AUTHOR Juuso O. Hakala, Katja Pahkala, Markus Juonala, Pia Salo, Mika Kähönen, Nina Hutri-Kähönen, Terho Lehtimäki, Tomi P. Laitinen, Eero Jokinen, Leena Taittonen, Päivi Tossavainen, Jorma S.A. Viikari, Olli T. Raitakari, Suvi P. Rovio

TITLE Repeatedly Measured Serum Creatinine and Cognitive Performance in Midlife
The Cardiovascular Risk in Young Finns Study

YEAR 2022

DOI 10.1212/WNL.0000000000200268

VERSION Author's accepted manuscript

CITATION Hakala, J.O., Pahkala, K., Juonala, M., Salo, P., Kähönen, M., Hutri-Kähönen, N., Lehtimäki, T., Laitinen, T.P., Jokinen, E., Taittonen, L., Tossavainen, P., Viikari, J.S.A., Raitakari, O.T., Rovio, S.P., 2022. Repeatedly Measured Serum Creatinine and Cognitive Performance in Midlife. Neurology 98, e2268. https://doi.org/10.1212/WNL.0000000000200268

REPEATEDLY MEASURED SERUM CREATININE AND COGNITIVE PERFORMANCE IN MIDLIFE: THE CARDIOVASCULAR RISK IN YOUNG FINNS STUDY

Juuso O. Hakala[1,2,3], MD; Katja Pahkala[1,2,3], PhD; Markus Juonala[4], MD, PhD; Pia Salo[1,2], MD, PhD; Mika Kähönen[5], MD, PhD; Nina Hutri-Kähönen[6], MD, PhD; Terho Lehtimäki[7], MD, PhD; Tomi P. Laitinen[8], MD, PhD; Eero Jokinen[9], MD, PhD; Leena Taittonen[10,11], MD, PhD; Päivi Tossavainen[11], MD, PhD; Jorma SA. Viikari[4], MD, PhD; Olli T. Raitakari[1,2,12], MD, PhD; Suvi P. Rovio[1,2], PhD

[1]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland;

[2]Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland;

[3]Paavo Nurmi Centre, Sports & Exercise Medicine Unit, Department of Physical Activity and Health, University of Turku, Turku, Finland;

[4]Department of Medicine, University of Turku and Division of Medicine, Turku University Hospital, Turku, Finland;

[5]Department of Clinical Physiology, Tampere University Hospital and Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;

[6]Department of Pediatrics, Tampere University Hospital and Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;

[7]Department of Clinical Chemistry, Fimlab Laboratories and Finnish Cardiovascular Research Center-Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;

[8]Department of Clinical Physiology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland;

[9]Department of Paediatric Cardiology, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland;

[10]Department of Pediatrics, Tampere University Hospital, Tampere, Finland;

[11]Department of Pediatrics, PEDEGO Research Unit and Medical Research Center, University of Oulu, and Oulu University Hospital Oulu, Finland;

[12]Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland;

Corresponding author: MD. Juuso O. Hakala, Research Centre of Applied and Preventive Cardiovascular Medicine and Centre for Population Health Research, University of Turku and Turku University Hospital, Kiinamyllynkatu 10, 20520 Turku, Finland. Email: juolhak@utu.fi, tel: +358 29 450 4373

ACKNOWLEDGEMENTS

This work was supported by the Academy of Finland: grants 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), 41071 (Skidi) and 322098 (T.L); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Diabetes Research Foundation of Finnish Diabetes Association; and EU Horizon 2020 (grant 755320 for TAXINOMISIS and grant 848146 for TO-AITION); and European Research Council (grant 742927 for MULTIEPIGEN project); Tampere University Hospital Supporting Foundation; Finnish Society of Clinical Chemistry (T.L). KP is supported by Academy of Finland research fellowship (322112).

Expert technical assistance in data management and statistical analyses by Irina Lisinen and Johanna Ikonen is gratefully acknowledged.

The authors report no relationships with industry. The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit the manuscript for publication.

ABSTRACT

Background and Objectives: Serum creatinine is typically used to assess kidney function. Impaired kidney function and thus high serum creatinine increases risk of poor cognitive performance. However, serum creatinine might have a non-linear association because low serum creatinine has been linked to 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 with latent class growth mixture modeling. Overall cognitive function and four specific domains—working memory, episodic memory and associative learning, reaction time, and information processing—were assessed with a computerized cognitive test.

Results: Four serum creatinine trajectory groups 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 34 to 49 years of age (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 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 be associated with better memory and learning function in midlife.

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

INRODUCTION

Having an effective means for enhancing cognitive health before appearance of cognitive deficits is paramount as the dementia prevalence increases[1]. Pathophysiological processes leading to cognitive deficits are known to begin years or decades before clinical symptoms manifest. Simultaneously, there is currently no cure, and very few medical treatments are available to slow the disease process after a patient becomes 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, non-linear associations of eGFR have been reported; high eGFR (i.e. low serum creatinine) has been linked to increased risk of all-cause and cardiovascular mortality[5]. In addition, some studies have suggested that high eGFR in midlife[6] and older 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. It is important to note that 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]. In addition, glomerular hyperfiltration is hypothesized to be linked to poor cognitive performance[9,22]. However, prior systematic evidence for 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 by 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 is associated 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) 3, 6, 9, 12, 15, and 18 years of age 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) were 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). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Cognitive Performance

Cognitive performance was assessed in 2,026 participants 34 to 49 years of age (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. In addition, 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 indicates 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 validation of the cognitive data is given elsewhere[24].

Serum Creatinine and Covariates

Serum creatinine was determined spectrophotometrically (Creatinine reagent, Olympus, Ireland, Dublin) on an AU400 analyzer (Olympus, Japan, Tokyo) 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 BPs[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 with the Friedewald formula for participants with triglycerides <4mmol/l. Antihypertensive medication use was obtained from the questionnaires in 2001, 2007, and 2011. 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 and height were measured, and body mass index (BMI) was calculated as weight divided by height squared[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 were estimated with the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) formula, which was calculated as fasting insulin multiplied by fasting glucose divided by 22.5. The analyses for serum creatinine

trajectories were adjusted for diabetes and impaired fasting glucose; 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 World Health Organization criteria[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 gram per day and grams per 1,000 kcal[30]. The mean values of the cardiovascular risk factor measurements, metabolic equivalent indices, and diet scores in adulthood follow-up studies were calculated. 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 with group-based trajectory modeling performed with SAS PROC TRAJ procedure (SAS Institute Inc, Cary, NC)[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 (N=12) diagnosis 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. Last, 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, and (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, and (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.

Analysis of variance 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 replacing education with annual income (Model 4). The possible effect modification of age and those risk factors that are known to be associated 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 with SAS 9.4 (SAS Institute Inc).

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 nonparticipants (eTable 7). Participants lost to follow-up were more often men and younger; therefore, further attrition analyses were adjusted for sex and age. Non-participants had higher childhood diastolic BP, had higher adulthood systolic and diastolic BPs, 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 in Table 1 and women in 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. In addition, 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); the ‘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). In addition, 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 the addition of 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 in which 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, and episodic memory and associative learning in middle-aged men. However, similar associations were not observed in women. In addition, low serum creatinine was associated with low childhood school performance, low education, low annual income, smoking, and low physical activity in men and women. An important note is that all serum creatinine levels were within clinically normal range.

To the best of 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 the Tromsø Study of >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, for example, processing speed, working

memory, and associative learning, i.e., cognitive domains that were found to be associated 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 >2 million participants ≥45 years of age (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. From 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 that were not observed to be associated with serum creatinine levels in the present study. However, physical activity is associated with high serum creatinine; thus, physical activity might be linked to better memory function and learning via high serum creatinine levels and other pathways.

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 has 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 nonenzymatic 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 because, to the best of 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 its associations with cognitive performance[6–9]. Furthermore, several factors are linked to glomerular hyperfiltration such as renin-angiotensin-aldosterone system activation[12] and high renal generation and low systemic bioactivity of nitric oxide[41], which also have 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]. In addition, 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 be associated with subclinical cardiovascular disease markers such as carotid atherosclerosis and left ventricular hypertrophy[43] while high eGFR was found to be associated with coronary artery calcification[44]. However, glomerular hyperfiltration is typically defined using 95th percentile of GFR as the cutoff, 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; therefore, glomerular hyperfiltration may not entirely explain the present results.

Low serum creatinine could be a secondary indicator of adverse risk factors known to be associated 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 be associated 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 to high GFR because 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% to 50% of the patients have glomerular hyperfiltration[14]. Obesity also has been suggested to link with high GFR as it was observed to be associated with high GFR in teenaged and young adult White populations[15], as well as middle-aged Black Americans[19]. In addition, 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 40 to 55 years of age, 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 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.

There are limitations to be addressed. First, we did not have data to assess kidney function more accurately, for example, 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; 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 a unique and large population-based cohort, long follow-up, and repeatedly measured risk factor exposure several years before the cognitive testing.

We observed that within clinically normal range of serum creatinine, higher levels during adulthood are associated 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 an 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.

REFERENCES

1. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396:413–446.
2. 2020 Alzheimer's disease facts and figures. Alzheimer's Dement. 2020;16:391–460.
3. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–612.
4. Brodski J, Rossell SL, Castle DJ, Tan EJ. A systematic review of cognitive impairments associated with kidney failure in adults before natural age-related changes. J Int Neuropsychol Soc. 2019;25:101–114.
5. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet [online serial]. Elsevier Ltd; 2010;375:2073–2081. Accessed at: http://dx.doi.org/10.1016/S0140-6736(10)60674-5.
6. Rogne SO, Solbu MD, Arntzen KA, Herder M, Mathiesen EB, Schirmer H. Albuminuria and carotid atherosclerosis as predictors of cognitive function in a general population. Eur Neurol. 2013;70:340–348.
7. Kurella Tamura M, Wadley V, Yaffe K, et al. Kidney Function and Cognitive Impairment in US Adults: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis. Epub 2008.
8. Antunes JPV, Bulhões C, Fonte P, Abreu MJ, Oliveira R. Renal function and cognitive dysfunction: cross-sectional study of users enrolled at Ponte Family Health Unit. J Bras Nefrol. 2015;37:79–90.
9. Kang MW, Park S, Lee S, et al. Glomerular hyperfiltration is associated with dementia: A nationwide population-based study. PLoS One. 2020;15:1–12.
10. Baxmann AC, Ahmed MS, Marques NC, et al. Influence of muscle mass and physical

activity on serum and urinary creatinine and serum cystatin C. Clin J Am Soc Nephrol. 2008;3:348–354.

11. Sabia S, Nabi H, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Health behaviors from early to late midlife as predictors of cognitive function. Am J Epidemiol. 2009;170:428–437.
12. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: Definitions, mechanisms and clinical implications. Nat Rev Nephrol. Nature Publishing Group; 2012;8:293–300.
13. Inrig JK, Gillespie BS, Patel UD, et al. Risk for cardiovascular outcomes among subjects with atherosclerotic cardiovascular disease and greater-than-normal estimated glomerular filtration rate. Clin J Am Soc Nephrol. 2007;2:1215–1222.
14. Kanbay M, Ertuglu LA, Afsar B, et al. Renal hyperfiltration defined by high estimated glomerular filtration rate: A risk factor for cardiovascular disease and mortality. Diabetes, Obes Metab. 2019;21:2368–2383.
15. Turer CB, Baum M, Dubourg L, Selistre LS, Skinner AC. Prevalence of hyperfiltration among US youth/young adults with overweight and obesity: A population-based association study. Obes Sci Pract. 2019;5:570–580.
16. Melsom T, Mathisen UD, Ingebretsen OC, et al. Impaired fasting glucose is associated with renal hyperfiltration in the general population. Diabetes Care. 2011;34:1546–1551.
17. Okada R, Yasuda Y, Tsushita K, Wakai K, Hamajima N, Matsuo S. Glomerular hyperfiltration in prediabetes and prehypertension. Nephrol Dial Transplant. 2012;27:1821–1825.
18. Tomaszewski M, Charchar FJ, Maric C, et al. Glomerular hyperfiltration: A new marker of metabolic risk. Kidney Int [online serial]. Elsevier Masson SAS; 2007;71:816–821. Accessed at: http://dx.doi.org/10.1038/sj.ki.5002160.

19. Wuerzner G, Pruijm M, Maillard M, et al. Marked association between obesity and glomerular hyperfiltration: A cross-sectional study in an African population. Am J Kidney Dis [online serial]. Elsevier Inc.; 2010;56:303–312. Accessed at: http://dx.doi.org/10.1053/j.ajkd.2010.03.017.

20. Maeda I, Hayashi T, Sato KK, et al. Cigarette smoking and the association with glomerular hyperfiltration and proteinuria in healthy middle-aged men. Clin J Am Soc Nephrol. 2011;6:2462–2469.

21. Reboldi G, Verdecchia P, Fiorucci G, et al. Glomerular hyperfiltration is a predictor of adverse cardiovascular outcomes. Kidney Int [online serial]. Elsevier Inc; 2018;93:195–203. Accessed at: https://doi.org/10.1016/j.kint.2017.07.013.

22. Småbrekke S, Schirmer H, Melsom T, Solbu MD, Eriksen BO. Low-grade impairments in cognitive and kidney function in a healthy middle-aged general population: A cross-sectional study. BMC Nephrol. BMC Nephrology; 2019;20:1–9.

23. Raitakari OT, Juonala M, Rönnemaa T, et al. Cohort profile: The cardiovascular risk in young Finns study. Int J Epidemiol. 2008;37:1220–1226.

24. Rovio SP, Pahkala K, Nevalainen J, et al. Cognitive performance in young adulthood and midlife: Relations with age, sex, and education—The Cardiovascular Risk in Young Finns Study. Neuropsychology [online serial]. 2016;30:532–542. Accessed at: http://doi.apa.org/getdoi.cfm?doi=10.1037/neu0000239.

25. Liu RS, Burgner DP, Sabin MA, et al. Childhood Infections, Socioeconomic Status, and Adult Cardiometabolic Risk. Pediatrics [online serial]. 2016;137:934–942. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/27235447.

26. Mononen N, Lyytikäinen LP, Seppälä I, et al. Whole blood microRNA levels associate with glycemic status and correlate with target mRNAs in pathways important to type 2 diabetes. Sci Rep. 2019;9:1–14.

27. WHO Global Report on Diabetes. Global Report on Diabetes. Isbn [online serial]. 2016;978:6–86. Accessed at: https://sci-hub.si/https://apps.who.int/iris/handle/10665/204874%0Ahttps://apps.who.int/iris/bitstream/handle/10665/204874/WHO_NMH_NVI_16.3_eng.pdf?sequence=1%0Ahttp://www.who.int/about/licensing/copyright_form/index.html%0Ahttp://www.who.int/about/licens.

28. Mansikkaniemi K, Juonala M, Taimela S, et al. Cross-sectional associations between physical activity and selected coronary heart disease risk factors in young adults. The Cardiovascular Risk in Young Finns Study. Ann Med [online serial]. 2012;44:733–744. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/21721849.

29. Laitinen TT, Pahkala K, Magnussen CG, et al. Lifetime measures of ideal cardiovascular health and their association with subclinical atherosclerosis: The Cardiovascular Risk in Young Finns Study. Int J Cardiol. Elsevier Ireland Ltd; 2015;185:186–191.

30. Lounassalo I, Hirvensalo M, Kankaanpää A, et al. Associations of leisure-time physical activity trajectories with fruit and vegetable consumption from childhood to adulthood: The cardiovascular risk in young finns study. Int J Environ Res Public Health. 2019;16:1–17.

31. Karjalainen JP, Mononen N, Hutri-Kähönen N, et al. The effect of apolipoprotein E polymorphism on serum metabolome – a population-based 10-year follow-up study. Sci Rep. 2019;9:1–14.

32. Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure for estimating them. Sociol Methods Res. 2007;35:542–571.

33. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol. 2010;6:109–138.

34. Rovio SP, Pahkala K, Nevalainen J, et al. Cardiovascular Risk Factors From Childhood and Midlife Cognitive Performance: The Young Finns Study. J Am Coll Cardiol. 2017;69:2279–2289.

35. Hakala JO, Pahkala K, Juonala M, et al. Cardiovascular Risk Factor Trajectories Since Childhood and Cognitive Performance in Midlife: The Cardiovascular Risk in Young Finns Study. Circulation [online serial]. Lippincott Williams & WilkinsHagerstown, MD; 2021;143:1949–1961. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/33966448. Accessed May 24, 2021.

36. Hakala JO, Rovio SP, Pahkala K, et al. Physical Activity from Childhood to Adulthood and Cognitive Performance in Midlife. Med Sci Sports Exerc. 2019;51:882–890.

37. De Rover M, Pironti VA, McCabe JA, et al. Hippocampal dysfunction in patients with mild cognitive impairment: A functional neuroimaging study of a visuospatial paired associates learning task. Neuropsychologia [online serial]. Elsevier Ltd; 2011;49:2060–2070. Accessed at: http://dx.doi.org/10.1016/j.neuropsychologia.2011.03.037.

38. Spellman T, Rigotti M, Ahmari SE, Fusi S, Gogos JA, Gordon JA. Hippocampal-prefrontal input supports spatial encoding in working memory. Nature. Epub 2015.

39. Van Der Velpen V, Teav T, Gallart-Ayala H, et al. Systemic and central nervous system metabolic alterations in Alzheimer's disease. Alzheimer's Res Ther. Alzheimer's Research & Therapy; 2019;11:1–12.

40. Béard E, Braissant O. Synthesis and transport of creatine in the CNS: Importance for cerebral functions. J Neurochem. 2010;115:297–313.

41. Cherney DZI, Reich HN, Jiang S, et al. Hyperfiltration and effect of nitric oxide inhibition on renal and endothelial function in humans with uncomplicated type 1 diabetes mellitus. Am J Physiol - Regul Integr Comp Physiol. 2012;303:710–718.

42. Toda N. Age-related changes in endothelial function and blood flow regulation. Pharmacol Ther [online serial]. 2012;133:159–176. Accessed at: http://dx.doi.org/10.1016/j.pharmthera.2011.10.004.

43. Eriksen BO, Løchen ML, Arntzen KA, et al. Subclinical cardiovascular disease is associated

with a high glomerular filtration rate in the nondiabetic general population. Kidney Int [online serial]. Elsevier Masson SAS; 2014;86:146–153. Accessed at: http://dx.doi.org/10.1038/ki.2013.470.

44. Choi HM, Hyun YY, Lee KB, Kim H. High estimated glomerular filtration rate is associated with coronary artery calcification in middle-aged Korean men without chronic kidney disease. Nephrol Dial Transplant. 2015;30:996–1001.

45. Cachat F, Combescure C, Cauderay M, Girardin E, Chehade H. A systematic review of glomerular hyperfiltration assessment and definition in the medical literature. Clin J Am Soc Nephrol. 2015;10:382–389.

46. Gong X, Liang L, Chen Q, et al. Association Between Body Composition and Glomerular Hyperfiltration Among Chinese Adults. Ther Apher Dial. 2020;24:439–444.

47. Chakkera HA, Denic A, Kremers WK, et al. Comparison of high glomerular filtration rate thresholds for identifying hyperfiltration. Nephrol Dial Transplant. 2020;35:1017–1026.

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% CIs from linear regression models. All modelswere 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 4 CANTAB tests.

*The association of 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 by 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% 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 4 CANTAB tests.