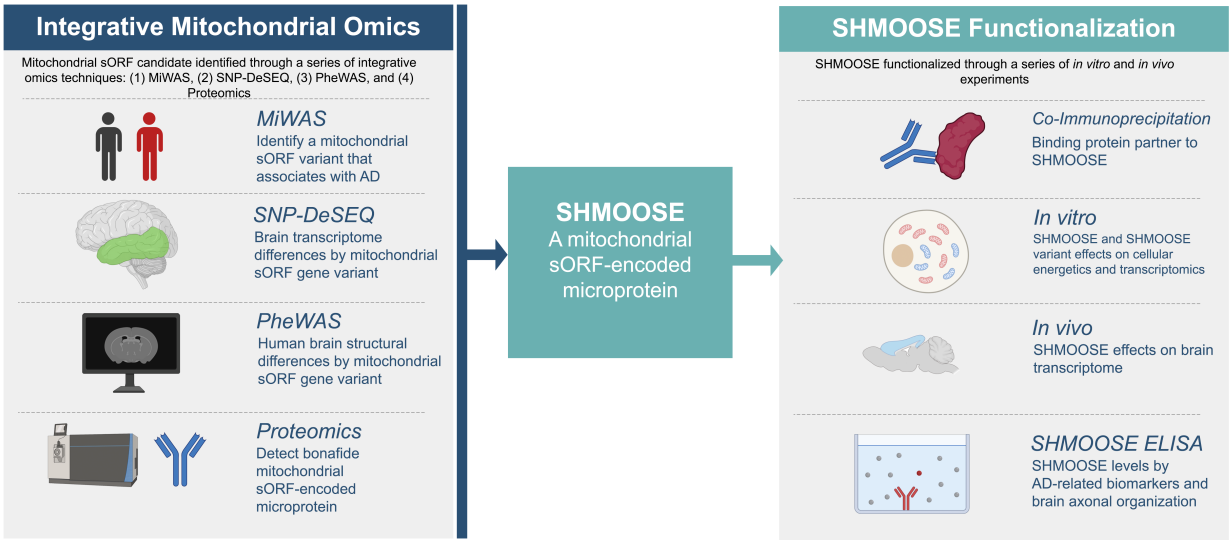

Fig. S1. Implemented workflow starting with human omics data to microprotein functionalization

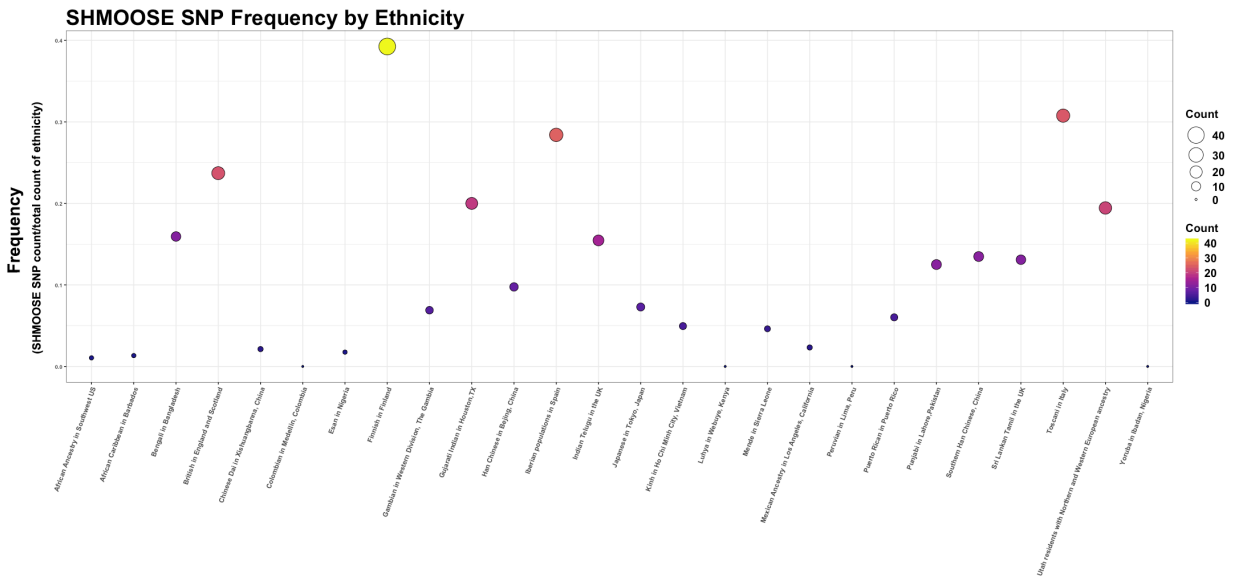

Fig. S2. SHMOOSE mtSNP (at base pair position 12372) frequency in 1000 Genomes Project.

On the x-axis are individuals sampled from respective locations. Count and size of the bubble per population indicates number of individuals with the SHMOOSE mtSNP. On the y-axis is frequency of the SNP within the population. For example, Finnish individuals from Finland have nearly a 40% frequency of the SHMOOSE mtSNP.

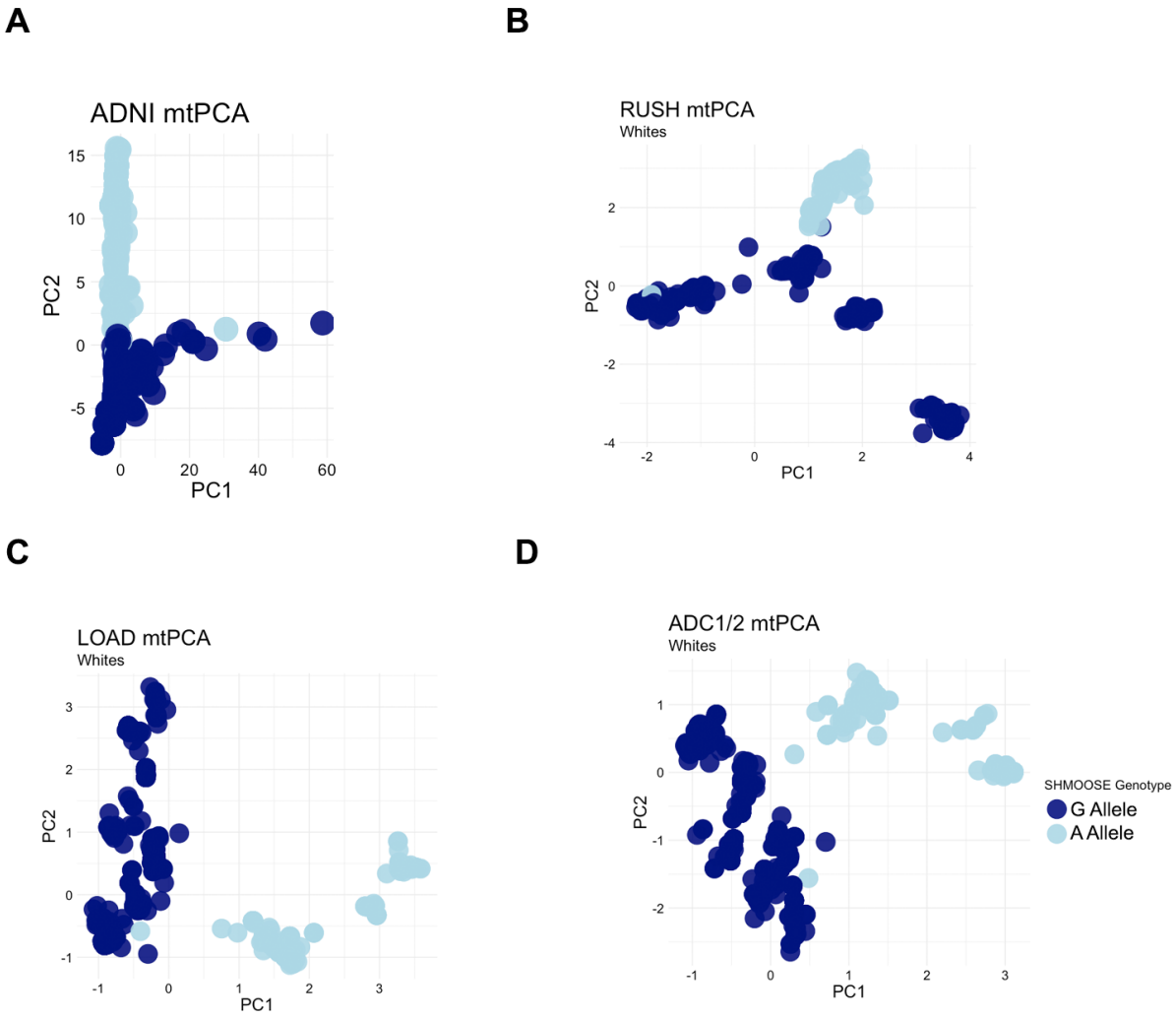

Fig. S3. Mitochondrial-DNA principal component analyses per cohort.
(A) mtPCA within the ADNI cohort. SHMOOSE A allele carriers cluster together. **(B)** RUSH ROSMAP mtPCA. SHMOOSE A allele carriers also appear to cluster together. **(C)** mtPCA within the LOAD cohort. SHMOOSE A allele carriers are within three distinct clusters. **(D)** mtPCA within the ADC1/2 cohort. SHMOOSE A allele carriers are within three distinct clusters.

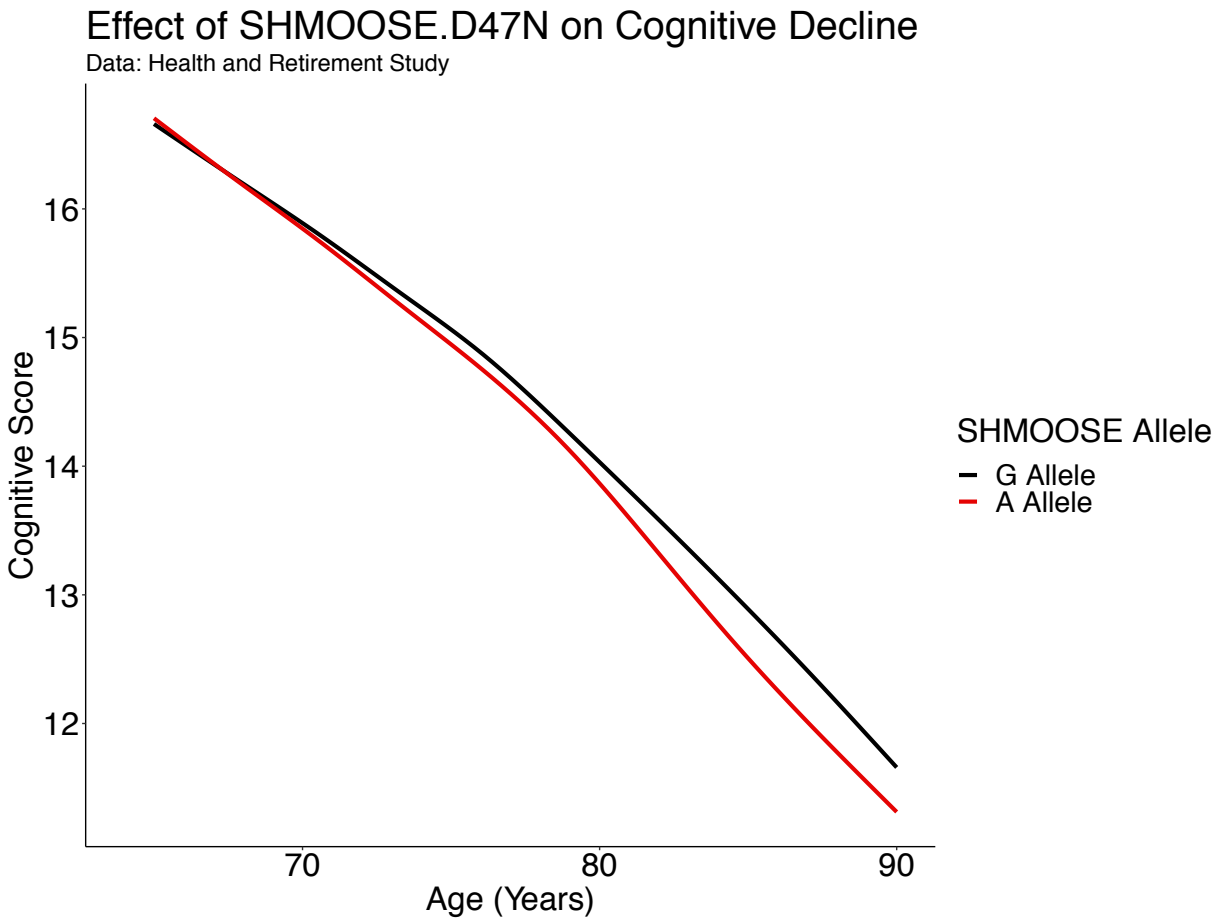

Fig. S4. SHMOOSE mtSNP associates with faster cognitive decline.
Individuals with the SHMOOSE mtSNP (A allele) were predicted to have accelerated cognitive decline. Model shows effects estimated from a mixed effects growth model. Red trajectories represent *SHMOOSE.D47N* carriers. Effects estimated starting at age 65 years old.

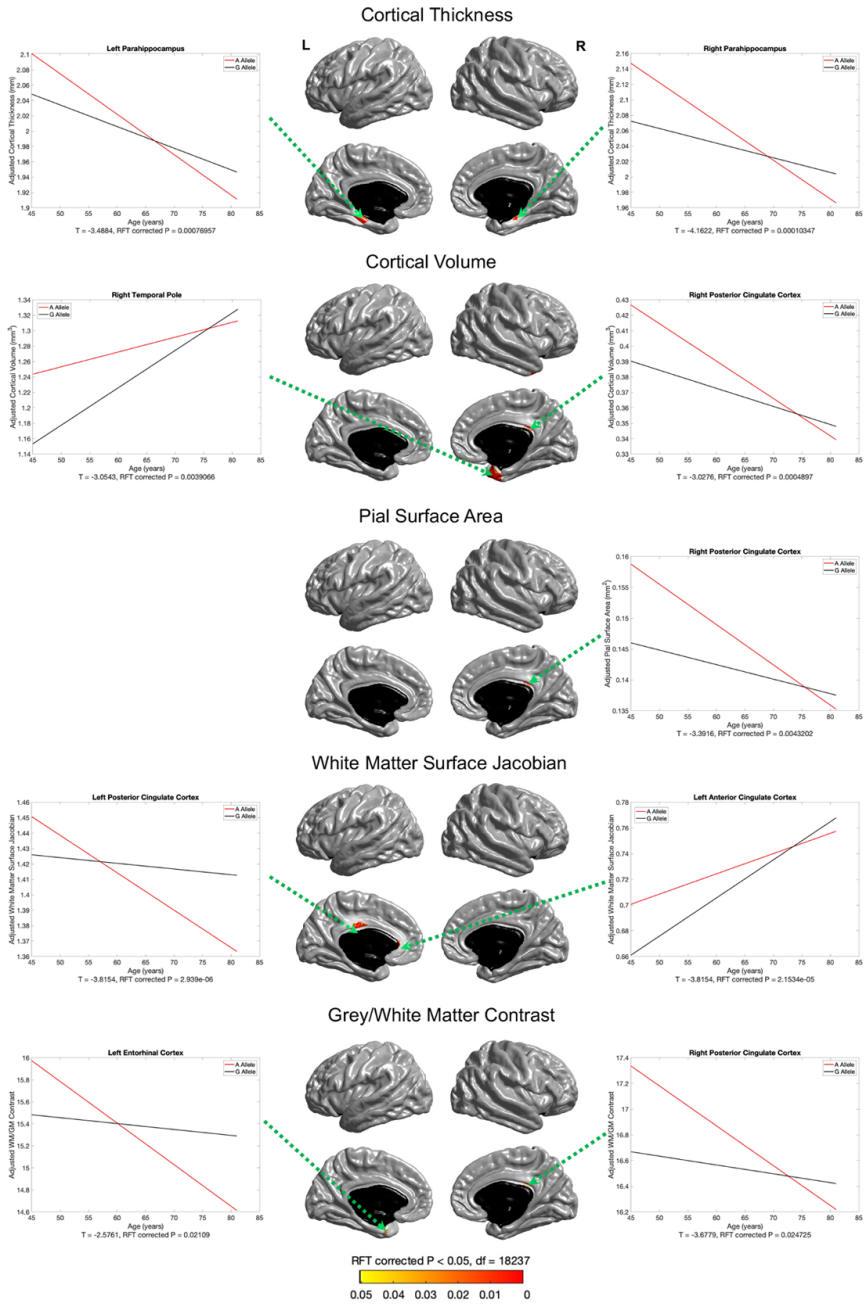

Fig. S5. Neuroimaging-based PheWAS in UK Biobank that illustrates the significant effects of SHMOOSE.D47N and age on respective neuroimaging markers. *SHMOOSE.D47* significantly associated with cortical thickness, volume, pial surface area, WM surface Jacobian, and GM/WM contrast in several paralimbic regions, including the parahippocampal gyri, the entorhinal cortex (EC), the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC), and the temporal pole (TPO) (clusterwise, RFT-corrected p value < 0.05. Color represents p value.

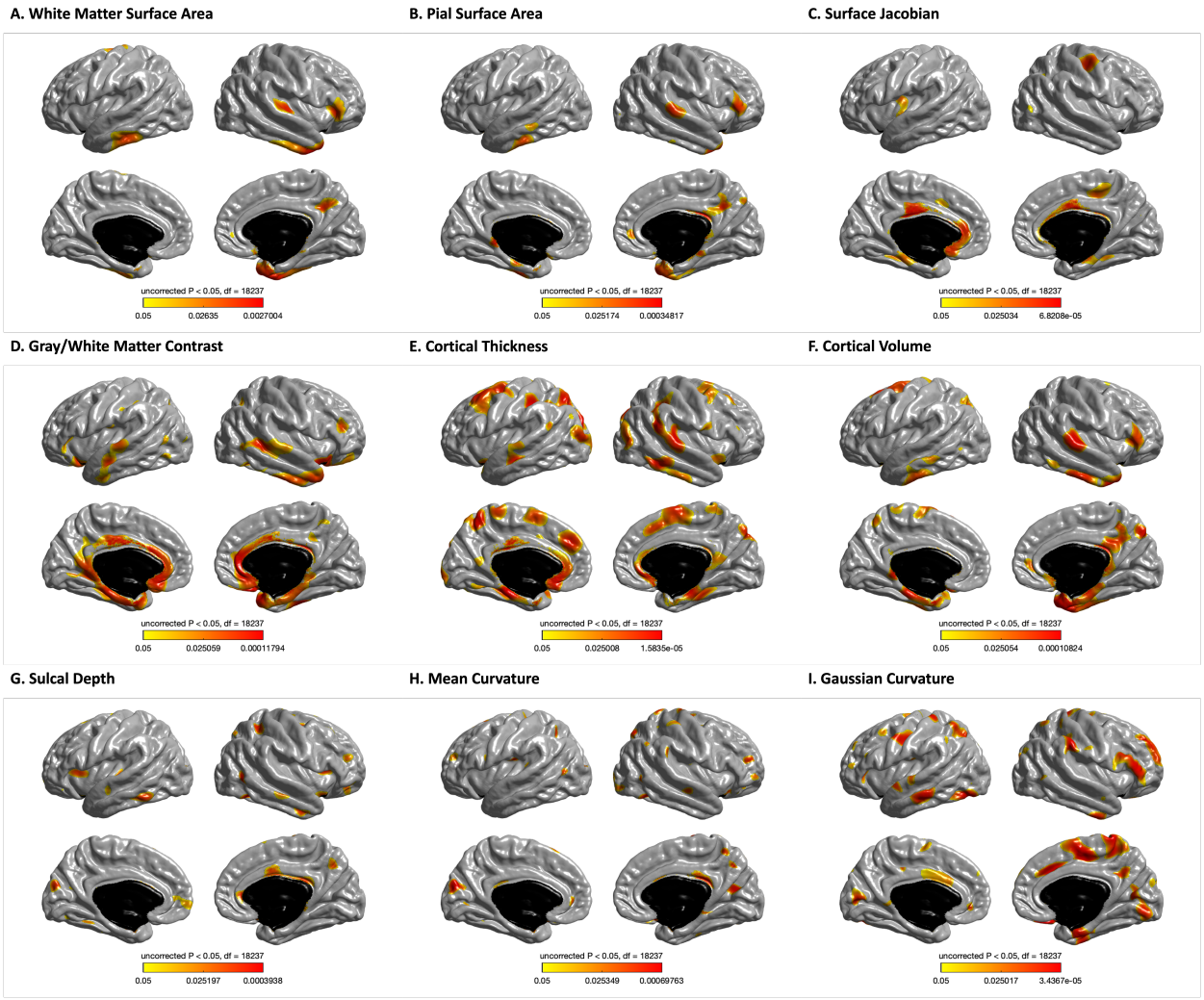

Fig. S6. In UKB, the effects of *SHMOOSE.D47N* in the language centers (superior temporal and inferior frontal gyri), dorsolateral and medial prefrontal cortex, central motor, and occipital visual cortices. (A-I) In order, white matter surface area, pial surface area, surface jacobian, gray/white matter contrast, cortical thickness, cortical volume, sulcal depth, mean curvature, and gaussian curvature modeled. Color indicates *p* value. Effects are shown with lenient, uncorrected *p* value < 0.05.

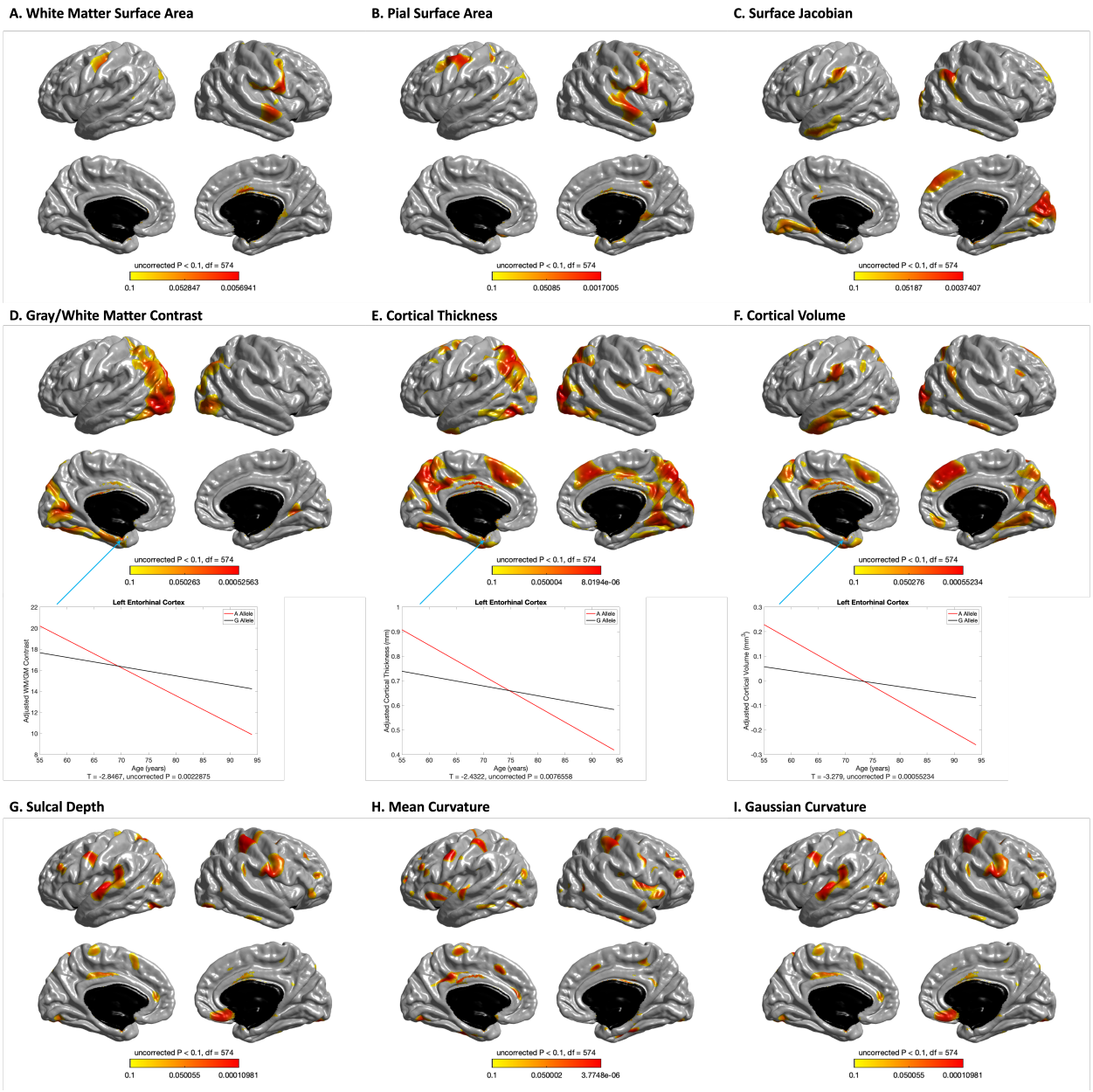

Fig. S7. In ADNI, effects of *SHMOOSE*.D47N limbic regions such as the medial temporal cortex and posterior cingulate cortex at a lenient threshold of uncorrected p value < 0.05. (A-I). In order, white matter surface area, pial surface area, surface jacobian, gray/white matter contrast, cortical thickness, cortical volume, sulcal depth, mean curvature, and gaussian curvature modeled. Color indicates *p* value. Effects are shown with lenient, uncorrected *p* value

< 0.05. In **(D-F)**, interactions between SHMOOSE mtSNP and age are shown.

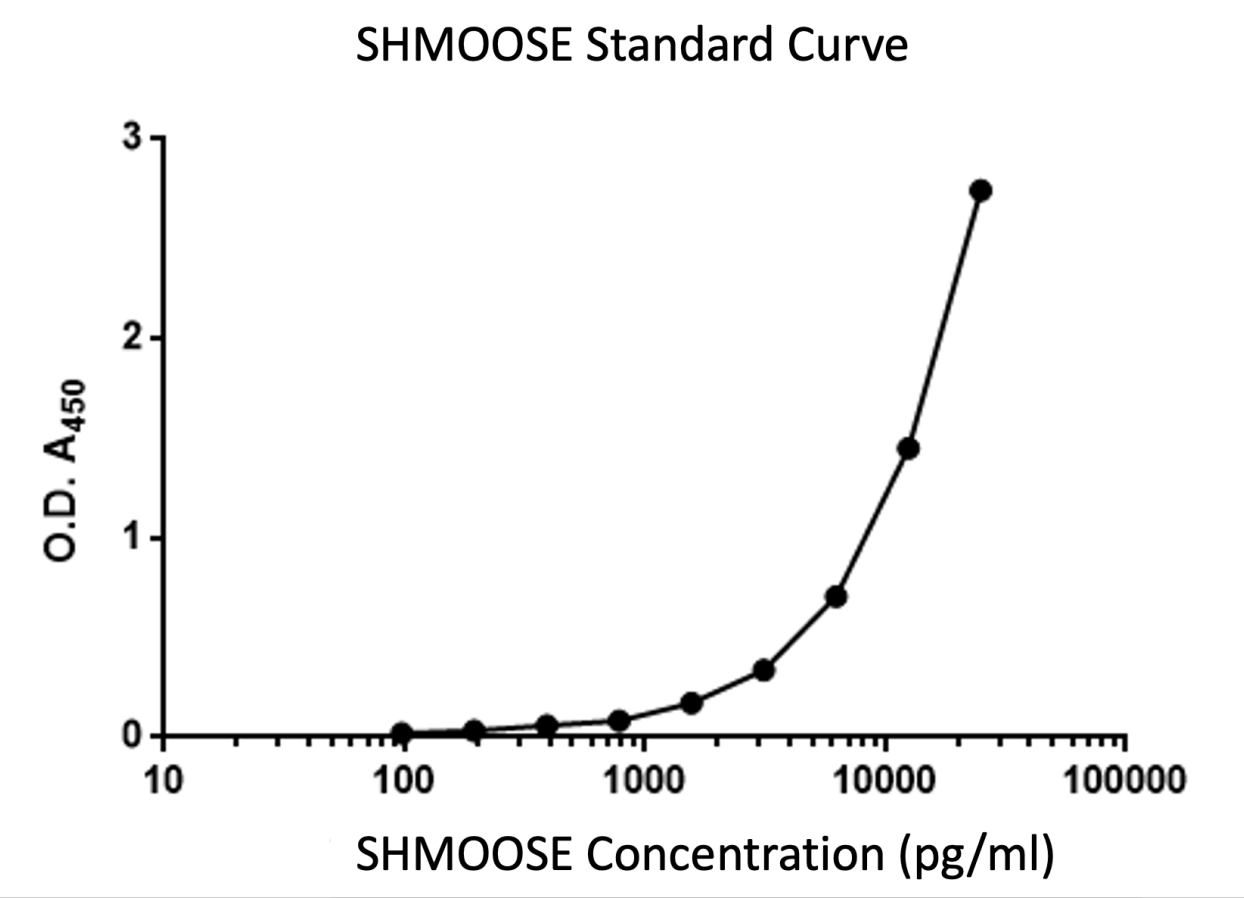

Fig. S8. Standard Curve of SHMOOSE ELISA.
The range of the standard curve is 100-250,000 pg/ml.

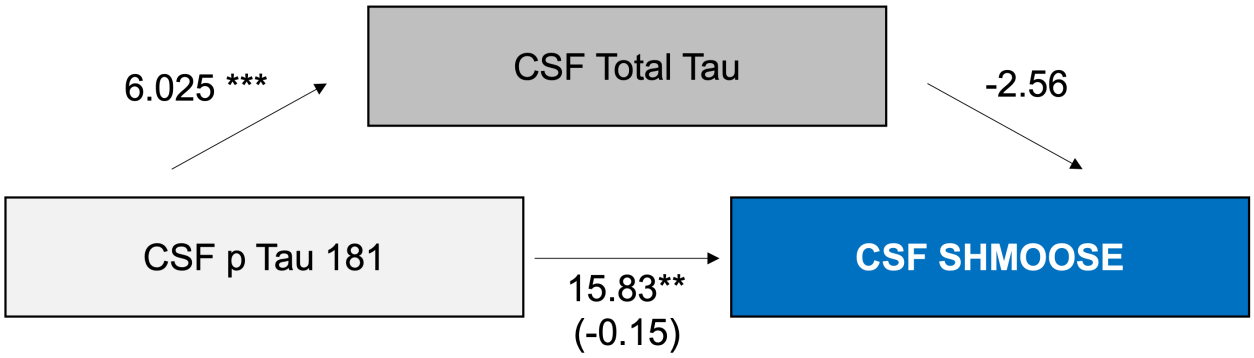

Fig. S9. Effects of p Tau 181 on SHMOOSE with tau as a mediator.
The indirect effect (ACME) is not significant (-0.15) below the combined indirect and direct (ADE) (15.83; *p* value < 0.01). The effect of p tau 181 on total was significant (6.025; *p* value < 0.01), while the effect of total tau on SHMOOSE when controlling for p tau 181was not significant (-2.56).

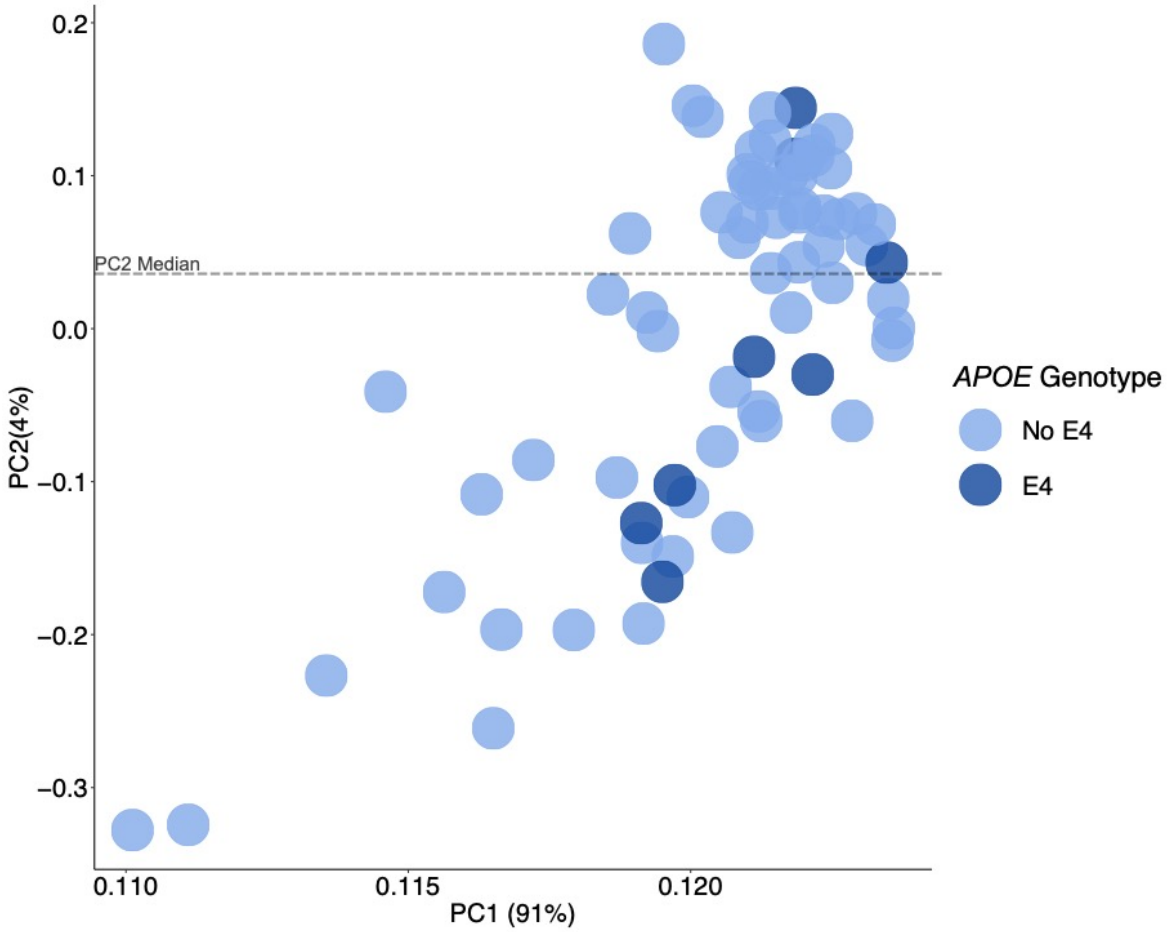

Fig. S10. Principal component analysis (PCA) color coded to represent the 8 *APOE4* carriers. Dashed line represents the median value of PC2. While not statistically significant, 5 of the 8 *APOE4* carriers fall below the PC2 median.