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RESEARCH ARTICLE

Clinical features, biomarker profiles, and neuroimaging characteristics in patients from memory clinic in china: The Shanghai Memory Study

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Abstract

INTRODUCTION: Despite advances in biomarker assessment, molecular neuroimaging, and disease-modifying therapies for cognitive disorders, China lacks well-characterized clinical cohorts integrating comprehensive clinical assessments and multimodal biomarkers.

METHODS: The Shanghai Memory Study (SMS), an ongoing hospital-based cohort, enrolled participants undergoing clinical/neuropsychological assessments, genotyping, multimodal imaging, and biospecimen collection.

RESULTS: From 2012 to 2024, 2001 participants were enrolled: 115 cognitively unimpaired (CU), 938 with mild cognitive impairment (MCI), and 948 with dementia. Positron emission tomography (PET) scan revealed A+/T+ positivity rates of 15.8% in CU, 51.2% in MCI, and 100% in Alzheimer's disease dementia (ADD). Plasma tau phosphorylated at threonine 181 (p-tau181) level increased gradually across the AD continuum. Blood p-tau181 and 18F-Florzolotau PET showed comparable utility for amyloid status identification. In a subcohort of 251 amnestic MCI (aMCI) patients, low Aβ42/Aβ40 and elevated p-tau181 predicted 4.7-year ADD risk.

DISCUSSION: By offering an integrated framework, SMS will facilitate the exploration of AD pathogenesis and the understanding of cognitive disorders.

KEYWORDS
Alzheimer's disease, biomarker, dementia, epidemiology, hospital-based study, neuroimaging

Highlights

- The SMS is an ongoing prospective cohort study based on a memory clinic in China.

- The SMS has established a relatively large-scale dataset that includes clinical data, biofluid markers, MRI and PET imaging, and novel biomarkers.
- By offering an integrated framework, SMS aims to facilitate the exploration of AD pathogenesis and deepen our understanding of cognitive disorders.

1 | BACKGROUND

Dementia is a leading cause of disability among individuals over the age of 65 years worldwide. The number of dementia cases in China accounts for 25% of the global patients.[1] Alzheimer's disease (AD), a primary cause of dementia, represents approximately 63% to 70% of all dementia cases.[2] There are about 9.83 million AD patients in China.[3] The complex pathological mechanisms underlying AD have been conceptualized within the ATN(X) framework, which includes the amyloid beta (Aβ) pathway (A), tau-mediated pathophysiology (T), neurodegeneration (N), and additional pathophysiological mechanisms (X), such as neuroimmune dysregulation, synaptic dysfunction, and blood–brain barrier alterations.[4] Over the past few decades, rapid socio-economic development has propelled China into a deeply aging society, with the population aged 65 and above now reaching approximately 210 million,[3] which has placed a substantial economic burden on families and society while also posing a significant challenge to global health-care systems.

Well-organized cohorts have played a pivotal role in advancing research on cognitive disorders. While community-based cohorts typically aim to identify protective and risk factors associated with the disease in large populations, hospital-based cohorts offer a concentrated patient population with pre-existing cognitive complaints. This focus enables more detailed and frequent examinations and comprehensive follow-up assessments. The availability of extensive medical records in a clinical setting significantly enhances the understanding of individual health profiles, thereby supporting more accurate diagnoses and the evaluation of disease progression. Furthermore, various diagnostic assessments can be readily performed in hospitals, facilitating a more nuanced exploration of the relationships between clinical outcomes and pathological biomarkers. Importantly, hospital-based cohorts also serve as a valuable resource for clinical trials.

In recent years, hospital-based cohorts have proliferated rapidly. Studies such as the Australian Imaging, Biomarkers and Lifestyle Study (AIBL)[5] and the Alzheimer's Disease Neuroimaging Initiative (ADNI)[6] aim to track AD progression and explore preventive strategies. Similarly, the China Aging and Neurodegenerative Initiative (CANDI),[7] the Chinese Alzheimer's Biomarker and Lifestyle (CABLE) study,[8] and the CHina registry study on cOgnitiveimPairment in the Elderly (HOPE)[9] all target early detection and diagnosis of cognitive impairment through clinical, imaging, and fluid biomarkers. COhort study to identify predictors for the clinical progression to mild cognitive impairment (MCI) or dementia from Subjective COgnitive decline (CoSCo), a multicenter study in South Korea, investigates risk factors for the progression from subjective cognitive decline (SCD) to MCI or AD.[10] Moreover, cohorts such as the China Alzheimer's Disease and Neurodegenerative Disorder Research (CANDOR) study[11] and the Vascular, Imaging, and Cognition Association of China (VICA) study[12] expand the scope by targeting the pathology and biomarkers of vascular cognitive impairment.

The Shanghai Memory Study (SMS) is an ongoing longitudinal, hospital-based cohort study that was established in 2012. Participants in the SMS underwent comprehensive neuropsychological assessments, biospecimen collection, magnetic resonance imaging (MRI), and positron emission tomography (PET) scans. It offered invaluable data to support both epidemiological research and clinical trials. The primary objectives of the study include (1) identifying potential biomarkers for early diagnosis of MCI, AD, and other dementias to explore the pathological mechanisms of cognitive disorders using a cross-sectional design and (2) monitoring the natural history of cognitive decline and assessing the predictive values of pathological biomarkers for disease outcomes by a longitudinal design.

In this article, we provide an overview of the SMS, including its aims, study design, and data collection, as well as the participants' clinical features, biomarker profiles, and neuroimaging characteristics. Moreover, we summarize major research findings and discuss future directions for the SMS.

2 | METHODS

2.1 | Study design and participants

SMS is an ongoing prospective cohort study launched in 2012. Multidimensional data (including cognitive function and imaging) and biospecimens were collected at baseline and regular longitudinal follow-ups. Since 2018, the study has expanded to include PET imaging and various biomarkers related to blood, urine, retina, and gut microbiota (Table S1). Cross-sectional data collection integrated clinical characteristics, neuroimaging, and biospecimens to explore potential biomarkers for early diagnosis. Longitudinal assessments were conducted to track the trajectory of disease progression and to evaluate the predictive value of biomarkers. Participants were followed up every 1–2 years primarily through proactive in-person visits conducted by clinical staff. Structured telephone interviews were used when severe health conditions prevented clinic attendance.

Participants were individuals with memory complaints seeking medical consultation at the memory clinic in Huashan Hospital, Shanghai,

China. The inclusion criteria of SMS were as follows: (1) age ≥ 40 years, (2) presence of memory complaints for at least 6 months, (3) compliance with comprehensive clinical data collection, (4) ability to complete a battery of neuropsychological assessments, (5) comply with biospecimens samples collection, and (6) good compliance with longitudinal follow-up. The exclusion criteria were as follows: (1) unwillingness to participate in the study; (2) cognitive dysfunction due to developmental disorders or mental retardation; (3) physical incapability (e.g., visual or hearing impairments) or serious mental illness (e.g., major depressive disorder, bipolar disorder, or schizophrenia) that impeded completing the questionnaire interviews and examinations; or (4) presence of contraindications for MRI or PET.

This study has been approved by the Institutional Review Board of Huashan Hospital, Fudan University. All participants or their legal guardians provided written informed consent.

2.2 | Demographic characteristics and comorbid disease

All participants underwent detailed clinical interviews and examinations at baseline and at each follow-up visit (Figure 1). Standardized, questionnaire-based surveys were administered through face-to-face interviews. These questionnaires collected information on demographic characteristics (age, gender, education level, address), socioeconomic status, lifestyle factors (smoking and alcohol consumption), medical history, current medication use, and family history of dementia.

2.3 | Ophthalmic examinations

Ophthalmic examinations included visual acuity (VA), intraocular pressure (IOP), slit-lamp examination, fundus photography, and optical coherence tomography (OCT) imaging. The OCT imaging was performed using the Optovue Angiovue system. Both the optic nerve head and three-dimensional disk were assessed to analyze the thickness of the peripapillary retinal nerve fiber layer (p-RNFL).[13] Optical coherence tomography angiography (OCTA) was also conducted, allowing for the visualization and quantification of retinal and choroidal vessels. The macular and peripapillary regions were the primary areas of focus for the scans.[14] All images were independently reviewed by two ophthalmologists.

2.4 | Olfactory identification test

An olfactory identification test was conducted using the Chinese version of Sniffin' Sticks Screening test (SSST-12),[15] which involves 12 common odors (orange, cinnamon, leather, banana, mint, licorice, lemon, clove, coffee, rose, pineapple, and fish). Participants were required to sniff the odor within 3 to 4 s and select the correct answer from four options.

RESEARCH IN CONTEXT

Systematic review: The authors conducted a search on PubMed for cohort studies related to cognitive disorders. Few clinical cohorts in China thoroughly profiled patients from memory clinics integrating comprehensive clinical assessments and multimodal biomarkers.

Interpretation: Establishing a prospective hospital-based cohort is crucial for advancing dementia research. We initiated the SMS to explore AD pathogenesis and enhance understanding of cognitive disorders through a large-scale dataset, including clinical data, biofluid markers, MRI and PET imaging, and novel biomarkers. The study protocol and major findings of SMS were detailed.

Future directions: The SMS provides the foundation for monitoring the natural history of cognitive disorders and identifying biomarkers for early diagnosis and interventions. Multicenter collaborations should be facilitated to support epidemiological research and clinical trials in future research.

2.5 | Neuropsychological, behavioral, and psychiatric assessment

Each participant was administered a battery of comprehensive neuropsychological tests including (1) Mini-Mental Status Examination (MMSE), (2) Montreal Cognitive Assessment (MoCA), (3) Auditory Verbal Learning Test (AVLT), (4) Rey–Osterrieth Complex Figure Test (ROCFT), (5) Boston Naming Test (BNT), (6) Verbal Fluency Test (VFT), (7) Trail Making Test (TMT), (8) Stroop Color–Word Test (SCWT), (9) Symbol Digit Modalities Test (SDMT), and (10) Clock Drawing Test (CDT). All tests were in Chinese, and normative data and detailed descriptions of these tests have been reported elsewhere.[16–20]

The total scores of MMSE or MoCA was used to assess global cognitive function.[16] Memory performance was evaluated using the subscores from AVLT, including the first to third immediate recalls, short-term delayed recall, and long-term delayed recall.[17] The recall score in ROCFT was adopted as a measure for memory as well. Language function was measured using the scores of BNT[18] and VFT.[21] Attention was reflected by the score of the SDMT.[22] Executive function was assessed by the completion time of TMT[19] or the SCWT.[23] Visuospatial function was evaluated using the score of copy in ROCFT.[20]

Behavioral and psychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI),[24] Hamilton Depression Scale (HAMD),[25] and Hamilton Anxiety Scale (HAMA).[26] Functional Activities Questionnaire (FAQ) and Activity of Daily Living Scale (ADL) were employed to investigated functional impairment.[27,28] The Clinical Dementia Rating (CDR)[29] was used to evaluate the severity of disease.

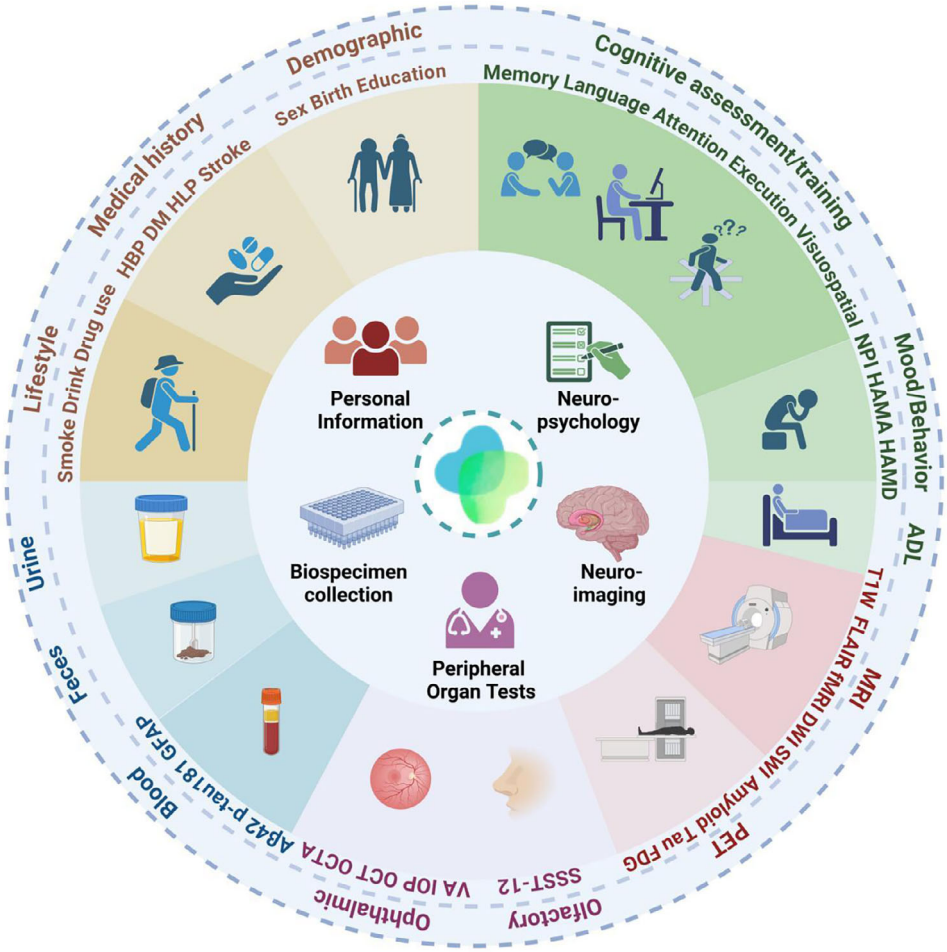

FIGURE 1 Categories and indices of measurements of SMS database. ADL, Activity of Daily Living scale; DM, diabetes mellitus; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; GFAP, glial fibrillary acidic protein; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; HBP, high blood pressure; HLP, hyperlipoproteinemia; IOP, intraocular pressure; MRI, magnetic resonance imaging; NPI, neuropsychiatric inventory; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; PET, positron emission tomography; p-tau, phosphorylated tau; SSST-12, 12-item Sniffin' Sticks Smell Test; SMS, Shanghai Memory Study; SWI, susceptibility-weighted imaging; VA, visual acuity.

2.6 | Cognitive diagnosis

The diagnosis encompassed the dementia, MCI, and cognitively unimpaired (CU). Diagnosing dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV).[30] The diagnosis of AD was made in accordance with the National Institute on Aging-Alzheimer's Association criteria.[31] Other dementias, including vascular dementia (VaD),[32] frontotemporal lobar dementia (FTLD),[33] Parkinson's disease dementia (PDD),[34] dementia with Lewy bodies (DLB),[35] general paresis of the insane (GPI),[36,37] progressive supranuclear palsy (PSP),[38] multiple system atrophy (MSA),[39] normal pressure hydrocephalus (NPH),[40] trauma-related dementia,[41] and dementia due to mental disorders[30] were diagnosed based on their respective diagnostic criteria. Only patients without dementia were considered for a diagnosis of MCI according to the Petersen criteria.[42] We further classified amnestic MCI (aMCI) or non-amnestic MCI (naMCI) into subtypes as single-domain or multidomain,[43] which depended on the number of affected cognitive domains. CU participants were defined as having intact cognitive function confirmed by neuropsychological assessment, ADL, and with a CDR score of 0. Among CU individuals, those exhibiting SCD were defined by the research framework for pre-MCI proposed by Jessen et al. in 2014.[44] A panel of cognitive disorder specialists synthesized neurological, psychiatric, imaging, neuropsychological, and other medical data to reach a consensus diagnosis. They were blinded to the plasma biomarkers results to ensure an unbiased evaluation.

2.7 | Biospecimens collection and storage

Blood samples were collected from participants who provided consent at baseline and during each follow-up. A total of 5 mL of venous blood was drawn into an ethylene diamine tetraacetic acid (EDTA) tube, which was gently inverted and mixed 10 to 12 times to ensure

thorough mixing of the blood and anticoagulant. The mixed blood was then placed in an incubator at 4°C and centrifuged at 1000 rpm for 15 min within 8 h of collection. After centrifugation, 300 µL of plasma and red blood cells were aliquoted into separate tubes. Additionally, 2 mL of venous blood was collected in a serum separator tube and allowed to stand at room temperature for at least 30 min. After centrifugation at 4000 rpm for 8 min, the supernatant (serum) was aliquoted into several 0.5-mL centrifuge tubes, each containing 300 µL of serum.

Participants were instructed to collect 20 g of morning fasting feces in aseptic containers on the day of their clinical visit, ensuring delivery to the hospital within 1 h. Then the samples were aliquoted into four tubes, each containing 5 g of feces. In addition, a 20-mL spot urine sample was collected and divided into two tubes, each containing 10 mL of urine.

All biospecimens were stored in −80°C refrigerators until analysis. The biorepository used for storing biological samples is equipped with appropriate alarm systems and emergency backup power to prevent accidental thawing.

2.8 | APOE genotyping

DNA was extracted from blood samples. Genotyping of apolipoprotein E (APOE) was accomplished using the Taqman single-nucleotide polymorphism method.[45] The presence of at least one $\varepsilon 4$ allele was treated as being APOE $\varepsilon 4$ positive.

2.9 | Blood-based AD biomarker assay

Plasma biomarkers, including Aβ40, Aβ42, total tau (t-tau), neurofilament protein light chain (NfL), and tau phosphorylated at threonine 181 (p-tau181) and p-tau217 were quantified using an ultra-sensitive single-molecule array (Simoa) technology (Quanterix, MA, USA) on the automated Simoa HD-X platform. The multiplex Neurology 3-Plex A kits (Catalog No. 101995), NF-light assay (Catalog No. 103186), p-tau181 Assay Kit V2 (Catalog No. 103714), and the ALZpath Simoa p-tau217 v2 (Catalog No: 104371) were obtained from Quanterix and used as directed. For all assays, serum and plasma samples were diluted at a 1:4 ratio. Technicians who performed the assay were blinded to the clinical data.

2.10 | Neuroimaging acquisition

MRI scans included T1-weighted (T1W), fluid-attenuated inversion recovery (FLAIR), functional MRI (fMRI), and susceptibility-weighted imaging (SWI) and diffusion-weighted imaging (DWI) sequences, which were acquired using a Siemens Verio 3T MRI scanner (Table 1). During MRI scans, participants were instructed to keep their eyes closed without falling asleep. As shown in Table 1, amyloid PET imaging was performed using the following tracers: 18F-Florbetapir (18F-AV-45), 18F-Flutemetamol (18F-AV-1), or 11C-Pittsburgh compound B (11C-PiB). Tau PET imaging was also conducted using 18F-Florzolotau (18F-PM-PBB3 or 18F-APN-1607). The 18F-fluorodeoxyglucose (18F-FDG) PET was adopted for cerebral glucose metabolism. Detailed procedures have been reported elsewhere.[46,47] The mean (standard deviation [SD]) interval from multimodal MRI and PET imaging to blood collection was 2.6 (5.0) weeks. The imaging was interpreted and evaluated visually by experienced neurologists and neuroradiologists.

2.11 | Image processing and analysis

Structural MRI and PET data were processed using a standardized pipeline as follows: (1) raw PET images were co-registered to the corresponding structural MRI scans; (2) PET images were spatially normalized to the Montreal Neurological Institute (MNI) standard space using the transformation parameters derived from segmentation of the structural MRI scans, followed by spatial smoothing with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel; (3) intensity normalization was performed using specific reference regions: whole cerebellum for 18F-florbetapir PET, cerebellar gray matter for 18F-Florzolotau PET, and pons for 18F-FDG PET. Standardized uptake value ratio (SUVR) values were calculated within predefined regions of interest (ROIs), based on previously established methods.[48–50] All imaging analyses were conducted using Statistical Parametric Mapping (SPM12) software (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), implemented in MATLAB (MathWorks, Natick, MA, USA).

2.12 | Statistical analysis

The normality of continuous variables was assessed using the Shapiro–Wilk test. Levene's test was performed to evaluate the homogeneity of variances. Descriptive statistics were presented as follows: mean ± SD for normally distributed variables, median and interquartile range (IQR) for skewed variables, and number (percentage) for categorical variables. For comparisons among multiple groups, one-way ANOVA followed by Tukey's post hoc test were applied for normally distributed variables with equal variance; however, Welch's ANOVA and the Games–Howell post hoc test were used when variances were unequal. The Kruskal–Wallis test, followed by Dunn's post hoc test with Bonferroni correction, was used for non-normally distributed variables. Categorical variables were analyzed using the chi-squared test and post hoc z-tests with Bonferroni correction. Pearson's correlation analysis was applied to the correlations between groups with continuous variables.

To examine the risk of progression from aMCI to AD dementia (ADD), we used Kaplan–Meier survival curves and the log-rank test to compare cumulative incidence across groups. Cox proportional hazard regression models were employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for age, sex, years of education, and APOE $\varepsilon 4$ carrier status. The follow-up period referred to the time between the participant's baseline assessment and either the last follow-up or the end of the observation period. Receiver oper-

TABLE 1 Parameters of multimodal MRI scans and tracers of PET scans.

MRI sequence	Voxel size (mm)	FOV (mm)	TR (ms)	TE (ms)	Flip angle (°)
T1W	1.0 × 1.0 × 1.0	256	2530	2.98	7
T2W	0.9 × 0.6 × 5.0	240	6000	95	150
T1-FLAIR	1.0 × 0.7 × 5.0	230	2000	9	150
T2-FLAIR	1.3 × 0.9 × 3.0	240	9000	94	150
DWI	1.4 × 1.4 × 5.0	210	7800	91	–
DTI	2.0 × 2.0 × 2.0	220	12,300	82	–
SWI	0.5 × 0.5 × 1.5	230	28	20	15
BOLD	3.3 × 3.3 × 4.0	210	2000	35	90
PET	**Tracers**				
FDG-PET	^{18}F-Fluorodeoxyglucose				
Amyloid PET	^{18}F-Florbetapir (^{18}F-AV-45), ^{18}F-Flutemetamol (^{18}F-AV-1), ^{11}C-Pittsburgh compound B				
Tau PET	^{18}F-Florzolotau (^{18}F-PM-PBB3 or ^{18}F-APN-1607)				

Abbreviations: BOLD-fMRI, blood oxygen level-dependent functional magnetic resonance imaging; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FDG, fluorodeoxyglucose; FLAIR, fluid attenuated inversion recovery; PET, positron emission tomography; SWI, susceptibility-weighted imaging; T1W, T1-weighted MRI; T2W, T2-weighted MRI.

ating characteristic (ROC) curve analysis was performed to evaluate biomarkers' diagnostic and predictive performance, with area under the curve (AUC) comparisons conducted using DeLong's test. Concordance between biomarkers was assessed using agreement rates and Cohen's kappa coefficients. All statistical tests were two-sided; a p value < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 27.0 for Windows (IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Characteristics of participants

As this was a hospital-based study, participants were consecutively enrolled from a memory clinic based on predefined inclusion and exclusion criteria. Based on approximately 180 individuals enrolled each year, we recruited 2001 participants (115 CU, 938 MCI, 948 dementia) from 2012 to 2024. The baseline characteristics were presented in Table 2. The average age of the cohort was 72.9 years, with 63.5% of participants aged between 60 and 79 years and 57.6% female. The cohort was generally well educated, with 54.7% of participants reporting 12 or more years of formal education. Compared to CU individuals, those with MCI or dementia had older ages, fewer years of education, a higher prevalence of APOE ε4 carriers, and lower MMSE and MoCA scores. Additionally, the dementia group exhibited significantly lower scores on both MMSE and MoCA than the MCI group. The CU demonstrated a higher prevalence of alcohol consumption, while the highest smoking rates were observed in the dementia group. Regarding comorbidities, the prevalence of hypertension, diabetes mellitus, and stroke was notably higher in the MCI and dementia groups compared to the CU group.

3.2 | Categories of cognitive diagnosis

A total of 115 participants (5.7%) were diagnosed with CU, 938 participants (46.9%) with MCI, and 948 participants (47.4%) with dementia. Within the MCI group, 886 participants (94.5%) were diagnosed with aMCI, significantly outnumbering those with naMCI. Among the aMCI cases, 579 were classified as multiple-domain aMCI (aMCI-MD), exceeding the 307 diagnosed with single-domain aMCI (aMCI-SD). Similarly, within the naMCI subgroup, 42 participants were identified as multiple-domain naMCI (naMCI-MD), which was more frequent than the 10 participants diagnosed with single-domain naMCI (naMCI-SD).

Among the dementia cases, 752 participants (79.3%) were classified as ADD. The majority of the remaining 196 non-ADD cases were attributed to other neurodegenerative diseases. Specifically, 37.8% were diagnosed with FTLD, 28.1% with PDD or DLB, and 15.3% with VaD. The remaining 18.9% were attributed to other etiologies, including GPI, PSP, MSA, NPH, trauma-related dementia, dementia due to mental disorders, and unspecified dementia (Figure 2A).

3.3 | Major findings

3.3.1 | Plasma biomarkers across disease stages

Blood-based biomarkers (BBMs) from a subset of 451 participants described based on the combination of CDR and clinical diagnosis were quantified (Table S2). As the CDR score increased, we found a decreasing trend in plasma levels of Aβ40, Aβ42, and the Aβ42/Aβ40 ratio but an increasing trend of t-tau, NfL, and p-tau181. There were significant differences observed in the levels of Aβ40, Aβ42, and NfL between participants who were CU (CDR = 0) and those with AD (CDR ≥ 1).

TABLE 2 Baseline characteristics of participants in SMS.

Characteristics	Overall ($n = 2001$)	CU ($n = 115$)	MCI ($n = 938$)	Dementia ($n = 948$)	*P* value*
Age, year, median (IQR)	73 (66, 80)	65 (57,73)	76 (69,82)	72 (64,79)	**<0.001**
< 60, *n* (%)	206 (10.3)	41 (35.7)	44 (4.7)	121 (12.8)	
60–79, *n* (%)	1271 (63.5)	67 (59.1)	591 (62.9)	613 (64.7)	
≥ 80, *n* (%)	524 (26.2)	6 (5.2)	304 (32.4)	214 (22.6)	
Sex, female, *n* (%)	1153 (57.6)	65 (57.4)	533 (56.7)	555 (58.5)	0.729
Education, year, median (IQR)	11 (9, 13)	13 (12, 16)	12 (9, 14)	9 (6, 12)	**<0.001**
Illiteracy, *n* (%)	79 (4.0)	2 (1.7)	4 (0.4)	73 (7.7)	
Primary, *n* (%)	281 (14.0)	4 (3.5)	83 (8.9)	194 (20.5)	
Junior middle, *n* (%)	547 (27.3)	14 (12.2)	260 (27.7)	273 (28.8)	
Senior middle, *n* (%)	563 (28.1)	31 (27.0)	291 (31.0)	241 (25.4)	
College and higher, *n* (%)	531 (26.5)	64 (55.7)	300 (32.0)	167 (17.6)	
Smoke, *n* (%)	389 (19.4)	17 (14.8)	157 (16.7)	215 (22.7)	**0.002**
Drink, *n* (%)	390 (19.5)	25 (21.7)	160 (17.1)	205 (21.6)	**0.036**
Hypertension, *n* (%)	775 (38.7)	37 (32.2)	389 (41.5)	349 (36.8)	**0.038**
Diabetes, *n* (%)	286 (14.3)	9 (7.8)	155 (16.5)	122 (12.9)	**0.010**
Stroke, *n* (%)	295 (14.7)	14 (12.2)	113 (12.1)	168 (17.7)	**0.002**
ApoE ε4, *n* (%)					**<0.001**
Non-carrier	1149 (61.8)	77 (74.0)	590 (67.9)	482 (54.5)	
Heterozygous	571 (30.7)	21 (20.2)	231 (26.6)	319 (36.1)	
Homozygous	138 (7.4)	6 (5.8)	48 (5.5)	84 (9.5)	
MMSE, median (IQR)	24 (17, 27)	29 (28, 29)	26 (25, 28)	16 (10, 21)	**<0.001**
MoCA, median (IQR)	15 (9, 21)	27 (25,28)	20 (17, 23)	10 (6, 14)	**<0.001**

Abbreviations: ApoE, Apolipoprotein E; CU, cognitively unimpaired; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.
**P* values refer to comparisons among the three groups: CU, MCI, and dementia.
Bold indicates statistically significant results ($P < 0.05$).

The Aβ42/Aβ40 ratio and t-tau exhibited differences only between CU (CDR = 0) individuals and those with severe AD (CDR = 3). The concentration of p-tau181 increased progressively across different cognitive stages of AD.[51] A simplified diagnostic model incorporating plasma p-tau181, Aβ42, and clinical features effectively distinguished AD from cognitively normal individuals (AUC = 0.933).[52]

3.3.2 | ATN PET profiles and their correlation with cognitive status

The results from participants who underwent both Aβ and tau PET scans revealed the frequency distribution of A−/T−, A−/T+, A+/T−, and A+/T+ profiles (Figure 2b): A−/T− was observed in 78.9% of CU cases, 37.3% of MCI cases, and 44.8% of non-AD cases. A−/T+ was present in 8.1% of MCI cases and 55.2% of non-AD cases. A+/T− occurred in 5.3% of CU cases and 3.3% of MCI cases. Finally, A+/T+ accounted for 15.8% of CU cases, 51.2% of MCI cases, and 100% of ADD cases.

In Aβ-positive individuals, tau PET SUVR measurements in the medial temporal lobe (MTL) and temporal neocortex (NEO-T) increased progressively with advancing CDR global scores (all $p < 0.001$). In contrast, FDG PET SUVR values within the meta-analytically derived region of interest (metaROI) showed a significant decline with increasing disease severity ($p < 0.001$). Moreover, plasma p-tau181 level demonstrated strong concordance with tau PET SUVRs in both MTL and NEO-T regions for differentiating Aβ-positive from Aβ-negative individuals, with Cohen's kappa coefficients of 0.65 for MTL SUVR and 0.72 for NEO-T SUVR.[53]

3.3.3 | Prediction of long-term clinical outcomes in individuals with aMCI

An analysis was performed on a subcohort with 251 participants with aMCI at baseline, including 121 (48.2%) with aMCI-SD and 130 (51.8%) with aMCI-MD. Over a median follow-up duration of 4.7 years (range: 0.9 to 8.1 years), 88 participants (35.1%) progressed to ADD,

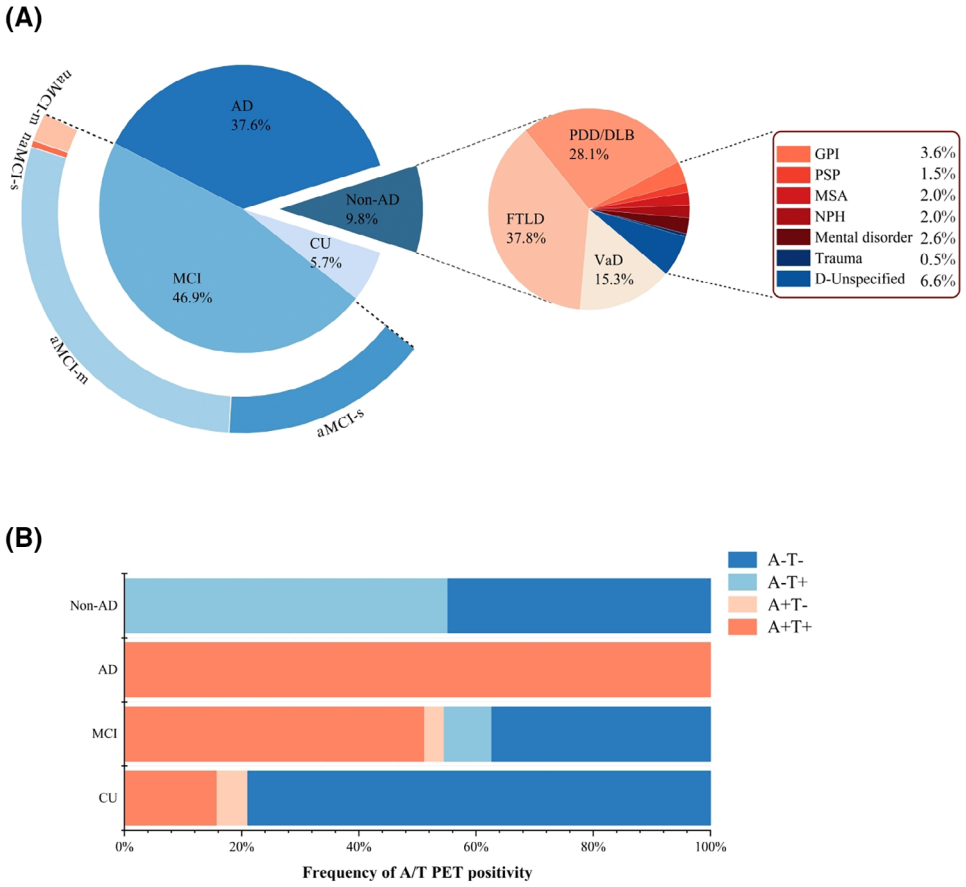

FIGURE 2 Proportion of participants with diagnostic types and A/T PET positivity between different clinical groups. Aβ, amyloid beta; AD, Alzheimer's disease; CU, cognitively unimpaired; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; GPI, general paresis insane; MCI, mild cognitive impairment; MSA, multiple system atrophy; NPH, normal pressure hydrocephalus; PDD, Parkinson's disease dementia; PSP, progressive supranuclear palsy; VaD, vascular dementia.

while eight participants were diagnosed with non-ADD (three cases of VaD, one case of PDD, one case of FTLD, and three cases of unspecified dementia). Among participants who did not progress to dementia, 62 reverted to normal cognitive function, whereas 93 remained classified as MCI. After adjusting for age, sex, years of education, and APOE ε4 status, participants with both low plasma Aβ42/Aβ40 ratio (< 0.056) and elevated p-tau181 level (> 2.41 pg/mL) at baseline exhibited the highest risk of progression to ADD (HR = 4.83, 95% CI 2.37–9.86).[54]

3.3.4 | Exploration of novel biomarkers

Retinal thickness was assessed using OCT in 73 individuals with AD, 51 with MCI, and 67 CU controls. Both the p-RNFL and the ganglion cell complex (GCC) were significantly thinner in individuals with AD and MCI compared to CU participants (AD vs CU, $p < 0.01$; MCI vs CU, $p < 0.01$). Additionally, MCI subjects exhibited significant thinning of the macular inner retinal layers relative to CU controls ($p < 0.001$). Retinal thickness was significantly correlated with total brain volume ($p < 0.05$), and the thickness of macular inner layers demonstrated a stronger association with hippocampal and entorhinal cortex volumes ($r = 0.427$ to 0.644, $p < 0.01$).[13]

We analyzed 302 fecal samples from CU ($n = 94$), MCI ($n = 125$), and AD ($n = 83$) subjects using 16S rRNA gene sequencing. At the genus level, the abundance of five taxa, including *Erysipelatoclostridiaceae*, *Erysipelotrichales*, *Saccharimonadales*, *Patescibacteria*, and *Saccharimonadia*, were positively associated with CDR scores and negatively correlated with memory performance (all $p < 0.001$). These taxa exhibited a progressive increase in abundance from CU to MCI to AD (all $p < 0.001$). Notably, all five taxa were more abundant in APOE ε4 carriers than in non-carriers (all $p < 0.05$).[55]

4 | DISCUSSION

SMS is one of the few clinical cohorts of cognitive disorders in China. The study incorporates a broad range of multidimensional biomarkers, both biological and clinical, with a particular focus on PET molecular imaging. Another key strength of the SMS is its nearly 10-year follow-up of the initial patient cohort, supported by well-defined diagnostic criteria, which provides opportunities to observe the prognosis

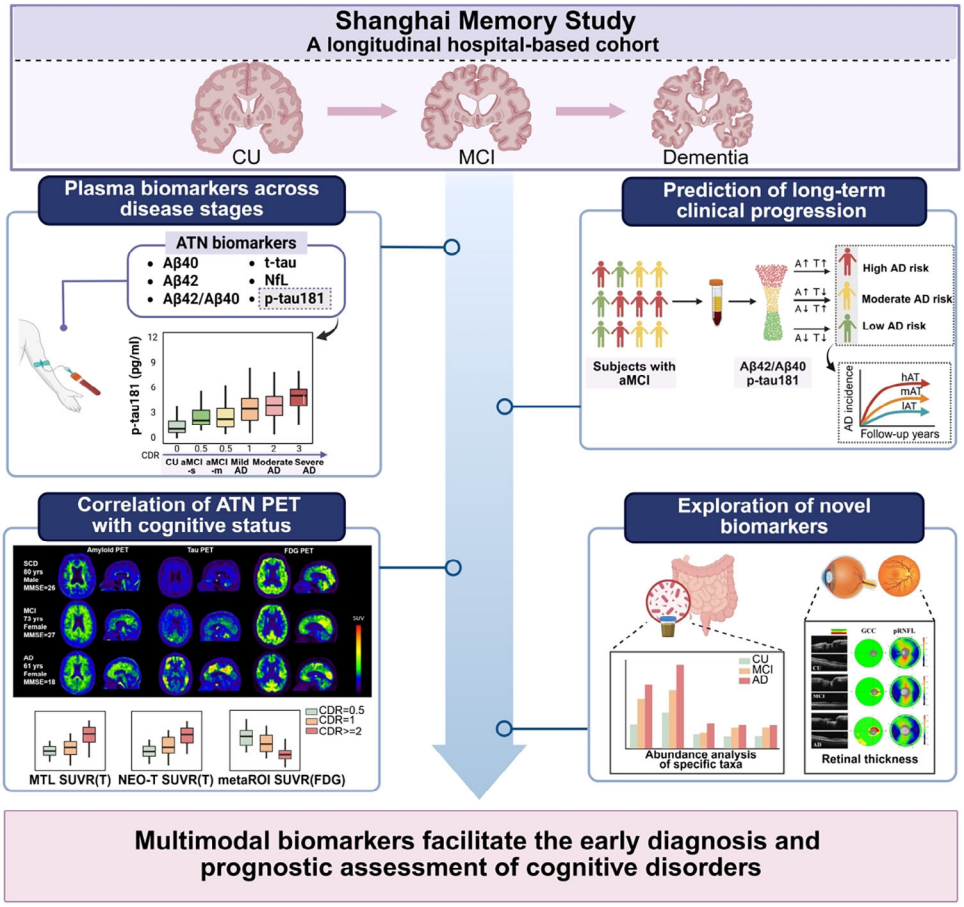

FIGURE 3 Overview of SMS. The SMS is a longitudinal, hospital-based cohort recruiting CU, MCI, and dementia participants across the cognitive spectrum. Major findings of SMS focus on the correlation of ATN biomarkers in plasma and PET with cognitive status, the prediction of long-term clinical outcomes, and the exploration of novel biomarkers. The primary objectives of SMS are to facilitate the early diagnosis and prognostic assessment of cognitive disorders by integrating multimodal biomarkers. AD, Alzheimer's disease; aMCI-m, amnestic mild cognitive impairment-multiple domains; aMCI-s, amnestic mild cognitive impairment-single domain; Aβ, amyloid beta; CDR, Clinical Dementia Rating scale; CU, cognitively unimpaired; FDG, fluorodeoxyglucose; FTLD, frontotemporal lobar degeneration; GCC, ganglion cell complex; hAT, high-risk AT (low plasma Aβ42/Aβ40 and high p-tau181); IAT, low-risk AT (high plasma Aβ42/Aβ40 and low p-tau181); mAT, moderate-risk AT (low plasma Aβ42/Aβ40 and low p-tau181, or high plasma Aβ42/ Aβ40 and high p-tau181); MCI, mild cognitive impairment; metaROI, meta-analytically derived region of interest; MMSE, Mini-Mental State Examination; MTL, medial temporal lobe; NEO-T, temporal neocortex; NfL, neurofilament protein light chain; PET, positron emission tomography; pRNFL, peripapillary retinal nerve fiber layer; p-tau 181, tau phosphorylated at threonine 181; SMS, Shanghai Memory Study; SUV, standard uptake value; t-tau, total tau.

of diseases. SMS has made major findings in the following areas: investigating blood biomarkers to assist the diagnosis and prediction of disease progression, integrating PET imaging with biofluid markers to assess disease severity, and identifying potential novel biomarkers for early detection of AD (Figure 3).

Among the blood-based ATN biomarkers assessed in our study, only plasma p-tau181 remained significantly elevated from CU to MCI and AD. This finding aligned with previous studies,[56,57] supporting the continuous involvement of tau pathology across the AD continuum. As a clinically relevant biomarker, plasma p-tau181 showed promise as a dynamic biomarker for disease progression monitoring and personalized disease-modifying therapy guidance.

We further compared plasma and PET ATN biomarkers to elucidate the association between peripheral biomarkers and neuroimaging measures. Previous studies demonstrated strong correlations between plasma p-tau biomarkers and both cerebrospinal fluid (CSF) and PET tau burdens, aligning with our findings.[58,59] Both 18F-Florzolotau and 18F-FDG PET robustly captured clinical severity. In contrast, neither plasma nor PET A biomarkers showed a significant association with cognitive impairment, reinforcing the hypothesis that Aβ pathology plateaus during the preclinical stage prior to symptom onset.[60]

Our 8-year longitudinal follow-up revealed that combining plasma Aβ42/Aβ40 and p-tau181 with demographic variables such as age, sex, years of education, and baseline MMSE scores improved predictive performance for identifying individuals at risk of AD conversion.[54] The AIBL cohort found that lower Aβ42/Aβ40 ratios and higher p-tau181 at baseline were associated with faster cognitive decline and increased cerebral amyloid deposition,[61] which aligned with our findings. Notably, approximately 25% of participants with aMCI reverted to CU status, consistent with a meta-analysis reporting an overall rever-

sion rate of 27.57%,[62] underscoring the inherent heterogeneity of MCI as a transitional clinical syndrome.

SMS also attempted to explore novel, non-invasive, and accessible biomarkers for AD. As an extension of the central nervous system, the retina offers a feasible window into neurodegenerative processes.[63] Our study demonstrated that retinal thickness, particularly the inner layer of the perifoveal retina, may serve as an early biomarker of AD, reflecting neurodegeneration or neuronal injury. Additionally, alterations in gut microbiota suggested their potential role as an "ignition" factor in early AD development and an "accelerator" in later disease progression.[55]

There are several limitations of SMS. First, the relatively small sample size, particularly in the longitudinal study, may reduce the statistical power and constrain our findings' robustness and generalizability. Future studies with larger sample sizes and longer follow-up durations are needed. Second, the educational level of SMS participants is relatively high, as most are from urban areas in Shanghai, which may limit the representativeness of the cohort. In future studies, we plan to increase the inclusion of individuals with lower educational attainment to improve cohort diversity. Third, the present analysis did not include blood biomarker data from each follow-up time point. We plan to incorporate longitudinal biomarker data from every follow-up visit in future studies to characterize temporal dynamics and improve understanding of disease progression. Fourth, the cut-off values of plasma biomarkers were used solely for risk stratification in the SMS. These thresholds were derived from a hospital-based population, primarily including individuals with MCI and AD. Therefore, their applicability to broader clinical or community-based populations requires further validation in more diverse populations in future studies. Fifth, there is significant heterogeneity among patients. While the cohort reflects real-world scenarios by including a diverse range of conditions, this variability increases the complexity of long-term follow-up and reduces response rates. Sixth, only 602 participants in the SMS cohort underwent PET scans, reflecting a relatively low acceptance rate for PET imaging. The high cost of PET and concerns about radiation exposure have limited participants' willingness to undergo the procedure. Last, since the SMS is based mainly on a memory clinic, CSF samples were not collected.

There are future plans for the SMS. First, SMS is ongoing, and there are plans to continue enrolling eligible individuals, particularly those in the preclinical stage of AD. We are also actively seeking collaborations to establish multicenter collaborative research. Second, future research needs to validate the utility of BBMs through large-scale longitudinal clinical studies. Meanwhile, the development of BBMs targeting synaptic dysfunction and inflammation, along with the advancement of molecular imaging research, will offer new opportunities for precision medicine. Third, "Memory Ever," a digital cognitive assessment and training program, has been developed by the SMS group. Future work will validate its diagnostic efficacy and evaluate its intervention efficacy. Lastly, SMS provides an ideal cohort for evaluating both pharmacological and non-pharmacological interventions for dementia. The efficacy and safety of various treatments, including medications and lifestyle interventions (such as exercise, diet, or cognitive training), could be thoroughly assessed through long-term follow-up.

In summary, the SMS has established a relatively large-scale dataset with comprehensive data collection, including clinical evaluation, biofluid markers, MRI and PET imaging, and novel biomarkers. By offering an integrated framework for investigating dementia, SMS will facilitate the exploration of AD pathogenesis and deepen the understanding of cognitive disorders.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare. Author disclosures are availaible in the Supporting Information.

CONSENT STATEMENT

This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University (Approval No. 2011-288, 2021-014, 2024-741), in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All participants or their legal guardians provided written informed consent.

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SUPPORTING INFORMATION

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