Accuracy of Tau Positron Emission Tomography as a Prognostic Marker in Preclinical and Prodromal Alzheimer Disease

A Head-to-Head Comparison Against Amyloid Positron Emission Tomography and Magnetic Resonance Imaging

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**IMPORTANCE**

Tau positron emission tomography (PET) tracers have proven useful for the differential diagnosis of dementia, but their utility for predicting cognitive change is unclear.

**OBJECTIVE**

To examine the prognostic accuracy of baseline fluorine 18 (\[^{18}\text{F}\]–flortaucipir and \[^{18}\text{F}\]RO948 (tau) PET in individuals across the Alzheimer disease (AD) clinical spectrum and to perform a head-to-head comparison against established magnetic resonance imaging (MRI) and amyloid PET markers.

**DESIGN, SETTING, AND PARTICIPANTS**

This prognostic study collected data from 8 cohorts in South Korea, Sweden, and the US from June 1, 2014, to February 28, 2021, with a mean (SD) follow-up of 1.9 (0.8) years. A total of 1431 participants were recruited from memory clinics, clinical trials, or cohort studies; 673 were cognitively unimpaired (CU group; 253 [37.6%] positive for amyloid-β [Aβ]), 443 had mild cognitive impairment (MCI group; 271 [61.2%] positive for Aβ), and 315 had a clinical diagnosis of AD dementia (315 [100%] positive for Aβ).

**EXPOSURES**

\[^{18}\text{F}\]Flortaucipir PET in the discovery cohort (n = 1135) or \[^{18}\text{F}\]RO948 PET in the replication cohort (n = 296), T1-weighted MRI (n = 1431), and amyloid PET (n = 1329) at baseline and repeated Mini-Mental State Examination (MMSE) evaluation.

**MAIN OUTCOMES AND MEASURES**

Baseline \[^{18}\text{F}\]flortaucipir/\[^{18}\text{F}\]RO948 PET retention within a temporal region of interest, MRI-based AD-signature cortical thickness, and amyloid PET Centiloid were used to predict changes in MMSE using linear mixed-effects models adjusted for age, sex, education, and cohort. Mediation/interaction analyses tested whether associations between baseline tau PET and cognitive change were mediated by baseline MRI measures and whether age, sex, and APOE genotype modified these associations.

**RESULTS**

Among 1431 participants, the mean (SD) age was 71.2 (8.8) years; 751 (52.5%) were male. Findings for \[^{18}\text{F}\]flortaucipir PET predicted longitudinal changes in MMSE, and effect sizes were stronger than for AD-signature cortical thickness and amyloid PET across all participants \(R^2, 0.35\) (tau PET) vs 0.24 (MRI) vs 0.17 (amyloid PET); \(P < .001\), bootstrapped for difference) in the Aβ-positive MCI group \(R^2, 0.25\) (tau PET) vs 0.15 (MRI) vs 0.07 (amyloid PET); \(P < .001\), bootstrapped for difference) and in the Aβ-positive CU group \(R^2, 0.16\) (tau PET) vs 0.08 (MRI) vs 0.08 (amyloid PET); \(P < .001\), bootstrapped for difference). These findings were replicated in the \[^{18}\text{F}\]RO948 PET cohort. MRI mediated the association between \[^{18}\text{F}\]flortaucipir PET and MMSE in the groups with AD dementia (33.4% [95% CI, 15.5%-60.0%] of the total effect) and Aβ-positive MCI (13.6% [95% CI, 0.0%-28.0%] of the total effect), but not the Aβ-positive CU group (3.7% [95% CI, −17.5% to 39.0%]; \(P = .71\)). Age (\(t = −2.28; P = .02\)), but not sex (\(t = 0.92; P = .36\)), or APOE genotype (\(t = 1.06; P = .29\)) modified the association between baseline \[^{18}\text{F}\]flortaucipir PET and cognitive change, such that older individuals showed faster cognitive decline at similar tau PET levels.

**CONCLUSIONS AND RELEVANCE**

The findings of this prognostic study suggest that tau PET is a promising tool for predicting cognitive change that is superior to amyloid PET and MRI and may support the prognostic process in preclinical and prodromal stages of AD.

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An accurate prognosis for individuals with Alzheimer disease (AD) is essential for patients and families to plan for the future, reduce uncertainty, increase safety, and optimize medical decision-making. Despite the development of several biomarkers for neurodegeneration and AD pathology in past decades, accurately predicting rates of cognitive decline in individuals with AD remains challenging. Given the strong links between tau pathology and key correlates of cognition (e.g., neuronal loss and synaptic dysfunction) observed in vitro and at autopsy, in vivo information about the magnitude of cerebral tau pathology might improve the prediction of future cognitive decline.

A variety of positron emission tomography (PET) ligands have been developed that bind with high affinity to the tau aggregates formed in AD. The degree and patterns of tau PET retention strongly overlap with regions affected by brain atrophy and hypometabolism and correlate with concurrent cognitive performance. In addition, tau PET has shown excellent diagnostic performance for distinguishing AD dementia from non-AD neurodegenerative disorders such as frontotemporal dementia or vascular dementia. Recently, elevated baseline tau PET levels have been associated with accelerated cognitive decline over time, but most studies had relatively modest sample sizes, lacked a replication cohort, and/or focused on 1 stage of the AD clinical continuum. The objectives of this prospective, longitudinal, multicenter study were to (1) examine the prognostic value of \(^{[18F]}\)flortaucipir and \(^{[18F]}\)RO948 tau PET in a large cohort of individuals with AD dementia, mild cognitive impairment (MCI), or normal cognition; (2) perform a head-to-head comparison of tau PET with established magnetic resonance imaging (MRI) and amyloid PET markers for predicting future cognitive change; and (3) investigate whether age, sex, and/or APOE genotype modify the association between baseline tau PET and cognitive change over time.

Methods

Participants

From an ongoing multicenter study, we included 1431 participants from the Memory Disorder Clinic of Gangnam Severance Hospital, Seoul, South Korea (n = 161); the Swedish BioFINDER-1 (n = 136) and BioFINDER-2 (n = 296) studies at Lund University, Lund, Sweden; University of California, San Francisco (UCSF [n = 44]); the Alzheimer Disease Neuroimaging Initiative (ADNI [n = 445]); Avid Radiopharmaceuticals studies (A05 [n = 160]) and the placebo arm of the Eli Lilly solanezumab Expedition-3 study (n = 79); and the Berkeley Aging Cohort Study (BACS [n = 110]). Data were collected from June 1, 2014, to February 28, 2021. Tau PET was performed using \(^{[18F]}\)flortaucipir-PET in the discovery cohort (1135 [79.3%] of the total sample) and \(^{[18F]}\)RO948-PET in the replication cohort (296 [20.7%] of the total sample from BioFINDER-2). Following National Institute on Aging-Alzheimer’s Association diagnostic criteria, we only included patients with AD dementia who were positive for amyloid-\(\beta\) (A\(\beta\)) on PET and/or cerebrospinal fluid (CSF) (n = 315); 34 individuals with clinically diagnosed AD dementia who were negative for A\(\beta\) were excluded. We also included A\(\beta\)-positive (n = 271) and A\(\beta\)-negative (n = 172) participants with MCI and A\(\beta\)-positive (n = 253) and A\(\beta\)-negative (n = 420) cognitively unimpaired individuals (CU group). In addition to tau PET, all participants underwent a medical history assessment and neurological examination, MRI, and a neuropsychological test battery including the Mini-Mental State Examination (MMSE). The MMSE is a diagnostic screening tool that measures a variety of cognitive abilities—including orientation to time and place, short-term episodic memory, attention, problem solving, visuospatial abilities, and language and motor skills—and is often used as a cognitive outcome measure in longitudinal studies and clinical trials. Inclusion criteria for this study were MMSE assessment (n = 1431), MRI scan (n = 1431), and amyloid-PET scan (n = 1329) less than 6 months from tau PET and at least 2 MMSE time points (including baseline) with a minimum follow-up duration of 12 months. Written informed consent was obtained from all participants, and local institutional review boards for human research approved the study. This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline.

PET/MRI Acquisition

We acquired PET images using the following PET/computed tomography (CT) scanners: Biograph mCT (Siemens) in Seoul; Discovery 690 (GE Healthcare) in BioFINDER-1, Discovery MI (GE Healthcare) in BioFINDER-2, Biograph 6 Truepoint (Siemens) at UCSF and BACS, and multiple scanners in the multicenter ADNI and Avid Radiopharmaceuticals cohorts. All PET data were reconstructed at the respective sites into 4 x 5-minute frames within the 80- to 100-minute (\(^{[18F]}\)flortaucipir) and 70- to 90-minute (\(^{[18F]}\)RO948) intervals after injection. Amyloid PET was performed using carbon 11 (\(^{11C}\))-Pittsburgh Compound B (BACS and UCSF), \(^{[18F]}\)florbetapir (Avid Radiopharmaceuticals and ADNI subsets), \(^{[18F]}\)florbetaben (Seoul and...
ADNI subsets, or \([^{18}\text{F}]\text{flutemetamol}\) (BioFINDER-1 and BioFINDER-2). Magnetic resonance images were acquired on the following scanners: 3.0-T Discovery MR750 (GE Healthcare) in Seoul,\(^{12}\) 3.0-T Tim Trio (Siemens) or 3.0-T Prisma (Siemens) in BioFINDER-1 and -2,\(^{13,17}\) 3.0-T Tim Trio or 3.0-T Prisma (Siemens) at UCSF,\(^{33}\) 1.5-T Magnetom Avanto (Siemens) for BACS,\(^{12}\) and multiple 1.5-T and 3-T scanners in the multicenter ADNI\(^{34}\) and Avid Radiopharmaceuticals\(^{33}\) cohorts.

**TI1-Weighted MRI Processing**

The MRI data were centrally processed at Lund University using previously reported procedures.\(^{13,17,18,28,29}\) Briefly, cortical reconstruction and volumetric segmentation were performed with FreeSurfer, version 6.0, image analysis pipelines (https://surfer.nmr.mgh.harvard.edu/). Magnetization-prepared rapid gradient-echo images underwent correction for intensity homogeneity, removal of nonbrain tissue, and segmentation into gray matter, white matter, and CSF with intensity gradient and connectivity among voxels.\(^{35}\) Cortical thickness was measured as the distance from the gray matter–white matter boundary to the perpendicular pial surface.\(^{36}\) Reconstructed data sets were visually inspected for accuracy, and segmentation errors were corrected.

**PET Processing**

Tau PET images were first resampled to obtain uniform image size (128 × 128 × 63 matrix) and voxel dimensions (2.0 × 2.0 × 2.0 mm) across centers. Next, \([^{18}\text{F}]\text{flortaucipir}/\text{[}^{18}\text{F}]\text{JR948}\) images were centrally processed at Lund University using previously reported procedures,\(^{18,28,29}\) followed by motion correction using AFNI’s 3-dimensional volume registration, calculation of mean time, and rigid coregistration to the skull-stripped MRI scan. Voxelwise standardized uptake value ratio (SUVR) images were created using inferior cerebral gray matter as the reference region.\(^{37}\) To extract mean regional SUVR values, FreeSurfer parcellation of the T1-weighted MRI scan was applied to the PET data transformed to participants’ native T1 space. For amyloid PET, we applied computational analysis of PET by AIBL (CapAIBL)\(^{38}\) and tracer-specific conversion formulas to convert PET images or SUVR values into a Centiloid scale, which is a standard framework for the quantification of amyloid PET scans across tracers and cohorts.\(^{39}\)

**Regions of Interest**

In line with previous work,\(^{17,18,28}\) we calculated the mean \([^{18}\text{F}]\text{flortaucipir}\) and \([^{18}\text{F}]\text{JR948}-\text{PET SUVR}\) in the entorhinal cortex,\(^{15,16}\) a temporal meta–region of interest (ROI) that is a weighted mean of entorhinal, amygdala, parahippocampal, fusiform, and inferior and middle temporal ROIs,\(^{40}\) and Braak stages V to VI encompassing widespread neocortical ROIs.\(^{41}\) For MRI, we computed hippocampal volumes (adjusted for intracranial volume), an AD-signature cortical thickness ROI consisting of bilateral entorhinal, inferior, and middle temporal and fusiform cortex\(^{40}\) and whole-brain cortical thickness (adjusted for surface area).\(^{40}\) The temporal meta-ROI for tau PET and AD-signature cortical thickness ROI for MRI are reported in the main text, whereas the other ROIs are presented in eFigures 2 and 4 in the Supplement.

**Statistical Analyses**

We first performed a head-to-head comparison between \([^{18}\text{F}]\text{flortaucipir-PET}\) and MRI for predicting change in MMSE over time. Therefore, single-participant slopes (representing annual change) for MMSE were calculated using linear regression models adjusted for age, sex, educational attainment, and cohort. These slopes were used as dependent variables in linear regression models, including continuous tau PET, MRI, or amyloid PET measures as predictors across the whole group and in the separate diagnostic groups. We performed bootstrapping with 1000 iterations to test whether the \(R^2\) value differed between PET and MRI models. To test whether tau PET and MRI provide complementary information, we applied linear mixed-effects models with random intercepts and fixed slopes using longitudinal MMSE as a dependent variable. Our longitudinal data set was characterized by many participants for whom only 2 MMSE measurements were available. Although linear mixed models are generally able to accommodate this, including random slopes for participants led to overfitting of our models, whereas fixed-participant slopes led to the most parsimonious model. Model 1 included age, sex, educational attainment, and cohort as predictors. In model 2, either baseline tau PET or baseline MRI was added to model 1 as a predictor. In model 3, both imaging modalities (and the predictors from model 1) were entered simultaneously in a single model. We assessed model fit (Akaike information criterion) and examined differences in Akaike information criterion between models 1 and 2 and models 2 and 3 using the \(\chi^2\) statistic. We also performed mediation analysis to examine whether associations between baseline tau PET and longitudinal change in MMSE are mediated by MRI, adjusting for age, sex, educational attainment, cohort, and \(\text{APOE}\varepsilon4\) status. All analyses described above were also performed in the \([^{18}\text{F}]\text{JR948-PET}\) replication cohort and were repeated for a head-to-head comparison between tau PET and amyloid PET (except for the mediation analysis). Finally, we tested whether the association between baseline tau PET and change in MMSE over time across all Aβ-positive participants is moderated by age, sex, or \(\text{APOE}\) genotype using linear mixed-effect models with a 3-way interaction term (time × tau PET × age/sex/\(\text{APOE}\)), adjusted for age, sex, educational attainment, and cohort. Significance level was set at 2-sided \(P < .05\). We used R, version 4.0.2 (R Program for Statistical Computing), for the statistical analyses.

**Results**

**Participants**

Participant characteristics across diagnostic groups are presented in Table 1 (and stratified by discovery/replication sample and by cohort in eTables 1 and 2 in the Supplement, respectively). The mean (SD) age of the study participants was 71.2 (8.8) years; 680 (47.5%) were female and 751 (52.5%) were male. As expected, the AD dementia group had worse baseline MMSE (21.2 [4.2]), annual decline in MMSE (−2.42 [1.87]), and base-
line imaging markers (eg, [{18F}]flortaucipir SUVR in the temporal meta-ROI, 1.83 [0.44]), followed by the MCI (baseline MMSE score, 27.0 [2.4]; annual decline in MMSE score, 1.38 [1.84]; [{18F}]flortaucipir SUVR in the temporal meta-ROI, 1.46 [0.36] in Aβ-positive MCI group) and then the CU groups (baseline MMSE score, 28.8 [1.3]; annual decline in MMSE score, −0.37 [0.84]; [{18F}]flortaucipir SUVR in the temporal meta-ROI, 1.22 [0.14] in Aβ-positive CU group). The mean (SD) follow-up duration for MMSE was 1.9 (0.8) years.

Head-to-Head Comparison: Tau PET vs MRI

When comparing [{18F}]flortaucipir SUVR in the temporal meta-ROI against MRI-based AD-signature cortical thickness in linear regression models with annual change in MMSE as dependent variable (Figure 1 and eTable 3 in the Supplement), greater [{18F}]flortaucipir uptake was more strongly associated with decline in MMSE over time than MRI across all participants ($R^2$, 0.35 [tau PET] vs 0.24 [MRI]; bootstrapped $R^2$ difference, $t = 80.3$ [P < .001]), the Aβ-positive MCI group ($R^2$, 0.25 [tau PET] vs 0.15 [MRI]; bootstrapped $R^2$ difference, $t = 30.8$ [P < .001]), the Aβ-positive CU group ($R^2$, 0.16 [tau PET] vs 0.08 [MRI]; bootstrapped $R^2$ difference, $t = 38.6$ [P < .001]), and the Aβ-negative CU group ($R^2$, 0.06 [tau PET] vs 0.03 [MRI]; bootstrapped $R^2$ difference, $t = 13.6$ [P < .001]). Magnetic resonance imaging performed better than tau PET in the Aβ-negative MCI ($R^2$, 0.04 [tau PET] vs 0.10 [MRI]; bootstrapped $R^2$ difference, $t = -11.4$ [P < .001]) and AD dementia ($R^2$, 0.16 [tau PET] vs 0.20 [MRI]; bootstrapped $R^2$ difference, $t = -7.2$ [P < .001]) groups. Comparable results were found in the [{18F}]RO9494 replication cohort (eFigure 1 and eTable 3 in the Supplement), with greater tau PET uptake being more strongly associated with annual decline in MMSE than MRI across all participants ($R^2$, 0.49 vs 0.34; bootstrapped $R^2$ difference, $t = 147.9$ [P < .001]), the Aβ-positive MCI group ($R^2$, 0.34 vs 0.20; bootstrapped $R^2$ difference, $t = 23.1$ [P < .001]), the Aβ-positive CU group ($R^2$, 0.53 vs 0.36; bootstrapped $R^2$ difference, $t = 16.7$ [P < .001]), and the Aβ-negative CU group ($R^2$, 0.04 vs 0.03; bootstrapped $R^2$ difference, $t = 15.4$ [P < .001]) and with better performance for MRI compared with PET in the Aβ-negative MCI group ($R^2$, 0.15 vs 0.16; bootstrapped $R^2$ difference, $t = -61.4$ [P < .001]). Contrary to the discovery cohort, in the AD dementia group, [{18F}]RO9494 SUVR was more strongly associated with MMSE change ($R^2$, 0.26 vs 0.17; bootstrapped $R^2$ difference, $t = 50.6$ [P < .001]). In sensitivity analyses assessing entorhinal and Braak stages V and VI ROIs, tau PET was more strongly associated with MMSE change than MRI across all participants, the Aβ-negative MCI group, and the Aβ-positive CU group (eFigures 2-5 in the Supplement).

Complementary Information by PET and MRI

The results presented in Table 2 indicate that the prediction of decline in MMSE over time improved with both tau PET ($R^2$ for all participants, 0.49; $R^2$ for Aβ-positive AD dementia group, 0.34; $R^2$ for Aβ-positive MCI group, 0.35; $R^2$ for Aβ-positive CU group, 0.17) and MRI ($R^2$ for all participants, 0.46; $R^2$ for Aβ-positive AD dementia group, 0.38; $R^2$ for Aβ-positive MCI group, 0.29; $R^2$ for Aβ-positive CU group, 0.12) compared with a basic model including age, sex, educational attainment, and

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### Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study group</th>
<th>Aβ-positive AD dementia (n = 315)</th>
<th>Aβ-positive MCI (n = 271)</th>
<th>Aβ-negative MCI (n = 172)</th>
<th>Aβ-positive CU (n = 253)</th>
<th>Aβ CU (n = 420)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td>71.2 (8.8)</td>
<td>72.3 (8.4)</td>
<td>71.7 (7.9)</td>
<td>70.1 (8.2)</td>
<td>73.6 (7.2)</td>
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<tr>
<td>Sex, %</td>
<td>Male</td>
<td>52.5</td>
<td>58.4</td>
<td>50.6</td>
<td>45.9</td>
<td>49.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>47.5</td>
<td>41.6</td>
<td>49.4</td>
<td>54.1</td>
<td>50.6</td>
</tr>
<tr>
<td>Educational attainment, y</td>
<td></td>
<td>13.4 (6.0)</td>
<td>12.5 (5.0)</td>
<td>12.2 (5.2)</td>
<td>12.5 (5.5)</td>
<td>15.5 (8.8)</td>
</tr>
<tr>
<td>APOE ε4-positive, No./total No. (%)</td>
<td></td>
<td>616/1378 (44.7)</td>
<td>200/296 (67.6)</td>
<td>162/261 (62.1)</td>
<td>34/166 (20.5)</td>
<td>137/247 (55.5)</td>
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<tr>
<td>MMSE, baseline score</td>
<td></td>
<td>26.7 (3.9)</td>
<td>21.2 (4.2)</td>
<td>27.0 (2.4)</td>
<td>28.0 (1.9)</td>
<td>28.8 (1.3)</td>
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<tr>
<td>MMSE, annual change</td>
<td></td>
<td>-1.01 (1.61)</td>
<td>-2.42 (1.87)</td>
<td>-1.38 (1.84)</td>
<td>-0.74 (1.31)</td>
<td>-0.37 (0.84)</td>
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<td>Follow-up duration, mo</td>
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<td>22.7 (9.8)</td>
<td>19.8 (10.2)</td>
<td>22.8 (10.4)</td>
<td>20.8 (9.0)</td>
<td>24.0 (10.1)</td>
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<td>Follow-up visits, median (range)</td>
<td></td>
<td>2 (2-6)</td>
<td>2 (2-5)</td>
<td>3 (2-5)</td>
<td>2 (2-5)</td>
<td></td>
</tr>
<tr>
<td>[{18F}]flortaucipir/{18F}RO948, No. of participants</td>
<td></td>
<td>1135/296</td>
<td>235/80</td>
<td>190/81</td>
<td>144/28</td>
<td>208/45</td>
</tr>
<tr>
<td>[{18F}]flortaucipir temporal meta-ROI, SUVR</td>
<td></td>
<td>1.39 (0.38)</td>
<td>1.83 (0.44)</td>
<td>1.46 (0.36)</td>
<td>1.18 (0.12)</td>
<td>1.22 (0.14)</td>
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<td>[{18F}]RO948 temporal meta-ROI, SUVR</td>
<td></td>
<td>1.49 (0.57)</td>
<td>2.15 (0.65)</td>
<td>1.35 (0.12)</td>
<td>1.16 (0.10)</td>
<td>1.24 (0.25)</td>
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<tr>
<td>AD-signature cortical thickness, mm</td>
<td></td>
<td>2.63 (0.22)</td>
<td>2.40 (0.20)</td>
<td>2.60 (0.20)</td>
<td>2.68 (0.20)</td>
<td>2.72 (0.17)</td>
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<td>Amyloid PET/CSF Aβ findings, No. of participants</td>
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<td>1329/102</td>
<td>224/91</td>
<td>264/7</td>
<td>170/2</td>
<td>252/1</td>
</tr>
<tr>
<td>Amyloid PET, Centiloids</td>
<td></td>
<td>43.4 (47.7)</td>
<td>95.5 (33.9)</td>
<td>77.0 (36.2)</td>
<td>-0.6 (11.6)</td>
<td>57.7 (34.8)</td>
</tr>
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</table>

Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; APOE, apolipoprotein E; CSF, cerebrospinal fluid; CU, cognitively unimpaired; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; ROI, region of interest; SUVR, standardized uptake value ratio.

* Unless otherwise indicated, data are expressed as mean (SD).
cohort ($R^2$ for all participants, 0.19; $R^2$ for Aβ-positive AD dementia group, 0.20; $R^2$ for Aβ-positive MCI group, 0.21; $R^2$ for Aβ-negative CU group, 0.08) (all $P < .001$). Furthermore, tau PET and MRI provide complementary information, because when adding tau PET to linear mixed-effects models assessing MRI measures, the $R^2$ value increased (all participants, 0.46 vs 0.55; Aβ-positive AD dementia group, 0.38 vs 0.41; Aβ-positive MCI group, 0.29 vs 0.36; Aβ-positive CU group, 0.12 vs 0.18) and Akaike information criterion decreased (all participants, 8309 vs 8166; Aβ-positive AD dementia group, 3266 vs 3251; Aβ-positive MCI group, 2904 vs 2873; Aβ-positive CU group, 1922 vs 8166; Aβ-positive AD dementia group, 3266 vs 3251; Aβ-positive MCI group, 2904 vs 2873; Aβ-positive CU group, 1922 vs 8166). Thus, adding tau PET to linear mixed-effects models assessing MRI provides complementary information, because when adding tau PET to linear mixed-effects models assessing MRI measures, the $R^2$ value increased (all participants, 0.46 vs 0.55; Aβ-positive AD dementia group, 0.38 vs 0.41; Aβ-positive MCI group, 0.29 vs 0.36; Aβ-positive CU group, 0.12 vs 0.18) and Akaike information criterion decreased (all participants, 8309 vs 8166; Aβ-positive AD dementia group, 3266 vs 3251; Aβ-positive MCI group, 2904 vs 2873; Aβ-positive CU group, 1922 vs 1901), and vice versa ($R^2$: 0.49 vs 0.56 for all participants, 0.34 vs 0.43 for Aβ-positive AD dementia group, 0.35 vs 0.39 for Aβ-positive MCI group, and 0.17 vs 0.19 for Aβ-positive CU group).
Table 2. Complementary Information Provided by Tau PET and MRI for Predicting Change in MMSEa

<table>
<thead>
<tr>
<th>Model by study group</th>
<th>β (SE)</th>
<th>P value</th>
<th>R² value</th>
<th>AIC</th>
<th>χ² For difference</th>
<th>P value for difference</th>
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<tbody>
<tr>
<td>All Aβ-positive participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1: age, sex, educational attainment, cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Model 2: model 1 plus tau PET</td>
<td>-0.21 (0.02)</td>
<td>&lt;.001</td>
<td>0.192</td>
<td>8678</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3: model 1 plus tau PET plus MRI</td>
<td>-0.21 (0.02)</td>
<td>&lt;.001</td>
<td>0.494</td>
<td>8188</td>
<td>483.9</td>
<td>&lt;.001</td>
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<tr>
<td>Model 2: model 1 plus MRI</td>
<td>0.27 (0.03)</td>
<td>&lt;.001</td>
<td>0.561</td>
<td>8085</td>
<td>115.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 3: model 1 plus MRI plus tau PET</td>
<td>0.27 (0.03)</td>
<td>&lt;.001</td>
<td>0.546</td>
<td>8166</td>
<td>146.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aβ-positive AD dementia group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1: age, sex, educational attainment, cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2: model 1 plus tau PET</td>
<td>-0.17 (0.03)</td>
<td>&lt;.001</td>
<td>0.337</td>
<td>3265</td>
<td>88.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 3: model 1 plus tau PET plus MRI</td>
<td>-0.17 (0.03)</td>
<td>&lt;.001</td>
<td>0.425</td>
<td>3224</td>
<td>42.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 2: model 1 plus MRI</td>
<td>0.22 (0.06)</td>
<td>&lt;.001</td>
<td>0.384</td>
<td>3266</td>
<td>87.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 3: model 1 plus MRI plus tau PET</td>
<td>0.23 (0.06)</td>
<td>&lt;.001</td>
<td>0.414</td>
<td>3251</td>
<td>17.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aβ-positive MCI group</td>
<td></td>
<td></td>
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<tr>
<td>Model 1: age, sex, educational attainment, cohort</td>
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</tr>
<tr>
<td>Model 2: model 1 plus tau PET</td>
<td>-0.25 (0.03)</td>
<td>&lt;.001</td>
<td>0.346</td>
<td>2852</td>
<td>92.9</td>
<td>&lt;.001</td>
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<td>Model 3: model 1 plus tau PET plus MRI</td>
<td>-0.26 (0.03)</td>
<td>&lt;.001</td>
<td>0.390</td>
<td>2838</td>
<td>19.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 2: model 1 plus MRI</td>
<td>0.23 (0.05)</td>
<td>&lt;.001</td>
<td>0.288</td>
<td>2904</td>
<td>41.0</td>
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<tr>
<td>Model 3: model 1 plus MRI plus tau PET</td>
<td>0.24 (0.05)</td>
<td>&lt;.001</td>
<td>0.356</td>
<td>2873</td>
<td>37.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aβ-positive CU group</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Model 1: age, sex, educational attainment, cohort</td>
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<tr>
<td>Model 2: model 1 plus tau PET</td>
<td>-0.18 (0.05)</td>
<td>&lt;.001</td>
<td>0.167</td>
<td>1902</td>
<td>35.3</td>
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</tr>
<tr>
<td>Model 3: model 1 plus tau PET plus MRI</td>
<td>-0.18 (0.05)</td>
<td>&lt;.001</td>
<td>0.188</td>
<td>1896</td>
<td>7.9</td>
<td>.005</td>
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<tr>
<td>Model 2: model 1 plus MRI</td>
<td>0.10 (0.04)</td>
<td>.005</td>
<td>0.117</td>
<td>1922</td>
<td>15.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 3: model 1 plus MRI plus tau PET</td>
<td>0.10 (0.04)</td>
<td>.005</td>
<td>0.180</td>
<td>1901</td>
<td>22.6</td>
<td>&lt;.001</td>
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Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; AIC, Akaike information criterion; CU, cognitively unimpaired; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NA, not available; PET, positron emission tomography.

a In this analysis, we used the temporal meta–region of interest (ROI) for [18F]flortaucipir (tau) PET and AD-signature cortical thickness as an MRI marker as predictors of change in MMSE scores. Reported values represent outputs from linear mixed-effects models with random intercepts and fixed slopes (β [SE] and R² value) and from analysis of variance comparing different models (AIC and χ²). The β (SE) values represent the interaction between the imaging modality and time; (marginal) R² value represents the explained variance by the fixed effects; and AIC represents the model fit. The χ² for difference compares a model with a less advanced model (thus model 2 vs model 1, and model 3 vs model 2).

Mediation Analyses

Figure 2 shows path diagrams assessing AD-signature cortical thickness as a potential mediator of associations between baseline [18F]flortaucipir temporal meta-ROI SUVR and MMSE slopes. There was a modest mediation effect in the total group (22.0% [95% CI, 13.9%-32.0%] of the total effect; P < .001), the AD dementia group (33.4% [95% CI, 15.5%-60.0%] of the total effect; P < .001), and the Aβ-positive MCI group (13.6% [95% CI, 0.0%-28.0%] of the total effect; P = .04), but not in the Aβ-positive CU group (3.7% [95% CI, −17.5% to 39.0%]; P = .71). In the replication cohort (eFigure 6 in the Supplement), the association between baseline [18F]JRO9484 temporal meta-ROI SUVR and decline in MMSE was only modestly mediated by AD-signature cortical thickness across all participants (21.0% [95% CI, 9.8%-35.0%]; P < .001), but not in the AD dementia (13.0% [95% CI, −0.5% to 41.0%]; P = .06), Aβ-positive MCI (9.0% [95% CI, −8.0% to 54.0%]; P = .24), and Aβ-positive CU (19.8% [95% CI, −50.9% to 56.0%]; P = .33) groups.
Figure 2. Mediation Analyses

Path diagrams indicate whether Alzheimer disease (AD)–signature cortical thickness mediates the associations between baseline fluorine 18-labeled flortaucipir standardized uptake value ratio (SUVR) in the temporal meta–region of interest (ROI) and Mini-Mental State Examination (MMSE) slopes, adjusted for age, sex, educational level, cohort, and APOE ε4 status. The direct effect (ie, coefficient c) reflects the extent to which MMSE slopes change when baseline tau positron emission tomography (PET) increases by 1 unit while baseline cortical thickness remains unaltered. The indirect effect (ie, coefficient a1 × b1) reflects the extent to which MMSE slopes change when baseline tau PET is held constant and baseline cortical thickness changes by the amount it would have changed had baseline tau PET increased by 1 unit. The coefficient c' represents the total effect (ie, direct plus indirect effects). AD indicates amyloid-β; CU, cognitively unimpaired; MCI, mild cognitive impairment.

Aβ-positive AD dementia

Aβ-positive MCI

Aβ-positive CU

Head-to-Head Comparison: Tau PET vs Amyloid PET

Figure 1 and eTable 5 in the Supplement indicate that [18F]flortaucipir-PET was more strongly associated with annual decline in MMSE than amyloid PET across all participants (R², 0.35 vs 0.17; bootstrapped R² difference, t = 147.1 [P < .001]), the AD dementia group (R², 0.17 vs 0.02; bootstrapped R² difference, t = 8.11 [P < .001]), the Aβ-positive MCI group (R², 0.25 vs 0.07; bootstrapped R² difference, t = 63.3 [P < .001]), the Aβ-positive CU group (R², 0.16 vs 0.08; bootstrapped R² difference, t = 47.0 [P < .001]), and the Aβ-negative CU group (R², 0.06 vs 0.04; bootstrapped R² difference, t = 21.7 [P < .001]). Comparable results were found in the [18F]RO948 replication cohort (eFigure 1 and eTable 5 in the Supplement). Tau PET always added information to models including amyloid PET (R² for all participants, 0.49 vs 0.25; R² for Aβ-positive AD dementia group, 0.33 vs 0.20; R² for Aβ-positive MCI group, 0.39 vs 0.24; R² for Aβ-positive CU group, 0.18 vs 0.11) (all P < .001) (eTable 6 in the Supplement), whereas amyloid PET did not improve tau PET models in the AD dementia (χ², 0.1 [P = .64]), Aβ-positive MCI (χ², 0.01 [P = .97]), and Aβ-positive CU (χ², 0.2 [P = .69]) groups.

Modification of Tau PET vs Cognitive Decline Associations by Age, Sex, and APOE Genotype

Linear mixed-effects models showed that age (t = −2.28; P = .02), but not sex (t = 0.92; P = .36) or APOE genotype (t = 1.06; P = .29), modified the association between baseline [18F]flortaucipir temporal meta–ROI SUVR and MMSE change, because older individuals showed faster cognitive decline at similar tau PET levels (Figure 3). In the [18F]RO948 cohort, modification by age was not replicated (t = −0.81; P = .42) (eFigure 7 in the Supplement). Consistent with the discovery cohort, there were no significant 3-way interactions for sex (t = −1.67; P = .10) and APOE genotype (t = −0.47; P = .64).

Discussion

The main finding of this multicenter prognostic study was that baseline tau PET predicts group-level changes in MMSE over time across the AD clinical spectrum. In a head-to-head comparison with established MRI and amyloid PET markers, tau PET showed stronger associations with cognitive change, especially in preclinical and prodromal stages of AD. Part of the association between baseline tau PET and cognitive decline over time was mediated by baseline cortical thickness, but tau PET and MRI also provided complementary prognostic information. We identified age as a potential moderator of the association between baseline tau PET and longitudinal cognitive change, because older individuals showed more rapid cognitive decline at similar levels of tau load compared with younger individuals. Altogether, our findings suggest that tau PET is a promising tool for predicting future cognitive change that could support the prognostic process, especially in preclinical and prodromal stages of AD.

Clinicopathological studies have identified strong associations between tau pathology and cognition as well as key correlates of cognition such as loss of neurons and synaptic ac-
...tau PET is a powerful predictor of cognitive change over time and outperformed MRI and amyloid PET markers. This is an important first step toward further investigation of the potential of tau PET to act as a prognostic marker, especially in the early stages of AD, when estimating rates of future decline is notoriously challenging. Future research directions include the use of more sensitive (eg, the preclinical Alzheimer cognitive composite) or domain-specific (eg, episodic memory or executive functioning) cognitive tests, functional measures (eg, Clinical Dementia Rating Scale Sum of Boxes) or diagnostic conversion (eg, from MCI to AD dementia) as clinical readouts, longer follow-up durations, assessment of individualized prognostic models, and head-to-head comparisons against fluid biomarkers (eg, plasma phosphorylated tau) that are more scalable and possibly more cost-effective. Furthermore, in a recent successful phase 2 clinical trial with the Aβ-antibody donanemab,44 more cost-effective. Furthermore, in a recent successful phase 2 clinical trial with the Aβ-antibody donanemab,44 more cost-effective. Furthermore, in a recent successful phase 2 clinical trial with the Aβ-antibody donanemab,44 more cost-effective. Furthermore, in a recent successful phase 2 clinical trial with the Aβ-antibody donanemab,44...
in predicting future cognitive change, which is in accordance with previous observations of modest cognitive correlates for levels of Aβ in stark contrast to associations of pathological tau burden.⁴,¹⁰,¹⁴-¹⁶,²³,²⁵ This can be explained by differences in the temporal evolution of Aβ and tau pathology. Widespread Aβ pathology may emerge approximately 20 years before symptom onset, but the rate of accumulation attenuates over the disease course, which reduces its clinicalpathological correlates.⁴,⁴⁸ In contrast, neocortical tau pathology is typically only observed when the disease has clinically manifested, and rates of tau accumulation are higher in symptomatic compared with asymptomatic individuals on the AD pathological continuum.¹⁸,⁴⁹

Age, sex, and APOE genotype have previously been shown to affect rates of tau accumulation and cognitive performance across the AD clinical spectrum.⁵⁰-⁵² In the present study, we examined whether age, sex, and APOE genotype act as modifiers of the association between baseline tau PET and cognitive change over time. In the discovery cohort, older individuals showed more rapid cognitive decline than younger individuals with a similar tau load. This could be explained by lower resilience against tau pathology (and/or associated neurodegeneration) in older individuals or by the presence of co-pathological features (eg, TAR DNA-binding protein 43 or vascular pathology) that are more likely to occur with advancing age. Sex did not affect the association between baseline tau PET and cognitive change over time. Previous work has suggested that this effect may only pertain to preclinical AD, wherein women showed faster rates of cognitive decline at similar (high) levels of tau pathology compared with men.⁵³ The association between baseline tau PET and cognitive change over time did not differ by APOE genotype.

Strengths and Limitations
The strengths of this study include the large sample size, coverage of the full AD clinical spectrum, and availability of tau PET, MRI, amyloid PET, and prospective longitudinal MMSE scores. There are also several limitations. First, MMSE served as an outcome measure because it is the only cognitive test available across all cohorts in this study. Although MMSE is a widely used measure in clinical practice and clinical trials, it is a relatively crude measure that is characterized by a ceiling effect, and the follow-up duration of this study was relatively short. Second, inherent to multicenter studies comprising multiple cohorts that were not codesigned at inception, several challenges exist regarding data harmonization and pooling. Moreover, additional complexities exist related to use of different criteria for study entry and differences in clinical assessment at each site. Similar to previous studies using this sample,¹⁸,²⁸-³⁰ we minimized variability by analyzing data centrally at Lund University using a uniform pipeline, and we adjusted for cohort effects in the statistical models. However, disparities in participant selection, data acquisition, and preprocessing remain. Third, despite geographical contributions from Europe, Asia, and the US, most study participants were non-Hispanic White individuals. Future studies should test whether the study findings are generalizable to more ethnically diverse populations. Fourth, we used a different tau PET tracer in the replication cohort, informed by previous studies demonstrating good correspondence between [¹⁸F]flortaucipir-PET and [¹⁸F]RO948-PET for neocortical tracer uptake and tau PET positivity rates.²⁸,⁵⁴

Conclusions
In this multicenter prognostic study, the tau PET tracers [¹⁸F]flortaucipir and [¹⁸F]RO948 demonstrated prognostic utility as strong predictors of cognitive change over time. Tau PET outperformed established MRI and amyloid PET markers in a head-to-head comparison, especially in the Aβ-positive MCI and Aβ-positive CU groups. Our findings suggest that although tau PET as a diagnostic marker is most valuable at the dementia stage of AD,¹⁷,¹⁸,²⁰ the optimal time window for tau PET as a prognostic marker is during the prodromal and preclinical stages of AD.
Research Original Investigation

Accuracy of Tau PET as a Prognostic Marker

Critical revision of the manuscript for important intellectual content: Smith, Mattsson-Carlgren, Gorn, Leysy, Strandberg, Palmqvist, Olsson, Jögi, Stormrud, Boxer, Gorno-Tempini, Soleiman-Meigooni, Iaccarino, La Joie, Baker, Klein, Pontecorvo, Devous, Jagust, Lyoo, Rabinovici, Hansson.

Supervision: Jagust, Lyoo, Hansson.

Obtained funding: Ossenkoppele, Palmqvist, Boxer, Mattsson-Carlgren, Groot, Strandberg, Iaccarino, Pontecorvo, Devous, Jagust, Lyoo, Rabinovici, Hansson.

Administrative, technical, or material support: Smith, Strandberg, Palmqvist, Olsson, Jögi, Cho, Ryu, Choi, Boxer, Miller, La Joie, Baker, Borroni, Jagust, Lyoo, Hansson.

Conflict of Interest Disclosures: Dr Boxer reported receiving research support from the National Institutes of Health (NIH), the Tau Research Consortium, the Association for Frontotemporal Degenaration, the Bluefield Project to Cure Frontotemporal Dementia, Avid Radiopharmaceuticals, Eisai Inc, Biogen Inc, and Roche and serving as a consultant for Applied Genetic Technologies Corporation, Alector, Inc, Arkuda Therapeutics, Arivanas, Inc, Bioage, Ionis Pharmaceuticals, Inc, H Lundbeck A/S, Passage Bio Inc, Samumed, Ono Pharmaceutical Co, Ltd, Sangamo Therapeutics, Inc, Stealth BioTherapeutics Inc, Third Rock Ventures, Transposon Therapeutics, Inc, UCB, and Wave Life Sciences. Dr Pontecorvo reported being a minor stockholder in El Lilly and Company. Dr Devous reported being a minor stockholder in El Lilly and Company. Dr Rabinovici reported receiving research support from the NIH, Alzheimer’s Association, American College of Radiology, Avid Radiopharmaceuticals, GE Healthcare, and Life Molecular Imaging and receiving consulting fees from AXON Neuroscience. Eisai Inc, GE Healthcare, Johnson & Johnson, and Merck & Co, Inc, in the past 2 years. Dr Hansson reported acquiring research support for (the institution) from Avid Radiopharmaceuticals, Biogen Inc, El Lilly and Company, Eisai Inc, GE Healthcare, Pfizer Inc, and Roche and receiving consultancy/speaker fees from AC Immune, ALZpath, Biogen Inc, Cereavea Technologies, and Roche in the past 2 years. No other disclosures were reported.

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Additional Contributions: A complete list of the Alzheimer Disease Neuroimaging Initiative (ADNI) investigators can be found in the eAppendix in the Supplement. Data used in preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report.

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Original Investigation  Research


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