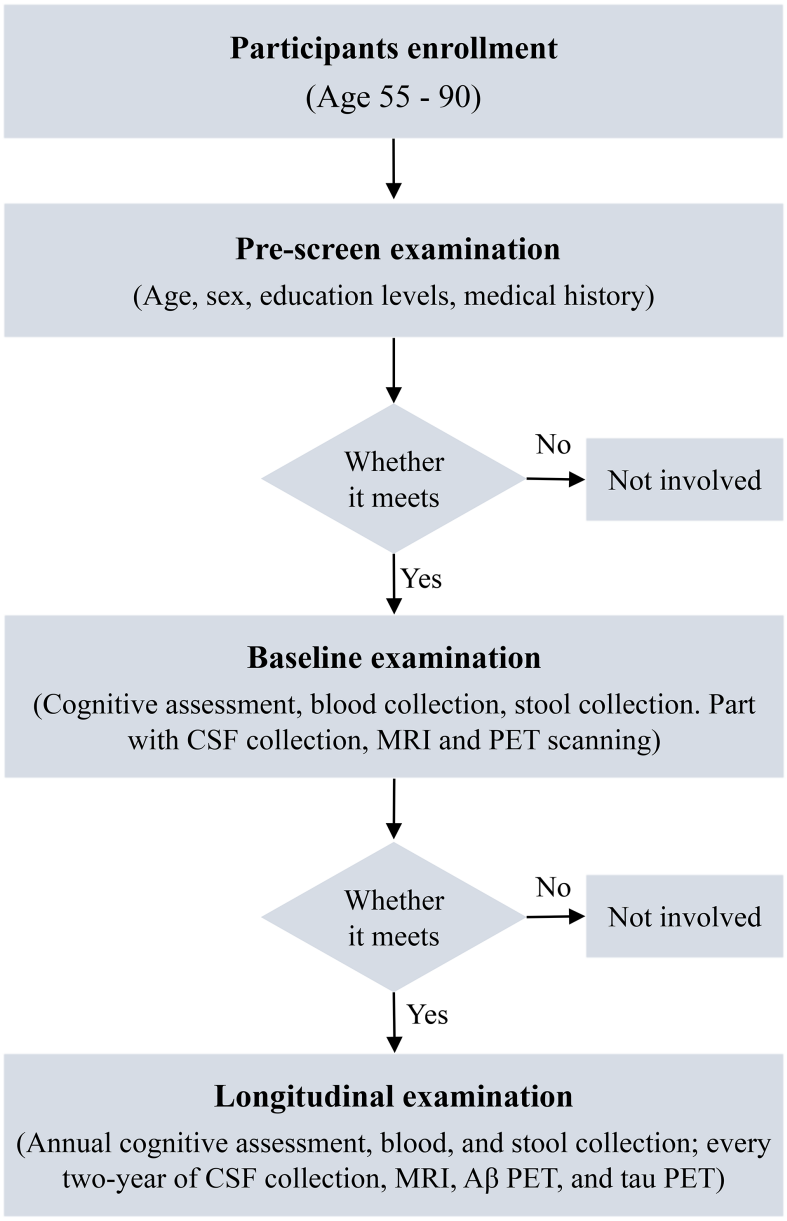
Supplementary Material

The participants' recruiting flowchart



Supplemental Figure 1. *The scheme of enrolment and follow-up of participants in the Greater-Bay-Area Healthy Aging Brain Study (GHABS).*

Inclusion and exclusion criteria

Briefly, the inclusion criteria of GHABS are as follows: (1) adults between the ages of 55 and 90 and speak Mandarin fluently (notably, individuals below 60 years old should have a family dementia history and meet the criteria of subjective cognitive decline (SCD)[25]); (2) the score on the Geriatric Depression Scale (GDS) is less than 6 points; (3) visual and auditory acuity is sufficient for neuropsychological testing (Including normal corrected vision and hearing); (4) participants are not pregnant, lactating, or have reproductive potential (that is, women must be two years after menopause or undergo sterilization surgery); (5) a modified version of the Hachinski Ischemic scores less than or equal to 4; (6) have completed primary school (6 years of education) or have good work experience (sufficient to rule out mental retardation). Individuals with an infection, infarction, or other focal lesions or multiple lacunes or lacunes in critical memory structures and who do not meet the MRI scanning requirements are excluded from the GHABS study. More details of the inclusion and exclusion criteria can be found in the supplemental materials.

This project intends to recruit men and women between the ages of 55 and 90. The inclusion criteria are as listed:

- Age 55-90 years old (including 55 and 90 years old).
- The score of the Geriatric Depression Scale (GDS) is less than 6 points.
- There is a caregiver who can maintain at least 10 hours of contact per week and can accompany volunteers to the test site for testing.
- Visual and auditory acuity is sufficient for neuropsychological testing. (Including normal corrected vision and hearing)
- Be in good health and are expected to be free of disease interference during the study.
- Volunteers are not pregnant, lactating or have reproductive potential (that is, women must be two years after menopause or undergo sterilization surgery).
- Willingness and ability to participate in longitudinal imaging studies.

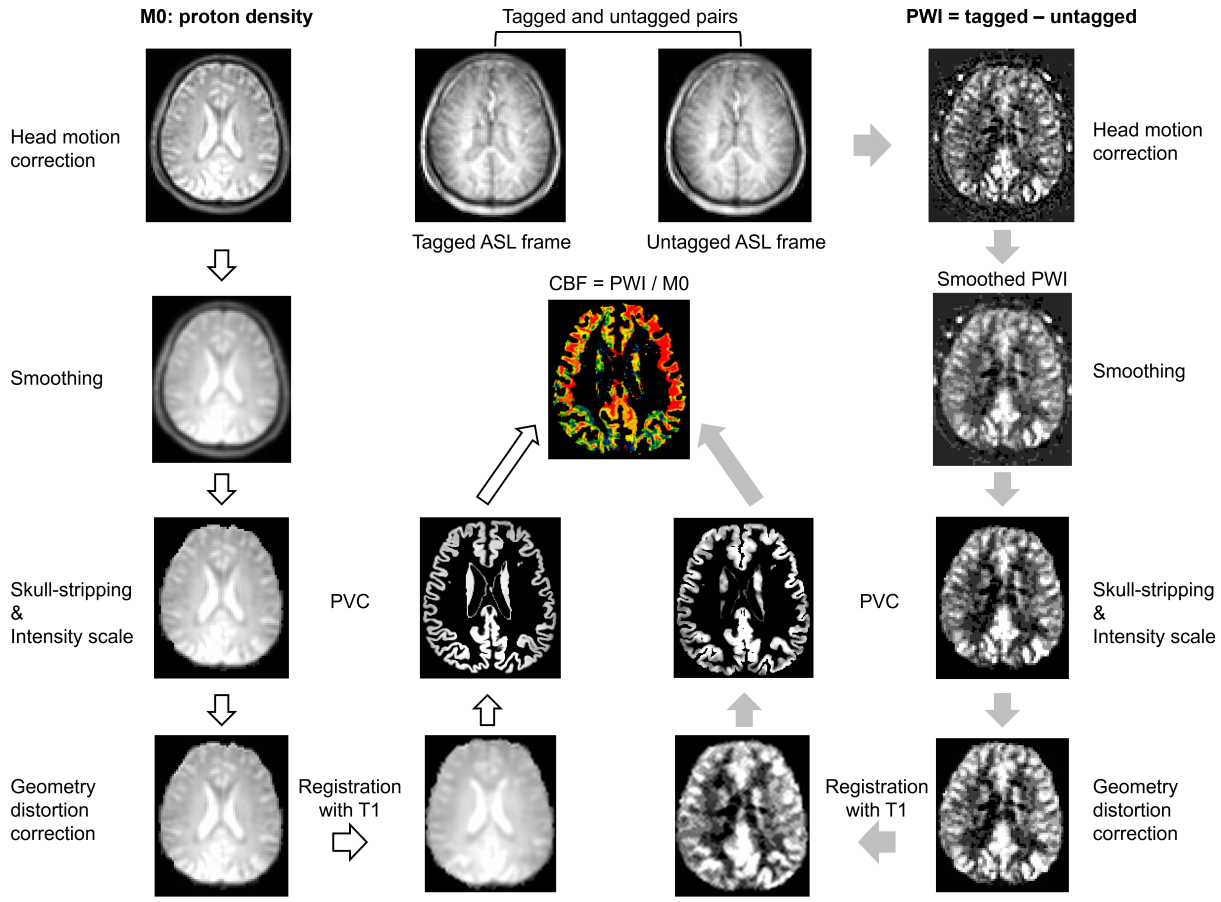
- A modified version of the Hachinski Ischemic scores less than or equal to 4.
- Have completed grade 6 education or have good work experience (sufficient to rule out mental retardation).
- Must be able to speak Mandarin fluently.
- Willing to undergo multiple 3T MRI scans and at least two PET scans.
- Agree to collect blood for genomic analysis (including GWAS sequencing and other analyses), AD risk and protective genes such as apolipoprotein E (APOE), klotho, etc., and biological sample storage.
- Agree to collect blood for biomarker detection.
- Agree to share genomic data and biomarker samples.

The exclusion criteria are as follows:

- MRI brain scan screening reveals infection, infarction or other focal lesions or multiple lacunes or lacunes in key memory structures.
- Any volunteers who do not meet the MRI scan requirements, including having a cardiac pacemaker, eyes, skin or metal fragments or foreign bodies in the body.
- Severe depression, bipolar affective disorder described in DSM-IV in the past year.
- Psychotic features, agitation or behavioral problems that may lead to difficulty complying with the protocol content in the past 3 months.
- Currently using medication to treat obsessive-compulsive disorder or attention deficit disorder.
- History of schizophrenia (meeting DSM-IV criteria).
- History of alcohol or drug abuse or dependence within the past 2 years (metting DSM-IV criteria).
- Any major systemic disease or unstable physical condition that may make longitudinal research difficult.
- Clinically significant abnormalities of B12 or TFTs may interfere with the study, low B12 will be excluded.

- Currently using certain psychoactive medications (e.g., certain antidepressants, neuro-depressants, chronic anxiolytics, or sedative-hypnotics). Currently using warfarin or other anticoagulants such as dabigatran, rivaroxaban, and apixaban (except lumbar puncture).
- Use of prohibited drugs.
- Simultaneously participating in other clinical studies involving neuropsychiatry.

Imaging analysis



Supplemental Figure 2*. Schematic diagram of ASL processing pipeline.*

The general imaging processing pipeline of ASL involved several steps (Supplemental Figure 2). First, ASL frames underwent head motion correction using SPM12. Second, the

perfusion images were obtained by subtracting the mean of tagged from untagged ASL images, and both perfusion and proton density images were smoothed using a Gaussian kernel with a full width at FWHM of 4mm. To correct EPI geometry distortion, a fieldmap with units of radians per second was obtained from raw fieldmap images using FSL (V6.0.3). The calculated fieldmap and structural T1 images were then used to correct for geometry distortion for perfusion and proton density images. Subsequently, perfusion and proton density images were co-registered with the T1 images, and underwent partial volume correction[1]. Finally, the quantitative CBF image was computed based on perfusion and proton density images[2], and regional mean CBF of 68 FreeSurfer-defined ROIs (regions of interest) defined by FreeSurfer were extracted in the native T1 space.

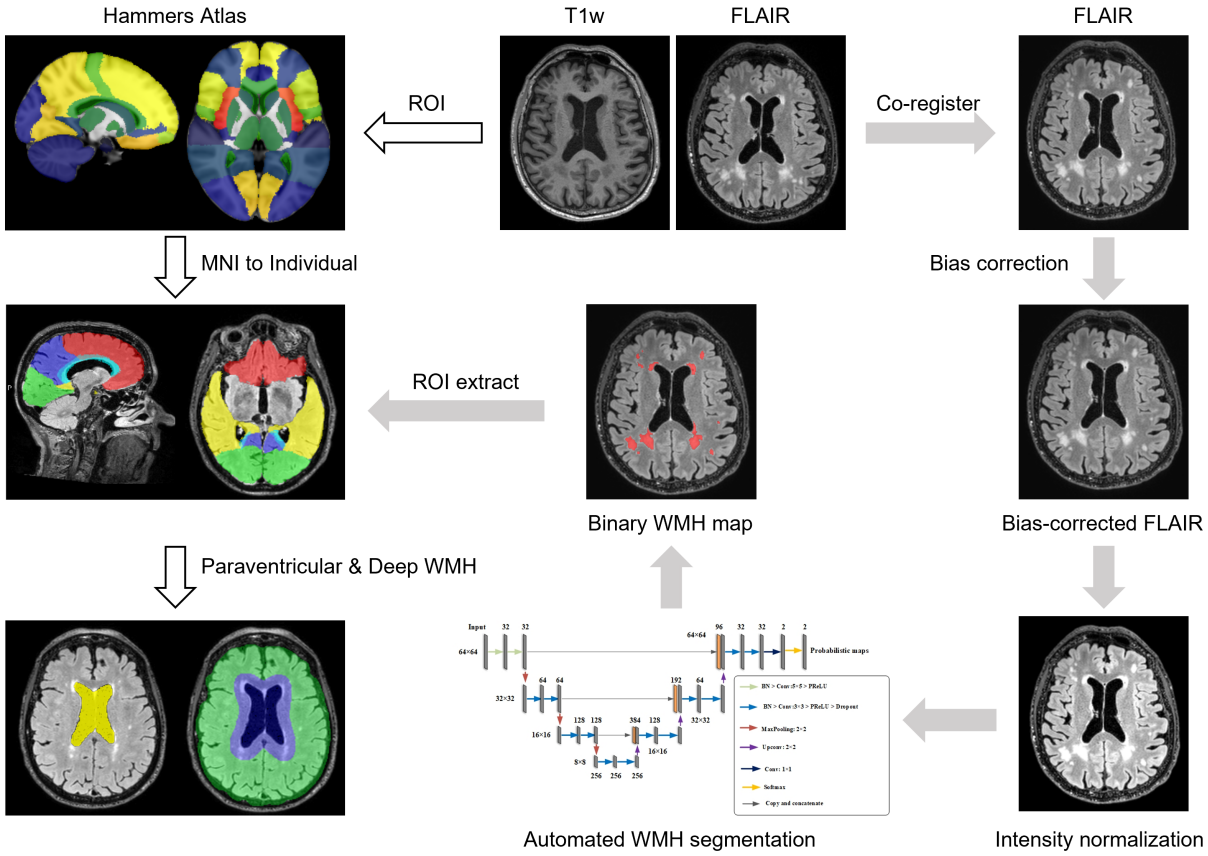
The general process of resting-state data preprocessing and brain functional connectivity construction are outlined in the third column of Figure 3. Preprocessing of resting-state image data was performed using the SPM12 software package in Matlab. The preprocessing steps are as follows: 1) first, the Dicom format of the original image data was converted to nii format using the built-in Dcm2nii module in SPM12; 2) the first 10 images of each data were removed to reduce the interference caused by magnetic field instability; 3) temporal layer correction; 4) head motion correction, with a maximum translation of less than 1mm in the X, Y, and Z axes and an average rotation angle of less than 1° around these three directions in this study; 5) resting-state fMRI data underwent the geometry distortion correction based on the fieldmap using a similar method in the ASL imaging processing; 6) spatial normalization: GHABS used individual T1 and standard space T1 structural images for joint segmentation-based spatial normalization; 7) spatial smoothing: this study used a Gaussian kernel function with a FWHM of 6mm to smooth the images to meet the distribution requirements of Gaussian random fields; 8)

band-pass filtering was used with a frequency range of 0.01 Hz-0.1 Hz. Based on the time series of AAL-116 brain regions obtained from the preprocessed data, a correlation analysis was performed to obtain a 116×116 time series correlation matrix. The Fisher's Z transformation was applied to the 116×116 time series correlation matrix to obtain the whole-brain functional connectivity matrix.

Diffusion-weighted data were denoised and corrected for Gibbs ring using Mrtrix3 (V3.0.3)[3], and then corrections were applied for head motion, eddy current and EPI susceptibility distortion using FSL (V6.0.3)[4]. Next, a brain mask was constructed using Brain Extraction Tool (BET)[5], and diffusion tensor model was reconstructed within the brain mask for estimation of fractional anisotropy (FA) parameter map with b=1000/mm^2. For the assessment of neurite orientation dispersion and density imaging (NODDI)[6], Accelerated Microstructure Imaging via Convex Optimization (AMICO)[7] was employed with b=1000 and 2000 s/mm^2. NODDI parameter maps, including neurite density index (NDI), orientation dispersion index (ODI), and isotropic volume fraction (ISO) were estimated. Subsequently, region of ROI-based analysis was performed respectively for FA, NDI, ODI and ISO, by non-linearly warping the JHU "Eve" WM atlas[8] to each participant. Furthermore, deterministic fiber tracking based on FA was conducted using DSI-studio[9] to construct a whole-brain structural connectivity map. The aforementioned functional connectivity brain region AAL-116 template was integrated with structural connectivity results, yielding the structural connectivity matrix.

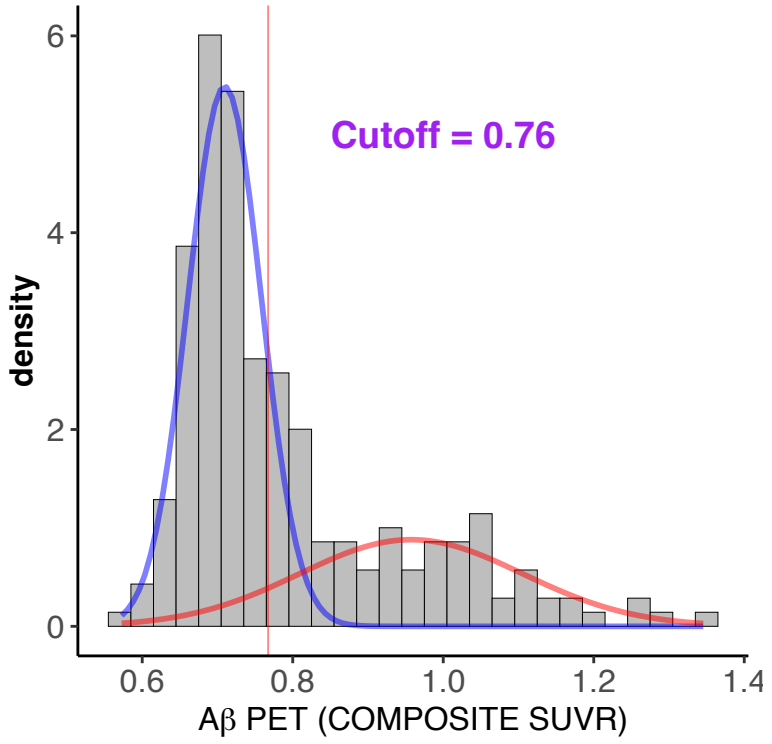
The white-matter hyperintensity (WMH) segmentation was processed using a custom pipeline developed by our lab based on the T2 FLAIR (Fluid-Attenuated Inversion Recovery) images. Briefly, T1 structural image was segmented using Freesurfer (v7.2.0) to derive the bias

field corrected T1 images and CSF mask, and the original T2 FLAIR image was co-registered to the corrected T1 image. Then, an anatomical-based MRI deep learning model (^{A}U-Net) was used with T2 FLAIR image as the input[10], and a binary WMH was obtained. The resulting WMH mask was further corrected for false positives in the choroid plexus of the lateral ventricle based on the CSF mask, and were manually edited by two senior physicians to ensure consistency and accuracy. Finally, the frontal, parietal, occipital, temporal atlas from the Hammer template (Hammers atlas[11]) were transformed to individual T1 space, and the regional WMH volumes were then extracted.



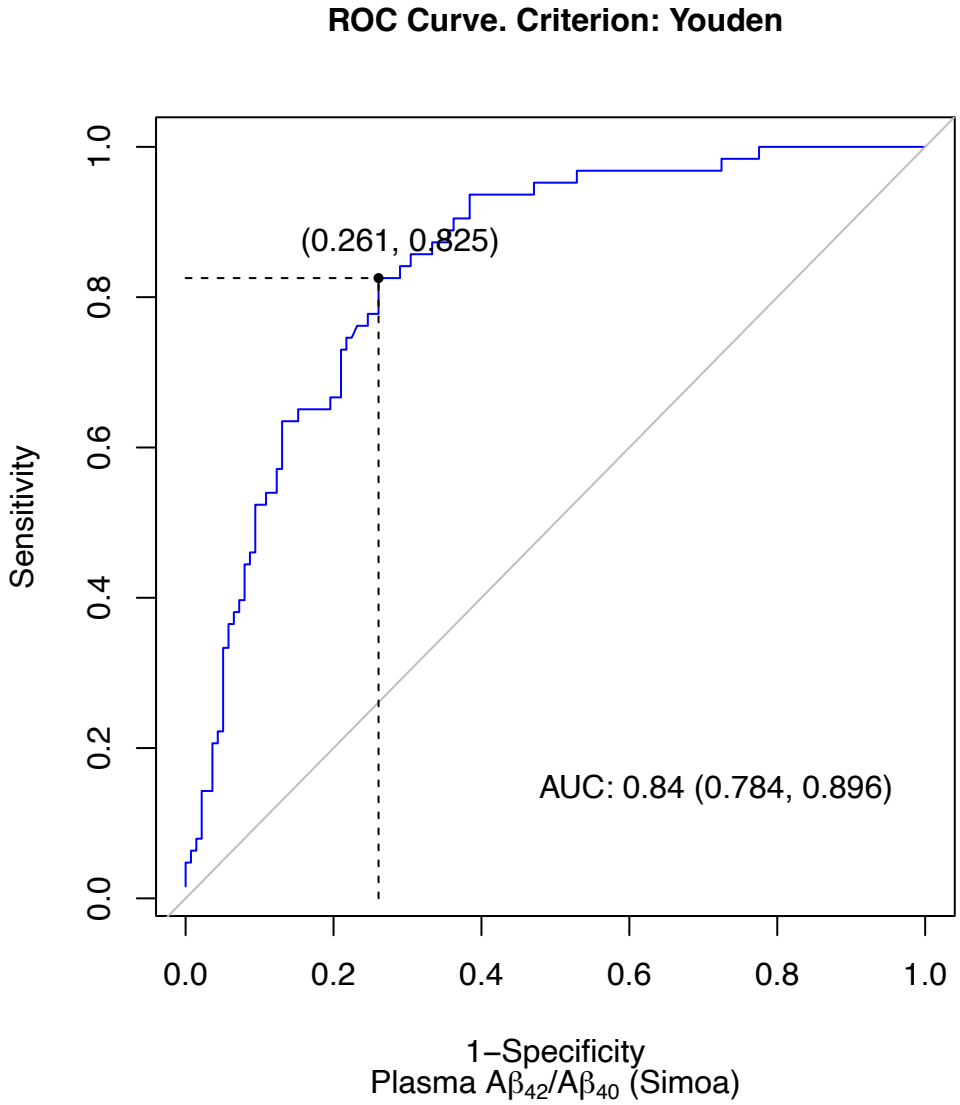
Supplemental Figure 3. *Schematic diagram of FLAIR processing pipeline.*

Cutoffs of Aβ PET FSP SUVR

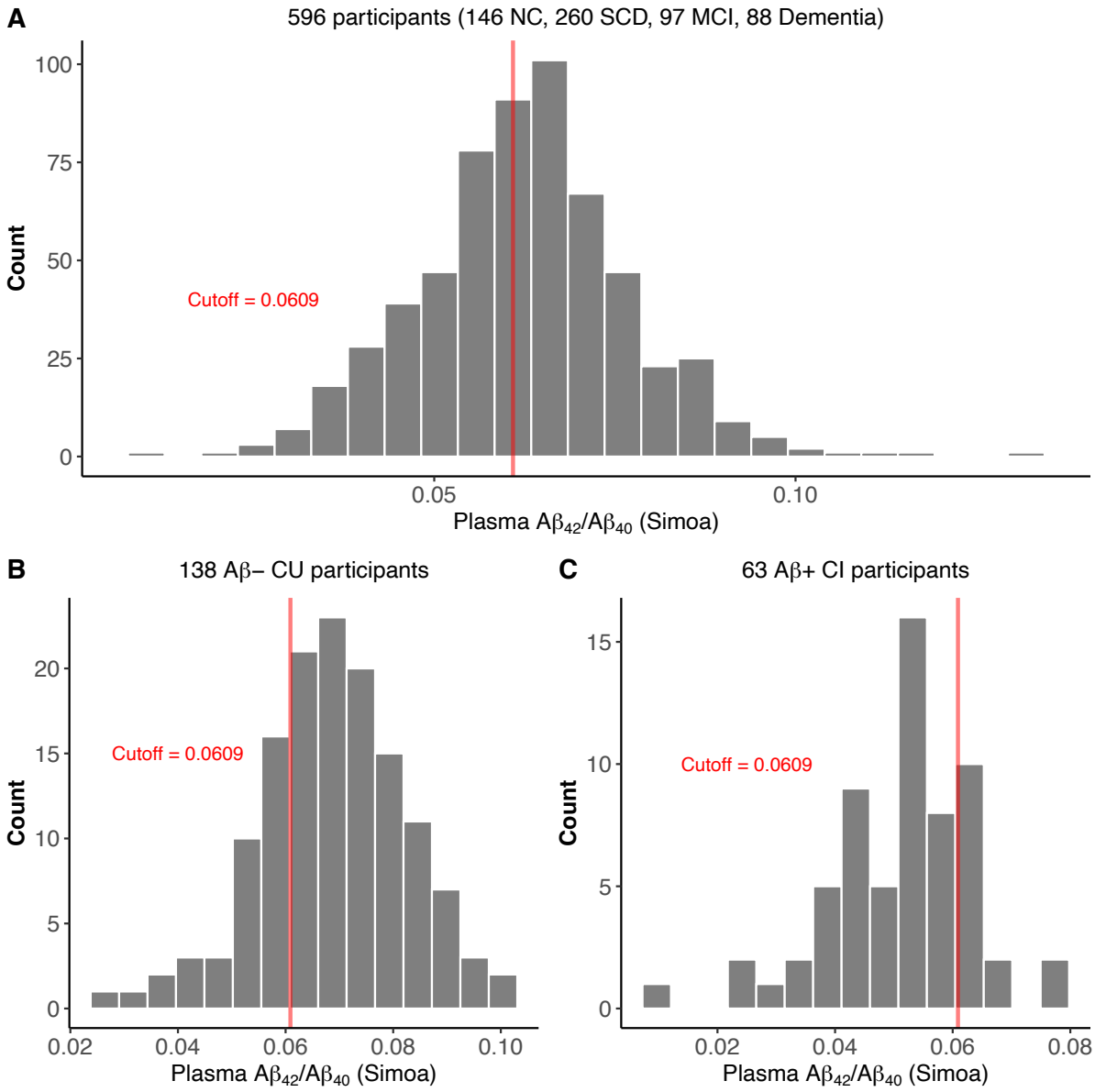


Supplemental Figure 4. *Estimates of two Gaussian distributions of low Aβ (blue curve) and high Aβ (red curve) for COMPOSITE FSP SUVRs of 233 individuals. The red dash vertical line reflects the Aβ+ threshold of COMPOSITE FSP SUVR 0.76, which corresponds to a 90% probability of belonging to the high Aβ distribution.*

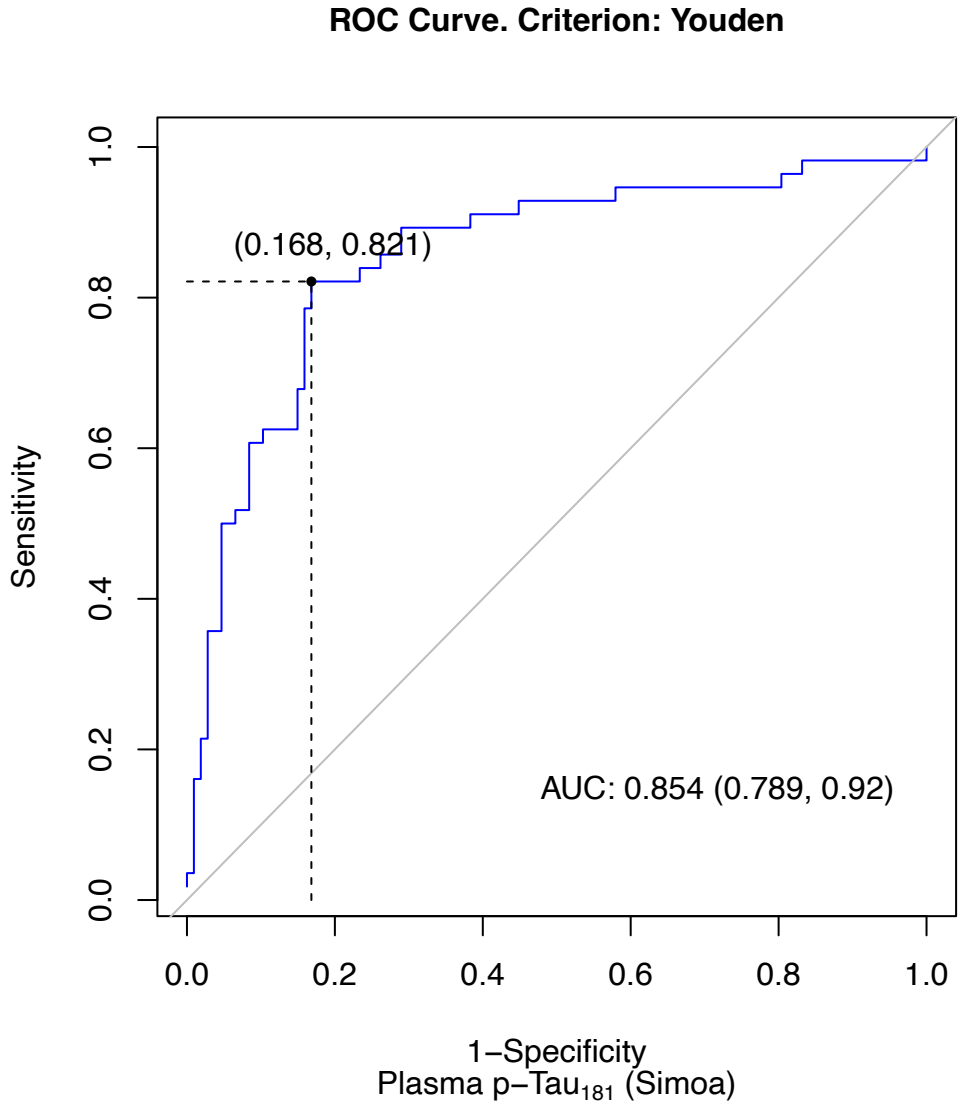
Cutoffs of plasma Aβ42/Aβ40 and plasma p-Tau181



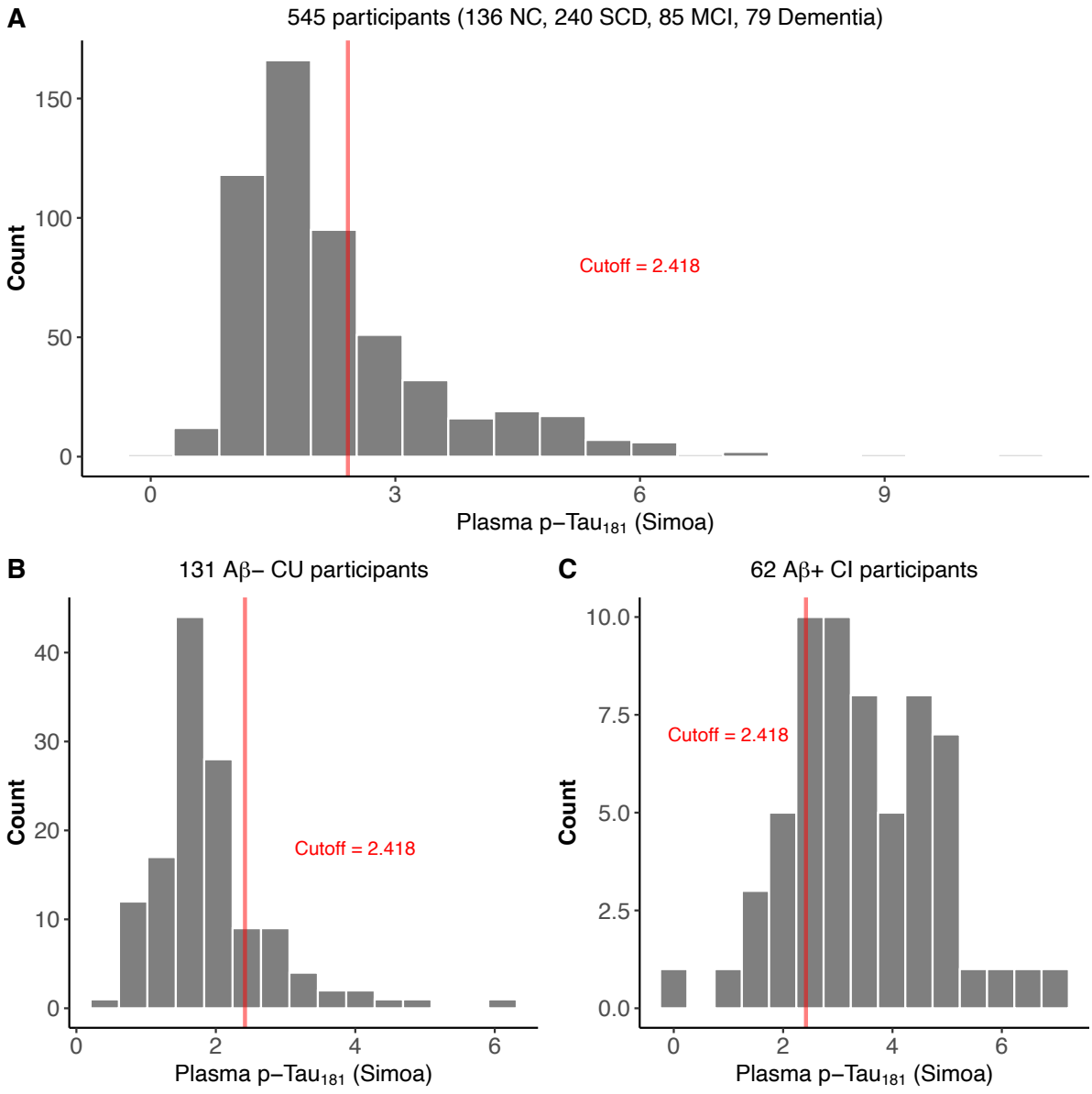
Supplemental figure 5. *The ROC analysis using the Youden index classifying 138 Aβ- cognitively unimpaired (CU) participants and 63 Aβ+ mild cognitive impairment (MCI) and dementia patients as the endpoint to define the cutoff ≤ 0.0609 for plasma $A\beta_{42}/A\beta_{40}$ ratio. AUC: 0.84 (95% CI, 0.83, 0.74).*



Supplemental figure 6. *Histograms of plasma $A\beta_{42}/A\beta_{40}$ for (A) all 596 GHABS participants, (B) 138 Aβ- GHABS CU participants and (C) 63 Aβ+ GHABS MCI and dementia patients. The red dotted line is the cutoff ≤0.0609 for the plasma $A\beta_{42}/A\beta_{40}$ ratio.*



Supplemental figure 7. *The ROC analysis using the Youden index classifying 131 Aβ- GHABS CU participants and 62 Aβ+ GHABS MCI and dementia patients as the endpoint to define the cutoff ≥ 2.418 for plasma p-Tau$_{181}$. AUC: 0.85 (95% CI, 0.82, 0.83).*



Supplemental figure 8. *Histograms of CSF p-Tau$_{181}$ for (A) all 545 GAHBS participants, (B) 131 Aβ- GHABS CU participants and (C) 62 Aβ+ GHABS MCI and dementia patients. Red dotted line is the 2.418 cutoff for the plasma p-Tau$_{181}$.*

References

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