**Supplementary Material**

**Longer Duration of Hypertension and MRI Microvascular Brain Alterations Are Associated with Lower Hippocampal Volumes in Older Individuals with Hypertension**

**Supplementary Table 1.** Characteristics of the study population undergoing visit 2 of the ADELAHYDE study, according to the MTA-scale for Medial Temporal lobe Atrophy (Scheltens)

|  |  |  |
| --- | --- | --- |
| *Population characteristics* | Scheltens scale | p |
| N=113 | 0(n=60) | ≥1(n=53) |
| *Socio-demographics* |
| Female gender, n (%) | 39 (65.0) | 22 (41.5) | 0.012 |
| Age (y) | 73.6±4.6 | 76.7±5.9 | 0.002 |
| Intermediate/high education level, n (%) | 42 (70.0) | 39 (73.6) | 0.67 |
| *Risk and hemodynamic factors* |
| Past/current smoker, n (%) | 18 (30.0) | 25 (47.2) | 0.061 |
| BMI (kg/m²) | 28.5±5.1 | 28.6±4.4 | 0.96 |
|  SBP (mmHg) | 140±17 | 142±18 | 0.45 |
| DBP (mmHg) | 72±10 | 74±10 | 0.28 |
| Pulse pressure (mmHg) | 67±13 | 68±14 | 0.85 |
| Heart rate (bpm) | 63±8 | 65±11 | 0.10 |
| *Biochemical examinations* |
| MDRD eGFR (ml/min/1.73 m2) | 70±16 | 70±15 | 0.84 |
| Sodium (mmol/L) | 140±2 | 140±2 | 0.83 |
| Total cholesterol (g/L) | 1.98±0.36 | 2.04±0.50 | 0.39 |
| LDL cholesterol (g/L) | 1.16±0.30 | 1.22±0.39 | 0.37 |
| HDL cholesterol (g/L) | 0.58±0.16 | 0.57±0.14 | 0.65 |
| Homocysteine (mmol/L) | 15.0±5.2 | 15.5±4.4 | 0.61 |
| C-reactive protein (mg/L) | 3.6±5.5 | 6.1±10.5 | 0.11 |
| HbA1c (%) | 6.1±1.1 | 6.1±1.0 | 0.85 |
| *Medical history* |
| Hypertension duration (y)\* | 20 (18 to 22) | 21 (19 to 23) | 0.73 |
| Diabetes, n (%) | 9 (15.0) | 10 (18.9) | 0.58 |
| *History of vascular events* |
| - myocardial infarction | 9 (15.0) | 9 (17.0) | 0.083 |
| - stroke | 3 (5.0) | 1 (1.9) | 0.80 |
| - transient ischemic attack | 5 (8.5) | 1 (1.9) | 0.13 |
| *Medications* |
| ACEi/ARBs, n (%) | 46 (76.7) | 35 (66.0) | 0.21 |
| Beta-blockers, n (%) | 21 (35.0) | 16 (30.1) | 0.59 |
| CCB, n (%) | 20 (33.3) | 20 (37.4) | 0.63 |
| Diuretics, n (%) | 31 (51.7) | 25 (47.2) | 0.63 |
| Statins, n (%) | 37 (61.7) | 27 (50.9) | 0.25 |
| Antithrombotic agents, n (%) | 16 (26.7) | 14 (26.4) | 0.98 |
| *Paraclinical Investigations and Psychometric assessment* |
| Gröber-Buschke test: |
| - free recall  | 28.6±6.7 | 22.1±9.7 | <0.001 |
| - total recall (free and cued) | 45.9±2.8 | 42.0±7.7 | 0.001 |
|  - composite score (“global memory”) | 0.7±1.1 | 1.4±1.3 | 0.003 |
| *Target organ damage* |
| Intima-media thickness (mm) | 0.72±0.22 | 0.73±0.24 | 0.84 |
| Carotid Atheromatous plaque, n (%) | 15 (25.4) | 14 (27.5) | 0.81 |
| Pulse wave velocity (m/s) | 11.8±3.1 | 12.8±4.5 | 0.18 |
| Augmentation index (%) | 38.7±19.6 | 37.6±17.5 | 0.76 |
| LV hypertrophy on ECG, n (%) | 10 (16.7) | 6 (11.8) | 0.54 |
| Microalbuminuria (mg/dL) | 23±60.3 | 43±117 | 0.27 |
| *MRI Fazekas Score* |
| Mean MRI Fazekas score | 2.7±1.4 | 3.8±1.6 | <0.001 |
| * grade I (0-1)
 | 9 (15.0) | 1 (1.9) | 0.002 |
| * grade II (2-3)
 | 36 (60.0) | 24 (45.3) |  |
| * grade III (4-6)
 | 15 (25.0) | 28 (52.8) |  |
| Mean hippocampal volumea | 2.79±0.30 | 2.45±0.40 | <0.001 |

For continuous variables, results are presented as mean ± standard deviation while; categorical variables are presented as numbers (n) and proportions (%).

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LV, left ventricular; ECG, electrocardiogram; MDRD, modified of diet in renal disease equation 4; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CCB, calcium channel blockers; MRI, magnetic resonance imaging.

aValues of hippocampal volume have been calculated by the division of HV in mm3 by the total intracranial volume (mm3) and multiplied by 1000.

**Supplementary Table 2.** Linear regression multivariate model to determine the factors at visit 1 associated with hippocampal volume at visit 2 assessed with FSS

|  |  |  |  |
| --- | --- | --- | --- |
| **Hippocampus volume** | **Beta coef.** | **95% CI** | **p** |
| ***Visit 1*** |  |  |  |
| Overall model fit (Adj. R2 =0.27) | - | - | <0.001 |
| Constant | -10.9 | -25.1 to -3.3 | 0.13 |
| Gender (male versus female) | -0.28 | -0.22 to 0.16 | 0.78 |
| Age (per each 10 y) | -0.38 | -0.54 to -0.23 | <0.001 |
| Hypertension duration (y) | -0.01 | -0.02 to -0.01 | 0.088 |

FSS, Free Surfer Software; BMI, body mass index; MRI, magnetic resonance imaging.

Values of hippocampal volume have been calculated by the division of HV in mm3 by the total intracranial volume (mm3) and multiplied by 1000).

**Supplementary Table 3.** Linear regression multivariate model in determining the factors at visit 2 associated with hippocampal volume also at visit 2

|  |  |  |  |
| --- | --- | --- | --- |
| **Hippocampal volume** | **Beta coef.** | **95% CI** | **p** |
| ***Visit 2*** |  |  |  |
| Overall model fit (Adj. R2 =0.41) | - | - | <0.001 |
| Constant | -15.4 | -28.3 to -2.5 | 0.020 |
| Gender (male versus female) | 0.01 | -0.18 to 0.18 | 0.99 |
| Age (per each 10 y) | -0.27 | -0.40 to -0.14 | <0.001 |
| BMI (Kg/m2) | 0.01 | -0.01 to 0.03 | 0.094 |
| Hypertension duration (y) | -0.01 | -0.02 to -0.01 | 0.026 |
| MRI Fazekas Score | -0.06 | -0.11 to -0.01 | 0.015 |
| Gröber-Buschke: Total Recall (Free & Cued) | 0.03 | 0.01 to 0.04 | <0.001 |

BMI, body mass index; MRI, magnetic resonance imaging.

Values of hippocampal volume have been calculated by the division of HV in mm3 by the total intracranial volume (mm3) and multiplied by 1000.

**Supplementary Table 4.** Logistic regression multivariate model to assess the factors associated with Scheltens score ≥1

|  |  |  |
| --- | --- | --- |
| **Variable** | **OR (95%CI)** | **p** |
| ***Model with MRI variables*** |  |  |
| MRI Fazekas scale (per 1 unit increase) | 1.56 (1.13 to 2.18) | 0.007 |
| Total hippocampus volume/TIV (per 1 unit\*1000 increase) | 0.12 (0.02 to 0.53) | 0.006 |
| Gender (male) | 3.06 (1.08 to 8.63) | 0.034 |
| ***Model without MRI variables***  |  |  |
| Age (per 10-year increase) | 2.85 (1.23 to 6.47) | 0.013 |
| Gröber-Buschke test: Free Recall  | 0.93 (0.88-0.98) | 0.012 |

The variables were selected on the basis of a p-value <0.15 from Table 1.

Two models were built: one with the MRI variables plus clinical variables and another with the clinical variables only. TIV, total intracranial volume.

**Supplementary Table 5.** Change (from V1 to V2) in clinical factors and respective association with the hippocampal volume

|  |  |  |  |
| --- | --- | --- | --- |
| ∆ Risk factors | Beta coef. | 95%CI | p |
| Age | 0.01 | -0.15 | 0.16 | 0.94 |
| BMI | 0.03 | -0.01 | 0.07 | 0.17 |
| SBP | 0.00 | -0.01 | 0.00 | 0.60 |
| HR | 0.00 | -0.01 | 0.01 | 0.96 |
| eGFR | 0.00 | 0.00 | 0.01 | 0.21 |
| LDLc | -0.15 | -0.38 | 0.09 | 0.23 |
| Homocystein  | -0.01 | -0.02 | 0.01 | 0.44 |
| Microalbuminuria | 0.00 | 0.00 | 0.00 | 0.93 |
| HTN years | -0.06 | -0.21 | 0.09 | 0.43 |
| HbA1c | 0.03 | -0.04 | 0.09 | 0.39 |

∆, delta (change from V1 to V2); BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate; LDLc, low density cholesterol; HTN, hypertension; HBA1c, glycated hemoglobin.

**Supplementary Table 6.** Allele frequencies of Alzheimer-related genes according to median hippocampal volume measured with the Free Surfer Software (adjusted for total intracranial volume)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Polymorphism** | **Candidate genes** | **Alleles** | **Total** | **Hippocampal volumea****(median)** | **p** |
|  | **SNP ID** | **protein** | **a** | **b** |  | **(n=113)** | **<2.7** **(n=57)** | **≥2.7** **(n=56)** |  |
| ApoE112 [1] | rs429358 | apolipoprotein E | Cys | Arg | aa | 81 (71.7) | 44 (78.6) | 37 (64.9) | 0.23 |
| ab | 28 (24.8) | 11 (19.6) | 17 (29.8) |
| bb | 4 (3.5) | 1 (1.8) | 3 (5.3) |
|  |  |  |  |  | aa | 99 (87.6) | 48 (85.7) | 51 (89.5) | 0.54 |
| ab | 14 (12.4) | 8 (14.3) | 6 (10.5) |
| bb | 0 (0) | 0 (0) | 0 (0) |
| MTHFR677 [2] | rs1801133 | Methylenetetra-hydrofolate reductase | C | T | aa | 49 (43.4) | 24 (42.9) | 25 (43.9) | 0.74 |
| ab | 39 (34.5) | 21 (37.5) | 18 (31.6) |
| bb | 25 (22.1) | 11 (19.5) | 14 (24.6) |
| PON1\_55 [3] | rs854560 | paraoxonase 1 | Met | Leu | aa | 16 (14.2) | 10 (17.9) | 6 (10.5) | 0.20 |
| ab | 56 (49.6) | 30 (53.6) | 26 (45.6) |
| bb | 41 (36.3) | 16 (28.6) | 25 (43.9) |
| PON1\_192 [3] | rs662 | paraoxonase 1 | Gln | Arg | aa | 53 (46.9) | 25 (44.6) | 28 (49.1) | 0.48 |
| ab | 49 (43.4) | 27 (48.2) | 22 (38.6) |
| bb | 11 (9.7) | 4 (7.1) | 7 (12.3) |
| PON2\_311 [4] | rs6954345 | paraoxonase 2 | Ser | Cys | aa | 63 (55.8) | 33 (58.9) | 30 (52.6) | 0.79 |
| ab | 41 (36.3) | 19 (33.9) | 22 (38.6) |
| bb | 9 (8) | 4 (7.1) | 5 (8.8) |
| CETP405 [5] | rs5882 | cholesterol ester transfer protein | Ile | Val | aa | 56 (49.6) | 28 (50) | 28 (49.1) | 0.99 |
| ab | 47 (41.6) | 23 (41.1) | 24 (42.1) |
| bb | 10 (8.8) | 5 (8.9) | 5 (8.8) |
| ACE [6] | rs1799752 | angiotensin-converting enzyme | I | D | aa | 30 (26.5) | 16 (28.6) | 14 (24.6) | 0.28 |
| ab | 49 (43.4) | 27 (48.2) | 22 (38.6) |
| bb | 34 (30.1) | 13 (23.2) | 21 (36.8) |
| TNFa308 [7] | rs1800629 | tumor necrosis factor-α | G | A | aa | 80 (70.8) | 36 (64.3) | 44 (77.2) | 0.12 |
| ab | 30 (26.5) | 17 (30.4) | 13 (22.8) |
| bb | 3 (2.7) | 3 (5.4) | 0 (0) |
| MMP3 [8] | rs3025028 | matrix metalloproteinase-3 | 5A | 6A | aa | 33 (29.2) | 18 (32.1) | 15 (26.3) | 0.74 |
| ab | 53 (46.9) | 26 (46.4) | 27 (47.4) |
| bb | 27 (23.9) | 12 (21.4) | 15 (26.3) |

aValues of hippocampal volume have been calculated by the division of HV in mm3 by the total intracranial volume (mm3) and multiplied by 1000.

Categorical variables are presented as numbers (n) and proportions (%).

SNP, Single nucleotide polymorphisms; rs, reference; Cys, Cysteine; Arg, Arginine; Met, Methionine; Leu, Leucine; Gln, Glutamine; Ser, Serine; Ile, Isoleucine; Val, Valine.

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