

Serum uric acid and cognitive function and dementia

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Uric acid is a risk factor of cardiovascular disease, as well as a major natural antioxidant, prohibiting the occurrence of cellular damage. The relation between uric acid and cognitive decline, in which both vascular mechanisms and oxidative stress are thought to play a role, is unknown. Therefore we assessed the relation between serum uric acid levels and the risk of subsequent dementia in a prospective population-based cohort study among 4618 participants aged 55 years and over. Additionally, we investigated the relation between serum uric acid and cognitive function later in life (on average 11.1 years later) in a subsample of 1724 participants who remained free of dementia during follow-up. All analyses were adjusted for age, sex and cardiovascular risk factors. Our data showed that only after correcting for several cardiovascular risk factors, higher serum uric acid levels were associated with a decreased risk of dementia (HR, adjusted for age, sex and cardiovascular risk factors, 0.89 [95% confidence interval (CI) 0.80–0.99] per standard deviation (SD) increase in uric acid). In participants who remained free of dementia, higher serum uric acid levels at baseline were associated with better cognitive function later in life, for all cognitive domains that were assessed [adjusted difference in Z-score (95% CI) per SD increase in uric acid 0.04 (0.00–0.07) for global cognitive function; 0.02 (–0.02 to 0.06) for executive function; and 0.06 (0.02–0.11) for memory function], but again only after correcting for cardiovascular risk factors. We conclude that notwithstanding the associated increased risk of cardiovascular disease, higher levels of uric acid are associated with a decreased risk of dementia and better cognitive function later in life.

Keywords: population-based cohort study; serum uric acid; cognitive function; dementia; cardiovascular risk factors

Introduction

Uric acid is associated with an increased risk for myocardial infarction, stroke, and cardiovascular mortality (Fang and Alderman, 2000; Niskanen *et al.*, 2004; Bos *et al.*, 2006). Suggested mechanisms for this are a uric-acid-induced stimulation of vascular smooth muscle cell proliferation; the inflammatory properties of soluble uric acid; and the direct effect of uric acid on endothelial function by impairing nitric oxide production (Fang and Alderman, 2000;

Johnson *et al.*, 2003; Niskanen *et al.*, 2004). However, as a major natural antioxidant, uric acid also accounts for a substantial part of the antioxidative capacity of the plasma (Miller *et al.*, 1993). This beneficial property might reduce oxidative stress and protect against the detrimental effect of free radicals.

Both vascular pathology and oxidative stress have been associated with an increased risk of dementia and cognitive impairment (Breteler, 2000; Christen, 2000; Zhu *et al.*, 2004). Therefore, the different properties of uric acid might have contradictory

effects on the risk of dementia and on cognitive function. Previous studies have shown that levels of serum uric acid in subjects with mild cognitive impairment and in patients with Alzheimer's disease are lower than those in healthy controls, suggesting that uric acid may have a protective effect (Rinaldi *et al.*, 2003; Kim *et al.*, 2006). To our knowledge, no prospective, population-based studies have investigated the relation between serum uric acid and the risk of dementia or cognitive function later in life.

We hypothesized an association between serum uric acid and a decreased risk of dementia and better cognitive function later in life, based on the antioxidative properties of uric acid, possibly masked by the uric acid-related vascular pathology that is associated with worse cognitive function. Therefore, we investigated the association between serum uric acid levels and the risk of dementia as well as the relation between serum uric acid levels and several domains of cognitive function later in life, in the Rotterdam Study, a large prospective population-based cohort study in subjects aged 55 years and over, for whom several known cardiovascular risk factors were available.

Methods

Population

The Rotterdam Study is a large ongoing prospective population-based cohort study that is being conducted among all inhabitants aged

55 years and over of Ommoord, a district of Rotterdam, the Netherlands (Hofman *et al.*, 2007). The study was conducted according to the Declaration of Helsinki, and the appropriate Medical Ethics Committees approved the study protocols. A written informed consent was obtained from all participants. Of 10 275 eligible subjects, 7983 individuals (78%) participated in the baseline examinations between 1990 and 1993 [mean age (SD) 71 (25) years, range 55–106 years]. All participants were interviewed at home, and visited the research centre for further examinations. At the fourth survey (2002–04) cognitive function was more extensively assessed with a dedicated neuropsychological test battery. The entire cohort was continuously monitored for incident dementia.

Study population

Uric acid assessments were performed only until December 31, 1992, when they were stopped because of financial constraints, leaving 5150 participants for whom baseline uric acid levels were available (Bos *et al.*, 2006). Participants with dementia ($n=278$), stroke ($n=126$) or missing cognitive test data ($n=128$) at baseline were excluded. This resulted in a sample of 4618 participants available for the analyses on the relation between uric acid and the risk of dementia (Fig. 1).

More than 10 years later, at the fourth survey in 2002–04, we assessed cognitive function with a neuropsychological test battery in all surviving, non-demented, consenting participants. Of these 4618 participants with uric acid assessments at baseline, 457 had developed dementia during follow-up; 1315 had died; 846 refused the in person examination; 186 had an incomplete cognitive test assessment; and 90 participants could not be contacted. The subsample available for the

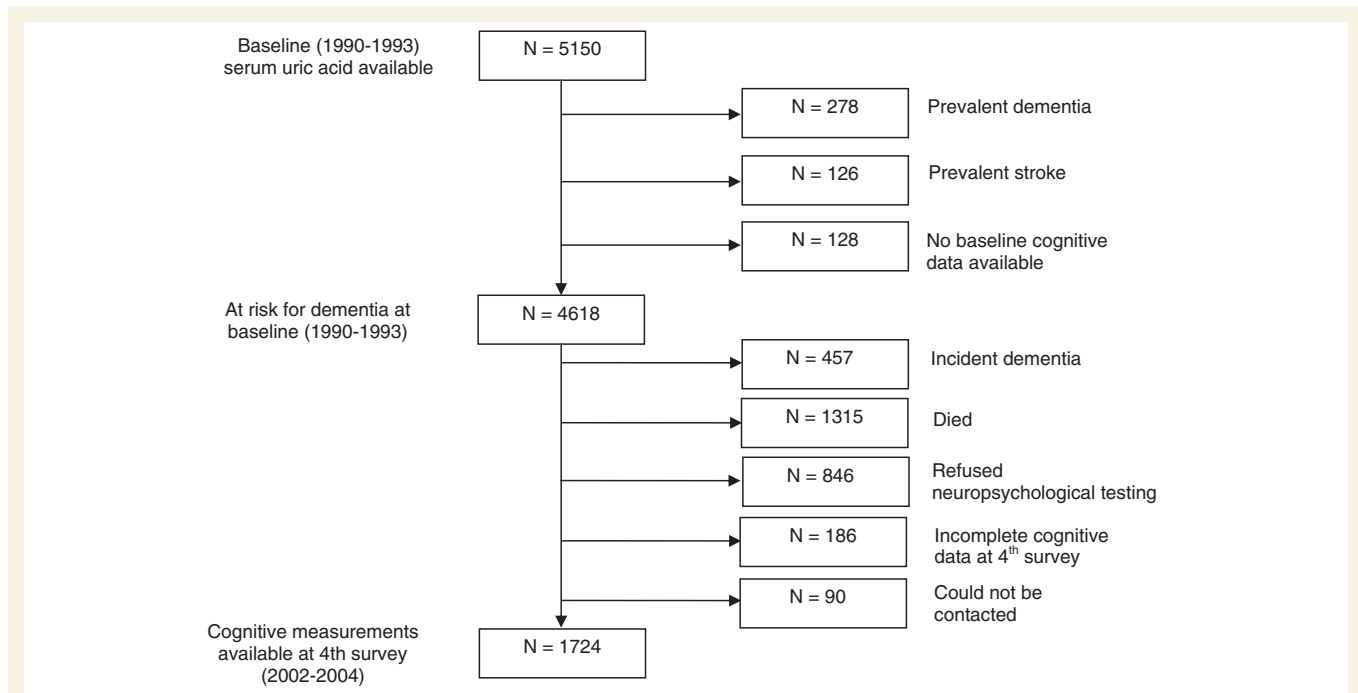


Fig. 1 Description of the study population. Of the 5150 participants whose serum uric acid measurements were available, 532 were excluded at baseline (1990–93): 278 were diagnosed with dementia, and 126 with a stroke; 128 did not have baseline cognitive measurements available. This resulted in 4618 participants in the total sample who were at risk for dementia at baseline. Of these 4618 participants, 2894 did not participate in the fourth survey: 457 had developed dementia during follow-up, 1315 had died, 846 refused the in person examination, 186 did not have a complete cognitive test assessment and 90 participants could not be contacted. This resulted in a sub-sample of 1724 participants who had complete data on the neuropsychological test battery available at the fourth survey.

analyses on the relation between uric acid levels and cognitive function later in life therefore consisted of 1724 participants who remained free of dementia during follow-up and had both baseline uric acid levels and cognitive test data available 11 years later (Fig. 1).

Uric acid

Non-fasting blood was collected and centrifuged. Within 30 min, the blood was centrifuged for 10 min at 3000 r.p.m. Subsequently, the serum was stored at -20°C for 1 week until uric acid activity was determined with a Kone Diagnostica reagent kit and a Kone autoanalyzer (Trivedi *et al.*, 1978). To check calibration, after every 10 samples, three control samples were included; if the average values of the control samples of each run (100 samples) were not within 2.5% of the true value, the run was repeated. Day-by-day variation had to be within 5%. Finally, we compared the serum uric acid levels in our population with those in two other large population-based studies (Fang *et al.*, 2000; Mazza *et al.*, 2001).

Diagnosis of dementia

At baseline and during follow-up examinations, dementia was diagnosed similarly according to a three-step protocol (Van Oijen *et al.*, 2006). The total cohort was continuously monitored for incident dementia through linkage between the study database and the digitalized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. The diagnosis of dementia was made in accordance with internationally accepted criteria for dementia (DSM-III) by a panel consisting of a neurologist, a neuropsychologist and a research physician.

Cognitive function

Global cognitive function was measured with the Mini Mental State Examination (MMSE) at baseline (Folstein *et al.*, 1975). In addition, a dedicated neuropsychological test battery was used to assess global cognitive function, executive function and memory function at the fourth survey (2002–04). Compound cognitive test scores were constructed by transforming individual test scores into standardized Z-scores ($Z\text{-score} = (\text{individuals score} - \text{mean population score})/\text{SD population score}$) (Prins *et al.*, 2005). Global cognitive function was calculated by averaging the Z-scores of the Letter Digit Substitution Task (Lezak *et al.*, 2004), the Word Fluency Test (Welsh *et al.*, 1994), the Stroop test (sum of the reading, colour naming and interference subtask) (Golden, 1976) and the 15-Word Learning Test immediate and delayed recall (Brand and Jolles, 1985). Executive function included the Z-scores of the Stroop test (interference subtask), the Letter Digit Substitution Task and the Word Fluency Test. Memory function included the Z-score of the 15-WLT immediate and delayed recall (Prins *et al.*, 2005).

Additional measurements

Blood pressure was measured twice at baseline with a sphygmomanometer after 5 min of seated rest. The average of these two measurements, separated by a count of the pulse rate, was used in the analyses. Total and high-density lipoprotein cholesterol levels were measured at baseline in nonfasting blood with an automated enzymatic procedure. During the home interview, smoking status (classified as current, former or never), history of diabetes mellitus and history of cardiovascular disease (defined as history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass

grafting, peripheral artery disease, cerebrovascular accident or atrial fibrillation) were assessed. Level of education was measured at baseline and dichotomized into primary education or less, and more than primary education. The waist/hip-ratio was calculated by dividing the waist circumference by the hip circumference.

Statistical analyses

We used Cox proportional hazard models to calculate hazard ratios with 95% CI for the association between uric acid and risk of dementia. Hazard ratios were calculated for quartiles of uric acid (with the lowest quartile as the reference) as well as continuously, per SD increase in uric acid level. Participants were followed from date of study entry until age of diagnosis of dementia, age at death or age at end of study, whichever came first. Because serum uric acid is associated with stroke (Bos *et al.*, 2006), and stroke is associated with risk of dementia (Ivan *et al.*, 2004), we censored incident stroke cases. The relation between baseline uric acid levels and cognitive function later in life was assessed with linear regression models, with uric acid as an independent, and cognitive function as the dependent variable, and with analyses of covariance (ANCOVA). All analyses were adjusted for age, sex, level of education and additionally for several known cardiovascular risk factors. Analyses were carried out using the SPSS statistical package (release 11.1; SPSS inc., Chicago, IL).

Results

The baseline characteristics of the total sample of 4618 participants and the subsample of 1724 participants for whom complete data on the neuropsychological test battery were available at the fourth survey, are shown in Table 1. The mean age of the total sample of 4618 participants was 69.4 years, 61% were female and the mean serum level of uric acid was $322.3 \mu\text{mol/l}$. Thirty-two percent of these participants had a history of cardiovascular disease. During a total of 41 651 person-years of follow-up [mean (SD) 9.0 (3.5)], 457 new cases of dementia were detected. Not surprisingly, the 1724 non-demented participants with complete cognitive test data at the fourth survey were at baseline younger, had lower levels of uric acid, less often a history of cardiovascular disease and a better cognitive function compared to the remainder of the cohort (Table 1). However, after adjustment for several vascular risk factors and markers of vascular disease (serum creatinine levels, systolic blood pressure, ever smoking, total cholesterol and HDL-cholesterol levels, diabetes mellitus, waist/hip ratio and prevalent cardiovascular disease), there was no significant difference in baseline uric acid levels anymore between the 1724 participants with complete cognitive test data at the fourth survey and the rest of the cohort.

In the total sample of 4618 participants, higher baseline levels of uric acid were not associated with the risk of dementia in the analyses that were adjusted for age, sex and level of education. However, when we accounted for vascular risk factors and markers of vascular disease (serum creatinine levels, systolic blood pressure, ever smoking, total cholesterol and HDL-cholesterol levels, diabetes mellitus, waist/hip ratio and prevalent cardiovascular disease) higher uric acid levels were associated with a lower risk of

Table 1 Baseline characteristics (1990–93)

	Total sample (n = 4618)	Complete data of cognitive function available at fourth survey(2002–04)					
		Yes (n = 1724)	No (n = 2894)				
			Incident dementia (n = 457)	Died (n = 1315)	Refused (n = 846)	Incomplete cognitive data (n = 186)	Could not be contacted (n = 90)
Age (years)	69.4 (8.6)	64.1 (5.7)	76.2 (7.3)	74.5 (8.7)	68.5 (7.0)	67.6 (7.0)	73.5 (8.8)
Gender (% female)	61	61	70	51	69	61	80
Serum uric acid level (µmol/l)	322.3 (80.5)	312.4 (73.4)	317.4 (78.9)	342.1 (87.8)	316.2 (77.6)	315.9 (78.3)	315.7 (86.6)
MMSE-score (points)	27.7 (1.9)	28.2 (1.4)	26.7 (2.2)	27.3 (2.1)	27.7 (1.8)	28.0 (1.7)	27.5 (2.1)
Low level of education (%)	40	29	55	47	44	37	51
Creatinine plasma level (µmol/l)	82.8 (21.9)	80.6 (14.0)	83.7 (25.5)	88.0 (31.3)	79.6 (14.0)	79.6 (12.7)	81.4 (18.1)
Systolic blood pressure (mm Hg)	138.9 (21.8)	133.5 (19.8)	141.9 (21.7)	144.2 (23.8)	141.0 (20.5)	133.5 (19.4)	142.8 (21.2)
Total cholesterol (mmol/l)	6.6 (1.2)	6.7 (1.2)	6.5 (1.2)	6.4 (1.3)	6.9 (1.2)	6.7 (1.2)	6.6 (1.1)
High-density cholesterol (mmol/l)	1.3 (0.4)	1.4 (0.4)	1.3 (0.3)	1.3 (0.4)	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)
Diabetes mellitus (%)	11	6	15	18	9	10	12
Smoking (% ever)	65	67	56	68	63	63	39
Waist/hip ratio	0.91 (0.09)	0.89 (0.09)	0.91 (0.09)	0.93 (0.09)	0.90 (0.09)	0.91 (0.09)	0.90 (0.09)
Cardiovascular disease (%)	32	19	42	48	29	27	39

Data are presented as means (SD) or percentages. The total sample represents the 4618 participants who were at risk of developing dementia. Of these 4618 participants, 1724 participated at the fourth survey (2002–04) and underwent cognitive assessments during this follow-up examination. Of the 2894 participants who did not have cognitive data available at the fourth survey, 457 had developed dementia, 1315 had died, 846 refused the in person examination, 186 did not have a complete cognitive test assessment and 90 participants could not be contacted.

Table 2 Uric acid and the risk of dementia

Uric acid	Model 1 ^a (457 cases)	Model 2 ^b (457 cases)
Per SD increase uric acid	0.93 (0.84–1.03)	0.89 (0.80–0.99)*
1 st Quartile	1 (reference)	1 (reference)
2 nd Quartile	0.97 (0.75–1.26)	0.95 (0.73–1.23)
3 rd Quartile	0.94 (0.73–1.22)	0.90 (0.69–1.18)
4 th Quartile	0.81 (0.62–1.05)	0.73 (0.55–0.97)*
P-trend	0.114	0.030

Estimates indicate hazard ratios with corresponding 95%.

^a Adjusted for age, sex and level of education. ^b Adjusted for age, sex, level of education serum creatinine levels, systolic blood pressure, ever smoking, total cholesterol and HDL-cholesterol levels, diabetes mellitus, waist/hip ratio, cardiovascular disease, all at baseline.

* $P < 0.05$.

dementia [hazard ratio (95% CI) for the highest versus the lowest quartile of uric acid 0.73 (0.55–0.97), Table 2].

In the subsample of 1724 participants, who survived without dementia and underwent complete cognitive testing at the follow-up examination (on average 11.1 years after baseline), higher baseline levels of uric acid were associated with better cognitive function later in life, but only after adjustment for cardiovascular risk factors (Fig. 2). The difference in Z-score (95% CI) per SD increase in uric acid was 0.04 (0.00–0.07) for global cognition; 0.02 (–0.02 to 0.06) for executive function; and 0.06 (0.02–0.11) for memory function. There was a significant trend ($P < 0.05$) over the quartiles of serum uric acid for global cognition and memory function, indicating better cognition for participants with higher levels of serum uric acid. These associations remained

significant after adjusting for baseline cognitive function (MMSE-score).

Furthermore, persons with higher levels of serum uric acid at baseline were more likely to have cardiovascular disease [age- and sex-adjusted odds ratio (95% CI) for cardiovascular disease for the highest versus the lowest quartile of uric acid 2.21 (1.82–2.67)], and had an increased risk to die from cardiovascular diseases [age- and sex-adjusted hazard ratio (95% CI) for cardiovascular mortality for the highest versus the lowest quartile of uric acid 1.73 (1.37–2.17)]. These associations remained after adjusting for serum creatinine, systolic blood pressure, ever smoking, total cholesterol, HDL-cholesterol, diabetes mellitus, waist/hip ratio and (for the cardiovascular mortality analysis only) prevalent cardiovascular disease.

Discussion

In this large, population-based cohort study, serum uric acid levels were not associated with the risk of dementia or with cognitive function later in life. However, after adjustment for several cardiovascular risk factors, higher serum uric acid levels were associated with a decreased risk of dementia and better cognitive function later in life. The age- and sex-adjusted analyses showed no clear association between serum uric acid levels and the risk of dementia, or cognitive function later in life. However, higher levels of uric acid were associated with an increased risk of cardiovascular disease and mortality. After adjustment for several cardiovascular risk factors, a possible protective effect of uric acid was unmasked: higher levels of uric acid were associated with a lower risk of dementia and better cognitive function later in life.

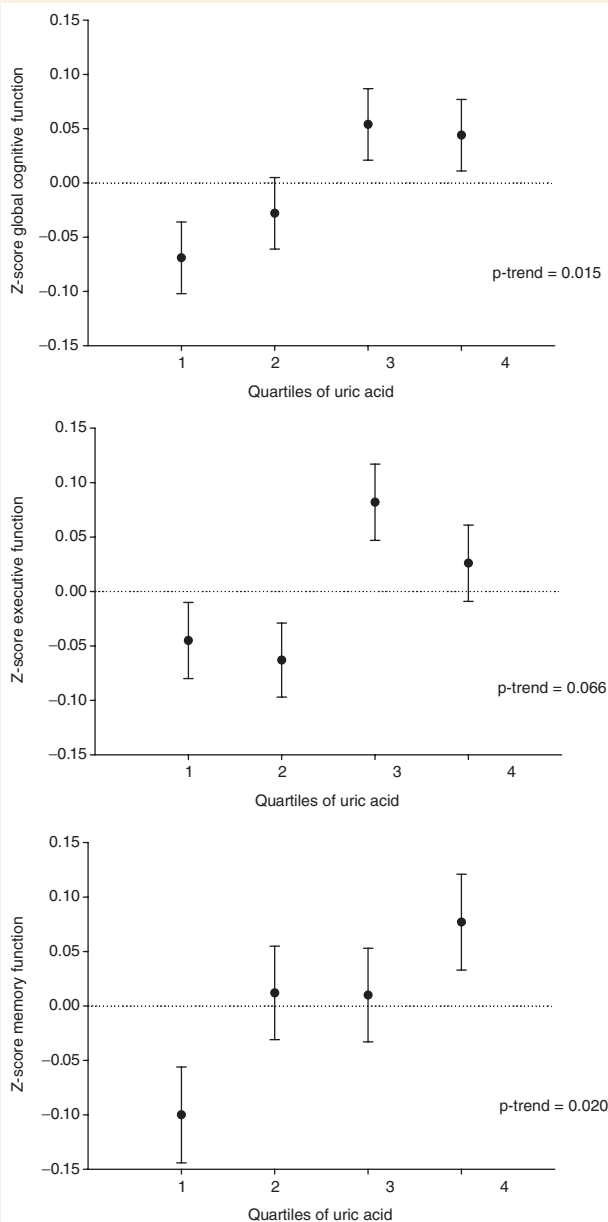


Fig. 2 Relation between plasma uric acid levels in quartiles and cognitive function later in life ($n = 1724$). Z-scores (SEM) for the different cognitive domains are plotted for the quartiles of plasma uric acid levels. Linear regression models and analyses of covariance (ANCOVA) were used, adjusted for age, sex, level of education, serum creatinine, systolic blood pressure, total cholesterol and high-density cholesterol levels, diabetes mellitus, ever smoking, waist/hip-ratio, prevalent cardiovascular disease.

Other explanations of the key findings are possible. First, although 90% of our study participants visit their family doctor at least once per year and we are confident that our general practitioners diagnose most incident cases of dementia, we cannot exclude that some very early incident cases who died from cardiovascular disease before they were recognized as having dementia, may have been missed. Especially patients with

mild vascular dementia may be at an increased risk of cardiovascular death. To the extent that these people had increased uric acid levels, it may have inflated the strength of the relation between high baseline uric acid levels with reduced risk of dementia. Second, the 1724 subjects who did not develop dementia at follow-up scored higher on the MMSE at baseline than the rest of the cohort. This suggests the possibility that individuals with elevated uric acid levels who survived to follow-up might have had more 'cognitive reserve' than those with high baseline uric acid levels who did not reach follow-up for various reasons. This selective attrition could have affected our analyses, although additional adjustment for baseline cognitive function (MMSE-score) did not markedly change these results.

We know of only one other population-based study that has examined the relation between serum uric acid and cognitive function. This study reported an association between higher levels of uric acid and impaired memory function in a sample of 96 community dwelling participants, which is not in line with our results (Schretlen *et al.*, 2007). The relatively small sample size and the limited number of cardiovascular risk factors for which the analyses were adjusted, may have made it hard to separate the contradictory properties of uric acid in relation to cognitive function in this study.

The strengths of our study include its prospective, population-based design with a large study population, the nearly complete dementia-follow-up, the dedicated neuropsychological test battery that was used and the large number of cardiovascular risk factors that were assessed.

Our study also had some limitations. First, the assessment of uric acid had been stopped before all participants could visit the research centre. However, because all participants were invited in random order, this is unlikely to have affected our results. Furthermore, the mean levels of serum uric acid measured in our study population were comparable with those in two other large population-based studies: NHANES I and the Cardiovascular Study in the Elderly (Fang *et al.*, 2000; Mazza *et al.*, 2001). Second, the association between uric acid and cognitive function later in life was based on the assessment of serum uric acid at baseline and the measurement of cognitive function >10 years later. Participants with relatively low levels of uric acid and good cognitive function at baseline were more likely to have complete data on the neuropsychological test battery at the fourth survey. The selective attrition of participants with relatively high levels of uric acid and concurrent worse cognitive function did not surprise us, as uric acid is an important risk factor for cardiovascular mortality, myocardial infarction and stroke (Fang and Alderman, 2000; Niskanen *et al.*, 2004; Bos *et al.*, 2006), but could have affected our results. However, after adjustment for several cardiovascular risk factors, there was no longer a significant difference in uric acid level between participants in the subsample and participants who did not have cognitive tests available at the fourth survey. Therefore, selective attrition is unlikely to be the only explanation for our results.

In conclusion, we found in a prospective population-based cohort study that higher serum uric acid levels are related to a decreased risk of dementia and better cognitive function later in life, but only after adjustment for several cardiovascular

risk factors. This corroborates the notion that oxidative stress is involved in the pathogenesis of dementia and cognitive impairment and suggests a possible protective role for antioxidants such as uric acid.

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