



Glucose metabolism in posterior cingulate cortex has supplementary value to predict the progression of cognitively unimpaired to dementia due to Alzheimer's disease: an exploratory study of ^{18}F -FDG-PET

Qi Zhang · Chunqiu Fan · Luyao Wang · Taoran Li · Min Wang · Ying Han · Jiehui Jiang · and for the Alzheimer's Disease Neuroimaging Initiative

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Abstract Amyloid- β ($\text{A}\beta$) and tau are important biomarkers to predict the progression of cognitively unimpaired (CU) to dementia due to Alzheimer's disease (AD), according to the diagnosis framework from the US National Institute on Aging and the Alzheimer's Association (NIA-AA). However, it is clinically difficult to predict those subjects who were already with $\text{A}\beta$ positive (A+) or tau positive (T+). As a typical characteristic of neurodegeneration in the diagnosis framework, the hypometabolism of the posterior

cingulate cortex (PCC) has significant clinical value in the early prediction and prevention of AD. In this paper, we proposed the glucose metabolism in the PCC as a biomarker supplement to $\text{A}\beta$ and tau biomarkers. First, we calculated the standard uptake value ratio (SUVR) of PCC based on fluorodeoxyglucose positron emission computed tomography (FDG PET) imaging. Secondly, we performed Kaplan–Meier (KM) survival analyses to explore the predictive performance of PCC SUVR, and the hazard ratio (HR) was calculated. Finally, we performed Pearson correlation analyses to explore the physiological significance of PCC SUVR. As a result, the PCC SUVR showed a consistent downward trend along the AD continuum. KM analyses showed better predictive performance when we combined PCC SUVR with cerebro-spinal fluid (CSF) $\text{A}\beta_{42}$ (from

Qi Zhang, Chunqiu Fan, and Luyao Wang contributed equally to the work.

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Q. Zhang
School of Communication & Information Engineering,
Shanghai University, Shanghai 200444, China

C. Fan · Y. Han (✉)
Department of Neurology, Xuanwu Hospital of Capital
Medical University, Beijing 100053, China
e-mail: hanying@xwh.ccmu.edu.cn

L. Wang · M. Wang · J. Jiang (✉)
School of Life Science, Shanghai University,
Shanghai 200444, China
e-mail: jiangjiehui@shu.edu.cn

T. Li
Department of Neurology, The First Affiliated Hospital
of Nanjing Medical University, Jiangsu 210029, China

Y. Han
School of Biomedical Engineering, Hainan University,
Haikou 570228, China

Y. Han
Center of Alzheimer's Disease, Beijing Institute for Brain
Disorders, Beijing 100053, China

Y. Han
National Clinical Research Center for Geriatric Diseases,
Beijing 100053, China

J. Jiang
Nuclear Medicine and Molecular Imaging Key Laboratory
of Sichuan Province, Sichuan 646000, China

HR=2.56 to 3.00 within 5 years; from HR=2.76 to 4.20 within 10 years) and ptau-181 (from 2.83 to 3.91 within 5 years; from HR=2.32 to 4.17 within 10 years). There was a slight correlation between $A\beta_{42}/A\beta_{40}$ and PCC SUVR ($r=0.14$, $p=0.02$). In addition, several cognition scales were also correlated to PCC SUVR (from $r=-0.407$ to 0.383 , $p<0.05$). Our results showed that glucose metabolism in PCC may be a potential biomarker supplement to the $A\beta$ and tau biomarkers to predict the progression of CU to AD.

Keywords Cognitively unimpaired · FDG PET · Kaplan–Meier analysis · Neurodegeneration · Posterior cingulate cortex

Introduction

Alzheimer's disease (AD) is the most common form of dementia. The course of AD is irreversible, which makes AD early diagnosis and prediction significant. The National Institute of Aging and Alzheimer's Association (NIA-AA) criteria for AD suggested three important biomarkers, including amyloid- β ($A\beta$), pathologic tau, and neurodegeneration [AT(N)] [1]. Researches on brain imaging biomarker genomics are also in full swing [2]. However, the current research showed that the AT(N) framework had limitations, especially the low predictive accuracy of the progression from cognitively unimpaired (CU) with evidence of $A\beta$ positive (A+) or tau positive (T+) [3]. Therefore, additional biomarkers are needed clinically.

Abnormal glucose metabolism is considered to be an important biomarker for AD [4–6]. The fluorine-18-labeled-fluorodeoxyglucose positron emission computed tomography (^{18}F -FDG PET) has been frequently used as an imaging technique to visualize abnormal glucose metabolism in the human brain in vivo [7]. Especially, the hypometabolism in the parietotemporal association area, posterior cingulate cortex (PCC), and precuneus were typical characteristics of AD [8]. Among these, as one part of the default mode network (DMN), PCC plays a certain role in spatial memory, morphological learning, and cognitive control [9].

Recently, several researchers have used glucose metabolism to predict the progression of CU to AD [10]. A small sample trial used the regional FDG PET standard uptake value ratio (SUVR) in predicting imminent progression to memory decline [11].

Another study showed that the transition status of individuals was significantly associated with some baseline periods of glucose metabolism in PCC [12]. However, few studies focus on the combination of glucose metabolism and $A\beta$ or tau biomarkers in predicting CU progression. Therefore, the study hypothesized that abnormal glucose metabolism was useful to predict the progression of CU to dementia due to AD. Especially, we supposed that abnormal glucose metabolism in PCC could be a supplement biomarker supplement to the $A\beta$ and tau biomarkers to predict the progression of CU to AD.

The purposes of this paper are as follows: (1) to test whether the glucose metabolism in PCC could be a potential biomarker for the prediction of CU progression. PCC SUVR was used to represent the glucose metabolism in PCC in this study. (2) To explore whether PCC SUVR combining $A\beta$ or tau biomarkers could improve the predictive performance for CU conversion. (3) To explore the physiological significance of glucose metabolism in PCC by correlation analyses between PCC SUVR existing biomarkers and cognition scales.

Materials and methods

Participants

A total of 849 participants were included in this study, including subjects from Alzheimer's Disease Neuroimaging Initiative (ADNI, cohort 1) and Xuanwu Hospital, Beijing, China (cohort 2). Cohort 1 is composed of 413 CU individuals, 76 patients with mild cognitive impairment (MCI), and 197 patients with AD from ADNI. Detailed inclusion information related to participant consent in ADNI is available at <https://adni.loni.usc.edu/>. All ADNI participants received baseline ^{18}F -FDG PET scans, T1-weighted structural MRI scans, and demographic information, including age, gender, apolipoprotein E (ApoE) status, Mini-Mental State Examination (MMSE) values, Functional Activities Questionnaire (FAQ), and Montreal Cognitive Assessment (MOCA). Among them, 253 subjects underwent quantitative measurements of cerebrospinal fluid (CSF) $A\beta_{42}$ and $A\beta_{40}$. In total, 302 subjects underwent quantitative measurement of CSF ptau-181. Standardization of measurement methods for CSF can be found at <https://adni.loni.usc.edu/>.

In addition, cohort 2 was enrolled as an independent test dataset, including 148 CU individuals and 15 patients with MCI. The entry criteria for CU individuals have been described previously [13]. The following exclusion criteria for CU subjects were applied: (1) a history of neurological or psychiatric illness; (2) prior exposure to neuroleptic agents or drug use; (3) an abnormal neurological examination; (4) a history of stroke, high blood pressure, brain disease, or mental illness. MCI participants were diagnosed using the Jak/Bondi actuarial neuropsychological test method [14]. Specifically, participants were considered to be MCI patients if any one of the following three criteria was met: (1) they had an impaired score, defined as >1 SD below the age-corrected normative mean, on both measures within at least one cognitive domain (i.e., memory, language, or speed/executive function); (2) they had one impaired score, defined as >1 SD below the age-corrected normative mean, in each of the three cognitive domains sampled; or (3) they had a score on the FAQ=9 indicating dependence in three or more daily activities. All participants in cohort 2 received baseline ^{18}F -FDG PET scans, T1-weighted structural MRI scans, and demographic information, including age, gender, ApoE status, MMSE, FAQ, and Montreal Cognitive Assessment Basic (MOCA-B). CSF was not collected in this cohort.

To validate PCC SUVR as a potential biomarker, we selected participants who converted from CU to cognitive impairment (CI, including MCI and AD) from the ADNI database as cohort 3. This cohort included 58 CU subjects who progressed to CI within 5 years and 84 CU subjects who progressed to CI within 10 years.

This study was approved by ADNI, Beijing Xuanwu Hospital Institutional Review Board, and written informed consent was obtained from all participants or authorized representatives.

Acquisition protocol and data preprocessing

Detailed information on the data acquisition of ADNI can be found on the website (<https://adni.loni.usc.edu/>). In cohort 2, all ^{18}F -FDG PET images were acquired from an integrated simultaneous 3.0-T TOF PET/MR (SIGNA PET/MR, GE Healthcare, Milwaukee, Wisconsin, USA) at Xuanwu Hospital. Each participant was instructed to fast for at least 6 h and must have a confirmed serum glucose level below 8 mmol/L. A 35-min dynamic scan was acquired approximately 40 min after the intravenous injection

of 3.7 MBq/kg of ^{18}F -FDG. 3D T1-weighted MRI images were adopted at the sagittal plane of the gradient-echo sequence. Parameters are as follows: FOV = $256 \times 256 \text{ mm}^2$, matrix = 256×256 , slice thickness = 1 mm^2 , gap = 0, slice number = 192, TR = 6.9 ms, TE = 2.98 ms, TI = 450 ms, flip angle = 12° , voxel size = $1 \times 1 \times 1 \text{ mm}^3$.

The preprocessing procedures contain format conversion, correction, spatial standardization, and smoothness. First, all DICOM images were converted into NIfTI format. Then the head movement correction of images was underway. Next, each PET image was co-registered to the T1 image and co-registered PET image was normalized into the Montreal Neurological Institute (MNI) standard space with $3 \times 3 \times 3 \text{ mm}^3$ voxel size. Finally, the images were smoothed using an 8-mm full width at half maximum Gaussian kernel to increase signal-to-noise ratios. All the above steps were performed by using Statistical Parametric Mapping 12 software (SPM12, Department of Imaging Neuroscience, Institute of Neurology, London, UK) implemented in MATLAB 2018b (Mathworks Inc.).

SUVR map calculation

For each participant, the standard uptake value (SUV) of the whole brain is calculated by using the automated anatomical labeling (AAL) atlas as a template, and then the SUV of each voxel is standardized with reference to the average SUV of the whole brain. The formula is as follows:

$$SUVR = \frac{SUV_{\text{voxel}}}{SUV_{\text{mean}}}$$

In the above formula, SUV_{voxel} is the SUV of each voxel, and SUV_{mean} is the average SUV of the whole brain. Then we obtain the SUVR map of each participant.

Definition of PCC hypometabolism in CU subjects

In this paper, the PCC brain region is defined throughout the AAL brain regions, numbered 35 and 36. The left side of PCC is with Talairach coordinates of $(-2, -36, 37)$, and the right side of PCC is with Talairach coordinates of $(3, -45, 11)$.

First, we calculated the PCC SUVR of 413 CU participants in cohort 1; the formula is as follows:

$$SUVR_{ROI} = \frac{SUV_{ROI}/num_{ROI}}{SUV_{mean}}$$

In the above formula, SUV_{ROI} is the sum of SUV in the ROI, num_{ROI} is the number of voxels in the ROI, and SUV_{mean} is the average SUV of the whole brain.

As there is no definition of the hypometabolism of CU, the median value of PCC SUVR in cohort 1 was proposed as the threshold according to previous studies [15, 16]. In this study, the PCC SUVR of 413 CU participants was ranked from the largest to smallest, and the median value was chosen as the partition threshold. The bottom 50% of the participants below the threshold were defined as CU (PCC+), and the top 50% of the participants above the threshold were defined as CU (PCC-). To verify the effectiveness of the median value method, we have performed cross-cohort verification of the rationality of the median division between cohorts 1 and 2 (see Additional file 1).

Distribution of PCC SUVR across the AD continuum

To observe the distribution of PCC SUVR in the AD continuum, we calculated the PCC SUVR of MCI and AD in cohorts 1 and 2. For cohort 1, we obtain PCC SUVR for CU (PCC-), CU (PCC+), MCI, and AD, and then we executed one-way ANOVA analysis and Tukey's multiple-comparisons test among different groups. The above analyses were also performed in cohort 2. For comparison, we also employed CSF $A\beta_{42}$ and ptau-181 as risk factors to repeat the above analyses in cohort 1. Positive status for these biomarkers is defined by <980 pg/mL for $A\beta_{42}$, and >21.8 pg/mL for ptau-181 [17]. Based on the dichotomized biomarkers, the participants were divided into a positive subgroup and a negative subgroup for each biomarker.

Validation of PCC SUVR as a predictor

In order to verify whether PCC SUVR can be used as an effective predictor, Kaplan–Meier (KM) analyses on CU (PCC+) and CU (PCC-) in cohort 3 were carried out. First, we collected the participants in the CU group who were converted to CI and recorded the conversion time. Then, we applied PCC SUVR as the predictor to conduct KM analysis between CU (PCC+) and CU (PCC-). The

differences in survival curves between groups were analyzed by the Log-rank test, and the hazard ratio (HR) was also calculated. As a comparison, $A\beta_{42}$ and ptau-181 were employed as $A\beta$ and tau predictors, and KM analyses were performed among CU (A+/A-) and CU (T+/T-), respectively. The differences in survival curves between groups were analyzed by the Log-rank test. Finally, we combined the PCC SUVR with $A\beta_{42}$ and ptau-181 respectively and performed KM analyses in CU (PCC+A+/ PCC- A-) and CU (PCC+T+/ PCC-T-) groups. In order to verify whether PCC SUVR is useful for prediction in different periods, the above analyses were carried out at two time points: the progression occurred within 5 years and the progression occurred within 10 years. In order to verify the effectiveness, we also calculated SUVR in cuneus, occipital, and parietal, repeated the above experiments, and compared them with PCC.

Correlation analyses

In this paper, Pearson correlation analyses of PCC SUVR and cognition scales were done in cohort 1, including MMSE, FAQ, MOCA, and Everyday Cognition scales (Ecog). The correlation analyses between PCC SUVR and CSF $A\beta_{42}$, $A\beta_{42}/A\beta_{40}$, and ptau-181 were also done.

Statistical analyses

Demographic and clinical characteristics are compared by analyses of variance, Chi-square test, and two-sample *t*-test as appropriate. The difference of PCC SUVR is compared using one-way ANOVA test, and the differences between groups are corrected by Tukey's multiple-comparisons tests. The level of significance is set at $p < 0.05$. Statistical analyses are carried out by using SPSS 23.0 software (SPSS Inc., Chicago, IL), MATLAB 2018b (Math Works Inc., Sherborn, MA), and GraphPad Prism version 9.4.1. (GraphPad Software, San Diego, California, USA).

Results

Participants

Table 1 presents the demographic information of the participants from each cohort. In cohort 1, the level of $A\beta_{42}/A\beta_{40}$ in the CU (PCC+) group is significantly lower than that in the CU (PCC-) group

($p < 0.01$). There is no statistical difference in other parameters between the above two groups. The age of the MCI group is significantly higher than that of the CU and AD groups, which has no significant difference between the AD group and the CU group. The scores of MMSE and MOCA in the MCI group and AD group are significantly lower than those in the CU group ($p < 0.001$). The scores of MOCA in the MCI group are significantly higher than AD group ($p < 0.05$). The FAQ scores in the MCI group and AD group are significantly higher than those in the CU group ($p < 0.001$). AD group is significantly higher than MCI group of FAQ ($p < 0.05$). The Chi-square test shows that the frequency of ApoE-4 carriers in the MCI group and the AD group is significantly

higher than that in the CU group ($p < 0.001$). The number of ApoE-4 carriers in the AD group is significantly higher than that in MCI group ($p < 0.01$). The deposition levels of ptau-181 in the MCI group and AD group are significantly higher than those in the CU group ($p < 0.001$). The level of ptau-181 deposition in AD group is significantly higher than that in MCI group ($p < 0.05$).

In cohort 2, the age of the MCI group is higher than that of the CU group, and the difference is statistically significant ($p = 0.026$). The Chi-square test shows that the frequency of ApoE-4 carriers in the MCI group is significantly higher than that in the CU group ($p = 0.025$), and the frequency of ApoE-4 carriers in the CU (PCC+) group is significantly higher

Table 1 Characteristics of participants

	Cohort 1 (ADNI)				Cohort 2 (Xuanwu hospital)			Cohort 3 (ADNI)	
	CU		MCI	AD	CU		MCI	CU converters (within 5 years)	CU converters (within 10 years)
	PCC+	PCC-			PCC+	PCC-			
Female / male	106 / 100	111 / 96	30 / 46 ^b	79 / 118 ^b	46 / 28	54 / 20	5 / 10	24 / 34	38 / 46
Age	73.40 (9.20)	72.60 (9.05)	78.90 (8.97) ^d	75.30 (11.80)	64.00 (6.00)	65.00 (7.00)	71.50 (20.00) ^c	78.60 (8.15)	80.00 (7.60)
SMC / CN	60 / 146	42 / 165	N/A	N/A	37 / 37	35 / 39	N/A	N/A	N/A
Converters / non-converters (within 5 years)	34 / 172	24 / 183	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Converters / non-converters (within 10 years)	48 / 158	36 / 171	N/A	N/A	N/A	N/A	N/A	N/A	N/A
A β_{42}	1115.00(996.25)	1486.00(739.00)	920.00(990.50)	718.00(368.00)	N/A	N/A	N/A	903.50(648.50)	802.50(635.25)
A β_{42} / A β_{40}	0.15 (0.10)	0.19 (0.07) ^a	0.12 (0.10) ^{c,d}	0.10 (0.03) ^c	N/A	N/A	N/A	0.11 (0.08)	0.11 (0.07)
ApoE-4 (noncarrier / carrier)	141 / 64	153 / 54	40 / 36 ^{b,c}	59 / 127 ^b	53 / 21	58 / 16	7 / 8 ^b	35 / 23	50 / 34
MMSE	29.00 (2.00)	30.00 (1.00)	25.50 (6.50) ^c	23.00 (4.00) ^c	29.00 (2.00)	29.00 (2.00)	21.50 (8.50) ^c	27.00 (3.50)	27.00 (5.00)
FAQ	0.00 (0.00)	0.00 (0.00)	8.50 (17.25) ^{c,d}	13.00 (11.00) ^c	0.00 (0.00)	0.00 (0.00)	6.50 (11.00) ^c	1.00 (4.00)	1.00 (6.00)
MOCA	26.00 (4.00)	26.00 (4.00)	22.00 (7.00) ^{c,d}	18.00 (7.00) ^c	26.00 (2.00)	26.00 (3.00)	14.50 (10.00) ^c	25.00 (3.50)	24.00 (2.00)
ptau-181	20.68 (10.56)	18.57 (12.98)	25.39 (5.12) ^{c,d}	33.17 (20.18) ^c	N/A	N/A	N/A	37.61 (22.26)	34.48 (22.50)

Age, A β_{42} /A β_{40} , MMSE, FAQ, MOCA, and ptau-181 are given as median (interquartile range). The MOCA of the Xuanwu cohort is MOCA-B

ADNI, Alzheimer Disease Neuroimaging Initiative; PCC, posterior cingulate cortex; CU, cognitively unimpaired; MCI, mild cognitive impairment; AD, Alzheimer's disease; SMC, significant memory concern; CN, cognitive normal; MMSE, Mini-Mental State Examination; FAQ, Functional Activities Questionnaire; MOCA, Montreal Cognitive Assessment

^aTwo-sample *t*-test, CU (PCC+) and CU (PCC-)

^b χ^2 test with CU

^cTwo-sample *t*-tests with CU

^dTwo-sample *t*-tests with AD

^e χ^2 test with AD

than that in the CU (PCC-) group ($p=0.043$). There is no significant difference in gender distribution between MCI and CU groups. There are no statistical differences in other parameters between the CU (PCC+) group and the CU (PCC-) group.

The real case of PCC + in CU subjects

We obtained the SUVR map of each participant. Figure 1 depicts the SUVR maps of the whole brain of two sample participants. The participant in Fig. 1a has SUVR results as follows: PCC SUVR=1.04, DMN SUVR=0.93; while the participant in Fig. 1b has SUVR results as follows: PCC SUVR=1.30, DMN SUVR=0.93. For the two participants, the SUVRs in the DMN region are similar, but the participant in Fig. 1a has obviously lower metabolism in the PCC brain region than the participant in Fig. 1b.

Distribution of PCC SUVR across the AD continuum

The PCC SUVR distributions of the two cohorts are shown in Fig. 2. In cohort 1, the CU group is divided into CU (PCC+) (SUVR=1.02±0.05) and CU (PCC-) (SUVR=1.16±0.05) with the median value as the segmentation threshold (SUVR threshold=1.092). The PCC SUVRs of MCI and AD are 1.00±0.13 and 0.98±0.11,

respectively. The results of one-way ANOVA test show that there are significant differences between the groups ($p<0.001$). PCC SUVR shows a downward trend in cohort 1. The threshold (SUVR=1.092) was applied to cohort 2 and it also indicates a downward trend. For comparison, we have applied the median PCC SUVR of cohort 2 to the two cohorts (see Additional file 1), and the results exhibit that cohort 1 does not show a stable downward trend. In addition, we pool the two cohorts to take the median, and both cohorts show a steady downward trend (see Additional file 1).

As a comparison, the PCC SUVR differences between CU (A+) and CU (A-) in cohort 1 are compared. The results of the two-sample *t*-test indicate that there is a significant difference ($p=0.009$) between CU (A+) (SUVR=1.07±0.84) and CU (A-) (SUVR=1.10±0.82). No significant difference ($p=0.434$) between CU (T+) (SUVR=1.08±0.83) and CU (T-) (SUVR=1.09±0.85) is observed. The relevant results can be found in the supplementary material (see Additional file 2).

Validation of PCC SUVR as a predictor

In this paper, KM survival analyses were performed on the two subgroups of CU based on whether the progression occurred within 5 or 10 years, and the

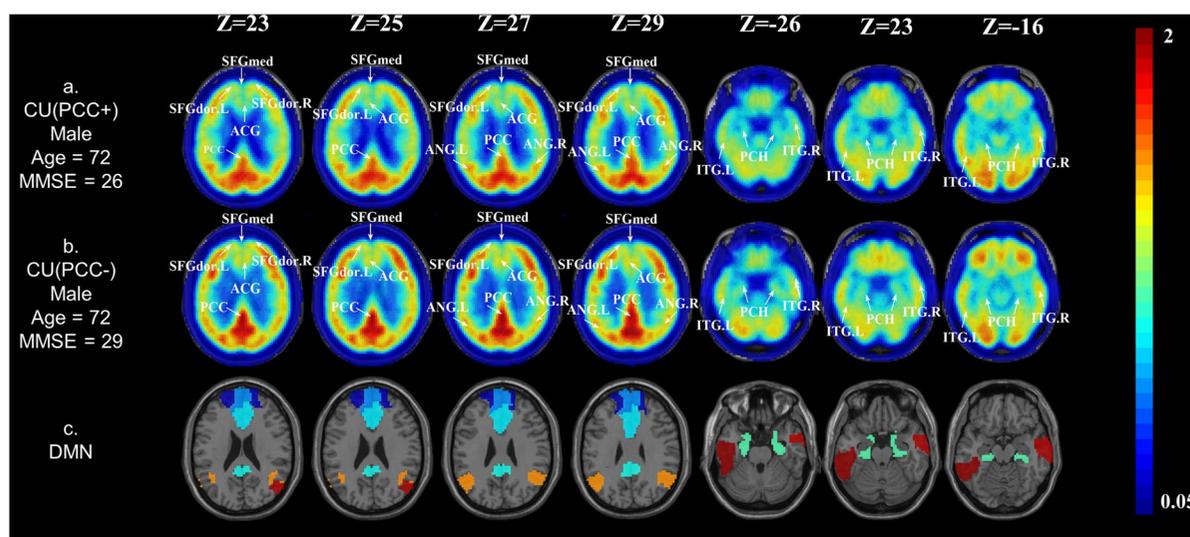


Fig. 1 Real cases of PCC hypometabolism in CU subjects. The age, gender, and ApoE of the two subjects matched. **a** A case of CU (PCC+), male, age=72.0 years, ApoE-4 noncar-

rier. **b** A case of CU (PCC-), male, age=72.0 years, ApoE-4 noncarrier. **c** The spatial location of DMN in the AAL template

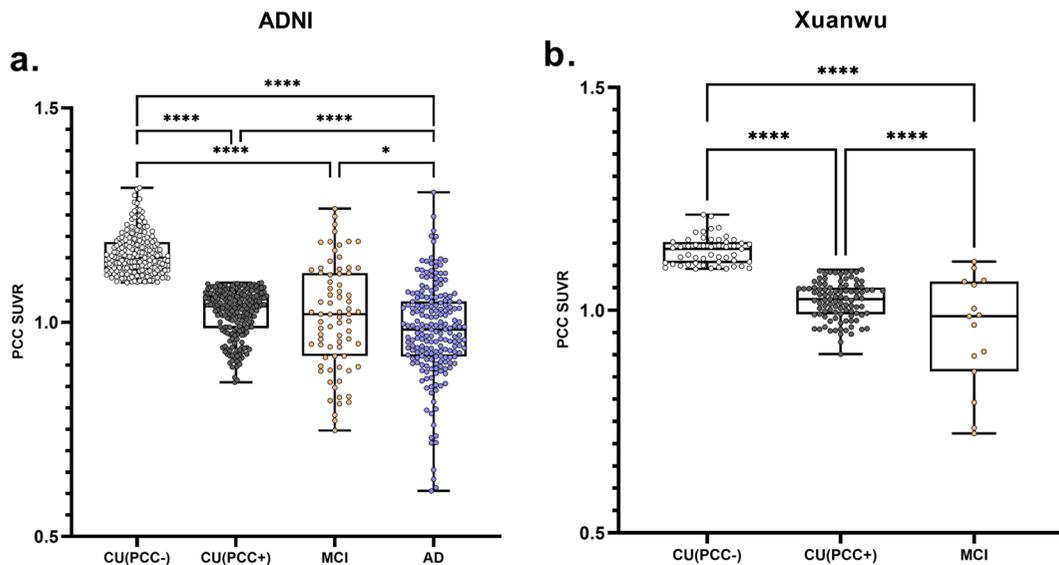


Fig. 2 The PCC SUVR distribution of ADNI cohort (a) and Xuanwu cohort (b). * $p < 0.05$; **** $p < 0.0001$. A two-sample t -test was performed

survival curves were statistically analyzed by the Log-rank test. As shown in Fig. 3a to c, the PCC SUVR cannot distinguish high risk and low risk in the 5 years group, while $A\beta_{42}$ and ptau-181 have a good ability to distinguish high-risk and low-risk groups, and the HRs are 2.561 and 2.828 respectively. In the 10 years group, the KM curves are shown in Fig. 3d to f. All three predictors are able to distinguish high risk and low risk, the HRs of PCC SUVR, ptau-181, and $A\beta_{42}$ are 1.635, 2.322, and 2.762, and the p values are smaller than the 5 years group.

Then we superimposed PCC SUVR with CSF $A\beta_{42}$ and ptau-181. KM curve results for the 5 years group are shown in Fig. 4a to b. Under the joint action of the two groups, the high- and low-risk groups are well distinguished. Among them, PCC SUVR combining ptau-181 has a stronger prediction ability (HR=3.913) and followed by PCC SUVR combining $A\beta_{42}$ (HR=3.002). The above steps were repeated in the 10 years group, and the similar results were obtained as shown in Fig. 4c to d. The prediction ability of PCC SUVR combining ptau-181 is weaker (HR=4.171) than PCC SUVR combining $A\beta_{42}$ (HR=4.199). The results demonstrated that $A\beta_{42}$ and ptau-181 had an impact on the survival prediction performance of PCC SUVR. The above experiments were repeated with cuneus, occipital, and parietal SUVR. None of the three brain regions

was able to predict CU transformation ($p > 0.05$), and the prediction performance was not improved after combing CSF $A\beta_{42}$ and ptau-181 (see Additional file 3).

Correlation analyses

There is a slight correlation between PCC SUVR and $A\beta_{42}/A\beta_{40}$ in the CU group ($r=0.179$, $p=0.004$) as shown in Fig. 5a. When we counted the CU (PCC+), MCI, and AD together, the correlation still existed ($r=0.140$, $p=0.02$) (Fig. 5b).

In addition, there is a slight correlation between PCC SUVR and Ecog scales in the CU group, including EcogPtLang ($r=-0.118$, $p=0.036$), EcogPtMem ($r=-0.166$, $p=0.003$), EcogPtTotal ($r=-0.137$, $p=0.014$), and ADASQ4 ($r=-0.128$, $p=0.009$). When we combined CU, MCI, and AD groups together, the correlations became stronger. The correlation coefficients between PCC SUVR and EcogPtLang, EcogPtMem, EcogPtTotal, and ADASQ4 are 0.129, 0.214, -0.191 , and -0.407 respectively ($p < 0.01$ for all) in cohort 1. For relevant charts, please refer to the supplementary materials (see Additional file 4).

In cohort 1, in addition to the clinical information mentioned above, PCC SUVR also has a significant correlation with EcogPtPlan ($r=-0.179$, $p < 0.001$),

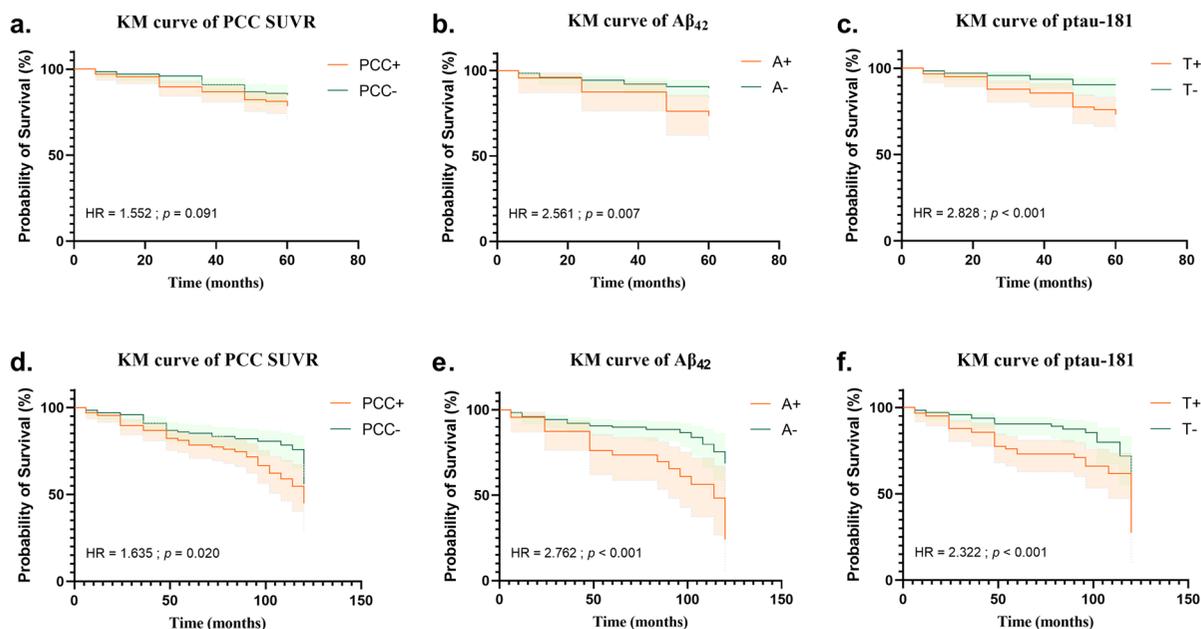


Fig. 3 Kaplan–Meier survival curve based on PCC SUVR, $A\beta_{42}$, and ptau-181 respectively. The top row is the Kaplan–Meier survival curve of subjects whose conversion occurred

within 5 years. The bottom row is the Kaplan–Meier survival curve of subjects whose conversion occurred within 10 years

EcogPtDivatt ($r = -0.113$, $p = 0.006$), and EcogPt-Visspat ($r = -0.190$, $p < 0.001$). Significant correlations between PCC SUVR and clinical neurological test questionnaires, including FAQ ($r = -0.369$, $p < 0.001$), MOCA ($r = 0.348$, $p < 0.001$), and MMSE ($r = 0.383$, $p < 0.001$), were observed. For relevant charts, please refer to supplementary materials (see Additional file 5).

Discussion

In this paper, we found that glucose metabolism in PCC could be used as a potential biomarker for the prediction of CU conversion. The results of survival analyses showed that the supplementation of PCC SUVR to $A\beta_{42}$ and ptau-181 could improve the predictive performance of CU progression. The correlation results found a slight correlation between PCC SUVR and participants' subjective cognition. The results suggested that glucose metabolism in PCC had potential to be used as a complement to $A\beta$ and tau biomarkers. Notably, two cross-racial cohorts were included in this paper.

It has been well known that brain histopathological changes preceded cognitive symptoms for many years. Although the evidence obtained by FDG PET in the CU stage is limited, glucose metabolism from FDG PET scans plays an important role in both clinical and preclinical diagnoses [8]. According to previous studies, hypometabolism in PCC was observed in identifying individuals at high risk of AD [15]. In this study, the PCC SUVR showed the same trend in the AD continuum in both Chinese and Western cohorts as shown in Fig. 2, which is consistent with the literature. Cross-cohort experiments showed that almost each cohort showed a stable downward trend when the median value of PCC SUVR was used to distinguish the CU(PCC+) and CU(PCC-) (please refer to Additional file 1). Therefore, we believed that it was reasonable to divide CU(PCC+) and CU(PCC-) by the median value method. We applied the median value of PCC SUVR from cohort 2 to the two cohorts and the results showed that cohort 1 did not show a stable downward trend, which may be due to a smaller sample size in cohort 2.

The cingulate gyrus is an area of early AD-associated pathological protein deposition [18], as well

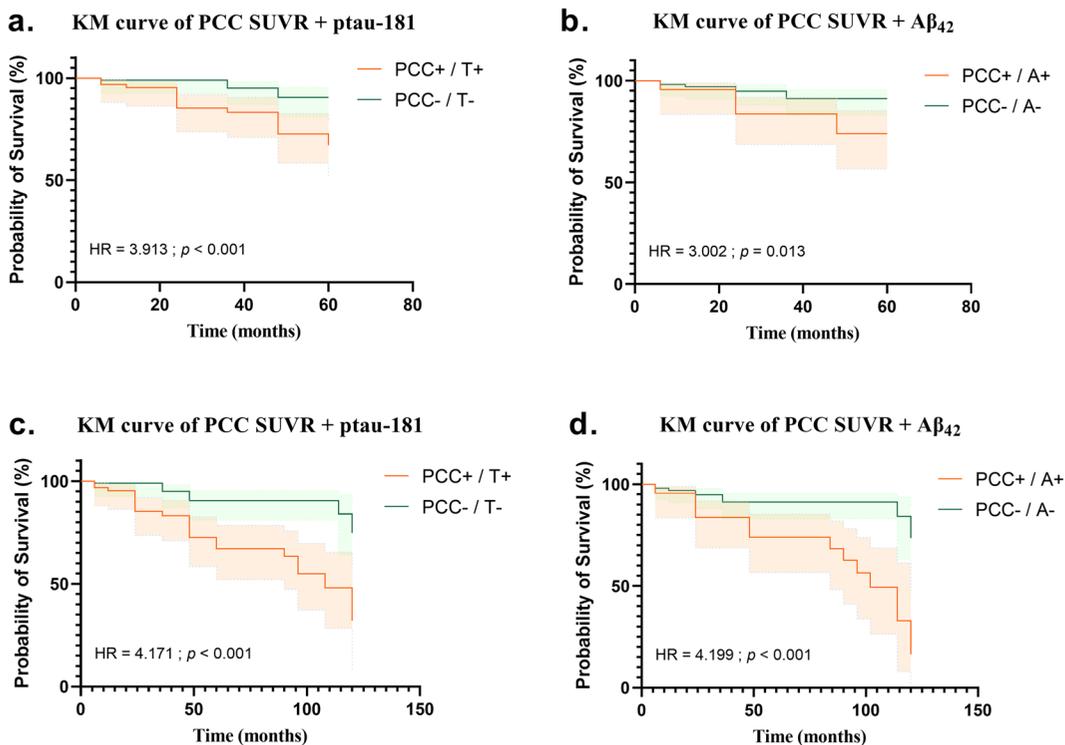


Fig. 4 Kaplan–Meier survival curve based on PCC SUVR combining $A\beta_{42}$ and ptau-181, respectively. The top line is the Kaplan–Meier survival curve of whose conversion occurred

within 5 years. The bottom line is the Kaplan–Meier survival curve of whose conversion occurred within 10 years

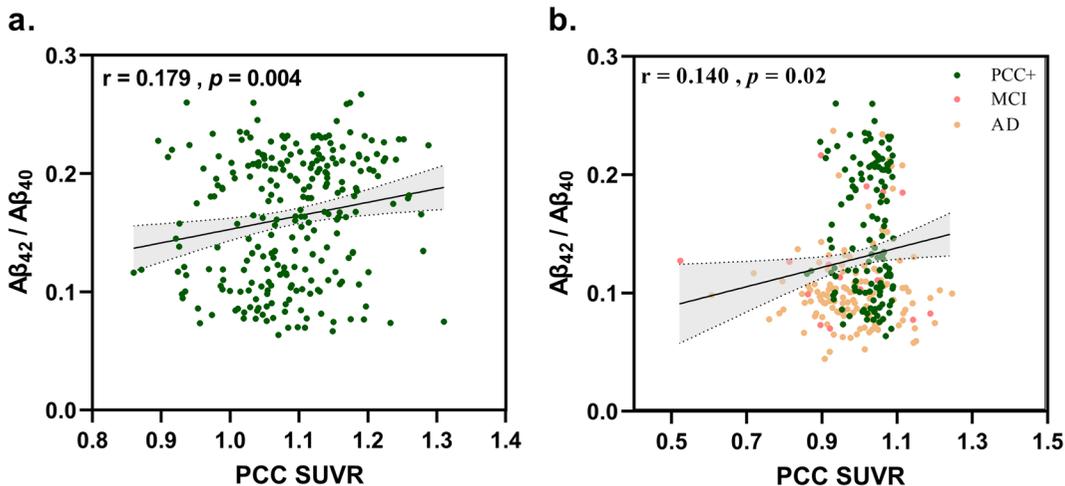


Fig. 5 Pearson correlation between PCC SUVR and $A\beta_{42}/A\beta_{40}$. **a** In CU group. **b** In CU (PCC+), MCI, and AD groups

as an area of early atrophy, reduced thickness, or reduced metabolism [8, 19]. $A\beta$, tau, and metabolic damage are common phenomena of AD, but there are

differences for the three kinds of biomarkers in time distribution. Available studies suggested that the pre-clinical stage of AD was characterized by amyloid

deposition [18], which was followed by the spread of neurofibrillary tangle tau pathology from the medial temporal lobes into the neocortex. We found that CSF $A\beta_{42}$ plus PCC SUVR could improve the predictive performance of CU progression as shown in Figs. 3 and 4. We speculated that it was the ceiling effect of $A\beta$, which made them not sensitive enough to the progression of the disease course when they were used as predictors alone. The ceiling effect may have occurred in the CU phase. To verify our conjecture, we performed the KM survival analyses of CU under two time points of 5 and 10 years. First, in Fig. 3, the predictive performance of the 10 years group was better than that of the 5 years group when we used $A\beta_{42}$ and PCC SUVR alone as the predictor, which indicated that the predictive performance of the biomarker deposition level in the baseline was different for different time points and that the time point of CU progression was closer to 10 years. However, when ptau-181 was used as an independent predictor, the prediction performance of 5 years was better than that of 10 years. We hypothesized that it was because tau was accumulated along with the course of the disease, and tau deposition level in the baseline period had less influence on tau deposition level after 10 years than that after 5 years, so the prediction performance was weaker. Secondly, when PCC SUVR was combined with $A\beta_{42}$ or ptau-181 as predictors as Fig. 4 shows, the predictive performance was significantly improved compared with that used alone, indicating the effectiveness of PCC SUVR as a supplementary biomarker for $A\beta$ or tau biomarkers. In addition, the predictive performance of the 10 years group was still better than that of the 5 years group.

In CU subjects, we found a slight correlation between $A\beta_{42}/A\beta_{40}$ and PCC SUVR as Fig. 5 shows. Considering that the ADNI cohort included in this study covers multiple countries and centers, under the influence of several complicated factors, we got these acceptable results compared to reported literatures [20–22]. Another large study in elderly cognitive normal subjects showed a significant negative correlation between local amyloid levels and metabolic signaling in several AD-typical regions, including PCC [15]. Two other studies showed correlations between local amyloid and PCC SUVR [23, 24]. These studies were consistent with the results of this paper. These results suggested that glucose metabolism in PCC and $A\beta$ deposition

already existed at the cognitive normal stage. However, we did not find a correlation between PCC SUVR and tau. Some investigators have previously found an inverse correlation between CSF tau levels and glucose metabolism in the right frontal, temporal, and parietal lobes of the brain [25, 26]. Other studies demonstrated no significant correlation between glucose metabolism and CSF tau levels [27, 28]. This may be due to pathological heterogeneity. Some studies found that CSF tau levels remained stable during dementia [29], whereas cognitive symptoms and hypometabolism deteriorated during the progression of the disease [30]. This made the mechanism of correlation between CSF tau and metabolism more complex. Therefore, the relationship between the two upstream and downstream in the CU phase needs further research.

Besides, we found that there was a certain correlation between PCC SUVR and several items of the Ecog scale in the stage of CU (please refer to Additional file 4). The Ecog can be used to measure relatively mild functional changes that may predate loss of independence in major activities of daily living, and assess functional abilities that are clearly linked to specific cognitive abilities, in other words, the everyday correlates of specific neuropsychological impairments [31]. Studies have shown that subjective cognitive decline is the first clinical manifestation on the AD continuum, manifesting as a decline in the self-experience of cognitive function without evidence of objective cognitive impairment [32–34]. The results indicated that the change of metabolic damage occurred in the subject cognitive impairment period.

This study had some limitations. First, the median value threshold (to divide PCC+ and PCC-) used in this paper was obtained by the data-driven method, which was reasonable, but there may be the problem of false positives or false negatives. Further study can be considered by expanding the sample size and including follow-up FDG PET data to test the threshold. Second, the value of CSF $A\beta_{42}$ and $A\beta_{40}$ from ADNI was not a commercially available IVD assay. It was an assay that was currently under development and for investigational use only. The measuring range of the assay is 200 (lower technical limit)–1700 pg/mL (upper technical limit). The performance of the assay beyond the upper technical limit has not been formally established. Therefore, the values above the upper technical limit were restricted to exploratory research purposes and

were excluded for clinical decision-making. This may have an impact on the results of this study. And biological sex differences, as an important phenotype in the study of neurodegenerative diseases [35, 36], may lead to different degrees of hypometabolism, which may be a direction of future research. Finally, in addition to AD-like pathology, many factors may affect PCC SUVR, such as vascular stenosis, inflammation, and tumor, but such information was lacking and not investigated in this study, and we plan to further investigate the other possible contributing factors in the future.

Conclusions

Cross-cohort experiments indicated that PCC SUVR exhibited a steady downward trend across the disease continuum. The results of survival analysis showed that the supplement of A β ₄₂ and ptau-181 by PCC SUVR could improve the prediction performance of CU progress. In summary, we found the important role of glucose metabolism in PCC in AD prediction. The PCC SUVR can be used as a supplement to the prediction of CU progression for A β and tau biomarkers. The results of this study are helpful for researchers to understand the early pathology of AD and provide theoretical support for the early prevention of AD clinically.

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The Alzheimer's Disease Neuroimaging Initiative

Michael W. Weiner⁹, Paul Aisen¹⁰, Ronald Petersen¹¹, Clifford R. Jack¹¹, William Jagust¹², John Q. Trojanowski¹³, Arthur W. Toga¹⁴, Laurel Beckett¹⁵, Robert C. Green¹⁶, Andrew J. Saykin¹⁷, John Morris¹⁸, Leslie M. Shaw¹³, Zaven Khachaturian^{15, 19}, Greg Sorensen²⁰, Lew Kuller²¹, Marcus Raichle¹⁸, Steven Paul²², Peter Davies²³, Howard Fillit²⁴, Franz Hefti²⁵, David Holtzman¹⁸, Marek M. Mesulam²⁶, William Potter²⁷, Peter Snyder²⁸, Adam Schwartz²⁹, Tom Montine³⁰, Ronald G. Thomas³⁰, Michael Donohue³⁰, Sarah Walter³⁰, Devon Gessert³⁰, Tamie Sather³⁰, Gus Jiminez³⁰, Danielle Harvey¹⁵, Matthew Bernstein¹¹, Paul Thompson³¹, Norbert Schuff^{9, 15}, Bret Borowski¹¹, Jeff Gunter¹¹, Matt Senjem¹¹, Prashanthi Vemuri¹¹, David Jones¹¹, Kejal Kantarci¹¹, Chad Ward¹¹, Robert A. Koeppe³², Norm Foster³³, Eric M. Reiman³⁴, Kewei Chen³⁴, Chet Mathis²¹, Susan Landau¹², Nigel J. Cairns¹⁸, Erin Householder¹⁸, Lisa Taylor-Reinwald¹⁸, Virginia Lee¹³, Magdalena Korecka¹³, Michal Figurski¹³, Karen Crawford¹⁴, Scott Neu¹⁴, Tatiana M. Foroud¹⁷, Steven G. Potkin³⁵, Li Shen¹⁷, Kelley Faber¹⁷, Sungeun Kim¹⁷, Kwang-sik Nho¹⁷, Leon Thal¹⁰, Neil Buckholtz³⁶, Marylyn Albert³⁷, Richard Frank³⁸, John Hsiao³⁶, Jeffrey Kaye³⁹, Joseph Quinn³⁹, Betty Lind³⁹, Raina Carter³⁹, Sara Dolen³⁹, Lon S. Schneider¹⁴, Sonia Pawluczyk¹⁴, Mauricio Beccera¹⁴, Liberty Teodorou¹⁴, Bryan M. Spann¹⁴, James Brewer¹⁰, Helen Vanderswag¹⁰, Adam Fleisher^{10, 34}, Judith L. Heidebrink³², Joanne L. Lord³², Sara S. Mason¹¹, Colleen S. Albers¹¹, David Knopman¹¹, Kris Johnson¹¹, Rachele S. Doody⁴⁰, Javier Villanueva-Meyer⁴⁰, Munir Chowdhury⁴⁰, Susan Rountree⁴⁰, Mimi Dang⁴⁰, Yaakov Stern⁴⁰, Lawrence S. Honig⁴⁰, Karen L. Bell⁴⁰, Beau Ances¹⁸, Maria Carroll¹⁸, Sue Leon¹⁸, Mark A. Mintun¹⁸, Stacy Schneider¹⁸, Angela Oliver¹⁸, Daniel Marson⁴¹, Randall Griffith⁴¹, David Clark⁴¹, David Geldmacher⁴¹, John Brockington⁴¹, Erik Roberson⁴¹, Hillel Grossman⁴², Effie Mitsis⁴², Leyla de Toledo-Morrell⁴³, Raj C. Shah⁴³, Ranjan Dura⁴⁴, Daniel Varon⁴⁴, Maria T. Greig⁴⁴, Peggy Roberts⁴⁴, Chiadi Onyike³⁷, Daniel D'Agostino³⁷, Stephanie Kiehl³⁷, James E. Galvin⁴⁵, Brittany Cerbone⁴⁵, Christina A. Michel⁴⁵, Henry Rusinek⁴⁵, Mony J. de Leon⁴⁵, Lidia Glodzik⁴⁵, Susan De Santi⁴⁵, P Murali Doraiswamy⁴⁶, Jeffrey R. Petrella⁴⁶, Terence Z. Wong⁴⁶, Steven E. Arnold¹³, Jason H. Karlawish¹³, David Wolk¹³, Charles D. Smith⁴⁷, Greg Jicha⁴⁷, Peter Hardy⁴⁷, Partha Sinha⁴⁷, Elizabeth Oates⁴⁷, Gary Conrad⁴⁷, Oscar L. Lopez²¹, MaryAnn Oakley²¹, Donna M. Simpson³⁷, Anton P. Porsteinsson⁴⁸, Bonnie S. Goldstein⁴⁸, Kim Martin⁴⁸, Kelly M. Makino⁴⁸, M Saleem Ismail⁴⁸, Connie Brand⁴⁸, Ruth A. Mulnard³⁵, Gaby Thai³⁵, Catherine McAdams-Ortiz³⁵, Kyle Womack⁴⁹, Dana Mathews⁴⁹, Mary Quiceno⁴⁹, Ramon Diaz-Arrastia⁴⁹, Richard King⁴⁹, Myron Weiner⁴⁹, Kristen Martin-Cook⁴⁹, Michael DeVous⁴⁹, Allan I Levey⁵⁰, James J. Lah⁵⁰, Janet S. Cellar⁵⁰, Jeffrey M. Burns⁵⁰, Heather S. Anderson⁵¹, Russell H. Swerdlow⁵¹, Liana Apostolova³¹, Kathleen Tingus³¹, Ellen Woo³¹, Daniel H. S. Silverman³¹, Po H.

- Lu³¹, George Bartzokis³¹, Neill R. Graff-Radford⁵², Francine Parfitt⁵², Tracy Kendall⁵², Heather Johnson⁵², Martin R. Farlow¹⁷, Ann Marie Hake¹⁷, Brandy R. Matthews¹⁷, Scott Herring¹⁷, Cynthia Hunt¹⁷, Christopher H. van Dyck⁵³, Richard E. Carson⁵³, Martha G. MacAvoy⁵³, Howard Chertkow⁵⁴, Howard Bergman⁵⁴, Chris Hosein⁵⁴, Ging-Yuek Robin Hsiung⁵⁵, Howard Feldman⁵⁵, Benita Mudge⁵⁵, Michele Assaly⁵⁵, Charles Bernick⁵⁶, Donna Munic⁵⁶, Andrew Kertesz⁵⁷, John Rogers⁵⁷, Dick Trost⁵⁷, Diana Kerwin²⁶, Kristine Lipowski²⁶, Chuang-Kuo Wu²⁶, Nancy Johnson²⁶, Carl Sadowsky⁵⁸, Walter Martinez⁵⁸, Teresa Villena⁵⁸, Raymond Scott Turner⁵⁹, Kathleen Johnson⁵⁹, Brigid Reynolds⁵⁹, Reisa A. Sperling¹⁶, Keith A. Johnson¹⁶, Gad Marshall¹⁶, Meghan Frey¹⁶, Barton Lane¹⁶, Allyson Rosen¹⁶, Jared Tinklenberg¹⁶, Marwan N. Sabbagh⁶⁰, Christine M. Belden⁶⁰, Sandra A. Jacobson⁶⁰, Sherye A. Sirrel⁶⁰, Neil Kowall⁶⁰, Ronald Killiany⁶¹, Andrew E. Budson⁶¹, Alexander Norbash⁶¹, Patricia Lynn Johnson⁶¹, Joanne Allard⁶¹, Alan Lerner⁶³, Paula Ogrocki⁶³, Leon Hudson⁶³, Evan Fletcher¹⁵, Owen Carmichael²⁵, John Olchney¹⁵, Charles DeCarli¹⁵, Smita Kittur⁶⁴, Michael Borrie⁶⁵, T-Y. Lee⁶⁵, Rob Bartha⁶⁵, Sterling Johnson⁶⁶, Sanjay Asthana⁶⁶, Cynthia M. Carlsson⁶⁶, Adrian Preda³¹, Dana Nguyen³¹, Pierre Tariot³³, Stephanie Reeder³³, Vernice Bates⁶⁷, Horacio Capote⁶⁷, Michelle Rainka⁶⁷, Douglas W. Scharre⁶⁸, Maria Katakaki⁶⁸, Anahita Adeli⁶⁸, Earl A. Zimmerman⁶⁹, Dzintra Celmins⁶⁹, Alice D. Brown⁶⁹, Godfrey D. Pearlson⁷⁰, Karen Blank⁷⁰, Karen Anderson⁷⁰, Robert B. Santulli⁷¹, Tamar J. Kitzmiller⁷¹, Eben S. Schwartz⁷¹, Kaycee M. Sink⁷², Jeff D. Williamson⁷², Pradeep Garg⁷², Franklin Watkins⁷², Brian R. Ott⁷³, Henry Querfurth⁷³, Geoffrey Tremont⁷³, Stephen Salloway⁷⁴, Paul Malloy⁷⁴, Stephen Correia⁷⁴, Howard J. Rosen⁹, Bruce L. Miller⁹, Jacobo Mintzer⁷⁵, Kenneth Spicer⁷⁵, David Bachman⁷⁵, Stephen Pasternak⁵⁷, Irina Rachinsky⁵⁷, Dick Drost⁵⁷, Nunzio Pomara⁷⁶, Raymundo Hernando⁷⁶, Antero Sarrae⁷⁶, Susan K. Schultz⁷⁷, Laura L. Boles Ponto⁷⁷, Hyungsub Shim⁷⁷, Karen Elizabeth Smith⁷⁷, Norman Relkin²², Gloria Chaing²², Lisa Raudin^{19, 22}, Amanda Smith⁷⁸, Kristin Fargher⁷⁸, Balebail Ashok Raj⁷⁸, Thomas Neylan⁹, Jordan Grafman²⁶, Melissa Davis¹⁰, Rosemary Morrison¹⁰, Jacqueline Hayes⁹, Shannon Finley⁹, Karl Friedl⁷⁹, Debra Fleischman⁴³, Konstantinos Arfanakis⁴³, Olga James⁴⁶, Dino Massoglia⁷⁵, J Jay Fruehling⁶⁶, Sandra Harding⁶⁶, Elaine R. Peskind³⁰, Eric C. Petrie⁶⁸, Gail Li⁶⁸, Jerome A. Yesavage⁸⁰, Joy L. Taylor⁸⁰ & Ansgar J. Furst⁸⁰
- ⁹ UC San Francisco, San Francisco, CA 94143, USA. ¹⁰ UC San Diego, San Diego, CA 92093, USA. ¹¹ Mayo Clinic, Rochester, NY 14603, USA. ¹² UC Berkeley, Berkeley, CA 94720, USA. ¹³ UPenn, Philadelphia, PA 9104, USA. ¹⁴ USC, Los Angeles, CA 90089, USA. ¹⁵ UC Davis, Davis, CA 95616, USA. ¹⁶ Brigham and Women's Hospital/Harvard Medical School, Boston, MA 02115, USA. ¹⁷ Indiana University, Bloomington, IN 47405, USA. ¹⁸ Washington University in St Louis, St Louis, MI 63130, USA. ¹⁹ Prevent Alzheimer's Disease 2020, Rockville, MD 20850, USA. ²⁰ Siemens, Munich 80333, Germany. ²¹ University of Pittsburgh, Pittsburgh, PA 15260, USA. ²² Weill Cornell Medical College, Cornell University, New York City, NY 10065, USA. ²³ Albert Einstein College of Medicine of Yeshiva University, Bronx, NY 10461, USA. ²⁴ AD Drug Discovery Foundation, New York City, NY 10019, USA. ²⁵ Acumen Pharmaceuticals, Livermore, CA 94551, USA. ²⁶ Northwestern University, Evanston and Chicago, IL 60208, USA. ²⁷ National Institute of Mental Health, Rockville, MD 20852, USA. ²⁸ Brown University, Providence, RI 02912, USA. ²⁹ Eli Lilly, Indianapolis, IN 46225, USA. ³⁰ University of Washington, Seattle, W A 98195, USA. ³¹ UCLA, Los Angeles, CA 90095, USA. ³² University of Michigan, Ann Arbor, MI 48109, USA. ³³ University of Utah, Salt Lake City, UT 84112, USA. ³⁴ Banner Alzheimer's Institute, Phoenix, AZ 85006, USA. ³⁵ UC Irvine, Irvine, CA 92697, USA. ³⁶ National Institute on Aging, Bethesda, MD 20892, USA. ³⁷ Johns Hopkins University, Baltimore, MD 21218, USA. ³⁸ Richard Frank Consulting, Washington, DC 20001, USA. ³⁹ Oregon Health and Science University, Portland, OR 97239, USA. ⁴⁰ Baylor College of Medicine, Houston, TX 77030, USA. ⁴¹ University of Alabama, Birmingham, AL 35233, USA. ⁴² Mount Sinai School of Medicine, New York City, NY 10029, USA. ⁴³ Rush University Medical Center, Chicago, IL 60612, USA. ⁴⁴ Wien Center, Miami, FL 33140, USA. ⁴⁵ New York University, New York City, NY 10003, USA. ⁴⁶ Duke University Medical Center, Durham, NC 27710, USA. ⁴⁷ University of Kentucky, Lexington, KY 0506, USA. ⁴⁸ University of Rochester Medical Center, Rochester, NY 14642, USA. ⁴⁹ University of Texas Southwestern Medical School, Dallas, TX 75390, USA. ⁵⁰ Emory University, Atlanta, GA 30322, USA. ⁵¹ Medical Center, University of Kansas, Kansas City, KS 66103, USA. ⁵² Mayo Clinic, Jacksonville, FL 32224, USA. ⁵³ Yale University School of Medicine, New Haven, CT 06510, USA. ⁵⁴ McGill University/Montreal-Jewish General Hospital, Montreal, QC H3T 1E2, Canada. ⁵⁵ University of British Columbia Clinic for AD & Related Disorders, Vancouver, BC V6T1Z3, Canada. ⁵⁶ Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV 89106, USA. ⁵⁷ St Joseph's Health Care, London, ON N6A 4V2, Canada. ⁵⁸ Premiere Research Institute, Palm Beach Neurology, Miami, FL 33407, USA. ⁵⁹ Georgetown University Medical Center, Washington, DC 20007, USA. ⁶⁰ Banner Sun Health Research Institute, Sun City, AZ 85351, USA. ⁶¹ Boston University, Boston, MA 02215, USA. ⁶² Howard University, Washington, DC 20059, USA. ⁶³ Case Western Reserve University, Cleveland, OH 20002, USA. ⁶⁴ Neurological Care of CNY, Liverpool, NY 13088, USA. ⁶⁵ Parkwood Hospital, London, ON N6C0A7, Canada. ⁶⁶ University of Wisconsin, Madison, WI 53706, USA. ⁶⁷ Dent Neurologic Institute, Amherst, NY 14226, USA. ⁶⁸ Ohio State University, Columbus, OH 43210, USA. ⁶⁹ Albany Medical College, Albany, NY 12208, USA. ⁷⁰ Hartford Hospital, Olin Neuropsychiatry Research Center, Hartford, CT 06114, USA. ⁷¹ Dartmouth-Hitchcock Medical Center, Lebanon, NH 03766, USA. ⁷² Wake Forest University Health Sciences, Winston-Salem, NC 27157, USA. ⁷³ Rhode Island Hospital, Providence, RI 02903, USA. ⁷⁴ Butler Hospital, Providence, RI 02906, USA. ⁷⁵ Medical University South Carolina, Charleston, SC 29425, USA. ⁷⁶ Nathan Kline Institute, Orangeburg, NY 10962, USA. ⁷⁷ University of Iowa College of Medicine, Iowa City, IA 52242, USA. ⁷⁸ University of South Florida: USF Health Byrd Alzheimer's Institute, Tampa, FL 33613, USA. ⁷⁹ Department of Defense, Arlington, V A 22350, USA. ⁸⁰ Stanford University, Stanford, CA 94305, USA.

Author contribution QZ took part in data collection, performed all analyses, and generated the first and final drafts. CF took part in generating the final drafts, and critically reviewed the manuscript. LW critically reviewed the manuscript. TL

took part in designing the study and data collection and critically reviewed the manuscript. YH took part in designing the study and data collection, and critically reviewed the manuscript. JJ took part in the study designed, provided funding, and critically reviewed the manuscript.

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Data availability All data are available upon request from the authors.

Declarations

Conflict of interest The authors declare no competing interests.

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