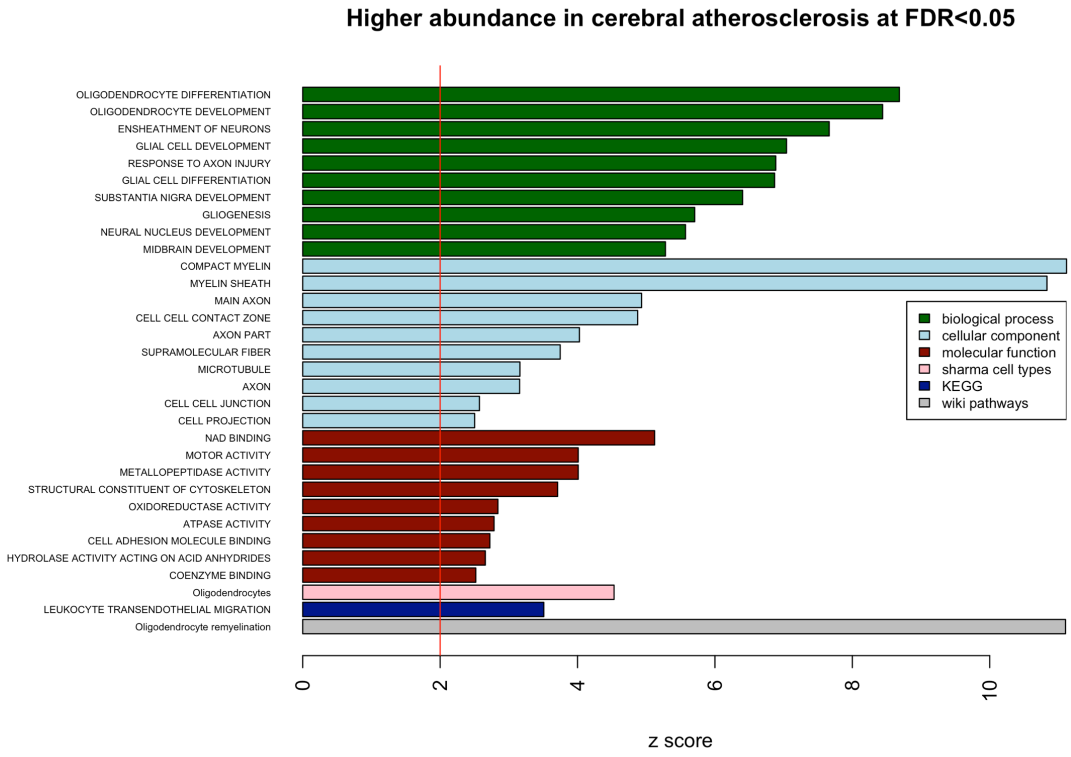
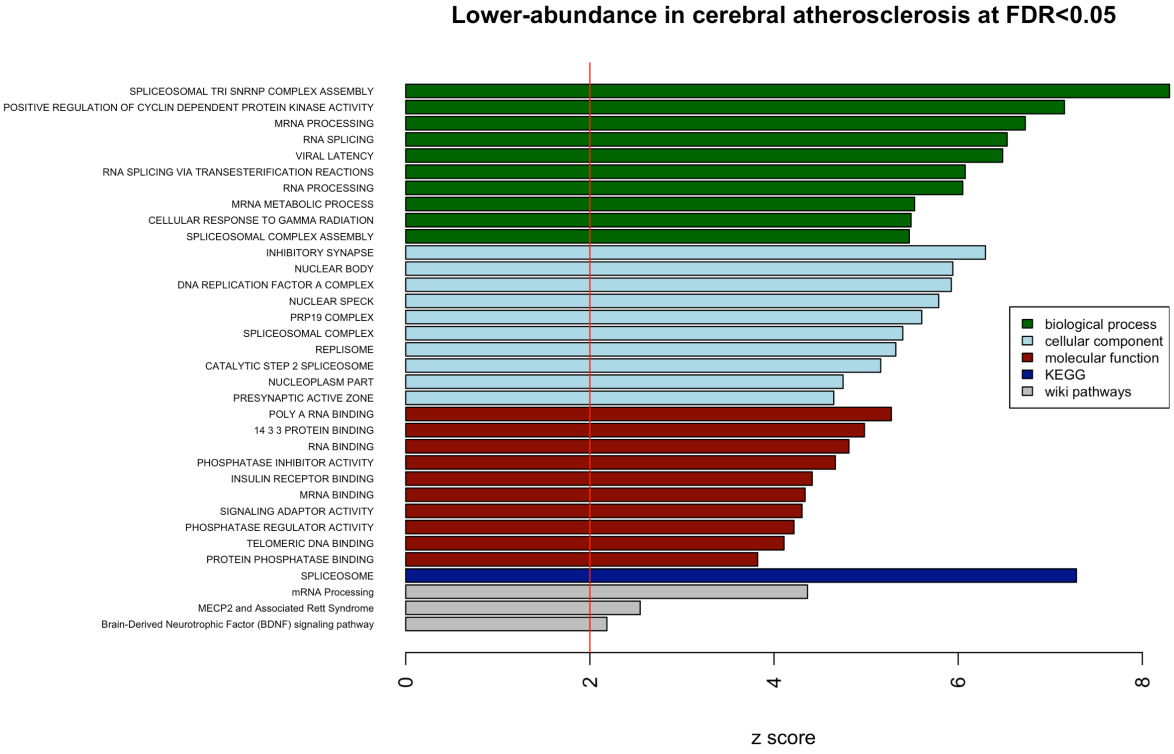
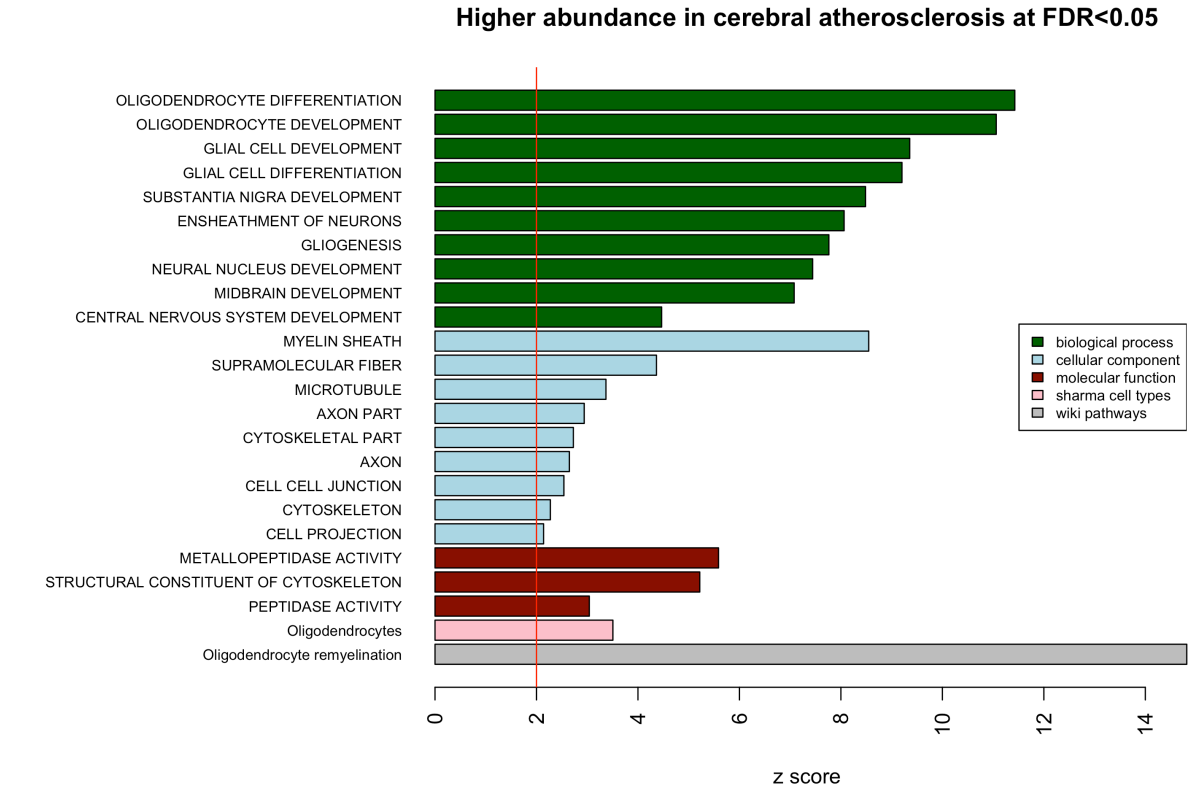
**Supplementary Figure 1:** Correlations between measured brain pathologies and CA and vascular risk factors. **a)** This plot summarizes the Spearman rank-based correlation between cerebral atherosclerosis and microinfarcts, gross infarcts, β-amyloid, tangles, cerebral amyloid angiopathy (CAA), Lewy 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.

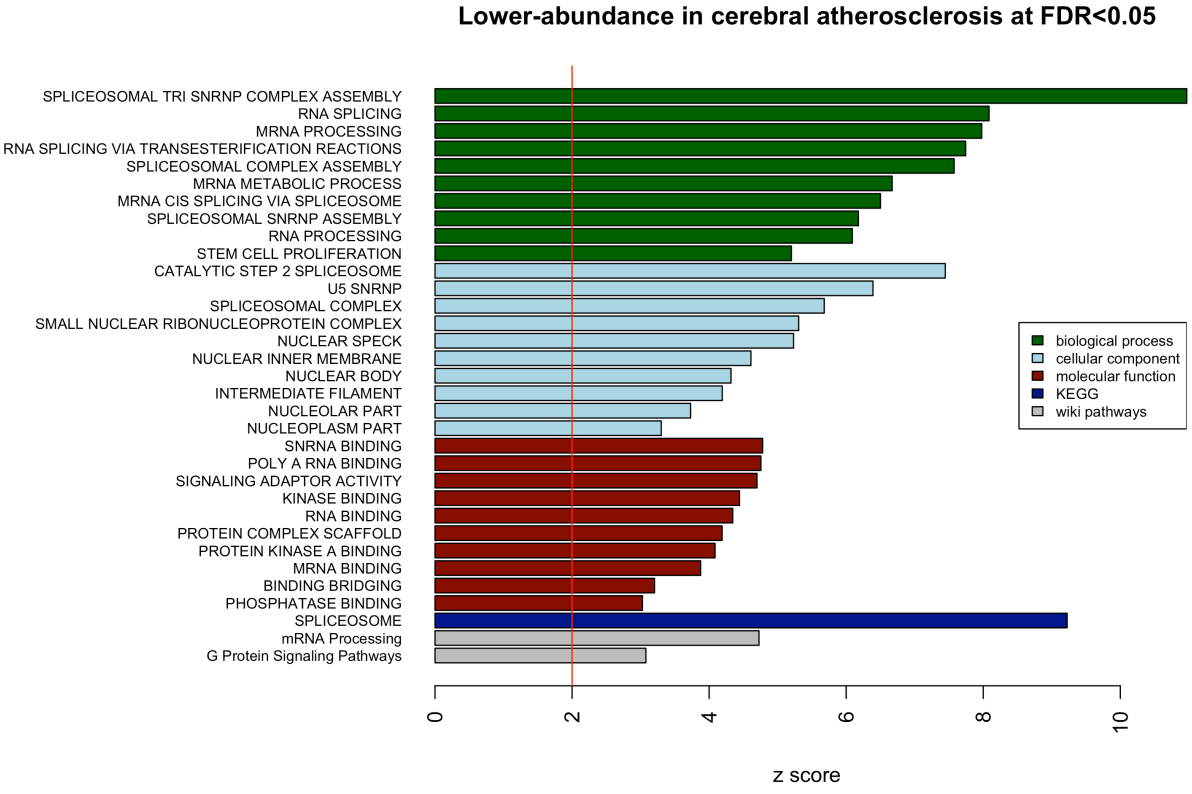
**Supplementary Figure 2**: This figure summarizes the gene set enrichment analysis of the 237 proteins associated with cerebral atherosclerosis after adjusting for the 7 other measured pathologies but not gross infarcts at proteome-wide adjusted p <0.05 in the discovery dataset. These 237 proteins were 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.



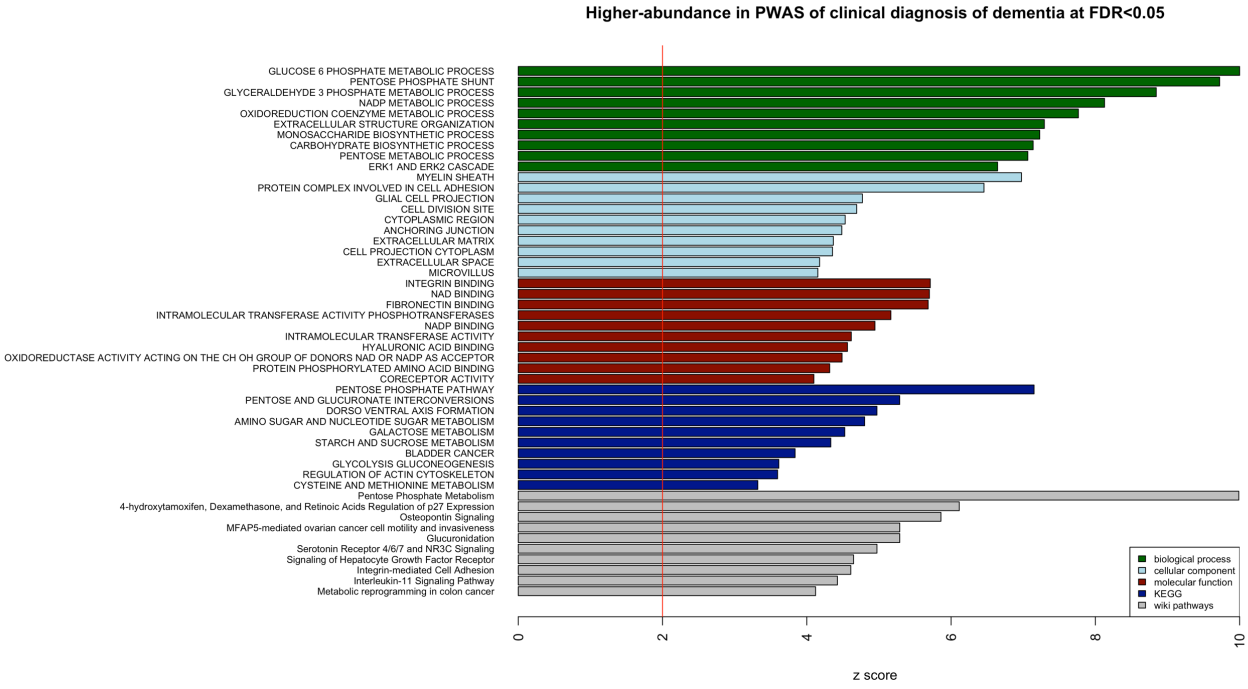



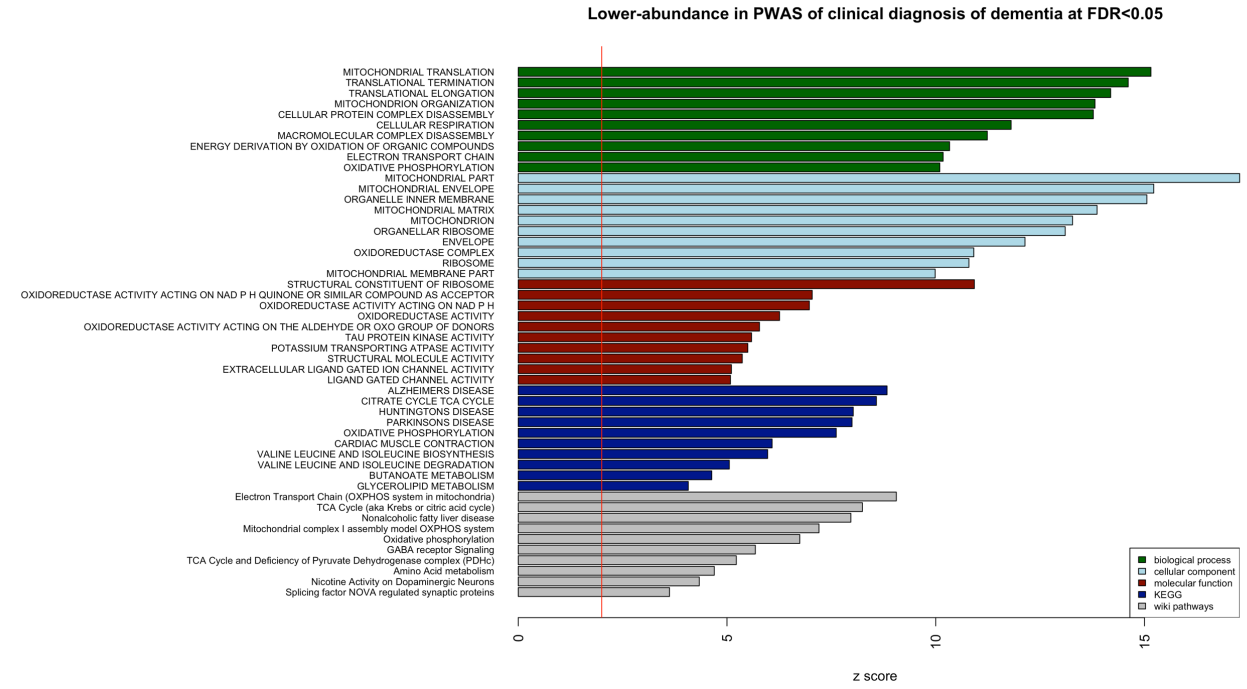
**Supplementary Figure 3**: This figure summarizes the gene set enrichment analysis of the 142 proteins associated with cerebral atherosclerosis after adjusting for the 7 other measured pathologies but not microinfarcts at proteome-wide adjusted p <0.05 in the discovery dataset. These 142 proteins were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



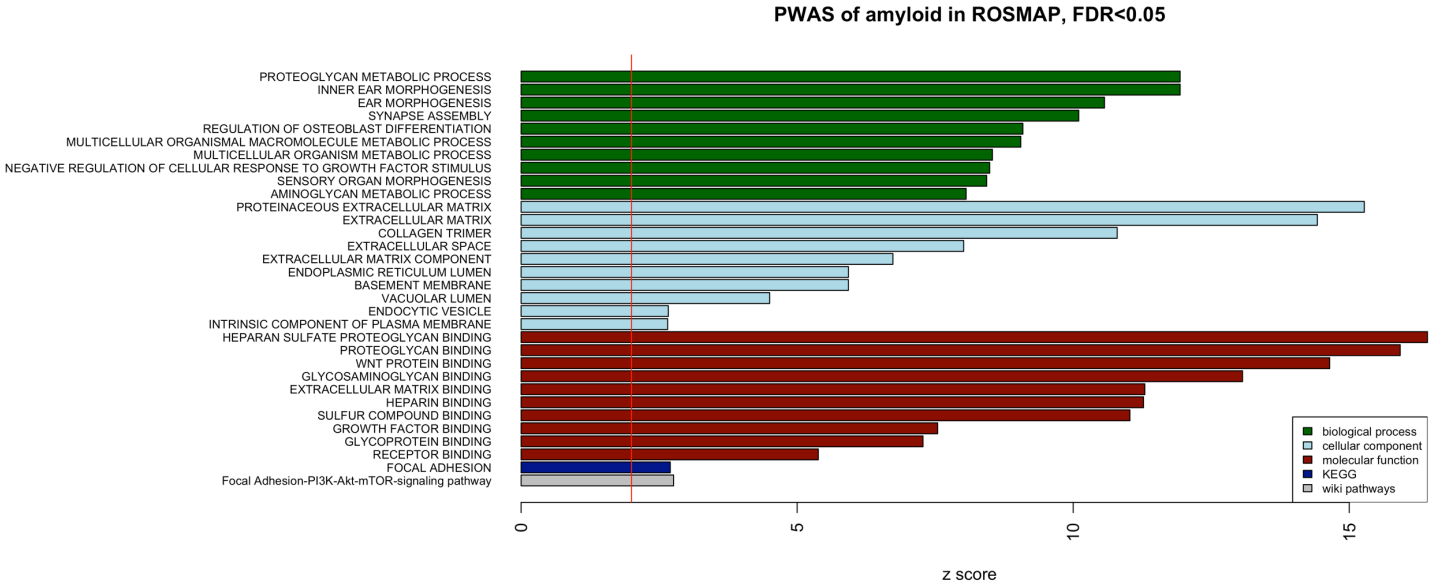



**Supplementary Figure 4**: This figure presents the gene set enrichment analysis of the 856 proteins associated with cognitive diagnosis at proteome-wide adjusted p <0.05 in the discovery dataset. These 856 proteins were divided into higher-abundance and lower-abundance proteins for the gene set enrichment analysis. Enrichment was determined using a one-sided *Z* test.

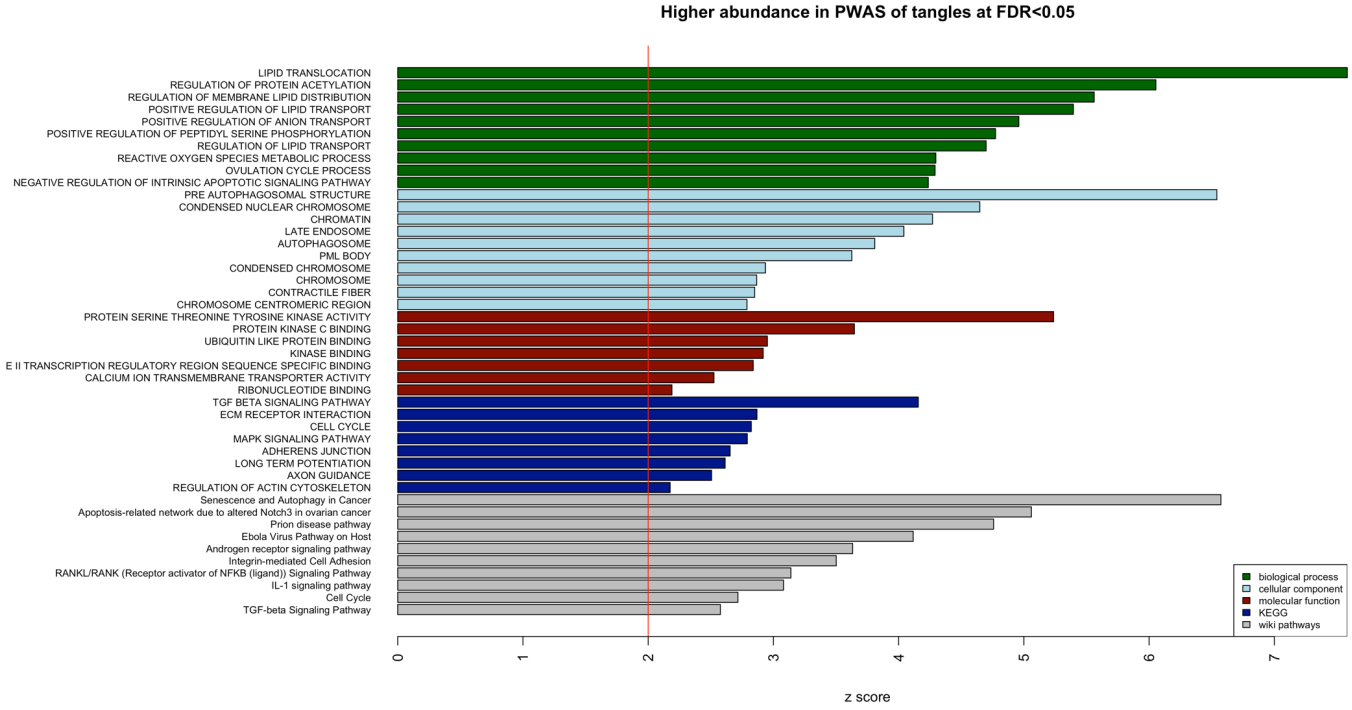


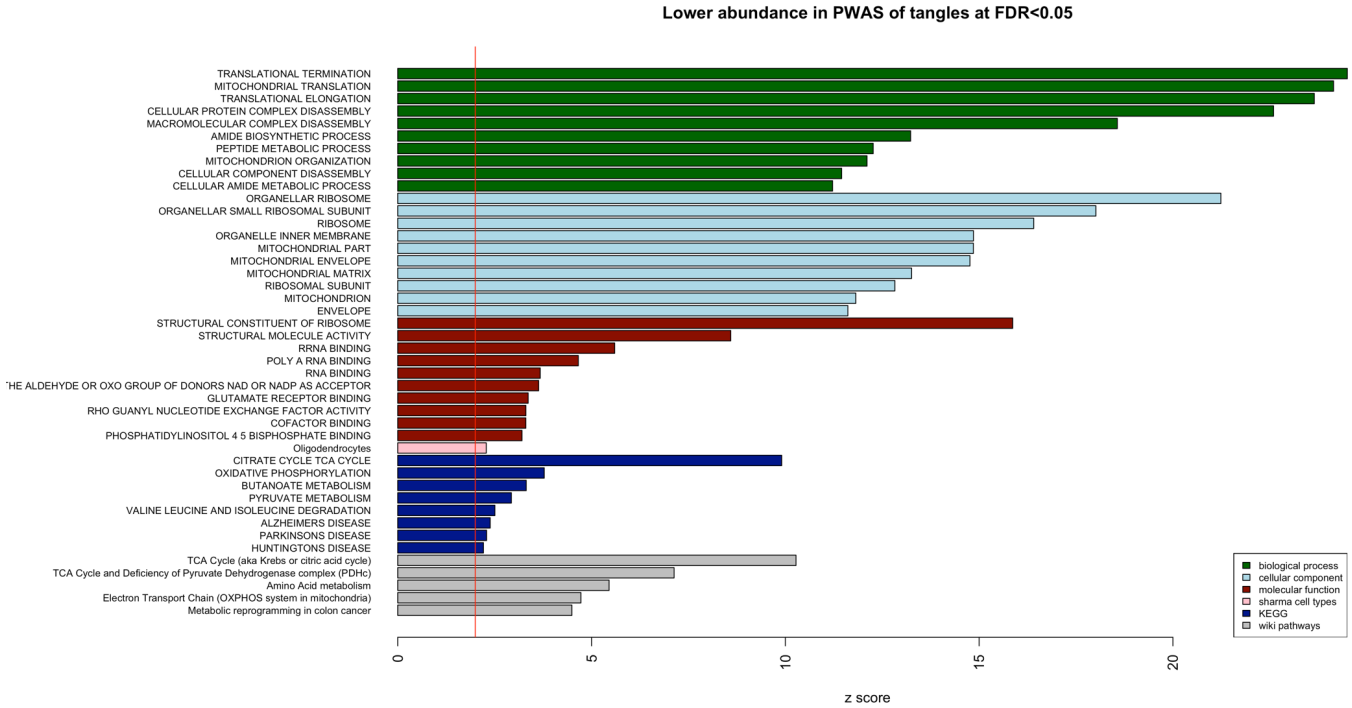



**Supplementary Figure 5**: This figure summarizes the gene set enrichment analysis of the 23 proteins associated with β-amyloid after adjusting for the 8 other measured pathologies at proteome-wide adjusted p <0.05 in the discovery dataset. Enrichment was determined using a one-sided *Z* test.

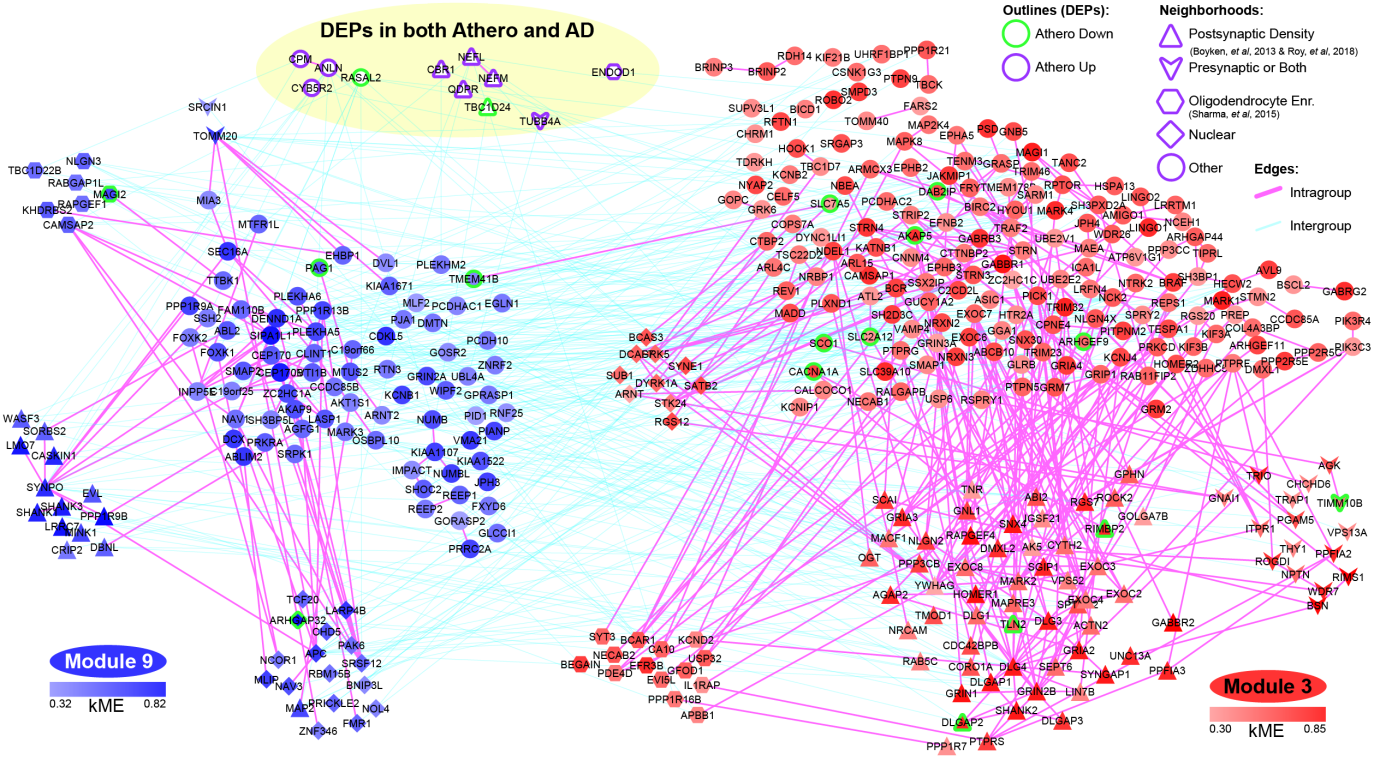


**Supplementary Figure 6**: This figure summarizes the gene set enrichment analysis of the 244 proteins associated with neurofibrillary tangles after adjusting for sex, age at death, cell type composition, and the eight other measured pathologies at proteome-wide adjusted p <0.05 in the discovery dataset. 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 | | | |
| Normal cognition | 160 | 40.9 | |
| Mild cognitive impairment | 101 | 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 | 1.7 [0.8] | 1.0 | [0.0-3.0] |
| Alzheimer's disease pathology | | | |
| β-Amyloid | 4.8 [4.7] | 3.2 | [0.0-19.9] |
| Tangles | 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** | | ***p*-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 | 64 | 27.1 | | |
| Other dementia | 6 | 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 |
| | **N** | **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.