Pathophysiology characterization and early detection of Alzheimer's disease in South China's Aging Population: for the Greater-Bay- Area Healthy Aging Brain Study (GHABS)

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Abstract

INTRODUCTION

Alzheimer's disease (AD) affects approximately 100 million aged 60 or above older adults in China. However, a community-based longitudinal neuroimaging AD cohort is rarely available in China, particularly in the Guangdong-Hong Kong-Macao Great-Bay-Area of South China.

METHODS

Following the standard protocols of the Alzheimer's Disease Neuroimaging Initiative, the Greater-Bay-Area Healthy Aging Brain Study (GHABS) was initiated in Shenzhen in May 2021. The GHABS cohort focuses on the pathophysiology characterization and early detection of AD in the Guangdong-Hong Kong-Macao Greater Bay Area, one of the largest population regions in China.

RESULTS

The aims, study design, data collection, and potential applications of GHABS are summarized. Currently, 565 participants have completed cognitive assessments and blood sample collection in the GHABS cohort by June 23, 2023, and 68% of the cohort were cognitively unimpaired or had a subjective cognitive decline. Additionally, 276 and 65 participants completed stool and CSF sample collection. So far, 396, 346, and 70 participants had MRI, Aβ PET, and tau PET imaging scans, respectively.

DISCUSSION

The GHABS cohort aims to: 1) summarize the characteristic and evolution of AD pathologies across the clinical and biological stages of AD in the Guangdong-Hong Kong-Macao Greater Bay Area; 2) determine the earliest abnormal signs of AD using biofluid markers and neuroimaging; 3) identify and validate novel blood biomarkers and imaging techniques for the early detection and prevention trials of AD.

Background

Alzheimer's dementia patients suffer from memory loss, cognitive dysfunction, behavioral abnormalities, and social disorders[1]. Alzheimer's disease (AD) is the leading cause of Alzheimer's dementia, accounting for 60–80% of all cases[2]. Extracellular β-amyloid (Aβ) plaques and neurofibrillary tau tangles are the two key hallmarks of AD[3]. AD patients have reduced $A\beta_{42}$ concentrations in cerebrospinal fluid (CSF) or plasma, elevated cortical Aβ plaques, CSF or plasma phosphorylated Tau (p-Tau) concentrations, and cortical tau tangles, which eventually result in synaptic loss[4][5], hippocampal atrophy[6], hypometabolism and cognitive decline[7–9]. Such abnormal changes in Aβ and tau can be detected by biomarkers or positron emission tomography (PET) imaging 15–20 years before the earliest clinical symptoms of AD[10–12]. According to the research framework proposed by the National Institute on Aging and Alzheimer's Association in 2018[13], cognitively unimpaired (CU) older adults with the evidence of Aβ pathology measured by either CSF Aβ biomarker[8] or Aβ PET imaging[14] are defined as

preclinical AD. Moreover, around 30% of the CU individuals aged 70 and over are at preclinical AD stage[15] and have a high risk of cognitive decline in the future[16][17].

The prevalence of dementia and mild cognitive impairment (MCI) among older adults aged 60 and above in China is 6.0% and 15.5%, respectively. Among those cases, the majority (65%) is dementia or MCI due to AD, followed by vascular dementia (26.7%) and other dementias (8.3%)[18]. Additionally, the prevalence of preclinical AD defined by Aβ PET imaging among adults aged 60 or older was around 18% [15]. Currently, approximately 260 million individuals are aged 60 years or older in China[19]. Among them, around 15 million, 39 million, and 47 million individuals are at stage of dementia, MCI, and preclinical AD, respectively. China's total expenditure on dementia treatment and nursing services is expected to be $1.89 trillion around 2050[20]. AD has become the fifth leading cause of death disease in China in 2019[21]. The age-standardized prevalence and the age-standardized death rate of AD and related dementias were 788.3/100 000 and 23.3/100 000, separately, which were slightly higher than that of the global levels (682.5/100 000 and 22.9/100 000, separately)[21]. China is severely challenged by the high prevalence and vast population of AD.

Recently, three anti-Aβ drugs, including Aducanumab[22], Lecanemab[23], and Donanemab[24] showed positive results in phase 3 clinical trials. Consequently, early AD diagnosis and intervention are critical for preventing AD progression. However, the standardization of biomarker measurements, magnetic resonance imaging (MRI), and PET image scanning and processing of AD are not fully established yet in China. Therefore, the neuroscientists, neurologists, pathologists, radio-pharmacist, biomedical engineers, and biochemists in Guangdong-Hong Kong-Macao Great-Bay-Area are working together to initiate the Greater-Bay-Area Healthy Aging Brain Study (GHABS) to investigate the pathological features and progression patterns of AD, especially in asymptomatic stage of AD. GHABS participants will undergo clinical neuropsychological assessments, biospecimen sample collection, MRI imaging, and PET imaging. The GHABS project aims to: 1) explore the risk factors of Aβ and tau aggregation in the early stage of AD among China's aging population; 2) determine the effect of Aβ and tau pathologies upon downstream neurodegeneration and cognitive decline in both Aβ negative (Aβ-) and Aβ positive (Aβ+) elderly adults; 3) identify novel approaches and techniques for early detection of AD and provides significant reference for the target brain region and appropriate time window for anti-AD treatments.

Methods

Study design

Shenzhen Bay Laboratory launched the community-based longitudinal cohort study GHABS in May 2021. The GHABS project was approved by the Shenzhen Bay Laboratory's and the collaborated hospitals' Ethical Committees. Each participant signed the written informed consent of the GHABS project before enrollment. The participants who met the inclusion and exclusion requirements were informed about the baseline and follow-up examinations. From 2021 to 2026, the GHABS cohort will recruit 1400 individuals aged 55 and older, including 1100 CU older adults, 200 MCI patients, and 100 dementia patients. The

scheme for recruiting GHABS participants is illustrated in Fig. 1. All the GHABS participants will undergo cognitive assessments, genetic screening, and blood sample collection. Some will have CSF collection, stool sample collection, MRI scanning, Aβ PET scanning, and tau PET scanning. All baseline examinations will be completed within three months. At follow-up, clinical assessments and blood sample collection will be conducted annually. CSF sample collection, MRI scan, Aβ PET scan, and tau PET scan are evaluated every two-year.

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.

Cognition core

The cognitive profiles are assessed via a series of cognitive ability tests, including the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), Logical Memory Test & (the Chinese version), Mini-mental State Examination (MMSE, the Chinese version), Montreal Cognitive Assessment Basic (MoCA-Basic), Shape Trail Test (STT), Clock Drawing Test (CDT), Auditory Verbal Learning Test (AVLT), Symbol Digit Modalities Test (SDMT), Digit Span Test (DST), Animal Verbal Fluency Test (AFT), Cognitive Change Index (CCI), SCD. Besides, functional and behavioral tests were also executed, including the Hachinski Incheinic Score, Clinical Dementia Rating (CDR), Neuropsychiatric Inventory (NPI), the Geriatric Depression Scale (GDS), Function Activities Questionnaire (FAQ), Activity of Daily Living Scale (ADL), measurement of everyday cognition (Ecog), Pittsburgh sleep quality index (PSQI), REM sleep behavior disorder screening questionnaire (RBDSQ), Epworth Sleepiness Scale (ESS).

Biospecimen core

Volunteers fasted for one night the day before (not less than 6 hours), and blood is drawn in the morning of the next day. The venous blood of the volunteers is drawn into two 10 ml EDTA blood collection tubes and gently inverted and mixed 10–12 times to ensure that the blood and anticoagulant are thoroughly mixed. The mixed blood was placed in an incubator at 4°C and shipped back to the laboratory within 4 hours for subsequent analysis. The blood is centrifuged at 1600g for 10 minutes in a refrigerated

centrifuge at 4°C. The upper plasma layer is transferred to several 2 ml centrifuge tubes using a sterile RNase-free pipette tip. To obtain more pure plasma, the separated plasma is centrifuged again at 16000 g for 10 minutes at 4°C, and then the supernatant is aliquoted into several 0.5 ml centrifuge tubes with labels, each with either 100 or 200 μl blood plasma. The aliquots are stored in a -80°C refrigerator for subsequent analysis. After the whole blood is centrifuged in the first step, the buffy coat in the middle layer is gently transferred to 2640 medium. Then, after density gradient centrifugation, erythrocyte lysis, and centrifugation steps, the isolated peripheral blood mononuclear cell sample is transferred to a 2ml RNase-free centrifuge tubes and stored in a gradient-cooled freezer box at -80°C for subsequent analysis. Samples will be used for genomic analysis (including GWAS sequencing and other analyses).

Before collecting the CSF sample, the volunteer must fast for one night (at least 6 hours), and the lumbar spinal fluid is performed on an empty stomach the following day. Lumbar puncture is performed strictly with clinical standards, and about 5 ml of CSF is collected. The collected CSF is sent to Shenzhen Bay Laboratory within 2 hours for biomarker analysis. CSF sample is quickly divided into 1.5 ml low protein adsorption centrifuge tubes. Afterward, they will be stored in a -80°C refrigerator for subsequent analysis.

The concentrations of $A\beta_{40}$, $A\beta_{42}$, p-Tau, neurofilament light (NfL), glial fibrillary acidic protein (GFAP), synaptosome associated protein 25 (SNAP25), YKL40, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), Neurogranin, platelet-derived growth factor receptor β (PDGFR-β), and growth-associated protein-43 (GAP43) in plasma and CSF are measured in GHABS cohort. These biomarkers are measured with the Simoa HD-X Analyzer™ (Quanterix Corp.), MESO SECTOR S 600MM (Meso Scale Diagnostics, LLC.), and enzyme-linked immunosorbent assay (ELISA). More details of fluid biomarker measurement processes are available in the supplementary material.

Fecal samples are collected on-site or at home after the volunteers' consent is obtained. The volunteer stool samples are labeled, sub-packaged, and frozen in a -80°C refrigerator. Fecal samples are used for 16S rDNA, metagenomic, metagenome, and metabolome detection of intestinal microorganisms.

MRI core

All the MRI scanning sequences will be conducted following the standard ADNI protocol here, and more details can be found in the supplemental materials. The MRI image data is collected on 3.0T scanners, and the scanning parameters vary slightly depending on the specifics of scanners from various clinical centers. A series of sequences are applied for head imaging of each volunteer, including 3 Plane Localizer positioning sequence, 3D T1 MPRAGE/IRSPGR, 3D T2 FLAIR, high resolution hippocampus (High Res Hippo), Susceptibility weighted imaging (SWI), Arterial Spin Label (ASL), Diffusion (Axial Diffusion Tensor Imaging, DTI), EPI-BOLD functional MRI (fMRI).

PET core

The Aβ PET radiotracer [^{18}F]-florbetapir (FBP)[26] or [^{18}F]D3FSP (FSP)[27] and tau PET radiotracer [^{18}F]-flortaucipir (FTP)[28] are used for PET imaging. The data acquisition is performed on either a GE Discovery™ MI Gen 2 PET/CT scanner or a Siemens Biograph™ TruePoint™ TrueV PET/CT scanner. The

spatial resolution of each PET scanner is quantified with PET imaging of a Hoffman phantom. For the Aβ PET imaging, the subjects are injected with either [^{18}F]-florbetapir or [^{18}F]-D3FSP intravenously at 370 MBq (10 mCi ± 10%), rested for 45 minutes and prepared for the scanning. PET/CT imaging is performed 50 minutes after injection, and the PET acquisition time is 20 minutes. For the tau PET imaging, the participants are injected with [^{18}F]-flortaucipir intravenously at 370 MBq (10 mCi ± 10%), rested for 75 minutes, and prepared for imaging. The dynamic acquisition of [^{18}F]-flortaucipir tau PET data is completed 80–100 minutes after the radiotracer administration.

A dedicated head scanning procedure covering the whole brain from vertex to cerebellum is used for imaging. A diagnostic dose CT scan of the brain is acquired beforehand for attenuation correction and fusion localization of PET images. The PET scans are acquired using 3D Listmode on the GE Discovery MI and Siemens BioGraph TruePoint scanners in two sites. For the GE scanner, the field of view (FOV) is 256 mm×256 mm×220 mm, the scanning matrix is 336×336×109, and the voxel size is 1.02 mm×1.02 mm×2.03 mm. For the Siemens scanner, FOV is 256 mm×256 mm×198 mm, the scanning matrix is 192×192×71, and the voxel size is 1.33 mm×1.33 mm×2.79 mm. All the correction options were selected for both scanners, and no filter or smooth was used during the reconstruction. A reconstruction offset is applied to ensure that the head is entirely in the field of view within the plane. Finally, 4 frames of dynamic images are generated according to 5 min/frame segmentation, with each PET scan corresponding to a 20-minute PET image.

Imaging analysis

The structural MRI images are segmented into different cortical and subcortical regions of interest (ROI) in Freesurfer (V7.2.0). The adjusted hippocampal volume is calculated using the hippocampal volume of both hemispheres and adjusted using the estimated total intracranial volume as we described previously[6]. In addition, the cortical thickness of AD-signature atrophy brain regions is obtained by calculating the surface area-weighted average thickness of the bilateral entorhinal, fusiform, inferior temporal, and middle temporal cortices[29].

The PET images were then preprocessed with the following steps before further analysis: 1) co-registering the 2nd, 3rd, and 4th frames to the 1st frame, respectively; 2) averaging the four frames into one; 3) the averaged frame resliced into a standard AC-PC space (anterior commissure-posterior commissure) with image size = 160×160×96, voxel dimension = 1.5mm×1.5 mm×1.5 mm; 4) smoothing with a uniform Gaussian kernel function with a full-width at half maximum (FWHM) of 6 mm. The PET and MRI images are processed using in-house Matlab algorithms as shown in Fig. 2. The PET images are co-registered with their corresponding structural MRI images in SPM12 (Statistical Parametric Mapping). Sixty-eight Freesurfer-defined cortical ROIs obtained from MRI segmentation extract regional FSP, FBP, and FTP measurements from the co-registered PET images.

The FSP and FBP standardized uptake value ratio (SUVR) of AD summary cortical regions (posterior cingulate cortex, precuneus, frontal lobe, parietal lobe, and lateral temporal) are obtained by dividing the

radiotracer uptake value of AD typical brain regions by that in the entire cerebellum[30]. For the [^{18}F]-flortaucipir images, FTP SUVR of 68 FreeSurfer-defined ROIs are calculated by normalizing the [^{18}F]-flortaucipir value to the value of the inferior cerebellar cortex[31]. The FTP SUVR of the AD Temporal-MetaROI[29] (entorhinal cortex, parahippocampal gyrus, amygdala, inferior temporal and middle temporal brain regions) is used to evaluate cortical tau deposition.

The general process of resting-state fMRI data preprocessing and brain functional connectivity construction are outlined in the third column of Fig. 2. Diffusion-weighted data were denoised and corrected for Gibbs ring using Mrtrix3 (V3.0.3)[32], and then corrections were applied for head motion, eddy current, and EPI susceptibility distortion using FSL (V6.0.3)[33]. 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. 3D pseudo-continuous ASL (pCASL) imaging was employed to calculate the cerebral blood flow (CBF) map. More details of fMRI, DTI, WMH, and pCASL can be found in Supplementary Material.

Results

Current Progress of the GHABS Cohort

Five hundred sixty-five participants have completed cognitive assessments and blood sample collection in the GHABS cohort by June 23, 2023 (Fig. 3). Among them, 23%, 45%, 19%, and 13% of the cohort were CU, SCD, MCI, and dementia, respectively. Additionally, 276 and 65 participants completed stool and CSF sample collection. So far, 396, 346, and 70 participants had MRI, Aβ PET, and tau PET imaging scans, respectively.

As shown in Table 1, MCI and dementia patients had older ages than CU (Vs. MCI: estimate = 6.05, 95% confidence interval (ci) [3.80, 8.23], $p < 0.001$; Vs. Dementia: estimate = 6.58, 95% ci [3.60, 9.55], $p < 0.001$) and SCD (Vs. MCI: estimate = 4.26, 95% ci [2.58, 6.08], $p < 0.001$; Vs. Dementia: estimate = 5.06, 95% ci [2.47, 7.57], $p < 0.001$) individuals. More females were found in the SCD group than the CU (odds ratio (OR) = 0.51, 95% ci [0.32, 0.82], $p = 0.004$), MCI (OR = 2.56, 95% ci [1.55, 4.25], $p < 0.001$), and dementia (OR = 2.62, 95% ci [1.47, 4.67], $p < 0.001$) groups. MCI and Dementia individuals had higher percentages of *APOE*-ε4 carriers than CU (Vs. MCI: OR = 0.38, 95% ci [0.20, 0.69], $p < 0.001$; Vs. Dementia: estimate = 0.34, 95% ci [0.17, 0.67], $p = 0.001$) and SCD (Vs. MCI: OR = 0.32, 95% ci [0.19, 0.55], $p < 0.001$; Vs. Dementia: estimate = 0.29, 95% ci [0.16, 0.54], $p < 0.001$). The SCD group had higher percentages of hyperlipidemia than the CU (OR = 2.40 [95% ci (1.44, 4.09)], $p < 0.001$), MCI (OR = 2.03 [95% ci (1.17, 3.62)], $p = 0.008$), and dementia (OR = 1.92 [95% ci (1.03, 3.72)], $p = 0.03$) groups. No other difference was found among the different groups.

Table 1
Profiles of the Greater-Bay-Area Healthy Aging Brain Study (GHABS) cohort

Characteristic at baseline	CU	SCD	MCI	Dementia
No. participants (%)	132 (23%)	256 (45%)	105 (19%)	72 (13%)
Age (years), *Median (IQR)*	63.9 (10.9)	65.3 (9.1)	69.0 (10.8)[b,d]	70.4 (16.8)[c,e]
Female, *n* (%)	79 (60%)	191 (75%)[a]	56 (53%)[d]	38 (53%)[e]
Education (years), *Median (IQR)*	13 (4.0)	14 (5.0)	12 (6.0)[b,d]	10 (6.25)[c,e,f]
APOE-ε4 carriers, *n* (%)	29 (23%)	50 (20%)	42 (44%)[b,d]	32 (46%)[c,e]
History of Hypertension, *n* (%)	31 (25%)	70 (28%)	32 (34%)	22 (33%)
History of Diabetes, *n* (%)	17 (14%)	33 (13%)	13 (14%)	13 (19%)
History of Hyperlipidemia, *n* (%)	28 (23%)	103 (41%)[a]	24 (26%)[d]	18 (27%)[e]

Significantly different from [a,b,c] CU, [d,e]SCD, [f]MCI, Mann-Whitney test, $p < 0.05$. Notably, 563, 538, 529, 529, 529 participants had education information, APOE genotyping results, History of Hypertension, History of Diabetes, and History of Hyperlipidemia, respectively.

Abbreviations: *CU = Cognitively unimpaired; SCD = Subjective Cognitive Decline; MCI = Mild Cognitive Impairment.*

As mentioned above, MRI and PET imaging were processed using the imaging processing pipeline. Sample images of Aβ PET and tau PET SUVR images of one A-T- CU, one A+/T- MCI, and one A+/T+ dementia due to AD were illustrated in Figure 4.

Discussion

There are approximately 47 million preclinical AD individuals, 39 million MCI patients, and 15 million dementia patients in China. In 2035, the elderly population aged 60 and above is expected to exceed 400 million, accounting for more than 30% of the total population. As long as there are no practical methods for the early detection and treatment of AD, the number of AD patients in China will continue to rise. To end this, the GHABS study was initiated in 2021. The GHABS study aims to understand the prevalence and progression of AD in the Guangdong-Hong Kong-Macao Great-Bay-Area of China. The ultimate goal is to develop novel biomarkers and neuroimaging approaches for early diagnosis of AD and support the early intervention of clinical trials in Guangdong-Hong Kong-Macao Great-Bay-Area (Figure 5).

Following the standard protocol of ADNI[34], the GHABS is supposed to be a high-standard AD community cohort in Guangdong-Hong Kong-Macao Great-Bay-Area of China, GHABS also referred to several well-organized cohorts in China, such as the Beijing Aging Brain Rejuvenation Initiative[35], China

Aging and Neurodegenerative Initiative [36], Chinese Alzheimer's Biomarker and LifestylE[37], the Chongqing Ageing & Dementia Study [38], the China Cognition and Ageing Study[39] and Sino Longitudinal Study on Cognitive Decline (SILCODE)[40]. Dr. Yin Han, the president of the “Pre-Alzheimer’s Disease Alliance of China”, is one of the principal investigators in GHABS. Dr. Han initiated the Pre-AD Alliance of China in 2017[41] and led two AD cohorts focused on the population of SCD for early AD diagnosis and investigation, the SILCODE and Cross-Cultural Longitudinal Study on Cognitive Decline[42]. The design of GHABS will be updated by the researchers if necessary. GHABS closely follows the latest academic and industry development in the field and tries to adapt and update protocols.

The primary goal of GHABS is to investigate the pathological characteristics, risk factors, protective indicators, and evolution of Aβ and tau pathologies in Guangdong-Hong Kong-Macao Great-Bay-Area older adults. The specific studies are as follows: 1) summarize the incidence of preclinical AD (Aβ+ CU) in the Guangdong-Hong Kong-Macao Great-Bay-Area, and reveal the characteristics and progression of AD pathologies; 2) clarify the feasibility of plasma biomarkers for detecting early AD in older adults; 3) determine the risk factors related to abnormal changes in Aβ and tau proteins; 4) reveal the spatiotemporal patterns of cortical Aβ plaques, tau tangles aggregation, synapse loss, and neuroinflammation and their relations to brain atrophy and cognitive decline; 5) investigate the roles of neuroinflammation, synaptic loss, vascular diseases, myelination, metabolic dysfunction across the spectrum of AD. Hopefully, these studies based on the GHABS cohort may provide novel insights into the early diagnosis and intervention of AD in China and the AD community.

Compared to CSF biomarkers and PET imaging, plasma biomarkers are the most promising early screening technology for AD by considering the advantages of simple sampling, low traumatic, and cost[43]. Recently, plasma $A\beta_{42}/A\beta_{40}$[44,45], p-Tau181[46], p-Tau217[47],p-Tau231[48], and GFAP[49] showed great potential in early diagnosis of AD. One of the primary goals of GHABS is to evaluate the performance of previously-reported plasma biomarkers and further explore novel plasma biomarkers in China’s aging population. For example, the GHABS research group has investigated the characteristics of CSF GAP43 in different clinical and pathological stages of AD[4] based on the ADNI cohort and demonstrated that presynaptic dysfunction measured by CSF GAP43 occurs prior to AD typical neurodegeneration and predicts faster cognitive decline [5]. We are currently measuring GAP43 concentrations in plasma in the GHABS cohort and evaluating its suitability as a plasma synaptic biomarker of AD in the Chinese aging population.

The GHABS project aims to support and fertilize new diagnosis methods for early AD diagnosis from academics and pharmaceutical industries. GHABS has been committed to co-developing early diagnostic tools since its inception, including fluid biomarkers, new antibodies, brain PET instruments, and new PET tracers. In Shenzhen Bay Laboratory, Dr. Qiyu Peng’s group are dedicated to developing high-performance and low-cost brain PET/CT scanner and wearable brain PET/CT scanner[50]. The GHABS plans to support the clinical verification of the novel brain PET/CT instruments, as AD is one of the main neurodegenerative diseases that require a brain-dedicated PET/CT instrument. GHABS is also exploring adjusting the Aβ PET imaging protocols for clinical diagnosis by shortening the scanning time or

reducing trace dose by using brain PET/CT scanners with high spatial resolution and detection sensitivity. In the future, GHABS will also facilitate AD clinical trials.

In summary, we adapt the standard ADNI protocols to collect cognitive assessments, fluid biomarkers, and neuroimaging data to create a community-based observable AD cohort in the Guangdong-Hong Kong-Macao Greater Bay Area of China. The GHABS cohort is expected to identify novel biomarkers and neuroimaging techniques for early detection, determine the appropriate time window for AD intervention, and understand the pathological features and progression patterns of AD, especially during the asymptomatic stage of AD in South China's aging population.

List Of Abbreviations

AD = Alzheimer's disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADL = Activity of Daily Living Scale; ADNI = Alzheimer's Disease Neuroimaging Initiative; AFT = Animal Verbal Fluency Test; ASL = Arterial Spin Label; AVLT = Auditory Verbal Learning Test; Aβ = β-amyloid; BOLD = Blood Oxygen Level Dependent; CBF = Cerebral Blood Flow; CCI = Cognitive Change Index; CDR = Clinical Dementia Rating; CDT = Clock Drawing Test; CI = Cognitive Impaired; ci = confidence interval; CSF = Cerebrospinal Fluid; CU = Cognitively Unimpaired; DST = Digit Span Test; DTI = Diffusion Tensor Imaging; Ecog = Everyday cognition; ELISA = Enzyme-linked Immunosorbent Assay; EPI = Echo-planar Imaging; ESS = Epworth Sleepiness Scale; FAQ = Function Activities Questionnaire; FBP = [^{18}F]-florbetapir; FLAIR = Fluid-attenuated Inversion Recovery; fMRI = functional MRI; FSP = [^{18}F]D3FSP; FTP = [^{18}F]-flortaucipir; FWHM = Full-width at Half Maximum; GAP43 = Growth-associated Protein-43; GDS = Geriatric Depression Scale; GFAP = Glial Fibrillary Acidic Protein; GHABS = Greater-Bay-Area Healthy Aging Brain Study; GWAS = Genome-wide Association Studies; High Res Hippo = High Resolution Hippocampus; IQR = Interquartile Range; MCI = Mild Cognitive Impairment; MMSE = Mini-mental State Examination; MoCA-Basic = Montreal Cognitive Assessment Basic; MRI = Magnetic Resonance Imaging; NfL = Neurofilament Light; NPI = Neuropsychiatric Inventory; OR = Odds Ratio; pCASL = 3D pseudo-continuous Arterial Spin Labeling; PDGFR-β = Platelet-derived Growth Factor Receptor β; PET = Positron Emission Tomography; PSQI = Pittsburgh Sleep Quality Index; p-Tau = Phosphorylated Tau; RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire; rHCV = residual Hippocampal Volume; ROC = Receiver Operating Characteristic Curve; ROI = Region of Interest; SCD = Subjective Cognitive Decline; SDMT = Symbol Digit Modalities Test; SILCODE = Sino Longitudinal Study on Cognitive Decline; SNAP25 = Synaptosome Associated Protein 25; sTREM2 = Soluble Triggering Receptor Expressed on Myeloid Cells 2; STT = Shape Trail Test; SUVR = Standardized Uptake Value Ratio; SWI = Susceptibility Weighted Imaging; WMH = White-matter Hyperintensity.

Declarations

Ethics approval and consent to participate: All the GHABS participants provided informed consent.

Consent for publication: Not applicable.

Availability of data and material: All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests: The authors declare no conflicts of interest.

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Figures

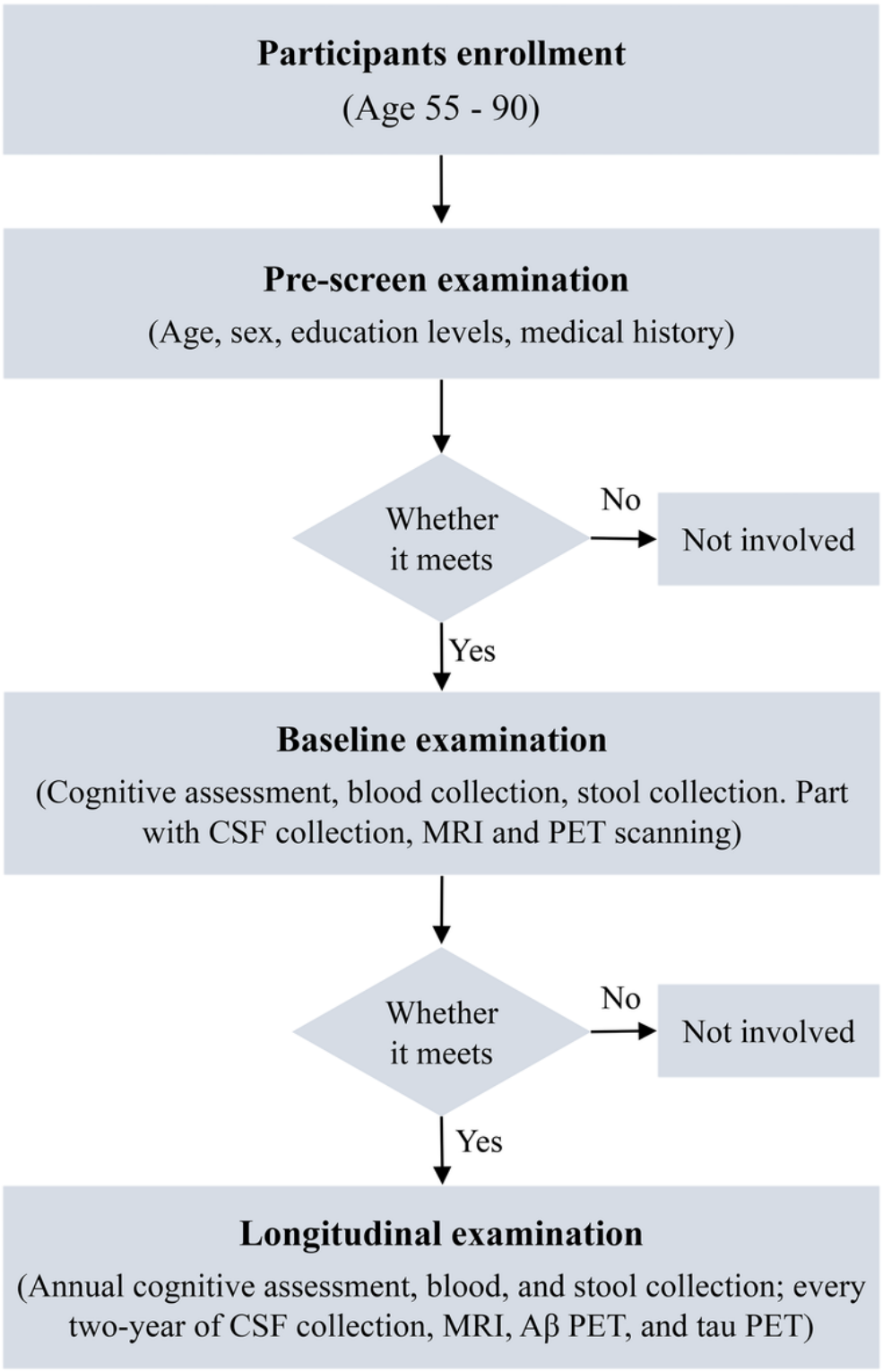

Figure 1

The scheme of enrolment and follow-up of participants in the Greater-Bay-Area Healthy Aging Brain Study.

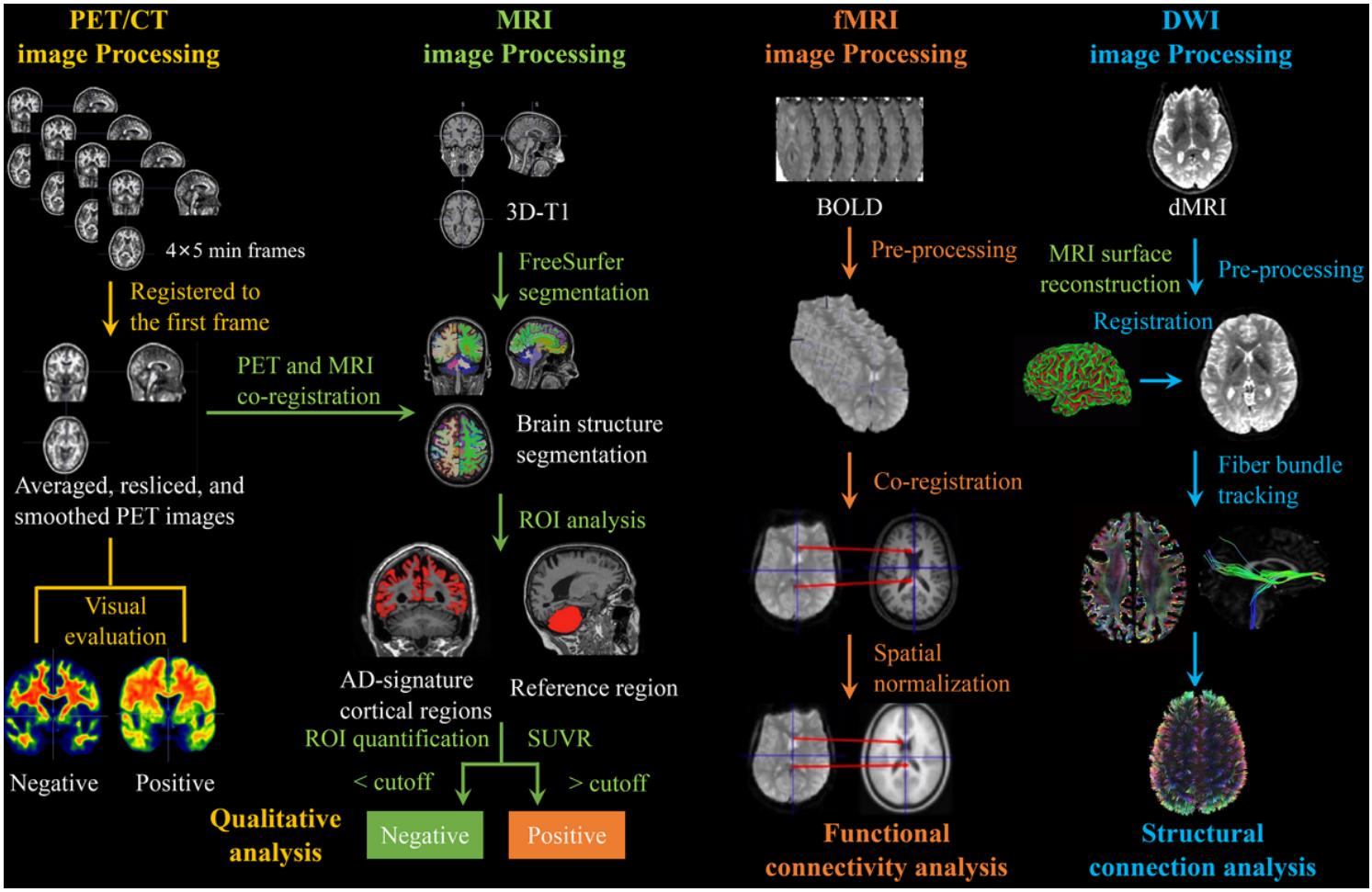

Figure 2

The image processing pipelines of PET, structural MRI, functional MRI (fMRI), and diffusion tensor imaging (DTI) images of the Greater-Bay-Area Healthy Aging Brain Study.

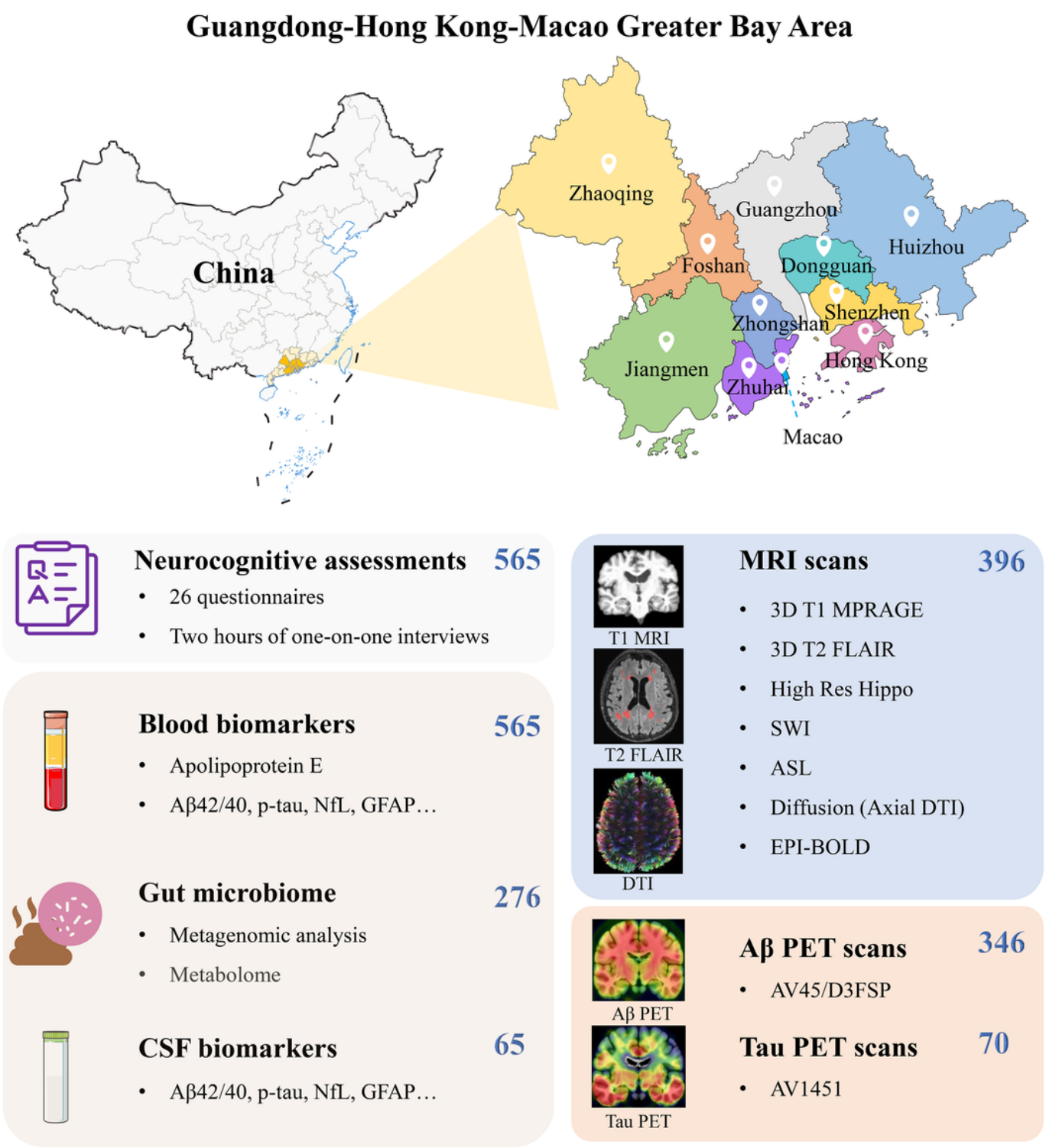

Figure 3

The current sample sizes of neurocognitive assessments, blood samples, CSF samples, stool samples, multimodal MRI scans, Aβ PET scans, and tau PET scans of the Greater-Bay-Area Healthy Aging Brain Study (By June 21, 2023).

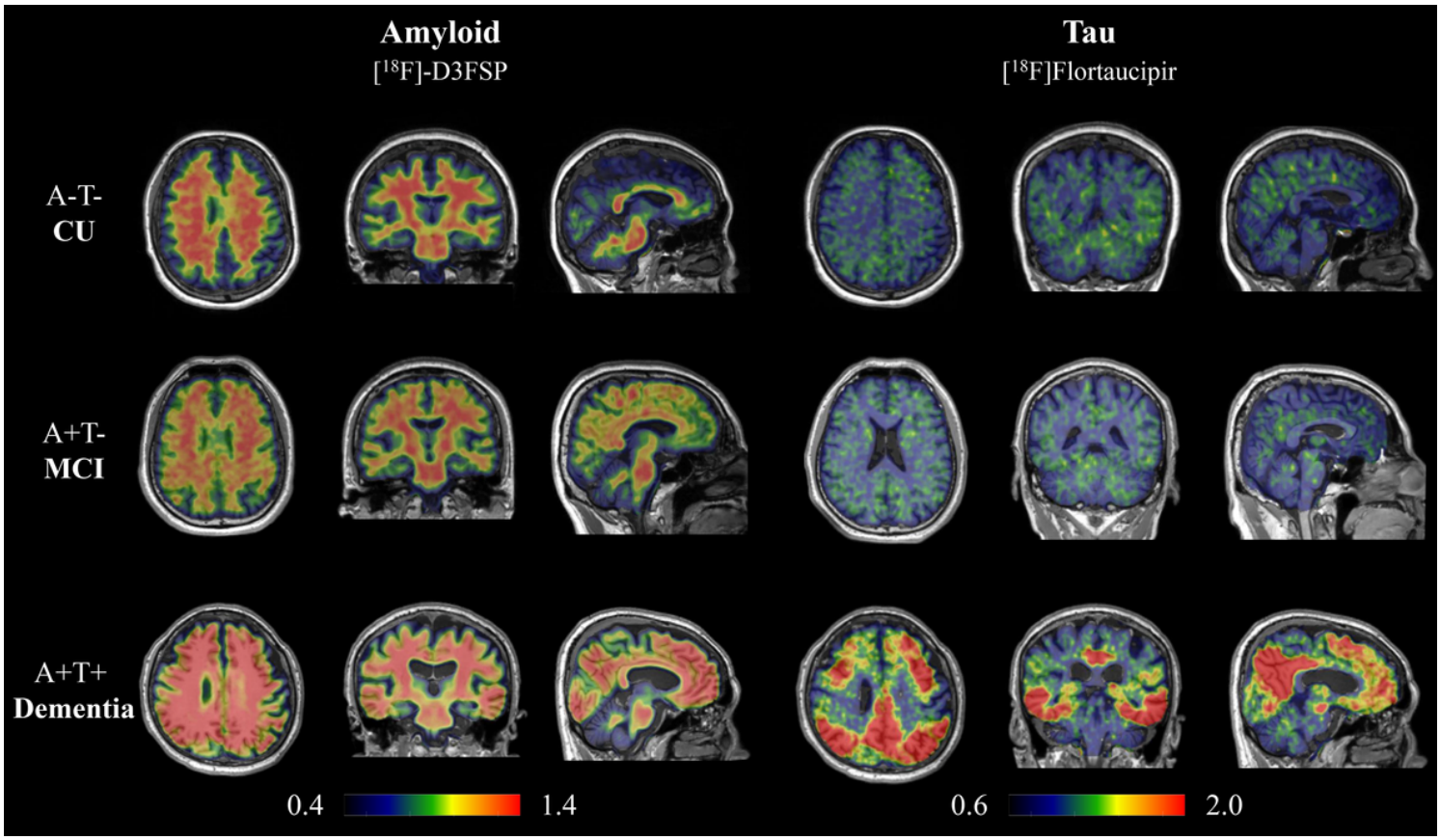

Figure 4

Sample images of Aβ PET and tau PET of one A-T- cognitively unimpaired (CU) individual, one A+T- mild cognitive impairment (MCI)patient, and one A+T+ dementia due to Alzheimer's disease (AD) in the Greater-Bay-Area Healthy Aging Brain Study.

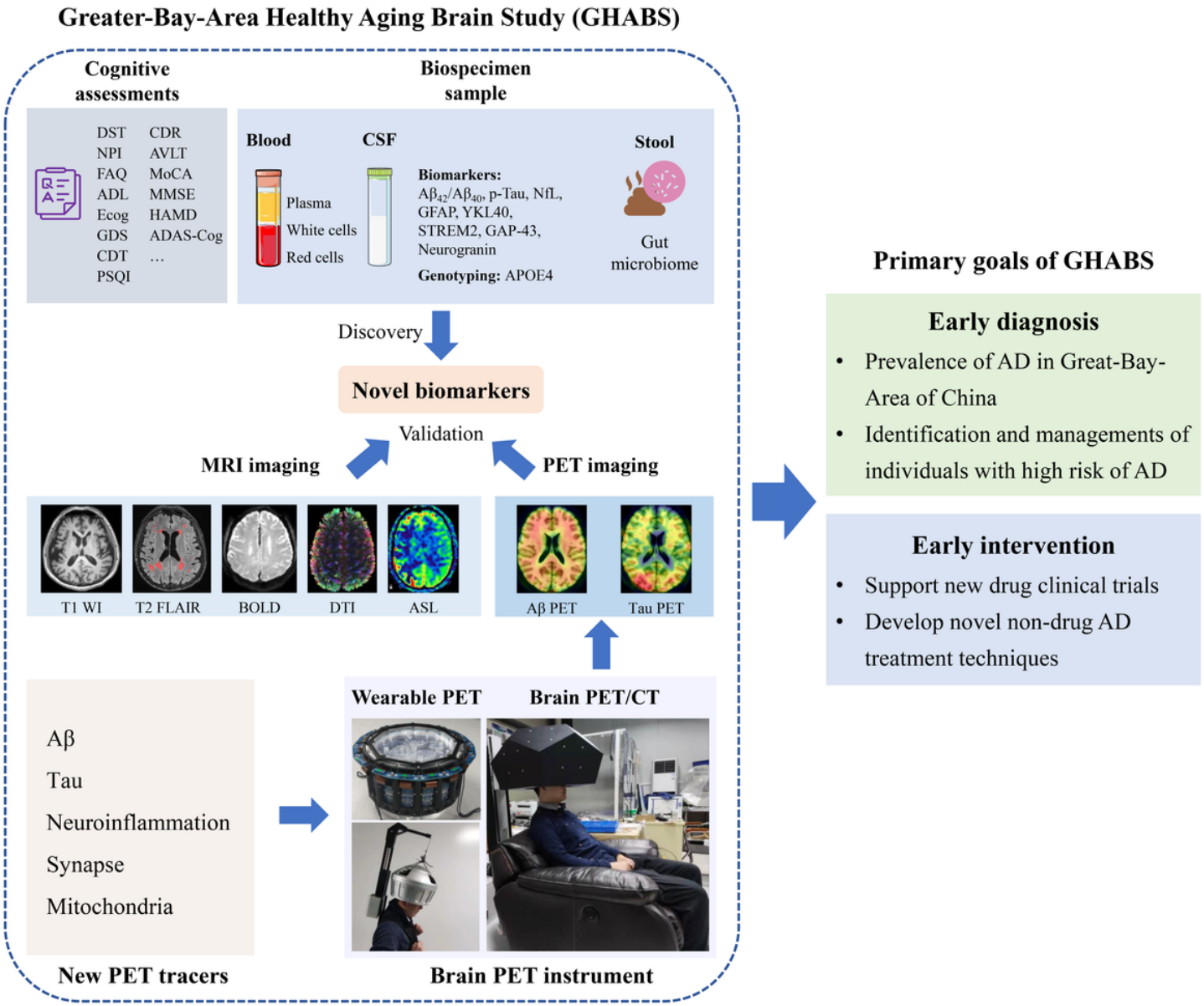

Figure 5

The general design and goals of the Greater-Bay-Area Healthy Aging Brain Study cohort.

Supplementary Files

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- SupplementalMaterialsv1.pdf