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Amyloid PET in Dementia Syndromes: A Chinese Multicenter Study

Zhihong Shi[1], Li-ping Fu[2,3], Nan Zhang[4], Xiaobin Zhao[5], Shuai Liu[1], Chuantao Zuo[6], Li Cai[7], Ying Wang[7], Shuo Gao[7], Lin Ai[5]*, Yi-Hui Guan[6]*, Baixuan Xu[2]*, Yong Ji[1,8,9]*

1 Tianjin Key Laboratory of Cerebrovascular and of Neurodegenerative diseases, Tianjin Dementia institute, Department of Neurology, Tianjin Huanhu Hospital, Tianjin, China

2 Department of Nuclear Medicine, the 1st Medical Center，Chinese PLA (People's Liberation Army) General Hospital, Beijing, China

3 Department of Nuclear Medicine, China-Japan Friendship Hospital, Beijing, China.

4 Department of Neurology, General Hospital of Tianjin Medical University, Tianjin, China

5 Department Nuclear medicine, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

6 PET center, Huashan hospital, Fudan University, Shanghai, China

7 Department of PET-CT Diagnostic, Tianjin Medical University General Hospital, Tianjin, China.

8 China National Clinical Research Center for Neurological Diseases, Beijing, China.

9 Department of neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Running Title: Amyloid PET study in China

Corresponding Authors: Yong Ji. MD, PhD. 1. Department of neurology, Beijing Tiantan Hospital, Capital Medical University, No. 199, W.Section of S.4th Ringroad, Fengtai District, Beijing, China.100070; 2. Tianjin Huanhu Hospital, Tianjin, China 300350. Email: jiyongusa@126.com.Tel: +86 13612048681. Fax: +86 022 59065662. Lin Ai. MD, PhD. Department Nuclear medicine, Beijing Tiantan Hospital, Capital Medical University, Beijing, China. Email: ailin@bjtth.org.Yi-Hui Guan. MD,

PhD. PET center, Huashan hospital, Fudan University, Shanghai, China. Email: guanyihui@hotmail.com. Baixuan Xu. MD. Department of Nuclear Medicine, the 1st Medical Center，Chinese PLA (People's Liberation Army) General Hospital, Beijing, China. Email: xbx301@163.com.

First author: Zhihong Shi. MD, PhD. Tianjin Key Laboratory of Cerebrovascular and of Neurodegenerative diseases, Tianjin Dementia institute, Department of Neurology, Tianjin Huanhu Hospital, No.6 Jizhao Road, Jinnan District,Tianjin, China. 300350. Email: shzhh1204@126.com. Tel: +86 13299945151.

Zhihong Shi, Li-ping Fu, Nan Zhang, and Xiaobin Zhao contributed equally to this work.

ABSTRACT

Cerebral β-amyloid deposits and regional glucose metabolism assessed by positron emission tomography (PET) are used to distinguish between Alzheimer's disease (AD) and other dementia syndromes. In the present multicenter study, we estimated the prevalence of β-amyloid deposits on PET imaging in a wide variety of dementia syndromes and mild cognitive impairment (MCI) within a memory clinic population.

Methods: Of the 1193 consecutive patients with cognitive impairment (CI) who received combined ^{18}F-AV45 and/or ^{11}C-PIB PET, 960 were diagnosed with AD, 36 with frontotemporal dementia (FTD), 5 with dementia with Lewy bodies (DLB), 144 with MCI, 29with vascular dementia (VaD), 4 with corticobasal syndrome (CBS) and 15 with unclassifiable dementia. Baseline clinical diagnoses were independently established without access to PET imaging results. ApoE genotype analysis was performed in CI patients and 231 gender- and age-matched controls.

Results: Of the 1193 CI patients, 860 (72.1%) were amyloid-positive. The prevalence of amyloid positivity in AD and MCI patients was 86.8% (833/960) and 9.7% (14/144), respectively. In FTD patients, the prevalence of β-amyloid deposits was 5.6% (2/36). In the 4 CBS patients, two were amyloid-positive. Three of the 5 DLB patients showed amyloid positivity, as did 6 of the 29 VaD (20.7%) patients. The ApoEε4 allele frequency was significantly increased in amyloid-positive CI patients (30.5%) as compared with other amyloid-negative CI patients (14%) or controls (7.3%).

Conclusions: Amyloid imaging may potentially be the most helpful parameter for differential diagnosis in dementia, particularly to distinguish between AD and FTD. Amyloid PET can be used in conjunction with the ApoEε4 allele genetic risk test for amyloid deposits.

Keywords: amyloid PET, dementia, multicenter

INTRODUCTION

Owing to the aging of the world's population, the prevalence of dementia is increasing, with the number of individuals living with dementia currently estimated at 50 million worldwide and projected to increase to 75 million by 2030. Moreover, the number of dementia cases are estimated to almost triple by 2050 (*1*). β-Amyloid positron emission tomography (PET) imaging allows *in vivo* detection of fibrillar plaques, a core neuropathological feature of Alzheimer's disease (AD). Several amyloid ligands have been studied *in vivo*, two of which, ^{11}C-PIB (*2*) and ^{18}F-Florbetapir (AV-45), are widely used in current clinical research (*3*) and have now been proven as reliable tools for assessing the amyloid burden in the brain of AD patients.

PET imaging with ^{18}F (^{18}F-FDG PET) highlights the differential distribution of pathology in dementia disorders and has been used to study neurodegenerative diseases for over 3 decades (*4,5*). AD causes hypometabolism predominantly in the posterior regions, including the posterior temporoparietal association cortex and posterior cingulate cortex (*6,7*). ^{18}F-FDG PET images of patients with frontotemporal dementia (FTD) show decreased metabolism in the frontal and anterior temporal areas, cingulate gyri, uncus, insula and subcortical areas, including the basal ganglia and medial thalamic regions (*7-9*).

Due to the invasive nature of lumbar puncture for the collection of cerebrospinal fluid, neuroimaging modalities such as^{18}F-FDG PET and ^{11}C-PIB PET/AV-45 PET are more accepted in routine clinical practice to improve the diagnosis of dementia subtypes. To date, most amyloid PET studies have been conducted in single centers with smaller sample sizes. Therefore, we performed a multicenter study including 5 clinics with a view to: 1) estimating the prevalence of amyloid positivity in a large sample encompassing a variety of dementia syndromes; 2) evaluating the association between ^{18}F-FDG PET and amyloid scans in this cohort of patients; and 3)analyzing the association between the apolipoprotein E (ApoE) ε4 gene and amyloid deposits on PET scans.

MATERIALS AND METHODS

Subjects

A total of 1193 consecutive patients with cognitive impairment (CI) were recruited at the PET/CT Center of Beijing Tiantan Hospital, the General Hospital of the People's Liberation Army, Shanghai Huashan Hospital and the General Hospital of Tianjin Medical University between December 2012 and December 2018. All participants were aged 19–92 years old. The inclusion criteria were a clinical diagnosis of mild cognitive impairment (MCI), dementia of any type or unclassifiable dementia and ^{11}C-PIB PET or ^{18}F-AV45 PET with or without ^{18}F-FDG PET having been performed within 1 month of the initial clinical diagnosis. Sixty patients were excluded whose clinical data were not recorded in detail by their clinicians.

The clinical assessment was performed by neurologists experienced in dementia care and included detailed history taking from primary caregivers of the patient, physical examination, cognitive assessment and laboratory studies including a thyroid function test, vitamin B12 level, folate level and syphilis serology.

Clinical criteria for AD, FTD, dementia with Lewy bodies (DLB) and vascular dementia (VaD) were employed to establish the initial clinical diagnosis without the use of any biomarker. The diagnosis of different dementia subtypes was based on the respective diagnostic guidelines using brain magnetic resonance imaging (MRI) and laboratory tests. The diagnosis of AD was made according to the criteria of the National Institute on Aging and the Alzheimer’s Association workgroup for the diagnosis of probable AD dementia (*10*). Patients with DLB were diagnosed using the McKeith criteria (*11*). Behavioral variant of FTD was diagnosed using revised diagnostic criteria reported by the International behavioral variant of FTD Criteria Consortium (*12*). Language variant of FTD and primary progressive aphasia were diagnosed according to the classification of primary progressive aphasia and its variants (*13,14*). Corticobasal syndrome (CBS) was diagnosed according to the criteria published in 2013

(*15*). Patients with VaD were diagnosed according to the criteria of the NINDS–AIREN (National Institute of Neurological Disorders and Stroke/Association International pour la Recherche et l'Enseignement en Neurosciences) (*16*). MCI was diagnosed according to the criteria published in 2004 (*17*). Subjects who had any contraindications to MRI or PET scanning were excluded from the present study.

The ApoE genotype was determined from venous blood samples. Controls were group-matched to patients with respect to age and gender.

Neuropsychological testing

Subjects were examined using a battery of tests during the two weeks prior to PET imaging. These tests included Minimum Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Activity of Daily Living Scale (ADL), and Clinical Dementia Rating (CDR).

Magnetic resonance imaging (MRI) acquisition

MRI scans were obtained on a 3.0 Tesla General Electric scanner or 3.0T SIEMENS Trio a Tim MR scanner. The time interval between MRI and amyloid PET was no longer than two weeks. T1-weighted coronal images were acquired using a three-dimensional spoiled gradient-recalled-echo inversion-recovery prepped sequence (1-mm slice thickness). All images from the 3T were reconstructed to a size of 256 × 256, with an isotropic resolution of 1 × 1 × 1 mm. These scans were used to define regions of interest (ROIs) for PET data analysis.

PET imaging

^{11}C-PIB PET imaging was conducted at the PET/CT centers using a GE Discovery LS PET/CT scanner or Siemens Biograph mCT Flow PET/CT scanner (Huashan hospital) in the 3D scanning mode. PIB was administered into an antecubital vein as a bolus injection at a mean dose of 370-555 MBq. ^{11}C-PIB PET images were acquired during a 90-min

dynamic PET scan. ^{11}C-PIB uptake in each cortical region and across the whole cortical region was calculated. Cerebellar cortex was chosen as reference tissue. ^{11}C-PIB integral images were co-registered to each subject's T1-weighted MR images. An MRI-based automated region of interest technique was used to sample each individual's PIB images. Imaging data at 40−60 min post-injection were used for the analysis of PIB uptake to get parametric images of PIB standard uptake value ratios (SUVRs). Patients were diagnosed as PIB-positive based on both visual interpretations of elevated binding in the neocortex and semi-quantitative assessment (SUVR> 1.40) (*18*).

^{18}F-AV45 PET scans were obtained on a Discovery Elite scanner (GE Healthcare) at Tiantan Hospital or Siemens Biograph mCT Flow PET/CT scanner (Huashan hospital). ^{18}F-AV45 PET was acquired for 20 min, 50 min post-injection of 248±58 MBq.^{18}F-AV45 PET data were reconstructed using an ordered subset expectation maximization algorithm with weighted attenuation. Images were smoothed using a 5-mm Gaussian kernel with scatter correction, and evaluated prior to analysis of patient motion and adequacy of statistical counts. SUVRs were calculated using the cerebellar gray matter reference region to normalize mean activity from 50 to 70 minutes. Patients were diagnosed as AV45-positivebased on both visual interpretations of elevated binding in the neocortex and semi-quantitative assessment (SUVR > 1.11).

Subjects were injected intravenously with 240-333 MBq ^{18}F-FDG, and a 10-min static PET scan was performed 40 min post-injection of ^{18}F-FDG. Voxel-based statistical analysis was performed on ^{18}F-FDG PET images using Statistical Parametric Mapping (SPM) 8 and Matlab2010b for Windows. Regions that reached an uncorrected *p*-value < 0.001 were considered statistically significant. Anatomical localization was based on the superimposition of SPM-T maps onto the ch2bet template brain and identification of the localization using the AAL software and anatomical atlases (http://www.talairach.org/) (*19*). The findings were rendered using the publicly available MRIcron software (http://www.sph.sc.edu/comd/rorden/mricron/).

Statistical analysis

Categorical variables were examined using Chi-square or Fisher's exact test. Data are expressed as the median, mean ± standard deviation (SD), or a number and percentage. ANOVA and independent Student's *t*-tests were used to determine the statistical differences in images and the duration of symptoms between amyloid-positive and -negative patients. *P*-values < 0.05 were considered statistically significant.

Ethics

Detailed written informed consent was obtained from all subjects and their relatives. The present study was approved by the Ethics Committees of Tianjin Huanhu Hospital, Beijing Tiantan Hospital, the General Hospital of the People's Liberation Army, Shanghai Huashan Hospital and the Tianjin Medical University. The procedures were performed in accordance with the ethical standards of the Committee on Human Experimentation.

RESULTS

A total of 1193 patients (55.4% males) were recruited, of whom 960 had AD, 36 had FTD, 5 had DLB, 4 had CBS, 29 had VaD, 144 had MCI, and 15 had unclassifiable dementia. ^{11}C-PIB PET data were available for 562 (47.1%) patients, ^{18}F-AV45 PET data were available for 643 (53.9%) patients, and both ^{18}F-FDG PET and ^{11}C-PIB PET or ^{18}F-AV45 PET data were available for 616 (51.6%) patients. Of the 12 patients with both ^{11}C-PIB PET and ^{18}F-AV45 PET scans, 3 were both PIB- and AV45-negative, and 9 were positive for both. The observations were consistent in the ^{11}C-PIB and ^{18}F-AV45 PET scans in these 12 patients.

Table 1 displays the demographic characteristics of all patients with CI. Most patients (85.2%) were aged 50−79 years old.

Table 2 shows the probability of amyloid positivity on PET imaging across diagnostic

and age groups. Of the 1193 CI patients, 860 (72.1%) were amyloid-positive. The prevalence of amyloid positivity in AD and MCI was 86.8% (833/960) and 9.7% (14/144), respectively. In FTD patients, the prevalence of β-amyloid deposits was 5.6% (2/36). Of the 4 CBS patients, 2 were amyloid-positive, as did 3 of the 5 DLB patients and 6 of the 29 (20.7%) VaD patients. All 15 patients with unclassifiable CI were amyloid-negative. In AD patients, those who were amyloid-positive had lower MMSE and MoCA scores than those who were amyloid-negative (MMSE: 16.8±6.1 vs 21.3±5.7, *P*= 0.001; MoCA: 11.6±5.8 vs 14.9±6.8, *P*= 0.024).In CBS, DLB, and VaD patients, those who were amyloid-positive also had lower MMSE and MoCA scores than those who were amyloid-negative (MMSE: 19.2±6.3vs23.9±6.1, *P*= 0.036; MoCA: 13.7±6.1 vs 16.9±7.0, *P*= 0.032).

Table 3 shows that the prevalence of amyloid positivity in all CI patients was significantly different among age groups, but in AD patients, this difference was not present.

Of all the CI patients, ^{18}F-FDG PET data were available for 463 AD and 36 FTD patients. Of all the clinically diagnosed AD patients, 80.6% (373/463) showed AD-pattern hypometabolism predominantly in the posterior regions, including the posterior temporoparietal association cortex and posterior cingulate cortex, with or without frontal lobe involvement. In all 396 clinical AD patients with a positive amyloid scan, 340 (85.9%) showed AD-pattern hypometabolism, and in all 373 clinical AD patients with AD-pattern hypometabolism, 340 (91.2%) showed amyloid positivity.A total of 4.5% (21/463) showed hypometabolism in the frontal and anterior temporal areas, cingulate gyri and insula, and in these patients only 12(57.1%) were amyloid-positive. A total of 14.9% (69/463) showed non-specific hypometabolism, but only 44(63.7%) were amyloid-positive (Supplemental Table 1).

Of the 36 FTD patients, 77.8% (28/36) showed FTD-pattern hypometabolism predominantly in the anterior regions, including the frontal and anterior temporal areas,

anterior cingulate gyrus, and insula, 13.9% (5/36) showed AD-pattern hypometabolismand 8.3% (3/36) showed non-specific hypometabolism. Only 2 (40%) FTD patients with AD-pattern hypometabolism were amyloid-positive (Supplemental Table 2).

The frequency of the ApoEε4 allele was 30.5% in β-amyloid-positive CI, 14.0% in β-amyloid-negative CI and 7.3% in the control. The ApoEε4 allele frequency was significantly increased in CI patients with AD pathology as compared with those with other CI without AD pathology or the controls (Supplemental Table 3).

DISCUSSION

The main findings of the present multicenter PET imaging study are that the prevalence of amyloid deposition PET images was 86.8% in clinically diagnosed AD patients, 9.7% in MCI patients and5.6% in FTD patients. Of the 4 CBS patients, 2 were amyloid-positive, as were 3 of the 5 (60%) DLB patients and 6 of the 29 (20.7%) VaD patients. The significant difference in amyloid positivity across dementia types suggests that amyloid imaging may potentially be the most helpful parameter for differential diagnosis in dementia, particularly in distinguishing between AD and FTD. Furthermore, amyloid deposits in non-AD dementia, including CBS, DLB and VaD may be clinically important, since amyloid positivity was associated with worse global cognition.

In the present study, a negative amyloid PET scan was observed in 13.2% of clinically diagnosed AD patients, which is consistent with a system meta-analysis performed in 2015 (*20*). In our clinically diagnosed AD patients aged 80 years old or older, 81.4% were amyloid-positive, which was lower than the 88.4% seen in the 50–59-year-old patients. The “AD phenocopy” was most prevalent in older patients and may be best explained by a mixture of age-related pathologies (e.g., hippocampal sclerosis, argyrophilic grain disease or tangle-predominant dementia (*21-23*)) that preferentially

target the limbic system, resulting in a memory-predominant presentation that may be mistaken for AD, in addition to false-negative PET scans. This requires more tracers to further detect the pathological changes *in vivo*.

Of the 4 clinically diagnosed CBS patients, 2 showed amyloid positivity, which is consistent with a change to AD pathology. In recent years, CBS with AD pathology has been reported in pathology and neuroimaging studies (*24-27*). Due to this clinicopathological diversity, Boeve et al., introduced the term CBS to distinguish the clinical syndrome from the pathological entity, corticobasal degeneration (*28*). Amyloid PET imaging is the optimal modality for the detection of AD pathology in CBS patients, which can direct future medical treatment.

Cerebrovascular disease is the second most common cause of age-related cognitive impairment and dementia and is widely recognized as VaD (*29*). Autopsy findings have revealed subjects with AD-type pathological changes (*30,31)* in VaD patients. For instance, a U.S. study (*32*) reported that 87% of patients enrolled to examine VaD in a dementia clinic setting were found to have AD, either alone (58%) or in combination with cerebrovascular disease (42%). Of our 29 VaD patients, 6 (20.7%) were amyloid-positive, indicating that these patients have AD alone or in combination with VaD.

In our 144 MCI patients, only 9.7% showed amyloid positivity. The rate of amyloid positivity waslower than previous studies, which have reported that 41–75% of MCI patients show beta amyloid retention on amyloid PET imaging (*33-35*). The criteria provided for MCI by Winblad et al. used in our study are relatively general, which may explain the low rate of amyloid positivity found in MCI patients in the present study.

Of all the clinically diagnosed AD patients in the present study, 80.6% showed hypometabolism predominantly in the posterior regions, including the posterior temporoparietal association cortex and posterior cingulate cortex, with or without frontal lobe involvement. Retrospective studies have illustrated that ^{18}F-FDGPET has 94% sensitivity and 73% specificity for predicting AD pathology (*36*). Hypometabolic

regions spread to the frontal association cortices in moderate-to-severe AD.

Of the 36 FTD patients, 77.8% showed FTD-pattern hypometabolism, 13.9% showed AD-pattern hypometabolism, and 8.3% showed non-specific hypometabolism. In FTD patients, frontal and temporal regions as well as the striatum and thalamus show decreased glucose metabolism (*37*). Metabolic and morphological changes occur in bilateral frontal and temporal lobes, whereas regions of metabolism are more severely affected than regions of atrophy in the frontal lobe (*38*). As the disease progresses to advanced stages, hypometabolism spreads from localized frontal lobe areas to the parietal and temporal cortices in some patients (*39*); thus, the advanced stage may mimic frontal variant AD-pattern hypometabolism. Therefore, ^{18}F-FDG PET could be used to differentiate between a diagnosis of FTD and AD in mild-to-moderate dementia patients.

ApoEε4 as a strong risk factor for AD has been studied for many years. In our 150 patients, the frequency of the ApoEε4 allele was 30.5% in those with amyloid-positive CI, which was higher than that in those with amyloid-negative CI and the controls. Human and animal studies have shown that brain β-amyloid levels and plaque loads are ApoE isoform-dependent (ε4 >ε3 >ε2), suggesting that ApoE isoforms differentially affect β-amyloid aggregation, clearance and deposition (*40-42*). The meta-analysis showed that the likelihood of amyloid positivity was associated with age and ApoEε4 status. In most non-AD dementia types, amyloid positivity increases with both age (60–80 years) and ApoEε4 carriership (*20*). A recent study showed that the ApoEε4 genotype influences the brain amyloid deposition pattern, with the ApoE genotype and age being associated with an increased β-amyloid deposition rate (*43*). The main limitation of the present study is that only 160 patients were tested for ApoE genotype; thus, we could not analyze the relationship among age, ApoE genotype and amyloid deposit pattern in detail.

CONCLUSION

Among patients with dementia, the significant difference in amyloid positivity across dementia types suggests that amyloid imaging may potentially be the most helpful parameter for differential diagnosis in dementia, particularly in distinguishing between AD and FTD. Furthermore, amyloid deposits in non-AD dementia, including CBS, DLB and VaD may be clinically important, since amyloid positivity was associated with worse global cognition. The ApoEε4 allele is a genetic risk factor for amyloid deposits.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

KEY POINTS

QUESTION: Is amyloid PET imaging a valuable test for the differential diagnosis of a variety of dementia syndromes?

PERTINENT FINDINGS: In our multicenter study including 1193 patients with cognitive impairment, 860 were amyloid-positive. Among patients with dementia, the prevalence of amyloid positivity was significantly different across dementia types.

IMPLICATIONS FOR PATIENT CARE: Amyloid imaging may potentially be the most helpful parameter for differential diagnosis in dementia, particularly in distinguishing between AD and FTD.

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Table 1. Participant characteristics in each dementia diagnostic group

	Total (n=1193)	AD (n = 960)	FTD (n = 36)	MCI (n= 144)	DLB (n = 5)	CBS (n = 4)	VaD (n=29)	UN-D (n=15)
Age, median (range)	65.0 (19-92)	65.1 (32-92)	60.4 (38-79)	61.5 (30-90)	71.0 (61-77)	63.5 (51-77)	70.0 (53-81)	56.5 (19-74)
Age groups								
<40	18	13	1	1	0	0	0	3
40-49	64	39	6	16	0	0	0	3
50-59	300	241	9	43	0	1	4	2
60-69	395	316	15	46	1	2	10	5
70-79	322	265	5	31	4	1	14	2
80-	94	86	0	7	0	0	1	0
Men, %	661 (55.4)	525 (54.7)	15 (41.7)	91 (63.2)	3 (60.0)	2 (50.0)	15 (51.7)	10 (66.7)
Education level	11.2 ± 3.7	10.9 ± 3.5	10.3 ± 3.1	13±3.3	14.7 ± 2.3	8.8±6.2	10.8 ± 4.2	13.7 ± 4.0
MMSE	19.2 ± 6.7	17.4 ± 6.3	19.0 ± 7.5	24.7 ± 4.0	20.3 ± 6.7	18.0 ± 4.0	22.8 ± 6.9	26.7 ± 3.2
MoCA	13.8 ± 6.9	12.0 ± 6.0	12.3 ± 7.7	19.3 ± 5.6	15.0 ± 11.7	7.3±3.1	17.5 ± 8.5	21.7 ± 5.1
ADL	28.0 ± 9.7	29.6 ± 8.9	28.3 ± 11.1	21.3 ± 1.8	28.0 ± 7.5	40.0 ± 2.0	27.9 ± 13.8	25.3 ± 6.1

AD, Alzheimer's disease; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; VaD, vascular dementia; CBS, corticobasal syndrome; UN-D, unclassifiable dementia; MMSE, Minimum Mental State Examination; MoCA, Montreal Cognitive Assessment; ADL, Activity of Daily Living Scale

Table 2. Observed probabilities of amyloid positivity on PET across diagnostic and age groups

	Total (n=1193)	AD (n = 960)	FTD (n = 36)	MCI (n= 144)	DLB (n = 5)	CBS (n = 4)	VaD (n=29)	UN-D (n=15)
Total n(%)	860(72.1)	833 (86.8)	2 (5.6)	14 (9.7)	3(60.0)	2 (50.0)	6 (20.7)	0
Age group								
<40y	12/18 (66.7)	12/13(92.3)	0/1	0/1	0	0	0	0/5
40-49 y	32/64 (50.0)	32/39 (82.1)	0/6	0/16	0	0	0	0/3
50-59 y	221/300 (73.7)	213/241 (88.4)	1/9 (11.1)	6/43 (14.0)	0	0/1	1/4 (25.0)	0/2
60-69 y	286/395 (72.4)	275/316 (87.0)	1/15 (6.7)	6/46 (13.0)	1/1 (100)	1/2 (50.0)	2/10 (20.0)	0/5
70-79 y	239/322 (74.2)	231/265 (87.2)	0/5	2/31 (6.5)	2/4 (50.0)	1/1 (100)	3/14 (21.4)	0/2
80y-	70/94 (74.5)	70/86 (81.4)	0	0/7	0	0	0/1	0
sex								
men	454/661 (68.7)	441/525 (84.0)	0/15	8/91 (8.8)	2/3 (66.7)	1/2 (50.0)	2/15 (13.3)	0/10
women	406/532 (76.3)	392/435 (90.1)	2/21 (9.5)	6/53 (11.3)	1/2 (50.0)	1/2 (50.0)	4/14 (28.6)	0/5

Table 3. Prevalence of amyloid positivity on PET scans across diagnostic, gender, and age groups

	Amyloid positive, n(%)	p-value
Diagnostic		<0.001
AD	833 (86.7)	
FTD	2 (5.6)	
MCI	14 (9.7)	
DLB+CBS	5(55.6)	
VaD	6(20.7)	
Total		
Age group		0.004
<40y	12 (66.7)	
40-49y	32 (50.0)	
50-59y	221 (73.7)	
60-69y	286 (72.4)	
70-79y	239 (74.2)	
80y-	70 (74.5)	
Sex		0.002
Men	454 (68.7)	
Women	406 (76.3)	
AD		
Age group		0.569
<40y	12 (92.3)	
40-49y	32 (82.1)	
50-59y	213 (88.4)	
60-69y	275 (87.0)	
70-79y	231 (87.2)	
80y-	70 (81.4)	
Sex		0.004
Men	441 (83.4)	
Women	392 (90.1)	