, where albuminuria was more strongly associated with poor cognitive performance in *APOE* e4 carriers vs. noncarriers. Although polymorphisms in the *APOE* gene are included in the polygenic risk score used here, we did not directly assess interaction with *APOE* e4. Taken together, the current study and that of Shin et al. suggest that a genetic susceptibility to poor cognitive performance and the presence of albuminuria may have synergistic adverse effects on brain function. Whether the current association is mediated by gene variants that further exacerbate the risk of microvascular dysfunction related to albuminuria is topic for further study. Albuminuria has both genetic and environmental components [58]. The environmental component can be targeted for intervention to reduce cognitive risk. Similarly, stratification based on polygenic scores may allow clinicians to better target individuals for more aggressive treatment and intervention strategies.

Due to the unique nature of the UK Biobank cognitive tests, the clinical significance of our findings is not clear. Based on cross-sectional age coefficients, differences in reaction time with eGFRcre<60, eGFRcys<60 and albuminuria are comparable to an additional 1.5, 2.7, and 1.7 years of age, respectively. A similar comparison would not be appropriate to interpret the verbal-numerical reasoning scores due to cohort effects, however differences in verbal-numeric reasoning with eGFRcre<60, eGFRcys<60 and albuminuria are comparable to 0.8, 1.6, and 0.9 fewer years of education, respectively.

There are several strengths to our study. The large size of the study population allowed us to examine gene by environment interaction which typically requires considerable sample size. We leveraged an alternate control selection approach to account for potential unmeasured confounding through propensity-score matching without extensive loss of information due to

inadequate matching which may occur in smaller samples. In addition, the extensive biochemical data allowed comparison of multiple measures of kidney function within one cohort.

Some limitations of our study should also be noted. Our analysis was restricted to participants of European ancestry which may limit generalizability to other ethnic groups. Additionally, given the voluntary nature of UKBB recruitment, the participants were generally healthier with higher socioeconomic levels than the general population [59]. It follows that the prevalence of CKD may also be comparatively lower in the UKBB Biobank population. However, the large overall sample size allowed for identification of an adequate number of individuals with kidney disease to characterize associations that may be applicable to broader populations. The cognitive tests in the UKBB were developed to be administered on a large scale and without supervision and may therefore not be sensitive to cognitive differences. However, the tests used here have been shown to have substantial correlation with previously validated tests in an independent sample of individuals [60]. Finally, this was a cross-sectional study limiting our ability to draw causal inferences. Longitudinal follow-up is required to better elucidate the temporal associations between kidney function, potential mediators such as cardiovascular disease and subsequent cognitive impairment.

CONCLUSION

In summary, this study confirms prior associations between reduced kidney function and reduced cognitive ability. We also show that the association between albuminuria and reaction time may be modified by genetic risk, but results need to be replicated in independent cohorts. Cognitive performance was inversely associated with eGFR, and associations appeared stronger when GFR was estimated based on cystatin C rather than creatinine.

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Table 3.1. Characteristics of study population overall and according to sex

	All Participants	Female	Male
	n=341,208	n=183,822	n=157,386
Age (years)	56.69 (8.01)	56.50 (7.91)	56.91 (8.11)
Smoking status			
Current	34,882 (10.2)	16,086 (8.8)	18,796 (11.9)
Never	184,846 (54.2)	108,045 (58.8)	76,801 (48.8)
Past	121,480 (35.6)	59,691 (32.5)	61,789 (39.3)
Some university education	193,791 (56.8)	100,608 (54.7)	93,183 (59.2)
Alcohol drinking status			
Current	319,390 (93.6)	169,577 (92.3)	149,813 (95.2)
Never	10,307 (3.0)	7,725 (4.2)	2,582 (1.6)
Past	11,511 (3.4)	6,520 (3.5)	4,991 (3.2)
Body mass index (kg/m^2)	27.34 (4.73)	26.94 (5.11)	27.80 (4.20)
LDL-c (mmol/L)	3.57 (0.87)	3.64 (0.87)	3.49 (0.86)
Triglycerides (mmol/L)	1.75 (1.02)	1.55 (0.85)	1.98 (1.14)
Hypertension	188,082 (55.1)	88,941 (48.4)	99,141 (63.0)
Type II diabetes	16,596 (4.9)	6004 (3.3)	10,592 (6.7)
Coronary artery disease	12,044 (3.5)	2569 (1.4)	9,475 (6.0)
History of stroke	5,489 (1.6)	2264 (1.2)	3,225 (2.0)
Heart failure	947 (0.3)	231 (0.1)	716 (0.5)
Cholesterol-lowering medication	57,130 (16.7)	22,065 (12.0)	35,065 (22.3)
Antihypertensive medication	68,615 (20.1)	30,859 (16.8)	37,756 (24.0)
Hormone replacement therapy	NA	13,325 (7.5)	NA
Albuminuria	17,006 (5.0)	6,886 (3.7)	10,120 (6.4)
eGFRcre<60 ml/min	7,605 (2.2)	4,071 (2.2)	3,534 (2.2)
eGFRcys<60 ml/min	14,986 (4.4)	7,882 (4.3)	7,104 (4.5)
Verbal-numeric reasoning score	6.17 (2.10)	6.07 (2.03)	6.32 (2.18)
Reaction time (ms)	555.14 (113.15)	563.14 (113.51)	545.80 (112.01)
Visual memory score	4.11 (3.26)	4.11 (3.18)	4.10 (3.35)

Abbreviations: eGFRcre, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; LDL-C, LDL-cholesterolValues are shown as n (%) for categorical variables and mean (SD) for continuous variables. Albuminuria was defined as a urine albumin to creatinine ratio (ACR) ≥2.5 mg/mmol for men and ACR ≥3.5 mg/mmol for womenAll characteristics are significantly different by sex except eGFRcre<60ml/min (p-value=0.55)

Verbal-numeric reasoning	Total n	β (95%CI)	β (95%CI)	p-value
Albuminuria				
All data	118,146		-0.09 (-0.14 to -0.04)	<0.001
Matched data	12,254		-0.08 (-0.14 to -0.01)	0.02
eGFRcr < 60ml/min				
All data	118,146		-0.11 (-0.18 to -0.03)	0.01
Matched data	5,334		-0.06 (-0.16 to 0.03)	0.19
eGFRcys < 60ml/min				
All data	118,146		-0.21 (-0.27 to -0.16)	<0.001
Matched data	10,180		-0.15 (-0.22 to -0.09)	<0.001

Reaction time	Total n	β (95%CI)	β (95%CI)	p-value
Albuminuria				
All data	340,887		7.06 (5.42 to 8.69)	<0.001
Matched data	33,992		7.23 (5.18 to 9.27)	<0.001
eGFRcr < 60ml/min				
All data	340,887		6.08 (3.66 to 8.49)	<0.001
Matched data	15,206		5.71 (2.46 to 8.95)	<0.001
eGFRcys < 60ml/min				
All data	340,887		11.21 (9.44 to 12.99)	<0.001
Matched data	29,948		10.67 (8.37 to 12.98)	<0.001

Visual memory	Total n	β (95%CI)	β (95%CI)	p-value
Albuminuria				
All data	341,208		0.013 (0.003 to 0.023)	0.01
Matched data	34,012		0.018 (0.006 to 0.029)	0.002
eGFRcre < 60ml/min				
All data	341,208		-0.005 (-0.02 to 0.009)	0.47
Matched data	15,210		-0.011 (-0.028 to 0.006)	0.21
eGFRcys < 60ml/min				
All data	341,208		-0.002 (-0.013 to 0.008)	0.71
Matched data	29,972		0.001 (-0.011 to 0.013)	0.85

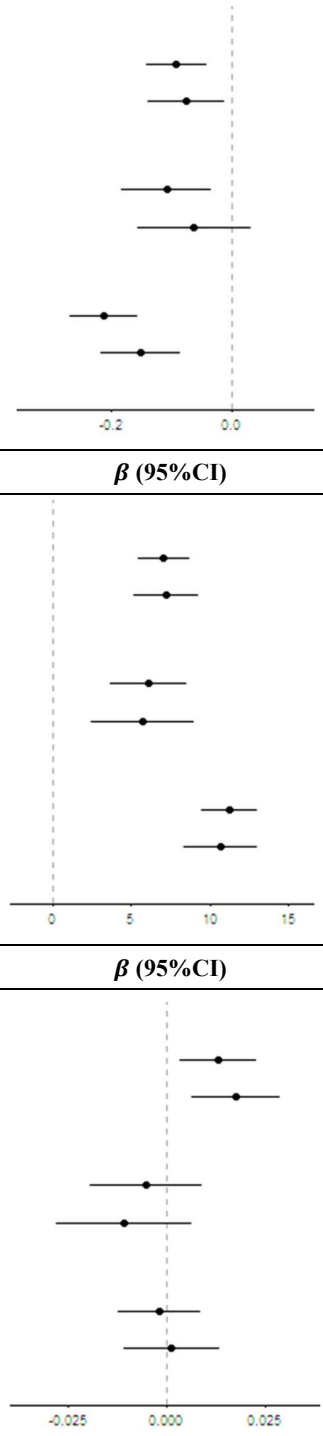

Figure 3.1. Adjusted beta estimates and 95% confidence intervals for association between kidney function exposures and cognitive performance. Models using all data were adjusted for age, sex, education, Townsend deprivation index, country of birth, physical activity, hypertension, diabetes, alcohol use, smoking, body mass index, lipid lowering and antihypertensive drugs. Matched data based on 1:2 propensity score matching was based on the same covariate set as models using all data. Albuminuria was defined as ACR≥2.5mg/mmol for men and ACR ≥3.5mg/mmol for women. Abbreviations: eGFRcre, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate.

Table 3.S1. Cardiovascular disease variable definitions

Variable	**Definition**
Coronary heart disease (CHD)	Self-report of myocardial infarction (MI), coronary artery bypass grafting, coronary artery angioplasty or triple heart bypass from nurse-administered verbal interview or Hospitalization for ICD-10 codes: (I21.0-21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0-23.6, I23.8) or ICD-9 codes: (410-412.9, 414) or Hospitalization for OPCS-4 coded procedure: (K40-K46, K49-K50, and K75)
Stroke	Stroke history was centrally adjudicated by UK Biobank as self-report of stroke from nurse-administered verbal interview or hospitalization for ICD-10 codes: (I60-64) or ICD-9 codes: (430, 431, 434, 436) *(http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=462)*
Heart failure	Self-report of heart failure from nurse-administered verbal interview or Hospitalization for ICD-10 codes: (I50, I110, I130, I132) or ICD-9 codes: (428.0, 428.9)

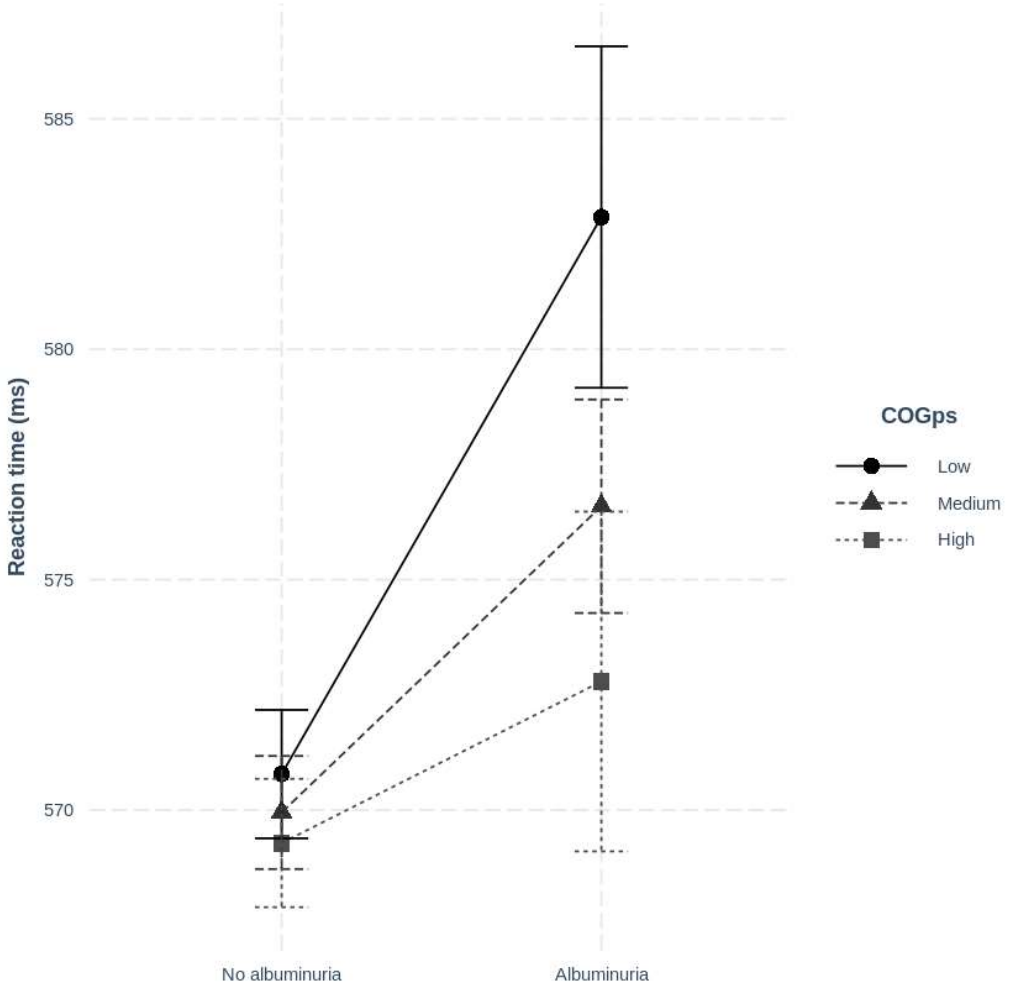

Figure 3.2. Predicted mean reaction time and 95% confidence intervals using albuminuria status as a predictor grouped by cognitive function polygenic score category. Higher scores represent worse performance. Abbreviations: PRS_{COG}, cognitive function polygenic score

Table 3.S2. Characteristics of study population according to albuminuria status: the UK Biobank

	Albuminuria	**No albuminuria**
	n=17,006	n=324,202
Age (years)	58.98 (7.74)	56.57 (8.00)
Male	10,120 (59.5)	147,266 (45.4)
Smoking status		
Current	2,360 (13.9)	32,522 (10.0)
Never	7,759 (45.6)	177,087 (54.6)
Past	6,887 (40.5)	114,593 (35.3)
Some university education	8,790 (51.7)	185,001 (57.1)
Alcohol drinking status		
Current	15,671 (92.1)	303,719 (93.7)
Never	568 (3.3)	9,739 (3.0)
Past	767 (4.5)	10,744 (3.3)
Body mass index (kg/m^2)	28.83 (5.68)	27.26 (4.66)
LDL-c (mmol/L)	3.43 (0.93)	3.58 (0.86)
Triglycerides (mmol/L)	2.03 (1.25)	1.73 (1.00)
Hypertension	13,468 (79.2)	174,614 (53.9)
Type II diabetes	2,835 (16.7)	13,761 (4.2)
Coronary artery disease	1,290 (7.6)	10,754 (3.3)
History of stroke	611 (3.6)	4,878 (1.5)
Heart failure	153 (0.9)	794 (0.2)
Cholesterol-lowering medication	5,630 (33.1)	51,500 (15.9)
Antihypertensive medication	7,132 (41.9)	61,483 (19.0)

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterolValues are shown as n (%) for categorical variables and mean (SD) for continuous variables. Albuminuria was defined as a urine albumin to creatinine ratio (ACR) ≥2.5mg/mmol for men and ACR ≥3.5mg/mmol for women. All characteristics are significantly different by albuminuria status

Table 3.S3. Characteristics of study population according to eGFRcre category: the UK Biobank

	eGFRcre <60 ml/min	**eGFRcre ≥60 ml/min**
	n=7,605	n=333,603
Age (years)	62.79 (5.76)	56.55 (8.00)
Male	3,534 (46.5)	153,852 (46.1)
Smoking status		
Current	599 (7.9)	34,283 (10.3)
Never	3,665 (48.2)	181,181 (54.3)
Past	3,341 (43.9)	118,139 (35.4)
Some university education	3,558 (46.8)	190,233 (57.0)
Alcohol drinking status		
Current	6,783 (89.2)	312,607 (93.7)
Never	419 (5.5)	9,888 (3.0)
Past	403 (5.3)	11,108 (3.3)
Body mass index (kg/m^2)	29.10 (5.23)	27.30 (4.71)
LDL-c (mmol/L)	3.32 (0.95)	3.58 (0.86)
Triglycerides (mmol/L)	2.04 (1.09)	1.74 (1.02)
Hypertension	5,895 (77.5)	182,187 (54.6)
Type II diabetes	1,002 (13.2)	15,594 (4.7)
Coronary artery disease	912 (12.0)	11,132 (3.3)
History of stroke	397 (5.2)	5,092 (1.5)
Heart failure	159 (2.1)	788 (0.2)
Cholesterol-lowering medication	3,249 (42.7)	53,881 (16.2)
Antihypertensive medication	4,080 (53.7)	64,535 (19.3)

Abbreviations: eGFR, estimated glomerular filtration rate; LDL-C, LDL-cholesterolValues are shown as n (%) for categorical variables and mean (SD) for continuous variablesAll characteristics are significantly different by eGFRcre category except sex (p-value=0.55)

Table 3.S4. Characteristics of study population according to eGFRcys category: the UK Biobank

	eGFRcys<60 ml/min	**eGFRcys ≥60 ml/min**
	n=14,986	n=326,222
Age (years)	63.21 (5.28)	56.39 (7.98)
Male	7,104 (47.4)	150,282 (46.1)
Smoking status		
Current	2,466 (16.5)	32,416 (9.9)
Never	6,356 (42.4)	178,490 (54.7)
Past	6,164 (41.1)	115,316 (35.3)
Some university education	6,163 (41.1)	187,628 (57.5)
Alcohol drinking status		
Current	12,912 (86.2)	306,478 (93.9)
Never	1,011 (6.7)	9,296 (2.8)
Past	1,063 (7.1)	10,448 (3.2)
Body mass index (kg/m^2)	30.62 (5.97)	27.19 (4.61)
LDL-c (mmol/L)	3.37 (0.96)	3.58 (0.86)
Triglycerides (mmol/L)	2.12 (1.11)	1.73 (1.01)
Hypertension	12,012 (80.2)	176,070 (54.0)
Type II diabetes	2,224 (14.8)	14,372 (4.4)
Coronary artery disease	1,735 (11.6)	10,309 (3.2)
History of stroke	789 (5.3)	4,700 (1.4)
Heart failure	269 (1.8)	678 (0.2)
Cholesterol-lowering medication	5,955 (39.7)	51,175 (15.7)
Antihypertensive medication	8,105 (54.1)	60,510 (18.5)

Abbreviations: eGFR, estimated glomerular filtration rate; LDL-c, LDL-cholesterol. Values are shown as n (%) for categorical variables and mean (SD) for continuous variablesAll characteristics are significantly different by eGFRcys category

Table 3.S5. Multivariable linear regression analyses of association between kidney marker exposure categories and cognitive performance

	Verbal-numeric memory		Reaction time		Visual memory	
	β **(95%CI)**	**p-value**	***β*** **(95%CI)**	**p-value**	***β*** **(95%CI)**	**p-value**
Albuminuria						
All	-0.09 (-0.14 to -0.04)	<0.001	7.06 (5.42 to 8.69)	<0.001	0.013 (0.003 to 0.023)	0.01
Women	-0.08 (-0.15 to -0.01)	0.03	5.32 (2.79 to 7.85)	<0.001	0.014 (-0.001 to 0.029)	0.06
Men	-0.08 (-0.15 to -0.02)	0.02	8.75 (6.62 to 10.89)	<0.001	0.012 (-0.001 to 0.025)	0.07
p-interaction[a]		0.52		0.29		0.89
eGFRcr < 60ml/min						
All	-0.11 (-0.18 to -0.03)	<0.001	6.08 (3.66 to 8.49)	<0.001	-0.005 (-0.02 to 0.009)	0.47
Women	-0.05 (-0.15 to 0.05)	0.32	4.67 (1.36 to 7.98)	0.005	-0.011 (-0.031 to 0.008)	0.25
Men	-0.18 (-0.29 to -0.07)	0.002	7.79 (4.26 to 11.33)	<0.001	0.002 (-0.019 to 0.023)	0.86
p-interaction[a]		0.01		0.69		0.20
eGFRcys < 60ml/min						
All	-0.21 (-0.27 to -0.16)	<0.001	11.21 (9.44 to 12.99)	<0.001	-0.002 (-0.013 to 0.008)	0.71
Women	-0.18 (-0.25 to -0.11)	<0.001	11.29 (8.84 to 13.75)	<0.001	-0.001 (-0.015 to 0.014)	0.92
Men	-0.25 (-0.33 to -0.16)	<0.001	11.15 (8.58 to 13.72)	<0.001	-0.004 (-0.019 to 0.012)	0.65
p-interaction[a]		0.09		0.31		0.82

Models adjusted for age, sex, education, Townsend deprivation index, country of birth, physical activity, hypertension, diabetes status, alcohol use, smoking status, body mass index, lipid lowering drugs, and antihypertensive drugs. Abbreviations: eGFRcre, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate. [a]p-value for marker by sex interaction.

Table 3.S6. Multivariable linear regression analyses of association between kidney marker exposure categories and cognitive performance adjusted for cardiovascular disease

	Verbal-numeric memory		Reaction time		Visual memory	
	β **(95%CI)**	**p-value**	***β*** **(95%CI)**	**p-value**	***β*** **(95%CI)**	**p-value**
Albuminuria						
All	-0.09 (-0.14 to -0.04)	<0.001	5.54 (3.03 to 8.05)	<0.001	0.013 (0.004 to 0.023)	0.01
Women	-0.08 (-0.15 to 0.004)	0.04	4.99 (2.46 to 7.52)	<0.001	0.014 (-0.001 to 0.029)	0.06
Men	-0.08 (-0.15 to -0.01)	0.02	8.27 (6.14 to 10.40)	<0.001	0.012 (-0.001 to 0.025)	0.07
p-interaction[a]		0.61		0.27		0.90
eGFRcr < 60ml/min						
All	-0.09 (-0.16 to -0.01)	0.02	5.03 (1.75 to 8.31)	0.003	-0.005 (-0.020 to 0.009)	0.47
Women	-0.04 (-0.13 to 0.06)	0.50	3.73 (0.42 to 7.04)	0.03	-0.012 (-0.031 to 0.007)	0.22
Men	-0.15 (-0.26 to -0.04)	0.008	5.83 (2.29 to 9.37)	0.001	0.002 (-0.019 to 0.024)	0.83
p-interaction[a]		0.03		0.08		0.82
eGFRcys < 60ml/min						
All	-0.20 (-0.25 to -0.14)	<0.001	11.52 (9.1 to 13.93)	<0.001	-0.002 (-0.013 to 0.008)	0.69
Women	-0.17 (-0.25 to -0.1)	<0.001	10.46 (8.0 to 12.92)	<0.001	-0.001 (-0.016 to 0.013)	0.85
Men	-0.23 (-0.31 to -0.15)	<0.001	9.50 (6.92 to 12.08)	<0.001	-0.003 (-0.019 to 0.012)	0.68
p-interaction[a]		0.08		0.81		0.20

Models adjusted for age, sex, education, Townsend deprivation index, country of birth, physical activity, hypertension, diabetes status, alcohol use, smoking status, body mass index, lipid lowering drugs, antihypertensive drugs, coronary artery disease, stroke and heart failure. Abbreviations: eGFRcre, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate. [a]p-value for marker by sex interaction.

Table 3.S7. Multivariable linear regression analyses of association between kidney marker exposure categories and cognitive performance excluding those with type II diabetes

	Verbal-numeric memory		Reaction time		Visual memory	
	β (95%CI)	**p-value**	**β (95%CI)**	**p-value**	**β (95%CI)**	**p-value**
Albuminuria						
All	-0.11 (-0.16 to -0.05)	<0.001	5.89 (4.13 to 7.65)	<0.001	0.010 (-0.001 to 0.02)	0.07
Women	-0.10 (-0.17 to -0.02)	0.01	4.15 (1.51 to 6.79)	<0.001	0.011 (-0.005 to 0.026)	0.17
Men	-0.10 (-0.17 to -0.02)	0.01	7.76 (5.4 to 10.11)	<0.001	0.008 (-0.007 to 0.022)	0.29
p-interaction[a]		0.64		0.13		0.88
eGFRcr < 60ml/min						
All	-0.11 (-0.19 to -0.03)	0.007	5.54 (2.96 to 8.11)	<0.001	-0.006 (-0.021 to 0.01)	0.46
Women	-0.05 (-0.16 to 0.05)	0.30	4.07 (0.61 to 7.53)	0.02	-0.015 (-0.035 to 0.005)	0.14
Men	-0.18 (-0.3 to -0.06)	0.003	7.53 (3.68 to 11.39)	0.001	0.006 (-0.017 to 0.03)	0.61
p-interaction[a]		0.02		0.80		0.09
eGFRcys < 60ml/min						
All	-0.21 (-0.27 to -0.15)	<0.001	10.45 (8.54 to 12.35)	<0.001	-0.003 (-0.014 to 0.009)	0.65
Women	-0.19 (-0.27 to -0.11)	<0.001	10.8 (8.21 to 13.40)	<0.001	-0.003 (-0.018 to 0.012)	0.74
Men	-0.23 (-0.32 to -0.14)	<0.001	10.08 (7.27 to 12.88)	<0.001	-0.003 (-0.02 to 0.014)	0.76
p-interaction[a]		0.07		0.07		0.60

Models adjusted for age, sex, education, Townsend deprivation index, country of birth, physical activity, hypertension, alcohol use, smoking status, body mass index, lipid lowering drugs, and antihypertensive drugs. Abbreviations: eGFRcre, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate. [a]p-value for marker by sex interaction.

Table 3.S8. Multivariable linear regression analyses of association between kidney marker exposure categories and cognitive performance excluding those with past stroke

	Verbal-numeric memory		Reaction time		Visual memory	
	β (95%CI)	**p-value**	**β (95%CI)**	**p-value**	**β (95%CI)**	**p-value**
Albuminuria						
All	-0.08 (-0.13 to -0.03)	<0.001	6.41 (4.77 to 8.06)	<0.001	0.008 (-0.002 to 0.019)	0.13
Women	-0.08 (-0.15 to -0.001)	0.05	4.42 (1.88 to 6.97)	0.01	0.009 (-0.006 to 0.025)	0.23
Men	-0.08 (-0.14 to -0.01)	0.03	8.35 (6.2 to 10.51)	<0.001	0.006 (-0.008 to 0.021)	0.39
p-interaction[a]		0.56		0.12		0.86
eGFRcr < 60ml/min					-0.002 (-0.023 to 0.019)	
All	-0.1 (-0.18 to -0.02)	0.01	4.91 (2.45 to 7.37)	<0.001	-0.006 (-0.022 to 0.01)	0.46
Women	-0.04 (-0.14 to 0.06)	0.40	4.12 (0.78 to 7.46)	0.04	-0.013 (-0.034 to 0.007)	0.19
Men	-0.17 (-0.29 to -0.05)	0.004	5.95 (2.31 to 9.58)	0.004	0.004 (-0.02 to 0.029)	0.73
p-interaction[a]		0.01		0.85		0.14
eGFRcys < 60ml/min						
All	-0.20 (-0.25 to -0.14)	<0.001	9.98 (8.17 to 11.79)	<0.001	-0.004 (-0.015 to 0.008)	0.51
Women	-0.18 (-0.26 to -0.1)	<0.001	10.60 (8.11 to 13.08)	<0.001	-0.004 (-0.019 to 0.012)	0.62
Men	-0.22 (-0.3 to -0.13)	<0.001	9.27 (6.64 to 11.91)	<0.001	-0.004 (-0.021 to 0.014)	0.66
p-interaction[a]		0.08		0.08		0.60

Models adjusted for age, sex, education, Townsend deprivation index, country of birth, physical activity, hypertension, diabetes status, alcohol use, smoking status, body mass index, lipid lowering drugs, and antihypertensive drugs. Abbreviations: eGFRcre, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate. [a]p-value for marker by sex interaction.

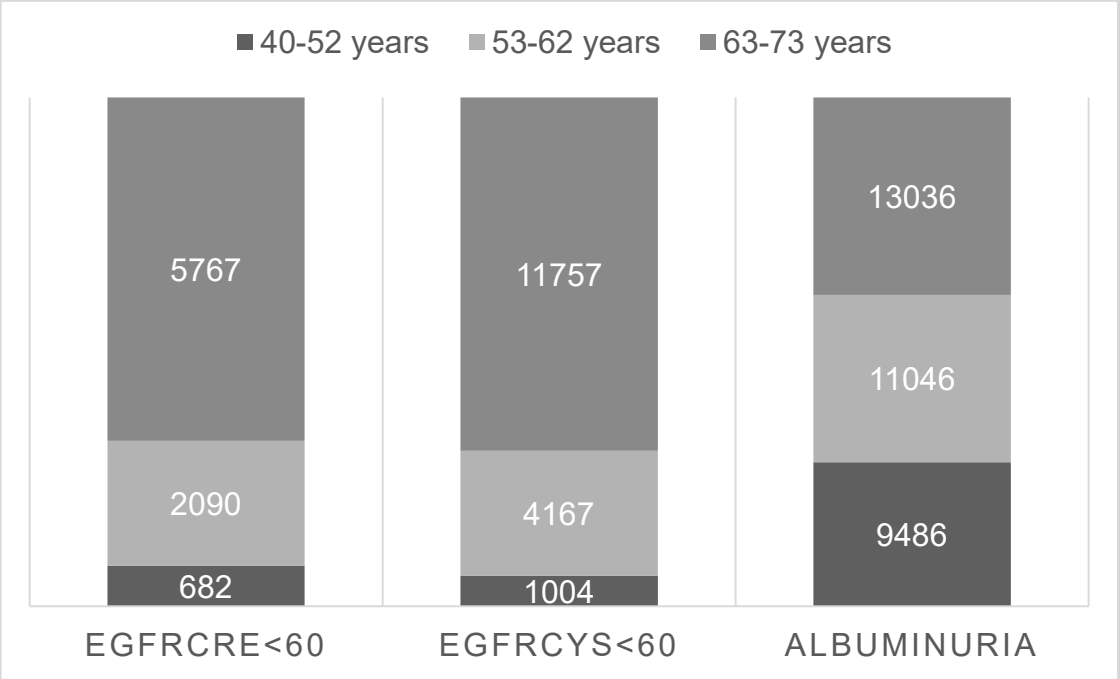

Figure 3.S1. 100% bar chart illustrating the distribution of age tertiles by kidney function marker. Age groups correspond to age tertiles of total study population. Values represent the number of individuals from each specific age tertile that fit the criteria for each kidney function marker.

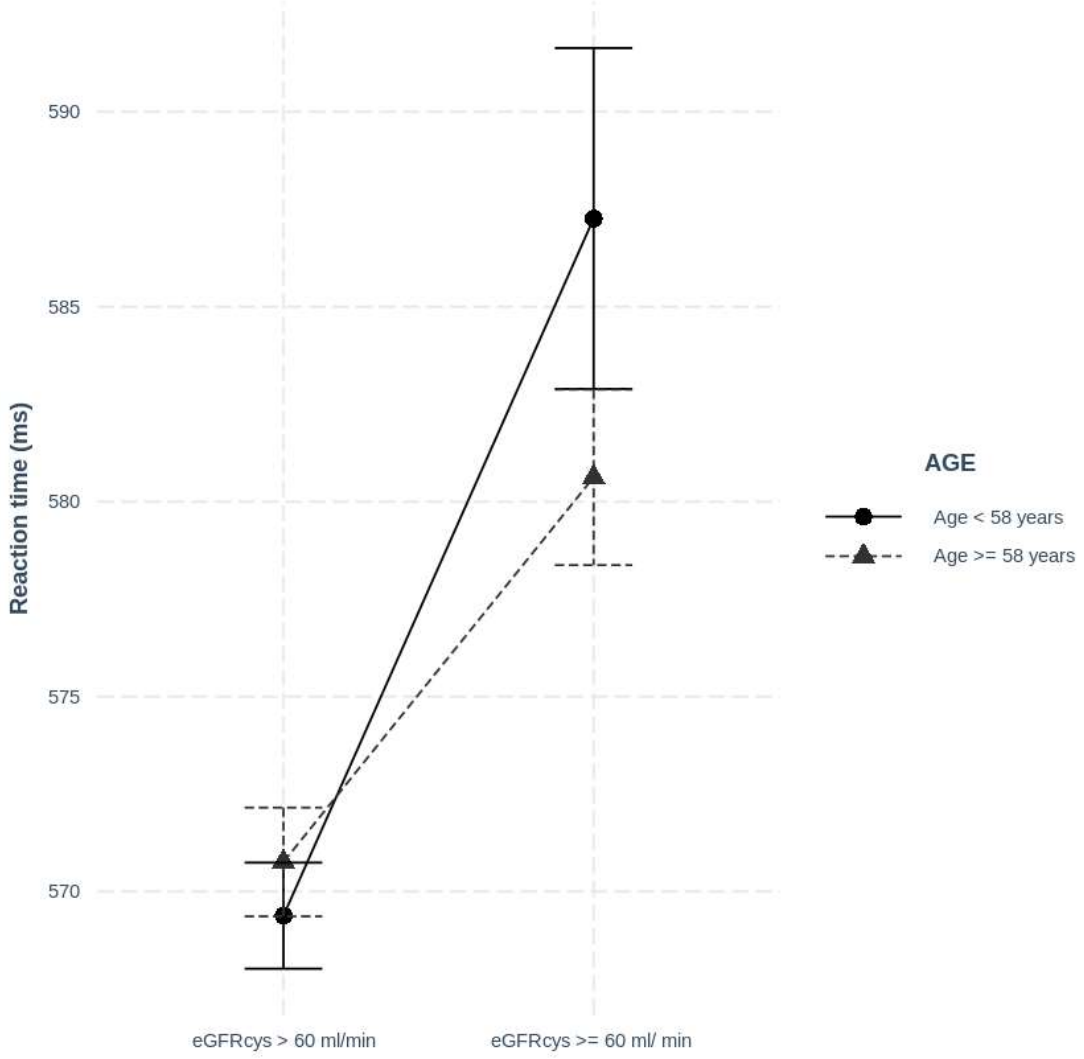

Figure 3.S2. Predicted mean reaction time and 95% confidence intervals using eGFRcys category as a predictor grouped by age category. Abbreviations: eGFRcys, cystatin C-based estimated glomerular filtration rate

CHAPTER 4: BIOMARKERS OF KIDNEY FUNCTION AND COGNITIVE ABILITY: A MENDELIAN RANDOMIZATION STUDY

ABSTRACT

Background: Estimated glomerular filtration rate (eGFR), albuminuria and serum uric acid (SUA) are markers of kidney function that have been associated with cognitive ability. However, whether these associations are causal is unclear.

Methods: We performed one-sample Mendelian randomization (MR) to estimate the effects of kidney function markers on cognitive performance using data from the UK Biobank. Polygenic scores for serum uric acid (SUA), urine albumin to creatinine ratio (ACR), estimated glomerular filtration rate based on serum creatinine (eGFRcre) and serum cystatin-c (eGFRcys) were used as instruments, and cognitive function outcomes included a test of verbal-numeric reasoning and reaction time.

Results: We found no evidence of a causal effect of genetically determined SUA, eGFRcre or eGFRcys on either cognitive function outcomes. There was no association between a polygenic score for ACR and verbal-numeric reasoning. However, there was suggestive evidence of a relationship between genetically increased ACR and slower reaction time. Pleiotropy adjusted estimates were directionally consistent with those of the principal analysis but overlapped with the null perhaps as a result of inadequate power.

Conclusions: This MR study does not support causal effects of SUA, eGFRcre or eGFRcys on cognitive performance. Genetically-increased ACR was associated with lower processing speed, but results need confirmation in independent samples.

INTRODUCTION

Dementia imposes significant societal and economic burdens. It is a leading cause of disability and was estimated to cost the equivalent to 1.1% of global gross domestic product in 2015 [1]. As no effective therapeutic treatment is currently available, identification and mitigation of modifiable risk factor remain of central importance. Chronic kidney disease (CKD) has emerged as a possible risk indicator for cognitive impairment [2,3]. Individuals living with chronic kidney disease experience higher rates of cognitive impairment and dementia compared to healthy adults [4]. Observational studies of associations between common biomarkers of kidney function suggest that this risk may extend to individuals with only mild kidney impairment [5,6]. Most common of these biomarkers, estimated glomerular filtration rate based on serum creatinine (eGFRcre) has been associated with cognitive performance [4,6–8] but studies have been conflicting [2]. Though less studied, cystatin C based GFR estimates (GFRcys) have shown stronger associations with cognitive performance compared to creatinine-based measurements [9,10]. An increased urine albumin to creatinine ratio (ACR) or albuminuria, which reflects kidney damage and is highly indicative of vascular dysfunction has been associated with higher odds of cognitive impairment and dementia [2,11]. However, whether this reflects a causal effect of albuminuria independent of concomitant cardiovascular disease is unclear. Higher serum SUA levels are correlated with diabetes, cardiovascular and kidney disease [12] but associations with cognitive ability are conflicting [13–15]. Somewhat paradoxically, case-control and cross-sectional studies have reported lower levels of SUA in individuals with Alzheimer's disease compared to those with normal cognition [16–18]. This finding has been attributed to a potential neuroprotective role of SUA through its anti-oxidant properties [19].

However, observational studies are susceptible to confounding and reverse causation to varying degrees and are therefore not appropriate for inferring causation. For example, in this context associations may have been confounded by environmental factors such as socio-economic status or comorbid disease. Reverse causation whereby the state of dementia leads to alterations in biomarker concentrations may also explain some of the observed inconsistencies in past studies, particularly with respect to the relationship between serum uric acid and Alzheimer's disease as individuals with Alzheimer's may change their eating habits.

The Mendelian randomization approach attempts to provide evidence of a causal association using genetic variants as instrumental variables for the exposure of interest. Analogous to randomization in clinical trials, the random assortment of alleles during meiosis allows confounding factors to be distributed evenly across genotypes. Furthermore, genotype at conception confers a lifelong increase or decrease in the exposure of interest minimizing the effects of reverse causation. The validity of the instrumental variable in Mendelian randomization relies on three key assumptions: (1) the genetic variant is strongly associated with the exposure, (2) the variant is not associated with confounders of exposure-outcome association, and (3) the variant-outcome association is explained only through the effect of the exposure of interest. The second and third assumptions can be violated in the presence of pleiotropy, where a genetic variant is associated with factors on a different causal pathway [20]. However, sensitivity analyses have been developed to address pleiotropic effects.

Individual-level data from the UK Biobank (UKBB) and summary data from previous genome-wide association studies (GWAS) were used to construct polygenic scores for multiple markers of kidney function including SUA, eGFRcre, eGFRcys or ACR. We then performed a

one-sample MR using these scores as instrumental variables to test for causal associations between each kidney function biomarker and cognitive performance.

METHODS

Study population

The UKBB is a prospective cohort that enrolled 502,617 participants aged 40-73 years from across the United Kingdom between 2006 and 2010. Details of enrollment procedures have been previously described [21]. At the baseline assessment, participants completed a detailed, computerized questionnaire including a wide range of information pertaining to lifestyle and health characteristics. Participants completed a battery of cognitive function tests via touchscreen interface at this time. Blood and urine samples for the full cohort were collected and stored for biochemical tests and genotyping. Ethical approval for data collection was received from the North-West Multi-centre Research Ethics Committee and the research was carried out in accordance with the Declaration of Helsinki of the World Medical Association Helsinki and approved by the University of California San Diego Institutional Review Board. Written informed consent was obtained for all participants.

Genotyping

The UKBB study was genotyped on the Affymetrix (now part of ThermoFisher Scientific) UK BiLEVE Axiom array (n=49,950 participants) or the similar UKBB Axiom array (n=438,427). To facilitate use of the UKBB resource by the research community, genotyping, quality control (QC) and genotype imputation were performed centrally by the primary UKBB investigators [22]. Genotype imputation is a statistical technique that leverages directly genotyped variants and a reference panel to infer ungenotyped variants. Prior to imputation,

genetic data from two arrays was combined and a QC procedure performed. Post quality control, genetic data is available for 488,377 subjects on 805,426 genetic markers and 92,693,895 imputed variants. We carried out the following additional quality control and filtering steps. Individuals with the following characteristics were excluded: extreme heterozygosity or missingness (n=968), individuals with sex chromosome aneuploidy (n=651), individuals whose reported sex did not match genetically inferred sex (n=186), and individuals with high levels of cryptic relatedness (n=73). Principal components were then calculated for the remaining 486,387 participants using 1000 Genomes as the reference population [23]. We used the "aberrant" clustering package in R [24] with a lambda parameter of 8.2 to determine the European ancestry cluster. Subjects with self-report of non-British or non-European ancestry included in European ancestry cluster were excluded, resulting in, 454,488 participants with European ancestry. To avoid inflation in test statistics due to inclusion of related individuals, we used a custom script that implements a greedy algorithm to determine the unrelated subset. Relatedness was first determined by UKBB using identity by State (IBS). The algorithm sequentially breaks related pairs to retain only unrelated individuals while preferentially maximizing the number of individuals with a user defined characteristic. In this study we chose to maximize those with available verbal-numeric reasoning scores. We excluded those with approximately second degree or closer relatedness (pi-hat =0.0625, n= 69,378 removed). After additionally excluding those who had withdrawn consent at the time of this study, pregnant women (n=119), individuals with probable type 1 diabetes (n=1670) and participants missing data on kidney function exposures or cognitive test scores there remained 124,834 and 357,590 participants for analyses with verbal-numerical reasoning and reaction time, respectively.

Kidney function biomarkers

At the initial assessment (2006-2010), blood and spot urine samples were collected and analyzed at a centralized laboratory. Sampling, handling, and quality control of biochemical measures have been described in detail previously [25]. Briefly, serum creatinine, urine creatinine and urine albumin were measured on a Beckman Coulter AU5800 instrument. An enzymatic, IDMS-traceable method was used to measure serum and urine creatinine. Urine albumin was quantified using an immune-turbidimetric method (Randox laboratories) with a lower limit of detection of 6.7 mg/L. Measurements below the lower limit of detection were set to 6.7mg/L as done previously [26]. Serum cystatin-C was measured using an Immuno-turbidimetric assay on a Siemens ADVIA 1800 instrument. Estimated GFR was calculated using creatinine (eGFRcre) or cystatin-C (eGFRcys) by the CKD-EPI equation as described previously [27,28]. SUA was measured by uricase PAP analysis on a Beckman Coulter AU5800.

Cognitive function

Cognitive function was assessed using self-administered, computerized tests specifically designed for the UKBB [29]. The verbal-numeric reasoning test, originally labelled the 'fluid intelligence' test, (Field ID 20016) included 13 logic/reasoning-type questions. The score was the number of questions answered correctly within a two-minute time limit. The Cronbach alpha coefficient for this test has been previously reported elsewhere as 0.62 [30]. This test was added part-way through the initial assessment period and therefore was not administered to all participants.

The reaction time is similar to the card game "Snap". Participants were shown a series of card pairs with symbols on them and were instructed to press a large red button as quickly as possible when the cards matched (Field ID 20023). The score was the mean time, in milliseconds (ms), to press the button across all trials with a matching pair.

Statistical analysis

Polygenic scores

SNPs included in the SUA, eGFRcre and eGFRcys polygenic scores were identified from GWAS meta-analysis of 288,649, 567,460 and 32,861 participants of European ancestry, respectively [26,31,32]. We used European ancestry specific summary statistics from a meta-analysis (n=547,361) carried out by Teumer et al. to derive the polygenic score for ACR [26]. All summary statistics were downloaded from the data page maintained by the CKDGen consortium (ckdgen.imbi.uni-freiburg.de/). It should be noted that UKBB participants made up the largest proportion of individuals included in the Teumer et al. meta-analysis which may to contribute to the winner's curse phenomenon [33]. However, prior GWAS were underpowered and would be unlikely to yield a polygenic score with adequate instrument strength [34]. For each biomarker we constructed two polygenic scores based on SNPs that passed a p-value threshold $p<5 \times 10^{-8}$ or $p<1 \times 10^{-5}$ in prior GWAS. SNPs were pruned based on the 1000 Genomes data with an $R^2 <0.1$ and a 500kb clumping window to find the SNP with the with the lowest p-value for each clump. The variance explained by the polygenic scores was calculated as the adjusted R^2 from the association of each score with the biomarker adjusted for age, sex and the 10 principal components (PCs) of population structure minus the adjusted R^2 from the regression with age, sex and the 10 PCs only.

We performed mendelian randomization analyses through two-stage least squares (2SLS) regression using the ivreg command from the AER package in R [35]. In 2SLS the exposure of interest is regressed on the polygenic score and, the outcome is regressed on the predicted values of the exposure and the residuals from the first regression. All 2SLS models were adjusted for age, sex, and the first 10 PCs. ACR was log-transformed for normality before analysis. The

instrument strength of each polygenic score was assessed using the F-statistic from the first regression where an F-statistic less than 10 suggests a weak instrument.

Sensitivity analysis

Modification by sex or age was assessed by performing 2SLS stratified by sex and by the median age in the UKBB (<58 years vs 58 years or older). We repeated 2SLS analyses using an unweighted allele scores for ACR to minimize bias from the use of internally derived weights [36]**.** Although, 2SLS is the standard method for MR in one-sample settings it does not address the problem of pleiotropy which violates the assumption that the genetic variant-outcome association is explained only through the effect of the exposure of interest. Alternatively, methods to address pleiotropy have been developed for two-sample MR where the effect estimates for the SNP-exposure and SNP-outcome are gleaned from independent study populations [37]. Using the MendelianRandomization package in R [38], we applied two methods, MRegger [39] and weighted-median regression [40] to account for the potential effects of pleiotropic SNPs in the ACR polygenic score. First, the β-estimates for the associations between each SNP with ACR and reaction time were obtained and inverse-variance weighted fixed effects meta-analysis (IVW) was used to derive the MR estimate to approximate the 2SLS estimate [41]. The MR-Egger method was used to estimate the causal effect as the slope from the weighted regression and the average pleiotropic effect as the intercept. If the intercept from the MR-Egger analysis is not equal to zero this indicates directional pleiotropy. Weighted median regression was then used to estimate the causal effect assuming at least 50% of the SNPs in the polygenic score are valid and that there is not directional pleiotropy.

RESULTS

Characteristics of the study population are shown in **Table 4.1**. The mean age was 56.7 years and 54% were female. On average, participants had a mean verbal-numeric reasoning score of 6.18 (standard deviation (SD)=2.11) and a mean reaction time of 555ms (SD=113ms). Mean eGFR was slightly lower when estimated using cystatin-C rather than creatinine (mean (SD)=88.35 (15.93) ml/min for eGFRcys and 90.67 (13.09) ml/min for eGFRcre). SUA was higher in men compared to women (mean (SD)=5.96 (1.20) mg/dl vs 4.54 (1.10) mg/dl), but the median ACR was lower in men (median (IQR)=0.86 (0.85) mg/g in men and 1.37 (1.33) mg/g in women).

MR analysis

F-statistics for the eight polygenic scores ranged from 552 to 10,004 which suggests that they were not weak instruments. The number of SNPs included in each polygenic score, the variance explained by the score and the corresponding effect estimates from the 2SLS regression are shown in **Table 4.2**. We detected no evidence for a causal effect of SUA, eGFRcre, or eGFRcys on performance on the verbal-numeric reasoning or reaction-time tasks (all p-values ≥0.13). There was no apparent effect of ACR on verbal-numeric reasoning score, however increased ACR as predicted by the 293-snp score was significantly associated with slower reaction-time scores (β (95% confidence interval [CI])) for 1 SD logACR=4.93 (1.60 to 8.26), p=0.004). The association was slightly weaker using the 76-snp score (β (95%CI) =4.82 (0.95 to 8.68), p=0.01).

Sensitivity analysis

We found similar null associations between SUA, eGFRcre, and eGFRcys with cognitive function when 2SLS analyses was stratified by sex or age. ACR was not associated with verbal-

numerical reasoning in MR analysis. Associations between genetically increased ACR and slower reaction time were significant in men and women (β (95% CI)=5.69 (0.42 to 10.96), p=0.03 and 4.27 (0.06 to 8.48), p=0.048, respectively). The association between ACR and reaction time was slightly stronger in individuals younger than 58 years compared to those who were older (β (95% CI)=6.02 (1.37 to 10.67), p=0.01 vs 4.46 (0.05 to 8.87) p=0.047, respectively). The results of 2SLS, IVW, MREgger and weighted median regressions for the association between the 293-SNP ACR polygenic score and reaction time are shown in **Figure 4.2.** Genetically increased ACR estimated using the unweighted polygenic score was significantly associated with slower reaction time scores (β (95% CI)= 5.84 (2.08 to 8.30), p=0.001). The results of the analyses that control for pleiotropy (MREgger and weighted median regression) were directionally consistent with that of the main analysis, but not statistically significant. However, the precision of the estimates was much lower for these methods as they demand high statistical power. The MREgger regression did not indicate the presence of directional pleiotropy (β (95% CI) for intercept=0.01 (-0.73 to 0.95, p=0.79).

DISCUSSION

In this study, we used MR analyses to investigate the potential causal associations of four markers of kidney function and cognitive ability in a large population-based cohort of European descent. Genetically increased ACR was associated with reaction time, a measure of processing speed. Our study did not provide evidence to support a causal effect of genetically determined serum uric acid, eGFRcre or eGFRcys levels on cognitive performance despite the associations observed in observational studies [2,3,14,16].

In a recent two-sample MR using summary GWAS data, Efstathiadou et al. found no association between genetically increased SUA and global cognitive function in participants of

the UKBB and the Cognitive Genomics (COGENT) consortium (n= 110,347) [42]. We found a similar null association in a one-sample setting which is not affected by heterogeneity between the populations used to obtain the SNP-exposure and SNP-outcome association statistics. Furthermore, we extend these results to a test of reaction time. This conflicts with past studies that found lower levels of SUA in Alzheimer's disease cases versus controls [15,43]. However, the results of this study along with those of prospective studies that found an inverse association between SUA and cognitive performance [13,44] suggest that it is unlikely that increasing SUA would benefit cognition. It is important to note that the 2SLS regression assumes a linear relationship between the exposure of interest and the outcome and therefore may not capture threshold effects. We therefore could not fully characterize the potential effects of the hyperuricemic state on cognitive ability.

To our knowledge, this is the first study to examine the association between eGFR and cognitive ability using the MR approach. Our finding of a null association between genetically determined eGFR and cognitive performance is consistent with a recent meta-analysis of observational studies by Deckers et al. that showed no significant differences in cognitive impairment according to eGFRcre [2]. The authors attributed this result to substantial study heterogeneity which could reflect differential distributions or treatment of confounding factors between populations. Taken together, the results of this study and that of Deckers et al. suggest that past significant associations between eGFRcre and cognitive function may have been affected by residual confounding. However, because eGFR often has a nonlinear association with outcomes, we may have not been able to detect any threshold effects. Future MR studies should consider using genetic instruments for binary CKD traits.

In contrast with observational studies that support a positive association between eGFRcys and cognitive performance [9,45], genetically determined eGFRcys did not predict cognitive ability in this study. A large proportion (85%) of the total variance in eGFRcys that was explained by the polygenic score is attributable to one SNP (rs1158167) which is found near the cystatin-C precursor gene family (*CST3, CST4, CST9*) and explains 2.7% of the variance of serum cystatin-C in the UKBB. It is likely that this SNP reflects cystatin-C expression rather than renal filtration. Although this suggests cystatin-C concentrations do not causally affect cognition, a better understanding of the genetic underpinnings of eGFRcys independent of cystatin-C expression may be necessary to draw further conclusions.

Our finding that genetically determined ACR was associated with reaction time is consistent with prior observational studies [9,46,47]. While the mechanism for this association is not known, it may be mediated through increased blood pressure and cardiovascular risk. Using bidirectional MR, Haas et al. suggested that high blood pressure contributes to albuminuria which in turn leads to further increased blood pressure in a feed-forward loop [48]. Cognition may also be affected due to the consequences of kidney damage including anemia, hyperparathyroidism, acidosis, hyperhomocysteinemia, inflammation, and exposure to uremic toxins accumulation [49]. The ACR polygenic score was constructed using weights from GWAS that included UKBB participants. This can exacerbate weak instrument bias which can overestimate the exposure-outcome association in one-sample MR studies [50]. However, we also found a significant positive association with reaction time when an unweighted polygenic score was used. MREgger and median-weighted estimates were directionally consistent with 2SLS and IVW estimates but overlapped with the null. However, the MREgger intercept was not signitficantly different from zero suggesting a lack of directional pleiotropy.

Strengths and limitations

Key strengths of this study were the large sample size and access to individual level data for one-sample MR allowing for stratification by sex and age group. In addition, this avoids the problem of sample heterogeneity that affects two-sample MR. In addition, the extensive biochemistry measurements of the UKBB data allowed for the investigation of multiple measures of kidney function. Some limitations of our study should also be noted. First, due to the UKBB sample overlap in the discovery dataset, the weights used in the albuminuria polygenic score may have biased our results. To address this, we replicated associations using an unweighted score. Nonetheless, these results should be interpreted cautiously but do provide motivation for replication in other large independent cohorts. Furthermore, our analysis may not be able to detect nonlinear associations. Future studies should consider using polygenic scores for binary kidney function traits in this context. Though, results from adequately powered GWAS will be required. Our analysis was restricted to participants of European ancestry, so our results may not be generalizable to other ethnic groups. The cognitive tests in the UKBB were developed to be administered on a large scale and without supervision and may therefore not be highly sensitive to cognitive differences. However, the tests used showed substantial correlation with previously validated tests in an independent sample of individuals (56).

CONCLUSIONS

In conclusion, our MR analyses do not support a causal effect of SUA, eGFRcre or eGFRcys on cognitive function. A polygenic score for ACR was associated with reaction time, a measure of processing speed, but replication in independent cohorts is needed.

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Table 4.1. Characteristics of the study population overall and according to sex: the UK Biobank

	All Participants	Female	Male
	n=357,590	n=192,758	n=164,832
Age (years)	56.69 (8.01)	56.50 (7.91)	56.92 (8.11)
Smoking status			
Current	36,597 (10.2)	16,887 (8.8)	19,710 (12.0)
Never	193,763 (54.2)	113,333 (58.8)	80,430 (48.8)
Past	127,230 (35.6)	62,538 (32.4)	64,692 (39.2)
Some university education	203,071 (56.8)	105,513 (54.7)	97,558 (59.2)
Alcohol drinking status			
Current	334,718 (93.6)	177,812 (92.2)	156,906 (95.2)
Never	10,818 (3.0)	8,114 (4.2)	2,704 (1.6)
Past	12,054 (3.4)	6,832 (3.5)	5,222 (3.2)
Body mass index (kg/m^2)	27.34 (4.74)	26.94 (5.11)	27.80 (4.21)
LDL-c (mmol/L)	3.57 (0.87)	3.64 (0.87)	3.49 (0.86)
Triglycerides (mmol/L)	1.75 (1.02)	1.55 (0.85)	1.98 (1.14)
Hypertension	197,182 (55.1)	93,304 (48.4)	103,878 (63.0)
Type II diabetes	17,430 (4.9)	63,35 (3.3)	11,095 (6.7)
Coronary artery disease	12,626 (3.5)	2,698 (1.4)	9,928 (6.0)
History of stroke	5,744 (1.6)	2,369 (1.2)	3,375 (2.0)
Heart failure	996 (0.3)	249 (0.1)	747 (0.5)
Cholesterol-lowering medication	59,942 (16.8)	23,189 (12.0)	36,753 (22.3)
Antihypertensive medication	71,933 (20.1)	32,404 (16.8)	39,529 (24.0)
ACR (mg/mmol)	1.11 (1.17)	1.37 (1.33)	0.86 (0.85)
SUA (mg/dl)	5.20 (1.35)	4.54 (1.10)	5.96 (1.20)
GFRcre (ml/min)	90.67 (13.09)	90.80 (13.10)	90.52 (13.08)
GFRcys (ml/min)	88.35 (15.93)	88.72 (15.70)	87.91 (16.20)
Verbal-numeric reasoning score	6.18 (2.11)	6.07 (2.03)	6.32 (2.18)
Reaction time (ms)	555.18 (113.12)	563.19 (113.53)	545.82 (111.92)

Abbreviations: ACR, albumin-to-creatinine ratio; eGFRcre, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; SUA, serum uric acid; ACR shown as median (IQR). Other values shown as n (%) for categorical variables and mean (SD) for continuous variablesAll characteristics are significantly different by sex except eGFRcre (p-value=0.53)

Table 4.2. Results from two-stage least squares MR analyses for the association of kidney function biomarkers with cognitive performance

Exposure	P-value cutoff	No. of SNPs	Variance explained	Verbal-numeric reasoning			Reaction time (ms)		
				β	**95%CI**	**p-value**	**β**	**95%CI**	**p-value**
SUA (mg/dl)	$1x10^{-5}$	693	5.9%	-0.02	-0.06 to 0.02	0.26	0.39	-0.72 to 1.51	0.48
SUA (mg/dl)	$5x10^{-8}$	297	5.4%	-0.03	-0.07 to 0.01	0.13	0.24	-0.91 to 1.39	0.68
eGFRcre (10ml/min)	$1x10^{-5}$	1120	4.5%	0.02	-0.02 to 0.06	0.25	-0.65	-1.94 to 0.64	0.31
eGFRcre (10ml/min)	$5x10^{-8}$	453	4.0%	0.03	-0.01 to 0.07	0.15	-0.58	-1.95 to 0.79	0.40
eGFRcys (10ml/min)	$1x10^{-5}$	16	3.4%	0.007	-0.01 to 0.24	0.72	-0.47	-1.68 to 0.74	0.43
eGFRcys (10ml/min)	$5x10^{-8}$	4	3.0%	0.006	-0.01 to 0.25	0.77	-0.21	-1.87 to 1.45	0.79
Log ACR (1 SD)	$1x10^{-5}$	293	1.1%	-0.03	-0.17 to 0.12	0.72	4.93	1.56 to 8.30	**0.004**
Log ACR (1 SD)	$5x10^{-8}$	76	0.6%	-0.03	-0.17 to 0.11	0.69	4.82	0.92 to 8.72	**0.01**

Abbreviations: ACR, albumin-to-creatinine ratio; CI, confidence interval; eGFRcre, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; SUA, serum uric acid
1 SD logACR = 0.74 log(mg/g)

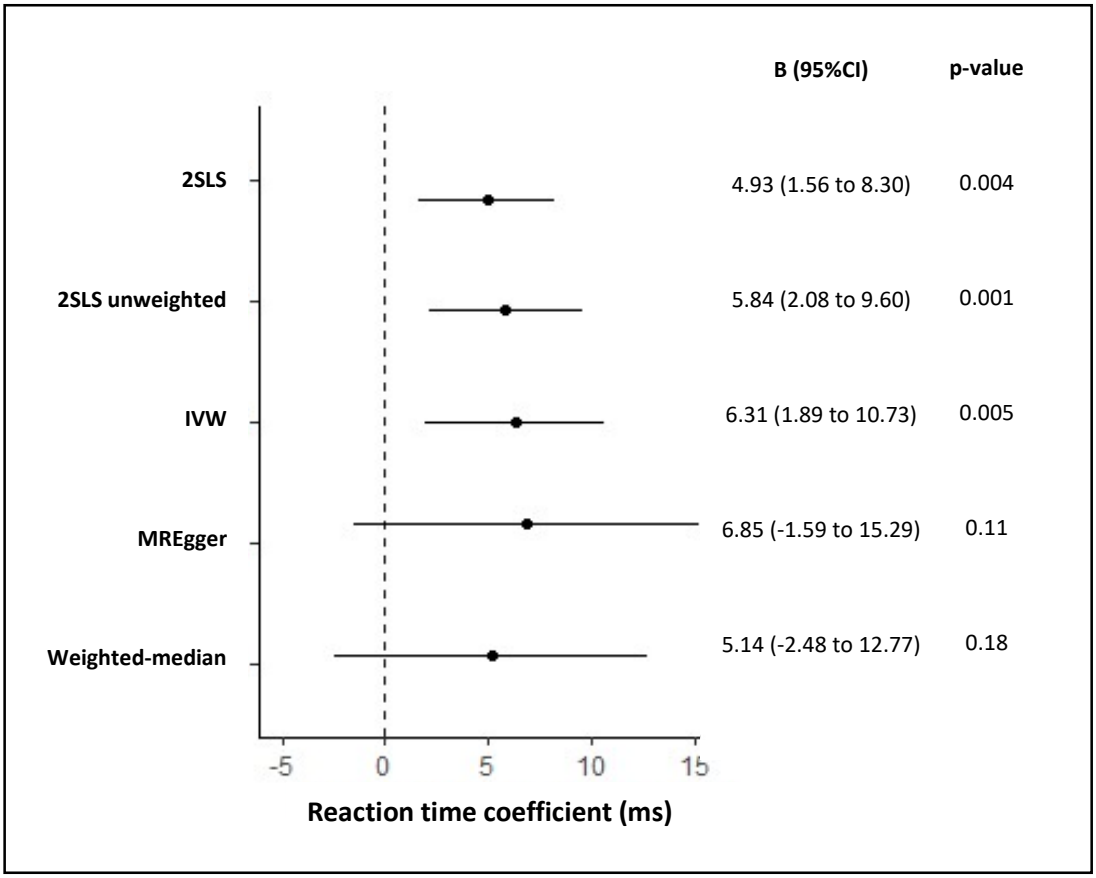

Figure 4.1. Mendelian randomization estimates for the effect of 1-standard deviation (SD) increase in genetically determined logACR on reaction time (ms).
CI, confidence interval; Con-Mix: IVW, inverse-variance weighted;
2SLS, Two-stage least-squares

CHAPTER 5: DISCUSSION

The prevalence of both chronic kidney disease (CKD) and dementia is increasing globally [1], and both are associated with an increased economic and societal burden [2,3]. Prior studies suggest that kidney dysfunction is a risk indicator of cognitive decline [4,5], however studies with extended follow-up and multiple markers of kidney function are lacking. Moreover, the extent to which these associations are modified by genetics has received little attention. In addition, whether these associations are potentially causal remains unclear. This dissertation addressed these knowledge gaps using three related yet distinct approaches as summarized below.

In chapter 2, we leveraged data from 1,634 older community-dwelling adults (mean age=71.7 years) with up to 24 years of cognitive follow-up to assess associations between three measures of kidney function and performance on a battery of cognitive tests. We found marked sex differences in the associations between albuminuria and hyperuricemia with cognitive decline. After adjusting for multiple demographic, lifestyle and health related **factors,** albuminuria was associated with steeper annual declines in global cognitive function (MMSE, β=-0.10, p = .003), executive function (Trails B, β=3.87, p < .0001) and episodic memory (Buschke total recall, β=-0.63, p = .02) scores in men. When a data-driven approach was used to identify groups of individuals with similar ACR patterns over time, we found a similar result. That is, men in the higher ACR trajectory group had greater cognitive decline compared to those in the lower ACR trajectory group. The rate of cognitive decline did not differ by hyperuricemia status, however men with hyperuricemia had lower baseline MMSE (β=-0.70, p = .009) compared to men with lower uric acid levels. In contrast, we found only null associations between albuminuria or hyperuricemia status and cognitive function in women. Creatinine-based

GFR (eGFRcre) <60ml/min was not associated with cognitive performance in men or women. Interestingly, the association between hyperuricemia and MMSE was attenuated after participants with a history of stoke were excluded suggesting a possible role of cerebrovascular disease in the causal pathway.

In the second study **(**chapter 3**)** which included cross-sectional data from up to 341,208 participants of the UK Biobank , albuminuria was associated with worse performance on tasks of verbal-numeric reasoning (β=-0.09, p<0.001), reaction time (β=7.06, p<0.001) and visual memory (β=0.013, p=0.01. Results were similar when propensity-score matched analyses were used as alternative approach to control for confounding. The association between albuminuria and reaction time was modified by a polygenic score for global cognitive function, such that slower reaction times were observed in those with a lower polygenic score (p<0.001). Participants with eGFR<60ml/min had lower verbal-numeric reasoning scores and slower mean reaction times compared to those with higher eGFR, and observed associations were stronger when eGFR was calculated using cystatin-C rather than creatinine.

In chapter 4 a Mendelian randomization (MR) approach was used to estimate the effects of kidney function markers on cognitive performance using data from the UK Biobank. There was no evidence of a causal effect of SUA, eGFRcre or eGFRcys on performance on the verbal-numeric reasoning or reaction time tests. Likewise, there was no apparent effect of genetically-determined ACR on verbal-numeric reasoning score, however increased ACR as predicted by a 293-snp score was significantly associated with slower reaction-time scores (β (95% confidence interval [CI])) for 1 SD logACR=4.93 (1.60 to 8.26), p=0.004). The association was slightly attenuated but remained significant using a score with only 76 SNPs. In sensitivity

analyses, which adjusted for pleiotropy, estimates were directionally consistent with the main analysis but were not significant.

This dissertation expands upon the current knowledge of the association between kidney function and cognitive ability by revealing potential sex-differences across multiple domains when cognitive function was measured repeatedly over an extended follow-up period. Furthermore, we demonstrated for the first time that higher ACR trajectories estimated using a data-driven approach were associated with subsequent cognitive decline in men. Using UKBB data, we found that albuminuria was also predictive of cognitive performance and that this association was modified by a polygenic score for cognitive function. In addition, we provide evidence that eGFRcys may have a more robust association with cognitive function than eGFRcre. Our MR results support prior two-sample MR studies that did not find a causal association between SUA and cognitive function or Alzheimer's disease [6,7] and suggest for the first time that albuminuria may be causally associated with cognitive performance.

In RBS participants, the association between albuminuria and cognitive decline was significant only in men. However, we did not detect significant sex differences in the association between albuminuria and cognitive performance in the UKBB cohort. There are several notable distinctions in both the study design and study populations that may explain this difference. First, the RBS had a much smaller sample size than UKBB, therefore small effect sizes in women may not have been detected. Second RBS participants were older on average than the UKBB cohort and sex differences may become more evident with age. Finally, associations in UKBB were cross-sectional while those in the RBS study were prospective reflecting cognitive decline over time. Interestingly, among UKBB participants, stronger associations between albuminuria and

reaction time were observed in men compared to women (8.75 (6.62 to 10.89) in men vs 5.32 (2.79 to 7.85) in women). However, this difference did not reach statistical significance (p for interaction=0.29). Follow-up studies within the UKBB could confirm whether or not sex differences emerge as the population ages.

The RBS and UKBB cohorts are different in many respects, but each offers distinct advantages. The RBS cognitive assessments included validated instruments that were administered under supervision and have been shown to be responsive to the effects of aging in the RBS cohort [8]. Comparatively, the UKBB cognitive tests were novel, brief and administered without supervision which could have made them less sensitive to cognitive differences. However, this was likely counterbalanced by the precision granted by the large sample size. It is not only notable that we detected a similar association between albuminuria and cognitive function in two methodologically diverse study cohorts, but it also demonstrates how the power of a study may be influenced both by the quality of the instruments used and the sample size.

It is possible that the association between kidney dysfunction and cognitive ability is mediated through clinically diagnosed or underlying CVD. In both the RBS and UKBB, we observed some attenuation of the associations between albuminuria or eGFR after controlling for cardiovascular disease including stroke. With the exception of the association between albuminuria and visual memory, associations remained significant. This suggests that kidney dysfunction could confer additional risk of cognitive impairment independently of overt CVD. Indeed, nontraditional risk factors such as inflammation, increased oxidative stress, and accumulation of uremic toxins such as homocysteine have also been linked to cognitive impairment [9,10]. In MR analysis we found a potentially causal role of ACR for cognitive ability. It is important to note, however, that this does exclude the possibility mediation by CVD,

an example of vertical pleiotropy, which does not violate the basic assumptions of MR [11]. It is also likely that kidney and the brain are affected by a common pathophysiology such as endothelial dysfunction or transvascular leakage of serum proteins [12] that affect the kidney and the brain concurrently but independently. In this way, kidney function biomarkers may serve as a marker of biological aging, particularly vascular aging. Investigating the associations between markers of kidney function and subclinical measures of cardiovascular disease such as coronary artery calcium (CAC) and subclinical measures of cerebrovascular disease including white-matter hyperintensities may add clarity to this association. It is important to note that it may be difficult to distinguish age-related declines in kidney function from progressive CKD. Therefore, these results should not be generalized to individuals with more severe CKD.

Strengths and limitations

There were several strengths to this dissertation. Given the extensive phenotyping of both the RBS and UKBB studies, we were able to examine multiple kidney function exposures and control for many potential confounders. In addition, the study described in chapter 2 which used RBS data was one of few studies to include repeated measures of kidney function and compared to similar studies, had the longest cognitive follow-up to date. To our knowledge, the study outlined in chapter 3 is the first to describe the association between measures of kidney function and cognitive ability using UKBB data. Finally, we were able to leverage the genotype and phenotype data available in the UKBB dataset to perform one-sample MR which avoids the problem of sample heterogeneity that affects two-sample MR.

This dissertation had some limitations worth noting. First, it was limited to individuals of European ancestry, so results are not generalized to other ethnicities. As Blacks are

disproportionately affected by both chronic kidney disease and dementia compared to whites [13,14], this is an important racial group to consider for future study. Furthermore, RBS and UKBB participants tended to be healthier compared to the general population [15,16]. A key limitation of this dissertation was the cross-sectional design of the UKBB study described in chapter 3, which makes results vulnerable to reverse-causation (e.g., poor cognitive function led to kidney disease diabetes). However, the results of longitudinal analysis in the RBS cohort along with those similar prospective studies suggest that poor kidney function precedes cognitive decline [17,18].

Future Directions

Future studies should aim to characterize the association between kidney function biomarkers and cognitive change over time in the UKBB. Between 2009 and 2013, a subset of 20,112 UKBB participants returned for a repeat assessment, and in 2014, the UKBB began an imaging study in which 100,000 participants were asked to complete the baseline assessment again and undergo brain, heart and abdominal scanning [19]. Interim data for ~40,000 participants is available at this time. The addition of the interim data will allow for the investigation of cognitive change over an extended time period and may be powered to detect gene by environment interaction.

This dissertation focused on the results of psychometric tests rather than clinical outcomes, i.e. dementia, Alzheimer's disease. While examining subtle cognitive changes even in midlife could provide opportunities for early detection for preventative interventions, it is also important to know if the lower cognitive test performance associated with kidney dysfunction translates to increased downstream risk of clinical dementia. In the RBS these hard outcomes

could be approximated by comparison of MMSE scores to population-specific norms with additional capture of Alzheimer's disease cases through death certificates. Due to the bespoke nature of the majority of the UKBB cognitive tests, such an approach would be questionable for UKBB. It should be noted, however, that a study using inpatient data by Calvin et al. showed that cognitive tests included in this dissertation were predictive of incident dementia and Alzheimer's disease 3-8 years later [17]. As of March 2020, 0.5% and 0.2% of the UKBB cohort had at least one inpatient visit related to dementia and Alzheimer's disease, respectively. With full integration of primary care data, case detection will increase as will the actual prevalence of these "hard outcomes" as the cohort ages.Although the positive predictive value for dementia has been estimated to be adequate using UKBB data [20], the sensitivity to detect dementia cases remains uknown. Individuals who are less likely to seek medical care or those who have more limited access to care may be less likely to be diagnosed with dementia. Prospective studies of these outcomes will become more feasible in the UKBB as a result. Large cohort studies such as the Million Veterans Program (MVP) will also offer opportunities to study the interplay between kidney function, genetic variation and clinical outcomes [22].

GWAS of complex traits such as eGFR and albuminuria typically need a very large sample size to yield significant associations, and a relatively large number of SNPs may be necessary to explain even a small proportion of the variance in some complex traits. For example, in **chapter 4** a 293 SNP polygenic score explained just 1.1% of the variation in ACR. Ideally, the GWAS discovery population and the population that the polygenic score is applied to would be independent, but this is not always possible as there are currently few studies at the UKBB scale. Methods to overcome the problem of overfitting by using internal weights are currently in development but not yet widely implemented [22]. Future studies should explore

such approaches to leverage large sample sizes and produce better performing polygenic scores for both MR and gene by environment analyses.

In chapter 4, the polygenic score for eGFRcys was largely driven by one SNP that was proximal to the cystatin C precursor gene family, so may have reflected cystatin C production rather than renal filtration. As an alternative approach to creating a polygenic score that more directly reflects kidney function, investigators could consider including only SNPs that are associated with both eGFRcre and eGFRcys thereby excluding variants that may reflect only creatinine or cystatin C expression.

Although the precise mechanisms explaining these associations is unclear, this dissertation underscores the importance of monitoring markers of kidney function, particularly albuminuria and eGFRcys as we age. The relationship between these markers and cognitive function is apparent even before clinical symptoms of CKD or CVD may manifest. As such, kidney function markers may be a potentially useful tool for cognitive impairment risk stratification. This work should provide added motivation for more aggressive treatment through targeted hypertension control, as well as smoking cessation and dietary modification.

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