Changes of plasma A β and t-tau along with 18F-florbetapir PET in a cohort of cognitive decline

Feng-Feng Pan

Shanghai Sixth Peoples Hospital

Qi Huang

Huashan Hospital Fudan University

Ying Wang

Shanghai Sixth Peoples Hospital

Yi-Fan Wang

Shanghai Sixth Peoples Hospital

Yi-Hui Guan

Huashan Hospital Fudan University

Fang Xie

Huashan Hospital Fudan University

Qihao Guo (✉ qhguo@sjtu.edu.cn)

Shanghai Jiao Tong University

Research

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Abstract

Background

Blood based biomarkers for Alzheimer's disease (AD) are becoming increasingly promising. Although plasma amyloid- β (A β) and total tau (t-tau) showed a potential ability in identifying cerebral amyloid deposition and AD. Comparisons of these plasma biomarkers along with A β -PET in a cohort of normal controls (NC), subjective cognitive decline (SCD), objectively-defined subtle cognitive decline (Obj-SCD), mild cognitive impairment (MCI) and AD remained lacking.

Methods

A total of 407 individuals aged from 40 to 90 years old were recruited, including 76 of NC, 77 of SCD, 61 of obj-SCD, 92 of MCI and 101 of AD. Plasma A β 40, A β 42 and t-tau were examined via single-molecule array (Simoa) immunoassay. A subset of 132 individuals underwent cerebral amyloid scans with 18F-florbetapir PET. Comparisons of plasma t-tau, A β 40, A β 42 and A β 42/A β 40 ratio were conducted between different diagnostic groups and cerebral A β burdens. Pearson correlation analysis was used to evaluate the correlation between A β 42, A β 42/A β 40 ratio and 18F-florbetapir SUVR. Receiver operating characteristic (ROC) curve analyses were carried out to evaluate the capacity of plasma biomarkers in identifying high brain A β burden and diagnosis of AD.

Results

Plasma A β 42 was significantly higher in SCD and obj-SCD than NC, MCI and AD. Plasma A β 40 was significantly higher in SCD and obj-SCD than NC and AD. The lowest levels of plasma A β 42 and A β 42/A β 40 ratio were found in AD. No significant difference of plasma t-tau was found among groups. Plasma A β 42 and A β 42/A β 40 ratio were inversely correlated with 18F-florbetapir SUVR ($r=-0.272$, $P=0.003$; $r=-0.211$, $P=0.021$ respectively). A β 42/A β 40 ratio performed well in predicting high brain A β burden (area under the curve, AUC = 0.762). Plasma A β 42 and A β 42/A β 40 ratio had acceptable diagnostic accuracy for AD (AUC = 0.714 and 0.706 respectively), even in A β -PET (+) individuals (AUC = 0.728 and 0.808 respectively).

Conclusions

Plasma A β 40 and A β 42 measured by Simoa immunoassay showed a significantly bidirectional trend of initially increasing from NC to SCD and obj-SCD, and then declining to MCI and AD. In addition, plasma A β was significantly correlated with 18F-florbetapir PET SUVR and showed potential value in predicting cerebral A β deposition and risk of AD.

Background

Deposition of amyloid- β (A β) plaques and neurofibrillary tangles (NFTs) of tau fibrils are still the primary neuropathological hallmarks of Alzheimer's disease (AD)(1). Though the examination of cerebrospinal fluid (CSF) and PET imaging provide the most reliable AD-related biomarkers of A β and tau in-vivo(2, 3), the invasive sampling procedure of CSF and high cost of PET image hinder their application in clinical trials and population screening, especially in the preclinical stages of AD. Blood-based biomarkers have the advantages of less invasive, more cost effective and easy to handle, potentially enabling its usage in population screening and follow-up. Owing to the emergence of ultrasensitive technologies such as Immunoprecipitation-mass spectrometry (IP-MS)(4) and single molecule array (Simoa)(5), measuring AD-related biomarkers in blood becomes increasingly promising. With these high sensitivity measurements, previous studies showed that plasma A β was significantly correlated with CSF(6-8), and had a high performance in predicting cerebral amyloid deposition (8-10). Consistent with the association between low plasma A β and increasing cerebral amyloid deposition, plasma A β isoforms and A β 42/A β 40 ratio were significantly lower in patients with AD (6, 11, 12). Even in the dementia-free populations, lower plasma levels of A β 42 or A β 42/A β 40 ratio are associated with steeper rate of cognitive decline or increased risk of AD and dementia(13-15).

Currently, even though the significant correlations between low plasma A β and AD were identified, confusing findings still remain. For example, in the large sample cohort of AIBL, plasma concentrations of A β 42 and A β 40 measured by ELISA showed an increasing trend from health controls to mild cognitive impairment (MCI), but decreased from MCI to AD(16). Similarly, a population based cross-sectional study found that plasma A β 42 and A β 42/A β 40 ratio in the possible cognitive impairment were higher than both the normal cognition group and probable cognitive impairment group(17). A recent longitudinal study showed that plasma A β 42 levels increased gradually before the stage of MCI and decreased just prior to clinical AD onset(18). Taken together, these data suggest a dynamic, nonlinear character of plasma amyloid- β over the course of cognitive decline. However, this trend of plasma amyloid- β was mostly derived from the cognitive status of MCI and

dementia, but not took into account the earlier status such as subjective cognitive decline (SCD) and objectively-defined subtle cognitive decline (Obj-SCD), which may lead to not accurately reflect the evolution of plasma biomarkers across a complete spectrum of cognitive decline.

The aims of this study were to examine plasma A β 42, A β 40 and t-tau with Simoa immunoassay in a cohort of cognitive decline, explore their evolution among normal controls (NC), SCD, Obj-SCD, MCI and AD, and investigate their abilities in identifying cerebral amyloid deposition and diagnosis of AD.

Methods

Study participants

In this monocentric retrospective cohort study, a total of 407 individuals were enrolled from Sixth People's Hospital, Shanghai, China, from January 2019 to January 2021. Participants were aged 40 to 90 years, educated more than one year. Individuals with a history of significant neurologic disease, psychiatric disorders, alcoholism, drug abuse and head trauma were excluded. Routine laboratory tests and cranial MRI scanning were carried out to preclude relevant diseases which may be adversely affecting cognitive function, such as abnormalities in folic acid, vitamin B12, thyroid function, cerebral infarction, subdural hematomas, hydrocephalus, intracranial tumors and infections. All the participants underwent a battery of standardized neuropsychological tests and examined plasma A β 42, A β 40 and t-tau via Simoa immunoassay. A total of 132 participants underwent 18F-florbetapir PET scan within 3 months after blood sampling. Written informed consent was obtained from all the participants or their caregivers. The ethics committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital approved this study.

Neuropsychological Assessment

General cognitive performance was assessed by Mini-Mental State Examination (MMSE)(19), Montreal Cognitive Assessment-Basic (MoCA-BC)(20) and Chinese version of Addenbrooke's Cognitive Examination-III (ACE-III-CV)(21). Global functional status was assessed by Everyday Cognition (ECOG)(22) and Functional Assessment Questionnaire (FAQ)(23). In addition, a battery of standardized neuropsychological tests including six neuropsychological indexes was carried out: Auditory Verbal Learning Test (AVLT)(24) 30-minute delayed free recall and AVLT recognition for memory, Boston Naming Test (BNT)(25) and Animal Verbal Fluency Test (AFT)(26) for language, Shape Trail Test Part A and B (STT-A, STT-B)(27) for executive function.

Cognitive groups

The clinical diagnosis of AD was made by experienced neurologists according to the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria for probable AD dementia(28). In the non-dementia participants, MCI and Obj-SCD was classified according to the criteria proposed by Jak and Bondi(29). Diagnosis of MCI was given if the participant met one of the following criteria: (1) impaired scores (defined as >1 standard deviation (SD) below the age-corrected normative mean) on two of the six neuropsychological indexes in the same cognitive domain; (2) impaired scores in each of the three cognitive domains; (3) FAQ score ≥ 9 . Participants were classified as Obj-SCD according to one of the following criteria: (1) impaired scores on two of the six neuropsychological indexes in the different cognitive domains; (2) impaired scores on one of the six neuropsychological indexes; (3) FAQ score of 6-8. Participants with self-reported experiences of cognitive decline but not met the criterion for MCI and Obj-SCD were classified as SCD according to the conceptual framework proposed by the Subjective Cognitive Decline Initiative (SCD-I) working group(30). Normal controls were recruited from caregivers or through advertisements, with no cognitive complaint and impairment determined by neuropsychological tests.

Blood processing and measurements of plasma A β 42, A β 40, t-tau

Blood samples were centrifuged at 500 g for 5 minutes at 4 °C to collect plasma. Then plasma was immediately aliquoted into ultra-low adsorption tubes (AXYGEN MCT-150-L-C) on ice and stored at -80 °C refrigerator. Before the test, plasma samples were transferred from the refrigerator to ice plate for 30 minutes, and then centrifuged at 10,000 g for 5 min at 4 °C. Total tau measurement was performed using Neurology 4-Plex A kit (Quanterix 102153), A β 42 and A β 40 were performed using Neurology 3-Plex A assay (Quanterix 101995) on the Simoa HD-1 platform (Quanterix)(31). Reagent pretreatment and sample loading were carried out according to the instructions of the manufacture. In brief, 350 μ L pre-diluted calibrator reagent (0–100pg/mL for t-tau, 0–50 ng/mL for A β 42 and 0–150 ng/mL for A β 40) and 320 μ L plasma sample (1:4 diluted) were loaded on the plate. Concentrations of each marker (pg/mL) were calculated from the calibration curve. All the biomarker measurements were performed by laboratory technicians who were blinded to the clinical data.

18F-florbetapir PET acquisition and analysis

Amyloid PET images were obtained from a PET/CT system (Biograph mCT Flow PET/CT, Siemens, Erlangen, Germany) at the PET center of Huashan hospital, Fudan University. Cerebral amyloid PET scans were carried out 50min after the intravenous injection of 7.4 MBq/kg(0.2mCi/kg) florbetapir and lasted for 20min. PET images were reconstructed using filtered back projection algorithm with corrections for decay, normalization, dead time, photon attenuation, scatter and random coincidences. PET images were coregistered to the individual structural MRI and partial volume error correction (PVC) was performed using the Muller-Gartner methods(32, 33), followed by spatially normalized in the Montreal Neurological Institute (MNI) template and Gaussian smoothing. Standard uptake value ratios (SUVR) were calculated for each cortical region of interest (ROI) relative to cerebellar crus. Global SUVR scores were calculated by weighted averaging of these ROIs. Subjects were diagnosis as 18F-florbetapir PET positive according to the visual interpretation by 3 physicians independently as previously reported.

Statistical Analyses

Quantitative variables were expressed as mean and standard deviation (SD). Categorical variables were expressed as percentage (%). Differences between the groups were assessed by one-way analysis of variance (ANOVA) or Chi-squared analysis according to the characteristics of data. Post hoc pairwise comparisons of plasma biomarkers between groups were assessed using the least significant difference (LSD) test. Pearson correlation analysis was used to evaluate the relationships between plasma biomarkers and values of 18F-florbetapir PET SUVR. Receiver operating characteristic (ROC) curve analyses were carried out to evaluate the capacity of plasma biomarkers in discriminating subjects with high composite 18F-florbetapir PET SUVR and subjects diagnosed with AD. All hypothesis testing was two-sided, and the level of significance was set at $\alpha = 0.05$. Statistical analyses were conducted using IBM SPSS Statistics 23.0 and MedCalc 19.1. A graphics package (GraphPad Prism, version 8.0) was used to create figures.

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics in the groups of NC, SCD, Obj-SCD, MCI and AD are shown in Table 1. Compared to other groups, subjects with AD were significantly older and had a lower education level. There was no significant difference of gender, diabetes and hypertension prevalence among the groups. Performances on all the neuropsychological tests gradually got worse along with the aggravation of cognitive impairment. Of the 132 subjects who underwent cerebral amyloid scans, the A β PET positive rates for each group were 7.6% (2/26, NC), 13.7% (4/29, SCD), 36.0% (9/25, Obj-SCD), 48.5% (17/35, MCI) and 94.1% (16/17, AD) respectively.

Plasma t-tau, A β 40, A β 42 and A β 42/A β 40 among diagnostic groups

The plasma levels of t-tau, A β 40, A β 42 and the ratio of A β 42/A β 40 in different diagnostic groups were shown in Table 2 and Figure 1. There were significant differences of plasma A β 40, A β 42 and A β 42/A β 40 ratio among the groups ($P=0.021$, $P<0.001$, $P=0.007$, respectively), though no significant difference was found for plasma t-tau ($P=0.762$). Post hoc analyses indicated that plasma A β 40 was significantly higher in SCD and Obj-SCD than in NC ($P=0.0101$ and 0.0105) and AD ($P=0.0326$ and 0.0313), while no significant difference was found between NC, MCI and AD. Plasma A β 42 was significantly higher in SCD and Obj-SCD than in NC ($P=0.0006$ and 0.0058), MCI ($P=0.0042$ and 0.0262) and AD (both $P<0.0001$), while no significant difference was found between NC and MCI. Significantly lower plasma A β 42 and A β 42/A β 40 ratio was observed in AD than all other groups, while no significant difference of A β 42/A β 40 ratio was found among NC, SCD, Obj-SCD and MCI.

Associations between plasma biomarkers and amyloid PET

Associations between plasma biomarkers and SUVR values of amyloid PET were first evaluated in all the subjects who underwent 18F-florbetapir PET scan. As a result, though no significant correlation was found between plasma t-tau, A β 40 and 18F-florbetapir SUVR, plasma A β 42 and A β 42/A β 40 ratio were significantly associated with 18F-florbetapir SUVR ($r=-0.272$, $P=0.003$; $r=-0.211$, $P=0.021$ respectively) (Figure 2. A-B). However, correlation vanished in the subgroup with A β -PET-negative (Figure 2. C-D). In the subgroup with A β -PET-positive, A β 42 but not A β 42/A β 40 ratio was still correlated with 18F-florbetapir SUVR ($r=-0.315$, $P=0.045$) (Figure 2. E-F). In view of plasma A β 40 and A β 42 showed bidirectional character along with aggravation of cognitive impairment in our study, we further explored the levels of plasma biomarkers in subgroups with different cerebral A β burden. 18F-florbetapir SUVR were classified as low SUVR (<1.20), moderate SUVR (1.20 to 1.35) and high SUVR (>1.35) according to the results of ROC analyses for SUVR in discriminating between A β -PET-positive and A β -PET-negative (1.20 and 1.35 for specificity 100% in identifying negative and positive A β -PET respectively). As shown in Table 3, plasma A β 42 and A β 42/A β 40 ratio were significantly lower in the subgroup of high SUVR than low and moderate SUVR (All $P<0.05$). Although not statistically significant, plasma A β 40 and A β 42 were both showed an initially increasing trend from low SUVR subgroup to moderate SUVR subgroup, and then decreased in high SUVR subgroup.

Plasma biomarkers as predictors of high brain A β burden and AD diagnosis

In a subset of individuals who underwent both amyloid PET and plasma biomarkers, ROC Analyses were carried out to evaluate the performances of plasma t-tau, A β 40, A β 42 and A β 42/A β 40 ratio in predicting high brain A β burden (18F-florbetapir SUVR >1.35). As shown in Figure 3. A, the highest value of area under the ROC curve (AUC) was seen with A β 42/A β 40 ratio (AUC=0.762), followed by plasma A β 42 (AUC=0.677), though relatively low values were observed with plasma t-tau and A β 40 (AUC=0.555 and 0.529 respectively).

Comparative diagnostic performances of plasma biomarkers in identifying AD were carried out in all participants regardless of the results of cerebral A β status first (Figure 3.B). ROC curves demonstrated the diagnostic accuracy of plasma A β 42 (AUC=0.714) and A β 42/A β 40 ratio (AUC=0.706) in discriminating AD from non-AD, though plasma t-tau and A β 40 showed relatively poor performances (AUC=0.613 and 0.563 respectively). Furthermore, in subjects with 18F-florbetapir PET positive, both plasma A β 42 (AUC=0.728) and A β 42/A β 40 ratio (AUC=0.808) showed even higher diagnostic accuracy in identifying AD, though no significant difference was found when compared to their performances in all subjects (Figure 3.C).

Discussion

The primary objective of this study was to compare plasma A β 40, A β 42 and t-tau examined by Simoa immunoassay in a continuum of cognitive decline including NC, SCD, Obj-SCD, MCI and AD. Consistent with the previous reports(6, 11, 12), concentration of plasma A β 42 and ratio of A β 42/A β 40 were significantly lower in AD patients, while plasma A β 40 was less distinct. Plasma t-tau showed no significant difference among the diagnostic groups, which was in agreement with the findings in the cohort of BioFINDER(34). It is worth noting that levels of plasma A β 40 and A β 42 were obviously higher in our groups of SCD and Obj-SCD, and showed a significant trend of initially increasing from NC to SCD and Obj-SCD, and then decreasing from SCD and Obj-SCD to MCI and AD. To a great extent, this change was similar to the findings that levels of plasma A β isoforms manifested as a bidirectional character over the course of cognitive decline, which was more likely to increase in the early stages of cognitive impairment and decrease prior to clinical AD onset(16–18). As in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, plasma A β 40 and A β 42 levels measured by double sandwich ELISA tended to be higher for MCI than both NC and AD, though were statistically less significant (16). However, with more detailed grouping criteria for cognitive decline, our results indicated that plasma A β 42 and A β 40 were significantly higher in SCD and Obj-SCD but not MCI. This may be partly due to the diagnosis of MCI in this study were based on an actuarial method with comprehensive neuropsychological tests, which may lead to less false positive and greater percentage of progression to dementia compared to conventional MCI diagnostic criteria(29). Compared to the marginal significance in AIBL, significant differences of plasma A β 40 and A β 42 between diagnostic groups in this study may also attribute to the ultrasensitive performance of SIMOA platform we used. On the other hand, given the bidirectional character of plasma A β 40 and A β 42 during the progression of cognitive decline in our study, no significant difference of plasma A β 40 and A β 42 between the groups of NC and MCI was not surprising, as observed in this study and previous report(35). In contrast, this study showed no biphasic evolution of A β 42/A β 40 ratio across the cognitive decline but significantly lower A β 42/A β 40 ratio in AD than all other groups. At this point, though the relative ratio of A β 42 and A β 40 may normalize the pre-analytical variability and eliminate the inter-individual differences for total A β concentrations(36, 37), as plasma A β 42 and A β 40 showed synchronous changes in SCD and Obj-SCD, the change of A β 42/A β 40 ratio would inevitably be weakened.

Previous studies demonstrated that plasma amyloid- β examined using the Simoa immunoassay could be useful as a potential surrogate for brain A β pathology, though the performances were not sufficient and discrepancies remained(6, 7, 9, 38, 39). In the present study, relationships between plasma amyloid- β and 18F-florbetapir SUVR were assessed not only in all the subjects with A β -PET scan, but also in subjects with different A β -PET status. As a result, both plasma A β 42 and A β 42/A β 40 ratio were significantly correlated with 18F-florbetapir SUVR in all the subjects, though the correlation became weak in the subgroup of A β -PET-positive, and no significant relationship was found in the subgroup of A β -PET-negative. We therefore speculate that significant correlation between plasma amyloid- β and 18F-florbetapir SUVR in all the subjects may due to their marked alteration between the subgroups of cerebral A β positive and negative. In view of the bidirectional character of amyloid- β with cognitive decline in our study, we further compared the levels of plasma biomarkers between different cerebral A β burden subgroups but not the simple status of positive or negative via visual interpretation of A β -PET. As a result, similar to their bidirectional character in the progression of cognitive decline, the levels of plasma A β 42 and A β 40 showed an increasing trend from low SUVR to moderate SUVR and decreasing from moderate SUVR to high SUVR, though only the decreasing of plasma A β 42 in the subgroup of high 18F-florbetapir SUVR had statistical significance. Taken together, as transportation of A β across blood–brain barrier (BBB) plays a major role in A β clearance(40), the bidirectional trend of plasma amyloid- β along with cognitive decline and cerebral A β burden may be associated with the alteration of equilibrium between amyloid- β production and clearance in AD continuum. A higher level of amyloid- β in peripheral blood may be attributed to the compensatory increased transportation of amyloid- β across blood–brain-barrier. At this point, though it is typically considered that decreased A β clearance contribute to the predominant pathogenesis of late-onset AD (LOAD)(41), the elevated plasma A β 40 and A β 42 in SCD and Obj-SCD, or not decreased plasma A β 40 and A β 42 in the group of moderate A β -PET SUVR indicated that amyloid- β clearance from brain by the BBB was not initially impaired, at least in preclinical AD. However, plasma amyloid- β showed significantly decreased with disease progression, consistent with the change in CSF. This may, at least in part, be due to the dysfunction of clearance systems for removing A β from brain, such as BBB clearance, Interstitial fluid bulk-flow clearance and CSF absorption clearance(40). In

addition, this can also be explained by the acceleration of A β aggregation in brain(42), rather than an intrinsic defect of clearance system. On the other hand, whether the initially elevated level of plasma A β in SCD and Obj-SCD represents more soluble forms of amyloid- β in brain and be a potential window period for anti-A β immunotherapy still need more studies to confirm. Either way, the ratio of A β 42/A β 40 showed a gradually decreasing but not bidirectional trend with the increasing of SUVR. This may contribute to the fact that A β 42 is more likely to form hard-to-clear aggregates than A β 40 in the progression of cerebral amyloid deposition according to their structural characteristics(43).

Owing to the invasive procedure of CSF and high cost of PET image, blood-based assessments with comparable accuracy in predicting cerebral pathology of AD are urgently needed, especially in population screening. In our current study, a lower ratio of plasma A β 42/A β 40 demonstrated acceptable value (AUC = 0.762) in identifying high brain A β burden. This was similar to the study in which amyloid-PET positivity was defined by composite SUVR (AUC = 0.79)(38), and higher than the study in which amyloid-PET positivity was defined by visually read (AUC = 0.68)(7). In any case, with the ultrasensitive technology of Simoa, plasma amyloid- β may be a potential surrogate in predicting cerebral A β deposition and could undoubtedly serve as a prescreening method to reduce the need of invasive or expensive methods such as lumbar puncture or PET scanning. In our whole cohort regardless the underlying A β pathology, both plasma A β 42 and A β 42/A β 40 ratio showed potential ability in discriminating the diagnosis of AD from non-AD. Furthermore, in the subset of AD continuum with A β positive determined by 18F-florbetapir PET, both plasma A β 42 and A β 42/A β 40 ratio showed even higher diagnostic accuracy in identifying AD. Thus, it can be seen that, even A β deposition reaches the threshold of positivity in PET imaging, plasma amyloid- β may continue to change along with cerebral A β deposition during the natural course of AD.

Several limitations should be noted in this study. First, only parts of our participants underwent 18F-florbetapir PET scan, which may have led to the non-significant differences of plasma amyloid- β between the groups of low and moderate 18F-florbetapir SUVR. By expanding the sample size of our cohort, we would like to re-assess the changes of plasma amyloid- β between different cerebral A β burdens or different distributions of A β in brain regions. In addition, the NC subgroup had relatively lower prevalence of A β -PET positivity in our study than previous reports, though this could contribute to the fact that SCD and Obj-SCD may be regarded as normal controls in previous studies. Second, as another primary neuropathological hallmarks of AD, phosphorylated tau in blood was not measured in this study. Plasma p-tau181 examination and cerebral tau PET scan will be carried out in our future studies to further increase our understanding of cerebral and peripheral biomarkers of AD. Third, designed as a cross sectional study, longitudinal data are needed to confirm the evolution of plasma biomarkers along with cognitive decline within our findings.

Conclusions

The present study demonstrated that plasma A β 42 and A β 42/A β 40 ratio were significantly lower in AD than all other groups. In addition, plasma amyloid- β was significantly correlated with 18F-florbetapir PET SUVR and showed potential value in predicting cerebral A β deposition and diagnosis of AD. Furthermore, plasma A β 40 and A β 42 measured by Simoa immunoassay showed a significantly bidirectional trend of initially increasing from NC to SCD and Obj-SCD, and then declining to MCI and AD. This may contribute to the status that more soluble forms of amyloid- β in brain, or compensatory increased clearance of amyloid- β from the brain to periphery in preclinical AD. Our findings encourage future longitudinal investigations on the changes of plasma A β along with cognitive decline and cerebral amyloid deposition, and to further explore the mechanisms of this bidirectional character of plasma A β with disease progression.

Abbreviations

A β : Amyloid- β ; AD: Alzheimer's disease; ACE-III-CV: Chinese version of Addenbrooke's Cognitive Examination III; AVLT: Auditory Verbal Learning Test; AFT: Animal Verbal Fluency Test; ANOVA: one-way analysis of variance; AUC: area under the curve; BBB: blood-brain barrier; BNT: Boston Naming Test; CSF: cerebrospinal fluid; ECOG: Everyday Cognition; FAQ: Functional Assessment Questionnaire; LOAD: late-onset AD; MMSE: Mini-Mental State Examination; MoCA-BC: Chinese version of Montreal Cognitive Assessment-Basic; NIA-AA: National Institute on Aging and Alzheimer's Association; NC: cognitively normal controls; MCI: mild cognitive impairment; Obj-SCD: objectively-defined subtle cognitive decline; PET: positron emission tomography; ROC: Receiver operating characteristic; SCD: subjective cognitive decline; STT-A and B: Shape Trail Test Part A and B; SUVR: standard uptake value ratios; Simoa: single-molecule array; t-tau: total tau

Declarations

Ethics approval and consent to participate

This study was approved by the Shanghai Jiao Tong University Affiliated Sixth People's Hospital Foundation Ethical Committee. Written informed consent was obtained from all individual participants or their caregivers included in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FFP analysed and interpreted the data, and was a major contributor in writing the manuscript. QH contributed to the PET experiments and drafted and revised the manuscript. YW performed the blood sample collection and processing. YFW had a major role in the acquisition of data. YHG had a major role in PET experiments and data analyses. FX assisted in the PET experiments and revised the manuscript. QHG designed and conceptualised the study, and revised the manuscript. All authors read and approved the final version of the paper.

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Authors' information

Not applicable.

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Tables

Table 1. Demographics, neuropsychological tests and 18F-florbetapir PET imaging for NC, SCD, Obj-SCD, MCI and AD						
Index	NC (n=76)	SCD(n=77)	Obj-SCD(n=61)	MCI (n=92)	AD n=101	F/x ² (P value)
Demographics						
Age(years)	60.08±9.44	61.82±7.68	64.85±7.06	63.87±6.88	69.78±7.78	20.05 (<0.001)
Education(years)	13.13±3.26	12.36±2.85	12.18±3.62	10.74±2.82	9.38±3.92	17.41 (<0.001)
Gender(M:F)	24:52	19:58	23:38	31:61	40:61	4.97(0.290)
Diabetes [n (%)]	4(5.2%)	7(9.0%)	2(3.2%)	4(4.3%)	9(8.9%)	5.55(0.235)
Hypertension [n (%)]	12(15.7%)	9(11.6%)	5(8.1%)	11(11.9%)	11(10.8%)	2.00(0.734)
neuropsychological tests						
MMSE	28.53±1.48	28.49±1.35	27.33±1.83	26.25±2.62	16.54±5.41	236.69(<0.001)
MoCA-BC	26.83±2.18	25.96±2.54	23.80±3.04	21.57±3.67	12.98±4.93	214.81(<0.001)
ACE-III-CV	84.67±7.04	81.13±6.58	76.33±7.68	70.92±10.64	50.25±11.44	110.31(<0.001)
AVLT delayed recall	7.08±2.30	6.21±2.24	3.75±2.11	2.44±2.09	0.19±0.47	93.99(<0.001)
AVLT recognition	21.00±4.99	20.75±5.04	19.19±5.87	17.00±4.45	14.5±5.31	14.03(<0.001)
BNT 30 items	24.94±2.98	24.44±2.86	23.53±3.03	21.64±4.19	20.39±3.57	13.20(<0.001)
AFT	18.02±4.17	16.68±3.50	13.73±3.23	12.97±4.48	10.61±3.72	20.22(<0.001)
STT-A	41.72±9.19	46.05±14.03	53.47±19.51	60.15±24.80	83.00±35.67	22.18(<0.001)
STT-B	113.83±30.20	116.89±36.88	139.57±46.67	153.52±46.66	190.91±71.97	18.54(<0.001)
FAQ	0.00±0.00	0.45±1.19	1.50±2.47	1.33±2.02	6.67±7.26	21.37(<0.001)
ECOG	16.47±4.08	21.17±5.89	21.07±5.81	22.11±6.80	32.13±10.11	27.79(<0.001)
Aβ-PET(n=132)	26	29	25	35	17	
18F-florbetapir PET positive [n (%)]	2(7.6%)	4(13.7%)	9(36.0%)	17(48.5%)	16(94.1%)	42.380(<0.001)
NC, cognitively normal controls; SCD, subjective cognitive decline; Obj-SCD, objectively-defined subtle cognitive decline; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; MoCA-BC, Chinese version of Montreal Cognitive Assessment-Basic; ACE-III-CV, Chinese version of Addenbrooke's Cognitive Examination III; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; AFT, Animal Verbal Fluency Test; STT-A and B, Shape Trail Test Part A and B; FAQ, Functional Assessment Questionnaire; ECOG, Everyday Cognition; 18F-florbetapir PET, 18F-florbetapir positron emission tomography						

Table 2. Plasma t-tau, A β 40, A β 42 and A β 42/A β 40 for NC, SCD, Obj-SCD, MCI and AD						
<i>Plasma biomarkers</i>	NC (n=76)	SCD(n=77)	Obj-SCD(n=61)	MCI (n=92)	AD (n=101)	F (P value)
T-tau (pg/ml)	1.46 $\pm$ 1.82	1.60 $\pm$ 1.75	1.43 $\pm$ 1.56	1.41 $\pm$ 1.39	1.67 $\pm$ 1.16	0.464(0.762)
A β 40 (pg/ml)	137.74 $\pm$ 42.25	160.04 $\pm$ 49.54	162.33 $\pm$ 44.23	144.96 $\pm$ 48.47	142.76 $\pm$ 61.38	2.932(0.021)
A β 42 (pg/ml)	9.22 $\pm$ 2.69	10.90 $\pm$ 2.84	10.72 $\pm$ 3.07	9.56 $\pm$ 2.91	7.90 $\pm$ 2.89	13.870(<0.001)
A β 42/A β 40(ratio)	0.0697 $\pm$ 0.0177	0.0712 $\pm$ 0.0165	0.0690 $\pm$ 0.0177	0.0686 $\pm$ 0.0141	0.0613 $\pm$ 0.0254	3.605(0.007)
NC, cognitively normal controls; SCD, subjective cognitive decline; Obj-SCD, objectively-defined subtle cognitive decline; MCI, mild cognitive impairment; AD, Alzheimer's disease; A β , Amyloid- β						

Table 3. Plasma biomarkers in the groups with different composite 18F-florbetapir SUVR				
Index	18F-florbetapir PET			F (P value)
	SUVR<1.2	1.2 $\leq$ SUVR<1.35	SUVR $\geq$ 1.35	
T-tau (pg/ml)	1.57 $\pm$ 2.29	1.66 $\pm$ 2.07	1.71 $\pm$ 2.27	0.037(0.964)
A β 40 (pg/ml)	131.50 $\pm$ 50.90	143.02 $\pm$ 53.74	134.89 $\pm$ 45.07	0.612(0.544)
A β 42 (pg/ml)	9.54 $\pm$ 3.45	9.90 $\pm$ 3.50	7.76 $\pm$ 2.59*†	3.621(0.030)
A β 42/A β 40(ratio)	0.0776 $\pm$ 0.0221	0.0732 $\pm$ 0.0201	0.0615 $\pm$ 0.0177*†	4.657(0.011)
18F-florbetapir PET, 18F-florbetapir positron emission tomography; A β , Amyloid- β ; SUVR, standard uptake value ratios				
Comparations between SUVR<1.2 and SUVR $\geq$ 1.35 are marked behind SUVR $\geq$ 1.35, * for P < 0.05				
Comparations between 1.2 $\leq$ SUVR<1.35 and SUVR $\geq$ 1.35 are marked behind SUVR $\geq$ 1.35, † for P < 0.05				

Figures

Figure 1

Comparisons of plasma biomarkers among the groups of cognitively normal controls (NC), subjective cognitive decline (SCD), objectively-defined subtle cognitive decline (Obj-SCD), mild cognitive impairment (MCI) and Alzheimer's disease (AD). *P<0.05; **P<0.01; ***P<0.001

Figure 2

Correlations between plasma Aβ42, Aβ42/40 and composite 18F-florbetapir PET SUVR A-B: all subjects; C-D: subjects with Aβ-PET-negative; E-F: subjects with Aβ-PET-positive

Figure 3

A. ROC curves for plasma A β 42 and A β 42/40 in discriminating composite 18F-florbetapir PET SUVR $\geq$ 1.35 from <1.35; B. ROC curves for plasma A β 42 and A β 42/40 in discriminating AD from non-AD; C. ROC curves for plasma A β 42 and A β 42/40 in discriminating AD from non-AD in subjects with A β -PET-positive