Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Participants and Study Design

Inclusion criteria per cohort:

PREVENT-AD: Enrollment criteria included: (1) having a parent or multiple siblings with a history of AD dementia; (2) age >60 years, or age between 55 and 59 years if the onset of symptomatic dementia of their youngest affected relative was within 15 years of their current age; (3) no major neurological diseases; and (4) no evidence of cognitive impairment at enrollment[1].

ADNI: see main text

HABS: Criteria for inclusion here included scores (1) of 0 on the Clinical Dementia Rating, (2) of 11 or less on the Geriatric Depression Scale, (3) of 27 or more on the education-adjusted Mini-Mental State Examination, and (4) performance within education-adjusted norms on Logical Memory–delayed recall test. HABS excluded persons who had a score of 5 or more on the Hachinski Ischemia Scale, a history of stroke with residual deficits, or a history of intracranial hemorrhage. We obtained data from the HABS data release 2.0 in October 2020 via habs.mgh.harvard.edu.

Exclusion criteria per cohort:

PREVENT-AD:

1. Cognitive disorders
2. Use of acetyl-cholinesterase inhibitors including tacrine, donepezil, rivastigmine, galantamine
3. Use of memantine or other approved prescription cognitive enhancer
4. Use of vitamin E at>600 iu. / day or aspirin at > 325 mg / day
5. Use of opiates (oxycodone, hydrocodone, tramadol, meperidine, hydromorphone)
6. Use of NSAIDs or regular use of systemic or inhalation corticosteroids
7. Clinically significant hypertension (accepted if controlled medically), anemia, significant liver or kidney disease
8. Concurrent use of warfarin, ticlopidine, clopidrogel, or similar anti-coagulant
9. Current plasma Creatinine > 1.5 mg/dl (132 mmol/l)
10. Current alcohol, barbiturate or benzodiazepine abuse/dependence

ADNI

1. Any significant neurologic disease, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities
2. Screening/baseline MRI scan with evidence of infection, infarction, or other focal lesions. Participants with multiple lacunes or lacunes in a critical memory structure are excluded.
3. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body.
4. Major depression, and bipolar disorder as described in DSM-IV within the past 1 year. Psychotic features, agitation or behavioural problems within the last 3 months could lead to difficulty complying with the protocol.
5. History of schizophrenia (DSM IV criteria).
6. History of alcohol or substance abuse or dependence within the past 2 years (DSM IV criteria).
7. Any significant systemic illness or unstable medical condition could lead to difficulty complying with the protocol.
8. Clinically significant abnormalities in B12, or TFTs might interfere with the study. A low B12 is exclusionary unless follow-up labs (homocysteine (HC) and methylmalonic acid (MMA)) indicate that it is not physiologically significant.
9. Residence in a skilled nursing facility.
10. Current use of specific psychoactive medications (e.g., certain antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.). Current use of warfarin (exclusionary for lumbar puncture).
11. Exclusion for amyloid imaging with 18F –AV-45: Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the participant in any given year would exceed the limits of annual and total dose commitment outlined in the US Code of Federal Regulations (CFR) Title 21 Section 361.1.
12. Exceptions to these guidelines may be considered on a case-by-case basis at the discretion of the protocol director (Dr. Petersen).

HABS

1. History of alcoholism, drug abuse, head trauma, or current serious medical/psychiatric condition.
2. Cholinesterase inhibitors and memantine are only allowed in MCI or AD patients if stable for three months before the screen.
3. > 0 score on the Clinical Dementia Rating Scale
4. A score of lower than 25 on the Mini-Mental State Examination
5. Scores below the age and education-adjusted cut-offs on the 30-Minute Delayed Recall of the Logical Memory Story A
6. A score of more than 11 on the Geriatric Depression Scale
7. Antidepressants are allowed for both normal and impaired participants if they are not depressed at the time of screen and do not have a history of major depression within the past 1 year.

***APOE* Genotyping**
For PREVENT-AD, genomic DNA was extracted at baseline from whole blood, and genotype at the polymorphic *APOE* locus was determined as recently described[2]. Similar baseline testing was performed for ADNI and HABS. Participants were classified as *APOE* ε4 carriers if they had at least one ε4 allele.

Cerebrospinal Fluid Biomarkers
Among the PREVENT-AD PET sample, 77 participants underwent a lumbar puncture ≤24 months before or after Aβ-PET (mean interval 10.4, s.d. 8.38 months). Cerebrospinal fluid (CSF) samples collected in the morning following an overnight fast were stored in cryovial tubes at −80°C. CSF $A\beta_{1-42}$, p-tau_{181} (phosphorylated at threonine 181) and total tau levels were assayed in duplicate using the INNOTEST ELISA kit (Fujirebio, Ghent, Belgium)[3,4].

In ADNI, CSF biomarkers were available for 276 participants within two years of their Aβ PET scans (mean interval 0.40, s.d. 0.75 months). ADNI CSF samples were frozen within 1 hour of collection and shipped overnight on dry ice to the Penn AD Biomarker Fluid Bank Laboratory. Aliquots of 500 µL were stored in polypropylene tubes at −80°C. CSF $A\beta_{1-42}$ and p-tau_{181} were measured using Elecsys immunoassays[5].

PET Acquisition
PET imaging in PREVENT-AD was performed using [^{18}F]NAV4694 (NAV; Navidea Biopharmaceuticals, Dublin, OH) for Aβ and Flortaucipir (FTP) (Eli Lilly & Co, Indianapolis, IN) for tau. Aβ scans were performed 40 to 70 minutes after injection (≈6 mCi) and tau scans 80 to 100 minutes after tracer injection (≈10 mCi). Most scans were conducted on 2 consecutive days. Imaging was performed at the McConnell Brain Imaging Centre at the Montreal Neurological Institute (Montreal, Canada) between February 2017 and May 2019. T1-weighted structural MRI scans had been acquired prior to the PET scans (median delay 9.06 [interquartile range (IQR): 0.03 - 34] months) on a 3T Siemens Trio scanner (Siemens, Munich, Germany) (repetition time of 2300 milliseconds, echo time of 2.98 milliseconds, 176 slices, and 1-mm slice thickness[4]).

Acquisition of the multicentric MRI and PET imaging data in ADNI has been described previously and is reported in detail at adni.loni.usc.edu/methods/. Briefly, Aβ PET scans were acquired using Florbetapir ([18F]-AV45) during a 50-to-70-minute interval following a 10 mCi bolus injection and FTP scans were acquired during a 75-to-105-minute interval following a 10 mCi bolus injection. T1-weighted structural MRI data were acquired on 3T scanning platforms using sagittal 3D magnetization-prepared rapid gradient-echo sequences. The T1 sequence was identical to that used for the PREVENT-AD cohort. A subsample of 176 participants (44%) also underwent tau-PET scans (median delay 5 [IQR: 0, 8] years). Aβ (2019-12-04 version) and tau (2020-02-04) regional SUVR data were downloaded from the ADNI database.

In HABS, PET data were acquired as described previously[6,7]. Aβ-PET scans were acquired using PIB (^{11}C-Pittsburgh Compound B) during a 60-minute dynamic acquisition starting directly after the injection, and FTP scans were acquired from 80-100 minutes after a 9.0 to 11.0 mCi bolus injection. MRI scans were performed on a 3T Tim Trio (Siemens) with a 12-channel phased-array head coil. The imaging measures were typically collected every two years (mean delay between FTP and PIB scans 3.5 months). Tau-PET was also added later on during the course of the study, with 195 participants (67%) having a FTP scan, on average 3 years [IQR: 0, 8] after PIB scans.

PET Processing

In all cohorts, T1-weighted MRIs were processed using FreeSurfer (version 5.3 or 6) and parcellated according to the Desikan-Killiany atlas[8].

PREVENT-AD: PET images were processed using a standard, in-house pipeline (available at https://github.com/villeneuvelab/vlpp). Briefly, the 4D PET images were realigned, averaged, and registered to the corresponding T1-weighted MRI. Images were then masked to exclude CSF signal and smoothed with a 6 mm^3 Gaussian kernel. Standardized uptake value ratios (SUVRs) were computed by dividing the tracer uptake in each voxel by the mean uptake in the cerebellum cortex for NAV scans[9] and the inferior cerebellum gray matter for FTP scans[10].

ADNI: PET images underwent standardized preprocessing steps to increase data uniformity across the multicenter data acquisition[11]. Briefly, Florbetapir-PET frames were re-aligned, co-registered, averaged, reoriented into a standardized image and voxel size, and smoothed to produce a uniform resolution. FTP frames were co-registered and resliced to the structural MRI closest in time to the FTP-PET. The whole cerebellum was used as the reference region for Florbetapir SUVRs, and the inferior cerebellum gray matter was used for FTP SUVRs. Aβ (2019-12-04 version) and tau (2020-02-04) regional SUVR data were downloaded from the ADNI database.

HABS: Following PET image acquisitions, a mean image was created (for PIB, at the 8-minute point following injection), and PET images were co-registered to the corresponding T1-weighted MRI with 6 DoF rigid body registration using spm_coreg from the SPM12 package. Bilateral cerebellum gray matter was used as the reference region for SUVR measurements.

Comparison with more traditional positivity classification

Global Threshold of Aβ Positivity

Each cohort had used a specific global threshold, as described previously, to categorize their participants into persons who were Aβ-positive and negative. Such thresholds were uniformly derived from the average SUVR of lateral and medial frontal, cingulate, parietal, and lateral temporal regions for PREVENT-AD and ADNI; while frontal, lateral temporal, and retrosplenial (FLR) regions were averaged for HABS. In PREVENT-AD, the NAV threshold for positivity was SUVR 1.37[12]. In ADNI, the Florbetapir threshold was SUVR 1.1[13,14]. The PIB threshold in HABS was DVR 1.19 [15,16].

Visual read binary classification

Visual reads were performed by KP on all regional participants as well as all participants with CL values higher than 8 or below 90. Visual reads were therefore performed on 129 PREVENT-AD, 206 ADNI and 171 HABS participants for a total of 506 visual reads. We classified individuals with CL < 8 in the visual read negative group and the ones with CL > 90 in the visual read positive group allowing us to present percentages for the full cohort that can be directly compared with the other methods to identify amyloid positivity.

3-tiered Centiloid global quantification

We calculated CL value for all participants and classified them as CL negative (≤20), CL intermediate (>20≤40) and CL positive (>40). This classification was based on the AHEAD trial (https://www.ahead-study.org) that aimed at intervening as early as possible in the disease cascade, when amyloidosis is at its early onset.

Statistical Analysis

All statistical analyses were conducted using RStudio, version 1.2.500124. The cutoff and mixtools packages (github.com/choisy/cutoff) were used for GMM and lme425 for mixed-effects models. Linear mixed-effects models included random slope and intercept, where the time-by-subject interaction estimated change in cognition or Aβ. The analyses were anchored at the participants' baseline visits for longitudinal cognition and at their first amyloid scan for longitudinal amyloid.

eResults

Additional Analyses.

Global quantitative thresholds of Aβ Positivity

Using the global quantitative thresholds, all negative group participants were categorized as Aβ-negative in all three cohorts (eTable 7). In the regional group, 79% of PREVENT-AD participants were classified as Aβ-negative while it's 56% in ADNI and 96% in HABS. All participants in the widespread group were classified as Aβ-positive on global quantitative thresholds in PREVENT-AD and in ADNI. One widespread group participant in HABS was classified as Aβ-negative (99%).

Visual read binary

Using a visual read binary classification one negative participant in PREVENT (99%) and one in ADNI (>99%) were classified as visual read negative (eTable 8). In the regional group, only 29% of the participants were classified as positive in PREVENT-AD, 25% in ADNI and 17% in HABS. All participants in the widespread group were classified as positive on visual read in the PREVENT-AD, 75% were classified as positive in ADNI and 91% in HABS.

3-tiered Centiloid global quantification

Finally, using a 3-tiered global quantification approach based on CL <20, 20-40 or >40, all negative participants had CL <20 (eTable 9). In the regional groups, 43% of PREVENT-AD participants has CL<20, 54% had CL>20<40 and 1% had a CL >40, these numbers were 56%, 36% and 0% in ADNI and 71%, 29% and 0% in HABS. The widespread group was composed of 95% of CL >40, 5% of CL >20<40 and 0% of CL <20 in PREVENT-AD, these numbers were 96%, 4% and 0% in ADNI and 80%, 19% and 1% in HABS.

Number of regions included to 5 or increasing to 10

Decreasing the number of regions included to 5 (by removing rostral middle frontal and inferior parietal) or increasing to 10 (by including insula, lateral orbitofrontal and isthmus cingulate)[17] did not change the main results. In all cohorts, while there was no difference between regional and negative groups, the widespread Aβ group had elevated tau-PET signal compared with both negative and regional groups across all regions investigated.

eTable 1. Regional Specific Thresholds

Cohort	Rostral Anterior Cingu-late	Precu-neus	Medial Or-bitofrontal	Rostral Middle Frontal	Inferior Parietal	Superior Frontal	Posterior Cingulate
PREVENT-AD	1.57	1.50	1.33	1.30	1.44	1.28	1.78
ADNI	1.19	1.18	1.12	1.12	1.09	1.15	1.25
HABS	1.53	1.47	1.41	1.41	1.40	1.46	1.70

GMM analyses provided SUVR thresholds for each region which correspond to a 90% probability of belonging to the low Aβ distribution in the PREVENT-AD and HABS cohorts and a 50% probability of belonging to the low Aβ distribution in the ADNI cohort.

eTable 2. Comparison of Biological and Clinical Characteristics across the Aβ Groups

A. PREVENT-AD	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread
Age	**F (2, 126) = 3.19** p < 0.05	F (2, 126) = 0.13 p=0.99	F (2, 126) = 3.07 p=0.07
Education	F (2, 125) = 2.12 p=0.035	F (2, 125) = 1.16 p=0.247	F (2, 125) = 0.97 p=0.333
Sex	X2 (1, N = 101) = 0.284 p=0.594	X2 (1, N = 109) = 0.37 p=0.544	X2 (1, N = 48) = 1.03 p=0.311
APOE ε4	**X2 (1, N = 101) = 8.54** p < 0.01	**X2 (1, N = 109) = 10.8** p < 0.01	X2 (1, N = 48) = 0.01 p=1
CSF Aβ1-42*	**F (2, 69) = 547** p<0.001	**F (2, 69) = 222** p<0.01	**F (2, 71) = 326** **p<0.01**
CSF pTau*	**F (2,74) = 20.43** p<0.05	F (2,74) = 11.67 p=0.304	F (2,74) = 8.76 p=0.293
B. ADNI	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread
Age	**F (1, 292) = 2.92** p < 0.05	F (1, 310) = 0.77 p=0.439	**F (1, 198) = 3.23** p < 0.01
Education	F (1, 292) = 2.16 p=0.078	F (1, 310) = 0.85 p=0.675	F (1, 198) = 1.20 p=0.451
Sex	**X2 (1, N = 292) = 3.48** p < 0.05	X2 (1, N = 310) = 1.05 p=0.305	X2 (1, N = 198) = 0.44 p=0.508
APOE ε4	**X2 (1, N = 292) = 29.11** p < 0.01	**X2 (1, N = 310) = 5.24** p < 0.05	**X2 (1, N = 198) = 6.98** p < 0.01
CSF Aβ1-42*	**F (2, 273) = 647** p < 0.001	**F (2, 273) = 290** p < 0.001	**F (2, 273) = 357** p<0.05
CSF pTau*	**F (2, 272) = 9.67** p < 0.001	F (2, 272) = 2.72 p=0.07	**F (2, 272) = 6.95** p < 0.001
C. HABS	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread
Age	**F (1, 207) = 2.49** p < 0.05	F (1, 211) = 0.838 p=0.680	F (1,144) = 1.47 p=0.305
Education	F (1,207) = 1.35 p=0.368	F (1,211) = 2.14 p= 0.096	**F (1, 144) = 3.04** p < 0.01
Sex	X2 (1, N = 207) = 0.08 p=0.779	**X2 (1, N = 211) = 6.46** p < 0.01	X2 (1, N = 144) = 3.31 p=0.069
APOE ε4	**X2 (1, N = 207) = 40.59** p < 0.001	X2 (1, N = 211) = 1.98 p=0.159	**X2 (1, N = 144) = 16.54** p < 0.001

We compared demographics, APOE ε4 status, and CSF findings across the three Aβ groups in the three cohorts separately using analysis of covariance and chi-squared tests for normally distributed continuous variables and categorical variables, respectively. We used the Tukey HSD post hoc test and Bonferroni correction to help interpret differences between the three Aβ groups. The negative group was assigned as a reference group while comparing negative to regional and negative to widespread; the regional group was set as a reference group when comparing regional to Widespread. Tukey HSD group mean difference values are reported above for each group comparison.

eTable 3. Baseline Cognition across the Aβ Groups

A. PREVENT-AD	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread	P<0.05
Immediate Memory Score	F (2,126) = 1.31, p=0.883	F (2,126) = 3.32, p=0.241	F (2,126) = 5.23, p=0.241	-
Delayed Memory Score	**F (2,126) = 6.53, p<0.05**	F (2,126) = 0.47, p=0.972	**F (2,126) = 6.06, p=0.076**	*b*
Total Index Score	F (2,126) =5.75, p=0.117	F (2,126) = 0.38, p=0.987	F (2,126) = 5.36, p=0.254	-
B. ADNI	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread	
Memory Score	F (2,397) = 0.13, p=0.171	F (2,397) = 0.04, p=0.859	F (2,397) = 0.17, p=0.105	-
Executive Function Score	F (2,397) = 0.33, p=0.063	F (2,397) = 0.11, p=0.465	F (2,397) = 0.22, p=0.120	-
C. HABS	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread	
PACC5	F (2,277) = 0.03, p=0.937	F (2,277) = 0.13, p=0.351	F (2,277) = 0.10, p=0.643	-

Cognitive test scores were compared at the baseline visit, corrected for age and sex; test scores are reported as Tukey HSD group mean differences for each group comparison. (**A)** As part of the PREVENT-AD battery, all participants undergo annual cognitive testing using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). (**B)** In ADNI, participants received detailed cognitive assessments from which composite scores are derived. All the composite scores have a mean of 0, and a standard deviation of 1. **(C)** HABS participants undergo annual cognitive testing with PACC5 to derive a cognitive composite score including memory, executive function, and semantic processing. Bold text represents the significant between-group differences: a = p<0.05 between Aβ-negative and regional Aβ groups; b = p<0.05 between Aβ-negative and widespread Aβ groups; c = p<0.05 between regional Aβ and widespread Aβ groups.

eTable 4. Change in Cognition Over Time Between the Aβ Groups

A. PREVENT-AD	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread
Immediate Memory Score (β [SE])	**-0.14 [0.04]**; p<0.01	-0.03 [0.04]; p=0.469	**-0.11 [0.04]**; p<0.05
Delayed Memory Score (β [SE])	**-0.13 [0.05]**; p < 0.01	0.03 [0.04]; p=0.357	**-0.11 [0.05]**; p < 0.05
Total Index Score (β [SE])	**-0.11 [0.03]**; p < 0.001	-0.03 [0.03]; p=0.304	**-0.08 [0.04]**; p < 0.05
B. ADNI	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread
Memory Score (β [SE])	**-0.10 [0.006]**; p < 0.001	**-0.03 [0.006]**; p < 0.001	**-0.07 [0.01]**; p<0.001
Executive Function Score (β [SE])	**-0.08 [0.008]**; p < 0.001	**-0.03 [0.008]**; p < 0.001	**-0.06 [0.01]**; p<0.001
C. HABS	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread
PACC5 (β [SE])	**-0.12 [0.02]**; p < 0.001	-0.03 [0.02]; p=0.142	**-0.09 [0.02]**; p < 0.001

Using linear mixed-effects models, we tested whether Aβ groups differed in terms of change in cognition score corrected for baseline age, sex, education, and time. Standardized estimates (Est.), standard errors (SE), and p-values are presented. The negative group was assigned as a reference group while comparing negative to regional and negative to widespread; the regional group was set as a reference group when comparing regional to widespread.

eTable 5. Aβ Accumulation Rate in ADNI and HABS

Cohorts	Variable	Rostral Anterior Cingulate	Precuneus	Medial Orbitofrontal	Rostral Middle Frontal	Inferior Parietal	Superior Frontal	Posterior Cingulate
ADNI	**Negative** *vs.* **Widespread**	0.028 (0.013), **p<0.05**	0.042 (0.012), **p<0.001**	0.044 (0.012), **p<0.001**	0.047 (0.012), **p<0.001**	0.040 (0.012), **p<0.01**	0.058 (0.013), **p<0.001**	0.028 (0.013), **p<0.05**
	Negative *vs.* **Regional**	0.049 (0.011), **p<0.001**	0.052 (0.010), **p<0.001**	0.056 (0.011), **p<0.001**	0.042 (0.010), **p<0.001**	0.030 (0.010), **p<0.01**	0.044 (0.011), **p<0.001**	0.050 (0.011), **p<0.001**
	Regional *vs.* **Widespread**	-0.020 (0.015), p=0.168	-0.010 (0.013), p=0.449	-0.014 (0.014), p=0.322	0.004 (0.013), p=0.762	0.009 (0.013), p=0.484	0.014 (0.014), p=0.329	-0.022 (0.014), p=0.135
HABS	**Negative** *vs.* **Widespread**	0.082 (0.015), **p<0.001**	0.073 (0.014), **p<0.001**	0.066 (0.016), **p<0.001**	0,066 (0.015), **p<0.001**	0.048 (0.016), **p<0.01**	0.057 (0.017), **p<0.001**	0.019 (0.018), p=0.280
	Negative *vs.* **Regional**	0.030 (0.015), **p<0.05**	0.034 (0.014), **p<0.05**	0.032 (0.016), **p<0.05**	0.035 (0.015), **p<0.05**	0.019 (0.016), p=0.257	0.031 (0.017), p=0.064	0.019 (0.018), **p<0.05**
	Regional *vs.* **Widespread**	0.052 (0.017), **p<0.01**	0.039 (0.016), **p<0.05**	0.033 (0.019), p=0.080	0.032 (0.017), p=0.064	0.030 (0.019), p=0.118	0.026 (0.020), p=0.185	-0.002 (0.021), p=0.903

Using linear mixed-effects models, we tested whether Aβ groups were associated with a change in accumulation rate throughout the whole brain (global) and in different regions of interest corrected for baseline age, sex, and time. Unstandardized estimates (Est.), standard errors (SE), and p-values are presented. The negative group was assigned as a reference group while comparing negative to regional and negative to widespread; the regional group was set as a reference group when comparing regional to widespread. Models employed *SUVR*: standardized uptake value ratio.

eTable 6. Tau-PET Uptake in Early Tau Regions

A. PREVENT-AD	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread	P<0.05
Entorhinal	F (2,126) = 0.18, p<0.001	F (2,126) = 0.06, p<0.05	F (2,126) = 0.12, p<0.01	*a,b,c*
Amygdala	F (2,126) = 0.18, p<0.001	F (2,126) = 0.02, p=0.822	F (2,126) = 0.16, p<0.01	*b,c*
Fusiform	F (2,126) = 0.15, p<0.001	F (2,126) = 0.04, p=0.285	F (2,126) = 0.11 , p<0.01	*b,c*
Inferior Temporal	F (2,126) = 0.16, p<0.001	F (2,126) = 0.05, p=0.197	F (2,126) = 0.12, p<0.01	*b,c*
Middle Temporal	F (2,126) = 0.14, p<0.001	F (2,126) = 0.06, p<0.05	F (2,126) = 0.07, p=0.063	*a,b*
Parahippocampal	F (2,126) = 0.12, p<0.001	F (2,126) = 0.04, p=0.215	F (2,126) = 0.08, p<0.05	*b,c*
B. ADNI	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread	
Entorhinal	F (2,173) = 0.14, p<0.001	F (2,173) = 0.03 , p=0.448	F (2,173) = 0.11, p<0.01	*b,c*
Amygdala	F (2,173) = 0.13, p<0.01	F (2,173) = 0.01, p=0.862	F (2,173) = 0.11, p<0.01	*b,c*
Fusiform	F (2,173) = 0.13, p<0.001	F (2,173) = 0.02, p=0.777	F (2,173) = 0.12, p<0.01	*b,c*
Inferior Temporal	F (2,173) = 0.15 , p<0.001	F (2,173) = 0.02 , p=0.655	F (2,173) = 0.13, p<0.01	*b,c*
Middle Temporal	F (2,173) = 0.14, p<0.001	F (2,173) = 0.04, p=0.241	F (2,173) = 0.10, p<0.01	*b,c*
Parahippocampal	F (2,173) = 0.12, p<0.001	F (2,173) = 0.02, p=0.473	F (2,173) = 0.09, p<0.01	*b,c*
C. HABS	Negative *vs.* Widespread	Negative *vs.* Regional	Regional *vs.* Widespread	
Entorhinal	F (2,192) = 0.14, p<0.001	F (2,192) = 0.03, p=0.196	F (2,192) = 0.11, p<0.001	*b,c*
Amygdala	F (2,192) = 0.13, p<0.001	F (2,192) = 0.03, p=0.241	F (2,192) = 0.10, p<0.01	*b,c*
Fusiform	F (2,192) = 0.08, p<0.001	F (2,192) = 0.01, p=719	F (2,192) = 0.07, p<0.001	*b,c*
Inferior Temporal	F (2,192) = 0.10, p<0.001	F (2,192) = 0.01, p=0.970	F (2,192) = 0.09, p<0.001	*b,c*
Middle Temporal	F (2,192) = 0.07, p<0.001	F (2,192) = 0.01, p=0.718	F (2,192) = 0.06, p<0.01	*b,c*
Parahippocampal	F (2,192) = 0.10, p<0.001	F (2,192) = 0.02, p=0.523	F (2,192) = 0.08, p<0.001	*b,c*

Using ANCOVA and multiple comparisons corrections for age and sex, we tested whether tau-PET uptake in early tau regions significantly differed between the Aβ groups in the **(A)** PREVENT-AD cohort, **(B)** ADNI cohort and **(C)** HABS cohort. For post-hoc analysis, Bonferroni correction was applied when comparing the pair of group means and Tukey HSD group mean difference SUVR are reported above for each group comparison. a = p<0.05 between negative Aβ and regional Aβ groups; b = p<0.05 between negative Aβ and widespread Aβ groups; c = p<0.05 between regional Aβ and widespread Aβ groups.

eTable 7. Global Binary Quantitative Classification by Spatial Extent groups

	Negative (n=81)	**Regional (n=28)**	**Widespread (n=20)**
PREVENT-AD	81 Negative Aβ 0 Positive Aβ	22 Negative Aβ 6 Positive Aβ	0 Negative Aβ 20 Positive Aβ
	Negative (n=202)	**Regional (n=108)**	**Widespread (n=90)**
ADNI	202 Negative Aβ 0 Positive Aβ	61 Negative Aβ 47 Positive Aβ	0 Negative Aβ 90 Positive Aβ
	Negative (n=139)	**Regional (n=76)**	**Widespread (n=73)**
HABS (DVR)	139 Negative Aβ 0 Positive Aβ	73 Negative Aβ 3 Positive Aβ	1 Negative Aβ 72 Positive Aβ

eTable 8. Visual Read Classification by Spatial Extent groups

	Negative (n=81)	Regional (n=28)	Widespread (n=20)
PREVENT-AD	80 Negative Aβ 1 Positive Aβ	20 Negative Aβ 8 Positive Aβ	0 Negative Aβ 20 Positive Aβ
	Negative (n=202)	**Regional (n=108)**	**Widespread (n=90)**
ADNI	201 Negative Aβ 1 Positive Aβ	81 Negative Aβ 27 Positive Aβ	17 Negative Aβ 73 Positive Aβ
	Negative (n=139)	**Regional (n=76)**	**Widespread (n=73)**
HABS	138 Negative Aβ 1 Positive Aβ	**63 Negative Aβ** 13 Positive Aβ	6 Negative Aβ 67 Positive Aβ

Individuals with Centiloids < 8 were automatically classified as visual read negative and the ones with Centiloids > 90 as positive.

eTable 9. Three-tiered Centiloid (CL) Classification by Spatial Extent groups

	Negative (n=81)	Regional (n=28)	Widespread (n=20)
PREVENT-AD	81 CL ≤20 CL 0 CL>20≤40 0 CL>40	12 CL ≤20 CL 15 CL>20≤40 1 CL>40	0 CL ≤20 CL 1 CL>20≤40 19 CL>40
	Negative (n=202)	**Regional (n=108)**	**Widespread (n=90)**
ADNI	202 CL ≤20 CL 0 CL>20≤40 0 CL>40	60 CL ≤20 CL 39 CL>20≤40 9 CL>40	0 CL ≤20 CL 4 CL>20≤40 86 CL>40
	Negative (n=139)	**Regional (n=76)**	**Widespread (n=73)**
HABS	139 CL ≤20 CL 0 CL>20≤40 0 CL>40	54 CL ≤20 CL 22 CL>20≤40 0 CL>40	1 CL ≤20 CL 14 CL>20≤40 58 CL>40

eTable 10. Biological and Clinical Characteristics excluding Regional Individuals that would have been classified as Positive based on Global Binary Classifications

	PREVENT-AD Aβ Groups				ADNI Aβ Groups			
	Negative (n = 81)	Regional (n = 22)	Widespread (n = 20)	*p < 0.05*	Negative (n = 202)	Regional (n =61)	Widespread (n =90)	*p < 0.05*
Age	**63 (4.61)**	64 (3.83)	**66 (5.62)**	b	**73 (5.81)**	**71 (5.93)**	**76 (5.35)**	b,c
Education	16 (3.53)	15 (2.75)	14 (2.46)		17 (2.59)	17 (2.56)	16 (2.70)	
Sex, female (%)	60 (74%)	17 (77%)	13 (65%)		**94 (47%)**	26 (46%)	**55 (61%)**	b
APOE ε4 carriership (%)	**22 (27%)**	**14 (64%)**	**13 (65%)**	a, b	**38 (19%)**	**16 (27%)**	**45 (50%)**	a,b,c
CSF $A\beta_{1-42}$*	**1265 (37.78)**	**1058 (72.38)**	**718 (71.53)**	a,b,c	**1448 (30.13)**	**1236 (49.65)**	**802 (45.69)**	a,b,c
CSF $pTau_{181}$*	**46 (3.14)**	53 (5.86)	**67 (6.15)**	b	**19 (0.72)**	**20 (1.19)**	**29 (1.10)**	b,c

The original analyses were replicated in PREVENT-AD and ADNI cohorts excluding the "global" Aβ+ participants in regional Aβ Groups. In HABS, no regional participants were classified as Aβ+ based on the cohort specific binary threshold (see eTable 7). Values reported as mean (SD) except for sex, and *APOE* ε4, which are reported as the number of participants (% of the group). Cognitive test scores were compared at the baseline visit and corrected for age and sex. Bold text represents the groups between which there were significant differences: *a* = p<0.05 between Aβ-negative and regional Aβ groups; *b* = p<0.05 between Aβ-negative and widespread Aβ groups; *c* = p<0.05 between regional Aβ and widespread Aβ groups. *In PREVENT-AD, CSF samples were available for 46 Aβ-negative, 19 regional, and 12 widespread; in ADNI, CSF samples were available for 138 Aβ-negative, 78 regional and 60 widespread. APOE ε4: Apolipoproteinε4; Aβ: beta-amyloid; CSF: cerebrospinal fluid.

eTable 11. Biological and Clinical Characteristics excluding Regional Individuals that would have been classified as Positive based on Visual Reads

	PREVENT-AD Aβ Groups				ADNI Aβ Groups				HABS Aβ Groups			
	Negative (n = 81)	Regional (n = 20)	Widespread (n = 20)	*p < 0.05*	Negative (n = 202)	Regional (n =81)	Widespread (n =90)	*p < 0.05*	Negative (n = 139)	Regional (n =63)	Widespread (n =73)	*p < 0.05*
Age	**63 (0.51)**	63 (1.05)	**66 (1.03)**	*b*	**73 (0.41)**	**72 (0.64)**	**76 (0.62)**	*b, c*	**73 (0.52)**	73 (0.85)	**75 (0.72)**	*b*
Education	16 (0.36)	15 (0.73)	14 (0.72)		17 (0.19)	17 (0.30)	16 (0.28)		16 (0.26)	**15 (0.38)**	**16 (0.35)**	*c*
Sex, female (%)	60 (74%)	16 (80%)	13 (65%)		**94 (47%)**	46 (60%)	**55 (61%)**	*b*	**75 (54%)**	**46 (73%)**	41 (56%)	*a*
APOE ε4 carriership (%)	**22 (27%)**	**12 (60%)**	**13 (65%)**	*a, b*	**38 (19%)**	**20 (25%)**	**45 (50%)**	*b, c*	**20 (14%)**	**15 (24%)**	**41 (56%)**	*b, c*
CSF $A\beta_{1-42}$*	**1265 (37.78)**	**1103 (73.97)**	**718 (71.53)**	*b, c*	**1448 (30.13)**	**1008 (93.19)**	**802 (45.69)**	*a, b*	*n/a*	*n/a*	*n/a*	
CSF pTau*	**46 (3.14)**	47 (5.61)	**67 (6.15)**	*b, c*	**19 (0.72)**	**26 (1.14)**	**29 (1.10)**	*b, c*	*n/a*	*n/a*	*n/a*	

The values are reported as mean (SD) except for sex and APOE ε4 which are reported as the number of participants (% of the group). Bold text represents the groups between which there were significant differences: a = p<0.05 between Aβ-negative and regional Aβ groups; b = p<0.05 between Aβ-negative and widespread Aβ groups; c = p<0.05 between regional Aβ and widespread Aβ groups. *In PREVENT-AD, CSF samples were available for 45 Aβ-negative, 10 regional, and 12 widespread; in ADNI, CSF samples were available for 125 Aβ-negative, 56 regional and 51 widespread. APOE ε4: Apolipoproteinε4; Aβ: beta-amyloid; CSF: cerebrospinal fluid.

eTable 12. Biological and Clinical Characteristics excluding Regional Individuals that would have been classified as having Intermediate and High Centiloid values (CL>20)

	PREVENT-AD Aβ Groups				**ADNI Aβ Groups**				**HABS Aβ Groups**			
	Negative (n = 81)	Regional (n = 13)	Widespread (n = 20)	*p < 0.05*	Negative (n = 202)	Regional (n =60)	Widespread (n =90)	*p < 0.05*	Negative (n = 139)	Regional (n =54)	Widespread (n =73)	*p < 0.05*
Age	**63 (0.51)**	63 (1.32)	**66 (1.03)**	*b*	**73 (0.41)**	**72 (0.77)**	**76 (0.62)**	*b, c*	**73 (0.52)**	73 (0.85)	**75 (0.72)**	*b*
Education	16 (0.36)	15 (0.61)	14 (0.72)		17 (0.19)	17 (0.34)	16 (0.28)		16 (0.26)	**15 (0.42)**	**16 (0.35)**	*c*
Sex, female (%)	60 (74%)	10 (77%)	13 (65%)		**94 (47%)**	25 (45%)	**55 (61%)**	*b*	**75 (54%)**	**37 (69%)**	41 (56%)	*a*
APOE ε4 carriership (%)	**22 (27%)**	**7 (54%)**	**13 (65%)**	*b, c*	**38 (19%)**	**16 (27%)**	**45 (50%)**	*b, c*	**20 (14%)**	**9 (17%)**	**41 (56%)**	*b,c*
CSF $A\beta_{1-42}$*	**1265 (37.78)**	**1160 (80.12)**	**718 (71.53)**	*b, c*	**1448 (30.13)**	**934 (101.34)**	**802 (45.69)**	*a, b*	*n/a*	*n/a*	*n/a*	
CSF $pTau_{181}$*	**46 (3.14)**	51 (6.41)	**67 (6.15)**	*b*	**19 (0.72)**	**21 (1.27)**	**29 (1.10)**	*b, c*	*n/a*	*n/a*	*n/a*	

The values are reported as mean (SD) except for sex and APOE ε4 which are reported as the number of participants (% of the group). Bold text represents the groups between which there were significant differences: a = p<0.05 between Aβ-negative and regional Aβ groups; b = p<0.05 between Aβ-negative and widespread Aβ groups; c = p<0.05 between regional Aβ and widespread Aβ groups. *In PREVENT-AD, CSF samples were available for 45 Aβ-negative, 10 regional, and 12 widespread; in ADNI, CSF samples were available for 101 Aβ-negative, 33 regional and 35 widespread. APOE ε4: Apolipoproteinε4; Aβ: beta-amyloid; CSF: cerebrospinal fluid.

eTable 13. Biological and Clinical Characteristics across the Aβ Groups with 5 Regions

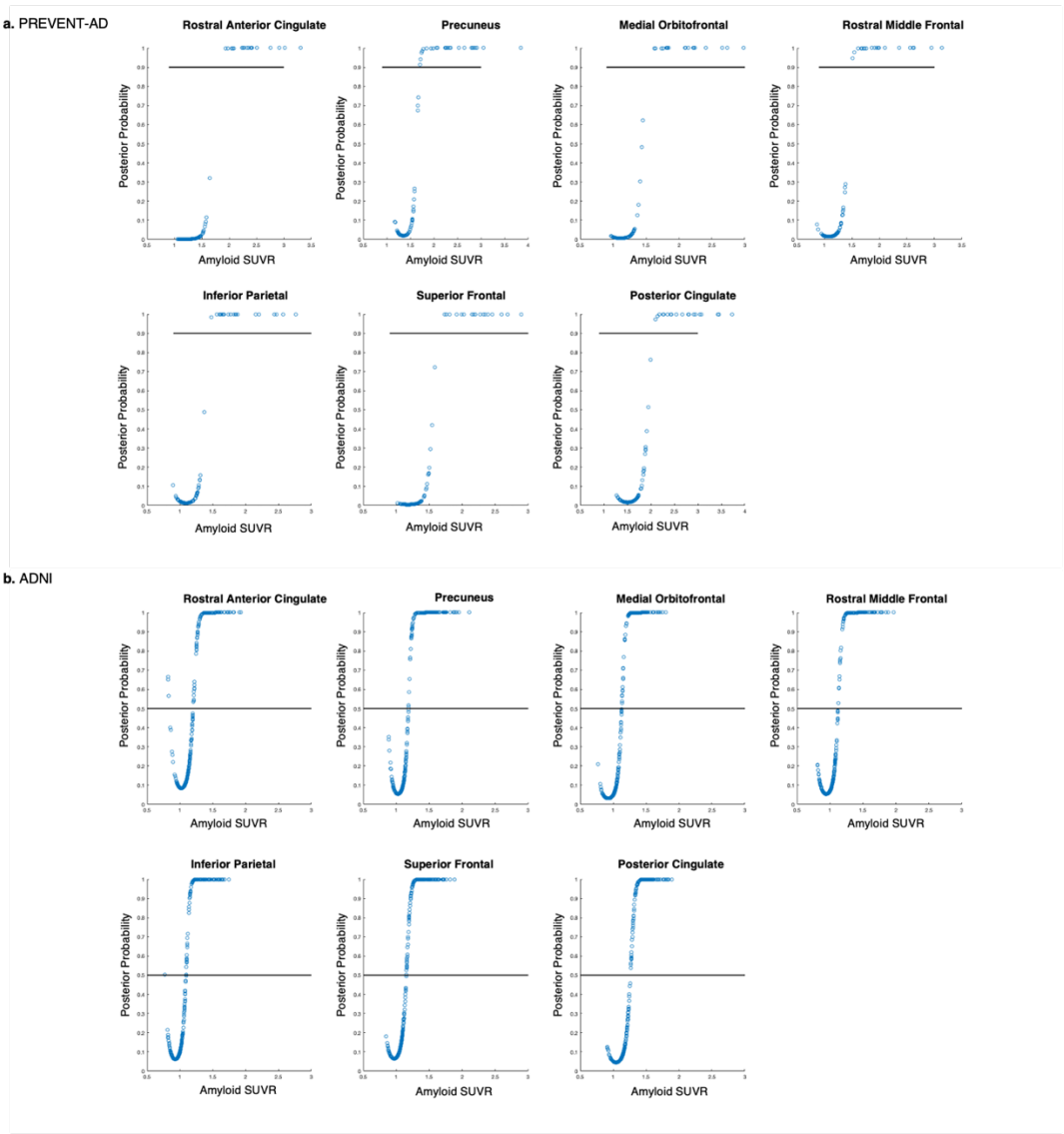
	PREVENT-AD Aβ Groups				ADNI Aβ Groups				HABS Aβ Groups			
	Negative (n = 89)	Regional (n = 18)	Widespread (n = 22)	*p < 0.05*	Negative (n = 235)	Regional (n =74)	Widespread (n =91)	*p < 0.05*	Negative (n = 152)	Regional (n =59)	Widespread (n =77)	*p < 0.05*
Age	**63 (0.49)**	63 (1.10)	**66 (0.99)**	*b*	**73 (0.38)**	74 (0.68)	**76 (0.61)**	*b*	**73 (0.50)**	74 (0.80)	**76 (0.70)**	*b*
Education	15 (0.35)	15 (0.77)	14 (0.70)		17 (0.17)	17 (0.31)	16 (0.28)		16 (0.25)	**15 (0.40)**	**16 (0.35)**	*c*
Sex, female (%)	66 (74%)	15 (83%)	15 (68%)		109 (49%)	36 (51%)	53 (60%)		**83 (55%)**	**44 (75%)**	44 (57%)	*a*
APOE ε4 carriership (%)	**27 (30%)**	**11 (61%)**	**15 (68%)**	*a, b*	**48 (21%)**	**22 (30%)**	**45 (50%)**	*b,c*	**20 (13%)**	**17 (30%)**	**42 (55%)**	*a,b, c*
CSF $A\beta_{1-42}$*	**1262 (39.55)**	**1125 (98.20)**	**712 (80.18)**	*b,c*	**1323 (58.63)**	**924 (99.60)**	**726 (99.60)**	*a,b*	*n/a*	*n/a*	*n/a*	
CSF $pTau_{181}$*	50 (2.76)	53 (6.58)	59 (5.81)		**19 (0.74)**	**25 (1.17)**	**30 (1.24)**	*a,b, c*	*n/a*	*n/a*	*n/a*	

The values are reported as mean (SD) except for sex and APOE ε4 which are reported as the number of participants (% of the group). Bold text represents the groups between which there were significant differences: a = p<0.05 between Aβ-negative and regional Aβ groups; b = p<0.05 between Aβ-negative and widespread Aβ groups; c = p<0.05 between regional Aβ and widespread Aβ groups. *In PREVENT-AD, CSF samples were available for 51 Aβ-negative, 12 regional, and 14 widespread; in ADNI, CSF samples were available for 101 Aβ-negative, 35 regional and 35 widespread. APOE ε4: Apolipoproteinε4; Aβ: beta-amyloid; CSF: cerebrospinal fluid.

eTable 14. Biological and Clinical Characteristics across the Aβ Groups with 10 Regions

	PREVENT-AD Aβ Groups				**ADNI Aβ Groups**				**HABS Aβ Groups**			
	Negative (n = 77)	Regional (n = 32)	Widespread (n = 20)	*p < 0.05*	Negative (n = 213)	Regional (n =125)	Widespread (n =62)	*p < 0.05*	Negative (n = 184)	Regional (n =57)	Widespread (n =47)	*p < 0.05*
Age	**63 (0.53)**	63 (0.82)	**66 (1.03)**	*b*	**73 (0.40)**	74 (0.52)	**75 (0.75)**	*a,b*	73 (0.45)	75 (0.82)	75 (0.90)	
Education	**15 (0.35)**	15 (0.57)	**14 (0.72)**	*b*	17 (0.18)	16 (0.24)	16 (0.34)		16 (0.23)	15 (0.41)	17 (0.45)	
Sex, female (%)	57 (74%)	26 (81%)	13 (65%)		101 (50%)	64 (53%)	33 (56%)		105 (57%)	34 (60%)	32 (68%)	
APOE ε4 carriership (%)	**22 (29%)**	**18 (56%)**	**13 (65%)**	*a, b*	**41 (19%)**	**39 (31%)**	**35 (57%)**	*b,c*	**28 (15%)**	**20 (36%)**	**31 (66%)**	*a,b, c*
CSF $A\beta_{1-42}$*	**1266 (38.36)**	**1053 (58.59)**	**718 (71.76)**	*a,b, c*	**1321 (64.78)**	**974 (80.03)**	**774 (116.28)**	*a,b*	*n/a*	*n/a*	*n/a*	
CSF $pTau_{181}$*	**46 (3.17)**	55 (4.76)	**67 (6.15)**	*b*	**20 (0.80)**	**24 (0.99)**	**30 (1.53)**	*a,b, c*	*n/a*	*n/a*	*n/a*	

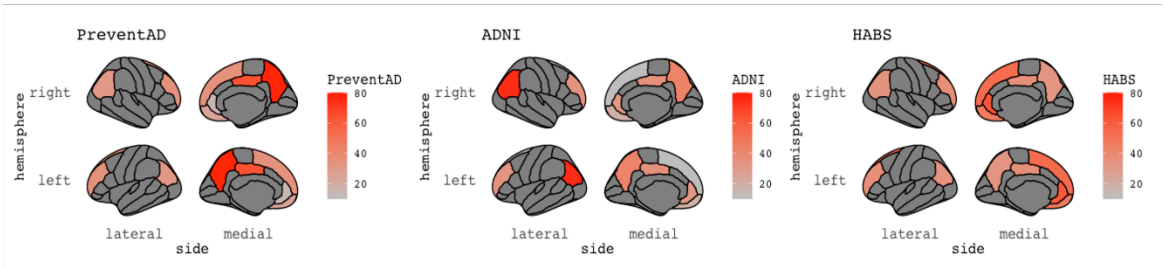
The values are reported as mean (SD) except for sex and APOE ε4 which are reported as the number of participants (% of the group). Bold text represents the groups between which there were significant differences: a = p<0.05 between Aβ-negative and regional Aβ groups; b = p<0.05 between Aβ-negative and widespread Aβ groups; c = p<0.05 between regional Aβ and widespread Aβ groups. *In PREVENT-AD, CSF samples were available for 45 Aβ-negative, 20 regional, and 12 widespread; in ADNI, CSF samples were available for 87 Aβ-negative, 57 regional and 27 widespread. APOE ε4: Apolipoproteinε4; Aβ: beta-amyloid; CSF: cerebrospinal fluid.



eFigure 1. Amyloid SUVR Distribution for the 7 Regions of Interest

Plotted is the posterior probability of the participants according to their Aβ SUVR values for regions of interest. (A) The NAV PET tracer (PREVENT-AD) GMM analyses provided a clear distinction between individuals with and without tracer binding using thresholds for each region which corresponds to a 90% probability of belonging to the low Aβ distribution. (B) The SUVR values from ADNI (Florbetapir tracer) participants followed a more continuous distribution without a distinctive cut-off between lower and higher distributions which complicate their probability of belonging to the low distribution compared to PREVENT-AD. The distributions for HABS are not shown but were extremely similar to the PREVENT-AD ones with a clear distinction between individuals with and without tracer binding using thresholds for each region which corresponds to a 90% probability of belonging to the low Aβ distribution. Prior to defining the groups in ADNI, we, therefore, used a 50-percent probability of belonging to the low- Aβ distribution as cut-off criteria solely depending on the distribution of regional SUVRs as previously reported in other studies[16,18,19].

A.



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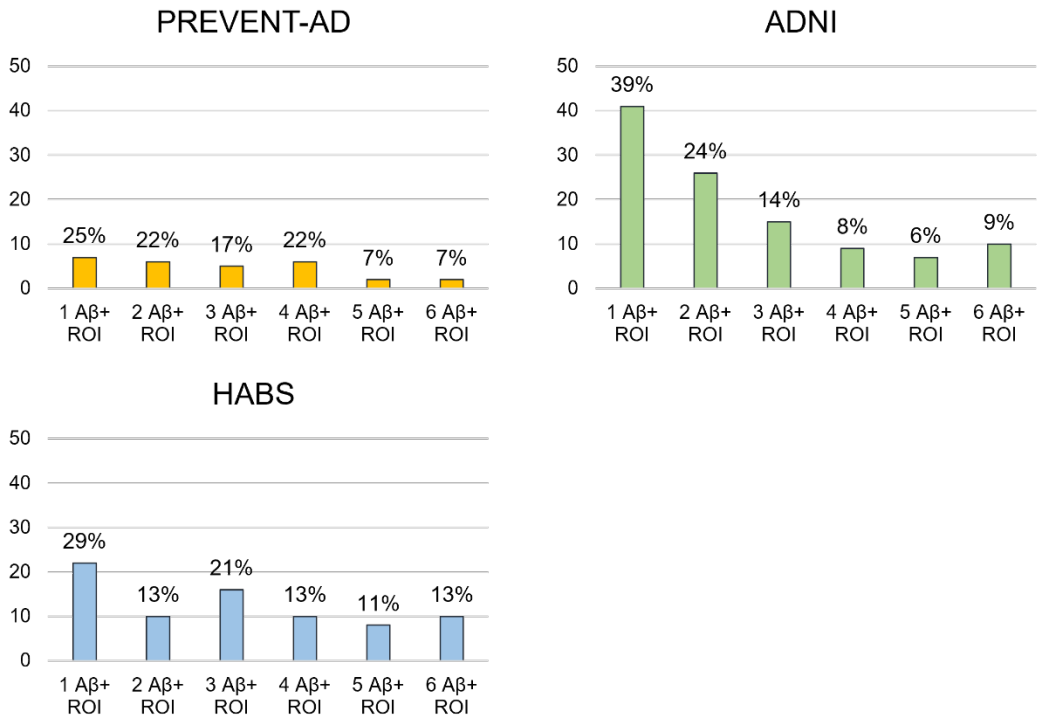
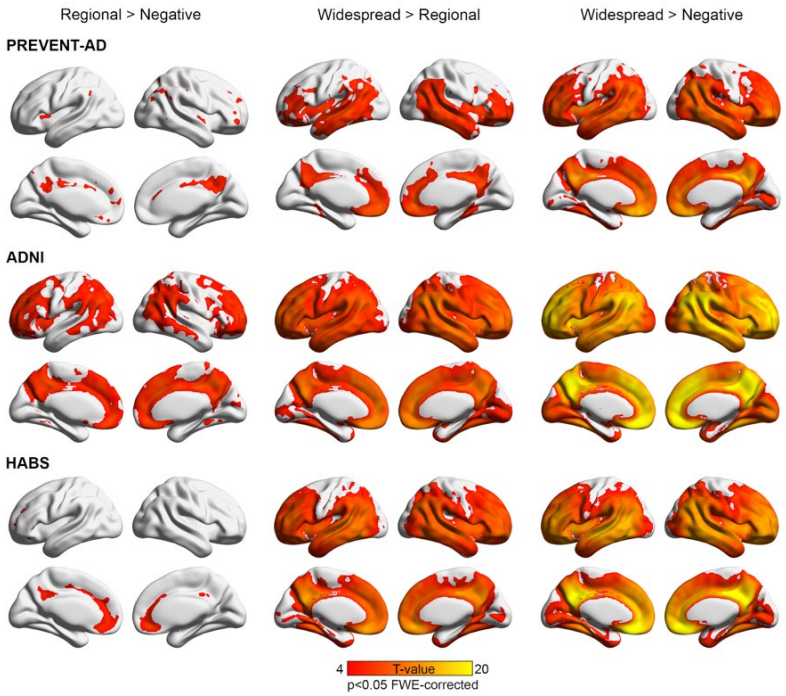


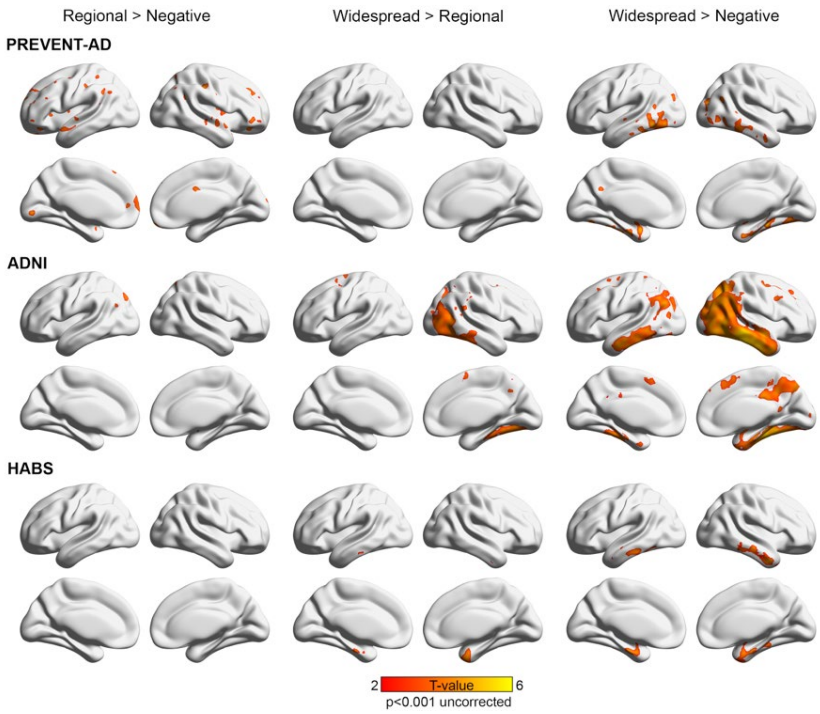
eFigure 2. Distribution of Abnormal Regions in Regional Aβ Groups

(A) Coloured clusters show the seven regions of interest, and the intensity indicates the percentage of regional Aβ group participants who are above the regional threshold on each ROI. The values were averaged across hemispheres. While PREVENT-AD showed more positivity in the precuneus and the posterior cingulate, ADNI regional group was more positive on inferior parietal. In HABS, rostral anterior cingulate and superior frontal were positive for more individuals compared to other ROIs. (B) Distribution of the positive ROIs in regional Aβ group. Overall, there were more participants who were only positive in only 1 ROI compared to others. The number of participants decreased as the number of positive regions increased across all 3 cohorts.

A. Aβ-PET

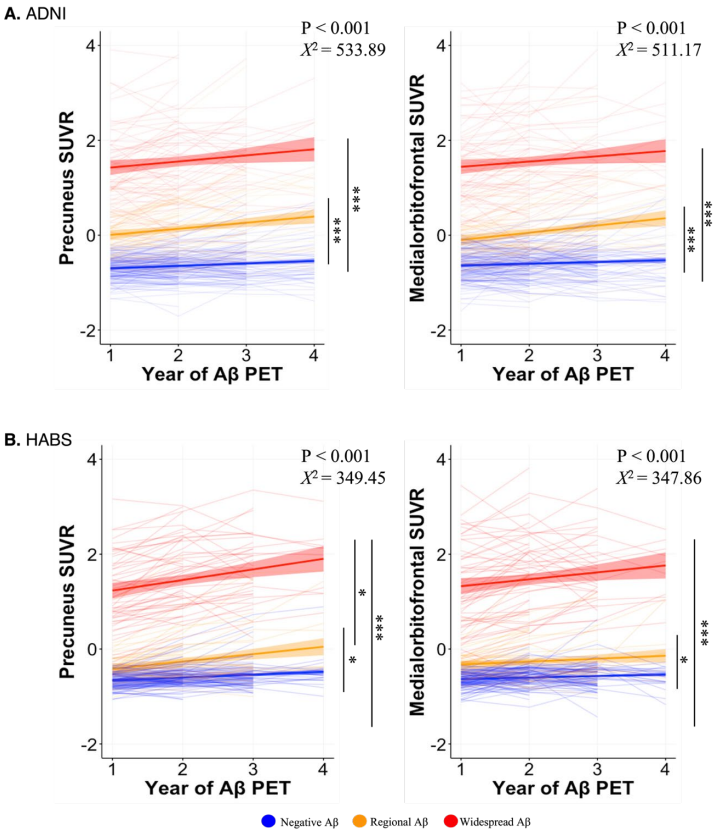


B. Tau-PET



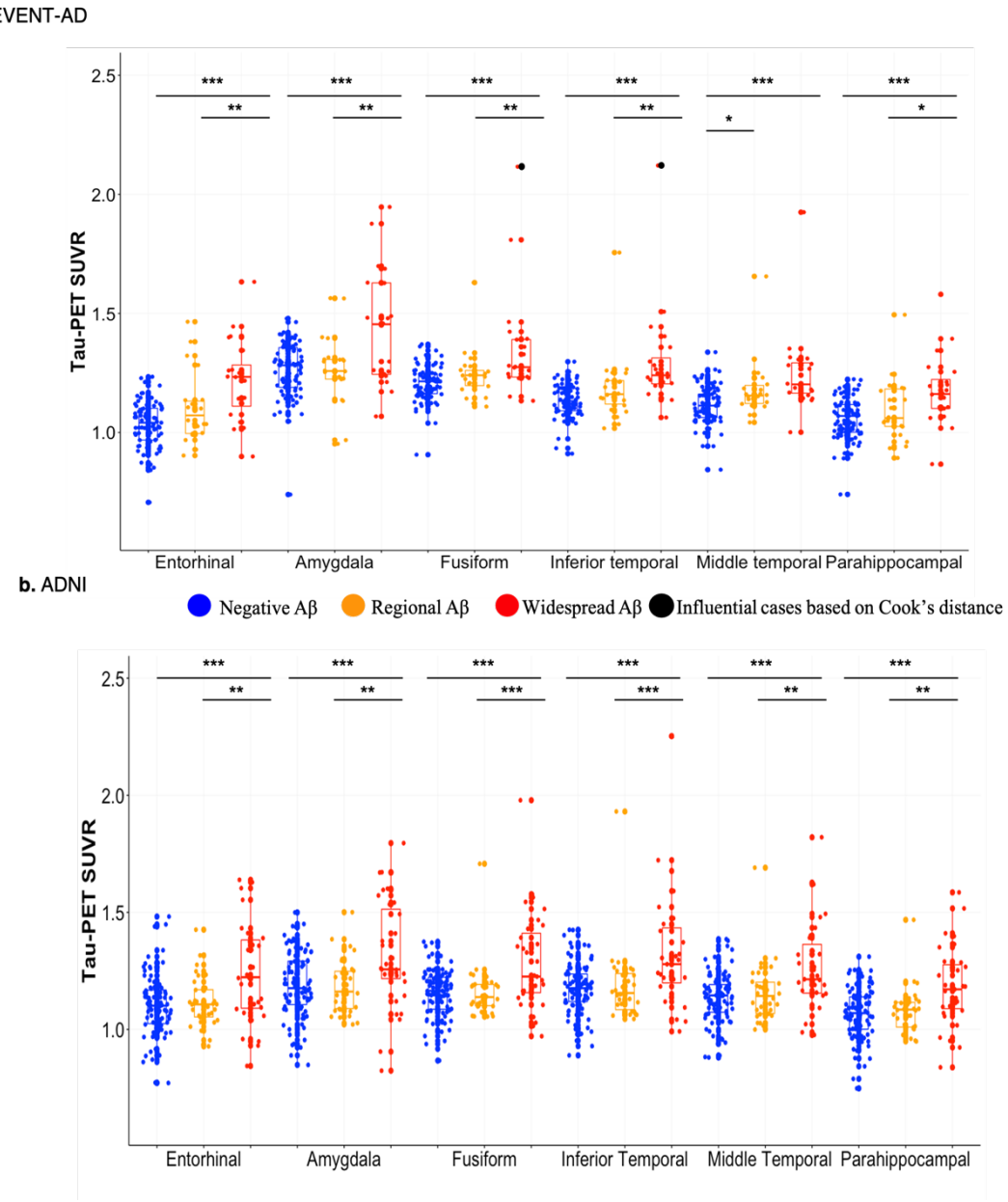
eFigure 3. Group-level Voxel-wise Analysis of Differences in Aβ-PET and tau-PET signals between the three Aβ Groups

Between groups analysis using two sample t-tests (A) for Aβ-PET and (B) for tau-PET. (A) Coloured clusters show those clusters indicating significant group differences (cluster threshold Z>200 p<0.05 FWE) and the intensity indicates the results of post-hoc tests. (B) Coloured clusters show clusters significantly different between groups (p<0.001 uncorrected).



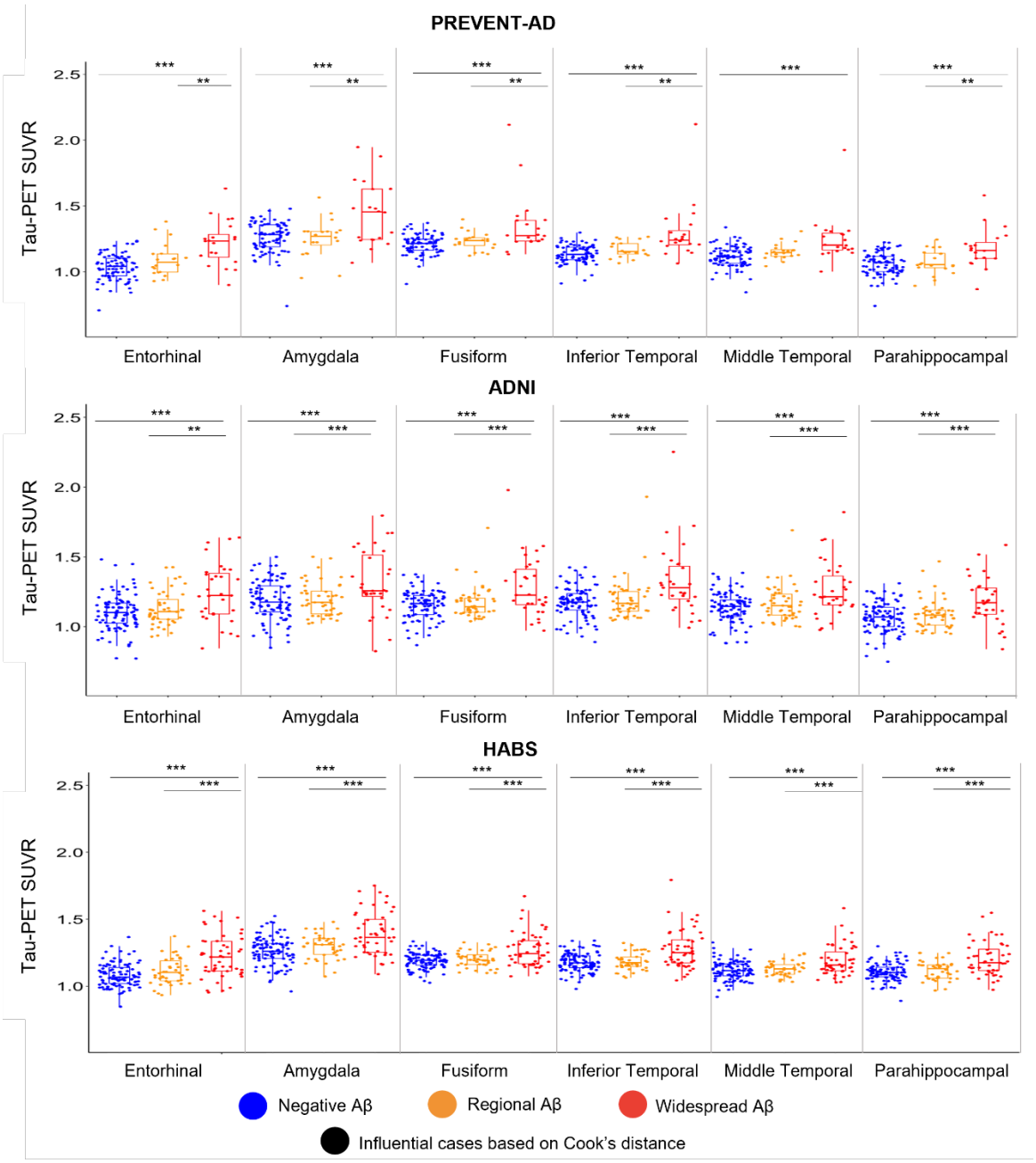
eFigure 4. Change in Aβ Uptake Over Time Between the three Aβ Groups in ADNI and HABS

Linear mixed-effect models investigating the effect of the groups on Aβ accumulation rate over time in ADNI and HABS cohorts corrected for age and sex. Plotted is the association between Aβ groups based on **(A)** precuneus SUVR score and **(B)** medial orbitofrontal SUVR score over the years from their first scan. While both the regional and widespread Aβ groups accumulated Aβ at a faster rate compared to the Aβ-negative group in both cohorts; while only in HABS, the widespread group accumulated Aβ at a faster rate compared to the regional Aβ group in precuneus. * p<0.05; ** p<0.01; ***p<0.001; etc. *SUVR*: standardized uptake value ratio.



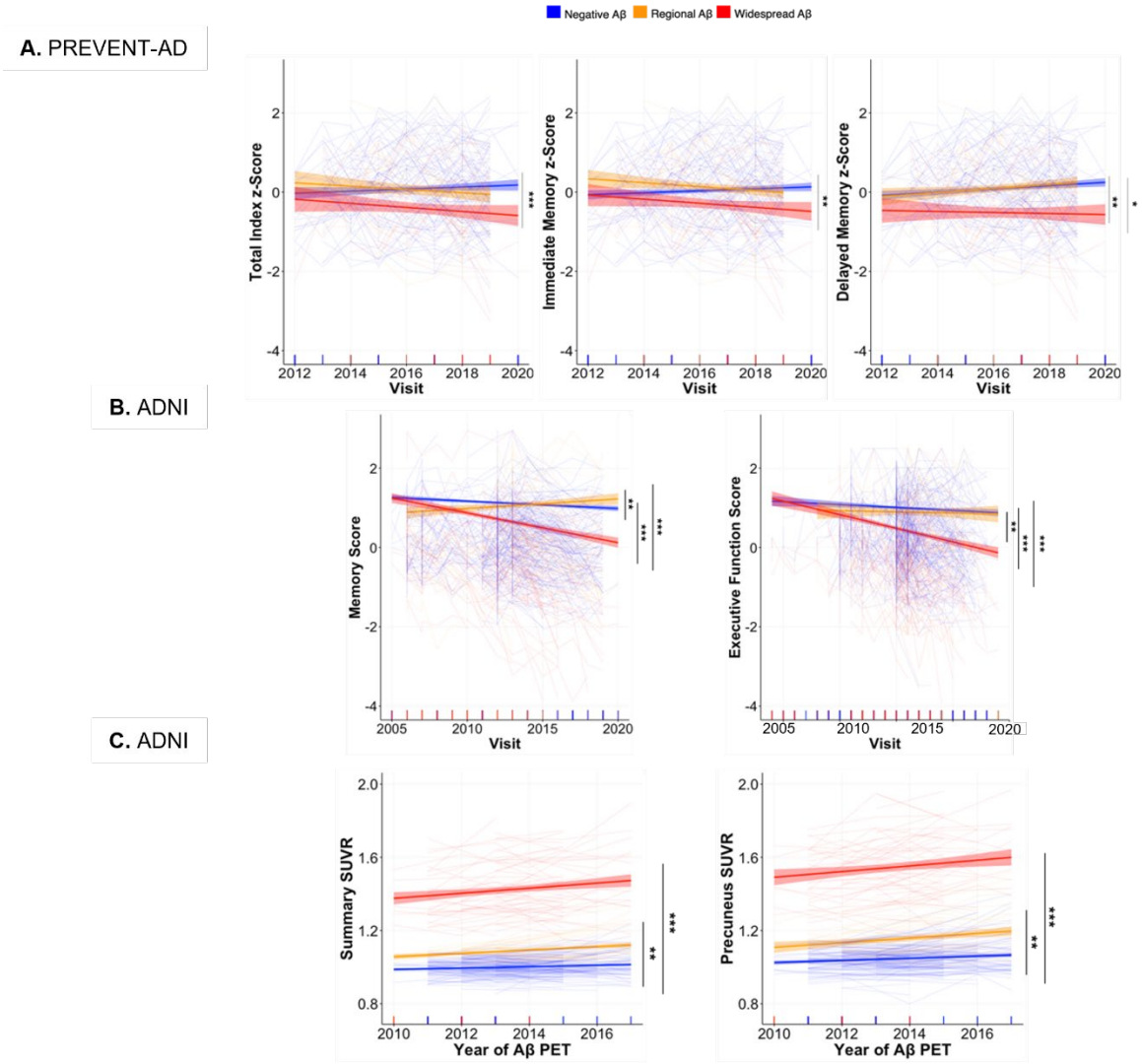
eFigure 5. Tau-PET Uptake Across the 3 Aβ groups excluding Regional Individuals that would have been classified as Positive based on Global Binary Classifications

The original analyses were replicated in PREVENT-AD (A) and ADNI (B) cohorts excluding the "global" Aβ+ participants in regional Aβ groups (no regional participants were classified as Aβ+ in HABS). Six regions were chosen to represent areas of early tau-PET accumulation[35]. Tau-PET scans were available for 123 PREVENT-AD participants and 157 ADNI participants. One PREVENT-AD widespread participant was considered an influential case based on Cook's distance. Removing this participant did not influence the results. Analyses were corrected for age and sex. * p<0.05; ** p<0.01; ***p<0.001. *SUVR*: standardized uptake value ratio.



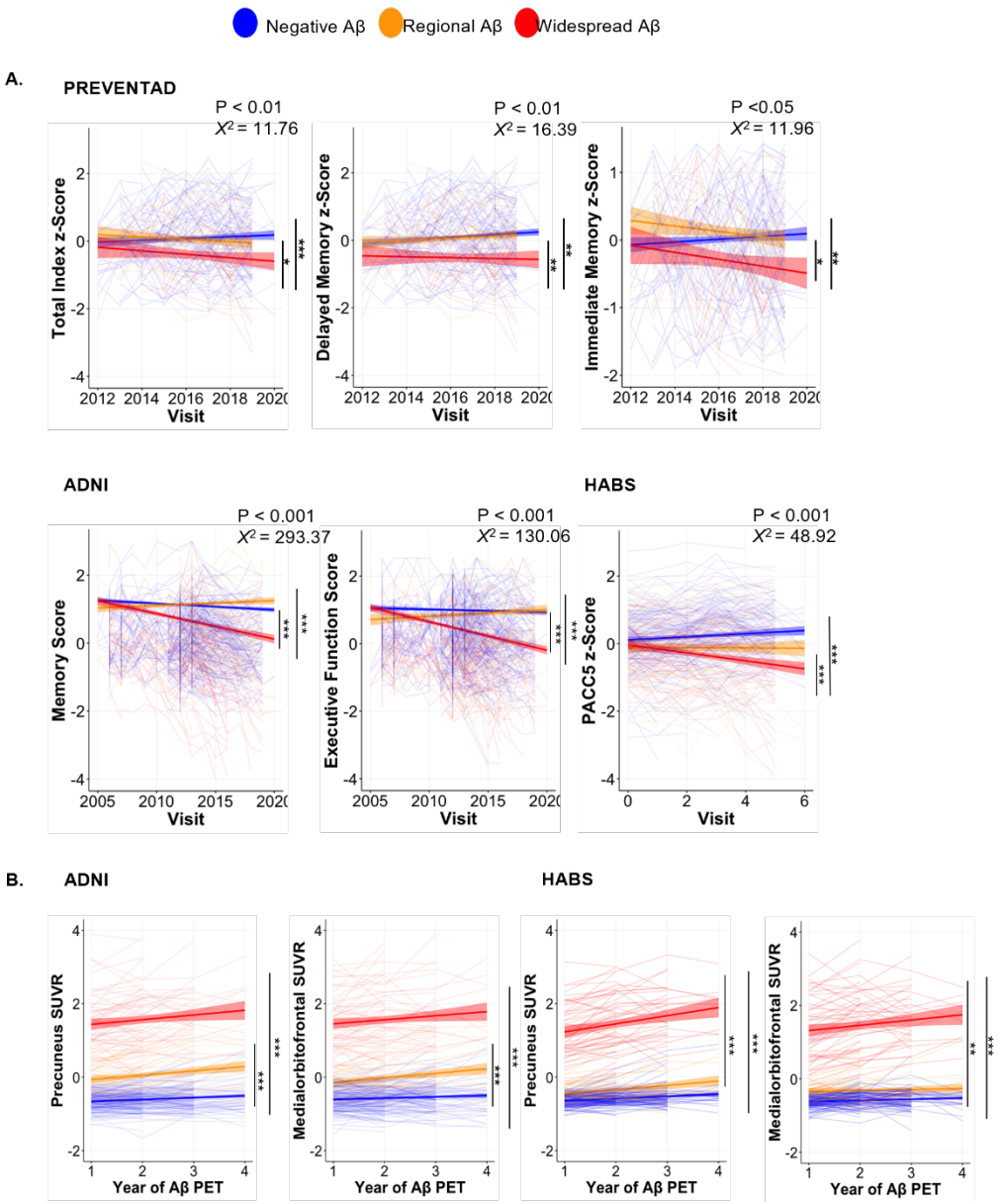
eFigure 6. Tau-PET Uptake Across the 3 Aβ groups excluding Regional Individuals that would have been Classified as Positive based on Visual Read

Six regions were chosen to represent areas of early tau-PET accumulation[35]. Tau-PET scans were available for 121 PREVENT-AD participants, 170 ADNI participants and 190 HABS participants. Analyses were corrected for age and sex. * p<0.05; ** p<0.01; ***p<0.001. *SUVR*: standardized uptake value ratio.



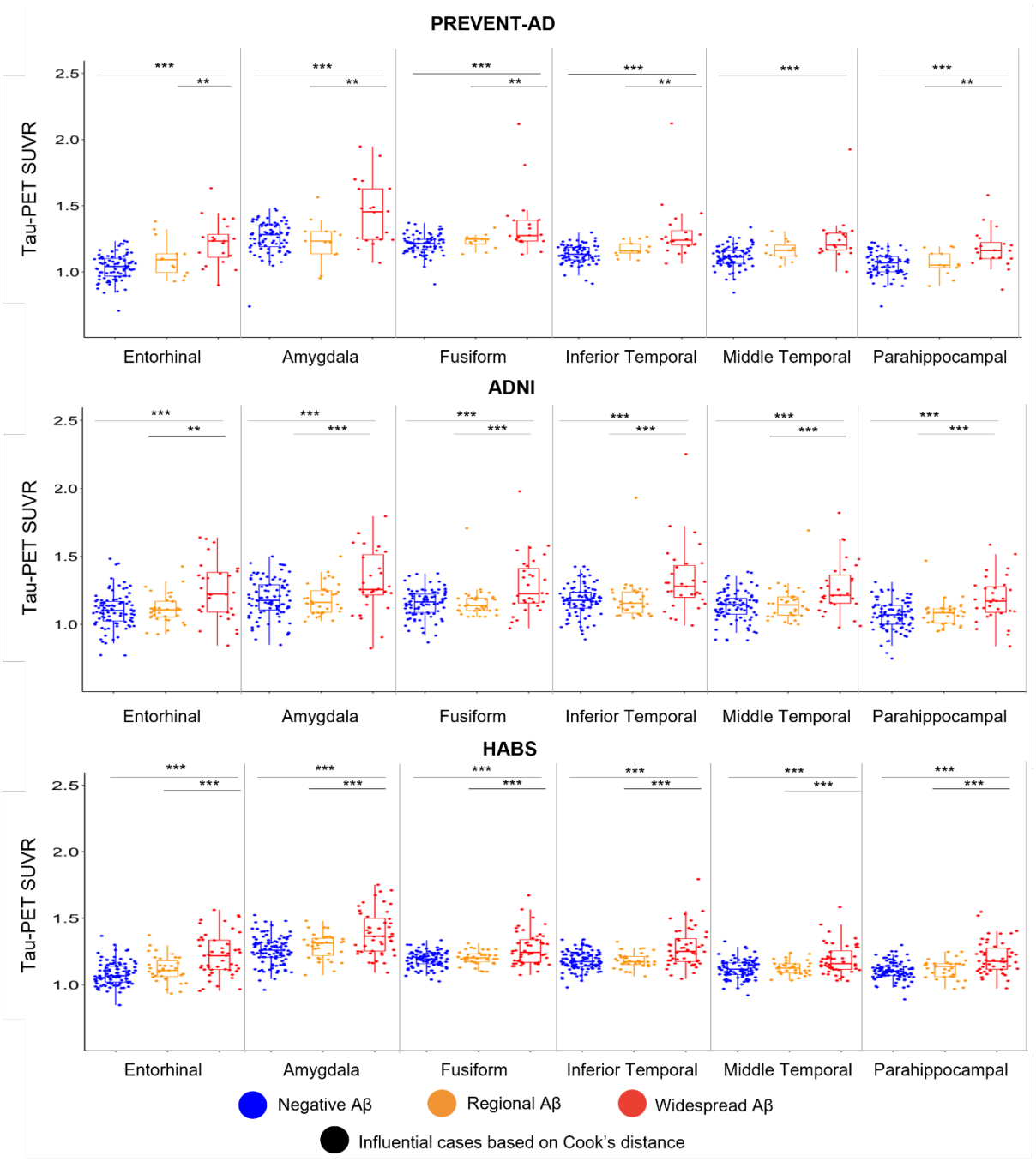
eFigure 7. Change in Cognition and Aβ Uptake over Time Between the Aβ Groups excluding Regional Individuals that would have been classified as Positive based on Global Binary Classifications

The original analyses were replicated in PREVENT-AD and ADNI excluding the "global" Aβ+ participants in the regional Aβ Groups. (A) For PREVENT-AD, cognitive test scores of Total Score, Immediate Memory and Delayed Memory on the RBANS. (B) In ADNI, cognitive test scores of Memory and Executive Function over time in the three different groups. (C) Plotted is the effect of the groups on Aβ accumulation rate over time in ADNI based on Aβ Summary SUVR and Precuneus SUVR. * p<0.05; ** p<0.01; ***p<0.001. SUVR: standardized uptake value ratio.



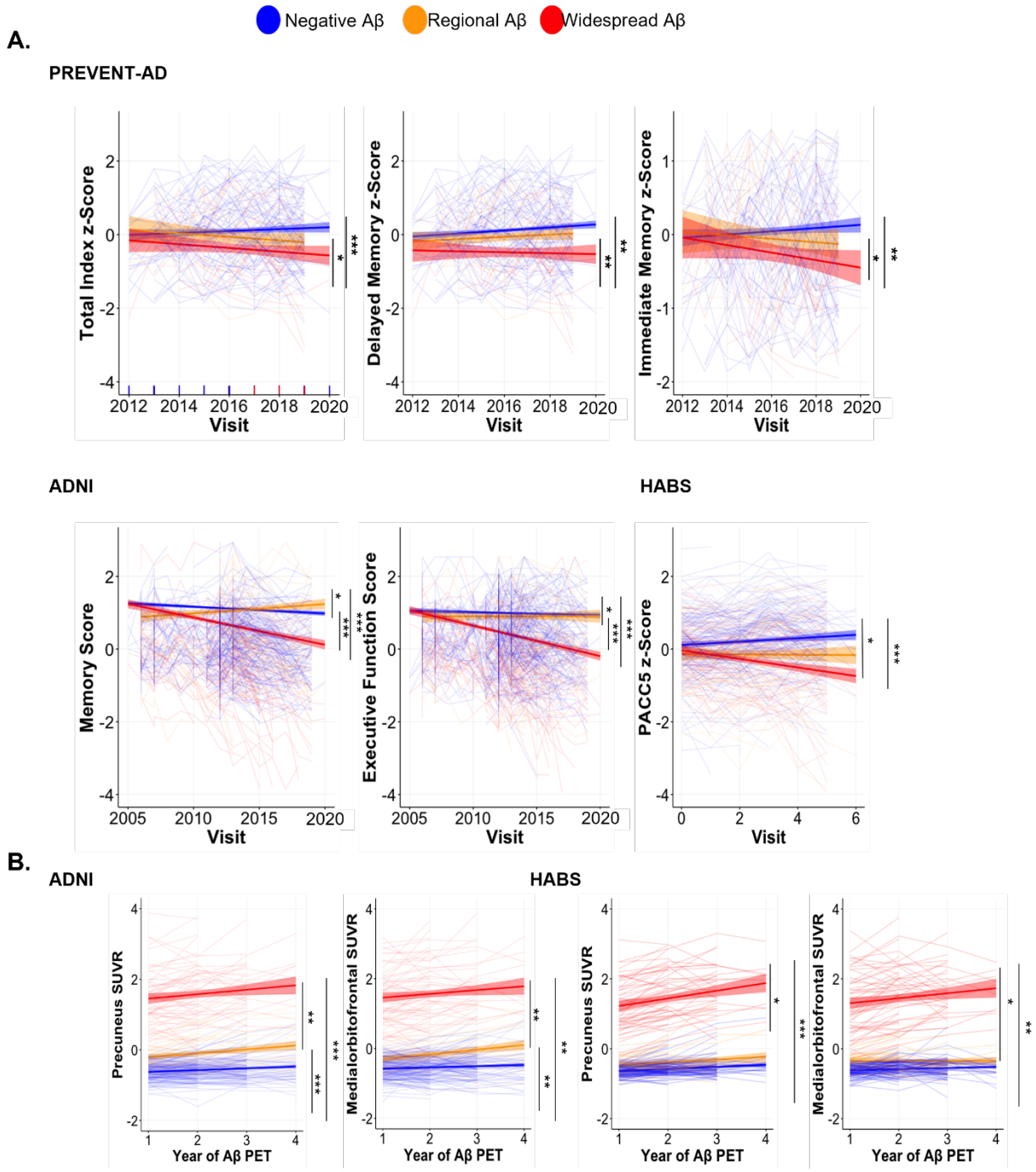
eFigure 8. Change in Cognition and Aβ Uptake over Time Between the Aβ Groups excluding Regional Individuals that would have been Classified as Positive based on Visual Read

The original analyses were replicated in all cohorts excluding the Regional group participants who would have been classified as positive bases on visual read. Linear mixed-effects models were used to assess the effect of Aβ status on longitudinal cognition in three cohorts (A), and on Aβ accumulation rate over time in ADNI and HABS (B) * p<0.05; ** p<0.01; ***p<0.001. SUVR: standardized uptake value ratio.



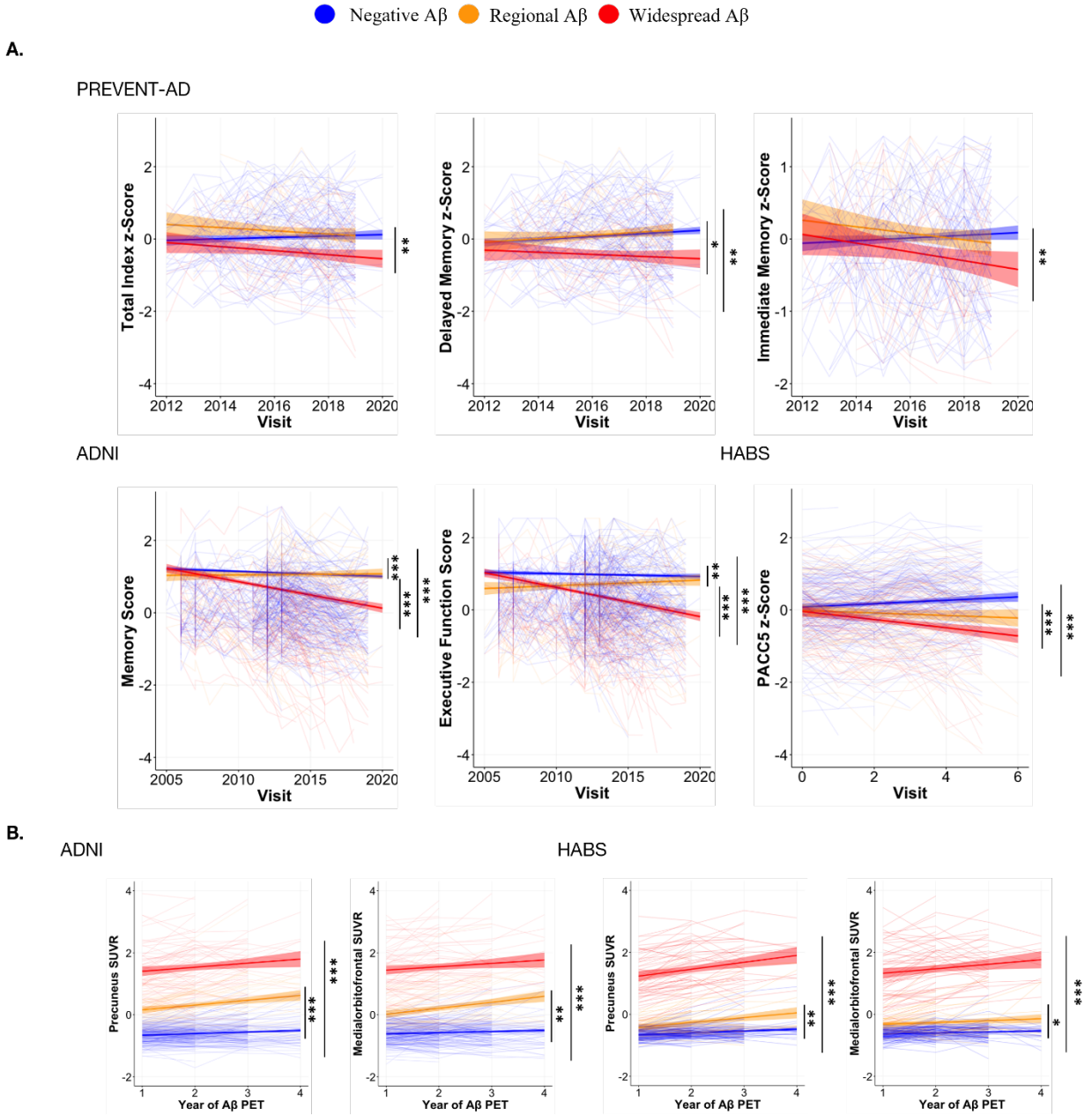
eFigure 9. Tau-PET Uptake Across the 3 Aβ groups excluding Regional Individuals with CL>20

Six regions were chosen to represent areas of early tau-PET accumulation[35]. Tau-PET scans were available for 115 PREVENT-AD participants, 157 ADNI participants and 183 HABS participants. Analyses were corrected for age and sex. * p<0.05; ** p<0.01; ***p<0.001. *SUVR*: standardized uptake value ratio.



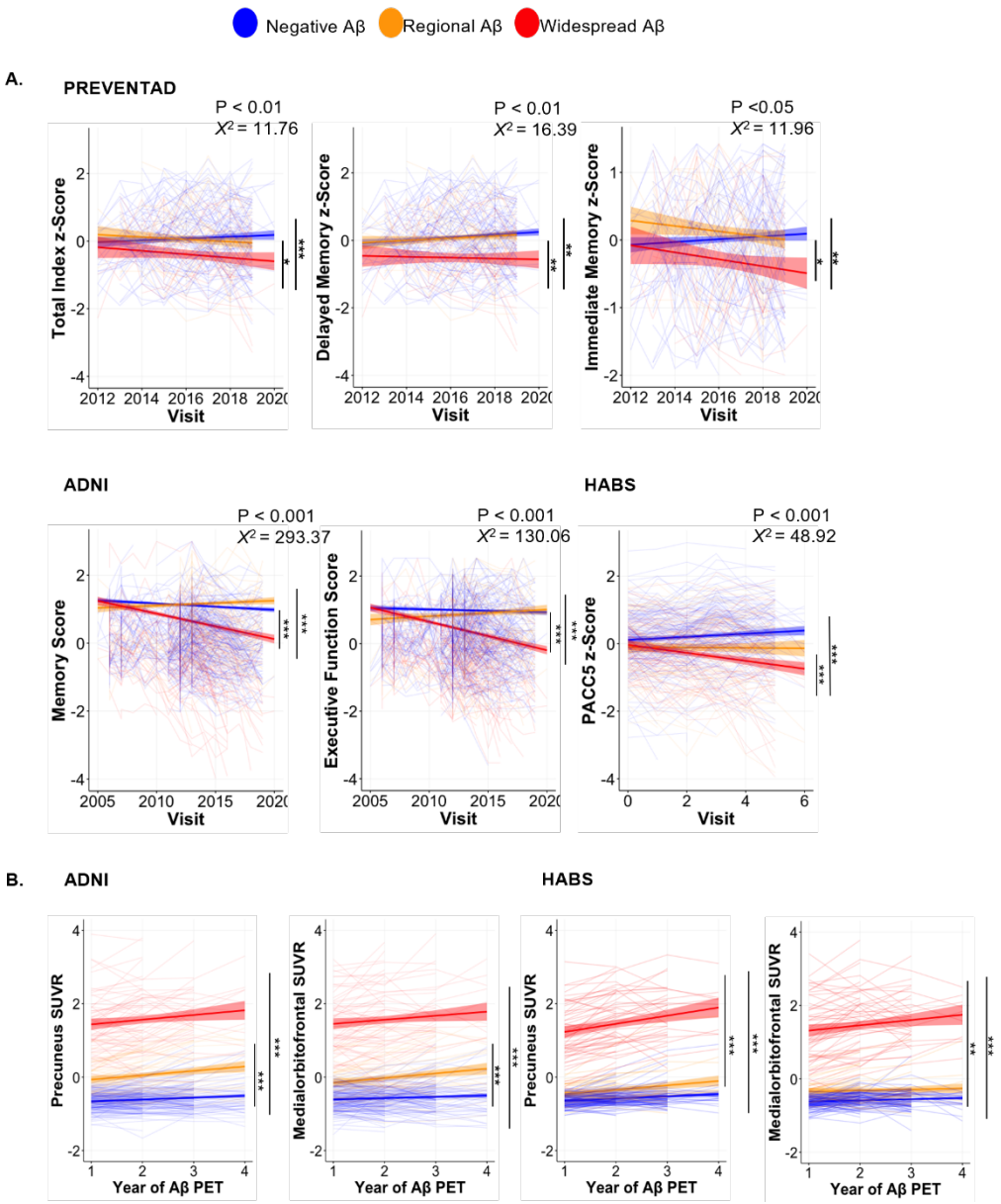
eFigure 10. Change in Cognition and Aβ Uptake Over Time Between the three Aβ Groups excluding Regional Group Participants with CL>20

The original analyses were replicated in all cohorts excluding the Regional group participants with CL>20. Linear mixed-effects models were used to assess the effect of Aβ status on longitudinal cognition in three cohorts (A), and on Aβ accumulation rate over time in ADNI and HABS (B). * p<0.05; ** p<0.01; ***p<0.001. SUVR: standardized uptake value ratio.



eFigure 11. Change in Cognition and Aβ Uptake Over Time Between the three Aβ Groups with 5 Regions

The original analyses were replicated in all cohorts decreasing the number of regions to 5 (by removing rostral middle frontal and inferior parietal) for the Aβ Groups. (A) For PREVENT-AD, cognitive test scores of Total Score, Immediate Memory, and Delayed Memory on the RBANS; in ADNI, cognitive test scores of Memory and Executive Function and in HABS cognitive score of PACC5 over time in the three different groups. (B) Plotted is the association in the ADNI and HABS cohorts between Aβ groups and Aβ accumulation rate over time-based on total Aβ precuneus and medial orbitofrontal SUVR. * p<0.05; ** p<0.01; ***p<0.001. SUVR: standardized uptake value ratio.



eFigure 12. Change in Cognition and Aβ Uptake Over Time Between the three Aβ Groups with 10 Regions

The original analyses were replicated in all cohorts increasing the numbers of regions to 10 (by including insula, lateral orbitofrontal and isthmus cingulate) for the regional Aβ Groups. (A) For PREVENT-AD, cognitive test scores of Total Score, Immediate Memory and Delayed Memory on the RBANS; in ADNI, cognitive test scores of Memory and Executive Function and in HABS cognitive score of PACC5 over time in the three different groups. (B) Plotted is the association in the ADNI and HABS cohorts between Aβ groups and Aβ accumulation rate over time based on total Aβ precuneus and medial orbitofrontal SUVR. * p<0.05; ** p<0.01; ***p<0.001. SUVR: standardized uptake value ratio.

eReferences

1. Breitner J, Poirier, J., Etienne, P. E., & Leoutsakos, J. M. . Rationale and structure for a new center for studies on prevention of Alzheimer's disease (STOP-AD). *J Prev Alzheimers Dis* 2016;3:36–42.
2. Miron J, Picard C, Lafaille-Magnan M, et al. Association of TLR4 with Alzheimer's disease risk and presymptomatic biomarkers of inflammation. *Alzheimers Dement.* 2019;15(7):951-960.
3. Meyer PF, Savard M, Poirier J, et al. Bi-directional Association of Cerebrospinal Fluid Immune Markers with Stage of Alzheimer's Disease Pathogenesis. *J Alzheimers Dis.* 2018;63(2):577-590.
4. Tremblay-Mercier J, Madjar C, Das S, et al. Open Science Datasets from PREVENT-AD, a Longitudinal Cohort of Pre-symptomatic Alzheimer's Disease. *bioRxiv.* 2020:2020.2003.2004.976670.
5. Bittner T, Zetterberg, H., Teunissen, C. E., Ostlund, R. E., Jr, Militello, M., Andreasson, U., Hubeek, I., Gibson, D., Chu, D. C., Eichenlaub, U., Heiss, P., Kobold, U., Leinenbach, A., Madin, K., Manuilova, E., Rabe, C., & Blennow, K. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* 2016;12(5):517–526.
6. Dagley A, LaPoint M, Huijbers W, et al. Harvard Aging Brain Study: Dataset and accessibility. *Neuroimage.* 2017;144(Pt B):255-258.
7. Johnson KA, Schultz A, Betensky RA, et al. Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Ann Neurol.* 2016;79(1):110-119.
8. Desikan RS, Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. . An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage.* 2006;31:968-980.
9. Villeneuve S, Rabinovici, G. D., Cohn-Sheehy, B. I., Madison, C., Ayakta, N., Ghosh, P. M., La Joie, R., Arthur-Bentil, S. K., Vogel, J. W., Marks, S. M., Lehmann, M., Rosen, H. J., Reed, B., Olichney, J., Boxer, A. L., Miller, B. L., Borys, E., Jin, L. W., Huang, E. J., Grinberg, L. T., … Jagust, W. . Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation. *Brain.* 2015;138:2020-2033.
10. Baker SL, Maass, A., & Jagust, W. J. . Considerations and code for partial volume correcting [18F]-AV-1451 tau PET data. *Data Brief.* 2017;15:648-657.
11. Clark CM, Schneider, J. A., Bedell, B. J., Beach, T. G., Bilker, W. B., Mintun, M. A., Pontecorvo, M. J., Hefti, F., Carpenter, A. P., Flitter, M. L., Krautkramer, M. J., Kung, H. F., Coleman, R. E., Doraiswamy, P. M., Fleisher, A. S., Sabbagh, M. N., Sadowsky, C. H., Reiman, E. P., Zehntner, S. P., Skovronsky, D. M., … AV45-A07 Study Group. Use of florbetapir-PET for imaging beta-amyloid pathology. . *JAMA.* 2011;305(3):275-283.
12. McSweeney M, Pichet Binette, A., Meyer, P. F., Gonneaud, J., Bedetti, C., Ozlen, H., Labonté, A., Rosa-Neto, P., Breitner, J., Poirier, J., Villeneuve, S., & PREVENT-AD Research Group Intermediate flortaucipir uptake is associated with Aβ-PET and CSF tau in asymptomatic adults. *Neurology.* 2020;94(11):e1190-e1200.
13. Jagust WJ, Landau SM, Koeppe RA, et al. The Alzheimer's Disease Neuroimaging Initiative 2 PET Core: 2015. *Alzheimers Dement.* 2015;11(7):757-771.

14. Schreiber S, Landau, S. M., Fero, A., Schreiber, F., & Jagust, W. J. . Comparison of visual and quantitative florbetapir F 18 positron emission tomography analysis in predicting mild cognitive impairment outcomes. *JAMA neurology.* 2015;72(10):1183-1190.
15. Buckley RF, Sikkes S, Villemagne VL, et al. Using subjective cognitive decline to identify high global amyloid in community-based samples: A cross-cohort study. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring.* 2019;11(1):670-678.
16. Farrell ME, Jiang S, Schultz AP, et al. Defining the Lowest Threshold for Amyloid-PET to Predict Future Cognitive Decline and Amyloid Accumulation. *Neurology.* 2021;96(4):e619-e631.
17. Fantoni E, Collij L, Lopes Alves I, Buckley C, Farrar G. The Spatial-Temporal Ordering of Amyloid Pathology and Opportunities for PET Imaging. *J Nucl Med.* 2020;61(2):166-171.
18. Buckley RF, Mormino EC, Amariglio RE, et al. Sex, amyloid, and APOE ε4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three well-characterized cohorts. *Alzheimer's & Dementia.* 2018;14(9):1193-1203.
19. Mormino EC, Betensky RA, Hedden T, et al. Amyloid and APOE ε4 interact to influence short-term decline in preclinical Alzheimer disease. *Neurology.* 2014;82(20):1760-1767.