**Association between Circulating Protein C Levels and Incident Dementia:**

**the Atherosclerosis Risk in Communities Study**

**Supplementary Tables 1 to 7**

**Supplementary Tables**

**Supplementary Table 1**. Ten cognitive and functional assessments administered at the late-life baseline (2011-13, visit 5) and subsequent visits

**Supplementary Table 2.** Association between the covariates and quintile of protein C weighted by stablized weights based on propensity scores at the midlife baseline

**Supplementary Table 3**. Association between the covariates and quintile of protein C weighted by stablized weights based on propensity scores at the late-life baseline

**Supplementary Table 4**. Data sources for the determination of incident dementia from the midlife baseline (1987-89, visit 1) to the midlife end point (up to 2013)

**Supplementary Table 5**. Association between protein C levels and incident dementia after excluding APOE Ɛ4 homozygotes or carriers

**Supplementary Table 6**. Population characteristics at the late-life baseline (2011-13, visit 5, n=3,614)

**Supplementary Table 7**. Data sources for the determination of incident dementia from the late-life baseline (2011-13, visit 5) to the late-life end point (December 31, 2017)

**Supplementary Table 1**. Ten cognitive and functional assessments administered at the late-life baseline (visit 5) and subsequent visits

Delayed word recall test

Digit symbol substitution test from the Wechsler Adult Intelligence Scale Revised (WAIS-R)

Letter fluency test

Neuropsychology test battery

Logical memory immediate and delayed recall

Incidental learning from the Wechsler Memory Scale-III

Trail making test parts A and B

WAIS-R digits span backward

Boston naming test and animal naming

Mini-mental state examination (MMSE)

**Supplementary Table 2**. Association between covariates and quintile of protein C weighted by stabilized weights based on propensity scores at the midlife baseline

|  |  |
| --- | --- |
| **Variable** | **P-value** |
| Male | 9.05E-01 |
| Race | 7.42E-01 |
| APOE Ɛ4 | 9.25E-01 |
| < High school | 9.97E-01 |
| High school graduate or vocational school | 9.98E-01 |
| College, graduate or professional school | 1.00E+00 |
| Current smoker | 8.90E-01 |
| Prevalent diabetes | 9.24E-01 |
| Prevalent hypertension | 1.00E+00 |
| Prevalent stoke | 8.64E-02 |
| Age | 6.26E-01 |
| Body mass index | 3.25E-01 |
| Estimated glomerular filtration rate | 8.64E-01 |
| Factor VIIIc | 7.84E-01 |
| Fibrinogen | 8.41E-01 |
| von Willebrand factor | 9.81E-01 |
| Platelet count | 6.26E-01 |

Generalized linear regression analyses were performed using each covariate as the outcome and the quintiles of protein C as predictors assuming a Gaussian distribution for continuous variable and pseudo-binomial distribution for binary variables. Pseudo-binomial distribution allows for the use of non-integer weights.

P-values were obtained using the anova function comparing a null model with the intercept as the only predictor and a model with the addition of quintiles of protein C as categorical predictors.

Factor VIII, fibrinogen, von Willebrand factor, and platelet count were log2 transformed.

**Supplementary Table 3**. Association between covariates and quintile of protein C weighted by stabilized weights based on propensity scores at the late-life baseline

|  |  |
| --- | --- |
| **Variable** | **P-value** |
| Male | 1.44E-02 |
| Race | 6.64E-01 |
| APOE Ɛ4 | 9.34E-01 |
| < High school | 7.41E-01 |
| High school graduate or vocational school | 7.07E-01 |
| College, graduate or professional school | 4.70E-01 |
| Current smoker | 7.53E-01 |
| Prevalent diabetes | 9.96E-01 |
| Prevalent hypertension | 9.01E-01 |
| Prevalent stoke | 7.94E-02 |
| Age | 9.80E-01 |
| Body mass index | 9.66E-01 |
| Estimated glomerular filtration rate | 7.78E-01 |
| Global cognition Z score | 8.83E-01 |
| Factor VIII | 9.87E-01 |
| von Willebrand factor | 9.70E-01 |
| Platelet count | 4.31E-01 |

Generalized linear regression analyses were performed using each covariate as the outcome and the quintiles of protein C as predictors assuming a Gaussian distribution for continuous variable and pseudo-binomial distribution for binary variables. Pseudo-binomial distribution allows for the use of non-integer weights

P-values were obtained using the anova function comparing a null model with the intercept as the only predictor and a model with the addition of quintiles of protein C as categorical predictors.

Factor VIII and von Willebrand factor and platelet count were log2 transformed.

**Supplementary Table 4**. Data sources for the determination of incident dementia from the midlife baseline (visit 1, 1987-89) to the midlife end point (visit 5, 2011-13)

|  |  |  |  |
| --- | --- | --- | --- |
| **Primary data source** | **Dementia incidence** | **%** | **Other data sources** |
| Comprehensive cognition assessment | 307 | 22.1 | 38 cases had hospital discharge code of dementia |
| TICS | 93 | 6.7 | 6 cases had hospital discharge code of dementia |
| CDR and or FAQ | 538 | 38.7 | 235 cases also had hospital discharge code of dementia, and 75 cases had ICD code of dementia on their death certificates |
| ICD code at hospitalization discharge | 374 | 26.9 |  |
| ICD code on death certificate | 77 | 5.5 |  |
| Total | 1389 | 100 |  |

Abbreviation. TICS, Telephone Interview for Cognitive Status; CDR, Clinical Dementia Rating; FAQ, Functional Activities Questionnaire; ICD, International Classification of Diseases.

**Supplementary Table 5.** Association between protein C levels and incident dementia after excluding APOE Ɛ4 homozygotes or carriers

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **N (% case)** | **Quintile 1** | **Quintile 2** | **Quintile 3** | **Quintile 4** | **Quintile 5** | **P-value for trend** | **Wald test p-value** |
| **Midlife baseline** | |  |  |  |  |  |  |  |
| Model 5\* | 14,462 (9.6) | Reference | 0.75 (0.61, 0.91) | 0.88 (0.73, 1.06) | 0.83 (0.69, 0.99) | 0.80 (0.66, 0.96) | 0.04 | 0.04 |
| Model 6 | 14,085 (9.1) | Reference | 0.73 (0.59, 0.90) | 0.85 (0.70, 1.03) | 0.80 (0.66, 0.97) | 0.78 (0.64, 0.95) | 0.03 | 0.03 |
| Model 7 | 10,010 (7.4) | Reference | 0.77 (0.59, 1.00) | 0.83 (0.64, 1.06) | 0.80 (0.63, 1.02) | 0.78 (0.60, 1.02) | 0.17 | 0.28 |
| **Late-life baseline** | |  |  |  |  |  |  |  |
| Model 5\*\* | 3,614 (9.8) | Reference | 1.26 (0.92, 1.72) | 0.78 (0.56, 1.10) | 0.73 (0.50, 1.07) | 0.84 (0.55, 1.28) | 0.04 | 0.02 |
| Model 6 | 3,542 (9.4) | Reference | 1.21 (0.88, 1.66) | 0.80 (0.56, 1.13) | 0.74 (0.50, 1.10) | 0.80 (0.52, 1.24) | 0.04 | 0.05 |
| Model 7 | 2,620 (8.3) | Reference | 1.01 (0.66, 1.53) | 0.79 (0.52, 1.22) | 0.71 (0.45, 1.11) | 0.62 (0.37, 1.04) | 0.01 | 0.20 |

\* The results of Model 5 at the midlife baseline were copied from Table 2 to facilitate the comparison of model results

\*\* The results of Model 5 at the late-life baseline were copied from Table 3 to facilitate the comparison of model results

Compared with Model 5, Model 6 removed APOE Ɛ4 homozygotes (midlife, n=377; late life, n=72)

Compared with Model 5, Model 7 removed APOE Ɛ4 carriers, both homozygotes and heterozygotes (midlife, n=4,452; late life, 994)

Models 5, 6 and 7 were evaluated incorporating stabilized weights based on the inverse of propensity scores.

Covariates:

Model 5: age, sex, race-center, education levels, APOE Ɛ4 carrier status, vascular factors (body mass index, current smoking status, prevalent stroke, diabetes and hypertension status, estimated glomerular filtration rate), coagulants (factor VIII, von Willebrand factor) + platelet count, incident stoke as time-varying covariate

Model 6 (same as Model 5):

Model 7: removed APOE Ɛ4 carrier status from the list of covariates in Model 5

**Supplementary Table 6**. Population characteristics at the late-life baseline (2011-13, visit 5, n=3,614)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Overall** | **Quintile 1** | **Quintile 2** | **Quintile 3** | **Quintile 4** | **Quintile 5** | **P-value** |
| Range, RFU/1000 | 38.18, 103.57 | 38.18, 66.11 | 66.13, 72.25 | 72.26, 77.64 | 77.64, 84.88 | 84.89, 103.57 |  |
| **Variable** |  |  |  |  |  |  |  |
| N | 3,614 | 723 | 723 | 722 | 723 | 723 |  |
| Age, year, mean (SD) | 75.1 (4.9) | 75.8 (5.1) | 75.5 (5) | 75.2 (5.1) | 74.7 (4.8) | 74.2 (4.5) | <0.001 |
| Male, n (%) | 1492 (41.3) | 343 (47.4) | 310 (42.9) | 304 (42.1) | 280 (38.7) | 255 (35.3) | <0.001 |
| Self-reported black, n (%) | 634 (17.5) | 179 (24.8) | 146 (20.2) | 139 (19.3) | 99 (13.7) | 71 (9.8) | <0.001 |
| *APOE* Ɛ4 carrier status, n (%) | 994 (27.5) | 201 (27.8) | 189 (26.1) | 207 (28.7) | 187 (25.9) | 210 (29) | 0.55 |
| Education level, n (%) |  |  |  |  |  |  | <0.001 |
| < High school | 419 (11.6) | 131 (18.1) | 73 (10.1) | 85 (11.8) | 81 (11.2) | 49 (6.8) |  |
| High school graduate or vocational school | 1555 (43.0) | 311 (43.0) | 315 (43.6) | 322 (44.6) | 283 (39.1) | 324 (44.8) |  |
| College, graduate or professional school | 1640 (45.4) | 281 (38.9) | 335 (46.3) | 315 (43.6) | 359 (49.7) | 350 (48.4) |  |
| BMI, kg/m2, mean (SD) | 28.6 (5.5) | 29.6 (6.1) | 29.1 (5.6) | 28.7 (5.3) | 27.9 (5.2) | 27.7 (5.0) | <0.001 |
| Current smoker, n (%) | 216 (6.0) | 49 (6.8) | 46 (6.4) | 35 (4.8) | 41 (5.7) | 45 (6.2) | 0.58 |
| Diabetes, n (%) | 1104 (30.6) | 256 (35.4) | 233 (32.2) | 221 (30.6) | 198 (27.4) | 196 (27.1) | 0.002 |
| Hypertension, n (%) | 2622 (72.6) | 579 (80.1) | 558 (77.2) | 516 (71.5) | 501 (69.3) | 468 (64.7) | <0.001 |
| Prevalent stroke, n (%) | 89 (2.5) | 29 (4.0) | 19 (2.6) | 16 (2.2) | 10 (1.4) | 15 (2.1) | 0.02 |
| Prevalent atrial fibrillation, n (%) | 113 (3.13) | 28 (3.9) | 22 (3) | 24 (3.3) | 22 (3) | 17 (2.4) | 0.58 |
| eGFR, mL/min/1.73m2, mean (SD) | 70.3 (16.6) | 63.7 (18.6) | 68 (16.7) | 70 (16.2) | 73.7 (14.6) | 75.8 (13.8) | <0.001 |
| Global cognition Z score, median (25th, 75th percentile) | -0.44 (-1, 0.08) | -0.70 (-1.22, -0.14) | -0.40 (-1.04, 0.07) | -0.50 (-1.04, 0.10) | -0.30 (-0.88, 0.13) | -0.30 (-0.79, 0.17) | <0.001 |
| Platelet count, K/uL, median (25th, 75th percentile) | 240 (198, 290) | 235 (192, 289) | 240 (199, 290) | 243 (199, 287) | 240 (198, 289) | 241 (201, 294) | 0.26 |
| Factor VIII, RFU/1000, median (25th, 75th percentile) | 9.3 (7.9, 11.1) | 9.3 (7.9, 11.2) | 9.5 (7.9, 11.2) | 9.3 (8.0, 11.0) | 9.4 (7.8, 11.1) | 9.3 (7.9, 11.0) | 0.77 |
| von Willebrand factor, RFU/1000, median (25th, 75th percentile) | 13.6 (10.1, 18.4) | 15.1 (11.4, 19.9) | 14.1 (10.8, 19.6) | 13.4 (10.0, 18.4) | 13 (9.5, 17.5) | 12.4 (9.0, 16.6) | <0.001 |

Abbreviation. BMI, body mass index; eGFR, estimated glomerular filtration rate; RFU, relative fluorescence unit

**Supplementary Table 7**. Data sources for the determination of incident dementia from the late-life baseline (2011-13, visit 5) to the late-life end point (December 31, 2017)

|  |  |  |  |
| --- | --- | --- | --- |
| **Primary data source** | **Dementia incidence** | **%** | **Other data sources** |
| Comprehensive cognition and functional assessment | 132 | 37.4 | 20 cases had hospital discharge code of dementia |
| Alzheimer's disease 8-Item Informant Questionnaire | 125 | 35.4 | 42 cases had hospital discharge code of dementia |
| Six Item Screener | 24 | 6.8 | 2 cases had hospital discharge code of dementia |
| ICD code at hospitalization discharge | 68 | 19.3 |  |
| ICD code on death certificate | 4 | 1.1 |  |
| **Total** | 353 | 100 |  |

Abbreviation. ICD, International Classification of Diseases.