Albuminuria and microalbuminuria as predictors of cognitive performance in a general population - an 11 year follow-up study

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Short running title: Albuminuria and cognitive decline

Abstract

Microalbuminuria, defined as urine albumin-to-creatinine ratio (UACR) > 3.0 mg/mmol and ≤ 30 mg/mmol, is an early marker of endothelial damage of the renal glomeruli. Recent research suggests an association among microalbuminuria, albuminuria (UACR > 3.0 mg/mmol) and cognitive impairment. Previous studies on microalbuminuria, albuminuria, and cognition in the middle-aged have not provided repeated cognitive testing at different time-points. We hypothesized that albuminuria (micro- plus macroalbuminuria) and microalbuminuria would predict cognitive decline independently of previously reported risk factors for cognitive decline, including cardiovascular risk factors. In addition, we hypothesized that UACR levels even below the cut-off for microalbuminuria might be associated with cognitive functioning. These hypotheses were tested in the Finnish nationwide, population-based Health 2000 Survey (*n*=5921, mean age 52.6, 55.0% women), and its follow-up, Health 2011 (*n*=3 687, mean age at baseline 49.3, 55.6% women). Linear regression analysis was used to determine the associations between measures of albuminuria and cognitive performance. Cognitive functions were assessed with verbal fluency, word-list learning, word-list delayed recall (at baseline and at follow-up), and with simple and visual choice reaction time tests (at baseline only). Here, we show that micro- plus macroalbuminuria associated with poorer word-list learning and a slower reaction time at baseline, with poorer word-list learning at follow-up, and with a steeper decline in word-list learning during 11 years after multivariate adjustments. Also, higher continuous UACR consistently associated with poorer verbal fluency at levels below microalbuminuria. These results suggest that UACR might have value in evaluating the risk for cognitive decline.

Keywords: cognition, cognitive decline, albuminuria, microalbuminuria, longitudinal study

Introduction

Midlife vascular risk factors, such as hypertension [1], dyslipidemia [1, 2], obesity [1], the metabolic syndrome [3], diabetes [4, 5], and insulin resistance even in non-diabetic individuals [6-8] increase the risk for cognitive decline and dementia later in life. Microalbuminuria is an early sign of endothelial damage of the renal glomeruli that has been associated with the aforementioned vascular risk factors [9]. It has been proposed that microalbuminuria would reflect not only renal, but also cerebral small vessel disease [10,11].

The vascular beds in the kidney and in the brain share many common features, since both the brain and the kidney are low resistance end-organs that are exposed to a high volume of blood flow [10]. More specifically, the vasculature of both the brain and the kidney are affected microscopically in similar ways by diseases such as diabetes or hypertension. In the kidneys the microscopic changes include gradual alterations of endothelial cells and the glomeruli, which result in the leakage of serum proteins into the urine. Possibly, a similar process at the blood-brain barrier could lead to the leakage of serum proteins into the brain tissue, presumably causing subtle cerebrovascular alterations [11].

Two recent meta-analyses on renal dysfunction, cognition and dementia risk suggest that albuminuria increases the risk for cognitive decline and dementia, but the evidence is still modest [12,13]. Microalbuminuria and albuminuria have been shown to increase the risk of poorer cognitive performance in elderly individuals in prospective studies [14-17]. Only a few longitudinal studies have assessed the association of albuminuria, microalbuminuria and cognition in middle-aged adults [18-20]. These studies showed an association among baseline albuminuria, increasing albuminuria, and poorer cognitive performance at follow-up.

To date, there are no studies with repeated cognitive testing in middle-aged individuals. We hypothesized that albuminuria (micro- plus macroalbuminuria) and microalbuminuria would

associate with poorer cognitive performance after 11 years, and with a greater decline in cognitive test scores from baseline to follow-up, independently of previously reported risk factors for cognitive decline. To test this hypothesis, we studied 3687 individuals who participated in the Finnish Health 2000 Survey and its 11-year follow-up, the Health 2011 Survey. In addition, we studied the cross-sectional associations among albuminuria, microalbuminuria, and cognition at baseline in 2000 (*n*=5921). The current cut-off for microalbuminuria is designed for risk-assessment and for treatment guidance, and it is not known if UACR levels below the cut-off for microalbuminuria are associated with cognitive performance [21]. To assess this question, we even evaluated the cross-sectional and longitudinal associations between continuous UACR and cognitive function in individuals with UACR levels below microalbuminuria.

Materials and methods

Study population

This study is based on data from the Finnish Health 2000 and Health 2011 Surveys, carried out in 2000–2001 and in 2011–2012 by the Finnish National Institute for Health and Welfare. In the Health 2000 Survey 8 028 individuals aged 30 years or older were randomly selected from the Finnish population registry, using a two-staged stratified cluster sampling procedure. The study population was a nationwide, representative sample of the Finnish adult population. 79% (*n*=6 354) attended the health examination proper [22]. In 2011 all the individuals who had been invited to participate in the original Health 2000 Survey, who were alive, and still lived in Finland, and who had not refused to participate, were invited to participate in the Health 2011 follow-up survey [23].

The studies were approved by the Ethics Committee for epidemiology and public health in the hospital district of Helsinki and Uusimaa, Finland. All participants gave written informed consent before attending the studies.

The baseline analyses of this study included 5921 individuals who attended the health examination proper in 2000–2001. Those with missing urine albumin-to-creatinine ratio (UACR) (*n*=96), with a fasting time < 4 hours (*n*=224), or with missing cognitive test scores at baseline (*n*=113) were excluded. In 2011–2012, 3687 of these 5921 individuals (62.2%) took part in the health examination proper or the home health examination and were included in the longitudinal analyses. A detailed flow chart of the study population is provided in Figure 1.

Clinical examination

At baseline, blood pressure was measured in sitting position from the right arm by a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany), and the average of two measurements was used for the analyses. Venous blood samples were drawn, the duration of fasting time was recorded, and the participants gave a spot urine sample [24].

Trained study nurses performed the cognitive tests in the Health 2000 and the Health 2011 Surveys. The participants were tested at baseline and at follow-up for verbal fluency, word-list learning, and word-list delayed recall according to the Finnish version of the CERAD test battery (The Consortium to Establish a Registry for Alzheimer´s Disease) [25, 26]. In the categorical verbal fluency test, the participants were asked to list as many animals as possible during one minute. This test represents language skills and executive functions. In the word-list learning test, ten words were shown to the participants. The participants were asked to read the words aloud, to memorize them and to repeat the words they remember within 90 seconds. In 2000, if all ten words were remembered after one round, the result was counted as

full 30 points. In 2011, all three rounds were repeated, regardless of whether all ten words had been remembered after the first round or not. The word-list learning test represents verbal learning and memory. After five minutes the participants were asked to recall all ten words (word-list delayed recall) [24, 27]. This test measures episodic memory, a part of cognition that is typically first impaired in AD.

The change in cognitive test scores during the follow-up was counted as cognitive test score in 2000 minus cognitive test score in 2011.

At baseline, the participants were also tested for simple and visual choice reaction time with a computer program (Good Response, Metitur Co., Jyväskylä, Finland). The participants had to react as quickly as possible by shifting the index finger of their writing hand from the waiting switch to a light that lit up 12 times at random intervals. In the simple reaction time test the same light lit up 12 times. In the visual choice reaction time test the light lit up 12 times at different parts of the panel. The participants were allowed to practice both tests three times, and more if needed, before the actual test runs. [24, 28]

The raw scores of the cognitive tests were used for the analyses.

Laboratory examinations

Urine albumin and urine creatinine were determined in 2015 from the frozen urine samples taken in 2000. Urine albumin (mg/l) was measured by an immunoturbidimetric method (Abbott Laboratories, Abbott Park, IL, USA) and urine creatinine (mmol/l) by an enzymatic method (Abbott Laboratories, Abbott Park, IL, USA). The detection limit for urine albumin was 1.0 mg/l and for urine creatinine 0.19 mmol/l. [24] Urine albumin to creatinine ratio (UACR, mg/mmol) was counted as urine albumin divided by urine creatinine. Microalbuminuria was defined as UACR >3.0 mg/mmol and ≤30.0 mg/mmol and

macroalbuminuria as UACR >30.0 mg/mmol. Albuminuria was defined as UACR >3.0 mg/mmol (microalbuminuria plus macroalbuminuria).

Plasma creatinine (μmol/l) was analyzed by an enzymatic method (Abbott Laboratories, Abbott Park, IL, USA) from the frozen plasma samples and the detection limit was 8.8 μmol/l. Glomerular filtration rate (eGFR) was estimated by the Modification of Diet in Renal Disease (MDRD) equation [29].

Serum total cholesterol values were determined by a CHOD PAP test (Olympus system reagent, Hamburg, Germany), and glucose by a hexokinase test (Olympus System Reagent, Germany). Serum insulin (μU/ml) was determined by a microparticle enzyme immunoassay (Abbott Laboratories, Dainabot, Tokyo, Japan). [24]. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was used to estimate insulin resistance and counted by the equation fasting insulin (μU/ml) times fasting glucose (mmol/l) divided by 22.5 [30].

Covariates

Information on years of formal education, smoking, medical history and medication were obtained by a questionnaire. Body mass index (BMI) was counted based on the weight and height measured in the health examination proper in 2000 by the equation (weight in kilograms)^2 divided by height in meters. Beck's Depression Inventory (BDI) score [31] was used to evaluate depressive symptoms. Hypertension was defined as systolic RR ≥140 or diastolic ≥90 mmHg or use of antihypertensive treatment. Individuals using oral diabetes medication or insulin or who had fasting glucose values >7.0 mmol/l were classified as having diabetes (either type 1 or type 2). History of stroke and myocardial infarction were obtained from medical records, national registries, by interview, and for myocardial infarction also based on ECG criteria. *APOEε4* genotype was available from 5637 (95.2%) individuals who had given written consent for DNA sampling. *APOE* epsilon genotyping was performed

with the MassARRAY system (Sequenom, San Diego, California) with a modified protocol which is described elsewhere [32]. *APOEε4* genotype was considered positive for subjects with one or two epsilon 4 alleles.

Statistical analysis

Only 1% (*n*=61) of our study population had macroalbuminuria at baseline and thus, these individuals were included in the original analyses. To evaluate if the small proportion of individuals with macroalbuminuria were driving the associations between albuminuria (microalbuminuria plus macroalbuminuria) and cognition, cross-sectional and longitudinal analyses were performed also after the exclusion of individuals with macroalbuminuria. Micro- plus macroalbuminuria and microalbuminuria were treated as dichotomous variables in the analyses. To evaluate if UACR levels below the 3.0 mg/mmol cut-off for microalbuminuria were associated with cognition, cross-sectional analyses between continuous UACR and cognitive test scores were performed in the 92% of the study population without micro- or macroalbuminuria, and longitudinal analyses in the 95% without micro- or macroalbuminuria.

Before the analyses the normality of the distributions of all the variables were evaluated by inspecting the histograms. The distributions of UACR, BDI score, HOMA-IR, and the simple and visual choice reaction time tests were skewed to the right. Thus, to achieve a normal distribution the skewed distributions were corrected with a logarithmic transformation ($\log_e$) before the analyses. Differences between individuals with and without albuminuria, and differences between the individuals who were included in the longitudinal analyses (*n*=3987) and those who did not participate in the health examinations at follow-up or had died (*n*=2234) were analyzed with Pearson´s ChiSquare test for categorical variables and with Student´s *t*-test for continuous variables.

The associations among dichotomous micro- plus macroalbuminuria and microalbuminuria, and continuous UACR with the cognitive tests were analyzed with linear regression analysis. In Model 1, adjustments were made for age, sex and years of education. In the multivariate adjusted Model 2, further adjustments were made for eGFR, APOEε4 genotype, depressive symptoms (BDI score), history of stroke, history of myocardial infarction, diabetes, current smoking, hypertension, medication for elevated serum lipids, serum total cholesterol and BMI. The analyses for the change in cognitive test scores from 2000 to 2011 were adjusted even for baseline cognitive test scores in both models.

Additional analyses where adjustments were made even for logarithmic HOMA-IR were performed for the analyses considering continuous UACR and cognitive tests (Model 3), because continuous UACR associated with poorer verbal fluency and we have previously found an association between HOMA-IR and verbal fluency in the same study population [8,33].

Statistical significance was set at $p<0.05$ for all other analyses except for interaction testing, where statistical significance was set at $p<0.1$.

The analyses were performed with SAS JMP 12.0 Pro (SAS Institute, Cary, NC, USA).

Interactions

The interactions of 'baseline albuminuria × diabetes', 'albuminuria × eGFR', 'albuminuria × hypertension', 'albuminuria × sex', 'albuminuria × *APOE*ε4 genotype' and 'albuminuria × age' on cognitive test scores at baseline, and on cognitive test scores at follow-up were tested in Model 2. The interactions of 'albuminuria × sex' were significant for verbal fluency ($p=0.05$) and for word-list delayed recall at baseline ($p=0.06$), and for word-list delayed recall at follow-up ($p=0.08$). The interaction of 'albuminuria × eGFR' was only significant for word-list delayed recall at follow-up ($p=0.08$). The interaction for 'albuminuria × diabetes'

was only significant for word-list learning at baseline (p=0.07). Albuminuria interacted significantly with age on the word-list learning (p=0.08) and the simple reaction time test (p=0.009) at baseline. The interactions of 'albuminuria × eGFR' (all p-values >0.19), 'albuminuria × hypertension' (all p-values >0.25), or 'albuminuria × *APOE*ε4 genotype' (all-p-values >0.51) were not significant for any of the cognitive tests at baseline. There were no further significant interactions for albuminuria and the aforementioned covariates on the cognitive test scores at follow-up. Stratified analyses were performed according to interaction testing.

Results

The individuals who participated in the follow-up analyses (n=3687) were younger (49.3 vs. 57.9 years at baseline, p<0.0001), more educated (12.0 vs. 9.9 years of formal education, p<0.0001), and had less often micro- or macroalbuminuria (4.6% vs. 13.2%, p<0.0001) than those who had died, had refused to be contacted or to participate, or who did not attend the health examination in 2011 (Figure 1, n=2234 in total). The proportion of women was similar in both groups (55.6% vs. 54.1%, p=0.26) (data not shown).

There were significant differences in the baseline characteristics between individuals with and without micro- plus macroalbuminuria (Table 1). Table 2 shows the characteristics at baseline of the individuals who attended the follow-up examination. Those with micro- or macroalbuminuria were older, less educated, more often female than male, and had lower eGFR than individuals without micro- or macro albuminuria. In addition, the prevalence of diabetes, hypertension, and treatment for elevated serum lipids were greater in the albuminuria group (for p-values, see Tables 1 and 2).

Micro- plus macroalbuminuria, microalbuminuria, and continuous UACR at levels below microalbuminuria were associated with poorer cognitive test scores at baseline and at follow-

up, and with a greater decline in cognitive test scores during 11 years when adjustments were made for age, sex and education (Model 1, Tables 3, 4, and 5, and Figures 2 and 3). After adjustments for previously reported risk factors for cognitive decline these associations were less clear, albeit still statistically significant for some of the cognitive tests at baseline and at follow-up (Model 2, Tables 3, 4, and 5).

Micro- plus macroalbuminuria, microalbuminuria, continuous UACR, and baseline cognition

At baseline, micro- plus macroalbuminuria was associated with poorer word-list learning (p=0.02) and with a slower simple (p=0.002) and visual choice reaction time (p=0.001), but not with verbal fluency (p=0.63) or word-list delayed recall (p=0.91) in Model 2. After excluding people with macroalbuminuria (n=61) from the baseline analyses, also microalbuminuria alone was associated with a slower simple (p=0.01) and visual choice reaction time (p=0.003) in the multivariate Model 2. Higher continuous logarithmic UACR at levels below microalbuminuria was associated with poorer performance on the verbal fluency test (p=0.03), and with a slower response on the simple reaction time test (p=0.005) in Model 2. These associations remained significant even after adjusting for HOMA-IR (Table 3).

Micro- plus macroalbuminuria, microalbuminuria, and continuous UACR as predictors of cognitive performance at follow-up

At follow up 11 years after baseline, baseline micro- plus macroalbuminuria was associated with a lower word-list learning score (p=0.02), but not with verbal fluency (p=0.15), or with word-list delayed recall (p=0.07) in Model 2. After excluding individuals with macroalbuminuria (n=15), the associations between microalbuminuria and cognition were no longer significant (all p-values >0.08).

Figure 3 shows the age, sex and education adjusted means of cognitive test scores according to tertiles of UACR at levels below microalbuminuria (Model 1). Higher continuous logarithmic UACR at levels below microalbuminuria predicted a poorer verbal fluency score in Model 2 (p=0.03), and in Model 3, further adjusted for HOMA-IR (p=0.04). The associations between continuous UACR and word-list learning (p=0.78), or word-list delayed recall (p=0.59) were not significant in Model 2. (Table 4).

Micro- plus macroalbuminuria, microalbuminuria and continuous UACR as predictors of cognitive decline during 11 years

Micro- plus macroalbuminuria predicted a greater decline during 11 years in word-list learning (p=0.02) in Model 2. The associations between micro- plus macroalbuminuria and verbal fluency (p=0.09) or word-list delayed recall (p=0.07) were no longer significant in the multivariate analyses in Model 2. The standardized estimates of all the parameters included in Model 2 are presented in Table 6, allowing the comparison of the independent value of each of the covariates. Smoking and diabetes accounted for the attenuation of the association between albuminuria and a decline in word-list learning. After the exclusion of individuals with macroalbuminuria (n=15), the association between microalbuminuria and a greater decline in word-list learning was no longer statistically significant (p=0.06). There was no association between microalbuminuria and a decline in verbal fluency (p=0.28) or word-list delayed recall (p=0.29). (Table 5).

Continuous UACR at levels below microalbuminuria associated with a greater decline in verbal fluency during the follow-up (p=0.03) in Model 2. In this model, continuous UACR was not associated with a decline on the other two cognitive tests (p-values 0.17 and 0.73 for word-list learning and word-list delayed recall, respectively). Further adjustments for HOMA-

IR yielded similar results (*p*-values 0.03, 0.19, and 0.71 for verbal fluency, word-list learning, and word-list delayed recall, respectively) (Table 5).

Analyses stratified by sex, age, eGFR and diabetes

Age-, sex-, eGFR- and diabetes stratified analyses were performed in the multivariate Model 2 according to the interaction analyses described in the Methods section.

In the analyses stratified by sex, no significant associations were found between micro- plus macroalbuminuria and verbal fluency (men: β=0.79, SE=0.68, *p*=0.25; women: β= -0.69, SE=0.45, *p*=0.12) or word-list delayed recall (men: β=0.24, SE=0.16, *p*=0.14; women: β= -0.14, SE=0.12, *p*=0.26) at baseline. In contrast, the association between micro- plus macroalbuminuria and word-list delayed recall at follow-up was significant in women only (men: β=0.14, SE=0.29, *p*=0.63; women: β= -0.47, SE=0.19, *p*=0.01).

Cross-sectional age-stratified analyses among micro- plus macroalbuminuria and the word-list learning and the simple reaction time tests were performed separately in individuals between 30 and 64 years of age (n=4607), and in individuals 65 years or older (n=1314). Continuous age was left as a covariate in the stratified analysis. The associations between albuminuria and word-list learning (30–64 years: β= -0.09, SE 0.27, p=0.73; ≥65 years: β= -0.43, SE 0.34, p=0.20), or reaction time was not significant in either group (30–64 years: β=0.03, SE 0.02, *p*=0.08; ≥65 years: β=0.02, SE 0.02, *p*=0.32).

For analyses stratified by eGFR the follow-up study population was divided into two groups according to the cut-off for normal eGFR i.e. 90 ml/min/1.73 m^3 (eGFR<90, *n*=917; eGFR≥90, *n*=2730). In these stratified analyses albuminuria was associated with lower word-list delayed recall at follow-up in individuals with impaired kidney function (eGFR < 90 ml/min/1.73m^3; β=-0.86, SE=0.36, *p*=0.02), but not in those who had normal kidney function (β=-0.17, SE=0.18, *p*=0.36). Only 24 individuals who participated in the follow-up

examination had eGFR <60 ml/min/1.73 m^3 at baseline, and therefore no statistical analyses were performed separately in these individuals with moderate loss of kidney function. Excluding individuals with eGFR <60 ml/min/1.73 m^3 did not change these results.

In the cross-sectional analyses of micro- plus macroalbuminuria stratified by diabetes status, the association between micro- plus macroalbuminuria and lower word-list learning was statistically significant only in individuals with diabetes (β= -1.61, SE=0.61, *p*=0.009; no diabetes: β= -0.32, SE=0.22, *p*=0.15).

Discussion

Our results showed that micro- plus macroalbuminuria, microalbuminuria alone, and even UACR at levels below microalbuminuria were associated with poorer cognitive performance cross-sectionally and longitudinally in the Finnish adult population. However, after multivariate adjustments for previously reported risk factors for cognitive decline and vascular risk factors, these associations were less clear. Also, the associations between micro- plus macroalbuminuria and cognition were largely driven by the very small proportion of individuals with macroalbuminuria at baseline. Nevertheless, we have shown that measures of albuminuria associate with poorer verbal fluency, word-list learning and with simple and visual choice reaction time cross-sectionally, and with poorer verbal fluency and word-list learning longitudinally.

Our results are consistent with the previous literature [14-20] indicating that microalbuminuria associates with poorer cognitive performance. We extend the findings of the previous longitudinal REGARDS [18], PREVEND [19] and Tromsø [20] studies on middle-aged populations by providing cognitive testing at two time points 11 years apart. The Tromsø study assessed cognitive functioning with five different cognitive tests at the follow-up visit, but no cognitive tests were performed at baseline [20]. The REGARDS study

used only the six-item screener, a crude screening test, to assess cognitive impairment, and this test was performed only at the follow-up visit [18]. The PREVEND study assessed cognitive function only at follow-up with the Ruff Figural Fluency Test [19].

In our study, the association between micro- plus macroalbuminuria and poorer cognition was most consistent for word-list learning, reflecting learning and verbal memory, and the simple and visual choice reaction time tests, reflecting psychomotor speed and executive function, respectively. In line with our results, albuminuria predicted poorer executive function (the digit-symbol test) and slower motor tempo (the finger-tapping test) in the Tromsø study. In contrast to our findings, the Tromsø study found no association with albuminuria and the 12-word test, an equivalent of the word-list learning test we used. [20]

Interestingly, higher UACR at levels below microalbuminuria consistently associated with a lower verbal fluency score at baseline and at follow-up. We have previously shown that insulin resistance, measured with HOMA-IR, associates with poorer verbal fluency in the same study population [8, 33]. In the present study, analyses adjusted even for HOMA-IR showed that both logarithmic UACR and HOMA-IR were independently associated with a lower verbal fluency score both cross-sectionally and longitudinally. This could indicate that the detrimental effects of insulin resistance on the vasculature [34] would result in low-grade albuminuria in the kidneys, and possibly a simultaneous leak of proteins to the brain tissue that could lead to cerebrovascular changes such as white matter lesions. Thus, the associations among both HOMA-IR and low-grade albuminuria with poorer cognitive function could reflect underlying subtle cerebrovascular changes. The difference in verbal fluency scores at follow-up between the highest and lowest tertile of UACR at levels below microalbuminuria was approximately 0.9 points (adjusted for age, sex, and education, Figure 3). This difference is subtle, and it does not imply cognitive impairment that would be clinically relevant. However, the estimated decline in verbal fluency per year of aging was 0.23 points in the

present study, which means that the difference in verbal fluency scores between the highest and lowest tertile of UACR would correspond to four years of aging.

The sex stratified analyses showed that baseline micro- plus macroalbuminuria predicted a lower word-list delayed recall score at follow-up in women only. The Tromsø study also reported sex differences, which varied according to cognitive tests. Higher UACR associated with a lower digit symbol test score in women only, whilst a greater change in UACR associated with a poorer finger-tapping test score only in men [20]. Analyses stratified for diabetes in the present study showed that the cross-sectional association between micro- plus macroalbuminuria and poorer word-list learning was significant only in individuals with diabetes. The lack of an interaction between albuminuria and age indicates that the associations between measures of albuminuria and cognition reported here were not age-dependent. Our results concerning the eGFR stratified analyses are partly in contrast with the findings from the REGARDS study, which reported that albuminuria associated with poorer cognitive performance only when kidney function was preserved (eGFR $\geq$60 mmol/min/1.73m^3) [18]. Our results indicated that albuminuria would associate with poorer word-list delayed recall only when kidney function was mildly impaired (eGFR was below 90 mmol/min/1.73m^3), and not in individuals with normal kidney function. However, we only found significant interactions between albuminuria and eGFR on one cognitive test at follow-up, indicating that the interaction between albuminuria and eGFR on cognition was mostly non-significant.

The theory of a kidney-brain connection, suggesting that microalbuminuria and albuminuria could possibly reflect a simultaneous leakage of proteins through the blood-brain barrier and changes in brain structure and pathology [11], is supported by brain magnetic resonance imaging studies. Microalbuminuria has been shown to associate with a greater risk for lacunar infarcts and cerebral white matter hyperintensities [35], and with cerebral microbleeds [36].

Also, greater UACR has been associated with lower gray matter volume in the frontal lobes and with poorer executive function [37], and with brain atrophy [38]. These structural changes could partly explain the cognitive decline associated with albuminuria.

Our study had limitations. The first is the single measurement of UACR at baseline from a spot urine sample. UACR is affected by exercise and the time of day the sample is given [39], which is why repeated measurements would be preferred. Also, the results concerning UACR values below the cut-off for microalbuminuria need to be interpreted with caution, since the detection of urine albumin and creatinine might not be accurate at these low levels. The proportion of individuals with micro- or macroalbuminuria was small in our study population, and 63.6% of the individuals who had micro- or macroalbuminuria at baseline did not attend the follow-up examination. Thus, the longitudinal results on micro- or macroalbuminuria and cognition are likely to be diluted. The word-list learning test was performed slightly differently at baseline and at follow-up, which may have affected the results of both word-list learning and word-list delayed recall. However, only 24 individuals had gained full 30 points in the word-list learning test at baseline, and thus it is unlikely that the difference in performing this test at baseline and at follow-up would have interfered with our results. Obvious strengths of our study are the large sample size of a nationally representative adult population sample; the 11-year follow-up time; the possibility to adjust for a wide variety of cardiovascular and other cognitive risk factors; and that the cognitive tests were performed at two time-points.

In conclusion, we showed that individuals with micro- and macroalbuminuria represent a risk group for cognitive decline. As the prevalence of micro- and macroalbuminuria was low, and many other vascular risk factors were more common in the individuals with micro- or macroalbuminuria than in those without, the added value of measuring micro- or albuminuria to predict future cognitive decline might be modest. However, we have shown that also

UACR values at levels below the cut-off for microalbuminuria associate with a decline in verbal fluency independently of other risk factors for cognitive decline. Thus, in the general population, the detection of very low levels of albuminuria could be an early sign of cognitive decline, possibly reflecting the early phases of brain microvascular disease. In the future, to assess the associations among low-grade albuminuria and cerebrovascular disease and/or Alzheimer´s disease neuropathology, longitudinal studies utilizing neuroimaging would be needed.

Conflicts of interest: The authors report no potential financial or other conflicts of interest relevant to this article.

Acknowledgements:
The authors sincerely thank all the volunteers who participated in the Health 2000 and the Health 2011 surveys for their generous contribution. The authors thank Kaisa Silander, Mari Kaunisto, and the staff of the Technology Centre, Institute for Molecular Medicine Finland (FIMM), University of Helsinki, for the APOE genotyping work.

Author contribution: L.L.E. and J.K.J. analyzed the data, and L.L.E. and S.T. wrote the manuscript. L.L.E., S.T., J.K.J., J.O.R., P.P., M.V., and A.J. planned this study. S.T., J.K.J., J.S., S.K., J.O.R., P.P., M.V., and A.J. critically revised and edited the manuscript for important intellectual content. J.S., S.K., and A.J. took part in designing the Health 2000 and 2011 surveys. All authors approved the final version of the manuscript to be published. L.L.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: This study was supported by personal grants from the Finnish Brain Foundation (Suomen Aivosäätiö) (L.L.E.), the Paulo Foundation (L.L.E.), the Orion Research Foundation (L.L.E), the Uulo Arhio Foundation (S.T.), and Finnish Governmental Research Funding for

Turku University Hospital and Turku City Hospital. The funders of this study had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

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Table 1. Characteristics of the study population at baseline according to baseline albuminuria.

	No albuminuria: UACR ≤ 3.0 mg/mmol	***Micro- plus macroalbuminuria: UACR > 3.0 mg/mmol***	***p-value***
n/%	5459/92.2	462/7.8	
Female (n/%)	2964/54.3	293/63.4	0.0002
Age (years)	51.7 (14.2)	62.8 (16.5)	<0.0001
Years of education	11.4 (4.1)	9.2 (3.9)	<0.0001
APOEε4 genotype[a]	1653/32.2	125/29.3	0.20
Beck's depression inventory score	6.9 (6.9)	8.8 (7.1)	<0.0001
VASCULAR RISK FACTORS			
UACR (mg/mmol)	0.55 (0.54)	17.8 (38.2)	<0.0001
Plasma creatinine (μmol/l)	72 (14)	75 (27)	0.02
eGFR (ml/min/1.73 m^2)	105 (24)	102 (31)	0.06
Diabetes (n/%)	196/3.4	91/19.7	<0.0001
Smokers (n/%)	1162/21.4	101/22.0	0.76
Hypertension (n/%)	2469/45.4	348/75.5	<0.0001
Treatment for elevated serum lipids (n/%)	312/6.2	44/10.1	0.002
Total cholesterol (mmol/l)	5.9 (1.1)	6.1 (1.2)	0.003
History of stroke (n/%)	173/3.2	49/10.6	<0.0001
History of myocardial infarct (n/%)	170/3.1	41/8.9	<0.0001
BMI (kg/m^2)	26.8 (4.5)	28.0 (5.7)	<0.0001
HOMA-IR	2.15 (2.20)	4.70 (16.5)	<0.0001
COGNITIVE TEST SCORES			
Verbal fluency	24.0 (7.2)	21.3 (7.1)	<0.0001
Word-list learning	20.8 (4.4)	18.4 (5.3)	<0.0001
Word-list delayed recall	7.1 (2.0)	6.1 (2.3)	<0.0001
Simple reaction time (ms)	33 (8)	37 (14)	<0.0001
Visual choice reaction time (ms)	47 (13)	55 (18)	<0.0001

The values are given as mean (SD), unless stated otherwise. UACR= urine albumin-to-creatinine ratio. *P*-values for differences between individuals with and without albuminuria, assessed with Student´s *t*-test for continuous variables and χ^2 test for categorical variables. A logarithmic transformation ($\log_e$) is used for the analyses of Beck´s depression inventory score, UACR, HOMA-IR and the simple and visual choice reaction time tests to achieve a normal distribution.

[a] APOEε4 genotype stands for an individual with one or two ε4 alleles.

Table 2. Characteristics of the participants of the follow-up analyses at baseline, and cognitive test scores at baseline and at follow-up, according to baseline albuminuria.

	No albuminuria: UACR ≤ 3.0 mg/mmol	***Micro- plus macroalbuminuria: UACR > 3.0 mg/mmol***	***p-value***
n/%	3519/95.4	168/4.6	
Female (%)	1933/54.9	116/69.0	0.0003
Age (years)	49.1 (11.9)	54.4 (14.0)	<0.0001
Years of education	12.1 (3.9)	10.8 (3.8)	<0.0001
APOEε4 genotype[a]	1065/32.2	51/32.2	0.99
Beck's depression inventory score	6.5 (6.6)	7.7 (6.8)	0.15
VASCULAR RISK FACTORS			
UACR (mg/mmol)	0.51 (0.49)	12.9 (23.8)	<0.0001
Plasma creatinine (µmol/l)	71 (13)	69 (16)	0.08
eGFR (ml/min/1.73 m^2)	106 (23)	111 (28)	0.05
Diabetes (n/%)	78/2.2	23/13.7	<0.0001
Smokers (n/%)	662/18.9	32/19.2	0.93
Hypertension (n/%)	1377/39.3	114/67.9	<0.0001
Treatment for elevated serum lipids (n/%)	180/5.6	20/12.6	0.0002
Total cholesterol (mmol/l)	5.9 (1.1)	6.1 (1.1)	0.01
History of stroke (n/%)	74/2.1	10/6.0	0.001
History of myocardial infarct (n/%)	51/1.4	7/4.2	0.006
BMI (kg/m^2)	26.6 (4.3)	28.7 (6.6)	<0.0001
HOMA-IR	1.94 (1.71)	4.83 (14.9)	<0.0001
COGNITIVE TEST SCORES AT BASELINE			
Verbal fluency	25.0 (7.0)	23.8 (7.0)	0.03
Word-list learning	21.6 (3.9)	20.7 (4.3)	0.009
Word-list delayed recall	7.5 (1.8)	7.1 (2.0)	0.02
COGNITIVE TEST SCORES AT FOLLOW-UP			
Verbal fluency	24.4 (7.4)	21.6 (7.5)	<0.0001
Word-list learning	21.3 (4.4)	19.5 (5.3)	<0.0001
Word-list delayed recall	7.3 (2.1)	6.5 (2.6)	0.0002

The values are given as mean (SD), unless stated otherwise. UACR= urine albumin-to-creatinine ratio. *P*-values for differences between individuals with and without albuminuria, assessed with Student´s *t*-test for continuous variables and χ^2 test for categorical variables. A logarithmic transformation ($\log_e$) is used for the analyses of Beck´s depression inventory score, UACR, and HOMA-IR to achieve a normal distribution.

[a] APOEε4 genotype stands for an individual with one or two ε4 alleles.

Table 3. Cross-sectional associations among dichotomous micro- or macroalbuminuria, microalbuminuria, continuous UACR, and cognitive test scores at baseline.

	Cognitive test score in 2000				
Predictors of cognitive performance (β(SE))	***Verbal fluency***	***Word-list learning***	***Word-list delayed recall***	***Simple reaction time [a]***	***Visual choice reaction time [a]***
Micro- and macroalbuminuria, n=5921					
Model 1	-0.58 (0.32)	-0.60 (0.18)***	-0.18 (0.08)	0.05 (0.01)***	0.05 (0.01)***
Model 2	-0.18 (0.37)	-0.46 (0.21)*	-0.02 (0.10)	0.04 (0.01)**	0.04 (0.01)**
Microalbuminuria (macroalbuminuria excluded), n=5860					
Model 1	-0.54 (0.34)	-0.48 (0.19)*	-0.12 (0.09)	0.05 (0.01)***	0.04 (0.01)***
Model 2	-0.09 (0.40)	-0.35 (0.22)	0.005 (0.10)	0.03 (0.01)*	0.04 (0.01)**
Continuous UACR in individuals without micro- or macroalbuminuria, n=5459					
Model 1	-0.29 (0.10)**	-0.09 (0.05)	-0.03 (0.03)	0.01 (0.003)***	0.006 (0.003)
Model 2	-0.25 (0.12)*	-0.03 (0.06)	-0.02 (0.03)	0.01 (0.004)**	0.005 (0.004)
Model 3	-0.24 (0.12)*	-0.03 (0.06)	-0.02 (0.03)	0.01 (0.004)**	0.005 (0.004)

Estimates (β) and standard errors (SE) are derived from multivariate linear regression analyses.

Model 1: Adjusted for age, sex and years of education.

Model 2: Further adjusted for APOEε4 genotype, Beck´s depression inventory score, diabetes, history of stroke and history of myocardial infarction, BMI, estimated GFR, current smoking, hypertension, serum total cholesterol, and treatment for elevated serum lipids.

Model 3: Adjusted even for HOMA-IR.

*P<0.05, **P<0.01, ***P<0.001.

[a] Note that a positive association with the reaction time tests indicates a slower i.e. a poorer reaction time for individuals with albuminuria, microalbuminuria or higher UACR.

A logarithmic transformation ($\log_e$) of the simple and visual choice reaction time tests, UACR, Beck´s depression inventory score and HOMA-IR is used for the analyses, to achieve a normal distribution.

Table 4. Longitudinal associations among baseline dichotomous micro- or macroalbuminuria, microalbuminuria, continuous UACR, and cognitive test scores at follow-up.

	Cognitive test score in 2011		
Predictors of cognitive performance (β(SE))	***Verbal fluency***	***Word-list learning***	***Word-list delayed recall***
Micro- and macroalbuminuria, n=3687			
Model 1	-1.39 (0.54)**	-0.94 (0.29)**	-0.41 (0.14)**
Model 2	-0.85 (0.60)	-0.77 (0.33)*	-0.29 (0.16)
Microalbuminuria (macroalbuminuria excluded), n=3672			
Model 1	-1.21 (0.56)*	-0.85 (0.30)**	-0.33 (0.15)*
Model 2	-0.57 (0.62)	-0.61 (0.34)	-0.18 (0.17)
Continuous UACR in individuals without micro- or macroalbuminuria, n=3519			
Model 1	-0.33 (0.13)*	-0.07 (0.07)	0.003 (0.93)
Model 2	-0.35 (0.16)*	-0.02 (0.09)	0.02 (0.04)
Model 3	-0.34 (0.16)*	-0.02 (0.09)	0.02 (0.04)

Estimates (β) and standard errors (SE) are derived from multivariate linear regression analyses.

Model 1: Adjusted for age, sex and years of education.

Model 2: Further adjusted for APOEε4 genotype, Beck´s depression inventory score, diabetes, history of stroke and history of myocardial infarction, BMI, estimated GFR, current smoking, hypertension, serum total cholesterol, and treatment for elevated serum lipids.

Model 3: Adjusted even for HOMA-IR.

*P<0.05, **P<0.01, ***P<0.001.

A logarithmic transformation ($\log_e$) of UACR, Beck´s depression inventory score and HOMA-IR is used for the analyses, to achieve a normal distribution.

Table 5. Longitudinal associations among baseline dichotomous micro- or macroalbuminuria, microalbuminuria, continuous UACR, and change in cognitive test scores from 2000 to 2011.

	Change in cognitive test scores from 2000 to 2011		
Predictors of cognitive performance (β(SE))	***Verbal fluency***	***Word-list learning***	***Word-list delayed recall***
Micro- and macroalbuminuria, n=3687			
Model 1	1.26 (0.44)**	0.81 (0.25)**	0.36 (0.12)**
Model 2	0.83 (0.49)	0.67 (0.29)*	0.26 (0.14)
Microalbuminuria (macroalbuminuria excluded), n=3672			
Model 1	1.10 (0.46)*	0.78 (0.26)**	0.29 (0.13)*
Model 2	0.55 (0.51)	0.56 (0.30)	0.16 (0.15)
Continuous UACR in individuals without micro- or macroalbuminuria, n=3519			
Model 1	0.19 (0.11)	0.11 (0.06)	0.02 (0.03)
Model 2	0.28 (0.13)*	0.10 (0.08)	0.01 (0.04)
Model 3	0.28 (0.13)*	0.10 (0.08)	0.01 (0.04)

Estimates (β) and standard errors (SE) are derived from multivariate linear regression analyses.

Model 1: Adjusted for age, sex and years of education.

Model 2: Further adjusted for APOEε4 genotype, Beck´s depression inventory score, diabetes, history of stroke and history of myocardial infarction, BMI, estimated GFR, current smoking, hypertension, serum total cholesterol, and treatment for elevated serum lipids.

Model 3: Adjusted even for HOMA-IR.

*P<0.05, **P<0.01, ***P<0.001.

Note that a positive association with the change in cognitive tests scores indicates a greater decline from 2000 to 2011 for individuals with micro- and macroalbuminuria, microalbuminuria, or higher levels of UACR.

A logarithmic transformation ($\log_e$) of UACR, Beck´s depression inventory score and HOMA-IR is used for the analyses, to achieve a normal distribution.

Table 6. Standardized estimates of all the parameters in Model 2 for the analyses between baseline albuminuria and the change in cognition from 2000 to 2011.

	Change in cognitive test scores from 2000 to 2011		
Baseline predictors of cognitive performance (standardized estimates)[a]	***Verbal fluency***	***Word-list learning***	***Word-list delayed recall***
Micro- and macroalbuminuria	0.03	0.04*	0.03
age	0.27***	0.32***	0.32***
education	-0.12***	-0.18***	-0.14***
sex[b]	-0.04	-0.13***	-0.18***
Baseline cognitive test score	0.47***	0.51***	0.47***
APOEε4 genotype	0.03	0.0006	0.02
BMI	-0.01	-0.01	-0.02
diabetes	0.02	0.04*	0.01
hypertension	0.03	0.02	0.02
stroke	0.003	0.005	0.003
myocardial infarction	-0.01	-0.01	-0.03
smoking	0.01	0.05**	0.05**
total cholesterol	0.01	0.003	0.02
medication for elevated serum lipids	0.02	0.02	0.03
Beck´s depression inventory	0.01	0.02	0.01
eGFR	0.03	0.006	0.05*

The analyses were performed with multivariate linear regression, adjusted for all the parameters shown in the table. A logarithmic transformation was used of Beck´s depression inventory score.

*P<0.05; **P<0.01, ***P<0.001.

[a]Note that a positive estimate indicates a greater decline during the follow up for individuals with albuminuria, higher age, BMI etc.

[b]Note that a negative estimate for sex indicates a greater decline in men than in women.

Figure 1. Flow chart of the study population.

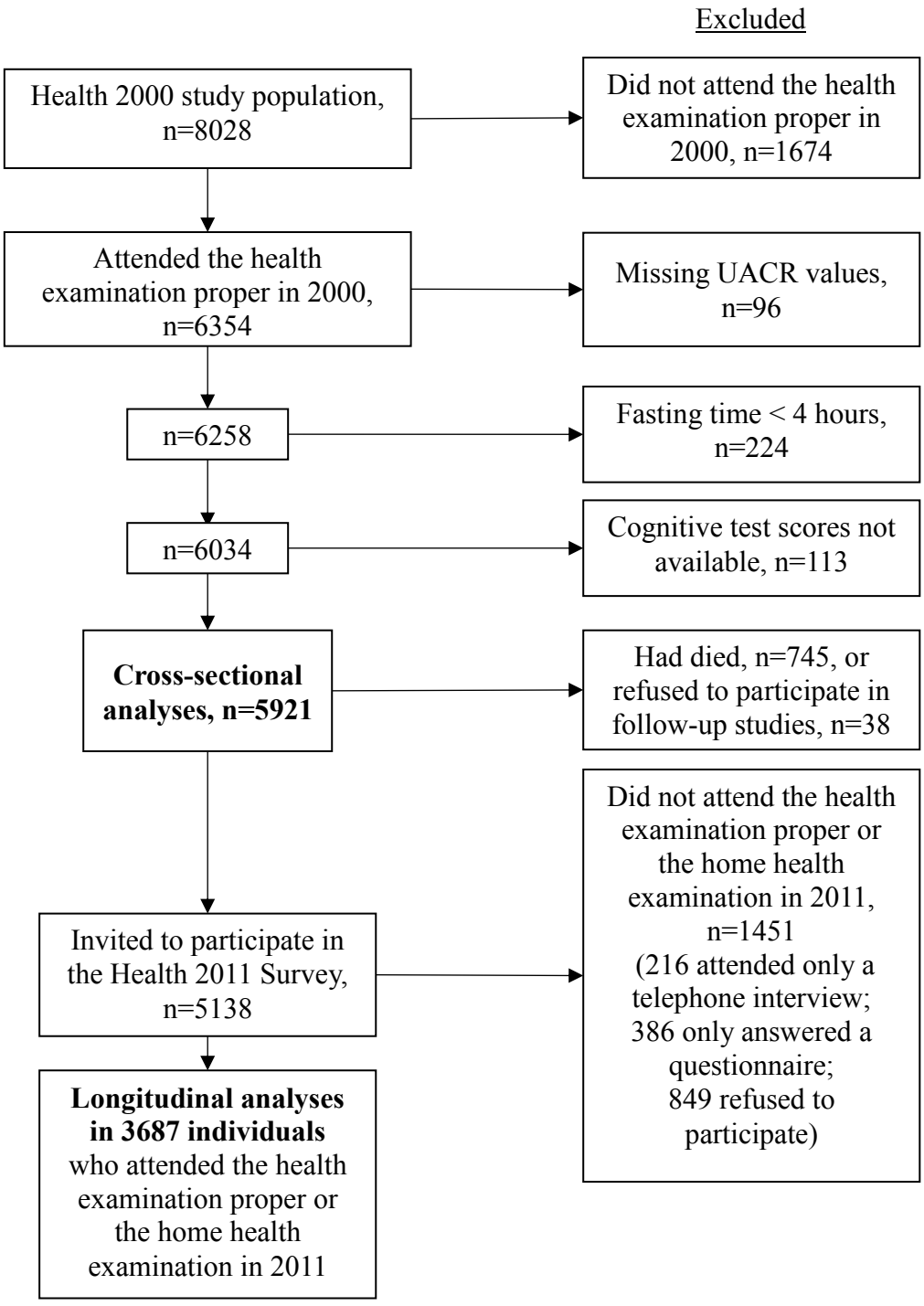
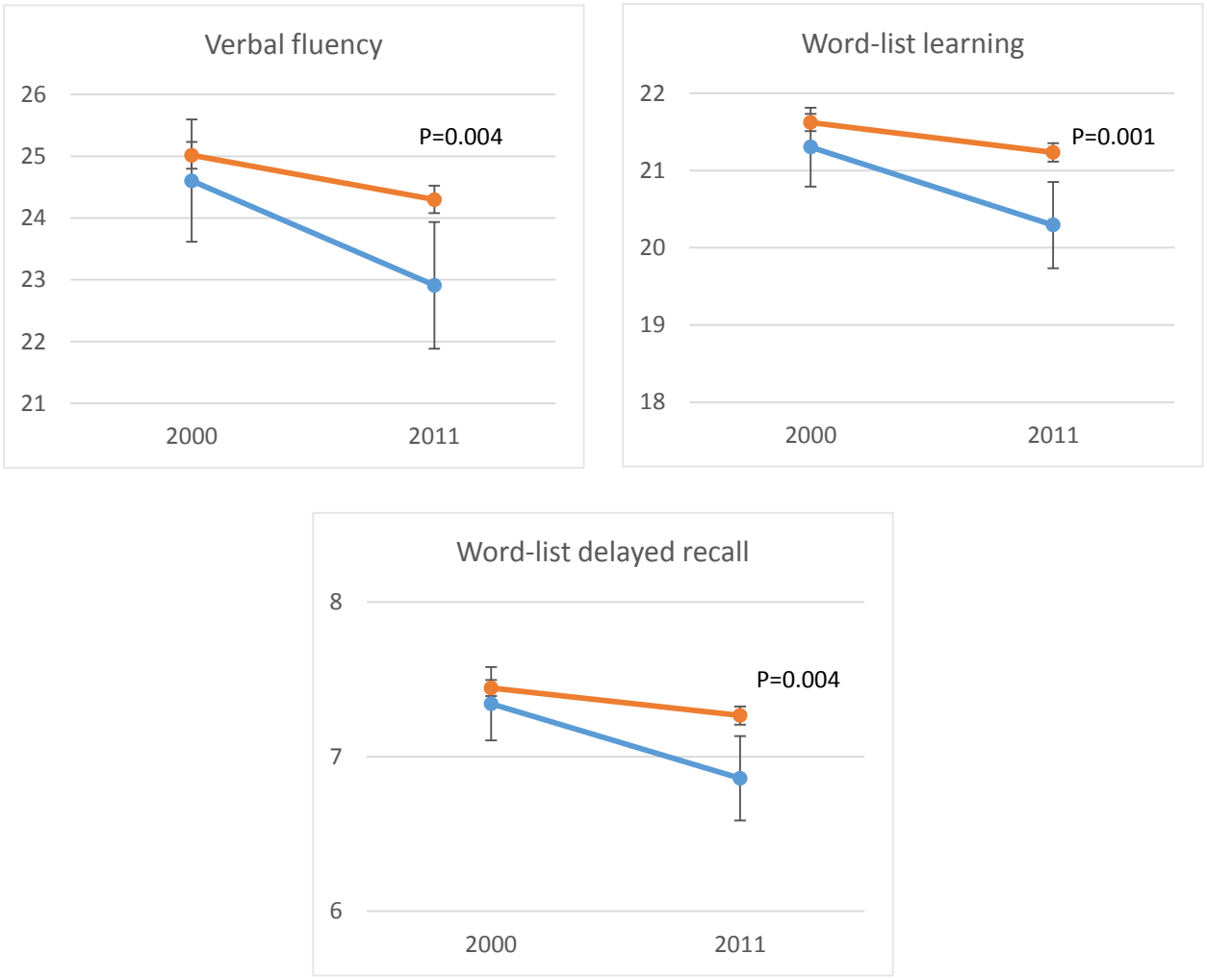


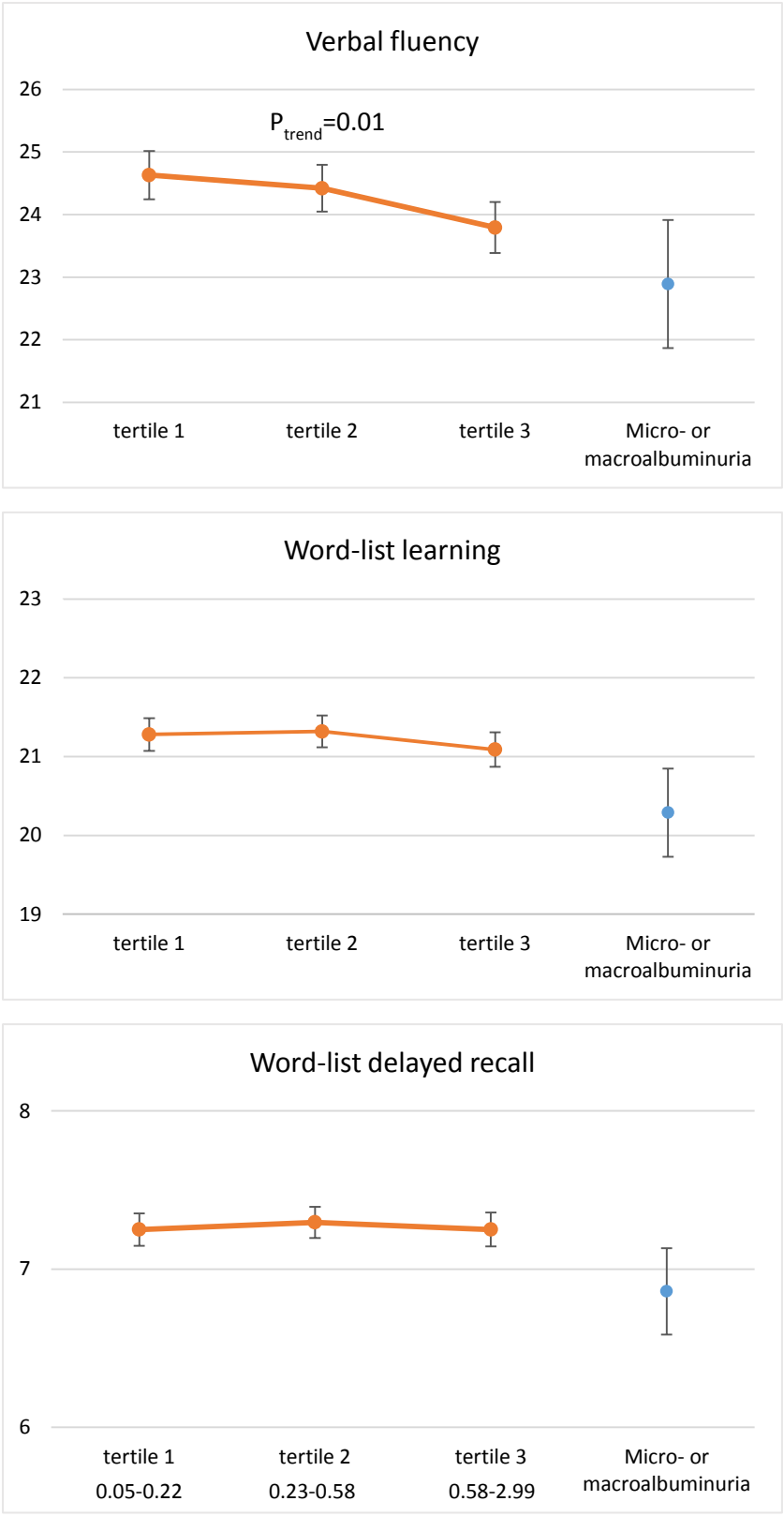
Figure 2. Age, sex, and education adjusted cognitive test scores at baseline and at follow-up in individuals with and without micro- or macroalbuminuria, in the study population that attended the follow-up examination, n=3687.



The results are shown as adjusted means with 95% confidence intervals. P-values for a difference in the rate of decline in cognitive test scores between the two groups from 2000 to 2011, assessed with linear regression analysis and adjusted for age, sex and education.

No albuminuria. Micro- or macroalbuminuria.

Figure 3. Age, sex and education adjusted cognitive test scores at follow-up according to baseline urine albumin-to-creatinine tertiles. N=3687.



The results are shown as adjusted means with 95% confidence intervals, according to tertiles of baseline urine albumin-to-creatinine ratio below microalbuminuria. The range of UACR

within each tertile are shown in mg/mmol. The test scores of individuals with micro- or macroalbuminuria are presented for comparison. P_{trend} for lower cognitive test scores according to UACR tertiles (individuals with micro- or macroalbuminuria not included in the analyses). Analyses are performed with linear regression, adjusted for age, sex and education.