**Supplement**

**Figure legends:**

Supplemental figure 1. Directed anticyclic graphs for Confounder identification of total effect of high sensitivity C-reactive protein on depressive symptoms using the Center for Epidemiologic Studies Depression Scale



Supplemental Table 1. – Patient characteristics stratified for follow-up point and depression defined as CES-D ≥ 16

|  | Follow-up Year 1 | Follow-up Year 2 | Follow-up Year 3 |
| --- | --- | --- | --- |
| CES-D Score < 16, n CES-D Score $\geq $ 16, n (%) No CES-D Score available, n No CES-D Score due to Death, n (%) Median CES-D (IQR) | 330 (80 %)86 (20%)16937 (21 %)7 (3 – 14) | 286 (79 %)77 (21 %)22245 (20 %)7 (3 – 15) | **271 (83 %)**56 (17 %)25855 (21 %)7 (3 – 14) |
| **Variable** | **N** | CES-D < 16 | CES-D ≥ 16 | **p-value1** | **N** | CES-D < 16 | CES-D ≥ 16 | **p-value1** | **N** | CES-D < 16 | CES-D ≥ 16 | **p-value1** |
| Age in years, mean (SD)  | 416 | 66 (13) | 65 (12) | 0.2 | 363 | 66 (12) | 63 (13) | 0.024 | 327 | 65 (12) | 68 (11) | 0.2 |
| Female sex, n (%)  | 416 | 115 (35%) | 46 (53%) | 0.002 | 363 | 97 (34%) | 35 (45%) | 0.062 | 327 | 88 (32%) | 28 (50%) | 0.013 |
| hs-CRP in mg/L1 | 416 | 4 (2, 11) | 5 (2, 12) | 0.15 | 363 | 4 (2, 10) | 6 (2, 15) | 0.021 | 327 | 3 (1, 8) | 6 (3, 19) | <0.001 |
| NIHSS Score, n (%)  | 416 |  |  | 0.3 | 363 |  |  | 0.2 | 327 |  |  | 0.006 |
|  0-4 |  | 257 (78%) | 62 (72%) |  |  | 225 (79%) | 55 (71%) |  |  | 223 (82%) | 36 (64%) |  |
|  5-15 |  | 73 (22%) | 24 (28%) |  |  | 61 (21%) | 22 (29%) |  |  | 48 (18%) | 20 (36%) |  |
|  median (IQR) | 416 | 2.0 (1.0, 4.0) | 2.0 (1.3, 5.0) | 0.047 | 363 | 2.0 (1.0, 4.0) | 3.0 (2.0, 5.0) | 0.008 | 327 | 2.0 (1.0, 4.0) | 3.0 (2.0, 5.2) | 0.004 |
| Habitual Alcohol Consumption n (%)  | 402 | 127 (40%) | 27 (32%) | 0.2 | 351 | 116 (42%) | 26 (35%) | 0.3 | 318 | 105 (40%) | 15 (28%) | 0.10 |
| Current smoker, n (%) | 411 | 82 (25%) | 25 (30%) | 0.3 | 358 | 76 (27%) | 24 (32%) | 0.3 | 324 | 74 (28%) | 16 (29%) | 0.9 |
| BMI in kg, n (%)  | 413 |  |  | 0.034 | 361 |  |  | 0.031 | 326 |  |  | 0.11 |
|  < 18,5  |  | 1 (0.3%) | 2 (2.4%) |  |  | 2 (0.7%) | 0 (0%) |  |  | 2 (0.7%) | 0 (0%) |  |
| ≥18,5 and < 25  |  | 110 (33%) | 27 (32%) |  |  | 102 (36%) | 24 (32%) |  |  | 90 (33%) | 19 (34%) |  |
| ≥25 and < 30  |  | 146 (44%) | 28 (33%) |  |  | 125 (44%) | 25 (33%) |  |  | 119 (44%) | 17 (30%) |  |
| ≥ 30  |  | 72 (22%) | 27 (32%) |  |  | 56 (20%) | 27 (36%) |  |  | 59 (22%) | 20 (36%) |  |
| median (IQR) | 413 | 27.0 (24.2, 29.4) | 27.3 (24.1, 31.3) | 0.8 | 361 | 26.8 (24.0, 29.3) | 28.0 (24.2, 31.6) | 0.030 | 326 | 26.9 (24.2, 29.4) | 27.4 (24.6, 32.0) | 0.3 |
| Cardiovascular risk factors, n (%) |  |  |  |  |  |  |  |  |  |  |  |  |
|  Diabetes mellitus | 416 | 64 (19%) | 21 (24%) | 0.3 | 363 | 60 (21%) | 16 (21%) | >0.9 | 327 | 49 (18%) | 16 (29%) | 0.073 |
|  History of myocardial infarction | 413 | 10 (3.0%) | 2 (2.4%) | >0.9 | 362 | 7 (2.4%) | 4 (5.3%) | 0.3 | 325 | 8 (3.0%) | 1 (1.8%) | >0.9 |
|  Coronary artery disease | 416 | 41 (12%) | 21 (24%) | 0.005 | 363 | 34 (12%) | 19 (25%) | 0.005 | 327 | 29 (11%) | 13 (23%) | 0.011 |
|  Peripheral artery disease  | 416 | 14 (4.2%) | 8 (9.3%) | 0.10 | 363 | 15 (5.2%) | 5 (6.5%) | 0.8 | 327 | 14 (5.2%) | 3 (5.4%) | >0.9 |
|  Arterial hypertension  | 416 | 202 (61%) | 59 (69%) | 0.2 | 363 | 181 (63%) | 49 (64%) | >0.9 | 327 | 162 (60%) | 38 (68%) | 0.3 |
| Atrial fibrillation | 416 | 63 (19%) | 19 (22%) | 0.5 | 363 | 48 (17%) | 17 (22%) | 0.3 | 327 | 45 (17%) | 11 (20%) | 0.6 |
| Stroke subtype according to TOAST, n (%) | 416 |  |  | 0.2 | 363 |  |  | 0.5 | 327 |  |  | 0.8 |
|  Large Artery Atherosclerosis  |  | 88 (27%) | 25 (29%) |  |  | 74 (26%) | 23 (30%) |  |  | 70 (26%) | 16 (29%) |  |
|  Cardioembolic |  | 73 (22%) | 22 (26%) |  |  | 61 (21%) | 17 (22%) |  |  | 59 (22%) | 10 (18%) |  |
|  Small Artery Occlusion  |  | 51 (15%) | 16 (19%) |  |  | 47 (16%) | 8 (10%) |  |  | 43 (16%) | 10 (18%) |  |
|  Other cause  |  | 14 (4.2%) | 0 (0%) |  |  | 8 (2.8%) | 4 (5.2%) |  |  | 8 (3.0%) | 3 (5.4%) |  |
|  Undefined  |  | 104 (32%) | 23 (27%) |  |  | 96 (34%) | 25 (32%) |  |  | 91 (34%) | 17 (30%) |  |
| Pre-stroke institutionalization, n (%) | 416 | 4 (1.2%) | 1 (1.2%) | >0.9 | 363 | 5 (1.7%) | 0 (0%) | 0.6 | 327 | 4 (1.5%) | 0 (0%) | >0.9 |
| ≤ 10 years Education, n (%)  | 403 | 204 (64%) | 68 (80%) | 0.013 | 353 | 167 (60%) | 60 (79%) | 0.003 | 318 | 159 (61%) | 47 (84%) | <0.001 |
| MRI findings for WahlundScore1 | 303 | 4.0 (2.0, 8.0) | 5.0 (3.2, 8.8) | 0.4 | 259 | 5.0 (2.0, 9.0) | 4.0 (2.8, 6.2) | 0.085 | 235 | 5.0 (2.0, 8.2) | 5.0 (4.0, 8.0) | 0.4 |
| Physical activity pre-stroke, n (%) | 414 |  |  | 0.6 | 360 |  |  | 0.2 | 324 |  |  | 0.090 |
|  None to occasional  |  | 211 (64%) | 58 (67%) |  |  | 170 (60%) | 53 (69%) |  |  | 163 (61%) | 40 (73%) |  |
| Regular to heavy  |  | 117 (36%) | 28 (33%) |  |  | 113 (40%) | 24 (31%) |  |  | 106 (39%) | 15 (27%) |  |
| MRI Infarct pattern, n (%) | 279 |  |  | 0.4 | 241 |  |  | 0.6 | 216 |  |  | 0.2 |
|  Territorial infarct  |  | 75 (33%) | 17 (34%) |  |  | 62 (31%) | 18 (42%) |  |  | 57 (30%) | 10 (34%) |  |
|  Subcortical infarct  |  | 60 (26%) | 11 (22%) |  |  | 49 (25%) | 10 (23%) |  |  | 54 (29%) | 8 (28%) |  |
|  Scattered infarct  |  | 47 (21%) | 15 (30%) |  |  | 43 (22%) | 8 (19%) |  |  | 36 (19%) | 9 (31%) |  |
|  Lacunar Infarct  |  | 0 (0%) | 0 (0%) |  |  | 0 (0%) | 0 (0%) |  |  | 0 (0%) | 0 (0%) |  |
|  Infratentorial Infarct  |  | 47 (21%) | 7 (14%) |  |  | 44 (22%) | 7 (16%) |  |  | 40 (21%) | 2 (6.9%) |  |
| 1 Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test |  |  |  |  |  |  |  |  |  |  |  |  |
|  |
|  |

Supplemental Table 2. Quartiles of high sensitivity C-reactive protein levels at baseline and depressive symptoms over time in patients with ischemic stroke

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Crude  | Adjusted  | Adjusted + male interaction  | Adjusted + female interaction  |
|  | Change in CES-D score over time |
|  | Beta | 95% CI | Beta | 95%- CI | Beta | 95% CI | Beta | 95% CI |
| hs-CRP<1.77 mg/l | Ref |  | Ref |  | Ref |  | Ref |  |
| hs-CRP1.77 – 4.77 | 1.34 | -0.50 – 3.17 | 0.44 | -1.34 – 2.23 | 0.22 | -1.96 – 2.40 | 1.33 | -1.74 – 4.40 |
| hs-CRP 4.77 – 12.5 | 1.67 | -0.17 – 3.51 | 0.77 | -1.05 – 2.59 | -0.82 | -3.03 – 1.39 | 3.87\* | 0.76 – 6.99 |
| hs-CRP 12.5-101 | 3.35\*\* | 1.47 – 5.24 | 1.96\* | 0.02 – 3.91 | 1.29  | -1.13 – 3.71 | 3.53 \* | 0.46 – 6.61 |

# adjusted for age, sex, physical activity pre stroke, diabetes mellitus, history of cardiovascular disease, stroke severity, BMI, regular alcohol consumption and smoking status; \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

Supplemental Table 3. high sensitivity C-reactive protein and depressive symptoms over time in ischemic stroke patients with subclinical level below 10 mg/L

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Crude  | Adjusted  | Adjusted + male interaction  | Adjusted + female interaction  |
|  | Change in CES-D score over time |
|  | Beta | 95% CI | Beta | 95%- CI | Beta | 95% CI | Beta | 95% CI |
| 10log hs-CRP | 1.53\* | 0.08–2.98 | 1.20 | -0.5 –2.9 | -0.36 | -2.52 –1.79 | 3.54\* | 0.91 –6.17 |

# adjusted for age, sex, physical activity pre stroke, diabetes mellitus, history of cardiovascular disease, stroke severity, BMI, regular alcohol consumption and smoking status; \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

Supplemental Table 4. Comprehensive Results Summary when including confounding for antidepressant and anti-inflammatory medication use

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Crude  | Adjusted  | Adjusted + male interaction  | Adjusted + female interaction  |
|  | Change in CES-D score over time |
|  | Beta | 95% CI | Beta | 95%- CI | Beta | 95% CI | Beta | 95% CI |
| Table 2.10log hs-CRP1 | 1.87\*\*\* | 0.88–2.86 | 1.26\* | 0.21 –2.32 | 0.63 | -0.67 –1.93 | 2.27\*\* | 0.67 –3.88 |
| Suppl. Table 3. 10log hs-CRP1 | 1.53\* | 0.08–2.98 | 1.06 | -0.59 –2.71 | -0.35 | -2.43 –1.73 | 3.23\* | 0.96 –5.80 |
| Table 3. 10log hs-CRP2 | 1.67\*\* | 0.53–2.81 | 1.41\* | 0.20 –2.62 | 0.61 | -0.89 –2.11 | 2.68\*\* | 0.81 –4.55 |

1 adjusted for age, sex, physical activity pre stroke, diabetes mellitus, history of cardiovascular disease, stroke severity, BMI, regular alcohol consumption and smoking status, use of antidepressant medication, use of anti-inflammatory medication

2 adjusted for age, sex, physical activity pre stroke, ARWMC (Wahlund Score), diabetes mellitus, history of cardiovascular disease, stroke severity, BMI, regular alcohol consumption and smoking status; use of anti-inflammatory medication, use of antidepressant medication,\*p<0.05, \*\*p<0.01, \*\*\*p<0.001