Elevated amyloid and tau PET signal is associated with near-term development of Alzheimer's disease symptoms in unimpaired older adults

Authors

Cherie Strikwerda-Brown, PhD[1,2], Diana A. Hobbs, PhD[3*], Julie Gonneaud, PhD[1,2,4*], Frédéric St-Onge, MSc[1,2], Alexa Pichet Binette, PhD[1,2.5], Hazal Ozlen, MSc[2], Karine Provost, MD, MSc[6], Jean-Paul Soucy, MD, MSc[7], Rachel F. Buckley, PhD[8,9,10], Tammie L.S. Benzinger, MD, PhD[3], John C. Morris, MD[3], Victor L. Villemagne, MD[11], Vincent Doré, PhD[12], Reisa A. Sperling, MD[8,9], Keith A. Johnson, MD[8,9], Christopher C. Rowe, MD[12], Brian A. Gordon, PhD[3], Judes Poirier, PhD[1,2], John C.S. Breitner, MD, MPH[1,2], Sylvia Villeneuve, PhD[1,2,8], for the AIBL, HABS and PREVENT-AD research groups

Affiliations

[1.] Department of Psychiatry, Faculty of Medicine, McGill University, Montreal, QC, H3A 1Y2, Canada

[2.] Douglas Mental Health University Institute, Montreal, QC, H4H 1R3, Canada

[3.] Washington University School of Medicine, St Louis, MO, USA

[4.] Inserm, Inserm UMR-S U1237, Université de Caen-Normandie, GIP Cyceron, Caen, France

[5.] Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Sweden

[6.] Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada

[7.] McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, QC, H3A 2B4, Canada

[8.] Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

[9.] Centre for Alzheimer Research and Treatment, Brigham and Women's Hospital, Boston, MA, USA

[10.] Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia

[11.] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

[12.] Department of Molecular Imaging & Therapy, Austin Health, Melbourne, Victoria, Australia

* These authors contributed equally

Corresponding Author

Sylvia Villeneuve

Douglas Mental Health University Institute

Perry Pavilion Room E3417.1, 6875 Boulevard LaSalle

Montreal, QC, Canada H4H 1R3

Phone: 514 761-6131 ext.: 3960, E-mail: Sylvia.villeneuve@mcgill.ca

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Key Points (85/100 words)

Question: What is the clinical relevance of the AT(N) biological classification of Alzheimer's disease (AD) in unimpaired older adults?

Findings: In this cohort study of 580 cognitively unimpaired participants from four independent cohorts, between 43 and 100% of A+T+(N+) participants progressed to mild cognitive impairment (MCI) within 2-3 years after PET. The majority of A+T+ non-progressors also showed cognitive decline.

Meaning: Cognitively unimpaired older adults with biological AD are at imminent risk of developing MCI. These individuals may be ideal candidates for disease modifying therapies.

Abstract (350/350 words)

Importance: National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups have proposed biological research criteria intended to identify individuals with preclinical Alzheimer's disease (AD).

Objective: Assess the clinical value of these biological criteria to identify cognitively unimpaired older individuals at near-term risk of cognitive impairment.

Design: This longitudinal cohort study used data from four independent cohorts (PREVENT-AD, HABS, AIBL, and Knight ADRC), collected between 2003 and 2021. Median clinical follow-up after Aβ and tau PET ranged from 1.94 to 3.66 years.

Setting: Population-based.

Participants: All cognitively unimpaired older adults with ≥1 year of clinical observation following Aβ and tau PET.

Exposures: Based on binary assessment of global amyloid burden (A) and a composite temporal region of tau PET uptake (T), participants were stratified into four groups (A+T+, A+T-, A-T+, A-T-). Presence (+) or absence (-) of neurodegeneration (N) was assessed using temporal cortical thickness.

Main Outcomes and Measures: Each cohort was analyzed separately. Primary outcome was clinical progression to mild cognitive impairment (MCI), identified by a CDR ≥ 0.5 in Knight ADRC and consensus committee review in the other cohorts. Clinical raters were blind to imaging, genetic, and fluid biomarker data. A secondary outcome was cognitive decline, based on a slope >1.5 SD below the mean of an independent subsample of cognitive unimpaired individuals. Outcomes were compared across the four biomarker groups.

Results: Among 580 participants (PREVENT-AD: 128; HABS: 153; AIBL: 48; Knight ADRC: 251), mean age ranged from 67 to 76 years across cohorts, with between 54 and 74% females. Across cohorts, 33-83% of A+T+ participants progressed to MCI during follow-up (mean progression time 2-2.72 years), compared with <12% of participants in other biomarker groups. Progression further increased to 43-100% when restricted to A+T+(N+) individuals. Cox proportional hazard ratios for progression to MCI in the A+T+ group vs. other biomarker groups were all ≥5. Many A+T+ 'non-progressors' also showed longitudinal cognitive decline, while cognitive trajectories in other groups remained predominantly stable.

Conclusions and Relevance: Clinical prognostic value of the NIA-AA research criteria was confirmed in four independent cohorts, with most A+T+(N+) cognitively unimpaired older individuals developing AD symptoms within ~2-3 years.

Introduction

The National Institute on Aging-Alzheimer's Association (NIA-AA) research criteria for Alzheimer's disease (AD) were revised in 2018 to add tau biomarkers. In the resulting AT(N) framework, amyloid-beta (A) and tau (T) are needed for the diagnosis of AD, while neurodegeneration (N) is used to stage disease severity [1]. These biomarkers can be classified as normal (-) and abnormal (+) such that individuals who are A+T+ can be said to have biological AD, even if they do not have cognitive symptoms. The clinical significance of biologically-defined AD in individuals without cognitive impairment remains debated [2], given that abnormal levels of amyloid-beta (Aβ) and tau are apparent in ~20% of cognitively unimpaired older adults both *in vivo* [3] and at autopsy [4]. As the cited studies are cross-sectional, however, it is unclear whether A+T+ individuals are at imminent risk of developing AD-related cognitive impairment. Frequent near-term development of mild cognitive impairment (MCI) in cognitively unimpaired A+T+ individuals would provide strong evidence favoring a biological definition of pre-clinical AD. It would also have important implications both for clinical trial recruitment and prognosis of early clinical disease.

Using positron emission tomographic (PET) signal for Aβ or tau deposition across four independent cohorts, we investigated whether elevation of both biomarker signals were associated with near-term progression from cognitively unimpaired to mild cognitive impairment (MCI). We also tested whether the evidence of neurodegeneration added clinical prognostic value to the amyloid and tau PET biomarkers. Analyses were performed separately for each cohort, to test the robustness of findings across methodologies and samples.

Methods

Participants and Study Design

Participants included 128 individuals from the family-history positive Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) cohort, 153 from the Harvard Aging Brain Study (HABS), 48 from the Australian Imaging, Biomarker & Lifestyle (AIBL) study, and 251 from the Knight Alzheimer Disease Research Center (ADRC) dataset (see eMethods in the Supplement). All participants included in this study had at least one Aβ and tau PET scan, were cognitively unimpaired at the time of PET, and had at least 12 months of clinical follow-up thereafter. Participants provided written informed consent, and research procedures were approved by the relevant ethics committees. All analyses were performed separately for each cohort.

Full details of all measures, outcomes, their relative timing, and analyses are contained within the eMethods in the Supplement. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies.

Cognitive evaluation

Participants completed the Mini Mental State Examination (MMSE) [5] at the time of tau PET and had longitudinal cognitive testing using a composite measure specific to each cohort. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [6] was used in PREVENT-AD, and the Preclinical Alzheimer's Cognitive Composite score (PACC) used in the other cohorts [7,8]. Performance was evaluated using cohort-derived z-scores. Tau PET was

introduced mid-study in all cohorts. All participants were required to be cognitively unimpaired both at cognitive baseline and at the time of PET.

Outcomes

The primary outcome measure was clinical progression to MCI following PET among cognitively unimpaired participants. This outcome was adjudicated in all instances by persons masked to PET and MRI data, and to *APOE* genotype, though not blind to MMSE performance in the PREVENT-AD, HABS, or AIBL cohorts. In PREVENT-AD, HABS, and AIBL, MCI classifications were made by consensus committees comprising expert clinical and research staff. In the Knight ADRC, MCI was defined by a Clinical Dementia Rating® (CDR®)[9] score of ≥0.5. Median follow-up after PET ranged from 1.94 to 3.66 years across cohorts. A secondary outcome was cognitive decline, as defined by a longitudinal slope in composite cognitive scores ≥ 1.5 SD below the mean of an independent subsample of cognitively normal participants within each cohort[10]. For this outcome, we took advantage of the full length of study follow-up (including pre-PET) to create the slopes and characterise participants as "decliners" vs "stable" (median follow-up across cohorts 5.10 - 6.31 yrs; minimum: 0.90 - 3.26 yrs; maximum: 7.26 - 14.47 yrs).

A/T/(N) classification

Aβ PET imaging was performed using [^{18}F]NAV4694 (NAV) in PREVENT-AD, [11C] Pittsburgh Compound B (PiB) in HABS, [^{18}F]AV45 (florbetapir) and NAV in AIBL, and PiB and florbetapir in Knight ADRC (processing details in eMethods in the Supplement). Tau PET was performed using [^{18}F]AV1451 (flortaucipir; FTP) in all cohorts [11-15]. T1-weighted structural MRI scans were collected on 3T scanners and segmented with the Freesurfer Desikan-Killiany atlas [16]. Pre-

processing was performed using cohort-specific pipelines, and did not include partial volume correction. Standardized uptake value ratios (SUVRs) (distribution volume ratios (DVRs) for PIB) for each Desikan-Killiany region were computed using the cerebellum grey matter for all scans except for tau PET in PREVENT-AD, which used inferior cerebellar grey matter [17].

Participants were allocated to four PET biomarker groups (A+T+, A+T-, A-T+, A-T-). Cohort-specific thresholds were employed to establish Aβ positivity based on a global amyloid index[18] (Centiloid values: PREVENT-AD = 22.32; HABS = 23.9; AIBL = 25; Knight ADRC = 27.1 and 21.9 for PiB and florbetapir, respectively; see eMethods in the Supplement for SUVR/DVR). A temporal meta-ROI was used as the primary measure of tau positivity. This comprised the average SUVR of the bilateral entorhinal cortex, amygdala, parahippocampal gyrus, fusiform gyrus, and inferior and middle temporal gyri[18]. Tau positivity was defined as meta-ROI uptake surpassing 2 SD from the mean of cognitively unimpaired (at baseline) Aβ- participants in each cohort (SUVR cut-offs: PREVENT-AD = 1.28; HABS = 1.29; AIBL = 1.28; Knight ADRC = 1.26).

In secondary analyses, the presence (+) or absence (-) of neurodegeneration (N) was designated based on average cortical thickness in a bilateral temporal meta-ROI comprising entorhinal cortex, fusiform, inferior temporal, and middle temporal gyri [17]. Participants were classified as neurodegeneration positive if temporal cortical thickness was below the 20th percentile of an independent subsample of cognitively normal participants within the respective cohorts.

Statistical Analysis

Analyses were performed separately for each cohort to assess replicability of results across samples and methodologies. The A-T+ group was excluded from statistical comparisons due to the low number of participants (PREVENT-AD: 0, HABS: 4; AIBL: 1; Knight ADRC: 4), though data from this group are presented visually for completeness. For demographic and clinical variables, we used one-way analyses of variance with Tukey's post hoc tests to compare biomarker groups on continuous variables, and Fisher's exact tests for categorical variables, including MCI progression status. Cox proportional hazard models tested whether the risk of MCI progression over time was higher in the A+T+ group relative to the other PET biomarker groups, including age, sex, education, and *APOE* ε4 status as covariates. In follow-up analyses, continuous measures of neurodegeneration (temporal cortical thickness or hippocampal volume) were added to the PET biomarker Cox models to test the additional clinical prognostic value of (N). These were used instead of categorical AT(N) status given the very small sample size of each AT(N) group. Using Concordance measures of model fit, we also compared the performance of each of these AT(N) models with clinical models that included MMSE, age, sex, education and *APOE* ε4 status. Finally, after confirming linearity of the longitudinal cognitive trajectories across cohorts, we employed linear mixed-effects models with random slopes and intercepts to investigate longitudinal cognitive decline across the different AT(N) groups. This secondary outcome was intended to explore whether individuals who had not yet progressed to MCI were nonetheless likely to be on a clinical pathway toward AD symptoms. To do so, participants were further divided into cognitively 'stable' versus 'decliners' based on individual longitudinal cognitive slopes (see Outcomes). The proportion of cognitive decliners versus cognitively stable in each biomarker group were then compared using Fisher's exact tests.

We also performed sensitivity analyses in which analyses were repeated using 1) harmonised Aβ and tau thresholds across cohorts, 2) other commonly used regions to define tau PET positivity, and 3) hippocampal volume to define neurodegeneration.

Alpha was set at $p < .05$ for all analyses. Analyses were performed using R Studio v1.1.463.

Results

Demographic and biological characteristics across biomarker groups

Across cohorts, between 7.17 and 12.50% of participants were classified as A+T+ using the tau temporal meta-ROI, compared with 20.83 to 25.78% as A+T-, 0 to 2.61% A-T+, and 64.58 to 68.13% A-T- (see eTables 4 and 5 in the Supplement for groupings using other regions to define T+, and harmonised Aβ and tau thresholds across cohorts). Characteristics of participants across cohorts and biomarker groups are presented in Table 1 (see eMethods and eTables 2 and 3 in the Supplement for statistics, and characteristics by MCI progression status).

Clinical progression rates across biomarker groups

Between 6.54% and 16.67% of participants across cohorts progressed from cognitively unimpaired to MCI after PET (mean progression time: PREVENT-AD = 2.00 years (SD = 1.10); HABS = 2.72 years (SD = 1.49), AIBL = 2.55 years (SD = 1.18), Knight ADRC = 2.67 years (SD = 1.18)). MCI progression status by biomarker group is displayed in Figure 1 and eTable 4 in the Supplement. Examples of Aβ and tau PET scans for each biomarker group and cognitive status from PREVENT-AD are presented in Figure 2. Across all cohorts, a greater proportion of A+T+ participants progressed to MCI (ADRC: 33.33%, HABS: 41.67%, PREVENT-AD: 54.55%, AIBL: 83.33%) compared with the other PET biomarker groups (<20%) (p values ≤ .004; Figure 1A-D & eTable 4 in the Supplement). Compared with other regions (entorhinal, inferior temporal, or 'any'), the meta-ROI for tau positivity detected the highest proportion of MCI progressors in the PREVENT-AD, HABS and Knight ADRC cohorts, whereas an inferior temporal ROI detected the highest proportion of MCI progressors in AIBL (100% vs 83.33%) (eTable 4 and eFigure 1 in the Supplement). Harmonised thresholds generally performed worse than cohort-specific thresholds in detecting MCI progressors (eTable 5 and eFigure 2 in the Supplement). In A+T+ participants, evidence of neurodegeneration (N+), defined using temporal cortical thickness, was associated with a 42.86 to 100% MCI progression rate (Figure 1E-H, eResults in the Supplement). Progression rates ranged from 50% to 75% using hippocampal volume to define (N+) (eResults and eFigure 3 in the Supplement).

Effect of biomarker group on probability of clinical progression across time

Survival curves representing progression time from CU to MCI for each AT biomarker group are displayed in Figure 3. Using the meta-ROI to define T+, the A+T+ group demonstrated a greater probability of progression to MCI over time compared with the other groups (Hazard Ratios > 4.75, Model Concordance Values > 0.68; Figure 3 & eTable 6 in the Supplement). Concordance (i.e., model fit) was typically reduced when other regions were used to define tau positivity (eTable 6 and eFigure4 in the Supplement), and when models used demographic/clinical information alone without the inclusion of biomarker groups (eTable 7 in the Supplement). Continuous measurement of neurodegeneration did not add significant prognostic value for MCI progression in the biomarker group models (*p* values > .07; eTable 8 in the Supplement).

Longitudinal cognition across biomarker groups

In all cohorts, A+T+ participants experienced greater longitudinal cognitive decline compared with the other groups (all β estimates > 0.03, *p* values < .04; Figure 4 and eResults in the Supplement; see eFigures 5-9 in the Supplement for performance stratified by MCI progression status and for specific RBANS cognitive indexes in PREVENT-AD). The strength of these associations was reduced when other regions were used to define tau abnormality in PREVENT-AD and HABS, whereas the inferior temporal lobe performed better in AIBL and Knight ADRC (eResults in the Supplement).

Cognitive decline status of non-progressors across biomarker groups

Cognitive status (declining versus stable) for non-progressors by biomarker group is displayed in eTable 9 and eFigure 10 in the Supplement. A greater proportion of A+T+ non-progressors showed cognitive decline compared with the A-T- group in PREVENT-AD (80% vs 27.63%, $p = .03$) and HABS (57.14% vs 13.86%, $p = .01$). No group difference reached significance in the other cohorts, but adding the decliners to the progressors in AIBL captured 100% of the A+T+ participants. Using different regions to classify tau positivity produced varying results across cohorts, with regions other than the temporal meta-ROI performing better at capturing decliners in some cases (eTable 9 and eFigure 10 in the Supplement).

Discussion

The AT(N) biological framework for AD has been proposed for research purposes, [1] but its clinical significance for individuals without cognitive impairment is unclear. We examined the implications of Aβ and tau positive PET signals for clinical progression from cognitively unimpaired to MCI over short-term intervals. Across four independent cohorts, 33% - 83% of cognitively unimpaired individuals with abnormal elevation of both Aβ and tau progressed to MCI within a mean of 2 to 2.7 years after PET scanning. These numbers increased across all cohorts when restricted to (N+) individuals, reaching 43-100% progression rate. Most of the remaining A+T+ participants also experienced cognitive decline, suggesting that they too are on a pathway towards AD symptoms.

AD clinical trials often require an abnormal amyloid biomarker for inclusion [19,20]. Here, positivity on both Aβ and tau PET was associated with an 7 to 29 times greater hazard of progression from cognitively unimpaired to MCI, as compared with a positive Aβ scan in the absence of a tau-positivity. The A-T+ group was not considered in analyses given this group represented <2% of all participants. These results suggest 1) that the presence of Aβ is typically needed as a precondition to tau-PET tracer binding detection, and 2) that tau pathology is critical for imminent decline. Models based on A+T+ PET biomarkers outperformed models based on demographic and clinical data alone in identifying risk of progression to MCI. Combining both tau and Aβ PET therefore greatly boosts associations with near-term clinical progression in preclinical disease stages – a finding that is highly relevant for future clinical trials. Examination of longitudinal cognitive trajectories further indicated that 22% - 100% of A+T+ participants who remained 'cognitively unimpaired' nonetheless demonstrated cognitive decline.

The research framework for the biological definition of AD uses dichotomous categories to define biomarker abnormality, i.e., (+) or (-)[1]. One challenge for this framework in PET studies is choice of anatomical region from which to define tau positivity [21]. While the entorhinal cortex (EC) is often the site of earliest tau deposition in AD [22], tau in this region is not necessarily specific to AD and may also occur with increasing age, independent of Aβ [23,24]. Accordingly, a temporal meta-ROI, comprising both medial and neocortical temporal regions, has been proposed as an alternative to the EC ROI for detecting AD-specific early tau deposition [18]. Here, use of a temporal meta-ROI to define T+ typically identified a larger percentage of MCI progressors in the A+T+ group and showed stronger associations with longitudinal cognitive decline when compared to EC and inferior temporal ROIs.

Evidence of neurodegeneration is not required for a diagnosis of biological AD, but is thought instead to reflect a non-specific marker of disease severity typical of more advanced stages. In the HABS cohort, A+T+ individuals with thinner temporal cortices had increased MCI progression rates. In the other cohorts, the progression rate was numerically, but not significantly, higher in the A+T+(N+) than the A+T+(N-) group when cortical thickness was used to define (N+), though it is notable that 100% of the A+T+(N+) AIBL participants progressed to MCI. The percentage of MCI progression was also numerically higher in the A+T+(N+) than A+T+(N-) groups in PREVENT-AD, HABS, and Knight ADRC cohorts when (N) was defined based on the hippocampal volume. The absence of a significant difference in AIBL, PREVENT-AD, and Knight ADRC may be attributable to the very high percentage of A+T+ progressors in AIBL (83%) and low statistical power in PREVENT-AD and Knight ADRC.

While the magnitude of the associations varied, the results were replicated across four independent cohorts using related but different methods. This replicability across methodologies and samples represents a key strength of our study, as does the robustness of the reported findings in multiple sensitivity analyses. Of note, the lowest progression rate for the A+T+ group was found in the Knight ADRC, the only cohort for which MCI was not defined on a consensus committee review but based on a CDR $\geq$ 0.5. We also found that cohort-specific biomarker thresholds performed better at detecting MCI progressors than harmonised cut-offs, likely due to between-sample differences such as participant age. The development of demographically-adjusted thresholds will be important for future clinical applicability of our findings. Study limitations include the modest sample sizes of the A+T+ groups, though the proportion of participants assigned to this biomarker group was similar to previous studies [25-27]. Given the majority of our participants were Non-Hispanic Whites, further studies are required to determine the applicability of our findings in more diverse and representative samples.

Conclusions

In four independent cohorts, we demonstrate that Aβ and tau PET positivity in cognitively unimpaired individuals is associated both with near-term progression to MCI and, among those who do not show such categorical change, longitudinal cognitive decline. Additional evidence of neurodegeneration (N) implies substantial additional probability of clinical progression, reaching a 100% progression rate over a ~3 year follow-up in one of the cohorts. Crucially, abnormality in both Aβ and tau PET was associated with a considerably greater risk of near-term clinical progression than abnormality of Aβ PET alone. These findings support the clinical validity of a

biological definition of AD in cognitively unimpaired subjects that is based on the presence of both Aβ and tau. When preventive treatments become available, the use of such a biological definition of AD to identify persons with probable pre-clinical AD could substantially mitigate the AD epidemic. Until then, elevations in both Aβ and tau PET indicate imminent clinical progression in most cognitively unimpaired individuals.

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CSB and DAH conducted the data analysis. SV and BAG had access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Jack CR, Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*. 2018;14(4):535-562.
2. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *The Lancet Neurology*. 2021;
3. Lowe VJ, Bruinsma TJ, Min H-K, et al. Elevated medial temporal lobe and pervasive brain tau-PET signal in normal participants. *Alzheimer's & dementia (Amsterdam, Netherlands)*. 2018;10:210-216. doi:10.1016/j.dadm.2018.01.005
4. Driscoll I, Troncoso J. Asymptomatic Alzheimers Disease: A Prodrome or a State of Resilience? *Current Alzheimer Research*. 2011;8(4):330-335. doi:http://dx.doi.org/10.2174/156720511795745348
5. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research*. Nov 1975;12(3):189-198. doi:0022-3956(75)90026-6 [pii]
6. Duff K, Humphreys Clark JD, O'Bryant SE, Mold JW, Schiffer RB, Sutker PB. Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: sensitivity, specificity, and positive and negative predictive powers. *Arch Clin Neuropsychol*. 2008;23(5):603-612. doi:10.1016/j.acn.2008.06.004
7. Papp KV, Rentz DM, Orlovsky I, Sperling RA, Mormino EC. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: The PACC5. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2017;3(4):668-677. doi:https://doi.org/10.1016/j.trci.2017.10.004
8. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA neurology*. 2014;71(8):961-970.
9. Morris JC. The clinical dementia rating (cdr): Current version and. *Young*. 1991;41:1588-1592.
10. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. May 2011;7(3):270-9. doi:S1552-5260(11)00104-X [pii]
10.1016/j.jalz.2011.03.008 [doi]
11. Johnson KA, Gregas M, Becker JA, et al. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. *Annals of neurology*. 2007;62(3):229-234. doi:https://doi.org/10.1002/ana.21164
12. Gordon BA, Friedrichsen K, Brier M, et al. The relationship between cerebrospinal fluid markers of Alzheimer pathology and positron emission tomography tau imaging. *Brain*. 2016;139(8):2249-2260. doi:10.1093/brain/aww139
13. McSweeney M, Pichet Binette A, Meyer P-F, et al. Intermediate flortaucipir uptake is associated with Aβ-PET and CSF tau in asymptomatic adults. *Neurology*. 2020;94(11):e1190-e1200. doi:10.1212/wnl.0000000000008905
14. Johnson KA, Schultz A, Betensky RA, et al. Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Annals of neurology*. 2016;79(1):110-119. doi:https://doi.org/10.1002/ana.24546

15. Fowler C, Rainey-Smith SR, Bird S, et al. Fifteen Years of the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study: Progress and Observations from 2,359 Older Adults Spanning the Spectrum from Cognitive Normality to Alzheimer's Disease. *Journal of Alzheimer's Disease Reports*. 2021;5:443-468. doi:10.3233/ADR-210005
16. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. Jul 1 2006;31(3):968-80. doi:10.1016/j.neuroimage.2006.01.021
17. Baker SL, Maass A, Jagust WJ. Considerations and code for partial volume correcting [(18)F]-AV-1451 tau PET data. *Data Brief*. Dec 2017;15:648-657. doi:10.1016/j.dib.2017.10.024
18. Jack CR, Jr, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimer's & Dementia*. 2017;13(3):205-216. doi:https://doi.org/10.1016/j.jalz.2016.08.005
19. Sperling RA, Rentz DM, Johnson KA, et al. The A4 Study: Stopping AD Before Symptoms Begin? *Science Translational Medicine*. 2014;6(228):228fs13-228fs13. doi:doi:10.1126/scitranslmed.3007941
20. Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature*. 2016/09/01 2016;537(7618):50-56. doi:10.1038/nature19323
21. Villemagne VL, Lopresti BJ, Doré V, et al. What Is T+? A Gordian Knot of Tracers, Thresholds, and Topographies. *Journal of Nuclear Medicine*. 2021;62(5):614-619. doi:10.2967/jnumed.120.245423
22. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta neuropathologica*. 1991;82:239-249. doi:10.1007/bf00308809
23. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta neuropathologica*. 2014/12/01 2014;128(6):755-766. doi:10.1007/s00401-014-1349-0
24. Yoon B, Guo T, Provost K, et al. Abnormal tau in amyloid PET negative individuals. *Neurobiol Aging*. Jan 2022;109:125-134. doi:10.1016/j.neurobiolaging.2021.09.019
25. Therriault J, Pascoal TA, Benedet AL, et al. Frequency of Biologically Defined Alzheimer Disease in Relation to Age, Sex, APOE ε4, and Cognitive Impairment. *Neurology*. 2021;96(7):e975-e985. doi:10.1212/wnl.0000000000011416
26. Betthauser TJ, Koscik RL, Jonaitis EM, et al. Amyloid and tau imaging biomarkers explain cognitive decline from late middle-age. *Brain : a journal of neurology*. 2020;143(1):320-335. doi:10.1093/brain/awz378
27. Jack CR, Jr, Therneau TM, Weigand SD, et al. Prevalence of Biologically vs Clinically Defined Alzheimer Spectrum Entities Using the National Institute on Aging-Alzheimer's Association Research Framework. *JAMA neurology*. 2019;76(10):1174-1183. doi:10.1001/jamaneurol.2019.1971

Table 1 Demographic, pathological and clinical characteristics of participants by biomarker group across cohorts

	PREVENT-AD					HABS					AIBL					Knight ADRC				
	Full sample (n = 128)	**A+T+** (n = 11)	**A+T-** (n = 33)	**A-T+** (n = 0)	**A-T-** (n = 84)	**Full sample** (n = 153)	**A+T+** (n = 12)	**A+T-** (n = 35)	**A-T+** (n = 4)	**A-T-** (n = 102)	**Full sample** (n =48)	**A+T+** (n = 6)	**A+T-** (n = 10)	**A-T+** (n = 1)	**A-T-** (n = 31)	**Full sample** (n = 251)	**A+T+** (n = 18)	**A+T-** (n = 58)	**A-T+** (n = 4)	**A-T-** (n = 171)
Demographics																				
Age, years	67.35 (4.87)	72.17. (5.12)[a,b]	66.72 (4.43)	NA	66.97 (4.71)	76.11 (6.33)	78.17 (5.08)	77.55 (6.24)	84.06 (3.72)	75.06 (6.26)	74.71 (6.87)	79.17 (6.55)[b]	79.50 (7.76)[c]	80	72.13 (5.40)	71.97 (5.73)	74.81 (4.79)[b]	72.21 (5.73)	70.79 (4.74)	71.62 (5.79)
Sex, F:M (% F)	95:33 (74.22)	9:2 (81.82)	26:7 (78.79)	NA	60:24 (71.43)	86:67 (56.21)	9:3 (75)	18:17 (51.43)	2:2 (50)	57:45 (55.88)	29:19 (60.42)	5:1 (83.33)	6:4 (60)	1:0 (100)	17:14 (54.84)	137:114 (54.58)	14:4 (77.78)[b]	37:21 (63.79)[c]	3:1 (75)	83:88 (48.54)
Education, years	15.17 (3.28)	13.09 (2.81)	15.21 (2.91)	NA	15.43 (3.41)	16.08 (3.06)	17.00 (2.00)	16.06 (2.91)	18 (1.63)	15.91 (3.23)	11.79 (2.97)	9.67 (2.73)	12.20 (2.86)	15	11.97 (2.96)	16.33 (2.38)	15.89 (1.94)	16.64 (2.34)	16.00 (1.63)	16.28 (2.45)
APOE ε4 carriers, n (%)	50 (39.06)	8 (72.73)[b]	19 (57.58)[c]	NA	23 (27.38)	46 (30.07)	11 (91.67)[a,b]	19 (54.29)[c]	1 (25)	15 (14.71)	12 (25)	2 (33.33)	3 (30)	0 (0)	7 (22.58)	76 (30.28)	13 (72.22)[a,b]	26 (44.83)[c]	0 (0)	37 (21.64)
Race/Ethnicity																				
Black/African American, n (%)	1 (0.78)	1 (9.09)	0 (0)	NA	0 (0)	21 (13.73)	2 (16.67)	3 (8.57)	0 (0)	16 (15.69)	NA	NA	NA	NA	NA	29 (11.55)	3 (16.67)	3 (5.17)	1 (25)	22 (12.87)
Hispanic, n (%)	2 (1.56)	0 (0)	0 (0)	NA	2 (2.38)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA	NA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
White, n (%)	125 (97.66)	10 (90.91)	33 (100)	NA	82 (97.62)	128 (83.66)	10 (83.33)	31 (88.57)	4 (100)	83 (81.37)	NA	NA	NA	NA	NA	222 (88.45)	15 (83.33)	55 (94.83)	3 (75)	149 (87.13)
Other*, n (%)	0 (0)	0 (0)	0 (0)	NA	0 (0)	4 (2.61)	0 (0)	1 (2.86)	0 (0)	3 (2.94)	NA	NA	NA	NA	NA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PET																				
Global Aβ Centiloid	26.59 (28.76)	73.62 (32.52)[a,b]	47.54 (33.57)[c]	NA	12.21 (5.13)	19.00 (20.52)	50.99 (13.85)[b]	43.66 (18.74)[c]	10.45 (1.42)	7.11 (4.05)	19.35 (38.44)	72.33 (34.33)[a]	64.10 (23.26)[c]	-16	-4.19 (10.60)	21.03 (33.51)	79.03 (38.64)[a,b]	56.12 (30.07)[c]	6.67 (7.95)	3.35 (10.09)
Temporal meta-ROI SUVR	1.17 (0.11)	1.42 (0.16)[a,b]	1.17 (0.06)	NA	1.14 (0.07)	1.18 (0.09)	1.39 (0.06)[a,b]	1.19 (0.06)[c]	1.31 (0.02)	1.15 (0.06)	1.19 (0.16)	1.51 (0.16)[a,b]	1.18 (0.10)	1.33	1.12 (0.09)	1.14 (0.09)	1.35 (0.09)[a,b]	1.15 (0.07)[c]	1.29 (0.02)	1.11 (0.07)
MRI																				
Temporal cortical thickness	2.89 (0.11)	2.81 (0.11)[a]	2.94 (0.09)[c]	NA	2.88 (0.11)	2.86 (0.16)	2.71 (0.19)[a,b]	2.85 (0.18)	2.88 (0.13)	2.88 (0.14)	2.88 (0.11)	2.82 (0.09)	2.86 (0.11)	3.02	2.90 (0.11)	2.84 (0.14)	2.80 (0.18)	2.86 (0.13)	2.83(0.13)	2.83 (0.14)
Hippocampal volume (% of TIV)	0.54 (0.06)	0.51 (0.04)[a]	0.56 (0.06)	NA	0.54 (0.06)	0.48 (0.06)	0.44 (0.06)[b]	0.47 (0.05)	0.46 (0.04)	0.49 (0.06)	0.51 (0.06)	0.50 (0.02)	0.48 (0.04)	0.57	0.52 (0.06)	0.51 (0.07)	0.47 (0.07)[a]	0.52 (0.07)	0.50 (0.07)	0.51 (0.07)
Cognition																				
MMSE (/30)	28.80 (1.26)	27.73 (1.56)[a,b]	29.15 (0.87)	NA	28.80 (1.29)	29.26 (0.98)	28.50 (1.17)[a,b]	29.31 (0.87)	29.75 (0.50)	29.31 (0.97)	28.46 (1.61)	25.83 (2.04)[a,b]	28.80 (1.48)	27	28.90 (1.01)	29.27 (1.08)	29.17 (1.20)	29.34 (1.04)	29.00 (1.41)	29.27 (1.09)
RBANS Global Cognition, baseline	-0.09 (0.88)	-0.41 (0.99)	0.00 (0.89)	NA	-0.09 (0.87)	NA	NA	NA	NA	NA										
PACC, baseline	NA	NA	NA	NA	NA	0.11 (0.61)	0.18 (0.55)	0.10 (0.55)	-0.02 (0.25)	0.11 (0.66)	-0.46 (0.89)	-0.59 (0.58)	-0.71 (0.95)	-1.40	-0.33 (0.92)	0.00 (0.69)	-0.14 (0.54)	0.04 (0.59)	0.15 (0.35)	0.00 (0.75)

Data are presented as mean (standard deviation) unless otherwise specified. Aβ = amyloid beta; *APOE* = apolipoprotein E genetic locus; DVR = distribution volume ratio; meta-ROI = meta region-of-interest; MCI = Mild Cognitive Impairment; MMSE = Mini

Mental State Examination; PACC = Preclinical Alzheimer's Composite Score; PET = Positron Emission Tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SUVR = standardized uptake value ratio; TIV = total intracranial volume.

Notes: Age and MMSE performance were calculated at the time of tau PET. Education data was collected in ranges in AIBL, with the lower boundary of the range used in current analyses. Years of education are therefore likely underestimated in this cohort (further details in eMethods in the Supplement). *APOE* ε4 carriers had at least one copy of the ε4 allele. Cognitive variables (RBANS, PACC) are reported as cohort-derived z-scores. [a] = significant difference between A+T+ and A+T- groups, [b] = significant difference between A+T+ and A-T-groups, [c] = significant difference between A+T- and A-T- groups at $p < .05$. * "Other" race included categories of Asian, Native American, or more than one race. The A-T+ group is presented for completion but was not included in statistical analysis owing to its small sample size.