Original Research Article

Dementia and Geriatric Cognitive Disorders

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Uric Acid and Dementia in Community-Dwelling Older Persons

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Key Words
Uric acid · Risk · Dementia · Inflammation · Aging

Abstract
Background: The biological action of uric acid (UA) in humans is controversial. UA is considered an antioxidant compound, but preclinical evidence suggests a proinflammatory action. Epidemiological studies found that hyperuricemia is associated with conditions leading to dementia. Our aim is to investigate the relationship between UA levels and dementia in older persons. ***Methods:*** Cross-sectional study performed in 1,016 community-dwelling older persons participating in the InCHIANTI study. Participants underwent determination of circulating UA levels and neuropsychological evaluation. A multivariate logistic regression model was used to estimate the probability of participants belonging to the highest and middle UA tertile to be affected by dementia compared to those in the lowest tertile. ***Results:*** Demented persons had higher UA levels ($p = 0.001$) and the prevalence of persons affected by dementia increased across UA tertiles ($p < 0.0001$). Independent of several confounders, persons belonging to the highest UA tertile had a threefold (OR = 3.32; 95% CI: 1.06–10.42) higher probability to suffer from a dementia syndrome while those in the middle UA tertile tended to have a higher probability of being demented compared to those in the lowest tertile. ***Conclusion:*** In a population-based sample, high circulating UA levels are associated with an increased likelihood to be affected by a dementia syndrome.

Introduction

The awareness of the public health burden of cognitive impairment and dementia has led to a worldwide effort to identify risk factors for these conditions and to develop strategies to prevent the onset or to slow down the progression of cognitive disorders.

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Many genetic, nutritional, and metabolic factors have been shown to influence the risk of cognitive impairment and dementia in older adults [1, 2]. Several pathways, including increased oxidative stress and inflammation, have been proposed to explain how these factors induce brain damage and dementia [3, 4].

Uric acid (UA) is a soluble blood circulating compound and a constituent of the cell cytosol whose role in human physiology remains controversial. Circulating UA levels, which mainly depend on nucleotide catabolism and cell turnover, are higher in humans and primates than in all other species due to an acquired mutation in the urate oxidase gene, which makes the enzyme nonfunctional [5]. Ames et al. [6] suggested that the inactivation of the urate oxidase gene is an evolutionary strategy to counteract the production of reactive oxygen species associated with the aerobic metabolism. Biochemical evidence and preclinical studies showing that UA is a reactive oxygen species scavenger support this hypothesis [7], and suggest that UA might play a protective role against dementia.

However, epidemiological studies show that UA is positively associated with several markers of systemic inflammation [8, 9], and is a risk factor for endothelial dysfunction [10], hypertension [11], metabolic syndrome [12], cardiovascular [13] and cerebrovascular diseases [14], and all-cause and specific-cause mortality [15–17].

Recently, some authors have suggested that UA independently contributes to neurovascular damage with negative effects on cognitive functions [18]. Whether this association depends on the presence of other diseases, mainly cerebrovascular or cardiovascular conditions, remains unclear.

The aim of this study was to evaluate the relationship between circulating UA levels and the dementia syndrome independent of lifestyle and health-related conditions in a large sample of older persons living in the community.

Material and Methods

Study Sample

The InCHIANTI (Invecchiare in Chianti; Aging in the Chianti area) Study is an epidemiological study conducted on a representative sample of the population living in two Italian towns located in Tuscany. The study was developed to investigate factors affecting mobility in late life. The rationale, design and data collection were described elsewhere [19]. The study protocol complies with the Declaration of Helsinki and was approved by the Ethical Committee of the Italian National Institute of Research and Care of Aging.

Briefly, in August 1998, 1,270 persons ≥65 years and 30 men and women in each decade of age between 20 and 60 years and in the age group 61–64 were randomly selected from the population registry. Of the 1,530 persons originally sampled, 1,453 (94%) agreed to participate in the study. Of these, 1,343 accepted to donate a blood sample and 1,325 (86% of those originally sampled eligible) completed the baseline data collection which started in September 1998 and ended in March 2000. The study population used for the analyses presented here consisted of 1,061 persons over 60 years of age (593 women and 468 men). Nobody was diagnosed with gout at enrolment or developed it before and at the time of clinical examination, and only 15 participants were taking drugs affecting UA serum levels (e.g. allopurinol, probenecid, sulfinpyrazone).

All subjects underwent a careful clinical examination and a detailed interview. A proxy was interviewed when the subject was unable to provide the required information. Blood samples were collected in the morning after overnight fasting and sitting for 15 min. The blood samples were centrifuged at 4°C to separate plasma. Plasma aliquots were protected from light with aluminum foil, stored at –80°C, and not thawed until analyzed.

Demographic, Behavioral and Health-Related Characteristics

Demographic data and information on formal education and smoking habit were collected using standardized questionnaires. Participants were classified as current, former and never-smokers. Pack-years, a measure of cigarette-smoking exposure that combines intensity and duration, was calculated as (packs smoked per day) × (years of smoking), based on self-report. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters.

Average energy intake (kcal/day) and alcohol consumption (g/day) were assessed using the European Prospective Investigation into Cancer (EPIC) and Nutrition food frequency questionnaire. The EPIC was the instrument developed and used by the Italian sites of the EPIC study conducted in 9 European Countries to study the relationship between diet and cancer [20]. The information provided by the questionnaire was transformed into average daily intake of macro- and micronutrients by custom software that uses as a reference the table of food composition for Italian epidemiological studies edited by the European Institute of Oncology [21]. The variables used in this study were: total energy and alcohol, all expressed as daily intake.

All participants were examined by a physician. Standard algorithms that combined information from physician diagnosis, medical and drug records, clinical and laboratory findings were used to diagnose hypertension, peripheral atherosclerosis, diabetes, stroke, heart and lung diseases [22]. Kidney function was estimated using the creatinine clearance (CrCl, ml/min) based on the formula proposed by Cockcroft and Gault, which incorporates measures of serum creatinine, age, sex and weight [23]. Kidney function was defined as impaired based on CrCl <70 ml/min or profoundly impaired if CrCl <30 mil/min [24]. Serum creatinine was measured using a modified Jaffé method and used to calculate and estimate CrCl. Peripheral atherosclerosis was defined as bilateral carotid atherosclerotic plaques, and/or any carotid stenosis >40%, and/or presence of peripheral arterial disease. Peripheral artery disease was defined as an ankle-brachial

index <0.90 [25]. Carotid atherosclerosis plaques and stenosis were estimated by Doppler flow ultrasonography.

Each subject was interviewed regarding disability in basic activities of daily living (ADL) and in instrumental activities of daily living (IADL). The number of activities that participants were unable to perform without help of another person is reported in the analysis.

Circulating Compounds

Plasma UA (mg/dl) was measured using an enzymatic-colorimetric method (Roche Diagnostics, GmbH, Germany). The lower limits of detection were 0.2 mg/dl, range 0.2–25.0 mg/dl, intra-assay and interassay coefficients of variation (CV) were 0.5 and 1.7%, respectively. According to the values provided by our laboratory, hyperuricemia was defined as a serum urate concentration >7.5 mg/dl (450 μmol/l) in men and >6.2 mg/dl (372 μmol/l) in women. For statistical analysis, UA was divided into tertiles according to the following cut-points: 4.6 and 5.6 mg/dl.

Circulating concentration of interleukin-6 (IL-6) was assayed performing an enzyme-linked immunosorbent assay (ELISA) using ultrasensitive commercial kits (Human Ultrasensitive, Biosource International Inc., Camarillo, Calif., USA). The minimum detectable concentration of IL-6 was 0.10 pg/ml and the interassay coefficient of variation was 7%. The average of two measures was used in the analyses.

Serum C-reactive protein (CRP) was measured in duplicate by an ELISA high-sensitivity test using purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, Calif., USA) with standardization according to the World Health Organization 1st International Reference Standard. The minimum detectable threshold was 0.03 mg/l, and the interassay coefficient of variation was 5%.

Plasma levels of α-tocopherol were measured by reverse-phase high-performance liquid chromatography using a 3-μm C_{18} reverse-phase column. A detailed description of the analytical method and procedures has been previously described and published [26]. Since vitamin E is carried in the bloodstream by lipoproteins and changes in lipid concentration should always be considered, and plasma levels of α-tocopherol were adjusted for total cholesterol levels in the multivariate analysis. Total cholesterol was measured using an automated enzymatic method [27].

Evaluation of Cognitive Status

Dementia was ascertained using a two-stage procedure, as already described [28]. During the interview, participants were screened using the Mini Mental State Examination (MMSE). Those with a score >26 were considered as nondemented, while those with a score ≤21 were considered as possibly demented and directly scheduled for the second-stage screening procedure. Participants with an MMSE score between 22 and 26 received additional neuropsychological tests assessing memory (Word-Pairing Test), concentration/attention (Digit Test – Number Memory) [29] and visuospatial ability (the Caltagirone drawings) [30]. The Word-Pairing and Number Memory Tests were taken from WAIS-R [29]. The Italian translation of the Word-Pairing Test is a subtest of the Wechsler Memory Scale battery [31] and consists in learning 10 pairs of words, 6 of them in a semantic relationship to each other (easy pairs) and 4 not in a semantic relationship to each other (difficult pairs). The Digit Test – Number Memory consists in the reading of series of figures that the subject is invited to repeat in the same order in which they are presented, starting with 3 digits. The Caltagirone drawing test consists in copying in succession a star, a house, and a cube. The education-adjusted normative data for these tests exist for the Italian population. Based on these additional tests, if the memory of the participant was considered normal, he or she was reattributed a full score on the MMSE memory items. Similarly, we reattributed 5 points to the item 'subtract 7 five times from 100' and 1 point to the 'pentagon drawing' when the performance in additional tests assessing analogous neuropsychological functions was considered normal. After these procedures, we re-analysed the MMSE score. The participants for whom the new score was >26 were considered 'not demented', while those for whom the newly calculated score remained between 22 and 26 were scheduled for the second-stage evaluation. The second-stage evaluation was performed by geriatricians and a psychologist with long-standing clinical experience in the evaluation of older patients with cognitive impairment. A diagnosis of 'dementia syndrome' independent of the etiology was established using a standard evaluation protocol based on the DSM-IV criteria (DSM-IV 1994). The authors can provide a detailed description of the neuropsychological battery used on request. A differential diagnosis between degenerative dementia, mainly represented by Alzheimer's disease, and vascular or mixed dementia, was not performed since neuroimaging was not available for all subjects. We divided the study population into two groups: (1) participants affected by a dementia syndrome (n = 60), and participants with normal cognitive functions (i.e. participants without a diagnosis of dementia and without any disability attributable to cognitive impairment) (n = 956). The remaining participants were excluded because they had mild ADL or IADL disabilities due to cognitive impairment but did not fulfill the DMS-IV criteria for dementia, or they had low cognitive performance on MMSE test, which in many cases might indicate the presence of cognitive impairment, but without any disability.

Statistics

Participants' characteristics were described for the entire sample, for the groups defined according to UA tertiles and according to their cognitive status. Variables with symmetric distribution were reported as means and standard deviations (SD). Asymmetrically distributed variables were summarized as medians and interquartile ranges and log-transformed in regression analyses and back-transformed for data presentation. Statistical comparisons across UA tertiles and across groups defined according to the participants' cognitive status were performed using the ANOVA test including post-hoc Bonferroni test, or the Mantel-Haenszel χ^2 test, as appropriate. The significance level used for 2-sided tests was $p < 0.05$.

The odds ratios and 95% confidence interval of having a 'dementia syndrome' compared to 'normal cognitive status' associated with being in the highest and middle tertile versus the lowest tertile of UA plasma levels were evaluated using a linear logistic regression model (proc logistic procedure SAS) adjusted for confounders. All analyses were performed using the SAS statistical package, version 8.2 (SAS Institute, Cary, N.C., USA).

Table 1. Baseline characteristics of InCHIANTI participants according to their cognitive status

	Dementia syndrome (n = 60)	Normal cognitive status (n = 956)	p
Demographics			
Women, n (%)	38 (63.33%)	523 (45.29%)	0.1926
Age, years	84.20 ± 7.33	73.26 ± 6.76	<0.0001
Education, years	3.02 ± 2.10	5.69 ± 3.33	<0.0001
Behavioral-related variables			
BMI, kg/m^2	26.53 ± 4.68	27.54 ± 4.02	0.1408
Alcohol, g/day	7.89 ± 10.93	15.11 ± 20.72	0.0080
Energy intake, kcal/day	1,701.74 ± 510.57	1,952.65 ± 563.33	0.0009
Smoking, pack-years	11.26 ± 22.74	12.52 ± 20.43	0.6454
Smoker, n (%)	4 (6.67%)	143 (14.96%)	<0.0001
Former smoker, n (%)	13 (21.67%)	263 (27.51%)	<0.0001
Never-smoker, n (%)	43 (71.67%)	550 (57.53%)	<0.0001
ADL disability score	2.20 ± 2.42	0.06 ± 0.42	<0.0001
IADL disability, score	5.33 ± 3.21	0.39 ± 1.13	<0.0001
MMSE score	11.12 ± 6.60	25.67 ± 2.92	<0.0001
Plasmatic parameters			
Uric acid, mg/dl	5.75 ± 1.90	5.13 ± 1.35	0.0010
IL-6, pg/ml	2.91 ± 2.48	2.13 ± 4.34	0.1795
CRP, μg/ml	5.84 ± 6.06	5.04 ± 9.36	0.5226
Vitamin E, μmol/l	25.64 ± 6.26	30.51 ± 8.42	<0.0001
Cholesterol, mg/dl	194.42 ± 45.50	219.51 ± 38.63	<0.0001
Health-related conditions			
Creatinine clearance, ml/min	45.82 ± 17.65	66.25 ± 18.93	<0.0001
Hypertension, n (%)	43 (71.67%)	630 (65.90%)	0.3597
Diabetes, n (%)	22 (36.67%)	165 (17.26%)	0.0002
Atherosclerosis, n (%)	9 (22.50%)	170 (19.43%)	0.6322
Cardiovascular disease, n (%)	24 (40.00%)	257 (26.88%)	0.0276
Cerebrovascular disease, n (%)	12 (20.00%)	52 (5.44%)	<0.0001

Data presented as mean ± SD, unless otherwise specified. Statistical comparisons of means by ANOVA including the Bonferroni post-hoc test; comparison of proportions by the Mantel-Haenszel χ^2 test for trend.

Results

Participants' demographic, behavioral, biological and health-related characteristics are presented according to their cognitive status in table 1. Persons affected by dementia syndrome were older, more likely women and had received less years of formal education compared to the other group. Concerning behavioral-related conditions, participants affected by dementia had lower energy and alcohol intake than those with normal cognitive functions. Although there was no significant difference in lifetime exposure to smoking between demented and normal current smokers, most of the never-smokers were affected by a dementia syndrome. There was no difference in BMI and circulating levels of IL-6 and CRP between the two groups, although persons affected by a dementia syndrome had significantly higher circulating levels of UA, but lower levels of vitamin E and cholesterol compared to those with normal cognitive functions. As expected, participants affected by dementia had significantly higher ADL and IADL disabilities, and a lower MMSE score. Additionally, persons with dementia had worse kidney function and were more likely to be affected by diabetes, cardiovascular and cerebrovascular diseases than those with normal cognitive functions (table 1).

In table 2, the biological characteristics of the participants are presented for the entire sample size (n = 1,061) and stratified according with the UA tertiles. Serum UA levels ranged from 1.8 to 10.9 mg/dl in men, and from 1.9 to 15.0 mg/dl in women. About 10% of participants were hyperuricemic, while about 1% of participants were

Table 2. Baseline characteristics of InCHIANTI participants according to uric acid tertiles

	Entire sample (n = 1,016)	Uric acid tertiles			p
		1 (n = 344)	2 (n = 340)	3 (n = 332)	
Demographics					
Women, n	593 (55.89%)	271 (74.25%)	181 (51.71%)	141 (40.75%)	<0.0001
Age, years	74.38 ± 7.58	73.84 ± 7.54	74.24 ± 7.33	74.47 ± 7.85	0.0775
Education, years, median and IQR	5.00 (4.00–6.00)	5.00 (3.00–5.00)	3.00 (4.00–7.00)	5.00 (3.00–5.00)	0.0021
Behavioral-related variables					
BMI, kg/m^2	27.44 ± 4.05	26.07 ± 3.58	27.90 ± 4.07	28.45 ± 4.12	<0.0001
Alcohol, g/day, median and IQR	6.58 (0.00–24.98)	3.95 (0.00–13.59)	1.90 (13.37–41.60)	7.64 (25.47–187.40)	<0.0001
Energy intake, kcal/day	1,925.42 ± 562.30	1,854.49 ± 537.32	1,957.16 ± 584.06	1,968.56 ± 560.13	0.0114
Smoking, pack-years, median and IQR	0.00 (0.00–20.00)	0.00 (0.00–3.75)	0.00 (0.00–23.50)	0.00 (0.00–30.25)	<0.0001
ADL disability score	0.23 ± 0.92	0.25 ± 0.97	0.14 ± 0.74	0.30 ± 1.04	0.0557
IADL disability score	0.86 ± 2.03	0.82 ± 2.01	0.71 ± 1.78	1.07 ± 2.27	0.0539
MMSE score	24.53 ± 4.87	24.53 ± 4.65	24.40 ± 4.76	24.64 ± 5.21	0.7990
Plasmatic parameters					
Uric acid, mg/dl	5.17 ± 1.43	3.82 ± 0.53	5.05 ± 0.27	6.72 ± 1.24	<0.0001
IL-6, pg/ml, median and IQR	1.43 (0.85–2.18)	1.18 (0.69–1.97)	1.46 (0.88–2.05)	1.66 (1.02–2.71)	0.0153
CRP, μg/ml, median and IQR	2.73 (1.31–5.67)	2.20 (1.09–4.85)	2.38 (1.26–5.08)	3.65 (1.79–6.33)	0.0303
Vitamin E, μmol/l	30.09 ± 8.37	29.57 ± 5.54	29.64 ± 7.70	31.10 ± 9.68	0.0246
Cholesterol, mg/dl	217.56 ± 39.54	219.50 ± 38.40	216.65 ± 37.52	216.44 ± 42.64	0.5117
Health-related conditions					
Creatinine clearance, ml/min	75.79 ± 17.18	78.62 ± 16.01	68.87 ± 24.58	74.14 ± 17.04	<0.0001
Hypertension, n	706 (66.54%)	218 (59.73%)	231 (66.00%)	257 (74.28%)	<0.0001
Diabetes, n	200 (18.85%)	69 (18.9%)	55 (15.71%)	76 (21.97%)	0.3104
Atherosclerosis, n	192 (20.27%)	50 (15.38%)	63 (20.13%)	79 (25.57%)	0.0015
Cardiovascular disease, n	303 (28.56%)	90 (24.66%)	97 (27.71%)	116 (33.53%)	0.0091
Cerebrovascular disease, n	76 (7.16%)	19 (5.21%)	22 (6.29%)	35 (10.12%)	0.0116
Dementia syndrome, n	60 (5.66%)	13 (3.56%)	21 (6.00%)	26 (7.51%)	0.0223

Data presented as mean ± SD, unless otherwise specified. Statistical comparisons are from ANOVA with Bonferroni post-hoc test, while those among proportions are from test for trend based on Mantel-Haenszel χ^2 tests. IQR = Interquartile range.

hypouricemic. As expected, high levels of UA were observed in older persons who had higher BMI, energy intake and alcohol consumption, and were heavier smokers. Participants belonging to the highest UA tertile had higher ADL and IADL disabilities compared to those belonging to the lowest and middle tertile. No difference was observed in cholesterol levels across the UA tertiles. Circulating levels of IL-6, CRP and vitamin E significantly increased across the UA tertiles, as well as the prevalence of hypertension, atherosclerotic disease, cardiovascular and cerebrovascular disease, and dementia. No difference in CrCl and distribution of renal failure was found among participants belonging the UA tertiles (table 2).

Compared to the participants in the lowest UA tertile and independent of age, sex, BMI, and education, those in the highest tertile, but not those in the middle tertile, had higher odds to be affected by a dementia syndrome (OR: 3.06; 95% CI: 1.10–5.52; p = 0.0323; OR: 2.34; 95% CI: 0.87–6.24; p = 0.0895, respectively) than having normal cognitive status (table 3, model 1). This association remained substantially unchanged after further adjustments for behavioral and health-related biological parameters, such as alcohol consumption, energy intake, smoking habit, serum cholesterol levels, vitamin E plasma levels (table 3, model 2). Although statistical significance was not reached (see model 2), participants belonging to the middle UA tertile were more likely to be demented compared to those in the lowest tertile (p = 0.0877). When confounders such as hypertension, renal disease, cerebrovascular and cardiovascular diseases were added in model 3, we found that participants in the highest UA tertile maintain a significant threefold higher probability to be affected by dementia syndrome (OR: 3.32; 95% CI: 1.06–10.42; p = 0.0262) compared to those in the lowest tertile. These findings were not substantially modified after adjustment for serum levels of IL-6 and CRP or after exclusion of 15 participants taking drugs affecting circulating UA levels (data not shown). We found no statistical evidence of an interaction be-

Table 3. Logistic regression model relating higher UA levels to dementia syndrome in the InCHIANTI participants

	UA tertile	OR	p
Model 1	1	1 (reference)	–
	2	2.34 (0.87–6.24)	0.0895
	3	3.06 (1.10–8.52)	0.0323
Model 2	1	1 (reference)	–
	2	2.73 (0.96–7.75)	0.0585
	3	3.63 (1.22–10.77)	0.0199
Model 3	1	1 (reference)	–
	2	2.62 (0.91–7.52)	0.1465
	3	3.32 (1.06–10.42)	0.0262
Model 4	1	1 (reference)	–
	2	11.02 (1.69–72.00)	0.0122
	3	18.89 (2.04–174.67)	0.0096

Odds ratio of dementia and 95% CI (in parentheses) in older subjects in the middle and the highest tertile of UA compared to those in the lowest tertile. Model 1: adjusted for age, sex, BMI, education; Model 2: adjusted for all variables in Model 1, and alcohol consumption, energy intake, smoking habit, cholesterol, vitamin E plasma levels; Model 3: adjusted for all variables in Model 2, and renal function, hypertension, cardiovascular diseases and cerebrovascular diseases; Model 4: adjusted for all variables in Model 3 and MMSE basal score.

tween UA and sex, BMI, cardiovascular, cerebrovascular disease and vitamin E in predicting prevalent dementia.

When the fully adjusted model was fitted in participants within the normal UA range (2–7.5 mg/dl in men and 2–5.7 in women), those in the highest UA tertile had a significantly higher probability of being demented compared with participants in the lowest UA tertile ($p = 0.0193$). Participants belonging to the middle UA tertile were still more likely to be demented compared to those in the lowest tertile, but the association was not statistically significant ($p = 0.0995$) (data not shown).

Discussion

Using data collected in the context of a population-based study, we evaluated whether having higher circulating levels of UA is associated with a higher probability of being affected by dementia syndrome in older persons. Our cross-sectional analysis suggests a positive association between high circulating levels of UA and the presence of a dementia syndrome. Persons with circulating UA levels in the highest tertile showed a threefold higher probability of being affected by a dementia syndrome. The probability of having dementia remained significantly higher independent of several confounders such as age, sex, education, BMI, smoking habit, total energy and alcohol consumption, vitamin E and cholesterol plasma levels, hypertension, renal function, cardiovascular and cerebrovascular diseases. Persons with UA levels within the middle UA tertile showed a clear tendency to be affected by a dementia syndrome with about twofold higher probability.

To the best of our knowledge, this is the first population-based study conducted to investigate the relationship between circulating levels of UA and dementia considering the confounding effects of behavioral and health-related conditions. Earlier studies reported a positive correlation between UA levels and cognitive performance estimated in adult persons using the IQ. However, these studies suffered from several methodological limitations such as the small sample size, the lack of information about confounders, and the limited neuropsychological evaluation [32, 33].

In a selected small sample of older subjects admitted to outpatient clinic, Rinaldi et al. [34] found lower plasma levels of UA and other antioxidants both in patients with mild cognitive impairment and Alzheimer's disease as compared to controls. Similarly, Nieto et al. [35] reported lower levels of UA and albumin in patients with Alzheimer's disease admitted to an acute-care ward compared to a control group, independent of age, BMI and sex. The authors interpreted the lower levels of UA as an attempt to counteract the increased oxidative stress associated with dementia [34, 35]. However, no information was available in these studies concerning potential confounders, in particular the major medical illnesses causing hospital admission, the presence of drug therapy or lifestyle factors affecting circulating UA levels.

More recently, Schretlen et al. [18] demonstrated that healthy older men and women with serum UA at the high end of the normal range perform worse in neuropsychological tests investigating several cognitive domains, i.e. processing speed, working memory and verbal memory, compared with those with low-intermediate UA concentrations.

To date, the biological mechanisms linking UA to cognitive functions are unknown. Some authors suggest that UA is a surrogate marker of metabolic and cardiovascular diseases leading to brain damage [35]. Moreover, it is speculated that the high levels of UA associated with these conditions may potentially counteract the oxidative stress associated with cardiovascular diseases, Parkin-

son's and Alzheimer's diseases [36, 37]. The biochemical data demonstrating antioxidant properties of UA against free radicals support this hypothesis [6].

In our study, high levels of UA are associated with dementia independent of underlying metabolic risk factors and cardiovascular diseases. However, the association was partially attenuated after adjustment for kidney disease and cardiovascular and cerebrovascular diseases.

The pathogenetic pathway linking UA to either dementia or conditions leading to dementia may be identified in its ability to increase inflammation, a condition well known to be involved in the pathogenesis of cognitive impairment. It has been demonstrated that soluble UA may exert a proinflammatory activity by mimicking an internal 'danger signal' that stimulates the maturation and the immunoactivity of dendritic cells [38]. Previous epidemiological data from our group showed that UA is positively associated with several proinflammatory markers, such as IL-6, TNF-α, CRP and white blood cells, and predicts the development of pathological levels over a 3-year period of follow-up [9, 39].

Our hypothesis that UA may have an independent detrimental effect on cognitive functions is also consistent with previous studies showing that high circulating UA levels may be causally involved in the development and progression of endothelial dysfunction [10], arteriolosclerosis, hypertension [11], atherothrombosis [40], metabolic diseases [12], and cardiovascular and cerebrovascular diseases [41].

The present study has some limitations. First, because of the cross-sectional nature of our data, a causal pathway from UA to dementia is suggested but could not be definitively proven. Indeed, a possible mechanism of reverse causality should be considered. We cannot exclude the possibility that serum UA increases in response to dementia because of accelerated cellular turnover due to the underlying pathological mechanisms. Then, we could only measure circulating UA levels whose relationship with brain tissue levels is currently unknown. However, on the other side, the available evidence suggests that serum UA levels are relatively stable over time in the same individual unless relevant changes occur in her or his health status or lifestyle [42, 43]. Moreover, since we did not perform a detailed neuropsychological evaluation of participants with an MMSE score >26, it is possible that the group considered as having normal cognitive functions also included participants with mild cognitive impairment.

In conclusion, our study points to a positive association between high circulating levels of UA and dementia syndome which, at least in part, is independent of most cardiovascular, cerebrovascular and metabolic risk factors. If these findings are confirmed in future studies, it would be worthwhile to perform clinical trials aimed at determining whether the pharmacological reduction in UA levels prevents the onset or delays the progression of dementia.

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