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Supplementary Methods

Assessment of plasma proteins
In Whitehall II and ARIC, proteins were analyzed using the SOMAscan version 4 assay. The analyses used plasma samples measured in 1995/1997 and stored in 0.25 mL aliquots at −80°C. Earlier studies describe performance of the SOMAscan assay and the modified aptamer binding in detail. In brief, the assay uses a 96-well plate including a mix of thousands of slow off-rate modified aptamers (SOMAmers). The SOMAmers are labeled with biotin and a 5′ fluorophore, photocleavable linker and immobilized on streptavidin-coated beads through biotin–streptavidin interaction. Participants’ plasma samples were diluted and added to each well, which resulted in formation of cognate and non-specific SOMAmer-protein complexes. After the unbound proteins were washed away, captured proteins were labelled with biotin. By using ultraviolet light photocleavage, the SOMAmer-protein complexes were released from the beads and incubated in a well containing dextran sulfate and unlabeled polyanionic competitor. This step separates the non-specific, fast off-rate SOMAmer-protein complexes from slow off-rate cognate and thus intended complexes and can be viewed as a second element of specificity analogous to the effect of adding a second antibody in a conventional immunoassay.

Cognate SOMAmer-protein complexes were then recaptured on a second set of streptavidin coated beads using biotin labelled proteins and additionally washed to further remove non-specific SOMAmer-protein interactions. In the next step, denaturing buffer released the SOMAmers from the proteins. The SOMAmers were then hybridized to complementary sequences on a DNA microarray chip and quantified by fluorescence for readout. In the SOMAscan assay, fluorescence intensity for each SOMAmer is related to the relative availability of the three-dimensional shape-charge epitope on each protein (the binding site of the SOMAmer reagent) in the original sample. This describes the concentration of each protein but can also reflect the shape of the protein (that may itself reflect a genetic variant or modification) and any potential circulating competitor (physiologic or a therapeutic antibody) to some extent. However, the specificity of the modified aptamer reagents is good and has been tested in several ways. Median intra- and inter-assay coefficients of variation for SomaScan version 4 are ~5% and assay sensitivity is comparable to that of typical immunoassays, with a median lower limit of detection in the femtomolar range.

Cognitive testing
The Whitehall II cognitive test battery covered four domains: executive function, memory, phonemic-, and semantic fluency. Executive function was assessed with the Alice Heim 4-I test that comprises a series of 65 verbal and mathematical reasoning items of increasing difficulty. It tests inductive reasoning, measuring the ability to identify patterns and infer principles and rules, and has time limit of 10 minutes. A 20-word free recall test assessed memory. Participants were presented a list of one or two syllable words at two-second intervals and were then asked to recall in writing as many of the words as possible in any order within two minutes. In assessment of phonemic and semantic fluency participants were asked to recall in writing as many words beginning with “s” (phonemic fluency) and as many animal names (semantic fluency) as they could. Time limit for this section was one minute per fluency area.
Based on these measures, we created a global cognitive score by first standardizing the distribution of each test domain measured in follow-up visits to the baseline score to create z-scores with mean 0 and SD 1. We then summed the domain specific scores at each phase and standardized the summary score to the baseline summary score; this approach minimizes measurement error inherent in individual tests. After dementia diagnosis, participants were rarely able to complete the cognitive tests and for this reason, their global test score was set to -3SD at the phase following the dementia diagnosis. Based on the global scores we derived a cognitive decline slope for each participant and used this as the outcome.

Comorbidities
The World Health Organization International Classification of Diseases (ICD) codes were retrieved from the National Health Services (NHS) Hospital Episode Statistics (HES) database records and from mortality registers using individual NHS identification numbers for linkage. The NHS provides nearly complete comprehensive health care coverage for all individuals legally resident in the UK. Cardiovascular disease diagnoses as ascertained via HES has shown 70% sensitivity and 96% specificity against standard biomedical examinations. Incident cardiovascular disease was denoted by atrial fibrillation (ICD-10 codes under I48.0, I48.1, I48.2, I48.3, I48.4, I48.9; ICD-9 codes 427.31, 427.32) stroke (ICD-10 codes under I60, I61, I63, and I64; ICD-9 codes 430, 431, 434, and 436), myocardial infarction (ICD-10 codes under I21; ICD-9 codes under 410), heart failure (ICD10-codes under 150), definite angina (ICD-10 codes under I20; ICD-9 codes under 410, both verified from medical records), peripheral artery disease (ICD-10 codes I70.2, I73.3, I73.9, I74.3-5, E10.5, E11.5, E12.5, E13.5, E14.5; ICD-9 codes 250.7, 440.2, 440.4, 443.8-9, 444.2, 444.81), coronary artery bypass graft, or percutaneous coronary intervention. In addition, ECG measurements in each 5-yearly visits screened atrial fibrillation. Definition for diabetes in each 5-yearly visits was use of diabetes medication, fasting glucose $\geq$ 7.0 mmol/L, 2h post-load glucose $\geq$ 11.1 mmol/L, or Hba1c% $\geq$ 6.5%.

Imputation model
In the Whitehall II study no participants were missing protein measurements but some covariates were missing; 26% had missing education status, 11% were missing APOE and 10% BMI. Education variable was introduced to questionnaire during data collection meaning that it is likely to be missing at random. APOE values were measured in a random sample, suggesting values are also missing at random. BMI values are missing due to lack of funds to cover sickness absences of the research nurse collecting height and weight at phase 5 and are also likely to be missing at random. Percentages of participants missing data for other variables were very low and unlikely to affect the imputation results regardless of the missing data mechanism. For these reasons, we used the missing at random assumption and conducted multiple imputation for covariate-adjusted analyses. Our imputation model included age, sex, education, socioeconomic status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medication, diabetes status, ApoE status, alcohol consumption, General Health Questionnaire, BMI, and smoking status. Continuous variables were imputed with linear regression, binary with logistic regression, categorical with ordered logistic regression, and right tailed integer data with negative binomial regression. Based on percentage of missing data and substantive model parameters from 100 iterations we chose to use 5 iterations and 30 imputations in the final analyses. We used an
imputation model based on substantive-model compatible fully conditional specification, which may be a better approach in survival analyses and in the presence of competing risks than the ordinary fully conditional model.\textsuperscript{130}

The two-step approach used to identify protein-dementia association for replication

We used a two-step approach in Whitehall II to identify dementia-related proteins for replication analyses in the ARIC study. The first step was designed to filter out proteins with no or only weak association with cognitive decline rate after false discovery rate correction of 5%; we had a 80% statistical power to detect a beta of 0.08. The outcome, cognitive decline slope, is sensitive to any decrease in cognition, including both impairments that precede dementia and those not reaching levels that meet criteria for clinical dementia. The second step was therefore designed to identify from the proteins that passed the first step those that are also associated with dementia. We used a dementia outcome derived from electronic health records from the National Health Services (NHS) Hospital Episode Statistics (HES) database, an outcome with a high positive predictive value. The analysis model in the second step was the Cox proportional hazards model which had 80% power to identify a beta of 0.27 with a p-value<0.05. The replication analysis used the ARIC study, which used different dementia ascertainment methods, had a different dementia conversion rate, different participant characteristics at baseline, and originated from a different continent. Of the 21 proteins that passed first and second step in Whitehall II study, 15 (71\%) were replicated in the ARIC study suggesting that our approach was successful within the limits of our dataset.
Supplementary Figures 1a and b. Sample size needed to detect a range of beta coefficients using linear regression or Cox proportional hazards model. Graph in part a is derived using sample size 2242 (dashed line), power 0.8, p-value 0.002, and standard deviation of 1 for both the covariate of interest and for the error term. Graph in part b is derived using outcome number of 106 (dashed line), power 0.8, p-value 0.05, and standard deviation 1 for covariate of interest.
**Supplementary Table 1. Beta for 1 standard deviation increase in amyloid, tau, and neurofilament related protein levels and cognitive decline.** Results are from a linear regression model with cognitive decline slope as the outcome. The number of individuals included is 2,242. FDR, false discovery rate correction of 5%.

| Protein                                          | Cognitive decline |        |        |
|--------------------------------------------------|-------------------|--------|--------|
| Protein                                          | Beta              | FDR p-value | Original p-value |
| Amyloid, tau, and neurofilament related proteins |                   |        |        |
| Amyloid-like protein 1                           | 0.016             | 0.646  | 0.449  |
| Amyloid-like protein 2                           | 0.031             | 0.354  | 0.137  |
| Serum amyloid A-1 protein                        | 0.046             | 0.187  | 0.030  |
| Serum amyloid A-2 protein                        | 0.052             | 0.133  | 0.015  |
| Serum amyloid A-4 protein                        | 0.020             | 0.556  | 0.347  |
| Serum amyloid P-component                        | 0.021             | 0.528  | 0.318  |
| Amyloid beta A4 protein                          | 0.015             | 0.672  | 0.483  |
| Amyloid beta A4 precursor protein-binding family B member 1 | 0.032 | 0.345 | 0.131 |
| Amyloid beta A4 precursor protein-binding family B member 2 | 0.053 | 0.123 | 0.013 |
| Amyloid beta A4 precursor protein-binding family B member 3 | 0.017 | 0.625 | 0.423 |
| Apolipoprotein E                                 | 0.002             | 0.951  | 0.915  |
| Microtubule-associated protein RP/EB family member 1 | -0.011 | 0.749 | 0.589 |
| Microtubule-associated protein RP/EB family member 2 | -0.011 | 0.765 | 0.612 |
| Microtubule-associated protein RP/EB family member 3 | -0.017 | 0.627 | 0.426 |
| Microtubule-associated proteins 1A/1B light chain 3A | 0.029 | 0.382 | 0.168 |
| Microtubule-associated proteins 1A/1B light chain 3B | 0.008 | 0.822 | 0.698 |
| Microtubule-associated protein tau                | 0.031             | 0.359  | 0.145  |
| Regulator of microtubule dynamics protein 1       | 0.007             | 0.859  | 0.757  |
| Regulator of microtubule dynamics protein 3       | 0.018             | 0.589  | 0.386  |
| Janus kinase and microtubule-interacting protein 3| 0.063             | 0.055  | 0.003  |
| MAP/microtubule affinity-regulating kinase 3      | 0.004             | 0.916  | 0.851  |
| Neurofilament light polypeptide                   | 0.014             | 0.694  | 0.512  |
| Neurofilament heavy polypeptide                   | 0.044             | 0.200  | 0.036  |
Supplementary Figure 2. Associations between each of the 4953 proteins and rate of cognitive decline by $-\log_{10} \text{p-values and beta coefficient}$. Inverse rank-based normal transformed proteins plotted by their betas and p-values from linear regression in which rate of cognitive decline was the outcome. The 15 proteins associated with cognitive decline and dementia in Whitehall II study and with dementia in the ARIC study are labelled.
Supplementary Figure 3. Associations between each of the 4953 proteins and dementia by \(-\log_{10} p\)-values and beta coefficient. Inverse rank-based normal transformed proteins plotted by their betas and p-values from Cox proportional hazards model in which binary dementia was the outcome. The 15 proteins that associated with cognitive decline and dementia in Whitehall II study and with dementia in the ARIC study are labelled.
Supplementary Figure 4. Violin plots describing differences in standardized protein levels by dementia status. All the 15 inverse rank-based normal transformed proteins were elevated in those who developed dementia. Blue, no dementia. Green, dementia.
Supplementary Table 2. Associations between the cognitive decline slope and a SD increase in the 15 proteins that survived replication. Results are from a linear regression model with cognitive decline rate as the outcome. The number of individuals included is 2,242.

| Protein          | HR (95% CIs)          | p-value | FDR corrected p-value |
|------------------|-----------------------|---------|-----------------------|
| N-terminal pro-BNP | 0.12 (0.08 to 0.17)  |  <0.001 |  <0.001               |
| CDCP1            | 0.16 (0.12 to 0.20)  |  <0.001 |  <0.001               |
| MIC-1            | 0.18 (0.14 to 0.22)  |  <0.001 |  <0.001               |
| CRDL1            | 0.09 (0.05 to 0.13)  |  <0.001 |  0.003                |
| RNAS6            | 0.07 (0.03 to 0.11)  |   0.001 |   0.023               |
| SAP3             | 0.08 (0.04 to 0.12)  |  <0.001 |   0.006               |
| HE4              | 0.12 (0.08 to 0.16)  |  <0.001 |  <0.001               |
| TIMP-4           | 0.08 (0.04 to 0.13)  |  <0.001 |   0.005               |
| IGFBP-7          | 0.10 (0.06 to 0.14)  |  <0.001 |  <0.001               |
| OPG              | 0.12 (0.08 to 0.16)  |  <0.001 |  <0.001               |
| Siglec-7         | 0.10 (0.05 to 0.14)  |  <0.001 |   0.001               |
| SVEP1            | 0.13 (0.09 to 0.17)  |  <0.001 |  <0.001               |
| TREM2            | 0.09 (0.05 to 0.13)  |  <0.001 |   0.003               |
| NPS-PLA2         | 0.07 (0.03 to 0.11)  |   0.001 |   0.035               |
| MARCKSL1         | 0.07 (0.03 to 0.11)  |   0.001 |   0.021               |
Supplementary Table 3. Associations between the decline slopes in all cognitive domains measured and a SD increase in the 15 proteins that survived replication. Results are from a linear regression model with cognitive domain decline rate as the outcome. The number of individuals included is 2,242.

| Protein                  | HR (95% CIs) | p-value | HR (95% CIs) | p-value |
|--------------------------|--------------|---------|--------------|---------|
| Executive function       |              |         |              |         |
| **Phonemic fluency**     |              |         |              |         |
| N-terminal pro-BNP       | 0.14 (0.10 to 0.18) | <0.001  | 0.10 (0.06 to 0.14) | <0.001  |
| CDCP1                    | 0.17 (0.12 to 0.21) | <0.001  | 0.08 (0.04 to 0.12) | <0.001  |
| MIC-1                    | 0.20 (0.16 to 0.24) | <0.001  | 0.08 (0.04 to 0.12) | <0.001  |
| CRDL1                    | 0.08 (0.04 to 0.12) | <0.001  | 0.04 (0.00 to 0.08) | 0.046   |
| RNAS6                    | 0.10 (0.06 to 0.14) | <0.001  | 0.03 (-0.02 to 0.07) | 0.225   |
| SAP3                     | 0.10 (0.06 to 0.14) | <0.001  | 0.04 (0.00 to 0.08) | 0.058   |
| HE4                      | 0.15 (0.10 to 0.19) | <0.001  | 0.05 (0.01 to 0.09) | 0.013   |
| TIMP-4                   | 0.11 (0.07 to 0.15) | <0.001  | 0.06 (0.02 to 0.10) | 0.005   |
| IGFBP-7                  | 0.06 (0.02 to 0.10) | 0.005   | 0.07 (0.02 to 0.11) | 0.002   |
| OPG                      | 0.14 (0.10 to 0.18) | <0.001  | 0.05 (0.01 to 0.09) | 0.021   |
| Siglec-7                 | 0.07 (0.03 to 0.11) | 0.001   | 0.03 (-0.01 to 0.07) | 0.134   |
| SVEP1                    | 0.13 (0.09 to 0.17) | <0.001  | 0.09 (0.05 to 0.13) | <0.001  |
| TREM2                    | 0.09 (0.05 to 0.13) | <0.001  | 0.06 (0.02 to 0.11) | 0.002   |
| NPS-PLA2                 | 0.09 (0.05 to 0.13) | <0.001  | 0.02 (-0.02 to 0.06) | 0.328   |
| MARCKSL1                 | 0.09 (0.04 to 0.13) | <0.001  | 0.06 (0.02 to 0.10) | 0.007   |
| **Memory**               |              |         |              |         |
| **Semantic fluency**     |              |         |              |         |
| N-terminal pro-BNP       | 0.01 (-0.03 to 0.05) | 0.734   | 0.04 (0.00 to 0.08) | 0.056   |
| CDCP1                    | 0.04 (0.00 to 0.08) | 0.050   | 0.04 (0.00 to 0.08) | 0.055   |
| MIC-1                    | 0.04 (0.00 to 0.08) | 0.064   | 0.06 (0.01 to 0.10) | 0.008   |
| CRDL1                    | 0.03 (-0.01 to 0.07) | 0.197   | 0.03 (-0.01 to 0.07) | 0.134   |
| RNAS6                    | -0.01 (-0.05 to 0.03) | 0.633  | 0.01 (-0.03 to 0.05) | 0.595   |
| SAP3                     | -0.02 (-0.06 to 0.02) | 0.356  | 0.05 (0.01 to 0.09) | 0.022   |
| HE4                      | 0.00 (-0.04 to 0.04) | 0.879   | 0.03 (-0.01 to 0.07) | 0.121   |
| TIMP-4                   | 0.02 (-0.02 to 0.06) | 0.325   | -0.01 (-0.05 to 0.04) | 0.794   |
| IGFBP-7                  | 0.06 (0.02 to 0.10) | 0.005   | 0.03 (-0.01 to 0.07) | 0.200   |
| OPG                      | 0.03 (-0.01 to 0.07) | 0.132   | 0.04 (0.00 to 0.08) | 0.068   |
| Siglec-7                 | 0.06 (0.01 to 0.10) | 0.009   | 0.02 (-0.02 to 0.07) | 0.256   |
| SVEP1                    | 0.02 (-0.02 to 0.07) | 0.245   | 0.04 (0.00 to 0.08) | 0.083   |
| TREM2                    | 0.01 (-0.04 to 0.05) | 0.786   | 0.02 (-0.03 to 0.06) | 0.469   |
| NPS-PLA2                 | 0.03 (-0.01 to 0.08) | 0.108   | 0.00 (-0.04 to 0.04) | 0.897   |
| MARCKSL1                 | 0.02 (-0.02 to 0.06) | 0.429   | 0.03 (-0.01 to 0.07) | 0.192   |
Supplementary Table 4. Protein expression levels in the brain tissue for 15 proteins that survived replication. The expression levels are derived from the Human Protein Atlas.

| Protein               | Expression in brain |
|-----------------------|---------------------|
| N-terminal pro-BNP    | Not known           |
| CDCP1                 | Low                 |
| MIC-1                 | Not detected        |
| CRDL1                 | Not known           |
| RNAS6                 | Not detected        |
| SAP3                  | High                |
| HE4                   | Low                 |
| TIMP-4                | Not known           |
| IGFBP-7               | Not known           |
| OPG                   | Not known           |
| SIGLEC-7              | Not known           |
| SVEP1                 | Low                 |
| TREM2                 | Medium              |
| NPS-PLA2              | Not detected        |
| MARCKSL1              | Medium              |
**Supplementary Table 5. Sensitivity analyses for the 15 proteins associated with both cognitive decline and dementia in the Whitehall II study.** The analyses include 2,262 individuals, 106 dementia cases and a mean follow-up of 20 years.

| Protein name          | Model 1       |       | Model 2       |       | Model 3       |       |
|-----------------------|---------------|-------|---------------|-------|---------------|-------|
|                       | HR (95% CIs)  | p-value | HR (95% CIs)  | p-value | HR (95% CIs)  | p-value |
| N-terminal pro-BNP    | 1.52 (1.24 to 1.88) | <0.001 | 1.49 (1.21 to 1.85) | <0.001 | 1.56 (1.26 to 1.94) | <0.001 |
| CDCP1                 | 1.42 (1.16 to 1.73) | <0.001 | 1.43 (1.17 to 1.76) | 0.001  | 1.38 (1.13 to 1.70) | 0.002  |
| MIC-1                 | 1.31 (1.04 to 1.65) | 0.021  | 1.30 (1.02 to 1.65) | 0.031  | 1.31 (1.03 to 1.67) | 0.029  |
| CRDL1                 | 1.30 (1.06 to 1.59) | 0.010  | 1.27 (1.04 to 1.55) | 0.021  | 1.30 (1.06 to 1.60) | 0.011  |
| RNAS6                 | 1.30 (1.07 to 1.57) | 0.007  | 1.28 (1.05 to 1.57) | 0.014  | 1.30 (1.06 to 1.59) | 0.011  |
| SAP3                  | 1.29 (1.06 to 1.57) | 0.012  | 1.28 (1.04 to 1.57) | 0.019  | 1.29 (1.05 to 1.58) | 0.016  |
| HE4                   | 1.29 (1.04 to 1.60) | 0.019  | 1.34 (1.07 to 1.69) | 0.012  | 1.34 (1.06 to 1.69) | 0.015  |
| TIMP-4                | 1.29 (1.05 to 1.59) | 0.017  | 1.24 (1.01 to 1.53) | 0.042  | 1.24 (1.00 to 1.54) | 0.051  |
| IGFBP-7               | 1.27 (1.05 to 1.54) | 0.015  | 1.22 (1.01 to 1.49) | 0.044  | 1.25 (1.03 to 1.53) | 0.027  |
| OPG                   | 1.26 (1.02 to 1.56) | 0.032  | 1.26 (1.02 to 1.56) | 0.030  | 1.27 (1.03 to 1.58) | 0.029  |
| SIGLEC-7              | 1.25 (1.03 to 1.52) | 0.025  | 1.23 (1.00 to 1.52) | 0.054  | 1.22 (0.99 to 1.50) | 0.068  |
| SVEP1                 | 1.24 (1.02 to 1.51) | 0.032  | 1.20 (0.98 to 1.47) | 0.077  | 1.24 (1.01 to 1.52) | 0.036  |
| TREM2                 | 1.24 (1.01 to 1.51) | 0.037  | 1.23 (1.00 to 1.50) | 0.046  | 1.25 (1.02 to 1.54) | 0.032  |
| NPS-PLA2              | 1.24 (1.01 to 1.51) | 0.038  | 1.20 (0.98 to 1.48) | 0.083  | 1.24 (1.00 to 1.53) | 0.049  |
| MARCKSL1              | 1.22 (1.01 to 1.48) | 0.041  | 1.20 (0.99 to 1.46) | 0.069  | 1.19 (0.98 to 1.45) | 0.084  |

| Protein name          | Model 4       |       | Model 5       |       |
|-----------------------|---------------|-------|---------------|-------|
|                       | HR (95% CIs)  | p-value | HR (95% CIs)  | p-value |
| N-terminal pro-BNP    | 1.53 (1.24 to 1.89) | <0.001 | 1.47 (1.18 to 1.83) | 0.001  |
| CDCP1                 | 1.41 (1.15 to 1.73) | 0.001  | 1.39 (1.13 to 1.71) | 0.002  |
| MIC-1                 | 1.31 (1.04 to 1.65) | 0.021  | 1.24 (0.98 to 1.57) | 0.069  |
| CRDL1                 | 1.30 (1.07 to 1.59) | 0.010  | 1.26 (1.03 to 1.55) | 0.027  |
| RNAS6                 | 1.30 (1.08 to 1.57) | 0.006  | 1.27 (1.04 to 1.54) | 0.016  |
| SAP3                  | 1.29 (1.06 to 1.57) | 0.011  | 1.28 (1.05 to 1.57) | 0.017  |
| HE4                   | 1.29 (1.04 to 1.60) | 0.019  | 1.27 (1.02 to 1.57) | 0.032  |
| TIMP-4                | 1.29 (1.05 to 1.59) | 0.017  | 1.25 (1.01 to 1.55) | 0.040  |
| IGFBP-7               | 1.27 (1.05 to 1.54) | 0.014  | 1.22 (1.00 to 1.49) | 0.045  |
| OPG                   | 1.27 (1.02 to 1.57) | 0.030  | 1.22 (0.99 to 1.51) | 0.067  |
| SIGLEC-7              | 1.25 (1.03 to 1.52) | 0.023  | 1.22 (1.00 to 1.49) | 0.054  |
| SVEP1                 | 1.24 (1.02 to 1.51) | 0.030  | 1.19 (0.98 to 1.46) | 0.084  |
| TREM2                 | 1.24 (1.01 to 1.51) | 0.039  | 1.24 (1.01 to 1.52) | 0.043  |
| NPS-PLA2              | 1.24 (1.01 to 1.51) | 0.035  | 1.23 (1.01 to 1.51) | 0.043  |
| MARCKSL1              | 1.22 (1.01 to 1.48) | 0.040  | 1.20 (0.99 to 1.47) | 0.064  |

Model 1 is adjusted for age, sex, and ethnicity in the Whitehall II study
Model 2 is multiple imputation model adjusted for age, sex, ethnicity, systolic blood pressure, total cholesterol, antihypertensive medication, smoking, diabetes, APOE genotype, BMI, alcohol consumption, education, and GHQ score
Model 3 is as model 2 but the first 10 years of follow-up has been excluded
Model 4 is as model 2 but controls for competing risk of death
Model 5 is as model 1 and additionally adjusted for stroke, heart failure, coronary heart disease, and atrial fibrillation, treated as time-varying covariates
Supplementary Table 6. Sensitivity analyses including all or only white participants of the ARIC study and the 15 proteins associated with both cognitive decline and dementia in the Whitehall II study. The associations for all are from age, sex, and race-study center adjusted Cox proportional hazards regression with 11,395 individuals, 1,942 dementia cases and 17 years of follow up. The second model includes white participants only and is age, sex, and study center adjusted Cox proportional hazards regression with 8,991 individuals, 1,438 dementia cases and 17 years of follow up.

| Protein name          | HR (95% CIs) | p-value | HR (95% CIs) | p-value |
|-----------------------|--------------|---------|--------------|---------|
| All                   |              |         |              |         |
| N-terminal pro-BNP    | 1.08 (1.03 to 1.13) | <0.001 | 1.04 (0.98 to 1.10) | 0.233 |
| CDCP1                 | 1.26 (1.17 to 1.37) | <0.001 | 1.20 (1.09 to 1.32) | <0.001 |
| MIC-1                 | 1.64 (1.49 to 1.82) | <0.001 | 1.67 (1.49 to 1.88) | <0.001 |
| CRDL1                 | 1.20 (1.01 to 1.42) | 0.039 | 1.20 (0.99 to 1.47) | 0.068 |
| RNAS6                 | 1.23 (1.11 to 1.37) | <0.001 | 1.18 (1.05 to 1.34) | 0.007 |
| SAP3                  | 1.32 (1.12 to 1.55) | 0.001 | 1.28 (1.05 to 1.57) | 0.015 |
| HE4                   | 1.44 (1.28 to 1.62) | <0.001 | 1.40 (1.22 to 1.62) | <0.001 |
| TIMP-4                | 1.12 (1.01 to 1.26) | 0.039 | 1.17 (1.03 to 1.34) | 0.018 |
| IGFBP-7               | 1.43 (1.18 to 1.72) | <0.001 | 1.37 (1.10 to 1.70) | 0.005 |
| OPG                   | 1.34 (1.20 to 1.50) | <0.001 | 1.39 (1.22 to 1.60) | <0.001 |
| SIGLEC-7              | 1.24 (1.06 to 1.45) | 0.008 | 1.41 (1.17 to 1.69) | <0.001 |
| SVEP1                 | 1.39 (1.23 to 1.58) | <0.001 | 1.33 (1.14 to 1.54) | <0.001 |
| TREM2                 | 1.13 (1.04 to 1.23) | 0.003 | 1.15 (1.03 to 1.27) | 0.010 |
| NPS-PLA2              | 1.13 (1.03 to 1.25) | 0.008 | 1.20 (1.07 to 1.35) | 0.002 |
| MARCKSL1              | 1.11 (1.01 to 1.22) | 0.035 | 1.03 (0.92 to 1.15) | 0.612 |
| SPONDIN-1             | 1.18 (1.00 to 1.40) | 0.055 | 1.05 (0.86 to 1.29) | 0.615 |
| IGFBP-2               | 1.06 (0.99 to 1.13) | 0.089 | 1.00 (0.93 to 1.08) | 0.932 |
| NEUROPEPTIDE W        | 1.03 (1.00 to 1.07) | 0.088 | 1.00 (0.96 to 1.04) | 0.963 |
| ST4S6                 | 0.96 (0.78 to 1.18) | 0.721 | 0.93 (0.73 to 1.19) | 0.554 |
| TPPP2                 | 1.04 (0.93 to 1.17) | 0.459 | 1.00 (0.88 to 1.14) | 0.984 |
| LEAP-1                | 1.02 (0.97 to 1.06) | 0.483 | 1.02 (0.97 to 1.07) | 0.533 |
Supplementary Table 7. Associations between common dementia risk factors and dementia in Whitehall II, and estimates from most recent meta-analyses. The results are from Cox proportional hazards model adjusted for age and sex. The mean follow-up is 20 years, total number of participants is between 1,950 and 2,262 and cases between 89 and 106 due to missing data in BMI and APOE variables. Reference 47, Sipilä, P. N. et al. Long-term risk of dementia following hospitalization due to physical diseases: A multicohort study. Alzheimers Dement. 16, 1686-1695 (2020). Reference 48, Stocker, H. et al. Prediction of clinical diagnosis of Alzheimer’s disease, vascular, mixed, and all-cause dementia by a polygenic risk score and APOE status in a community-based cohort prospectively followed over 17 years. Mol. Psychiatry (2020).

| Risk Factor                     | Whitehall II | Low estimate       | High estimate      |
|--------------------------------|--------------|--------------------|--------------------|
| Hypertension                   | 1.56 (1.04 - 2.33) | 1.18 (1.02 - 1.35) | 1.61 (1.16 - 2.24) |
| Obesity (BMI ≥30)              | 1.86 (1.18 - 2.94) | 0.91 (0.83 - 1.01) | 1.91 (1.40 - 2.62) |
| Smoking                        | 1.13 (0.59 - 2.17) | 1.27 (1.02 - 1.60) | 1.30 (1.18 - 1.45) |
| Depression (GHQ ≥5)            | 1.30 (0.83 - 2.03) | 1.08 (1.04 - 1.12) | 1.98 (1.50 - 2.63) |
| Physical inactivity            | 0.83 (0.53 - 1.28) | 1.01 (0.89 - 1.13) | 1.39 (1.16 - 1.67) |
| Diabetes                       | 1.24 (0.77 - 2.00) | 1.43 (1.33 - 1.53) | 1.73 (1.65 - 1.82) |
| Apolipoprotein E, 1 or 2 ε4 alleles | 2.05 (1.34 - 3.15) | 2.60 (1.60 - 4.00) | 3.34 (2.24 - 4.99) |
Supplementary Figure 5. Between protein correlations. Correlations are Spearman correlations and were all positive and $\leq 0.53$. 
**Supplementary Table 8.** Sensitivity analyses of dementia subtypes for the 15 proteins associated with both cognitive decline and dementia in the Whitehall II study. The associations are from age, sex, and ethnicity adjusted Cox proportional hazards model with 2,262 individuals, mean follow-up of 20 years, and 72 dementias with comorbid vascular disease or 34 dementias without comorbid vascular disease.

| Protein name          | Dementia with comorbid vascular disease | Dementia without comorbid vascular disease | p-value for difference |
|-----------------------|----------------------------------------|------------------------------------------|------------------------|
| N-terminal pro-BNP    | 1.44 (1.11 to 1.86) 0.006              | 1.74 (1.20 to 2.52) 0.004               | 0.392                  |
| CDCP1                 | 1.43 (1.11 to 1.83) 0.005              | 1.36 (0.95 to 1.96) 0.096               | 0.919                  |
| MIC-1                 | 1.23 (0.93 to 1.63) 0.147              | 1.41 (0.93 to 2.15) 0.104               | 0.377                  |
| CRDL1                 | 1.27 (0.99 to 1.63) 0.057              | 1.34 (0.94 to 1.92) 0.105               | 0.816                  |
| RNAS6                 | 1.27 (1.01 to 1.61) 0.044              | 1.35 (0.96 to 1.89) 0.081               | 0.606                  |
| SAP3                  | 1.21 (0.95 to 1.54) 0.127              | 1.50 (1.05 to 2.14) 0.026               | 0.257                  |
| HE4                   | 1.28 (0.99 to 1.67) 0.061              | 1.26 (0.86 to 1.85) 0.238               | 0.861                  |
| TIMP-4                | 1.31 (1.01 to 1.69) 0.044              | 1.16 (0.80 to 1.69) 0.426               | 0.806                  |
| IGFBP-7               | 1.27 (1.00 to 1.60) 0.050              | 1.28 (0.90 to 1.80) 0.166               | 0.856                  |
| OPN                   | 1.16 (0.89 to 1.50) 0.277              | 1.47 (1.00 to 2.17) 0.051               | 0.241                  |
| SIGLEC-7              | 1.27 (1.00 to 1.61) 0.049              | 1.23 (0.87 to 1.74) 0.251               | 0.809                  |
| SVEP1                 | 1.17 (0.92 to 1.49) 0.203              | 1.36 (0.96 to 1.93) 0.085               | 0.499                  |
| TREM2                 | 1.30 (1.01 to 1.66) 0.041              | 1.14 (0.80 to 1.63) 0.473               | 0.554                  |
| NPS-PLA2              | 1.27 (0.99 to 1.62) 0.057              | 1.25 (0.87 to 1.78) 0.226               | 0.903                  |
| MARCKSL1              | 1.17 (0.92 to 1.48) 0.205              | 1.35 (0.95 to 1.90) 0.091               | 0.512                  |
Supplementary Table 9. Spearman correlations between plasma proteins measures with SOMAscan version 4 and Olink Explore platform. RNAS6, SAP3, SVEP1, and MARCKSL1 were not available in Olink Explore platform.

| Protein        | Correlation |
|----------------|-------------|
| N-terminal pro-BNP | 0.46        |
| CDCP1          | 0.87        |
| MIC-1          | 0.84        |
| CRDL1          | 0.57        |
| RNAS6          | N/A         |
| SAP3           | N/A         |
| HE4            | 0.85        |
| TIMP-4         | 0.86        |
| IGFBP-7        | 0.65        |
| OPG            | 0.83        |
| Siglec-7       | 0.69        |
| SVEP1          | N/A         |
| TREM2          | 0.84        |
| NPS-PLA2       | 0.76        |
| MARCKSL1       | N/A         |
Supplementary Table 10. Validation of Somalogic aptamer-based protein measurements. DDA-MS = Data-dependent acquisition Tandem Mass Spectrometry, cis pQTL = cis protein quantitative loci, MRM-MS = Multiple reaction monitoring Tandem Mass Spectrometry, Indirect = association observed between MRM-MS measured SAP3 and Alzheimer’s diseases.  

| Full aptamer target name                                      | Aptamer target          | Entrez Gene Symbol | Method of validation      | Other comments from Somalogic                                      |
|---------------------------------------------------------------|-------------------------|--------------------|---------------------------|-------------------------------------------------------------------|
| N-terminal pro-BNP                                           | N-terminal pro-BNP      | NPPB               | cis pQTL data,           | Olink panel, sandwich immunoassay                                 |
|                                                               |                         |                    |                           | 10,25                                                              |
| CUB domain-containing protein 1                              | CDCP1                   | CDCP1              | cis pQTL data            |                                                                   |
|                                                               |                         |                    |                           | 10                                                                  |
| Growth/differentiation factor 15                             | MIC-1                   | GDF15              | cis pQTL data,           | Olink panel, sandwich immunoassay                                 |
|                                                               |                         |                    |                           | 10,25                                                              |
| Chordin-like protein 1                                        | CRDL1                   | CHRD1              | DDA-MS Data              |                                                                   |
|                                                               |                         |                    |                           | 10                                                                 |
| Ribonuclease K6                                               | RNAS6                   | RNASE6             | cis pQTL data            |                                                                   |
|                                                               |                         |                    |                           | 10,25                                                              |
| Ganglioside GM2 activator                                    | SAP3                    | GM2A               | Indirect MRM-MS Data     |                                                                   |
|                                                               |                         |                    |                           | 28                                                                 |
| WAP four-disulfide core domain protein 2                     | HE4                     | WFDC2              | DDA-MS Data, cis pQTL data|                                                                   |
|                                                               |                         |                    |                           | 10,10,25                                                           |
| Metalloproteinase inhibitor 4                                 | TIMP-4                  | TIMP4              | cis pQTL data,           | Olink panel                                                        |
|                                                               |                         |                    |                           | 10,25                                                              |
| Insulin-like growth-factor binding protein 7                  | IGFBP-7                 | IGFBP7             | DDA-MS Data, cis pQTL data|                                                                   |
|                                                               |                         |                    |                           | 10,25                                                              |
| Tumor necrosis factor receptor superfamily member 11B        | OPG                     | TNFRSF11B          | cis pQTL data            |                                                                   |
|                                                               |                         |                    |                           | 10                                                                 |
| Sialic acid-binding Ig-like lectin 7                         | Siglec-7                | SIGLEC7            | cis pQTL data            |                                                                   |
|                                                               |                         |                    |                           | 10,25                                                              |
| Sushi, von Willebrand factor type A, EGF and pentraxin domain-containing protein 1 | SVEP1                   | SVEP1              | MRM-MS Data, DDA-MS Data |                                                                   |
|                                                               |                         |                    |                           | cis pQTL data, cis pQTL data                                      |
|                                                               |                         |                    |                           | 10,10,25                                                           |
| Triggering receptor expressed on myeloid cells 2             | TREM2                   | TREM2              | MRM-MS Data, indirect sandwich immunoassay |                                                                   |
|                                                               |                         |                    |                           | 10,10,25                                                           |
| Phospholipase A2, membrane associated                         | NPS-PLA2                | PLA2G2A            | DDA-MS Data, cis pQTL data|                                                                   |
|                                                               |                         |                    |                           | 10,25                                                              |
| MARCKS-related protein                                        | MARCKSL1                | MARCKSL1           | -                         |                                                                   |
Supplementary Figure 6. Hypothesize dementia-related pathologies for 15 proteins associated with cognitive decline rate and dementia risk. A schematic overview of the potential processes linking the proteins with a. increased innate and b. adaptive immunity responses in blood circulation and the brain, c. dysfunction of the blood-brain barrier, d. atherosclerotic and thrombotic changes in cerebral capillaries, and e. central insulin resistance in the brain. BBB, blood brain barrier. CNS, central nervous system. GLUT4, Glucose transporter type 4. IGF-1, Insulin-like growth factor 1. IGF-2, Insulin-like growth factor 2. NK-cells, natural killer cells. NO, nitric oxide.
a) Innate immunity

1a) Inflammation and pathogens cause macrophages to secrete MARCKS1, NPS-PLA2, MIC-1, and TIMP-4.

2) Leukocytes secrete RNase6, a second line antimicrobial peptide.

3a) SVEP1 activates complement.

3b) Active complement promotes leukocyte infiltration.

3c) Chronic activation of complement damages endothelium and BBB.

4) Viral infection and inflammation causes NK-cells to release SIGLEC-7, an autoantibody recognition antigen. This leads to dysfunctional NK-cells. Plasma SIGLEC-7 is considered a marker of uncontrolled viral infection or inflammation.

5) Inflammation and pathogens increase OPG, which leads to decreased endothelial survival and angiogenesis.

6) Epithelial cells secrete HE4 that protects against proteolytic pathogens.

7) Infiltrating leukocytes and damaged BBB that passes through circulating toxins, complement, erythrocytes, TREM2, MARCKS1, CRDL1, SAP3, and NPS-PLA2 cause reduced neuronal plasticity, activate microglia, disrupt lipid metabolism, and cause neuroinflammation that leads to amyloid and tau accumulation and neurodegeneration.

CNS

Neuron

Oligodendrocyte

Microglia
b) Adaptive immunity

Capillary

1a) Inflammation, pathogens and related innate immune response cause macrophages and dendrocytes to present antigens to T-cells and lead to T-cell mobilisation.

1b) MARCKSL1, NPS-PLA2, and MIC-1 promote macrophage activation and antigen presentation, OPG and TIMP-4 promote T-cell survival, and CDCP1 activates T-lymphocytes via CD6.

1c) CDCP1 promotes T-cell adhesion, T-cell infiltration, and is associated with accumulation of myelinoligodendrocyte glycoprotein specific T-cells to central nervous system.

2) Infiltration of macrophages and neutrophils and subsequently T-cells causes neuroinflammation and microglia activation that lead to amyloid and tau accumulation and neurodegeneration.

CNS

Neuron

Amyloid

Neutrophil

Oligodendrocyte

Microglia
c) Blood brain barrier breakdown

1) CDCP1 is linked to tight junction degradation
2) HE4 and TIMP-4 decrease protease activity and may increase fibrin(ogen) accumulation into perivascular space
3) SAP3 is linked to pericyte degradation and plasma membrane degradation
4) Macrophages can cleave MARCKSL1 that maintains endothelial integrity, which leads to endothelial disruption
5) SVEP1 activates complement leading to endothelium and BBB damage. SVEP1 also cleaves E-selectin that induces apoptosis and dysfunction in endothelium and binds to integrin α9β1 linked with basement membrane dysfunction
6) MIC-1 and OPG are markers of endothelial dysfunction
7) Damaged BBB passes through circulating toxins, TREM2, MARCKSL1, CRDL1, SAP3, and NPS-PLA2 that leads to reduced neuronal plasticity, activation of microglia, disruption of lipid metabolism, and neuroinflammation that causes amyloid and tau accumulation and neurodegeneration
d) Atherosclerosis and thrombosis

1) TIMP-4 is associated with remodelling in labile atherosclerotic plaques, promotes thrombosis formation, and is apoptotic to damaged myocytes that is linked to arteriosclerosis.

2) OPG is associated with macrophage invasion, smooth cell hyperplasia and fibrosis in atherosclerosis.

3) NPS-PLA2 promotes macrophage mediated inflammation in atherosclerotic plaques.

4) SAP3 transports glycosphingo lipid to atherosclerotic plaques that relate to macrophages transfer to foam cells and causes smooth muscle cell hyperplasia.

5) SVEP1 activates neutrophils that promote thrombosis.

6) MIC-1 is associated with atherosclerosis but it is unclear whether it is a marker or a factor in its development.

7) HE4 and TIMP-4 increases protease activity and may increase fibrinogen accumulation in the perivascular space.

8) Atherosclerosis and small vessel disease reduce cerebral blood flow which is further reduced by IGFBP-7 via lower insulin availability and subsequent decrease in NO-mediated vasodilation.

9) HE4 and CRDL1 increase in response to ischemia leading to abnormal angiogenesis and endothelial disruption.

10) N-terminal pro-ENaC is a marker of atrial and ventricular overload that is associated with endothelial dysfunction.

11) Endothelial dysfunction, impairment of autoregulation, and dysfunction of neurovascular coupling, additionally mediated by oxidative stress and NO deficit further reduce cerebral blood flow resulting in hypo perfusion and tissue hypoxia. This leads to expression of adhesion molecules in endothelium and contributes to leucocyte infiltration, platelet adhesion, microvascular occlusion, and micro bleeds.

12) Damaged BBB passes through circulating toxins, TREM2, MARCKSL1, CRDL1, SAP3, and NPS-PLA2 that reduced neuronal plasticity, activate microglia, disrupt lipid metabolism, and cause neuroinflammation that leads to amyloid and tau accumulation and neurodegeneration.
e) Central insulin resistance

1) IGFBP-7 restricts mainly free insulin and to some extent free IGF-1 and IGF-2 levels in blood and inhibits their binding to their receptors.

2) Reduced insulin levels lead to decrease in NO-mediated vasodilation and subsequently decrease in cerebral perfusion.

3) IGFBP-7 restricts insulin availability and inhibits insulin and IGF-1 binding in neurons’ insulin receptor leading to apoptosis and reduced neurogenesis.

4) IGFBP-7 reduces availability of IGF-1 to IGF-1 receptor leading to neurodystrophic effects, neuroinflammation amyloid accumulation, and tau phosphorylation.

5) IGFBP-7 reduces IGF-2 availability to IGF-2 receptor leading to dysregulation of endocytosis, lysosomes, and apoptosis.

6) IGFBP-7 limits insulin availability to insulin dependent glucose transporter GLUT4 expressed in areas, such as hypothalamus, with high glucose demand.

7) IGFBP-7 limits insulin availability that leads to reduced oligodendrocyte proliferation, survival, differentiation, and myelination.

8) IGFBP-7 reduces insulin availability that increases inflammatory response, reduces glycogen storage, and reduces BBB glucose uptake in astrocytes.

9) IGFBP-7 reduces insulin availability to microglia that leads to inflammatory response and subsequent amyloid and tau accumulation and neurodegeneration.