Polygenic Risk for Alzheimer's Disease in Healthy Aging: Age-related and APOE-driven Effects on Brain Structures and Cognition

Fig. S1: Flow chart of the study

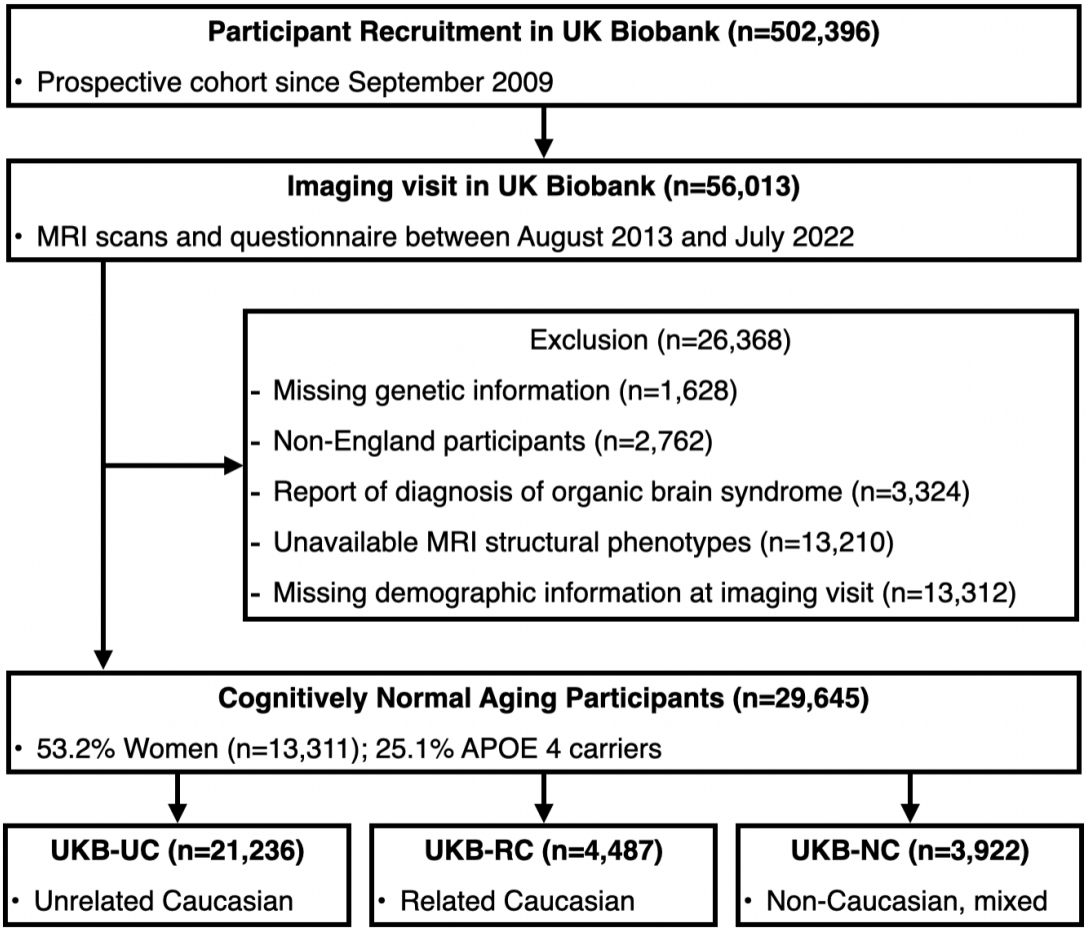

Fig. S1 Flow chart of the study. UKB-UC: Unrelated Caucasian; UKB-RC: Related Caucasian; UKB-MIX: Non-Caucasian.

Fig. S2: Correlations among AD-PRSs

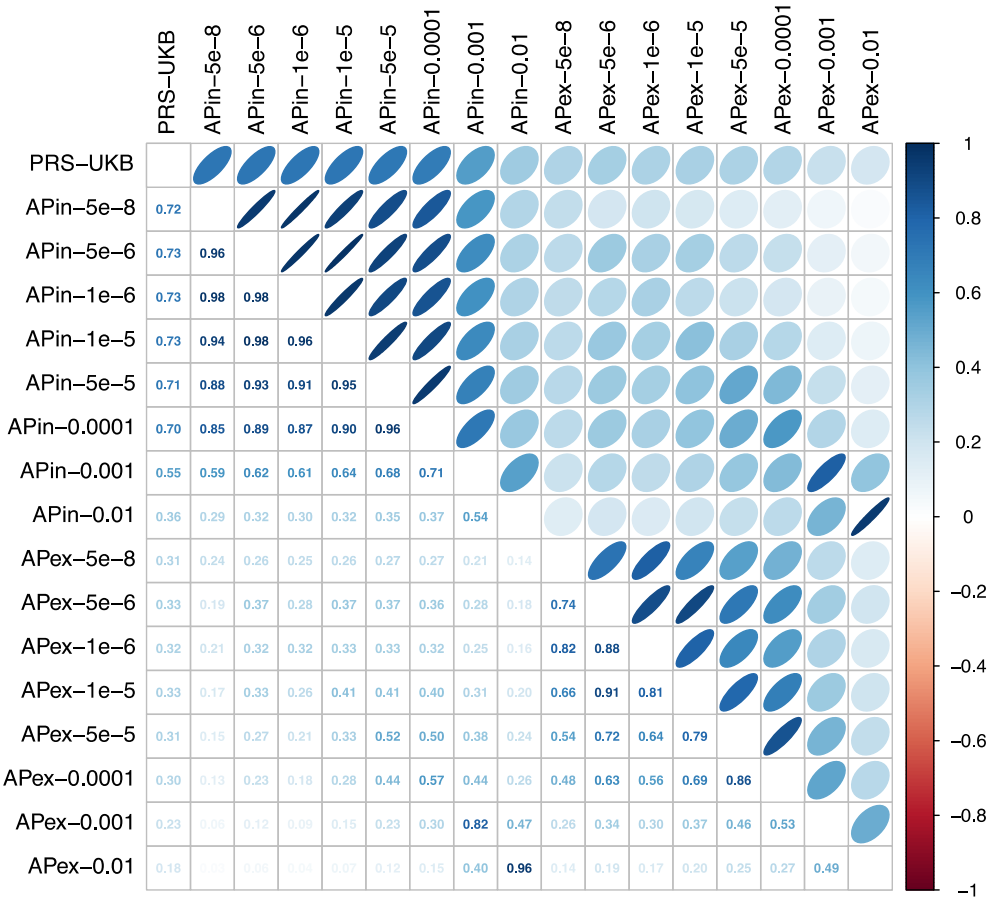

Fig. S2 Correlations among AD-PRSs across thresholds. AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S3 Window size selection of quantitative sliding window analysis

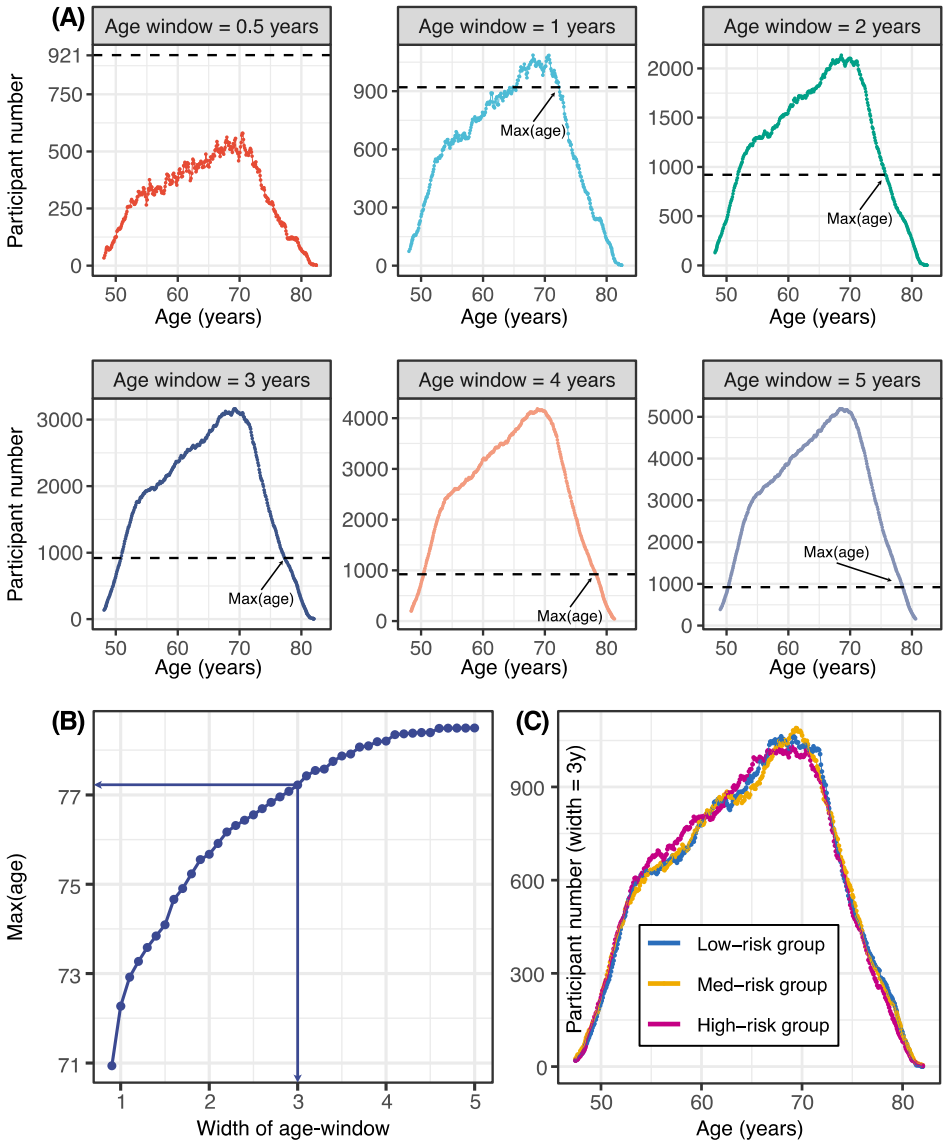

Fig. S3 Window size selection of quantitative sliding window analysis. (**A**) Participant number within each window across window sizes. (**B**) Maximum age of the windows meeting the statistical power of small polygenic effects (N=921). **(C)** The distribution of participants across age for each risk tertile, demonstrating a balanced risk distribution within the 3-year window. This window width was selected to optimize the balance between statistical power and age-specific resolution. The distribution of participant numbers as well as overlapping between consecutive windows across varied window widths are available in online Tables (See Availability of data and materials).

Fig. S4 Principal component analysis

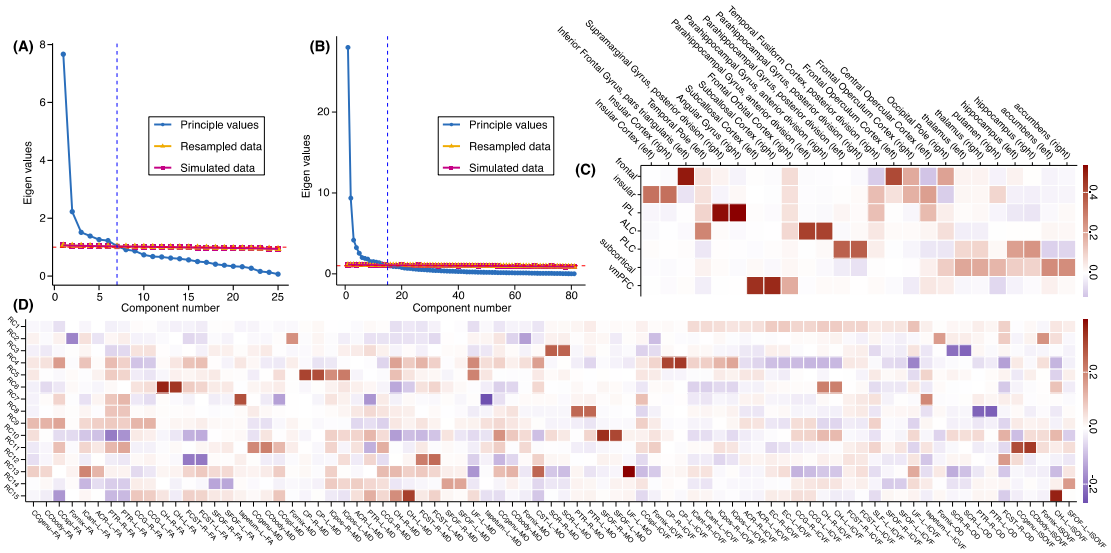

Fig. S4 Principal component analysis (PCA). (A) Scree plot for GM components. GM, grey matter. **(B)** Scree plot for WM components. WM, white matter. **(C)** Factor loadings for GM PCA. IPL, inferior parietal lobe; ALC: anterior limbic component; PLC: posterior limbic component; vmPFC: ventral medial prefrontal cortex. **(D)** Factor loadings for WM PCA. PCA was performed across regional imaging measures showed biologically plausible associations (p <0.05) with PRS-UKB among participants aged ≥75 years (N = 1,663). FA: fractional anisotropy; MD: mean diffusivity; MO: mode of anisotropy; ICVF: intracellular volume fraction; ISOVF: isotropic or free water volume fraction; OD: orientation dispersion index.

Fig. S5 Regional sensitive IDPs

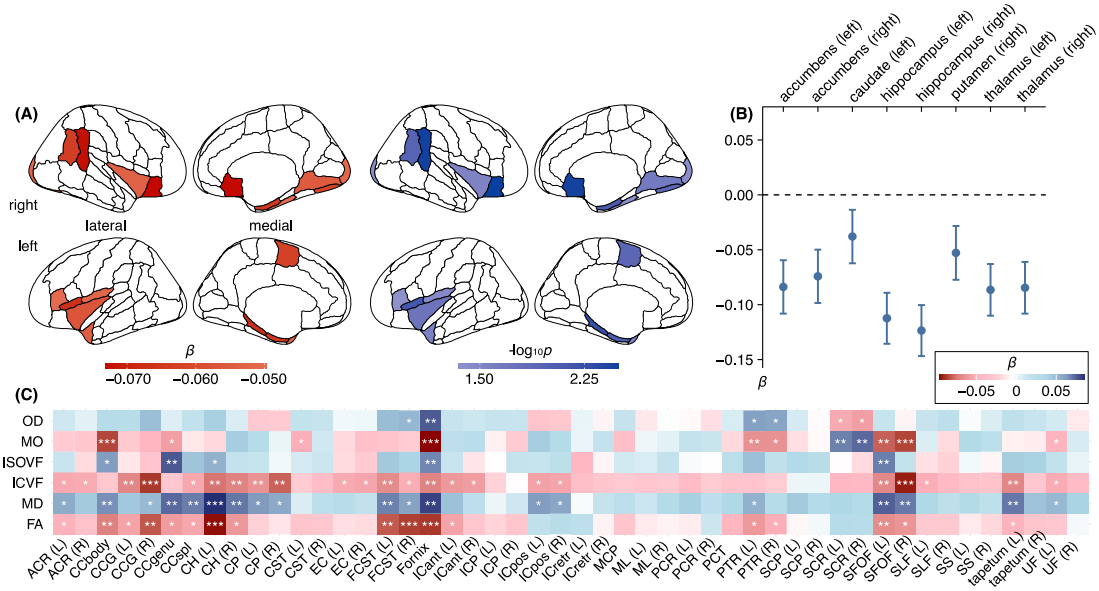

Fig. S5 Regional Sensitive IDPs. Defined as IDPs showed biologically plausible associations (p <0.05, sensitive IDPs) with AD-PRS among participants aged ≥75 years (N = 1,663). AD-PRS: Alzheimer's disease polygenic risk score with UK Biobank's standard PRS; IDP: imaging-derived phenotypes. **(A)** Regional distribution of the effect of AD-PRS on the cortical volumes of sensitive IDPs. **(B)** Regional distribution of the effect of AD-PRS on the tract-wise white matter integrity of sensitive IDPs. **(C)** Regional distribution of the effect of AD-PRS on the tract-wise white matter integrity of sensitive IDPs. FA: fractional anisotropy; MD: mean diffusivity; MO: mode of anisotropy; ICVF: intracellular volume fraction; ISOVF: isotropic or free water volume fraction; OD: orientation dispersion index. '***': $p < 0.001$; '**': $p < 0.01$; '*': $p < 0.05$

Fig. S6 Aging trajectories of the volumes of subcortical regions with different AD-PRS

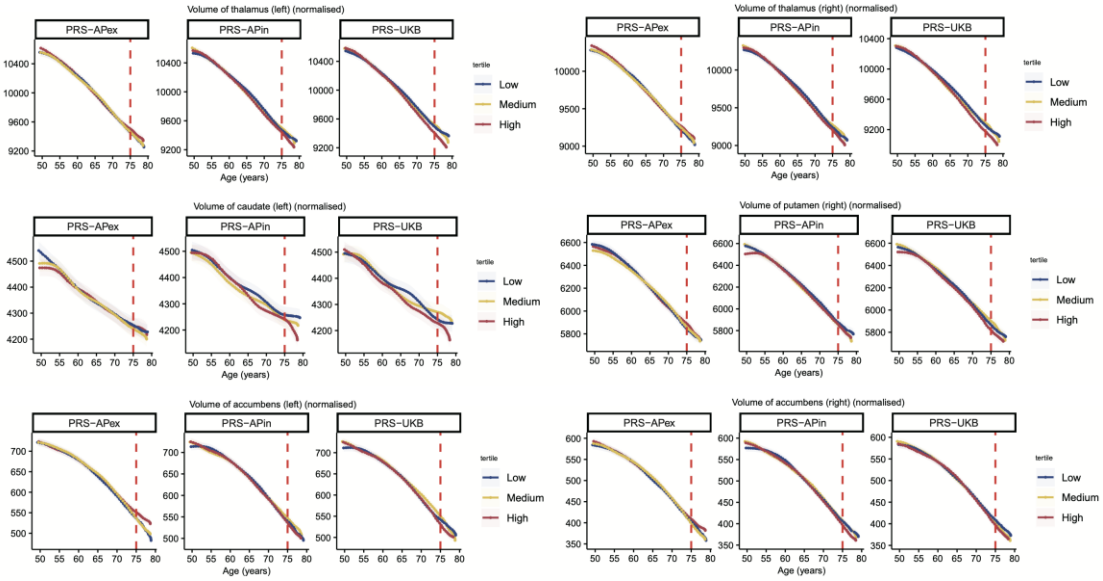

Fig. S6 Aging trajectories of the volumes of subcortical regions with different AD-PRS. AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S7 Aging trajectories of the volumes of parahippocampal regions with different AD-PRS

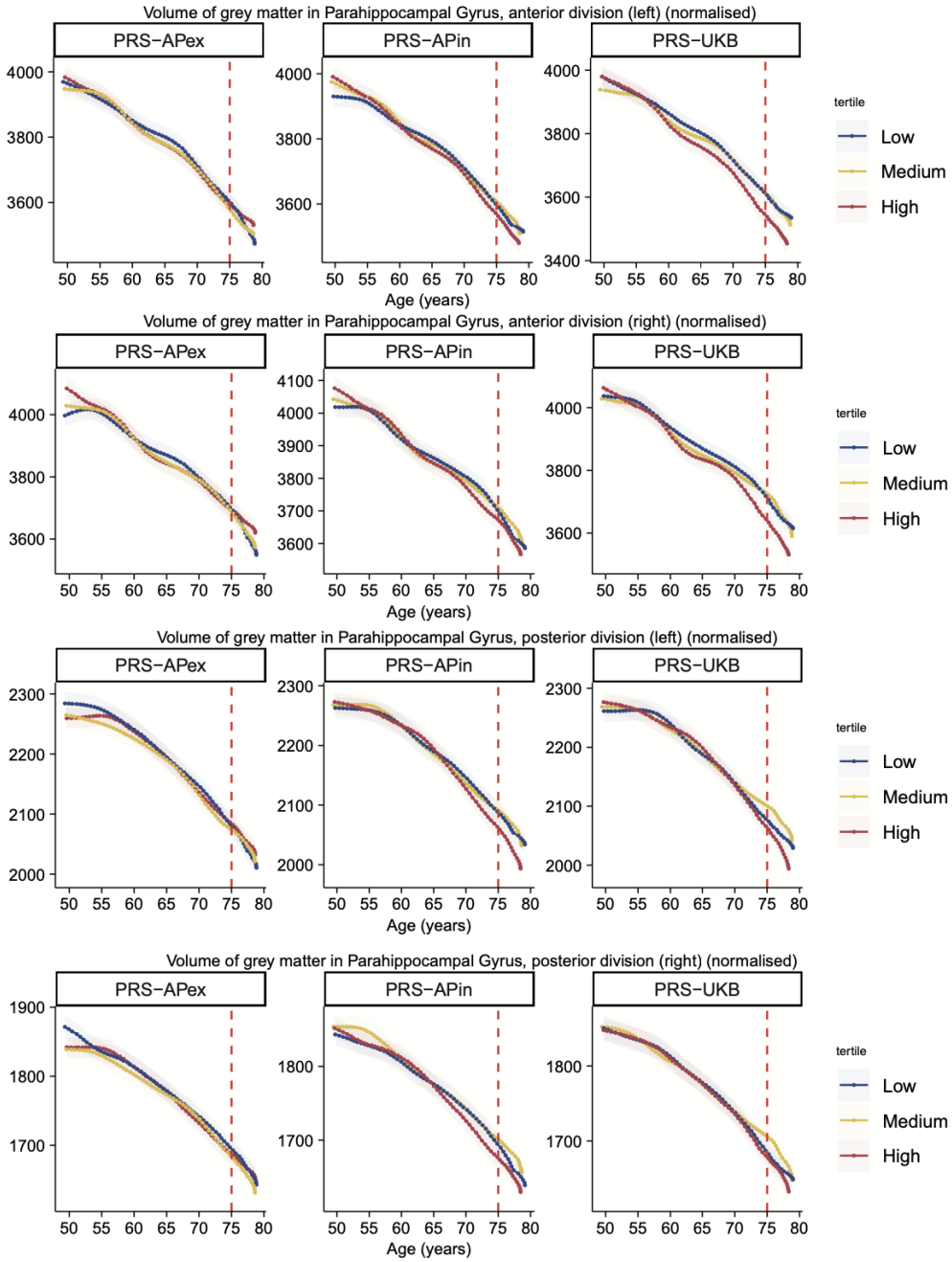

Fig. S7 Aging trajectories of the volumes of parahippocampal regions with different AD-PRS. AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S8 Aging trajectories of the volumes of cortical regions with different AD-PRS

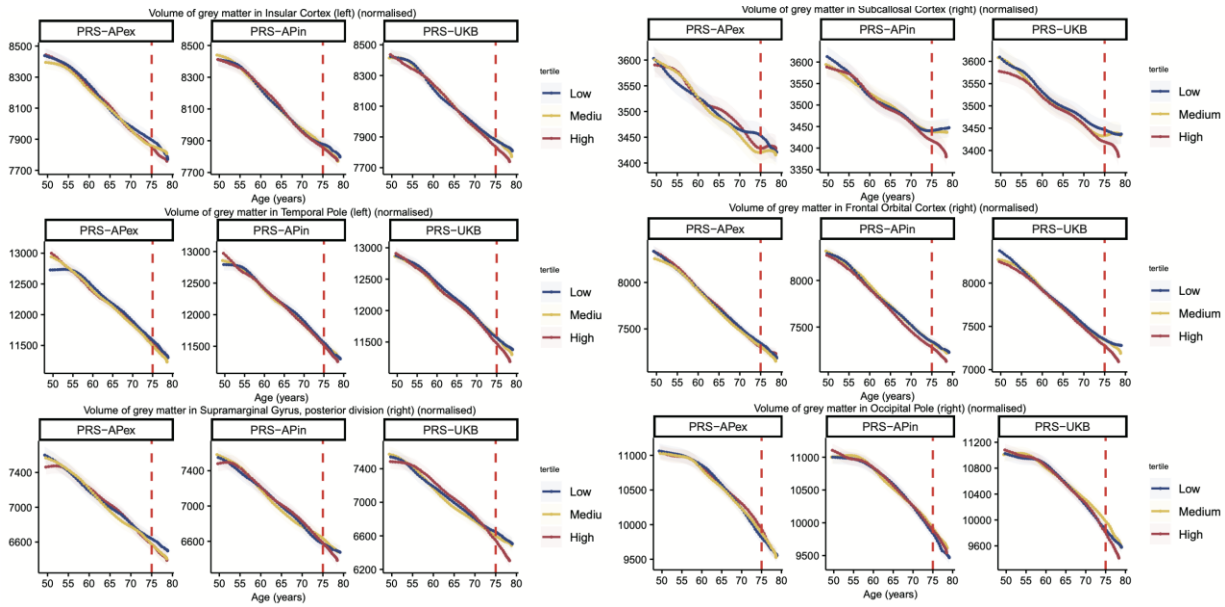

Fig. S8 Aging trajectories of the volumes of cortical regions with different AD-PRS. AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S9 Age-related standardized effects of different AD-PRS on the volumes of subcortical regions

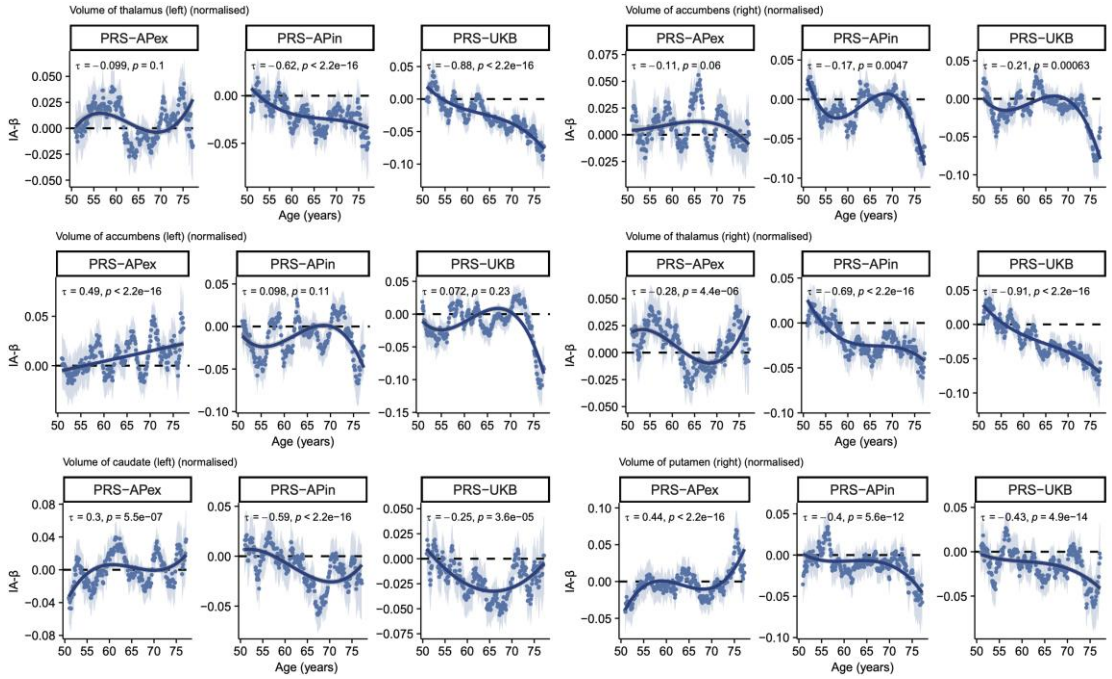

Fig. S9 Age-related standardized effects of different AD-PRS on the volumes of subcortical regions. IA-β: intra-age standard regression coefficient of AD-PRS; AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S10 Age-related standardized effects of different AD-PRS on the volumes of parahippocampal regions

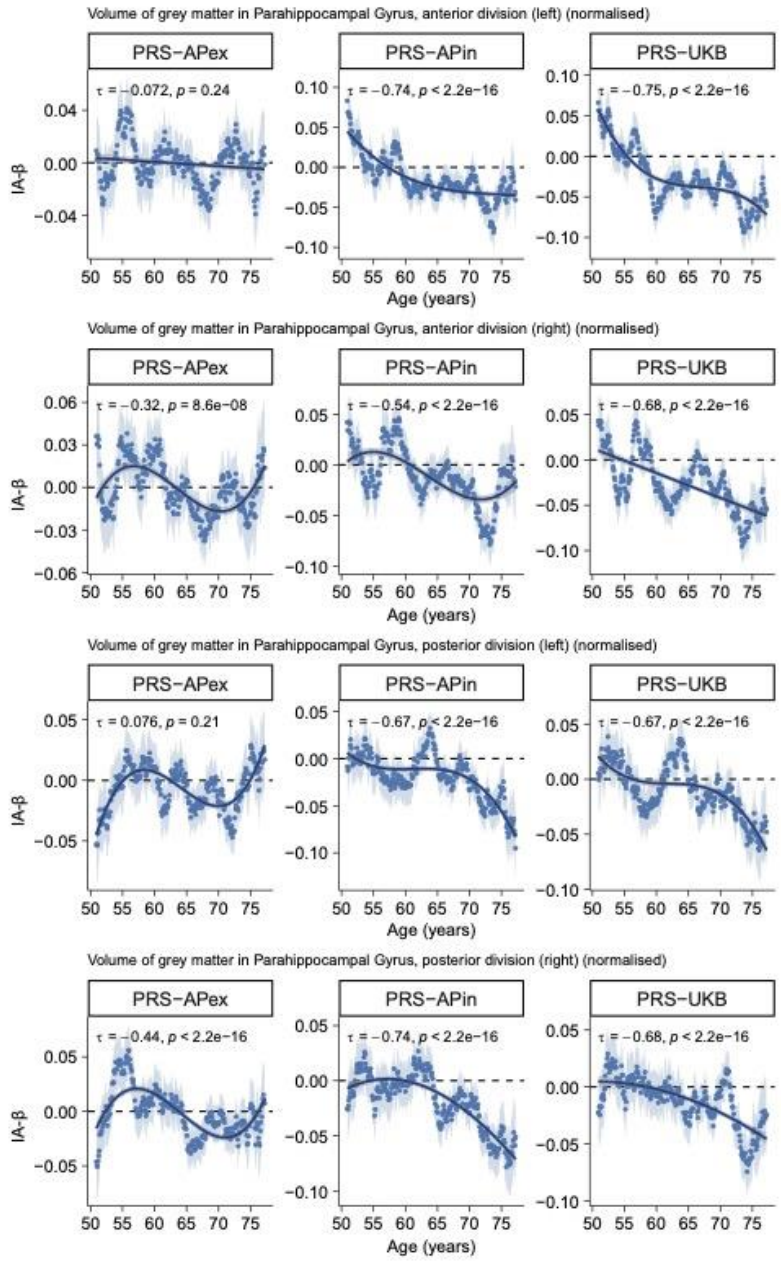

Fig. S10 Age-related standardized effects of different AD-PRS on the volumes of parahippocampal regions. IA-*β*: intra-age standard regression coefficient of AD-PRS; AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S11 Age-related standardized effects of different AD-PRS on the volumes of cortical regions

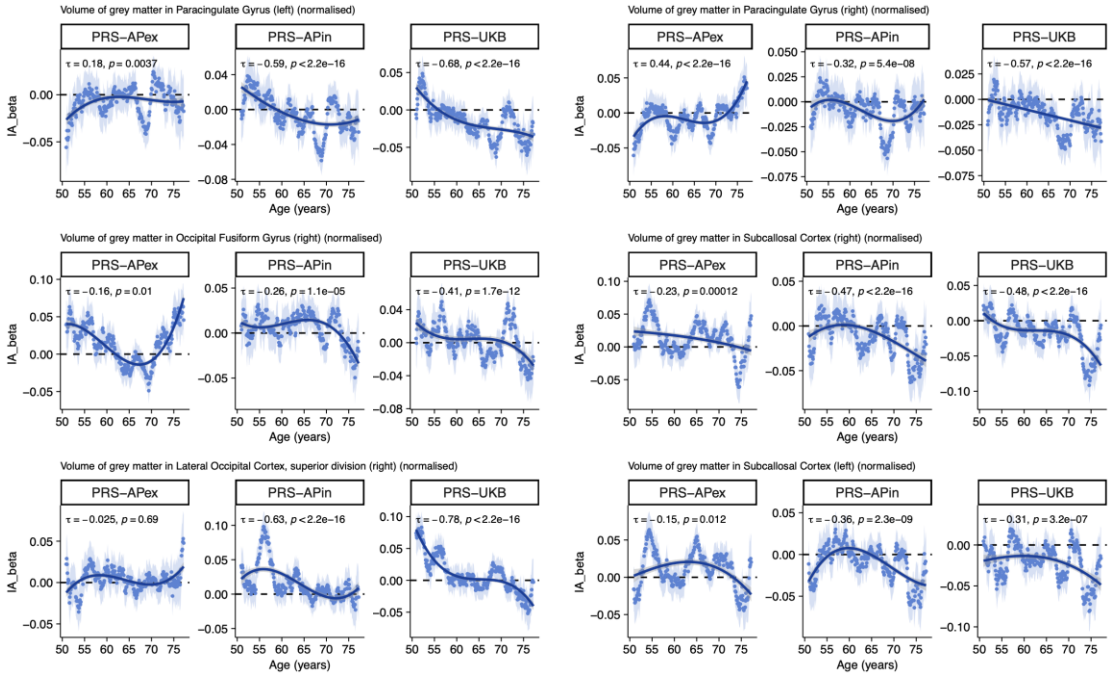

Fig. S11 Age-related standardized effects of different AD-PRS on the volumes of cortical regions. IA-β: intra-age standard regression coefficient of AD-PRS; AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S12 Age-related standardized effects of AD-PRS on the microstructural integrity of FCST and SFOF

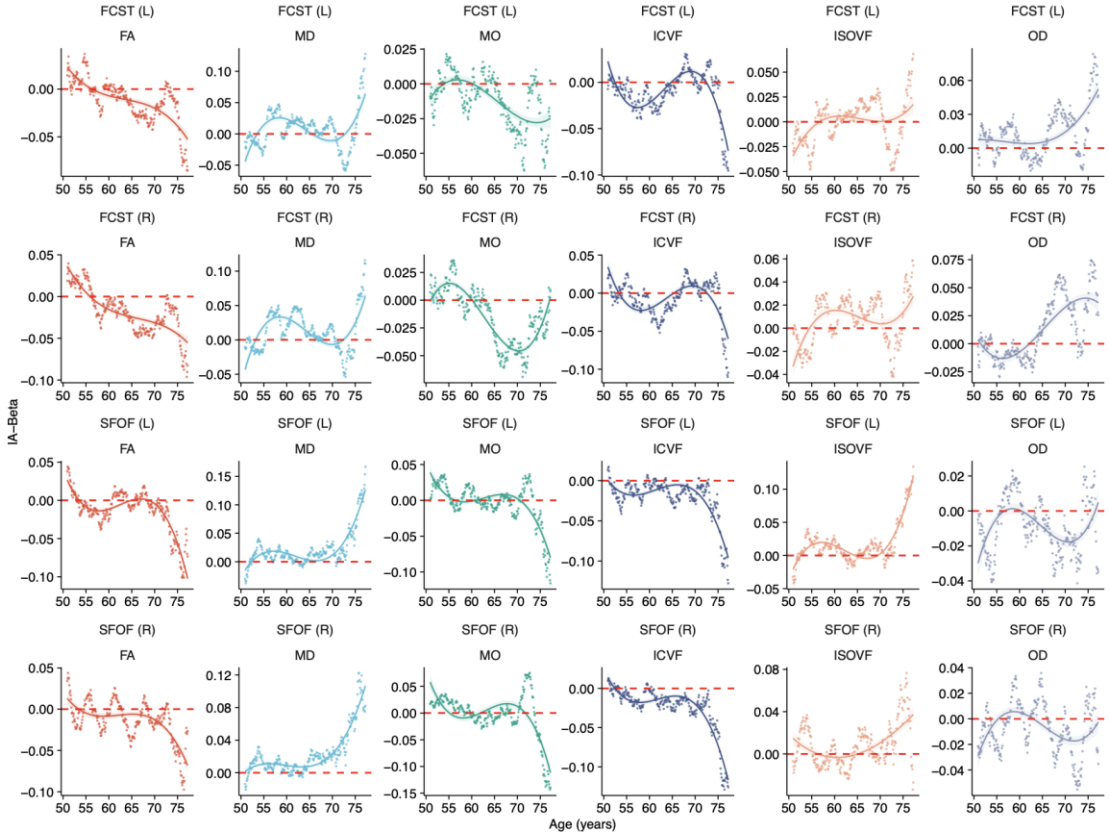

Fig. S12 Age-related standardized effects of AD-PRS on the microstructural integrity of FCST and SFOF. IA-*β*: intra-age standard regression coefficient of AD-PRS; AD-PRS: Alzheimer's disease polygenic risk score, using UK Biobank's standard AD-PRS; FCST: the fornix crus & stria terminalis; SFOF: superior fronto-occipital fasciculus; FA: fractional anisotropy; MD: mean diffusivity; MO: mode of anisotropy; ICVF: intracellular volume fraction; ISOVF: isotropic or free water volume fraction; OD: orientation dispersion index.

Fig. S13 Age-related standardized effects of different AD-PRS on the unnormalized volumes

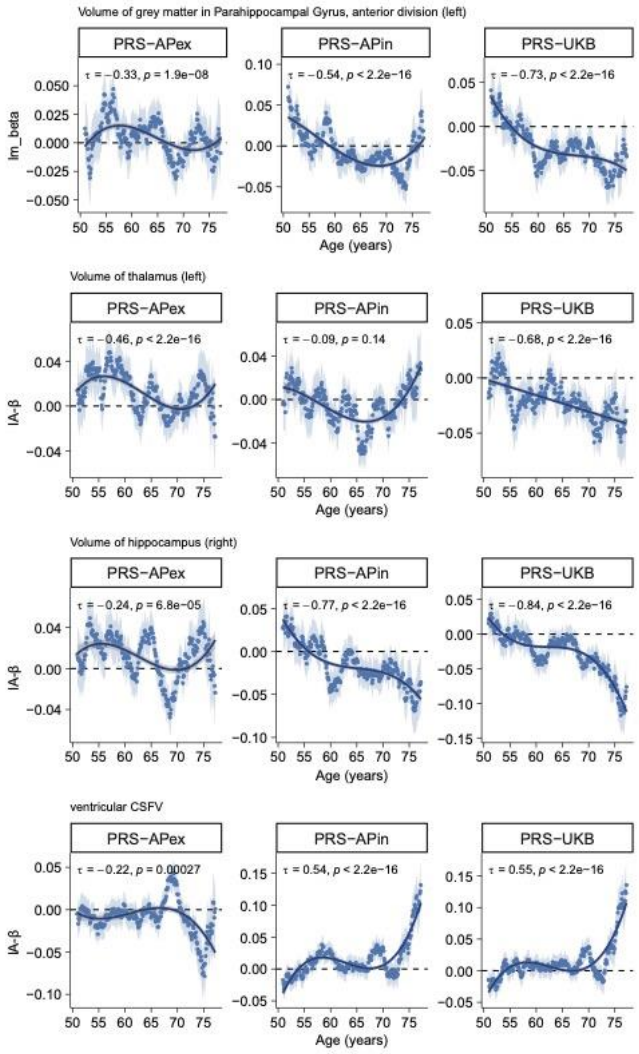

Fig. S13 Age-related standardized effects of different AD-PRS on the unnormalized volumes. IA-*β*: intra-age standard regression coefficient of AD-PRS; AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S14 Aging trajectories of the volumes of subcortical regions with different AD-PRS and FAST segmentation

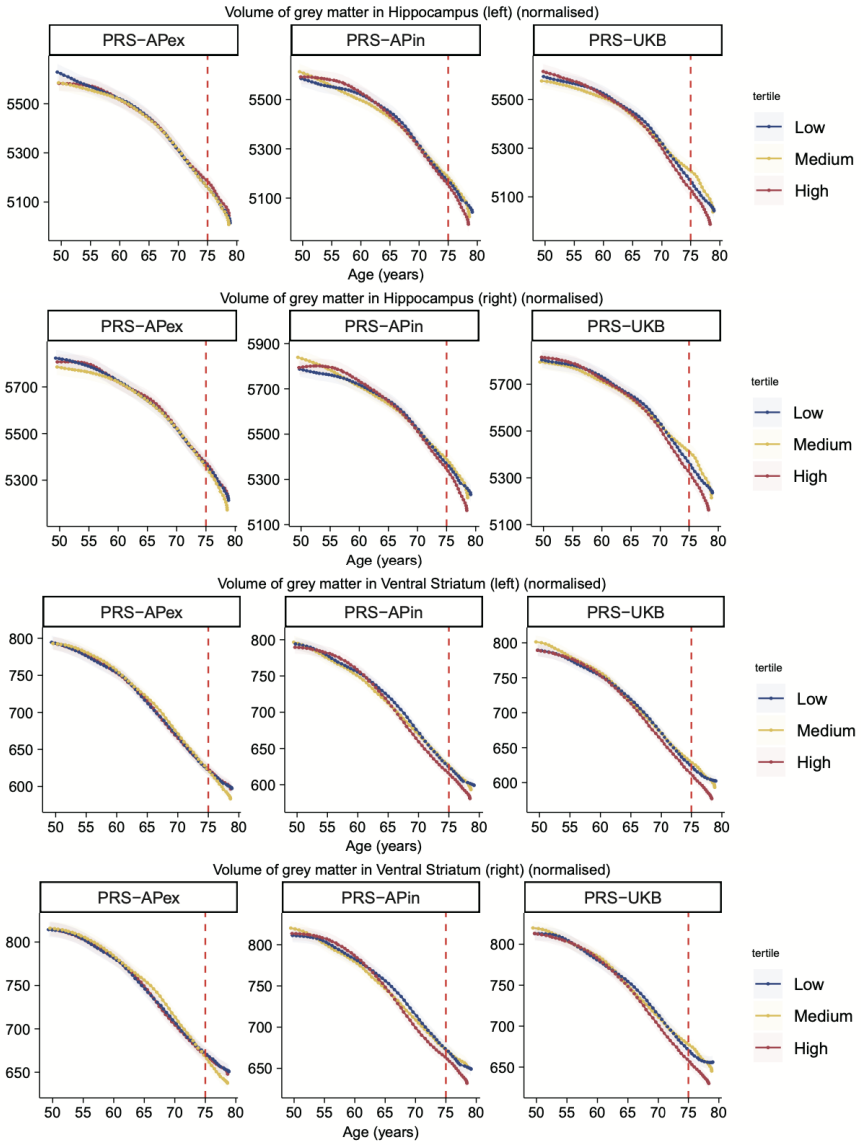

Fig. S14 Aging trajectories of the volumes of subcortical regions with different AD-PRS and FAST segmentation. AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S15 Age-related standardized effects of different AD-PRS on the volumes of subcortical regions with FAST segmentation

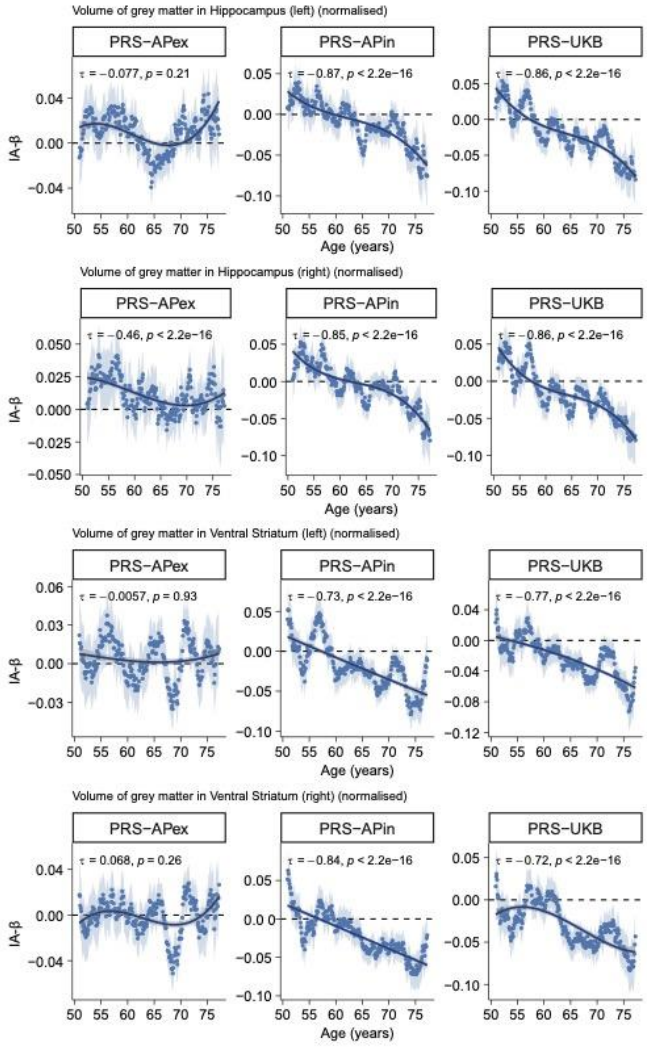

Fig. S15 Age-related standardized effects of different AD-PRS on the volumes of subcortical regions with FAST segmentation. IA-*β*: intra-age standard regression coefficient of AD-PRS; AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS

Fig. S16 Mediation analysis with GM components

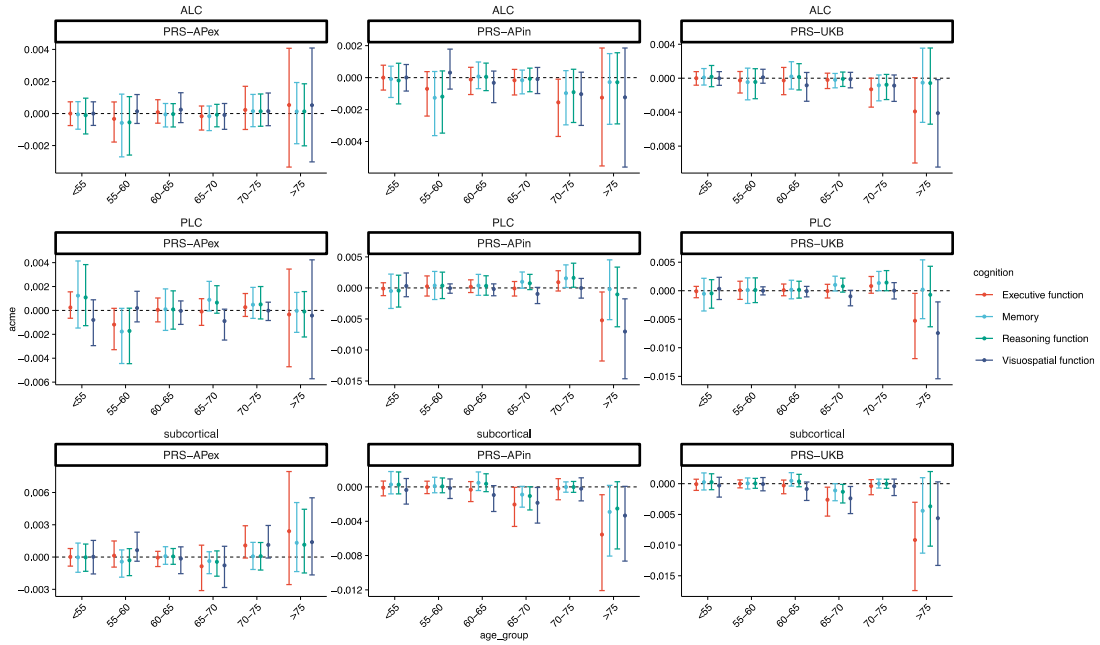

Fig. S16 Mediation analysis with GM components. GM: grey matter; ACME: average causal mediation effects; AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS; ALC, anterior limbic component; PLC, posterior limbic component

Fig. S17 Mediation analysis with WM components

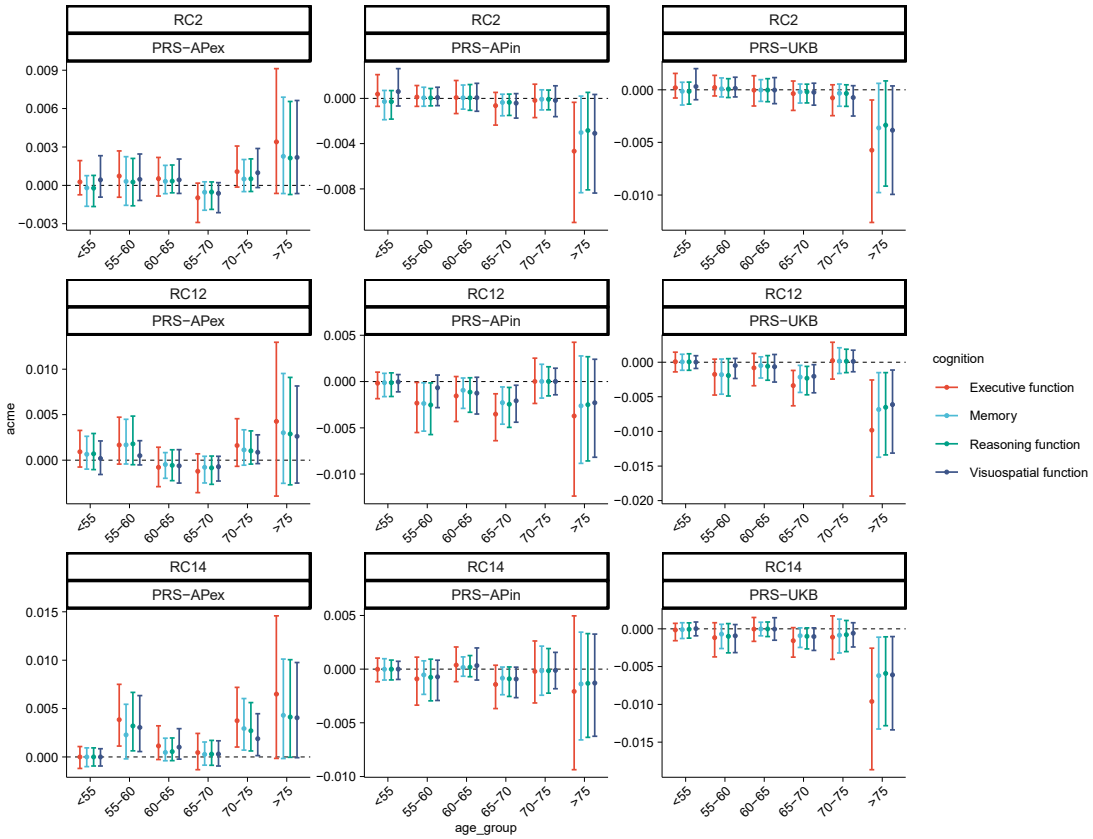

Fig. S17 Mediation analysis with WM components. WM: white matter; ACME: average causal mediation effects; AD-PRS: Alzheimer's disease polygenic risk score; PRS-APex: PRS excluding APOE; PRS-APin: PRS including APOE; PRS-UKB: UK Biobank's standard AD-PRS; ALC, anterior limbic component; PLC, posterior limbic component

Fig. S18 Age-related effects of PRS-APex on brain structures

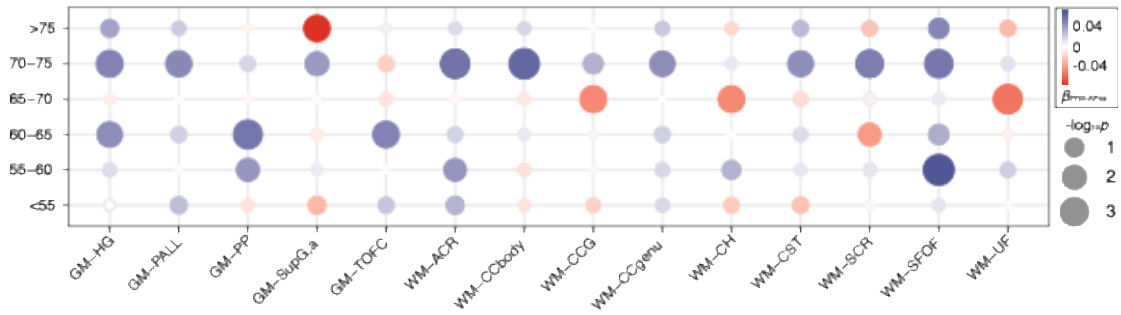

Fig. S18 Age-related effects of PRS-APex on brain structures. PRS-APex: PRS excluding APOE gene region threshed at 1×10^{-5}; APOE: apolipoprotein E; GM, grey matter; WM, white matter; HG: Heschl's gyrus; PALL: Pallidum; PP: Planum polare;SupG,a: Supramarginal gyrus, anterior division; TOFC: Temporal occipital fusiform cortex; ACR: Anterior corona radiata; CCbody: Body of corpus callosum; CCG: Cingulate gyruspart of cingulum; CCgenu: Genu of corpus callosum; CH: Cingulum hippocampus; CST: Corticospinal tract; SCR: Superior corona radiata; SFOF: Superior fronto-occipital fasciculus; UF: Uncinate fasciculus.