Repeatedly measured serum creatinine and cognitive performance in midlife: The Cardiovascular Risk in Young Finns Study

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ABSTRACT

Background and Objectives: Serum creatinine is typically used to assess kidney function. Impaired kidney function and thereby high serum creatinine increases risk of poor cognitive performance. However, serum creatinine might have a non-linear association as low serum creatinine has been linked with cardiovascular risk and impaired cognitive performance. We studied the longitudinal association between serum creatinine and cognitive performance in midlife.

Methods: Since 2001, participants from the Cardiovascular Risk in Young Finns Study were followed up for 10 years. Serum creatinine was measured repeatedly in 2001, 2007, and 2011. Sex-specific longitudinal trajectories for serum creatinine among participants without kidney disease were identified using latent class growth mixture modeling. Overall cognitive function and four specific domains such as 1) working memory, 2) episodic memory and associative learning, 3) reaction time, and 4) information processing were assessed using a computerized cognitive test.

Results: Four serum creatinine trajectory groups all with clinically normal serum creatinine were identified for both men (N=973) and women (N=1,204). After 10 years of follow-up, cognitive testing was performed for 2,026 participants aged 34 to 49 years (mean age 41.8 years). In men and women, consistently low serum creatinine was associated with poor childhood school performance, low adulthood education, low adulthood annual income, low physical activity, and smoking. Compared to the men in the low serum creatinine trajectory group, those in the high serum creatinine group had better overall cognitive performance (β=0.353 SD, 95%CI 0.022–0.684) and working memory (β=0.351 SD, 95%CI 0.034–0.668), while those in the moderate (β=0.247 SD, 95%CI 0.026–0.468) or the normal (β=0.244 SD, 95%CI 0.008–0.481) serum creatinine groups had better episodic memory and associative learning. No associations were found for women.

Discussion: Our results indicate that, in men, compared to low serum creatinine levels consistently high levels may associate with better memory and learning function in midlife.

Key words: cognitive performance, serum creatinine, cardiovascular risk, kidney function, adulthood, midlife, longitudinal, population-based

INRODUCTION

Effective means for enhancing cognitive health before appearance of cognitive deficits is paramount as the dementia prevalence is increasing[1]. Pathophysiological processes leading to cognitive deficits are known to begin years or decades before manifesting clinical symptoms. Simultaneously, there are currently no cure and very few medical treatments to slow down the disease process after becoming symptomatic[2]. Therefore, identifying early determinants of cognitive performance could have a key role both in identifying high-risk individuals and in reducing cognitive deficit burden[1].

Serum creatinine is a measure of kidney function and can be used to calculate estimated glomerular filtration rate (eGFR)[3]. Previous studies have demonstrated that low eGFR that is a result of high serum creatinine and indicates impaired kidney function is associated with poor cognitive performance[4] and higher all-cause mortality[5]. However, also non-linear associations of eGFR have been reported as high eGFR (*i.e.* low serum creatinine) has been linked with increased risk of all-cause and cardiovascular mortality[5]. In addition, some studies have suggested that high eGFR in midlife[6] and old age[7,8] is associated with poor cognitive performance and increased dementia incidence[9].

The mechanism that explains the link between low serum creatinine and impaired cognitive performance is unknown. Low muscle mass or poor dietary habits are possible explanations for low serum creatinine[10] and both factors have also been shown to associate with poor cognitive performance[11]. Low serum creatinine may indicate glomerular hyperfiltration, which physiologically occurs in pregnancy and after a high-protein meal[12]. Furthermore, increased filtration can occur as an adaptive response to nephron loss and cause glomerular hypertension with subsequent glomerulosclerosis leading to progressive kidney function decline and initiation of glomerular damage. Importantly, glomerular hyperfiltration has been proposed to be an early

manifestation of risk factors and such as diabetes[13–15], prediabetes[16,17], elevated blood pressure (BP)[17,18], obesity[15,19], and smoking[20] and to associate with cardiovascular end points (*i.e.* death, congestive heart failure hospitalization, myocardial infarction, stroke)[13,14,21]. Additionally, glomerular hyperfiltration is hypothesized to link with poor cognitive performance[9,22]. However, prior systematic evidence on the associations between longitudinal serum creatinine levels and cognitive performance in midlife is lacking.

We aimed to provide this evidence by elucidating the associations between repeatedly measured serum creatinine levels from young adulthood to midlife and cognitive performance in midlife leveraging the data from the Cardiovascular Risk in Young Finns Study (YFS). We hypothesized that low serum creatinine during adulthood and midlife among participants without kidney disease is a sign of poor cardiovascular health and associates with poor cognitive performance in midlife.

METHODS

Participants

The YFS is a national ongoing longitudinal population-based study focusing on cardiovascular risk factors from childhood to adulthood. The baseline study was conducted in five Finnish university cities and their rural surroundings in 1980, when 3596 randomly selected individuals (boys and girls, all White) aged 3, 6, 9, 12, 15, and 18 years participated in clinical examinations. Follow-up studies were conducted in 1983, 1986, 2001, 2007 and 2011. For this study, adulthood follow-up data (participants' age ≥24 years; follow-up years 2001, 2007, 2011) was used. In total, 2,284 individuals participated in clinical examination in 2001, 2,204 in 2007, and 2,062 in 2011. The YFS design, population, and protocol have been reported elsewhere[23].

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was reviewed and approved by Ethics Committees of each of the participating universities (medical schools of Helsinki, Turku, Tampere, Kuopio, and Oulu). The written informed consent was obtained from all participants in accordance with the Helsinki Declaration.

Cognitive Performance

Cognitive performance was assessed in 2,026 participants aged 34-49 years (1,105 women, 922 men; mean age 41.8 years) in 2011 with the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, United Kingdom). The test battery included four tests that reflect different cognitive domains: 1) the Spatial Working Memory (SWM) test measured short-term working memory, 2) the Paired Associates Learning (PAL) test assessed episodic memory and associative learning, 3) the Reaction Time (RTI) test measured reaction and movement time, and 4) the Rapid Visual Information Processing (RVP) test assessed visual processing and sustained attention. Each of the tests produced several variables. Principal component analysis was conducted applying all data derived from the cognitive tests to create an indicator for overall cognitive performance. Additionally, test-specific principal component analyses were conducted to obtain cognitive domain specific outcome variables. From the principal component analyses, the first components were considered to represent overall cognitive performance and performance in each cognitive domain. The principal components were normalized using a rank-order normalization procedure, resulting in five normally distributed components (mean=0 and SD=1), and transformed so that greater value in the components indicate better cognitive performance. All available data for each cognitive test were used. Therefore, the number of participants varies between the components (177 excluded due to technical reasons; 51 refused to participate in all/some of the tests). A detailed description of the cognitive testing is presented in the eMethods, and the validation of the cognitive data elsewhere[24].

Serum Creatinine and Covariates

Serum creatinine was determined spectrophotometrically (Creatinine reagent, Olympus, Ireland) on an AU400 analyzer (Olympus, Japan) in three follow-ups (2001, 2007, 2011). GFR was estimated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) serum creatinine-based equation[3]. Age was defined in full years in 2011. Childhood school performance expressed as grade point average (range 4–10) was queried (*i.e.* mean of grades in all school subjects at baseline or in the two subsequent follow-ups for those participants who were not of school age at baseline). Queried data on the maximum years of education until the cognitive testing and annual gross income on a 13-point scale, ranging from 1 (<5,000€) to 13 (>60,000€) in 2011[25] were used as indicators of socioeconomic status. In all follow-ups, standard methods were used for measuring systolic and diastolic BP[26]. Venous blood samples were taken after an overnight fast. Serum total cholesterol and triglyceride concentration were determined enzymatically with standard methods[26]. High-density lipoprotein (HDL) cholesterol was analyzed after precipitation of very low-density lipoprotein cholesterol and low-density lipoprotein (LDL) cholesterol. The LDL-cholesterol concentration was calculated using the Friedewald formula for participants with triglycerides <4mmol/l. Antihypertensive medication use was obtained from the questionnaires in 2001, 2007, and 2011. The participants were classified as having hypertension if they had antihypertensive medication, systolic BP ≥140mmHg, diastolic BP ≥90mmHg, or self-reported hypertension in any follow-up. Weight (kg) and height (m) were measured, and body mass index (BMI) was calculated as weight (kg)/height (m^2)[23]. Standard methods were used to analyze serum insulin with microparticle enzyme immunoassay kit, serum glucose with enzymatic method, and glycated hemoglobin (HbA1c) with immunoturbidimetric methods[26]. Insulin resistance and sensitivity was estimated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) formula which was calculated as fasting insulin (mU/l) multiplied by fasting glucose (mmol/l) divided by 22.5. The analyses for serum creatinine trajectories were adjusted for diabetes and impaired fasting

glucose, and therefore, individuals were categorized into three groups: 1) normal fasting glucose, 2) impaired fasting glucose, and 3) diagnosed diabetes (type 1 or 2) in any of the follow-up studies. The classification of impaired fasting glucose was based on the criteria of the WHO[27]. The participants were classified as having type 2 diabetes if they met one of the following criteria: fasting serum glucose ≥7mmol/, type 2 diabetes diagnosed by a physician, HbA1c ≥48mmol/mol at the 2011 follow-up visit, and the use of glucose-lowering medication in the 2007 or 2011 follow-ups or as confirmed by the National Social Insurance Institution Drug Reimbursement Registry. Smoking was queried, and smoking status was dichotomized into daily smokers (daily smoking in any of the follow-ups) and nonsmokers. Physical activity was assessed with a standardized questionnaire in all study phases and a metabolic equivalent index was calculated from the product of intensity*frequency*duration and commuting physical activity[28]. A standardized food frequency questionnaire was used to assess participants diet in 2007 and 2011. Leveraging the data obtained from the questionnaire, 1) a diet score was calculated on the basis of the American Heart Association's definition which included recommended ideal intake levels of fruits and vegetables, fish, whole grains, sodium, and sugar-sweetened beverages[29] and 2) daily consumption of red meat (pork, beef, lamb, game, meat products, offal, and sausage) was assessed and expressed as g/day and g/1000 kcal[30]. The mean values of the cardiovascular risk factor measurements, MET-indices, and diet scores in adulthood follow-up studies were calculated. Apolipoprotein E (APOE) was determined as described previously[31]. A detailed description of the covariates is presented in the eMethods.

Statistical Analysis

Heterogeneity in the longitudinal development of serum creatinine was investigated using group-based trajectory modeling performed with SAS PROC TRAJ procedure[32] to identify subgroups of YFS participants who shared similar underlying trajectories between 24 and 49 years of age. To

ensure that only the participants with clinically normal serum creatinine were included in trajectory modeling, those with self-reported (N=12) and register-based diagnosis (N=12) of kidney disease, and those with eGFR <60ml/min/1.73m^2 in any of the follow-up studies (N=6) were excluded from the trajectory modeling (total N=30). Furthermore, single serum creatinine measurements obtained after kidney injury (N=4) or during the participant's pregnancy[12] (N=74) were excluded from the trajectory modeling analyses. Finally, all participants with at least two of the three serum creatinine measurements were included in the trajectory analyses. Sex-stratified trajectory analyses were conducted because women and men have different serum creatinine levels and reference rages[3]. The decision on the number and shape of the trajectory groups (eTable 1) was based on clinical plausibility and standard criteria[33] which are the Bayesian Information Criterion indicating the goodness of fit of the models and the posterior probability indicating internal reliability of each participant belonging to a specific trajectory group. Participants were assigned to the group where they had the highest posterior probability to belong (eTables 2 and 3). For meaningful statistical analyses linking serum creatinine trajectories and cognitive performance, frequency of >5% was preferred for the groups. Last, individual trajectory models for serum creatinine in men and women were formed (Figure 1) with adequate fit to data, good classification accuracy, and a strong clinical interpretability (eTables 4, 5, and 6).

In men, a four-group trajectory solution was considered optimal (Figure 1 and eTables 4 and 6): (1) '***high serum creatinine***' (N=71, 7.3%) with serum creatinine levels close to 100μmol/l; (2) '***normal serum creatinine***' (N=295, 30.3%) with serum creatinine levels close to 90μmol/l; (3) '***moderate serum creatinine***' (N=432, 44.4%) with serum creatinine levels close to 80μmol/l; (4) '***low serum creatinine***' (N=175, 18.0%) with serum creatinine levels close to 70μmol/l. Similarly in women, a four-group trajectory solution was considered optimal (Figure 1 and eTables 5 and 6): (1) '***high serum creatinine***' (N=146, 12.1%) with serum creatinine levels close to 80μmol/l; (2) '***normal***

serum creatinine' (N=360, 29.9%) with serum creatinine levels close to 70μmol/l; (3) '***moderate serum creatinine***' (N=558, 46.3%) with serum creatinine levels close to 65μmol/l; (4) '***low serum creatinine***' (N=140, 11.6%) with serum creatinine levels below 55μmol/l. A detailed description of the creation of the serum creatinine trajectories is presented in the eMethods.

ANOVA or Kruskal-Wallis test were used for continuous variables and Cochran-Mantel-Haenszel test for categorical variables to investigate risk factor levels between the trajectory groups. Linear regression analyses were conducted to investigate the associations of sex-stratified serum creatinine groups and midlife cognitive performance. All regression analyses were conducted as multivariable models using the standardized principal components for cognitive performance as outcome variables. Analyses between serum creatinine groups and midlife cognitive performance were first adjusted for age, childhood school performance, and education (Model 1). Subsequently, the analyses were further adjusted for APOE, systolic BP, serum total cholesterol, BMI, smoking, physical activity, diet, antihypertensive medication, and diabetes and impaired fasting glucose (Model 2). Furthermore, additional analyses were conducted using the fully adjusted model (Model 2) but replacing first the diet score with proportional daily red meat consumption (Model 3) and secondly education with annual income (Model 4). The possible effect modification of age as well as those risk factors that are known to associate with glomerular hyperfiltration or serum creatinine (systolic BP, BMI, smoking, physical activity, diet, red meat consumption, antihypertensive medication, diabetes and impaired fasting glucose, HOMA-IR, and HbA1c) for the studied associations were analyzed by adding multiplicative interaction terms (*e.g.* age*serum creatinine groups, systolic BP*serum creatinine groups) into the fully adjusted models (Model 2). All statistical analyses were performed using SAS 9.4 (SAS Institute Inc. Cary, North Carolina, USA).

Data availability

Anonymized data are available on request from the YFS research group (https://youngfinnsstudy.utu.fi/).

RESULTS

Representativeness of the Study Population

Representativeness of the study population participating in the cognitive testing was examined by comparing the whole study baseline (1980) and the present study baseline (follow-up year 2001) data between the participants and non-participants (eTable 7). Participants lost to follow-up were more often men and younger and therefore, further attrition analyses were adjusted for sex and age. Non-participants had higher childhood diastolic BP, higher adulthood systolic and diastolic BP, and were more often adulthood smokers. No other differences were observed.

Serum Creatinine Trajectories Characteristics

Serum creatinine levels within each group in each follow-up are presented in the eTable 6. The descriptive characteristics for serum creatinine groups in 2001 and 2011 follow-ups are presented for men (Table 1) and women (Table 2). In men and women, consistently low serum creatinine was associated with poor childhood school performance, low education, low annual income, low physical activity, and smoking. Additionally, low serum creatinine was associated with higher antihypertensive medication use and higher systolic BP in men, while in women, low serum creatinine was associated with higher BMI and triglyceride levels.

Serum Creatinine Trajectories and Cognitive Performance

In men, serum creatinine was directly associated with overall cognitive performance and short-term working memory (SWM-test); ‘high serum creatinine’ group had better overall cognitive performance and short-term working memory compared with the ‘low serum creatinine’ group in

the age, childhood school performance, and education-adjusted analyses (Table 3, Model 1). Additionally, serum creatinine showed a weak direct association with episodic memory and associative learning (PAL-test); the 'normal serum creatinine' and 'moderate serum creatinine' groups had better episodic memory and associative learning compared with the 'low serum creatinine' group in the age, childhood school performance, and education-adjusted analyses (Table 3, Model 1). After adding APOE, systolic BP, serum total cholesterol, BMI, smoking, physical activity, diet, antihypertensive medication, and diabetes and impaired fasting glucose (Model 2), the associations for both short-term working memory and episodic memory and associative learning became stronger (Table 3). No associations were found for women (Table 4). In the additional analyses where diet score was replaced with proportional red meat consumption and education with annual income, the associations for serum creatinine and short-term working memory and episodic memory and associative learning in men remained substantially similar (eTable 8).

The possible effect modification was studied for those cognitive domains showing association with serum creatinine trajectories (*i.e.* short-term working memory and episodic memory and associative learning) in men by introducing multiplicative interaction terms for each possible modifier (*e.g.* age*serum creatinine groups) separately into the fully adjusted linear regression models (Model 2). No significant interactions were found.

Cognitive Aging

To increase the clinical interpretability of our findings, we transformed the associations of longitudinal serum creatinine trajectories to correspond with 'cognitive aging' by comparing the β estimates of the serum creatinine trajectory groups with the β estimates of age in the test-specific fully adjusted multivariable models (estimates for age: overall cognitive performance β=-0.049SD, SWM-test β=-0.042SD and PAL-test β=-0.050SD). Concluding, for overall cognitive performance

in men, the group with high serum creatinine had 7.1-year younger 'cognitive age' compared to the group with low serum creatinine (Table 3). For short-term working memory, men with high serum creatinine had 8.2-year younger 'cognitive age' compared to the group with low serum creatinine. For episodic memory and associative learning, men with normal or moderate serum creatinine had 5.0- and 5.1-year younger 'cognitive age' compared to the group with low serum creatinine.

DISCUSSION

We observed that, compared to low serum creatinine, consistently higher serum creatinine levels during a 10-year follow-up were associated with better overall cognitive performance, short-term working memory as well as with better episodic memory and associative learning in middle-aged men. However, similar associations were not observed in women. Additionally, low serum creatinine was associated with low childhood school performance, low education, low annual income, smoking, and low physical activity in men and women. Importantly, all serum creatinine levels were within clinically normal range.

Findings from the present study

To our knowledge, only a few prior studies have examined the association between low serum creatinine, high GFR, and cognitive performance. In two cross-sectional reports from Tromsø Study of over 1,500 middle-aged men and women (mean age 57 years), an inverse association was observed for high measured[22] and estimated[6] GFR with performance in the Digit Symbol Substitution Test after wide adjustments, including age and cardiovascular risk factors. Association for eGFR remained significant but diluted for measured GFR after controlling for education. In the Tromsø Study, the measured GFR was assessed as iohexol clearance, which is an accurate method for measuring GFR, and therefore, measures true hyperfiltration. The Digit Symbol Substitution Test assesses cognitive performance involving components from *e.g.* processing speed, working

memory and associative learning, *i.e.* cognitive domains that were found to associate with serum creatinine levels also in our study. In two different cross-sectional studies conducted in older populations, high eGFR was associated with cognitive impairment measured using either the Six-item Screener Test performed on telephone[7] or the Mini-Mental State Examination[8]. Furthermore, in a large-scale South-Korean study with over 2 million participants aged 45 years or older (mean age 59 years) and a median follow-up time of 3.1 years, high eGFR in midlife and old age was associated with all-cause dementia in men and women, and specifically, with Alzheimer's disease in men[9]. Supporting our observations, this study found stronger associations for men than women after controlling for age, sex, BMI, smoking, alcohol consumption, physical exercise, income, diabetes, hypertension, and hyperlipidemia. Based on this finding, it might be hypothesized that the association of low serum creatinine with cognitive performance is not yet visible in women in our young and cognitively healthy population. It is important to note, that neither of the previous studies have used longitudinal data on eGFR, and that the eGFR levels were measured during the age frame when the neuropathological process causing cognitive deficits could already be ongoing[2].

In the present study, no association was found for serum creatinine on reaction and movement time (RTI-test) or visual processing and sustained attention (RVP-test). The lack of associations suggests that these cognitive domains are plausibly determined via other factors not related to serum creatinine. This is supported by our previous studies on the YFS population which demonstrated inverse associations for systolic BP, serum total and LDL-cholesterol, obesity, and cardiovascular risk factor accumulation since childhood on episodic memory and associative learning, reaction and movement time, and visual processing and sustained attention[34,35]. Furthermore, muscle mass and physical activity have major role in serum creatinine levels. In this study, the found associations remained significant after taking into account BMI and physical activity. Moreover, our previous findings indicate that physical activity was directly associated with reaction time (RTI-test) in both

sexes and with visual processing and sustained attention (RVP-test) in men[36] – i.e. with cognitive domains which were not observed to associate with serum creatinine levels in the present study. However, physical activity is associated with high serum creatinine, and thereby, physical activity might be linked to better memory function and learning via high serum creatinine levels and other pathways.

Potential mechanisms

Findings from this study suggest a potential role of serum creatinine in crucial neural network areas for memory and learning functions. Performance in the PAL-test (episodic memory and associative learning) is localized mainly to medial temporal lobes, specifically to the hippocampus and parahippocampal gyrus[37] while performance in the SWM-test (short-term working memory) localizes mainly to prefrontal cortex[38]. It is important to note that the pathophysiology in these areas are typical in diseases causing cognitive deficits[2] and have a central role in cognitive reserve mechanisms via preserved metabolism or increased connectivity[1]. Furthermore, creatinine has been suggested to have a role in pathophysiological processes of Alzheimer's disease in a prior study where Alzheimer's disease patients (N=40) were observed to have higher cerebrospinal fluid levels of creatinine compared to the controls (N=34)[39]. However, there were no difference between the patients and controls in serum creatinine levels. In that study, the creatinine-related process was suggested to take place in the central nervous system where excessive phosphocreatine usage and/or disrupted creatine-phosphocreatine shuttle leads to non-enzymatical and irreversible degradation of both phosphocreatine and creatine into creatinine[40]. It might be speculated that in the conditions of impaired brain energy metabolism, higher level of whole-body creatine and creatinine may be beneficial for preserving cerebral energy metabolism. Moreover, specific pathophysiological mechanism behind the association of serum creatinine and cognitive performance remains uncertain as to our knowledge, there are no experimental data on this association.

Glomerular hyperfiltration is suggested to be a potential pathway linking low serum creatinine and cognitive performance[9]. Several previous studies have used high eGFR as an indicator of glomerular hyperfiltration and studied it's associations with cognitive performance[6–9]. Furthermore, there are several factors linked to glomerular hyperfiltration, such as renin-angiotensin-aldosterone system activation[12] as well as high renal generation and low systemic bioactivity of nitric oxide[41], that have also a role in endothelial dysfunction[42]. Low nitric oxide bioactivity and endothelial dysfunction are suggested to compromise vascular structure and function which might lead in cerebral hypoperfusion[42]. Additionally, other factors related to vascular hypothesis (e.g. arterial stiffness) are suggested to be associated with glomerular hyperfiltration[21]. This is supported by previous studies in healthy populations where high measured GFR levels were observed to associate with subclinical cardiovascular disease markers, such as carotid atherosclerosis and left ventricular hypertrophy[43] while high eGFR was found to associate with coronary artery calcification[44]. However, glomerular hyperfiltration is typically defined using 95th percentile of GFR as cut-off, but also other cut-offs have been used[45] which might have affected the previous results. In this study, the group with low serum creatinine levels was larger compared to 95th percentile and therefore, glomerular hyperfiltration may not entirely explain the present results.

Low serum creatinine could be a secondary indicator of adverse risk factors known to associate with poor cognitive performance such as smoking, obesity, prediabetes or diabetes, and low physical activity, which in the present study were associated with low serum creatinine. This hypothesis is supported by previous studies examining associations between high GFR and adverse cardiovascular risk factors. In a cross-sectional study in 1,572 healthy men (mean age 18.4 years), high eGFR, indicating glomerular hyperfiltration, was shown to associate with the accumulation of metabolic risk factors, including overweight, elevated BP, and low HDL-cholesterol[18]. Furthermore,

in a large-scale cross-sectional study in 99,140 participants with mean age of 52 years (range 20-89 years) high eGFR was associated with prediabetes and prehypertension[17]. Prediabetes and diabetes are possibly linked with high GFR as middle-aged participants with elevated eGFR were more likely to have diabetes[13] and impaired fasting glucose and HbA1c levels were associated with high measured GFR in participants without diabetes[16]. It has been reported that in the early course of diabetes, 20-50% of the patients have glomerular hyperfiltration[14]. Also obesity has been suggested to link with high GFR as to associate with high GFR in teenaged and young adult white populations[15], as well as middle-aged African Americans[19]. Additionally, in a cross-sectional study in 6,902 participants, a direct association between adiposity and high eGFR was shown in early midlife (mean age 38.6 years)[46]. Moreover, in a Japanese study conducted in 10,118 men aged 40-55 years, smoking was associated with high eGFR and thereby, low serum creatinine during a 6-year follow-up[20]. This finding reflects our present observation on the association between smoking and serum creatinine. As a plausible mechanism for this association, the Japanese study hypothesized that smoking may induce increase in insulin resistance, cause idiopathic nodular glomerulosclerosis, and increase creatinine excretion through renal tubules. In addition to the cardiovascular risk factors, general mechanisms behind low serum creatinine such as low muscle mass or poor diet[10], may reflect the plausible link for cognitive performance. Hence, it could be speculated that high eGFR and thereby low serum creatinine indicates adverse cardiovascular risk factor profile possibly before it has led into clinical manifestations, and thereof, accumulation of several risk factors may link to cognitive performance. However, the possible confounding role of cardiovascular risk factors on the association between serum creatinine and cognitive performance was taken into account in our analyses by adjusting for cardiovascular risk factors. Importantly, these adjustments did not alter our results.

Limitations and Strengths

There are limitations to be addressed. First, we did not have data to assess kidney function more accurately, e.g. measured creatinine clearance, cystatin C, or albuminuria levels. Therefore, we did not estimate eGFR trajectories because CKD-EPI equation is known to underestimate GFR in healthy populations[47]. Second, cognitive performance was assessed at a single time point, and therefore, we have no data on baseline cognitive performance. However, we have adjusted the analyses for childhood school performance indicating childhood cognitive ability and for adulthood education indicating socioeconomic status. Third, in observational studies, reverse causation could cause misinterpretation of the results. Therefore, it is not possible to make firm conclusions on the causal relations between serum creatinine and cognitive performance. However, longitudinal population-based cohorts are the only realistic ways to study these associations because no life-course randomized control trial exists. Fourth, latent class growth analysis is a data-driven longitudinal method to model serum creatinine and it applies no a priori hypothesis for creating the groups. Therefore, the data-driven method might lead to oversimplification of true variability in serum creatinine levels or result in groups that do not exist. However, if the diagnostic criteria related to the analyses are carefully followed, as in our study, latent class growth analysis offers an adequate method to model natural history of serum creatinine by discriminating participants into clinically meaningful groups. Fifth, results obtained from observational studies are prone to bias caused by residual confounding caused by unmeasured factors. Sixth, the association was observed only in men. Potential mechanisms for this remain undetermined. However, it may be hypothesized that the link between large muscle mass and high serum creatinine might explain why the benefits of creatinine on cognitive performance were observed in men but not in women. These limitations are outweighed by the strengths of the study including unique and large population-based cohort, long follow-up, and repeatedly measured risk factor exposure several years before the cognitive testing.

Conclusions

We observed that within clinically normal range of serum creatinine higher levels during adulthood associate with better overall cognitive performance, short-term working memory, and episodic memory and associative learning in men. Similar associations were not observed in women. If the found associations were causal and a sign of an independent risk factor, these results could provide a novel and interpretable way to evaluate risk for poor cognitive performance in young and healthy male individuals. Ultimately, our results provide evidence on the importance of primary and even primordial prevention of cognitive deficits.

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Figure 1. Serum Creatinine Levels in the Trajectory Groups in Men (A) and Women (B).

Values are means for serum creatinine in each follow-up year in the serum creatinine trajectory groups. Sex-specific serum creatinine trajectories from adulthood to midlife were identified using latent class growth mixture modeling. Four trajectory groups for men (A) and women (B) were identified. Participants with kidney disease or eGFR <60 ml/min/1.73 m^2 as well as serum creatinine values obtained after kidney injury or during pregnancy were excluded from the serum creatinine trajectory modeling.

Table 1. Background Characteristics of the Study Population and Serum Creatinine Trajectories in Men

	N	**All**		**Low Creatinine**		**Moderate Creatinine**		**Normal Creatinine**		**High Creatinine**		**P-value**
			N (%)	175	18.0	432	44.4	295	30.0	71	7.3	
		Mean/N	SD	**Mean/N**	SD	**Mean/N**	SD	**Mean/N**	SD	**Mean/N**	SD	
Age at baseline	973	31.7	5.0	31.9	4.9	31.7	5.0	31.8	5.1	31.0	5.0	0.630
Age at cognitive testing	973	41.7	5.0	41.9	4.9	41.7	5.0	41.8	5.1	41.0	5.0	0.630
Childhood school performance	842	7.57	0.72	**7.45**	**0.73**	**7.54**	**0.72**	**7.68**	**0.69**	**7.59**	**0.75**	**0.013**
Years of education	813	14.7	2.8	**13.7**	**2.6**	**14.6**	**2.8**	**15.3**	**2.8**	**14.7**	**3.0**	**<0.0001**
Annual income (range 1-13)	797	8.4	3.1	**7.6**	**2.8**	**8.1**	**3.1**	**9.2**	**3.0**	**9.0**	**3.3**	**<0.0001**
Smoking, N (%) yes	973	286	29.4	**74**	**42.3**	**125**	**28.9**	**71**	**24.1**	**16**	**22.5**	**<0.0001**
Antihypertensive medication, N (%) yes	973	103	10.6	**23**	**13.1**	**54**	**12.5**	**23**	**7.8**	**3**	**4.2**	**0.007**
Hypertension, N (%) yes	973	245	25.2	**56**	**32.0**	**113**	**26.2**	**61**	**20.7**	**15**	**21.1**	**0.006**
Impaired fasting glucose, N (%) yes	973	132	13.6	26	14.9	54	12.5	45	15.3	7	9.9	0.701
Apolipoprotein E ε4 carriers, N (%) yes	971	351	36.2	63	36.0	156	36.3	110	37.3	22	31.0	0.768
Cardiovascular risk factors in follow-up year 21 (2001)												
Systolic blood pressure, mmHg	852	121.1	12.0	122.3	12.7	121.5	11.8	119.6	12.2	121.0	10.8	0.176
Diastolic blood pressure, mmHg	852	72.8	11.0	72.5	12.2	73.3	10.6	72.1	10.8	74.1	11.0	0.434
Total cholesterol, mmol/l	858	5.25	1.02	5.23	0.96	5.29	1.02	5.19	1.04	5.27	1.12	0.639
LDL-cholesterol, mmol/l	836	3.43	0.90	3.42	0.86	3.47	0.92	3.37	0.88	3.50	0.97	0.550
HDL-cholesterol, mmol/l	856	1.15	0.27	1.15	0.25	1.15	0.27	1.15	0.28	1.13	0.30	0.917
Triglycerides, mmol/l	858	1.52	0.99	1.51	0.98	1.51	0.93	1.54	1.08	1.55	1.06	0.972
Body mass index, kg/m^2	854	25.71	3.94	25.80	4.73	25.77	4.02	25.41	3.08	26.38	4.37	0.355
Fasting serum insulin, mU/l	852	7.57	5.64	8.31	9.40	7.59	4.78	7.19	3.77	7.08	4.07	0.853
Fasting serum glucose, mmol/l	852	5.16	0.53	5.11	0.55	5.19	0.61	5.18	0.42	5.05	0.34	**0.067**
HOMA-IR, (mU/l*mmol/l)/22.5	852	1.77	1.55	1.98	2.82	1.77	1.18	1.68	0.95	1.61	0.96	0.841
Physical activity	850	19.23	21.09	**14.71**	**19.22**	**19.02**	**20.72**	**21.01**	**22.31**	**23.74**	**20.81**	**0.005**
Estimated GFR, ml/min/1.73 m^2	857	110.06	9.94	**120.33**	**4.81**	**113.20**	**5.43**	**103.73**	**7.01**	**91.18**	**8.39**	**<0.0001**

Table 1. Background Characteristics of the Study Population and Serum Creatinine Trajectories in Men (continued)

	N	**All**		**Low Creatinine**		**Moderate Creatinine**		**Normal Creatinine**		**High Creatinine**		**P-value**
			N (%)	175	18.0	432	44.4	295	30.0	71	7.3	
		Mean/N	SD	**Mean/N**	SD	**Mean/N**	SD	**Mean/N**	SD	**Mean/N**	SD	
Cardiovascular risk factors in follow-up year 31 (2011)												
Systolic blood pressure, mmHg	850	123.1	13.3	**124.9**	**12.9**	**123.6**	**13.5**	**121.4**	**12.9**	**122.6**	**13.7**	**0.050**
Diastolic blood pressure, mmHg	850	77.9	10.7	78.8	11.8	77.9	10.2	77.4	10.9	78.0	10.5	0.641
Total cholesterol, mmol/l	856	5.32	1.01	5.32	1.03	5.31	0.98	5.32	1.04	5.34	1.01	0.998
LDL-cholesterol, mmol/l	821	3.43	0.89	3.40	0.96	3.46	0.87	3.40	0.87	3.48	0.86	0.775
HDL-cholesterol, mmol/l	854	1.20	0.29	1.22	0.31	1.21	0.29	1.20	0.29	1.17	0.28	0.792
Triglycerides, mmol/l	856	1.58	1.23	1.72	1.29	1.47	1.03	1.65	1.49	1.56	0.89	0.174
Body mass index, kg/m^2	855	26.97	4.33	27.35	5.62	26.99	4.22	26.59	3.60	27.51	3.98	0.265
Fasting serum insulin, mU/l	849	9.89	8.70	10.79	11.78	9.59	7.64	9.59	8.24	10.59	7.22	0.366
Fasting serum glucose, mmol/l	851	5.52	0.75	5.60	1.23	5.51	0.65	5.48	0.54	5.52	0.43	0.739
HOMA-IR, (mU/l*mmol/l)/22.5	849	2.53	2.67	2.93	4.17	2.41	2.08	2.43	2.37	2.67	1.98	0.384
HbA1c, mmol/mol	845	36.68	4.46	37.04	6.62	36.63	4.10	36.46	3.19	37.05	4.33	0.733
Type 1 diabetes mellitus, N (%) yes	791	3	0.4	0	0.0	2	0.6	1	0.4	0	0.0	0.894
Type 2 diabetes mellitus, N (%) yes	968	33	3.4	11	6.3	10	2.3	10	3.4	2	2.8	0.214
Physical activity	780	20.99	21.46	16.91	21.25	19.67	21.17	23.26	20.64	28.86	23.97	**<0.0001**
Diet score	620	1.9	0.8	1.8	0.9	1.9	0.8	2.0	0.8	1.8	0.8	0.281
Red meat consumption, g/day	620	187.9	95.7	186.5	96.9	184.9	95.6	194.5	99.0	181	80.3	0.685
Red meat consumption, g/1000 kcal	620	71.1	26.9	70.2	25.6	69.2	25.9	73.7	28.6	73.6	28.0	0.310
Estimated GFR, ml/min/1.73 m^2	855	97.07	11.17	**109.39**	**4.88**	**100.80**	**6.54**	**89.27**	**6.97**	**76.33**	**5.59**	**<0.0001**

Values are means (standard deviations) for the continuous variables and numbers (percentages) for categorical variables. ANOVA or Kruskal-Wallis test were used for continuous variables and Cochran-Mantel-Haenszel test for categorical variables to investigate the risk factor levels between within the trajectory groups. Childhood school performance (range 4 – 10) was defined as grade point average (*i.e.* mean of grades in all

individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline). Years of education was determined as a continuous variable from self-reported data on total years of education attained in adulthood until the year 2011. Annual gross income in 2011 was queried using an ordinal scale ranging from 1 (<5000€) to 13 (>60,000€). Smoking status was dichotomized into daily smokers (daily smoking in any of the adulthood follow-up studies 2001, 2007, or 2011) and nonsmokers. The participants reporting use of antihypertensive medication in any follow-up studies were defined as those with antihypertensive medication. APOE ε4 carriers were the participants with either one or two ε4 alleles, while the non-carriers were those without any ε4 allele. Physical activity was measured with a standardized self-administered questionnaire and a metabolic equivalent index was calculated from the product of intensity*frequency*duration and commuting physical activity. Participants who had impaired fasting glucose in any of the follow-up studies were defined as those with impaired fasting glucose. Participants with current use of insulin medication were excluded from the analyses for serum insulin, serum glucose, HOMA-IR, HbA1c, and impaired fasting glucose. The diet score was based on intake levels of ideal five dietary metrics (range 0 – 5): fruits and vegetables, fish, whole grains, sodium, and sugar-sweetened beverages. The daily red meat consumption was summed based on the reported intakes of pork, beef, lamb, game, meat products, offal, and sausage. Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) serum creatinine-based equation. LDL = low-density lipoprotein. HDL = high-density lipoprotein.

Table 2. Background Characteristics of the Study Population and Serum Creatinine Trajectories in Women

	N	**All**		**Low Creatinine**		**Moderate Creatinine**		**Normal Creatinine**		**High Creatinine**		**P-value**
			N (%)	140	11.6	558	46.3	360	29.9	146	12.1	
		Mean/N	SD	**Mean/N**	SD	**Mean/N**	SD	**Mean/N**	SD	**Mean/N**	SD	
Age at baseline	1,204	31.9	5.0	32.0	5.1	31.6	4.9	32.1	4.9	32.2	5.1	0.333
Age at cognitive testing	1,204	41.9	5.0	42.0	5.1	41.6	4.9	42.1	4.9	42.2	5.1	0.333
Childhood school performance	1,072	7.94	0.69	**7.75**	**0.71**	**7.92**	**0.66**	**7.98**	**0.69**	**8.08**	**0.72**	**0.001**
Years of education	1,028	15.2	2.7	**14.2**	**2.6**	**15.2**	**2.8**	**15.5**	**2.6**	**15.8**	**2.6**	**<0.0001**
Annual income (1-13)	990	6.6	2.8	**5.7**	**2.3**	**6.6**	**2.7**	**6.7**	**2.9**	**7.0**	**2.9**	**0.001**
Smoking, N (%) yes	1,204	264	21.9	**40**	**28.6**	**139**	**24.9**	**65**	**18.1**	**20**	**13.7**	**0.0001**
Antihypertensive medication, N (%) yes	1,204	127	10.6	22	15.7	47	8.4	35	9.7	23	15.8	0.581
Hypertension, N (%) yes	1,204	205	17.0	36	25.7	80	14.3	54	15.0	35	24.0	0.941
Impaired fasting glucose, N (%) yes	1,204	64	5.3	5	3.6	29	5.2	21	5.8	9	6.2	0.339
Apolipoprotein E ε4 carriers, N (%) yes	1,194	430	36.0	63	45.7	194	35.1	120	33.6	53	36.3	0.136
Cardiovascular risk factors in follow-up year 21 (2001)												
Systolic blood pressure, mmHg	1,069	112.4	12.3	113.8	12.1	111.7	12.7	112.6	11.9	112.9	12.3	0.268
Diastolic blood pressure, mmHg	1,069	68.7	9.9	68.8	9.8	68.2	10.0	68.9	9.3	70.2	10.7	0.200
Total cholesterol, mmol/l	1,078	5.06	0.91	5.04	1.05	5.05	0.92	5.05	0.81	5.17	0.96	0.621
LDL-cholesterol, mmol/l	1,076	3.15	0.77	3.13	0.84	3.15	0.79	3.14	0.70	3.18	0.79	0.971
HDL-cholesterol, mmol/l	1,078	1.40	0.31	1.38	0.32	1.38	0.31	1.42	0.29	1.43	0.32	0.149
Triglycerides, mmol/l	1,078	1.15	0.57	**1.19**	**0.62**	**1.15**	**0.58**	**1.10**	**0.53**	**1.25**	**0.58**	**0.028**
Body mass index, kg/m^2	1,074	24.44	4.56	**25.35**	**5.72**	**24.59**	**4.70**	**23.73**	**3.81**	**24.79**	**4.23**	**0.003**
Fasting serum insulin, mU/l	1,072	7.60	4.97	8.31	5.66	7.77	4.90	7.15	5.02	7.41	4.23	**0.061**
Fasting serum glucose, mmol/l	1,072	4.87	0.44	4.90	0.46	4.86	0.45	4.88	0.4	4.85	0.45	0.745
HOMA-IR, (mU/l*mmol/l)/22.5	1,072	1.68	1.19	1.84	1.31	1.71	1.15	1.58	1.27	1.63	1.01	**0.092**
Physical activity	1,077	18.01	17.27	**15.15**	**15.86**	**17.3**	**17.21**	**18.84**	**17.12**	**21.76**	**18.74**	**0.005**
Estimated GFR, ml/min/1.73 m^2	1,038	105.61	11.72	**119.43**	**5.58**	**111.18**	**6.92**	**98.64**	**7.13**	**86.8**	**7.41**	**<0.0001**

Table 2. Background Characteristics of the Study Population and Serum Creatinine Trajectories in Women (continued)

	N	**All**		**Low Creatinine**		**Moderate Creatinine**		**Normal Creatinine**		**High Creatinine**		**P-value**
			N (%)	140	11.6	558	46.3	360	29.9	146	12.1	
		Mean/N	SD	**Mean/N**	SD	**Mean/N**	SD	**Mean/N**	SD	**Mean/N**	SD	
Cardiovascular risk factors in follow-up year 31 (2011)												
Systolic blood pressure, mmHg	1,045	115.5	13.7	117.5	14.2	114.9	13.3	116.4	14.7	114.0	12.5	**0.095**
Diastolic blood pressure, mmHg	1,045	72.4	9.5	72.3	9.3	72.3	9.4	72.5	9.7	72.4	9.9	0.970
Total cholesterol, mmol/l	1,048	5.06	0.87	5.12	0.95	5.08	0.92	5.01	0.78	5.02	0.78	0.544
LDL-cholesterol, mmol/l	1,040	3.13	0.73	3.20	0.79	3.15	0.75	3.10	0.68	3.10	0.72	0.560
HDL-cholesterol, mmol/l	1,048	1.43	0.32	1.41	0.31	1.42	0.33	1.44	0.30	1.41	0.33	0.705
Triglycerides, mmol/l	1,048	1.13	1.23	1.14	0.98	1.18	1.67	1.04	0.49	1.13	0.52	0.430
Body mass index, kg/m^2	1,046	26.09	5.48	**26.94**	**6.30**	**26.32**	**5.62**	**25.18**	**4.73**	**26.56**	**5.53**	**0.005**
Fasting serum insulin, mU/l	1,039	8.97	12.98	8.34	5.32	9.91	17.89	7.82	5.59	8.72	7.11	0.191
Fasting serum glucose, mmol/l	1,043	5.22	0.75	5.29	1.03	5.23	0.87	5.19	0.47	5.14	0.49	0.468
HOMA-IR, (mU/l*mmol/l)/22.5	1,039	2.29	6.93	2.01	1.41	2.69	10.01	1.86	1.45	2.08	1.94	0.221
HbA1c, mmol/mol	1,039	36.29	4.11	37	6.93	36.38	4.14	35.98	2.98	36.07	2.65	0.201
Type 1 diabetes mellitus, N (%) yes	996	7	0.7	1	0.9	3	0.7	1	0.3	2	1.6	0.680
Type 2 diabetes mellitus, N (%) yes	1,196	40	3.3	5	3.6	25	4.5	8	2.2	2	1.4	**0.059**
Physical activity	1,000	20.80	19.31	18.39	18.17	20.26	18.27	22.51	21.63	20.94	18.21	0.263
Diet score	852	2.3	0.9	2.3	1.0	2.4	0.9	2.2	0.9	2.3	0.9	0.306
Red meat consumption, g/day	852	111.2	66.0	116.7	74.2	107.8	57.5	114.7	78.3	110.3	54.6	0.893
Red meat consumption, g/1000 kcal	852	53.4	25.9	55.3	29.9	53.5	24.1	53.6	29.0	51.3	20.1	0.746
Estimated GFR, ml/min/1.73 m^2	1,039	93.17	12.53	**109.74**	**5.01**	**99.04**	**7.73**	**85.82**	**6.87**	**74.36**	**5.92**	**<0.0001**

Values are means (standard deviations) for the continuous variables and numbers (percentages) for categorical variables. ANOVA or Kruskal-Wallis test were used for continuous variables and Cochran-Mantel-Haenszel test for categorical variables to investigate the risk factor levels

between within the trajectory groups. Childhood school performance (range 4 – 10) was defined as grade point average (*i.e.* mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline). Years of education was determined as a continuous variable from self-reported data on total years of education attained in adulthood until the year 2011. Annual gross income in 2011 was queried using an ordinal scale ranging from 1 (<5000€) to 13 (>60,000€). Smoking status was dichotomized into daily smokers (daily smoking in any of the adulthood follow-up studies 2001, 2007, or 2011) and nonsmokers. The participants reporting use of antihypertensive medication in any follow-up studies were defined as those with antihypertensive medication. APOE ε4 carriers were the participants with either one or two ε4 alleles, while the non-carriers were those without any ε4 allele. Physical activity was measured with a standardized self-administered questionnaire and a metabolic equivalent index was calculated from the product of intensity*frequency*duration and commuting physical activity. Participants who had impaired fasting glucose in any of the follow-up studies were defined as those with impaired fasting glucose. Participants with current use of insulin medication were excluded from the analyses for serum insulin, serum glucose, HOMA-IR, HbA1c, and impaired fasting glucose. The diet score was based on intake levels of ideal five dietary metrics (range 0 – 5): fruits and vegetables, fish, whole grains, sodium, and sugar-sweetened beverages. The daily red meat consumption was summed based on the reported intakes of pork, beef, lamb, game, meat products, offal, and sausage. Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) serum creatinine-based equation. LDL = low-density lipoprotein. HDL = high-density lipoprotein.

Table 3. Associations Between Serum Creatinine Trajectories and Midlife Cognitive Performance in Men.

	Model 1		**Model 2**		**Difference in cognitive aging***
	β Estimate	**95% CI**	**β Estimate**	**95% CI**	
Overall cognition	N=610		N=599		
Low creatinine	Ref.		Ref.		Ref.
Moderate creatinine	0.173	-0.046 – 0.392	0.193	**-0.032 – 0.418**	
Normal creatinine	0.199	**-0.034 – 0.431**	0.223	**-0.018 – 0.464**	
High creatinine	**0.326**	**0.002 – 0.651**	**0.351**	**0.019 – 0.682**	7.1
SWM-test	N=681		N=670		
Low creatinine	Ref.		Ref.		Ref.
Moderate creatinine	0.097	-0.107 – 0.301	0.125	-0.085 – 0.335	
Normal creatinine	0.100	-0.118 – 0.318	0.140	-0.086 – 0.366	
High creatinine	**0.328**	**0.017 – 0.638**	**0.349**	**0.031 – 0.667**	8.2
PAL-test	N=628		N=616		
Low creatinine	Ref.		Ref.		Ref.
Moderate creatinine	0.212	**-0.003 – 0.426**	**0.251**	**0.030 – 0.472**	5.1
Normal creatinine	0.217	**-0.011 – 0.445**	**0.239**	**0.003 – 0.476**	5.0
High creatinine	0.205	-0.107 – 0.517	0.251	-0.068 – 0.570	
RTI-test	N=617		N=606		
Low creatinine	Ref.		Ref.		
Moderate creatinine	-0.097	-0.329 – 0.135	-0.154	-0.391 – 0.083	
Normal creatinine	0.050	-0.196 – 0.296	0.005	-0.248 – 0.258	
High creatinine	0.047	-0.295 – 0.390	-0.037	-0.384 – 0.310	
RVP-test	N=670		N=659		
Low creatinine	Ref.		Ref.		
Moderate creatinine	-0.040	-0.243 – 0.163	-0.063	-0.271 – 0.145	
Normal creatinine	0.024	-0.193 – 0.241	-0.022	-0.246 – 0.202	
High creatinine	0.060	-0.250 – 0.370	0.027	-0.288 – 0.343	

Values are β estimates and 95% confidence intervals (CIs) from linear regression models. All models were adjusted for age, childhood school performance, and education (Model 1). Model 2 was additionally adjusted for APOE, systolic blood pressure, serum total cholesterol, body mass index, smoking, physical activity, diet, antihypertensive medication, and diabetes and impaired fasting glucose. Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Cognitive tests measured short-term working memory (SWM-test), episodic memory and associative learning (PAL-test), reaction and movement time (RTI-test), and visual processing and sustained attention (RVP-test). Overall cognitive performance was determined from the data on all four CANTAB tests.

*The association of the serum creatinine was compared with the effect of age on the same cognitive domain to increase the clinical interpretation of the findings. For that, the difference in cognitive

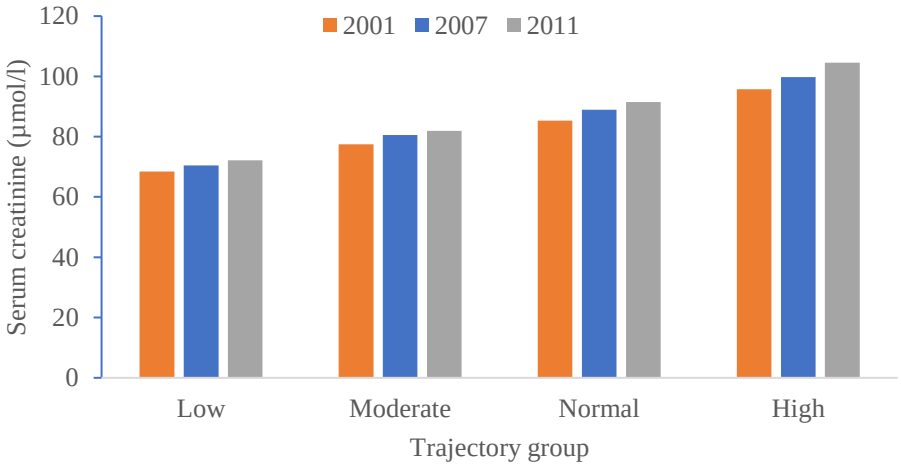
aging was estimated dividing the β estimates for the serum creatinine trajectory groups by the β estimate for age from the same statistical model (β estimates for age for the separate cognitive domains: Overall cognitive performance β=0.049; SWM-test β=–0.042 SD; PAL-test β=–0.050 SD).

Table 4. Associations Between Serum Creatinine Trajectories and Midlife Cognitive Performance in Women.

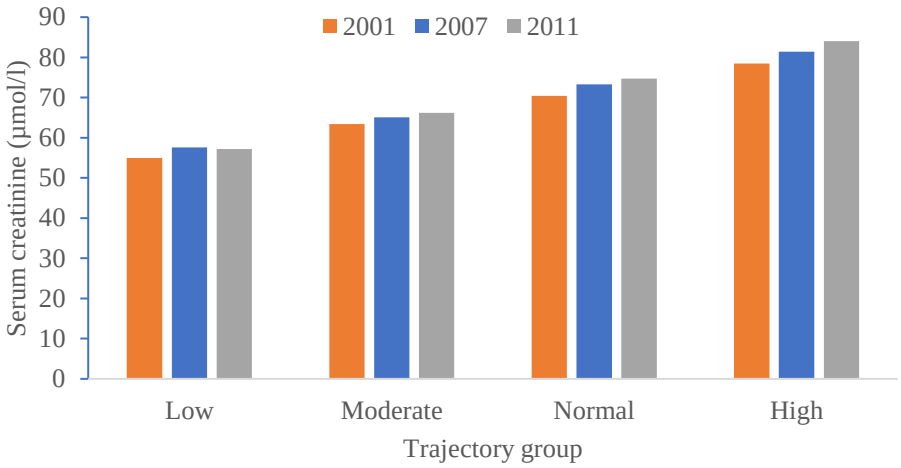
	Model 1		**Model 2**	
	β Estimate	**95% CI**	**β Estimate**	**95% CI**
Overall cognition	N=789		N=781	
Low creatinine	Ref.		Ref.	
Moderate creatinine	0.050	-0.171 – 0.272	0.041	-0.182 – 0.263
Normal creatinine	-0.091	-0.322 – 0.140	-0.081	-0.313 – 0.152
High creatinine	0.106	-0.162 – 0.374	0.096	-0.171 – 0.364
SWM-test	N=890		N=879	
Low creatinine	Ref.		Ref.	
Moderate creatinine	-0.048	-0.263 – 0.167	-0.046	-0.262 – 0.171
Normal creatinine	-0.057	-0.284 – 0.169	-0.046	-0.275 – 0.182
High creatinine	-0.020	-0.283 – 0.243	-0.054	-0.318 – 0.209
PAL-test	N=813		N=805	
Low creatinine	Ref.		Ref.	
Moderate creatinine	0.099	-0.134 – 0.332	0.088	-0.146 – 0.323
Normal creatinine	-0.126	-0.369 – 0.118	-0.109	-0.354 – 0.136
High creatinine	0.145	-0.136 – 0.427	0.153	-0.129 – 0.435
RTI-test	N=803		N=795	
Low creatinine	Ref.		Ref.	
Moderate creatinine	0.059	-0.175 – 0.292	0.016	-0.218 – 0.249
Normal creatinine	0.072	-0.172 – 0.316	0.010	-0.234 – 0.254
High creatinine	-0.111	-0.393 – 0.170	-0.147	-0.428 – 0.133
RVP-test	N=869		N=858	
Low creatinine	Ref.		Ref.	
Moderate creatinine	0.122	-0.091 – 0.335	0.112	-0.103 – 0.326
Normal creatinine	0.075	-0.150 – 0.299	0.051	-0.174 – 0.277
High creatinine	0.115	-0.146 – 0.377	0.111	-0.150 – 0.372

Values are β estimates and 95% confidence intervals (CIs) from linear regression models. All models were adjusted for age, childhood school performance, and education (Model 1). Model 2 was additionally adjusted for APOE, systolic blood pressure, serum total cholesterol, body mass index, smoking, physical activity, diet, antihypertensive medication, and diabetes and impaired fasting glucose. Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Cognitive tests measured short-term working memory (SWM-test), episodic memory and associative learning (PAL-test), reaction and movement time (RTI-test), and visual processing and sustained attention (RVP-test). Overall cognitive performance was determined from the data on all four CANTAB tests.

A. Men


120
100
80
60
40
20
0
Serum creatinine (µmol/l)
2001
2007
2011
Low
Moderate
Normal
High
Trajectory group

B. Women


90
80
70
60
50
40
30
20
10
0
Serum creatinine (µmol/l)
2001
2007
2011
Low
Moderate
Normal
High
Trajectory group