Association between Circulating Protein C Levels and Incident Dementia: the Atherosclerosis Risk in Communities Study

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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 ε4 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/m^2, 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.

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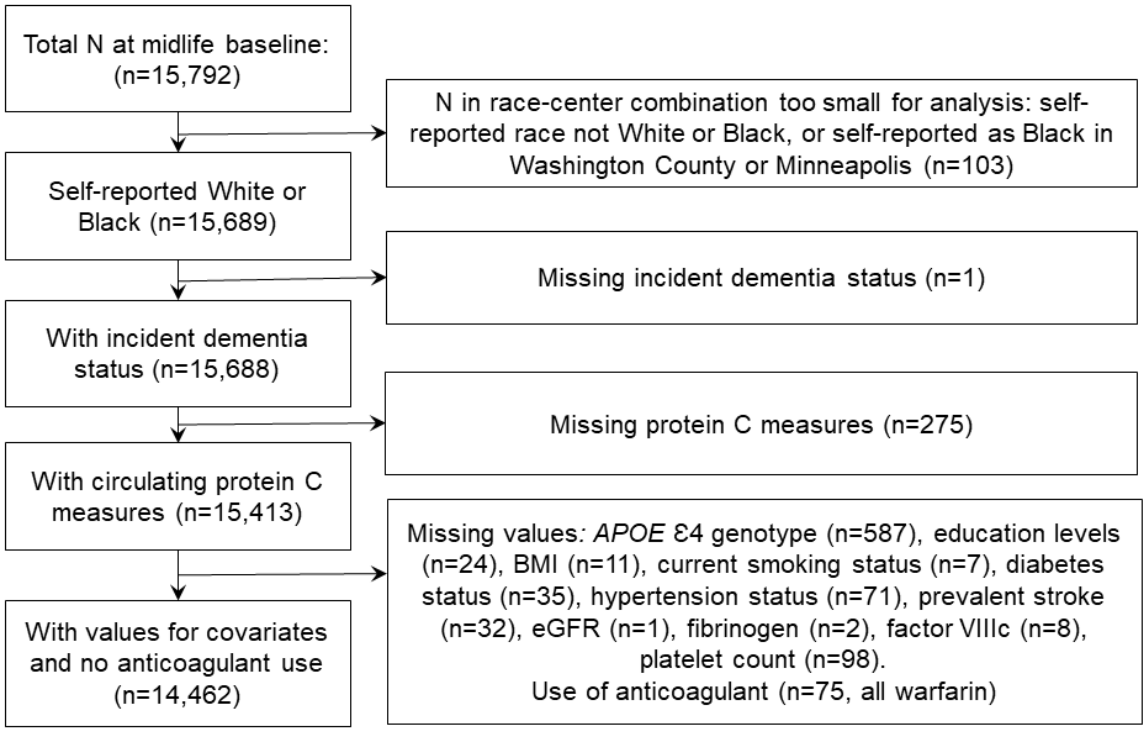
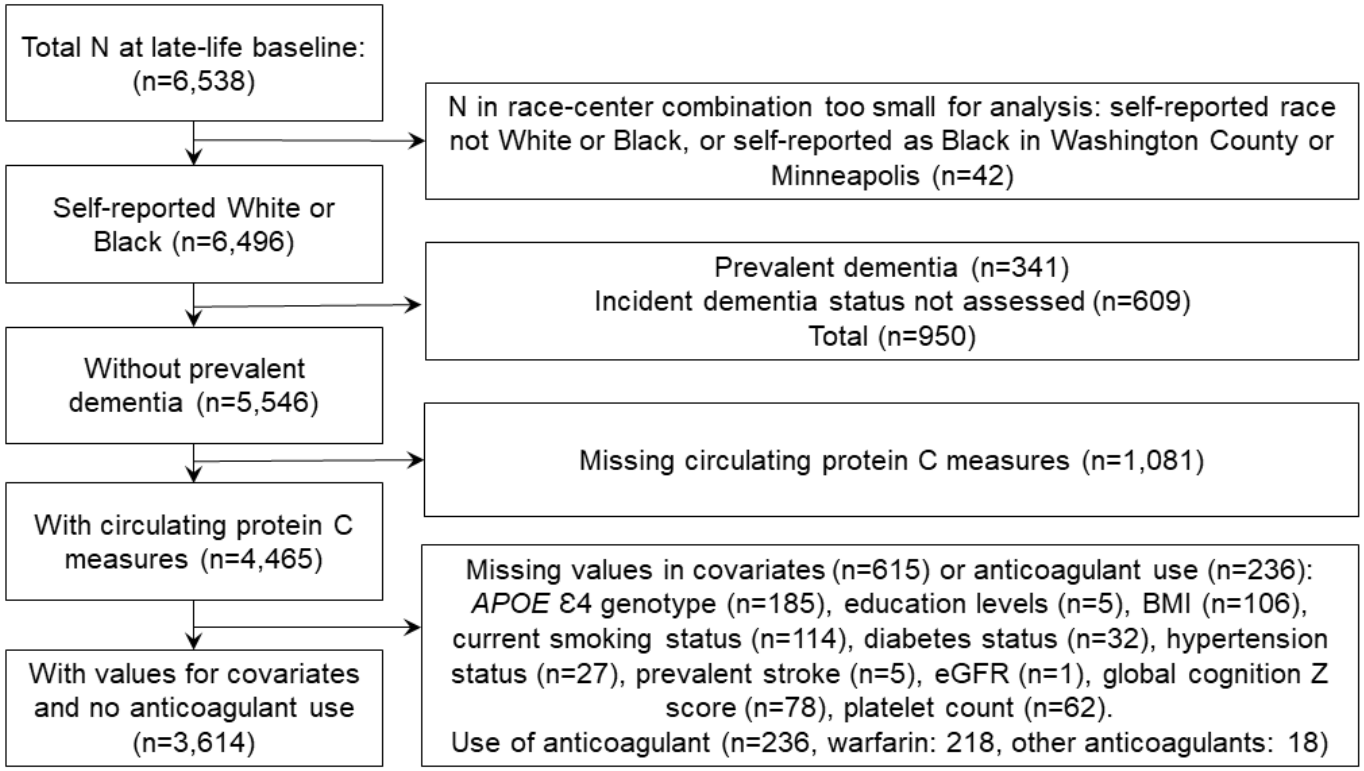
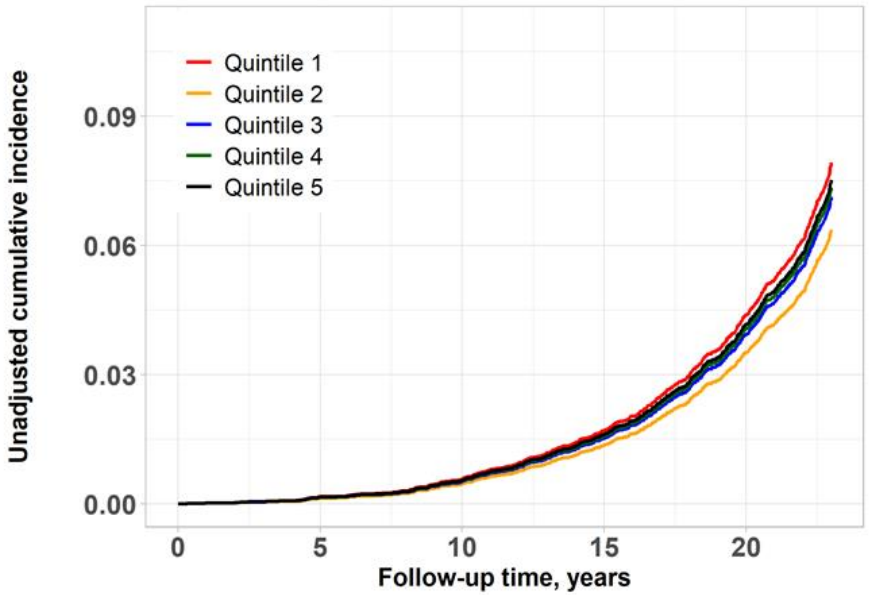
Supplementary Figures 1 to 4



Supplementary Figure 1. Flowchart of participant inclusion at the midlife baseline (1987-89, visit 1) with the number of participants excluded due to missing values in covariates, sample size in race-center combinations that were too small for analysis, and the use of warfarin. Prevalent dementia status at the midlife baseline was not assessed. Given that the age range of these participants at midlife were from 44 to 66, we assumed all participants did not have prevalent dementia at the midlife baseline.

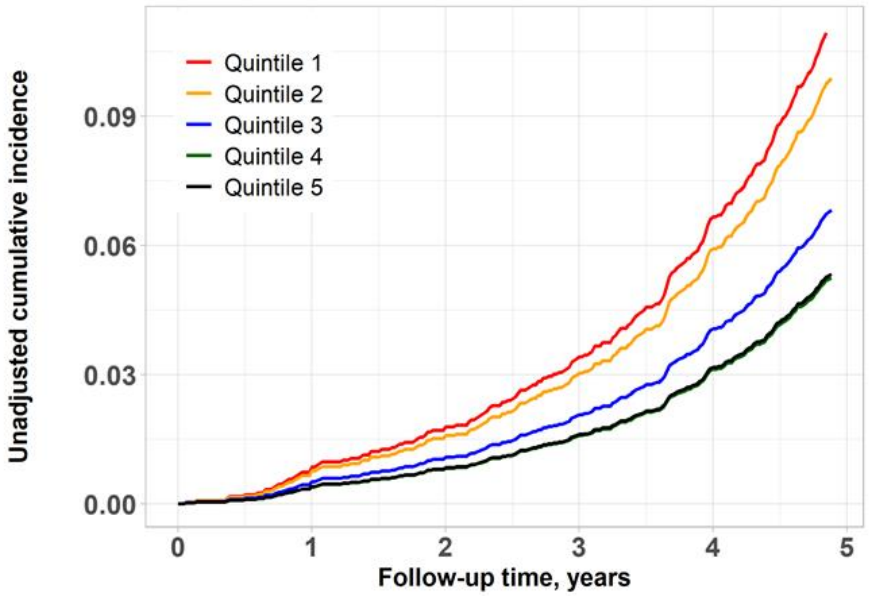


Supplementary Figure 2. Flowchart of participant inclusion at the late-life baseline (2011-13, visit 5) with the number of participants excluded due to missing values in covariates, sample size in race-center combinations that were too small for analysis, and the use of anticoagulant.



Number at risk					
Quintile 1	2809	2681	2487	2206	1904
Quintile 2	2738	2639	2454	2235	1939
Quintile 3	3011	2894	2717	2493	2156
Quintile 4	2963	2863	2698	2445	2125
Quintile 5	2941	2833	2674	2416	2122

Supplementary Figure 3. Crude cumulative incident from the midlife baseline by quintiles of protein C levels



Number at risk			
Quintile 1	723	708	593
Quintile 2	723	706	616
Quintile 3	722	717	627
Quintile 4	723	709	640
Quintile 5	723	716	635

Supplementary Figure 4. Crude cumulative incident from the late-life baseline by quintiles of protein C levels. The curves of quintiles 4 and 5 overlapped.