**SUPPLEMENTARY MATERIAL**

**Supplementary Methods**

**MRI acquisition and brain lesions assessment**

MRI acquisition was performed on 1.5-Tesla Magnetom scanner (Siemens, Erlangen). Exclusion criteria for MRI were presence of an internal electrical or magnetic device; presence of metal fragments in the eyes, brain, or spinal cord; history of neurosurgery or aneurysm; and claustrophobia. A 3D high-resolution T1-weighted brain volume was acquired by using a 3D inversion recovery fast spoiled-gradient echo sequence (3D IR-SPGR; repetition time [TR] =97 msec; echo time [TE] = 4 msec; inversion time [TI] = 600 msec; coronal acquisition). The axially reoriented 3D volume matrix size was 256×192×256 with a 1.0× .98× .98 mm3 voxel size. T2- and proton density (PD)-weighted brain volumes were acquired by using a 2D dual spin-echo sequence with two echo times (TR=4400 msec; TE1=16 msec; TE2=98 msec). T2 and PD acquisitions consisted of 35 axial slices 3.5 mm thick (0.5 mm between slices spacing), with a 256×256 matrix size, and a 0.98×0.98 mm2 in-plane resolution.

Concerning brain volume, T1- and T2-weighted images from every participant were aligned to each other and analyzed with use of SPM99 (http://www.fil.ion.ucl.ac.uk/spm/). A Voxel-Based Morphometry protocol modified to account for characteristics of aging brains and complemented with a modulation step was used [1 2]. For each participant, gray matter (GM), white matter, and CSF volume were computed as the integral of the voxel intensities over the corresponding modulated tissue partition image; total intracranial volume was generated as their sum [3]. GM volumes in specific regions of interest (ROIs) were computed by integrating the voxel intensities of the modulated GM partition images within each ROIs. Anatomical ROI limits were derived from a model of macroscopic neuroanatomical parcellation, the Automated Anatomical Labeling atlas, based on the high-resolution single-subject T1-weighted volume provided by the Montreal Neurological Institute [4 5]. The hippocampal volume (sum of left and right hippocampal regions) was computed automatically by integrating the voxel intensities of the modulated gray matter partition images obtained within this ROI by using a voxel-based morphometry method previously described [6].

A fully automated image processing software was used to detect and localize white matter hyperintensities (WMH), and measure WMH volume (WMHV) [7]. WMHV was studied as a dichotomized variable, with the top age-specific quartile (≥ 75th percentile) of the ratio of WMHV to white mask volume (age-strata: <70, 70-75, and ≥ 75 years) taken to represent extensive WMHV.

One experienced reader (Yi-Chen Zhu) blind to all clinical data analyzed all images and rated MRI-defined brain infarcts on T1, T2- and proton density-weighted images. Infarcts were defined as focal lesions ≥ 3 mm with the same signal characteristics as cerebrospinal fluid (CSF) on all sequences, located in basal ganglia, brainstem or subcortical white matter. Lacunes were defined as focal lesions 3 to 15 mm in diameter with the same signal characteristics as CSF on all sequences, located in basal ganglia, brainstem, or white matter [8], in agreement with the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria [9]. Subjects with cortical infarcts in the cerebrum, cerebellar infarcts, or large subcortical infarcts (> 15 mm) were excluded from analyses of lacunes. All infarct-like lesions were distinguished from perivascular spaces by using multiplanar reformatting, with lesions having a typical vascular shape and following perforating vessels orientation regarded as perivascular spaces [8].

**Stroke definitions**

At baseline, participants with reported hospitalization for stroke were excluded from the analysis. Information concerning suspicion of stroke occurrence was collected at each follow-up. Information on stroke symptoms and hospitalization was also obtained. For participants who reported an incident stroke, further medical data were collected from hospital records and neuroimaging examinations, general practitioners, and specialists. In case of fatal events, emergency medical services and hospital records were used and if unavailable, family physicians and family members were consulted. An incident stroke was defined as a new focal neurological deficit of sudden or rapid onset, of presumed vascular origin, that lasted 24 hr or more, or led to death. An endpoint adjudication committee reviewed source documentation for all participants with a suspected stroke or those who died during follow-up. Outcomes were coded according to the tenth revision of the International Classification of Diseases. A stroke was classified as non-fatal if the patient was alive 28 days after stroke onset, and an intermediary stroke was defined as a stroke occurring before dementia (for dementia cases). Both fatal and non-fatal strokes were included.

**Measurement of uric acid levels**

Baseline fasting blood samples were collected at the participants’ homes and then centrifuged to collect serum. Serum uric acid (SUA) level was determined by using a colorimetric enzymatic assay (Cobas C; Roche Diagnostics GmbH, Mannheim, DE). This method is based on the production of H2O2 after UA catalysis by uricase. In presence of peroxidase, amino-4 phénazone is oxidized by H202 to form colored quinone diimine. The intensity of coloration is directly related to the SUA levels. The detection limits were 11.9-1487 µmol/L. The intra-assay coefficients of variation reported by the manufacturers ranged from 0.7% to 1.6%.

**Other measurements**

A high education level was defined possessing a high school diploma or university degree. Body mass index (BMI) was calculated as the ratio of weight (kg) to height (m) squared. Smoking status was categorized as never, former, and current. Alcohol consumption was categorized as never, former, and current (≤ 2 or > 2 drinks per week). Past and present medical history was assessed from self-reported diseases, medication use, and objective biologic and physical measures. Diabetes mellitus was defined as intake of antidiabetic drugs or fasting blood glucose ≥ 7 mmol/L. Hypertension was defined by systolic blood pressure (BP) ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or antihypertensive drug intake. Presence of cardiovascular disease was defined as self-reported history of myocardial infarction, bypass cardiac surgery, angioplasty, stroke, or peripheral vascular disease. Renal function was evaluated by estimating the glomerular filtration rate (MDRD-IDMS equation). Methods for genotyping the APOEε polymorphism and for quantifying plasma interleukin 6 (IL-6), C-reactive protein (CRP) and lipids (high-, low-density lipoprotein cholesterol, triglycerides) were described previously.[10-12] APOE-ε4 carrier status was defined as the presence of at least one ε4 allele. All prescribed drugs taken during the preceding month were recorded after checking participants’ medical prescriptions and drug packages as much as possible. Drug names were coded according to the Anatomic Therapeutic Chemical classification recommended by the World Health Organization. Treatments affecting SUA level were classified as urate-lowering treatment (allopurinol, benzbromarone, probenicid, or febuxostat) based on ATC code M04. Other recorded treatments were anti-inflammatory agents (colchicine or nonsteroidal anti-inflammatory drugs), and diuretic or aspirin (concomitant use). Information concerning suspicion of stroke occurrence was collected at each follow-up and validated by a panel of expert neurologists. An interim stroke was defined as a stroke occurring before dementia (for dementia cases).

**Statistical analyses**

We assessed the proportional hazard assumption by testing the interaction between time (age at last follow-up or dementia occurrence) and all variables in the model. Since this assumption was not verified for hypertension and interleukin 6 [IL-6], all Cox models also include an interaction term for these covariates with time (the interaction with hypertension being present in all models adjusted for vascular risk factors, and the one with IL6 only in models adjusted for inflammatory markers). In preliminary analyses, we verified that age or gender would not modify the associations studied by stratified analyses according to median age or gender and testing for interaction of each of these parameters with SUA (≥ 75th percentile) in the association with dementia: all aforementioned interactions were not significant (all pinteraction ≥ 0.32) (data not shown). Then, analyses were performed in 4 steps. Models were initially adjusted for education level and gender (Model 1). Additional adjustments were made for: i) covariates associated with dementia and/or SUA level on univariate analyses or identified as their risk factors in the literature (i.e., BMI, tobacco and alcohol consumption, levels of low- and high-density lipoprotein cholesterol [LDL-c and HDL-c] and triglycerides, diabetes mellitus, hypertension, interaction between hypertension and time, history of cardiovascular disease, renal function, and APOE-ε4) (Model 2); ii) anti-inflammatory agents hereinafter referred to as nonsteroidal anti-inflammatory drugs (NSAIDs) – since the individual under colchicine was also taking ULT and thus was excluded from the analyzed sample – and other drugs affecting SUA: diuretic or aspirin (concomitant use) (Model 3); and iii) inflammatory markers (interleukin 6 [IL-6], C-reactive protein [CRP]) in a fourth model (Model 4). When examining dementia subtypes, all subtypes that were not the primary outcome of interest were censored at the age of their diagnosis.

To explore the cross-sectional association of SUA level with our secondary outcomes (i.e., MRI measurements [extensive WMHV, brain infarcts, lacunes and hippocampal volume]), we used logistic or linear regression with the 4 models described above minus the interaction terms with time. Analyses with hippocampal volume as the outcome were systematically adjusted for total intracranial volume.

To assess the robustness of our primary results, we performed several sensitivity analyses by: a) evaluating the association between SUA and dementia in subjects not taking NSAIDs since these medications might impact the risk of dementia related to the oxidative stress or systemic inflammation, some independent and some dependent on SUA; b) using the usual SUA threshold used to define hyperuricemia vs. normouricemia (360 µmol/l for men, 300 for women); c) altering dates of disease to date of diagnosis rather than midpoint; d) excluding participants with prevalent stroke (n=72) and adjusting all models on intermediary incident stroke, in order to examine whether our findings may have been confounded by the presence of this disease; and e) including individuals under ULT in order to have a sample that would be more representative of the general population. We also performed secondary analyses using gender-unified cut-offs. The influence of ULT was also looked upon for associations concerning MRI markers.

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**Supplementary Table 1. Baseline characteristics of the study sample: differences according to the intake of ULT**

|  |  |  |
| --- | --- | --- |
|  | **Intake of ULT** |  |
|  | **No (n=1,598)** | **Yes (n=61)** | **P**a |
| **Age, years, mean (SD)** | 72.4 (4.1) | 73.3 (4.3) | 0.07 |
| **Male** | 612 (38.3) | 50 (82.0) | <**0.0001** |
| **High education level** b | 654 (40.9) | 28 (45.9) | 0.72 |
| **Current drinker (> 2 drinks/week)** | 332 (22.6) | 24 (40.7) | 0.86 |
| **Current smoking** | 92 (5.8) | 2 (3.3) | 0.12 |
| **BMI, kg/m2, mean (SD)** | 25.4 (3.8) | 27.8 (2.9) | **<0.0001** |
| **Glomerular filtration rate, ml/min/1.73m2, mean (SD)** | 75.1 (13.7) | 69.8 (15.3) | **<0.0001** |
| **Hypertension** | 1,209 (75.7) | 55 (90.2) | 0.1 |
| **Diabetes mellitus** | 121 (7.6) | 14 (23.0) | **0.0004** |
| **History of cardiovascular disease** | 91 (5.7) | 13 (21.3) | **0.003** |
| **NSAIDs** | 239 (15.1) | 10 (16.4) | 0.34 |
| **Concomitant use of aspirin or diuretics**  | 424 (26.6) | 29 (48.3) | **0.0007** |
| **APOE ε4 carrier** | 347 (21.7) | 11 (18.0) | 0.31 |
| **LDL-c level, mmol/L, mean (SD)** | 3.58 (0.81) | 3.2 (0.75) | **0.002** |
| **Triglycerides level, mmol/L, mean (SD)** | 1.20 (0.56) | 1.57 (0.82) | **<0.0001** |
| **High CRP level**c | 537 (33.6) | 28 (45.9) | 0.09 |
| **High IL-6 level**d | 411 (25.7) | 20 (32.8) | 0.59 |
| **SUA level, μmol/L, mean (SD)** | 273.72 (70.41) | 299.56 (60.66) | 0.71 |
| Values are number (percentage) unless stated otherwise. a Logistic regression models adjusted for age and gender, with ULT as the dependent variable. b High school or university diploma. c C-reactive protein level ≥ 66th percentile of distribution (≥ 2.49 mg/L). d Interleukin-6 level ≥ median of distribution (≥ 4.0 pg/mL).NSAIDs, non-steroidal anti-inflammatory agents; LCL-c. low-density lipoprotein-cholesterol; HDL-c. high-density lipoprotein-cholesterol. |

**Supplementary Table 2. Baseline characteristics of the study sample and association with dementia status**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Total sample.** | **Incident dementia** |  |
|  | **N=1,598** | **No (n=1,488)** | **Yes (n=110)** | **P**a |
| **Age, years, mean (SD)** | 72.4 (4.1) | 72.2 (4.1) | 74.7 (4.1) | **<0.0001** |
| **Male** | 612 (38.3) | 574 (38.6) | 38 (34.5) | 0.40 |
| **High education level** b | 654 (40.9) | 613 (41.2) | 41 (37.3) | 0.42 |
| **Current drinker (> 2 drinks/week)** | 332 (22.6) | 315 (23.0) | 17 (17.3) | 0.48 |
| **Current smoking** | 92 (5.8) | 89 (6.0) | 3 (2.7) | 0.36 |
| **BMI, kg/m2, mean (SD)** | 25.4 (3.8) | 25.4 (3.8) | 26.0 (4.0) | 0.13 |
| **Glomerular filtration rate, ml/min/1.73m2, mean (SD)** | 75.1 (13.7) | 75.2 (13.7) | 73.8 (14.3) | 0.30 |
| **Hypertension** | 1,209 (75.7) | 1,123 (75.5) | 86 (78.2) | 0.52 |
| **Diabetes mellitus** | 121 (7.6) | 109 (7.3) | 12 (10.9) | 0.17 |
| **History of cardiovascular disease** | 91 (5.7) | 81 (5.4) | 10 (9.1) | 0.11 |
| **NSAIDs** | 239 (15.1) | 222 (15.0) | 17 (15.5) | 0.90 |
| **Concomitant use of aspirin or diuretics**  | 424 (26.6) | 385 (25.9) | 39 (35.8) | **0.025** |
| **APOE ε4 carrier** | 347 (21.7) | 306 (20.6) | 41 (37.3) | **<0.0001** |
| **LDL-c level, mmol/L, mean (SD)** | 3.58 (0.81) | 3.57 (0.81) | 3.64 (0.86) | 0.45 |
| **HDL-c level, mmol/L, mean (SD)** | 1.65 (0.40) | 1.65 (0.40) | 1.58 (0.35) | 0.10 |
| **Triglycerides level, mmol/L, mean (SD)** | 1.20 (0.56) | 1.19 (0.56) | 1.25 (0.56) | 0.14 |
| **High CRP level**c | 537 (33.6) | 502 (33.7) | 35 (31.8) | 0.76 |
| **High IL-6 level**d | 411 (25.7) | 381 (25.6) | 30 (27.3) | 0.51 |
| Values are number (percentage) unless stated otherwise. a Analysis of covariance for continuous variables; chi-square test for categorical variables. b High school or university diploma. c C-reactive protein level ≥ 66th percentile of distribution (≥ 2.49 mg/L). e Interleukin-6 level ≥ median of distribution (≥ 4.0 pg/mL).NSAIDs, non-steroidal anti-inflammatory agents; LCL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein-cholesterol.  |

**Supplementary Table 3. Association of baseline serum uric acid (SUA) level and incident all-cause dementia and by type using non-gender dependent quartiles**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **%** | **Model 1a** | **Model 2 b** | **Model 3 c** | **Model 4 d** |
| **SUA level (μmol/L)** | **(N event)** | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** |
| **All-cause dementia (n=110)** |  |  |  |  |  |  |  |  |
| < 75th percentile | 5.9 (71) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| ≥75th percentile | 9.7 (39) | 1.76 (1.16;2.66) | 0.007 | 1.84 (1.17;2.91) | 0.008 | 1.84 (1.17;2.92) | 0.009 | 1.89 (1.20;2.99) | 0.006 |
|  |  |  |  |  |  |  |  |  |  |
| Q1 | 5.5 (22) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| Q2 | 6.6 (26) | 1.25 (0.71;2.21) | 0.44 | 1.31 (0.73;2.34) | 0.37 | 1.32 (0.73;2.37) | 0.36 | 1.33 (0.74;2.40) | 0.34 |
| Q3 | 5.7 (23) | 1.13 (0.62;2.04) | 0.69 | 1.29 (0.69;2.41) | 0.42 | 1.31 (0.7;2.44) | 0.4 | 1.40 (0.75;2.62) | 0.29 |
| Q4 | 9.7 (39) | 1.99 (1.14;3.46) | 0.015 | 2.26 (1.22;4.2) | 0.01 | 2.28 (1.22;4.24) | 0.01 | 2.41 (1.29;4.48) | 0.006 |
| *P for linear trend* |  |  | 0.016 |  | 0.009 |  | 0.009 |  | 0.005 |
|  |  |  |  |  |  |  |  |  |  |
| **Alzheimer’s disease (n=76)** |  |  |  |  |  |  |  |  |
| < 75th percentile | 4.1 (48) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| ≥75th percentile | 7.2 (28) | 1.85 (1.13;3.04) | 0.015 | 1.93 (1.12;3.33) | 0.018 | 1.97 (1.13;3.41) | 0.016 | 2.03 (1.17;3.51) | 0.011 |
|  |  |  |  |  |  |  |  |  |  |
| Q1 | 4.1 (16) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| Q2 | 4.7 (18) | 1.19 (0.6;2.33) | 0.62 | 1.23 (0.61;2.47) | 0.56 | 1.23 (0.61;2.48) | 0.56 | 1.21 (0.60;2.45) | 0.60 |
| Q3 | 3.5 (14) | 0.93 (0.45;1.94) | 0.86 | 1.07 (0.50;2.29) | 0.87 | 1.08 (0.50;2.31) | 0.85 | 1.12 (0.52;2.41) | 0.78 |
| Q4 | 7.2 (28) | 1.92 (1.00;3.70) | 0.05 | 2.14 (1.03;4.48) | 0.042 | 2.19 (1.04;4.58) | 0.038 | 2.28 (1.09;4.76) | 0.029 |
| *P for linear trend* |  |  | 0.06 |  | 0.043 |  | 0.039 |  | 0.026 |
|  |  |  |  |  |  |  |  |  |  |
| **Vascular or mixed dementia (n=20)** |  |  |  |  |  |  |  |
| < 75th percentile | 1.2 (14) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| ≥75th percentile | 1.6 (6) | 1.41 (0.52;3.82) | 0.50 | 1.01 (0.31;3.28) | 0.98 | 0.97 (0.30;3.18) | 0.96 | 1.00 (0.30;3.33) | 0.99 |
|  |  |  |  |  |  |  |  |  |  |
| Q1 | 1 (4) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| Q2 | 1.1 (4) | 1.05 (0.26;4.22) | 0.40 | 1.2 (0.29;5.03) | 0.80 | 1.28 (0.30;5.36) | 0.74 | 1.29 (0.31;5.45) | 0.73 |
| Q3 | 1.6 (6) | 1.58 (0.44;5.72) | 0.48 | 2.21 (0.55;8.84) | 0.26 | 2.21 (0.54;8.95) | 0.27 | 2.24 (0.53;9.35) | 0.27 |
| Q4 | 1.6 (6) | 1.74 (0.47;6.48) | 0.41 | 1.54 (0.33;7.16) | 0.58 | 1.52 (0.32;7.17) | 0.59 | 1.58 (0.33;7.65) | 0.57 |
| *P for linear trend* |  |  | 0.34 |  | 0.49 |  | 0.53 |  | 0.51 |
| Q1: quartile 1 (lowest quartile); Q2: quartile 2; Q3: quartile 3; Q4: quartile 4 (highest quartile). Cutoffs for SUA: 75th percentile=315; Q1: < 225; Q2: [225-268[; Q3: [268-315[; Q4: ≥ 315. |
| a Model 1: adjusted for education level, gender. b Model 2: Model 1 + BMI, tobacco and alcohol consumption, cholesterol (LDL, HDL), triglycerides, diabetes mellitus, hypertension, interaction between hypertension and time (age at last follow-up or dementia occurrence), history of cardiovascular disease, glomerular filtration rate, and APOE-ε4. c Model 3: Model 2 + NSAIDs, aspirin or diuretics. d Model 4: Model 3 + CRP, IL-6 levels, and interaction between Il-6 and time (age at last follow-up or dementia occurrence). |

**Supplementary Table 4. Association of baseline serum uric acid (SUA) level and incident dementia: effect of interim stroke events**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **% (N event)** | **Model 1a** | **Model 2 b** | **Model 3 c** | **Model 4 d** |
| **UA level (μmol/L)** | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** |
| **All-cause dementia (n=105)** |  |  |  |  |  |  |  |  |
| < 75th percentile | 5.7 (66) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| ≥75th percentile | 10.3 (39) | 1.67 (1.12;2.49) | 0.012 | 1.77 (1.13;2.78) | 0.012 | 1.72 (1.09;2.70) | 0.019 | 1.80 (1.14;2.84) | 0.011 |
|  |  |  |  |  |  |  |  |  |  |
| Q1 | 5.0 (19) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| Q2 | 5.7 (22) | 1.01 (0.55;1.88) | 0.96 | 1.04 (0.55;1.99) | 0.90 | 1.05 (0.55;2.00) | 0.89 | 1.11 (0.58;2.12) | 0.76 |
| Q3 | 6.6 (39) | 1.31 (0.72;2.37) | 0.38 | 1.44 (0.76;2.70) | 0.26 | 1.48 (0.78;2.79) | 0.23 | 1.62 (0.86;3.08) | 0.14 |
| Q4 | 10.3 (39) | 1.84 (1.06;3.20) | 0.03 | 2.08 (1.12;3.86) | 0.02 | 2.04 (1.10;3.79) | 0.024 | 2.25 (1.21;4.18) | 0.01 |
| *P for linear trend* |  |  | 0.01 |  | 0.007 |  | 0.009 |  | 0.004 |
|  |  |  |  |  |  |  |  |  |  |
| **Alzheimer’s disease (n=75)** |  |  |  |  |  |  |  |  |
| < 75th percentile | 4.3 (49) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| ≥75th percentile | 7.1 (26) | 1.49 (0.92;2.41) | 0.11 | 1.58 (0.93;2.68) | 0.09 | 1.57 (0.92;2.66) | 0.10 | 1.58 (0.93;2.70) | 0.09 |
|  |  |  |  |  |  |  |  |  |  |
| Q1 | 4.0 (15) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| Q2 | 3.9 (15) | 0.87 (0.43;1.79) | 0.71 | 0.95 (0.45;2.01) | 0.89 | 0.94 (0.45;2.00) | 0.88 | 1.03 (0.48;2.20) | 0.94 |
| Q3 | 5.1 (19) | 1.26 (0.64;2.47) | 0.51 | 1.42 (0.69;2.90) | 0.34 | 1.42 (0.69;2.92) | 0.34 | 1.61 (0.78;3.35) | 0.20 |
| Q4 | 7.1 (26) | 1.54 (0.81;2.92) | 0.19 | 1.79 (0.87;3.68) | 0.11 | 1.77 (0.86;3.64) | 0.12 | 1.93 (0.94;3.98) | 0.08 |
| *P for linear trend* |  |  | 0.09 |  | 0.05 |  | 0.06 |  | 0.037 |
|  |  |  |  |  |  |  |  |  |  |
| **Vascular or mixed dementia (n=17)** |  |  |  |  |  |  |  |
| < 75th percentile | 0.6 (7) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| ≥75th percentile | 2.6 (9) | 3.38 (1.26;9.10) | 0.016 | 1.51 (0.36;6.34) | 0.57 | 0.95 (0.19;4.75) | 0.95 | 0.95 (0.18;4.90) | 0.95 |
|  |  |  |  |  |  |  |  |  |  |
| Q1 | 0.5 (2) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| Q2 | 0.8 (3) | 1.20 (0.20;7.17) | 0.85 | 1.06 (0.13;8.96) | 0.95 | 1.60 (0.18;14.07) | 0.67 | 1.63 (0.17;15.48) | 0.67 |
| Q3 | 0.6 (2) | 0.96 (0.13;6.82) | 0.97 | 2.20 (0.23;21.36) | 0.50 | 2.62 (0.27;25.91) | 0.41 | 2.66 (0.25;27.81) | 0.41 |
| Q4 | 2.6 (9) | 3.59 (0.77;16.68) | 0.10 | 2.01 (0.27;14.72) | 0.49 | 1.51 (0.18;12.41) | 0.70 | 1.53 (0.18;13.16) | 0.70 |
| *P for linear trend* |  |  | 0.033 |  | 0.44 |  | 0.75 |  | 0.75 |
| Participants with prevalent stroke (n=67) were excluded. Q1: quartile 1 (lowest quartile); Q2: quartile 2; Q3: quartile 3; Q4: quartile 4 (highest quartile). Cutoffs gender-specific for SUA: 75th percentile=345 for men, 292 for women; Q1: < 260 in men, < 209 for women; Q2: [260-299[ for men, [209-247[ for women; Q3: [299-345[ for men. [247-292[ for women; Q4: ≥ 345 for men, ≥ 292 for women. |
| a Model 1: adjusted for education level, gender. b Model 2: Model 1 + BMI, tobacco and alcohol consumption, cholesterol (LDL, HDL), triglycerides, diabetes mellitus, hypertension, interaction between hypertension and time (age at last follow-up or dementia occurrence), history of cardiovascular disease, glomerular filtration rate, APOE-ε4 and interim stroke events. c Model 3: Model 2 + NSAIDs, aspirin or diuretics. d Model 4: Model 3 + CRP, IL-6 levels, and interaction between IL-6 and time (age at last follow-up or dementia occurrence). |

**Supplementary Table 5. Association of baseline SUA level and incident all-cause dementia and by type: sensitivity analysis including participants taking urate-lowering treatments in the analyzed sample (n=1,659)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **%** | **Model 1a** | **Model 2 b** | **Model 3 c** | **Model 4 d** |
| **UA level (μmol/L)** | **(N event)** | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** |
| **All-cause dementia (n=113)** |  |  |  |  |  |  |  |  |
| < 75th percentile | 5.7 (71) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| ≥75th percentile | 9.9 (42) | 1.58 (1.07;2.32) | 0.02 | 1.74 (1.15;2.63) | 0.009 | 1.72 (1.13;2.61) | 0.012 | 1.71 (1.12;2.62) | 0.013 |
|  |  |  |  |  |  |  |  |  |  |
| Q1 | 5.1 (21) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| Q2 | 6.1 (25) | 1.08 (0.60;1.92) | 0.81 | 1.12 (0.62;2.02) | 0.71 | 1.13 (0.62;2.04) | 0.69 | 1.14 (0.63;2.08) | 0.66 |
| Q3 | 6.1 (25) | 1.17 (0.66;2.10) | 0.59 | 1.25 (0.69;2.26) | 0.47 | 1.29 (0.71;2.34) | 0.41 | 1.33 (0.73;2.42) | 0.36 |
| Q4 | 9.9 (42) | 1.71 (1.01;2.90) | 0.046 | 1.97 (1.11;3.49) | 0.021 | 1.97 (1.11;3.50) | 0.021 | 2.00 (1.12;3.56) | 0.019 |
| *P for linear trend* |  |  | 0.024 |  | 0.01 |  | 0.011 |  | 0.01 |
|  |  |  |  |  |  |  |  |  |  |
| **Alzheimer’s disease (n=78)** |  |  |  |  |  |  |  |  |
| < 75th percentile | 4.2 (51) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| ≥75th percentile | 6.6 (27) | 1.40 (0.87;2.25) | 0.16 | 1.48 (0.89;2.46) | 0.13 | 1.48 (0.89;2.47) | 0.14 | 1.47 (0.87;2.46) | 0.15 |
|  |  |  |  |  |  |  |  |  |  |
| Q1 | 4.2 (17) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| Q2 | 3.7 (15) | 0.79 (0.40;1.59) | 0.52 | 0.78 (0.38;1.59) | 0.49 | 0.80 (0.39;1.63) | 0.53 | 0.81 (0.39;1.66) | 0.56 |
| Q3 | 4.7 (19) | 1.10 (0.57;2.11) | 0.78 | 1.09 (0.55;2.14) | 0.81 | 1.13 (0.57;2.24) | 0.72 | 1.15 (0.58;2.28) | 0.68 |
| Q4 | 6.6 (27) | 1.34 (0.73;2.48) | 0.34 | 1.41 (0.72;2.75) | 0.32 | 1.44 (0.73;2.82) | 0.29 | 1.44 (0.74;2.84) | 0.29 |
| *P for linear trend* |  |  | 0.18 |  | 0.16 |  | 0.15 |  | 0.15 |
|  |  |  |  |  |  |  |  |  |  |
| **Vascular or mixed dementia (n=21)** |
| < 75th percentile | 0.9 (10) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| ≥75th percentile | 2.8 (11) | 2.82 (1.20;6.66) | 0.02 | 3.92 (1.46;10.54) | 0.007 | 4.07 (1.48;11.17) | 0.007 | 3.88 (1.41;10.69) | 0.009 |
|  |  |  |  |  |  |  |  |  |  |
| Q1 | 0.5 (2) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
| Q2 | 1.5 (6) | 2.45 (0.49;12.15) | 0.27 | 3.16 (0.62;16.06) | 0.17 | 3.12 (0.60;16.14) | 0.17 | 3.35 (0.65;17.21) | 0.15 |
| Q3 | 0.5 (2) | 0.96 (0.14;6.85) | 0.97 | 1.36 (0.18;10.09) | 0.76 | 1.48 (0.20;11.01) | 0.70 | 1.55 (0.20;11.69) | 0.67 |
| Q4 | 2.8 (11) | 4.33 (0.96;19.59) | 0.06 | 7.32 (1.42;37.67) | 0.017 | 7.77 (1.48;40.75) | 0.015 | 7.62 (1.46;39.91) | 0.016 |
| *P for linear trend* |  |  | 0.037 |  | 0.011 |  | 0.009 |  | 0.011 |
| Q1: quartile 1 (lowest quartile); Q2: quartile 2; Q3: quartile 3; Q4: quartile 4 (highest quartile). Cutoffs gender-specific for SUA: 75th percentile=345 for men, 292 for women; Q1: < 260 in men, < 209 for women; Q2: [260-299[ for men, [209-247[ for women; Q3: [299-345[ for men. [247-292[ for women; Q4: ≥ 345 for men, ≥ 292 for women. |
| a Model 1: adjusted for education level, gender. b Model 2: Model 1 + BMI, tobacco and alcohol consumption, cholesterol (LDL, HDL), triglycerides, diabetes mellitus, hypertension, history of cardiovascular disease, glomerular filtration rate, and APOE-ε4. c Model 3: Model 2 + urate-lowering treatment, anti-inflammatory agents (NSAIDs or colchicine), aspirin or diuretics. d Model 4: Model 3 + CRP and IL-6 levels. |

**Supplementary Table 6. Association of baseline SUA level and baseline MRI brain markers of cerebrovascular disease: sensitivity analyses including participants taking urate-lowering treatments in the analyzed sample (n=1,659)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Model 1a** | **Model 2 b** | **Model 3 c** | **Model 4 d** |
| **Extensive WMHV** | **UA (μmol/L)** | **% (N)** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** |
|  | < 75th percentile | 22.9 (271) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
|  | ≥75th percentile | 31.2 (125) | 1.52 (1.18;1.95) | 0.001 | 1.35 (1.03;1.78) | 0.03 | 1.31 (1.00;1.74) | 0.05 | 1.28 (0.97;1.17) | 0.08 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Brain infarcts** | **UA (μmol/L)** | **% (N)** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** |
|  | < 75th percentile | 9.5 (116) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
|  | ≥75th percentile | 11.4 (48) | 1.16 (0.80;1.66) | 0.44 | 0.92 (0.61;1.37) | 0.68 | 0.87 (0.58;1.32) | 0.52 | 0.86 (0.57;1.13) | 0.47 |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Lacunes** | **UA (μmol/L)** | **% (N)** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** |
|  | < 75th percentile | 7.4 (89) | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  | 1.00 (ref.) |  |
|  | ≥75th percentile | 9.2 (38) | 1.21 (0.80;1.81) | 0.37 | 0.95 (0.60;1.48) | 0.81 | 0.91 (0.57;1.44) | 0.69 | 0.89 (0.56;1.42) | 0.64 |
|  |  |  |  |  |  |  |  |  |  |  |
| Cutoffs gender-specific for SUA: 75th percentile=345 for men, 292 for women. Extensive white matter hyperintensity volume (WMHV) is defined as the age-specific top quartile (≥ 75th percentile) of WMHV over white mask volume (thresholds are calculated in 3 age-strata: <70, [70-75], and ≥ 75 years). Logistic regression models were used to assess the probability of having brain infarcts, lacunes or extensive WMHV at baseline by baseline UA level. |
| a Model 1: adjusted for age, gender. b Model 2: Model 1 + BMI, tobacco and alcohol consumption, cholesterol (LDL, HDL), triglycerides, diabetes mellitus, hypertension, history of cardiovascular disease, glomerular filtration rate. c Model 3: Model 2 + urate-lowering treatment, anti-inflammatory agents (NSAIDs or colchicine), aspirin or diuretics. d Model 4: Model 3 + CRP and IL-6 levels. |