Supplementary Figure 1: Correlations between measured brain pathologies and CA and vascular risk factors. **a)** This plot summarizes the Spearman rank-based correlation between cerebral atherosclerosis and microinfarcts, gross infarcts, β -amyloid, tangles, cerebral amyloid angiopathy (CAA), Lewy body, hippocampal sclerosis, and TDP-43 n the discovery dataset (N=375). Significance was based on adjusted p value less than 0.05 and noted with an asterisk. **b)** This plot summarizes the Pearson correlation between cerebral atherosclerosis and the mean plasma low-density lipoprotein (LDL; N=373), mean triglyceride (TG; N=374), and mean high-density lipoprotein (HDL; N=374) levels averaged across all available years of follow-up. Significance was based on an unadjusted p-value less than 0.05 and noted with the asterisk.





Α

Supplementary Figure 2: This figure summarizes the gene set enrichment analysis of the 237 proteins associated with cerebral atherosclerosis after adjusting for the 7 other measured pathologies but not gross infarcts at proteome-wide adjusted p < 0.05 in the discovery dataset. These 237 proteins were divided into higher-abundance and lower-abundance proteins in cerebral atherosclerosis for the gene set enrichment analysis. Enrichment was determined using a one-sided *Z* test.



Higher abundance in cerebral atherosclerosis at FDR<0.05



Lower-abundance in cerebral atherosclerosis at FDR<0.05

SPLICEOSOMAL TRI SNRNP COMPLEX ASSEMBLY POSITIVE REGULATION OF CYCLIN DEPENDENT PROTEIN KINASE ACTIVITY MRNA PROCESSING RNA SPLICING VIRAL LATENCY RNA SPLICING VIA TRANSESTERIFICATION REACTIONS RNA PROCESSING MRNA METABOLIC PROCESS CELLULAR RESPONSE TO GAMMA RADIATION SPLICEOSOMAL COMPLEX ASSEMBLY INHIBITORY SYNAPSE NUCLEAR BODY DNA REPLICATION FACTOR A COMPLEX NUCLEAR SPECK PRP19 COMPLEX SPLICEOSOMAL COMPLEX REPLISOME CATALYTIC STEP 2 SPLICEOSOME NUCLEOPLASM PART PRESYNAPTIC ACTIVE ZONE POLY A RNA BINDING 14 3 3 PROTEIN BINDING RNA BINDING PHOSPHATASE INHIBITOR ACTIVITY INSULIN RECEPTOR BINDING MRNA BINDING SIGNALING ADAPTOR ACTIVITY PHOSPHATASE REGULATOR ACTIVITY TELOMERIC DNA BINDING PROTEIN PHOSPHATASE BINDING SPLICEOSOME mRNA Processing MECP2 and Associated Rett Syndrome Brain-Derived Neurotrophic Factor (BDNF) signaling pathway

z score

Supplementary Figure 3: This figure summarizes the gene set enrichment analysis of the 142 proteins associated with cerebral atherosclerosis after adjusting for the 7 other measured pathologies but not microinfarcts at proteome-wide adjusted p < 0.05 in the discovery dataset. These 142 proteins were divided into higher-abundance and lower-abundance proteins for the gene set enrichment analysis. Enrichment was determined using a one-sided Z test.



Higher abundance in cerebral atherosclerosis at FDR<0.05

OLIGODENDROCYTE DEVELOPMENT GUAL CELL DEVELOPMENT GLIAL CELL DIFFERENTIATION SUBSTANTIA NIGRA DEVELOPMENT ENSHEATHMENT OF NEURONS GLIOGENESIS NEURAL NUCLEUS DEVELOPMENT MIDBRAIN DEVELOPMENT CENTRAL NERVOUS SYSTEM DEVELOPMENT MYELIN SHEATH SUPRAMOLECULAR FIBER MICROTUBULE AXON PART CYTOSKELETAL PART AXON CELL CELL JUNCTION CYTOSKELETON CELL PROJECTION METALLOPEPTIDASE ACTIVITY STRUCTURAL CONSTITUENT OF CYTOSKELETON PEPTIDASE ACTIVITY Oligodendrocytes Oligodendrocyte remyelination

Lower-abundance in cerebral atherosclerosis at FDR<0.05





SPLICEOSOMAL TRI SNRNP COMPLEX ASSEMBLY RNA SPLICING MRNA PROCESSING RNA SPLICING VIA TRANSESTERIFICATION REACTIONS SPLICEOSOMAL COMPLEX ASSEMBLY MRNA METABOLIC PROCESS MRNA CIS SPLICING VIA SPLICEOSOME SPLICEOSOMAL SNRNP ASSEMBLY RNA PROCESSING STEM CELL PROLIFERATION CATALYTIC STEP 2 SPLICEOSOME **U5 SNRNP** SPLICEOSOMAL COMPLEX SMALL NUCLEAR RIBONUCLEOPROTEIN COMPLEX NUCLEAR SPECK NUCLEAR BODY NUCLEOLAR PART NUCLEOPLASM PART SNRNA BINDING POLY A RNA BINDING SIGNALING ADAPTOR ACTIVITY KINASE BINDING RNA BINDING PROTEIN COMPLEX SCAFFOLD PROTEIN KINASE A BINDING MRNA BINDING **BINDING BRIDGING** PHOSPHATASE BINDING SPI ICEOSOME mRNA Processing G Protein Signaling Pathways **Supplementary Figure 4**: This figure presents the gene set enrichment analysis of the 856 proteins associated with cognitive diagnosis at proteome-wide adjusted p < 0.05 in the discovery dataset. These 856 proteins were divided into higher-abundance and lower-abundance proteins for the gene set enrichment analysis. Enrichment was determined using a one-sided *Z* test.



Higher-abundance in PWAS of clinical diagnosis of dementia at FDR<0.05

Supplementary Figure 5: This figure summarizes the gene set enrichment analysis of the 23 proteins associated with β -amyloid after adjusting for the 8 other measured pathologies at proteomewide adjusted p <0.05 in the discovery dataset. Enrichment was determined using a one-sided *Z* test.



PWAS of amyloid in ROSMAP, FDR<0.05

Supplementary Figure 6: This figure summarizes the gene set enrichment analysis of the 244 proteins associated with neurofibrillary tangles after adjusting for sex, age at death, cell type composition, and the eight other measured pathologies at proteome-wide adjusted p <0.05 in the discovery dataset. These 244 proteins were divided into higher-abundance and lower-abundance proteins in tangles for the gene set enrichment analysis. Enrichment was determined using a one-sided *Z* test.



Supplementary Figure 7: Protein-protein interactions among the 23 proteins differentially expressed in both cerebral atherosclerosis and AD at proteome-wide adjusted p<0.05 and the proteins composing the protein co-expression modules 3 and 9, both of which were also associated with cerebral atherosclerosis and AD. DEPs refer to the 23 proteins differentially expressed in both atherosclerosis and AD. Sixty percent of the proteins in module 9 and 58% of the proteins in module 3 have physical interactions. Interactions were based on BioGRID database (v3.5.179).



Supplementary table 1: Characteristics of discovery dataset (ROS/MAP cohorts; N=391)

Characteristic	N	Percent	
Sex			
Female	273	69.8	
Male	118	30.2	
Cognitive diagnosis at baseline			
Normal cognition	390	99.7	
Mild cognitive impairment	1	0.3	
Cognitive diagnosis at death	160	40.0	
Mild cognitive impairment	100	25.8	
Alzheimer's dementia	122	31.2	
Other dementia	8	2.1	
	Mean [SD]	Median	Range
Age at enrollment	79.7 [6.7]	79.9	[59.0-100.5]
Age at death	89.2 [6.5]	89.5	[65.9-106.5]
Education	15.8 [3.6]	16.0	[5.0-28.0]
Number of follow-up years	8.7 [4.5]	9.0	[1.0-20.0]
Post-mortem interval (PMI)	8.1 [5.5]	6.5	[2.3-61.5]
Vascular risk factors	1.1 [0.88]	1.0	[0.0-3.0]
	N	Percent	
Brain infarcts			
Gross infarct (Present)	125	32.0	
Microinfarct (Present)	131	33.5	
Hippocampal sclerosis (Present)	29	7.4	
Lewy Body (Present)	92	23.5	
TDP-43 (Present)	170	43.5	
	Mean [SD]	Median	Range
Cerebral atherosclerosis		1.0	
Alzheimer's disease pathology	1.7 [0.0]	1.0	[0.0-0.0]
	4 0 [4 7]	2.2	[0 0 40 0]
p-Anyou Tanalaa	4.0 [4.7]	J.Z	[0.0-19.9]
langles	4.8 [5.0]	3.4	[0.0-30.5]
Cerebral amyloid angiopathy	1.1 [0.9]	1.0	[0.0-3.0]

Cerebral atherosclerosis was rated as none (0), mild (1), moderate (2), or severe (3)

Supplementary table 2: Characteristics of the replication dataset (BLSA cohort).

Characteristic	N	Percent	
Sex			
Female	17	36.2	
Male	30	63.8	
Final cognitive diagnosis			
Normal cognition	27	57.4	
Alzheimer's disease	20	42.6	
	Mean [SD]	Median	Range
Age at death	85.6 [9.4]	86.0	[62.0-99.0]
Post-mortem interval (PMI)	14.5 [6.1]	14.5	[2.0-28.0]
			[]
	N	Percent	
Brain infarct			
Gross infarct (Present)	5	10.6	
Microinfarcts (Present)	7	14.9	
	Mean [SD]	Median	Range
Cerebral atherosclerosis	1.2 [0.9]	1.0	[0.0-3.0]
Alzheimer's disease pathology			
β-Amyloid	1.9 [1.2]	2.0	[0.0-3.0]
Tangles	4.2 [1.5]	4.0	[1.0-6.0]
Cerebral amyloid angiopathy	0.5 [0.9]	0.0	[0.0-3.0]

Cerebral atherosclerosis was rated as minimal (0), mild (1), moderate (2), or severe (3)

Supplementary table 3: Characteristics of the 236 ROS/MAP subjects with ex-vivo imaging data

Characteristic	N	Percent		<i>p</i> -value [#]
Sex				0.468
Female	172	72.9		
Male	64	27.1		
Cognitive diagnosis at baseline				1.000
Normal cognition	236	100.0		
Mild cognitive impairment	0	0.0		
Cognitive diagnosis at death				0.993
Normal cognition	74	31.4		
Mild cognitive impairment	92	39.0		
Alzheimer's dementia	6	27.1		
	0	2.5		
	Mean [SD]	Median	Range	
Age at enrollment	80.3 [6.4]	80.6	[59.0-96.3]	0.268
Age at death	90.2 [5.8]	90.0	[65.9-103.6]	0.054
Education	15.6 [3.6]	16.0	[5.0-27.0]	0.573
Number of follow-up years	9.8 [4.5]	9.0	[2.0-21.0]	0.396
Post-mortem interval (PMI)	8.2 [5.1]	6.7	[0.0-32.6]	0.715
Vascular risk factors	1.2 [0.89]	1.0	[0.0-3.0]	0.536
	Ν	Percent		
Brain infarcts				
Gross infarct (Present)	76	32.2		1.000
Microinfarct (Present)	71	30.1		0.717
Hippocampal sclerosis (Present)	22	9.3		0.451
Lewy Body (Present)	60	25.4		0.929
TDP-43 (Present)	107	45.3		0.801
	Mean [SD]	Median	Range	
Cerebral atherosclerosis	1.1 [0.8]	1.0	[0.0-3.0]	0.727
Alzheimer's disease pathology				
β-Amyloid	6.0 [5.0]	5.7	[0.0-19.9]	0.002
Tangles	5.5 [5.4]	3.8	[0.0-30.5]	0.129
Cerebral amyloid angiopathy	1.1 [0.8]	1.0	[0.0-3.0]	0.671

p-values for comparing the 236 subjects with ex-vivo imaging data with the 391 subjects with proteomic data using two-sided Fisher exact test for categorical variables and two-sided t-test for continuous variables.