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# Frequency and Clinical Outcomes Associated With Tau Positron Emission Tomography Positivity

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**IMPORTANCE** Tau positron emission tomography (PET) allows in vivo detection of neurofibrillary tangles, a core neuropathologic feature of Alzheimer disease (AD).

**OBJECTIVE** To provide estimates of the frequency of tau PET positivity and its associated risk of clinical outcomes.

**DESIGN, SETTING, AND PARTICIPANTS** Longitudinal study using data pooled from 21 cohorts, comprising a convenience sample of 6514 participants from 13 countries, collected between January 2013 and June 2024. Cognitively unimpaired individuals and patients with a clinical diagnosis of mild cognitive impairment (MCI), AD dementia, or other neurodegenerative disorders were included.

**EXPOSURES** Tau PET with flortaucipir F 18, amyloid-β (Aβ) PET, and clinical examinations. Tau PET scans were visually rated as positive according to a US Food and Drug Administration– and European Medicines Agency–approved method, designed to indicate the presence of advanced neurofibrillary tangle pathology (Braak stages V-VI).

**MAIN OUTCOMES AND MEASURES** Frequency of tau PET positivity and absolute risk of clinical progression (eg, progression to MCI or dementia).

**RESULTS** Among the 6514 participants (mean age, 69.5 years; 50.5% female), median follow-up time ranged from 1.5 to 4.0 years. Of 3487 cognitively unimpaired participants, 349 (9.8%) were tau PET positive; the estimated frequency of tau PET positivity was less than 1% in those aged younger than 50 years, and increased from 3% (95% CI, 2%-4%) at 60 years to 19% (95% CI, 16%-24%) at 90 years. Tau PET positivity frequency estimates increased across MCI and AD dementia clinical diagnoses (43% [95% CI, 41%-46%] and 79% [95% CI, 77%-82%] at 75 years, respectively). Most tau PET–positive individuals (92%) were also Aβ PET positive. Cognitively unimpaired participants who were positive for both Aβ PET and tau PET had a higher absolute risk of progression to MCI or dementia over the following ' 5 years (57% [95% CI, 45%-71%]) compared with both Aβ PET–positive/tau PET–negative (17% [95% CI, 13%-22%]) and Aβ PET–negative/tau PET–negative (6% [95% CI, 5%-8%]) individuals. Among participants with MCI at the time of the tau PET scan, an Aβ PET–positive/tau PET–positive profile was associated with a 5-year absolute risk of progression to dementia of 70% (95% CI, 59%-81%).

**CONCLUSIONS AND RELEVANCE** In a large convenience sample, a positive tau PET scan occurred at a nonnegligible rate among cognitively unimpaired individuals, and the combination of Aβ PET positivity and tau PET positivity was associated with a high risk of clinical progression in both preclinical and symptomatic stages of AD. These findings underscore the potential of tau PET as a biomarker for staging AD pathology.

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Supplemental content

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**Group Information:** The PREVENT-AD Research Group, Harvard Aging Brain Study, LEADS Consortium, and Alzheimer's Disease Neuroimaging Initiative members are listed in Supplement 2.

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The development of imaging and fluid biomarkers of amyloid-β (Aβ) plaques,[1,2] a core neuropathologic feature of Alzheimer disease (AD),[3] has had a major impact on AD research and drug development.[4] Positron emission tomography (PET) imaging of Aβ has also demonstrated clinical utility in patients with mild cognitive impairment (MCI) or dementia of uncertain etiology.[5] However, the precise clinical consequences of Aβ positivity in earlier stages of the disease remain uncertain because Aβ positivity can occur in asymptomatic older individuals[6] who remain symptom free over their lifetime.[7] This lack of strong correspondence between Aβ positivity and relevant outcomes has led some experts in the AD field to question the clinical utility of biological definitions of AD independent of symptoms,[8] although this opinion is not universally accepted.[9]

Contrary to Aβ, autopsy studies have found that the presence of widespread neocortical tau neurofibrillary tangles, another neuropathologic hallmark of AD,[3] was strongly associated with neurodegeneration and clinical symptoms.[10,11] This close relationship underscores the importance of detecting tau pathology in vivo, complementing the information provided by Aβ biomarkers. To date, the only biomarker of neurofibrillary tangles approved for clinical use by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) is tau PET imaging with flortaucipir F 18 (formerly known as [$^{18}$F]T807 or [$^{18}$F]AV1451).[12] When assessed using an approved visual interpretation method, a positive flortaucipir F 18 PET scan reflects the presence of advanced neurofibrillary tangle pathology, corresponding to Braak stages V and VI at autopsy.[13] Braak staging[14] is a neuropathological framework that describes the spatial progression of tau neurofibrillary tangle pathology in AD. In this system, stages I and II involve the transentorhinal region, III and IV extend to limbic areas, and V and VI represent the most advanced stages with widespread neocortical involvement. Clinically, Braak stages V and VI represent the neuropathological stage most closely associated with significant cognitive impairment and dementia.[3,10,11,15]

The investigation of tau PET imaging using an FDA- and EMA-approved method to establish positivity could provide valuable insights directly relevant for its use in clinical settings. However, previous studies on tau PET have relied on the use of varying, nonclinically applicable definitions of tau PET positivity, leading to conflicting results on crucial metrics that inform its potential utility. These include inconsistent frequency estimates of tau PET positivity (eg, ranging from 2%-3%[16,17] to 20%-50%[18-20] in Aβ-negative cognitively unimpaired individuals), as well as highly variable estimates of the risk of clinical progression associated with tau PET positivity, with some studies suggesting limited relevance[18] while others reported a high risk.[16,17] To clarify the potential of tau PET in clinical settings, it is essential to investigate the frequency of and outcomes associated with tau PET positivity when established using clinically applicable methods.

The purpose of this study was to contribute to a better understanding of the potential of tau PET by providing estimates of 2 key metrics: the frequency of tau PET positivity and its associated risk of clinical progression. For this, data were analyzed from a large convenience sample of participants who underwent tau PET imaging with an approved radiotracer, flortaucipir F 18, in whom tau PET positivity was determined using a clinically applicable visual interpretation method.

### Key Points

**Question** What is the frequency of tau positron emission tomography (PET) positivity, defined using a clinically applicable visual interpretation method, and its associated risk of cognitive decline?

**Findings** In this longitudinal cohort study that included a convenience sample of 6514 participants from 21 cohorts, 9.8% of cognitively unimpaired individuals had positive tau PET scans, and the frequency of positivity increased with age and across increasingly symptomatic stages of Alzheimer disease. Participants who were positive for both amyloid-β (Aβ) PET and tau PET had a higher risk of clinically relevant cognitive decline over the following 5 years compared with both Aβ PET–positive/tau PET–negative and Aβ PET–negative/tau PET–negative individuals.

**Meaning** These findings underscore the potential role of tau PET as a biomarker for staging Alzheimer disease neuropathologic changes across the spectrum of the disease.

## Methods

Local institutional review boards for human research at each participating institution approved use of data for this study. All participants provided written informed consent. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

### Participants

A convenience sample of 6514 participants pooled from 21 different cohorts was included (eMethods 1.1 and eTable 1 in Supplement 1). All participants underwent a tau PET scan with flortaucipir F 18 between January 2013 and June 2024 and had a concurrent clinical evaluation (**Table 1**). Participants were either cognitively unimpaired (defined as not MCI, dementia, or any other major neurological disorder; see eMethods 1.1 in Supplement 1) or met established clinical criteria for a syndromic diagnosis of MCI,[21] AD dementia (including posterior and logopenic variants),[22] dementia with Lewy bodies,[23] behavioral variant frontotemporal dementia,[24] semantic or nonfluent variant primary progressive aphasia,[25] Parkinson disease[26] with cognitive impairment, progressive supranuclear palsy,[27] or corticobasal syndrome.[28] This diagnostic categorization was based solely on the aforementioned clinical criteria, independent of biomarker results or dementia severity rating instruments.

In addition, to assess whether the frequency of visual tau PET positivity (a proxy of Braak stages V-VI) was consistent with the frequency of autopsy-confirmed Braak stages V and VI across different ages, we conducted an indirect comparison using an independent sample of participants from the National Alzheimer's Coordinating Center dataset. These participants were either cognitively unimpaired or had a clinical

Table 1. Characteristics of the Study Participants

| Baseline Characteristics | Cognitively unimpaired (n = 3487) | Mild cognitive impairment (n = 1326) | Alzheimer disease dementia (n = 1332) | Dementia with Lewy bodies (n = 81) | Behavioral-variant FTD (n = 69) | Semantic variant PPA (n = 29) | Nonfluent variant PPA (n = 29) | Parkinson disease (n = 31) | Progressive supra-nuclear palsy (n = 73) | Corticobasal syndrome (n = 57) |
|---|---|---|---|---|---|---|---|---|---|---|
| Age, median (IQR), y | 70 (65 to 77) | 72 (65 to 78) | 69 (60 to 76) | 70 (66 to 75) | 65 (58 to 69) | 67 (63 to 70) | 70 (58 to 75) | 71 (65 to 75) | 71 (66 to 74) | 70 (64 to 74) |
| Sex, No. (%) | | | | | | | | | | |
| Female | 1875 (53.8) | 565 (42.6) | 695 (52.2) | 17 (21.0) | 33 (47.8) | 9 (31.0) | 19 (65.5) | 11 (35.5) | 36 (49.3) | 29 (50.9) |
| Male | 1612 (46.2) | 761 (57.4) | 637 (47.8) | 64 (79.0) | 36 (52.2) | 20 (69.0) | 10 (34.5) | 20 (64.5) | 37 (50.7) | 28 (49.1) |
| APOE ε4 carrier, No (%) | 1069 (34.2) | 453 (44.4) | 617 (63.3) | 24 (42.1) | 6 (27.3) | 2 (25.0) | 1 (33.3) | NA | NA | 0 |
| Not assessed | 363 | 305 | 358 | 24 | 47 | 21 | 26 | | | 56 |
| CDR, median (range) | | | | | | | | | | |
| Global[a] | 0 (0 to 0.5) | 0.5 (0 to 2) | 1 (0 to 3) | 1 (0 to 3) | 1 (0 to 2) | 0.5 (0 to 2) | 0.5 (0 to 3) | 0.5 (0 to 2) | 0.5 (0 to 3) | 0.5 (0 to 2) |
| Sum of Boxes[b] | 0 (0 to 4) | 1.5 (0 to 12) | 4.5 (0 to 18) | 4.8 (1.5 to 17) | 5.5 (0.5 to 12) | 3 (0 to 7.5) | 1.5 (0 to 14) | 4 (0 to 12) | 4 (0 to 15) | 1.5 (0 to 10) |
| Not assessed | 534 | 148 | 211 | 32 | 15 | 10 | 9 | 0 | 40 | 22 |
| Aβ PET | | | | | | | | | | |
| Centiloid, mean (range)[c] | 26 (−37 to 212) | 49 (−39 to 248) | 88 (−31 to 196) | 50 (−6 to 157) | 10 (−32 to 122) | 25 (−7 to 113) | 16 (−14 to 141) | 4 (−5 to 44) | 9 (−11 to 69) | 8 (−34 to 127) |
| Aβ positive (>24.4 Centiloids or positive visual read), No. (%) | 1074 (34.1) | 695 (57.9) | 1050 (90.8) | 35 (59.3) | 8 (18.2) | 5 (29.4) | 3 (16.7) | 1 (10.0) | 5 (19.2) | 9 (17.0) |
| Not assessed | 342 | 126 | 175 | 22 | 25 | 12 | 11 | 21 | 47 | 4 |
| Tau PET | | | | | | | | | | |
| Positive, No. (%)[d] | 343 (9.8) | 605 (45.6) | 1165 (87.5) | 29 (35.8) | 23 (33.3) | 20 (69.0) | 9 (31.0) | 9 (29.0) | 3 (4.1) | 15 (26.3) |
| Follow-up characteristics[e] | | | | | | | | | | |
| Participants with follow-up data, No. | | | | | | | | | | |
| Clinical diagnosis | 1977 | 490 | NA | NA | NA | NA | NA | NA | NA | NA |
| CDR | 2253 | 647 | 560 | NA | NA | NA | NA | NA | NA | NA |
| Follow-up time, median (maximum), y[f] | | | | | | | | | | |
| Clinical diagnosis | 3.8 (7.1) | 2.9 (6.8) | NA | NA | NA | NA | NA | NA | NA | NA |
| CDR | 4.0 (8.1) | 1.7 (7.0) | 1.5 (6.4) | NA | NA | NA | NA | NA | NA | NA |

Abbreviations: Aβ, amyloid-β; APOE ε4, apolipoprotein ε4 allele; CDR, Clinical Dementia Rating; FTD, frontotemporal dementia; NA, not assessed/available; PET, positron emission tomography; PPA, primary progressive aphasia.

[a] CDR-Global scores range from 0 (best) to 3 (worst).

[b] CDR–Sum of Boxes scores range from 0 (best) to 18 (worst).

[c] Assessed with [$^{18}$F]florbetapir, [$^{18}$F]florbetaben, [$^{18}$F]NAV4694, or [$^{11}$C]PiB.

[d] Assessed using the approved visual interpretation method for flortaucipir F 18 PET.

[e] Longitudinal analyses included only participants with Aβ status available at baseline. For those with mild cognitive impairment or Alzheimer disease dementia, a baseline CDR-G score of 0.5 or 1 was also required.

[f] Median follow-up times were estimated using the reverse Kaplan-Meier method.[42]

diagnosis of AD dementia within 1 year of death, and were assessed neuropathologically post mortem (neuropathology cohort, n = 3178).[29] None of these participants had available tau PET scans.

## PET Imaging

All tau PET scans were performed with flortaucipir F 18 and classified as either positive or negative using its FDA- and EMA-approved visual interpretation method.[12] This method defines a scan as positive if it exhibits increased signal in posterolateral temporal, occipital, and/or parietal/precuneus regions, with or without elevated signal in frontal areas. A visually positive flortaucipir F 18 PET scan reflects Braak stages V and VI.[13] Additional details can be found in eMethods 1.2 in Supplement 1.

To visually assess the large number of tau PET scans in our sample, we gathered a team of 18 readers, including nuclear medicine physicians and neuroimaging researchers,

who were trained using materials provided by Avid Radiopharmaceuticals to interpret flortaucipir F 18 PET scans (eMethods 1.3-1.4 in Supplement 1). The robustness of our visual interpretation procedure was validated in interrater agreement analyses (Cohen κ across readers; mean, 0.89; range, 0.78-0.97; eResults 2.1 and eFigure 1 in Supplement 1).

Aβ PET scans were available for most of the study participants (n = 5729, 87.9%). Aβ PET positivity was defined as a Centiloid[30] higher than 24.4[31] or with visual reads.

## Outcomes

The outcomes were (1) frequency of visual tau PET positivity as a function of clinical diagnosis, age, Aβ PET status, sex, and apolipoprotein E (APOE) ε4 carriership; and (2) clinically relevant progression among tau PET-positive individuals. For the latter, we studied 3 different definitions of relevant progression as perceived by patients, caregivers, and clinicians[32,33]: (1) progression to a clinical diagnosis of MCI or dementia among initially cognitively unimpaired individuals or progression to dementia among individuals with MCI; (2) progression on the Clinical Dementia Rating (CDR) Global score (CDR-G), defined as any increase in the score[34]; and (3) group-level mean CDR Sum of Boxes (CDR-SB) score after 5 years (baseline age, 70 years) higher than 1 for cognitively unimpaired, 5 for MCI (baseline CDR-G, 0.5-1), and 10 for mild AD dementia (baseline CDR-G, 0.5-1), which correspond to scores consistent with MCI, mild AD dementia, and moderate AD dementia,[35] respectively. The CDR-G score ranges from 0 to 3, with higher values indicating more severe cognitive and functional impairment. The CDR-SB score ranges from 0 to 18, based on the sum of ratings across 6 domains; higher scores reflect greater overall impairment.

Clinical progressions to MCI or dementia at follow-up visits were established by the respective study clinicians and committees based on published criteria.[21,22,36] The CDR was administered through a semistructured interview with both the participant and their study partner. While outcome assessors were not fully blinded to tau PET scans, clinical assessments were conducted independently of biomarker and CDR results, and tau PET visual reads were performed only after outcome ascertainment.

## Statistical Analysis

We used generalized additive models to derive frequency estimates of tau PET positivity conditional on covariates (age, sex, APOE ε4 carriership, and Aβ PET status) and diagnostic categories. Educational attainment was not included as a covariate due to its limited association with clinical decline,[37,38] age-cohort differences, and the lack of a standardized education metric across the included studies. Of note, the models account for the impact of studies that overrepresent Aβ-positive individuals, such as the A4 study, on the frequency of tau PET positivity. Ninety-five percent confidence intervals were calculated using either the Wald approximation when estimates were derived directly from model predictions or using the bootstrap method (n = 1000 repetitions) when estimates involved combining predictions from multiple models. Additional details can be found in eMethods 1.5 in Supplement 1.

Generalized additive mixed models were used to estimate mean temporal trajectories of the CDR-SB score (eMethods 1.6 in Supplement 1). Ninety-five percent confidence intervals were calculated using the Wald approximation.

The probability of clinical progression over the next 5 years (for cognitively unimpaired and MCI) or 3 years (for AD dementia) across different Aβ PET/tau PET profiles was estimated using illness-death models, which is the simplest form of a multistate Markov model.[39] This approach combines the naive hazard functions for clinical progression and mortality to account for the competing risk of death during follow-up precluding clinical progression, allowing for the estimation of unbiased probabilities of progression (eMethods 1.7 in Supplement 1). The naive hazard functions describing clinical progression were estimated using either Kaplan-Meier estimators (for global absolute risk estimates) or Cox proportional hazards regression (for age- and sex-specific absolute risk estimates). Because death events were not consistently recorded across all cohorts included in this study, we followed a previously published approach[40] and estimated naive hazard functions for mortality based on publicly available life tables from the 2019 US general population (https://mortality.org/). These estimates were further adjusted to account for the increased mortality risk associated with MCI or dementia[41] (eMethods 1.7 in Supplement 1). Ninety-five percent confidence intervals of the estimated absolute risks were computed using bootstrap (n = 1000 repetitions). Median follow-up times were estimated using the reverse Kaplan-Meier method.[42]

Analyses of the clinical outcomes of the Aβ PET-negative/tau PET-positive groups were regarded as exploratory due to reduced sample size and reported in eFigure 9 in Supplement 1.

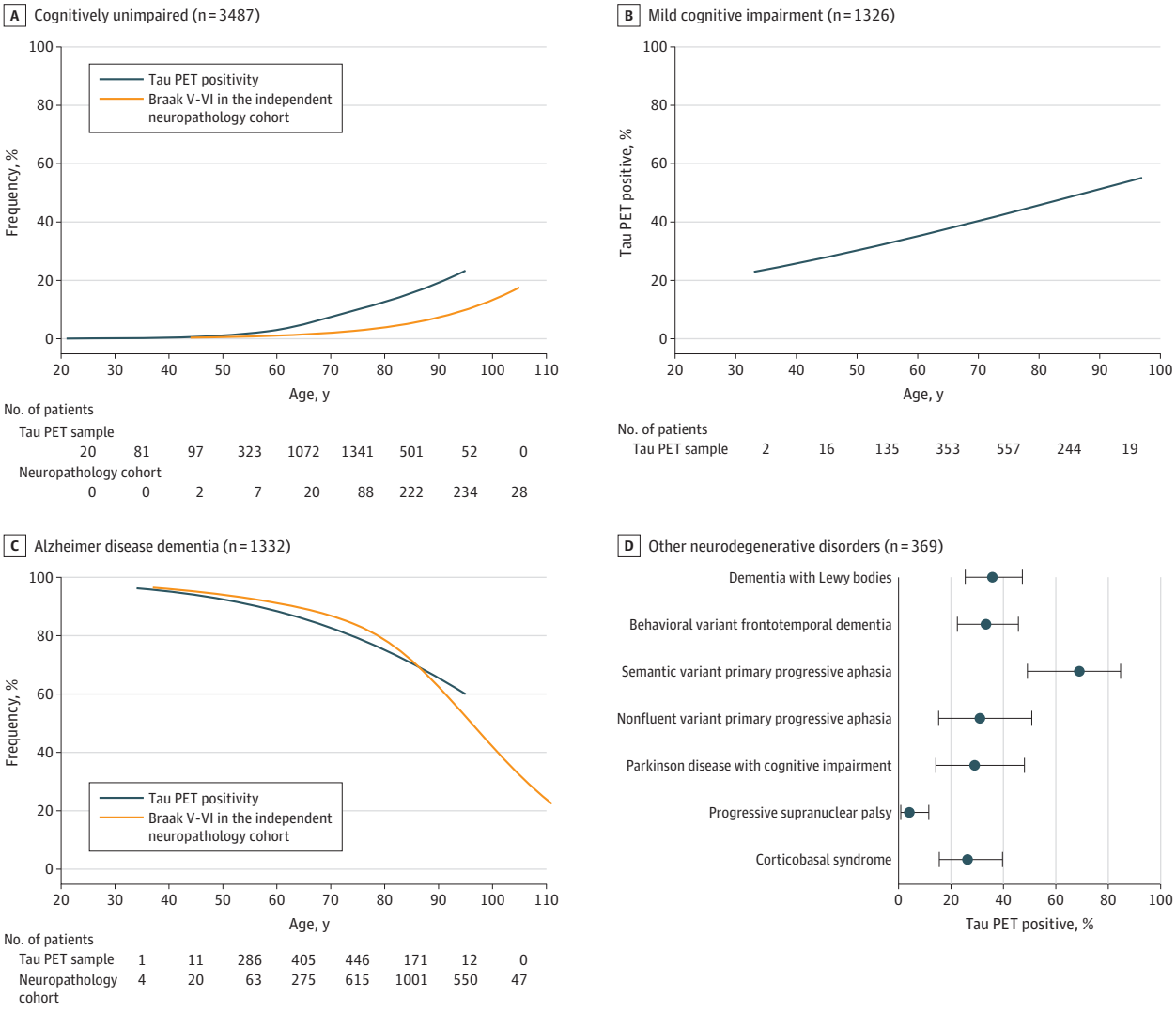
Analyses of between-cohort variability in the frequency of positivity and risk estimates were performed by estimating the additional explained variation that can be attributed to cohort membership (eMethods 1.8 in Supplement 1).

All analyses were conducted using the full pooled dataset, with statistical models run separately for cognitively unimpaired and cognitively impaired individuals. A complete-case approach was applied, as the proportion of missing Aβ PET, APOE ε4, and CDR data was relatively small compared with the overall dataset. Sensitivity analyses using multiple imputation yielded results consistent with the primary findings, indicating that the impact of the missing data was minimal. A 2-sided *P* value less than .05 was considered statistically significant. R version 4.3.2 (R Foundation for Statistical Computing) and MATLAB 2023b (The MathWorks) were used for all statistical analyses.

# Results

A total of 6514 participants with tau PET scans (mean age, 69.5 years; 50.5% female) pooled from 21 different cohorts were included. Baseline and follow-up characteristics of the included participants are reported in Table 1 and eTables 2-9 and eFigure 2 in Supplement 1.

**Figure 1. Frequency of Tau Positron Emission Tomography (PET) Positivity in Cognitively Unimpaired Individuals, Mild Cognitive Impairment, and Patients With a Clinical Diagnosis of Various Neurodegenerative Disorders**




Estimated frequency of tau PET positivity, established using the approved visual interpretation method for flortaucipir F 18, as a function of age in cognitively unimpaired individuals (A), participants with mild cognitive impairment (B), and Alzheimer disease dementia (C). The cognitively unimpaired, mild cognitive impairment, and Alzheimer disease dementia groups were defined based solely on the respective clinical symptoms, independent of amyloid-β status or other biomarker results. Benchmark estimates of the frequency of Braak stages V and VI (orange lines) in cognitively unimpaired individuals and participants with Alzheimer disease dementia were derived using data from an independent sample of participants from the neuropathology cohort (n = 3178).

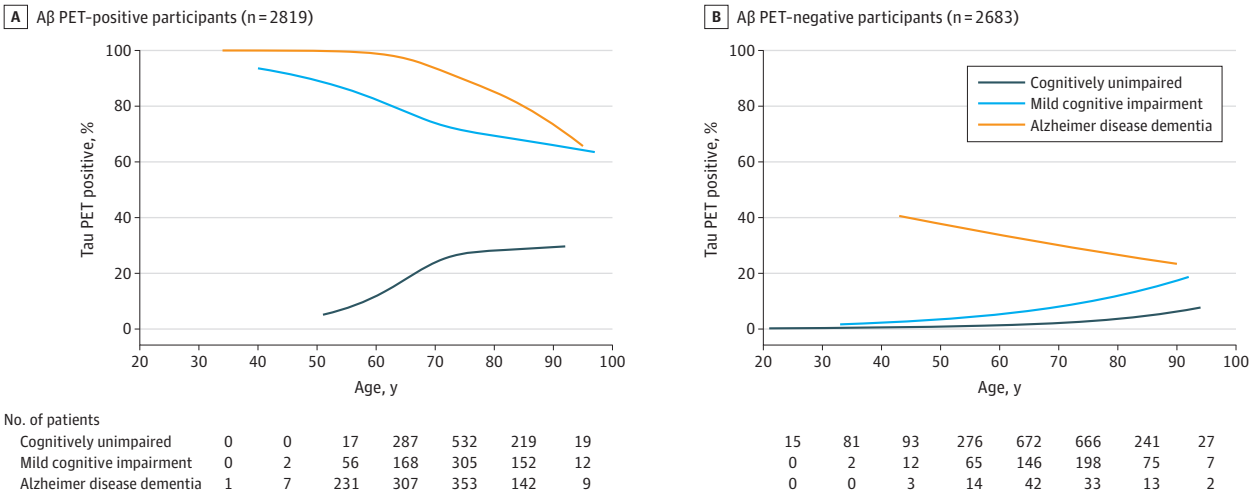
Panel D shows the overall frequency of tau PET positivity in other clinically diagnosed (ie, independent of amyloid-β status or other biomarker results) neurodegenerative disorders. Whiskers represent 95% confidence intervals. The number of participants with other neurodegenerative disorders were (tau PET positive/total): dementia with Lewy bodies, 29/81; behavioral variant frontotemporal dementia, 23/69; semantic variant primary progressive aphasia, 20/29; nonfluent variant primary progressive aphasia, 9/29; Parkinson disease with cognitive impairment, 9/31; progressive supranuclear palsy, 3/73; and corticobasal syndrome, 15/57. The numbers in the tables in A-C present the number for the decile they lie within.

## Frequency of Tau PET Positivity

Of 3487 cognitively unimpaired participants, 349 (9.8%) were tau PET positive. Quantitative neuroimaging analyses revealed significantly elevated tau PET signal in temporoparietal and frontal regions (eResults 2.2 and eFigure 3 in Supplement 1). The estimated frequency of tau PET positivity in cognitively unimpaired individuals younger than 50 years was below 1%, and increased from 3% (95% CI, 2%-4%) at 60 years to 19% (95% CI, 16%-24%) at 90 years (**Figure 1**A; eTable 10 in Supplement 1). The estimated frequency of Braak stages V and VI in cognitively unimpaired participants from the neuropathology cohort paralleled that of tau PET positivity until approximately 60 years of age but was consistently lower for older ages (Figure 1A; eTable 10 in Supplement 1).

Tau PET positivity was more frequent among the 1326 patients with MCI and 1332 patients with AD dementia. In patients with MCI, the estimated frequency at 40 years was 26% (95% CI, 20%-33%) and increased with age (from 35%

Figure 2. Frequency of Tau Positron Emission Tomography (PET) Positivity Among Amyloid-β (Aβ) PET-Positive and Aβ PET-Negative Individuals, Stratified by Clinical Diagnosis




No. of patients

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cognitively unimpaired | 0 | 0 | 17 | 287 | 532 | 219 | 19 | 15 | 81 | 93 | 276 | 672 | 666 | 241 | 27 |
| Mild cognitive impairment | 0 | 2 | 56 | 168 | 305 | 152 | 12 | 0 | 2 | 12 | 65 | 146 | 198 | 75 | 7 |
| Alzheimer disease dementia | 1 | 7 | 231 | 307 | 353 | 142 | 9 | 0 | 0 | 3 | 14 | 42 | 33 | 13 | 2 |

Panels A and B show the estimated frequency of tau PET positivity as a function of age among Aβ PET-positive and Aβ PET-negative individuals, separately for cognitively unimpaired (dark blue), mild cognitive impairment (light blue), and patients with a clinical diagnosis of Alzheimer disease dementia (orange). The numbers in the tables present the number for the decile they lie within.

[95% CI, 32%-39%] at 60 years to 51% [95% CI, 46%-57%] at 90 years; Figure 1B; eTable 10 in Supplement 1). Among participants with clinically diagnosed AD dementia, tau PET positivity frequency was estimated to be more than 85% for those younger than 65 years of age; however, its estimated frequency decreased with advancing age (from 88% [95% CI, 86%-91%] at 60 years to 65% [95% CI, 58%-72%] at 90 years; Figure 1C; eTable 10 in Supplement 1). This decreasing trend was also observed for the frequency estimates of Braak stages V and VI in the neuropathology cohort, which closely matched the frequency curve of tau PET positivity (Figure 1C; eTable 10 in Supplement 1).

Estimates of tau PET positivity for other neurodegenerative disorders are displayed in Figure 1D. The estimated frequency of positivity was relatively high in patients with frontotemporal dementia, particularly in those with semantic variant primary progressive aphasia (20/29, 69% [95% CI, 49%-85%]), the majority of whom were Aβ PET negative (eFigure 4D in Supplement 1).

Among cognitively unimpaired participants and those with a clinical diagnosis of MCI and AD dementia, tau PET positivity was more frequently observed in Aβ PET-positive than in Aβ PET-negative individuals (Aβ PET positive vs Aβ PET negative, cognitively unimpaired: 268/1074, 25% [95% CI, 22%-28%] vs 46/2071, 2% [95% CI, 2%-3%]; MCI: 511/695, 74% [95% CI, 70%-77%] vs 43/505, 9% [95% CI, 6%-11%]; AD dementia: 976/1050, 93% [95% CI, 91%-94%] vs 33/107, 31% [95% CI, 22%-40%]; eFigure 4A-C in Supplement 1). Older age was associated with higher frequency estimates of tau PET positivity among Aβ PET-positive cognitively unimpaired individuals, but with lower frequencies among Aβ PET-positive participants with MCI or AD dementia (**Figure 2**A; eTable 11 in Supplement 1). In Aβ PET-negative participants, the estimated frequency of positivity increased with age in the cognitively unimpaired and MCI groups, while it remained approximately constant or decreased slightly for Aβ PET-negative participants with AD dementia (Figure 2B; eTable 11 in Supplement 1). Higher Aβ levels (Centiloids) were associated with increased probability of a positive tau PET scan in a dose-dependent manner (eFigure 5 in Supplement 1).

Frequency estimates of tau PET positivity according to age, Aβ PET status, sex, and APOE ε4 carriership can be seen in eFigures 6 and 7 and eTables 12 to 15 in Supplement 1. The estimated frequency of tau PET positivity was higher in Aβ PET-positive cognitively impaired females than in males (75-year-old with MCI, 74% for females vs 62% for males, difference, 12% [95% CI, 6%-19%]; 75-year-old with AD dementia, 91% for females vs 85% for males, difference, 6% [95% CI, 3%-9%]; eFigure 6 in Supplement 1), but this association was not statistically significant in cognitively unimpaired individuals (eFigure 6C-D and eTables 12-14 in Supplement 1). APOE ε4 carriership was associated with increased probability of tau PET positivity in both Aβ PET-negative and Aβ PET-positive cognitively unimpaired individuals (75-year-old Aβ PET negative: 4% for carriers vs 2% for noncarriers, difference, 2% [95% CI, 0%-3%]; 75-year-old Aβ PET positive: 32% for carriers vs 21% for noncarriers, difference, 11% [95% CI, 7%-17%]) and Aβ PET-positive impaired individuals (75-year-old with MCI, 71% for carriers vs 59% for noncarriers, difference, 12% [95% CI, 5%-19%]; 75-year-old with AD dementia, 90% for carriers vs 85% for noncarriers, difference, 5% [95% CI, 2%-10%]) (eFigure 6A-B and eTables 12-14 in Supplement 1). These associations were largely attenuated in Aβ PET-negative cognitively impaired individuals (eFigure 7 and eTable 15 in Supplement 1).

The percentage deviance attributable to cohort differences was 0.8% for cognitively unimpaired and 11.1% for symptomatic participants, indicating relatively low cohort-related

variability in frequency estimates. Visual inspection of study-specific estimates also confirmed low variability (eFigure 8 in Supplement 1).

### Clinical Outcomes

The Aβ PET-positive/tau PET-positive profile was associated with a significantly increased estimated risk of experiencing all the evaluated clinical outcomes compared with both the Aβ PET-negative/tau PET-negative and Aβ PET-positive/tau PET-negative profiles (**Figure 3**, **Table 2**; eTables 16-17 in Supplement 1). For example, among initially cognitively unimpaired individuals with an Aβ PET-positive/tau PET-positive profile, the cause-specific hazard ratio for progression to MCI or dementia was 8.1 (95% CI, 5.5-12.0; $P < .001$) compared with Aβ PET-negative/tau PET-negative cognitively unimpaired individuals, and 3.8 (95% CI, 2.6-5.6; $P < .001$) compared with those with an Aβ PET-positive/tau PET-negative profile. Similar findings were observed for Aβ PET-positive/tau PET-positive individuals with MCI, with a hazard ratio of 6.8 (95% CI, 4.1-11.0; $P < .001$) for progression to dementia compared with the Aβ PET-negative/tau PET-negative MCI group, and a hazard ratio of 4.7 (95% CI, 2.6-8.4; $P < .001$) compared with the Aβ PET-positive/tau PET-negative MCI group.

The Aβ PET-positive/tau PET-positive profile was associated with a high absolute risk of progression to MCI or dementia among initially cognitively unimpaired individuals (5-year absolute risk: 57.4% [95% CI, 45.4%-70.8%]; Figure 3A; Table 2) as well as to progression to dementia among participants with MCI (5-year absolute risk: 69.9% [95% CI, 59.3%-81.2%]; Figure 3B; Table 2). Moreover, the 5-year absolute risk estimates of progression were dependent on baseline age and sex for both Aβ PET-positive/tau PET-positive cognitively unimpaired participants (60 years: 30% [95% CI, 17%-43%] for females vs 31% [95% CI, 17%-45%] for males; 80 years: 63% [95% CI, 52%-75%] for females vs 62% [95% CI, 50%-74%] for males; eTable 18 in Supplement 1) and Aβ PET-positive/tau PET-positive participants with MCI (60 years: 77% [95% CI, 59%-90%] for females vs 74% [95% CI, 55%-88%] for males; 80 years: 71% [95% CI, 55%-84%] for females vs 66% [95% CI, 55%-76%] for males; eTable 19 in Supplement 1). Similarly, Aβ PET-positive/tau PET-positive individuals were at high risk of progression on all the CDR-G outcomes (Figure 3C-D, Table 2; eTables 17 and 20-22 in Supplement 1). Additional estimates of the absolute risks of clinical progression, conditional on age and sex, are provided in eTables 18 to 22 in Supplement 1. At the group level, only the Aβ PET-positive/tau PET-positive groups surpassed specified thresholds on the CDR-SB at 5 years (Figure 3E-F).

The outcomes of the Aβ PET-positive/tau PET-negative groups were more similar to those of the corresponding Aβ PET-negative/tau PET-negative groups, particularly among symptomatic (MCI or AD dementia) participants (Figure 3; eTable 23 in Supplement 1). Analyses of the Aβ PET-negative/tau PET-positive groups revealed numerically higher rates of clinical decline compared with their Aβ PET-negative/tau PET-negative counterparts (eFigure 9 in Supplement 1).

Explainable variation in risk of clinical progression attributable to cohort membership ranged from 13.1% to 32.9% (eTable 24 in Supplement 1). Percentage deviance on CDR-SB trajectories attributable to cohort membership was low (0.2% for cognitively unimpaired and 0.3% for symptomatic participants), and visual inspection of cohort-specific trajectories confirmed limited variability (eFigure 10 in Supplement 1).

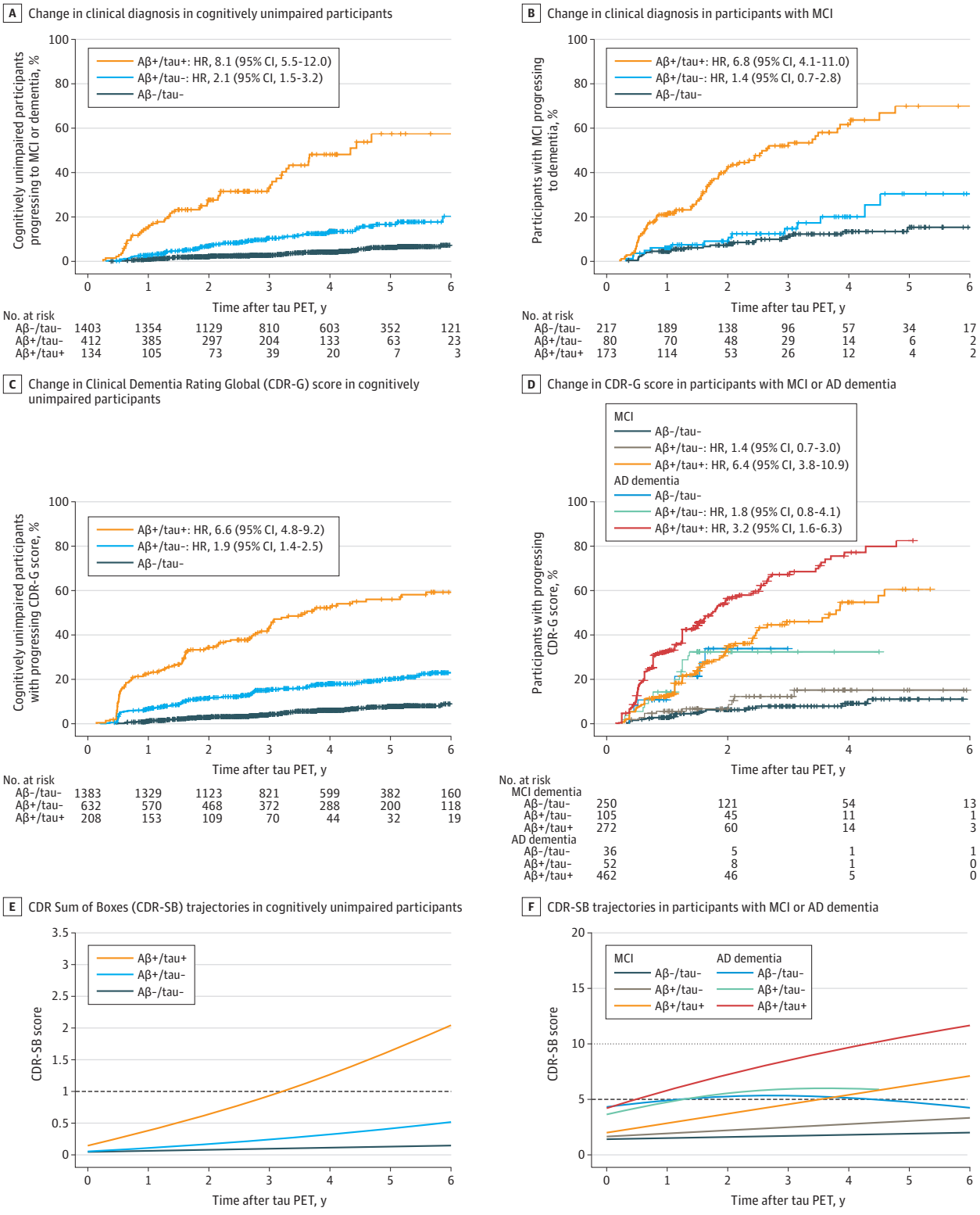
## Discussion

In this study that applied an FDA- and EMA-approved method for determining tau PET positivity in a large convenience sample from 21 pooled cohorts, the findings suggest that cognitively unimpaired older individuals have visually positive tau PET scans more frequently than previously suggested,[43] exceeding frequencies of 10% in those aged 75 years and older. Tau PET positivity in the cognitively unimpaired group was also systematically higher than the prevalence of Braak stages V and VI in an independent cognitively unimpaired sample from the neuropathology cohort (Figure 1A). This discrepancy likely reflects selection bias in the neuropathology cohort,[44] which overrepresents healthy older individuals who reached old age (median age at death, 88 years) without experiencing cognitive decline. As a result, this population tends to have a lower AD neuropathologic burden, leading to a lower frequency of Braak stages V and VI.[29] Moreover, the fact that most of the tau PET-positive cognitively unimpaired individuals were also Aβ positive (85%), exhibited elevated tau PET signal in regions consistent with Braak V and VI stages (eFigure 3 in Supplement 1), and were at high risk of clinical progression (Figure 3) suggest that the FDA- and EMA-approved method for defining tau PET positivity is indeed reflecting neurofibrillary tangle pathology in these individuals.

Previous studies have reported conflicting findings on the clinical outcomes of Aβ PET-positive/tau PET-positive cognitively unimpaired individuals,[16-18] leaving the implications of this biomarker profile unclear. These discrepancies may stem from substantial differences in how tau PET positivity was defined across studies, including variations in cut points, brain regions, quantification methods, and radiotracers. Consequently, these studies may lack generalizability to clinical practice, where only approved methods for visual tau PET assessment are used. In the present study that used an FDA- and EMA-approved method for determining tau PET positivity, an Aβ PET-positive/tau PET-positive profile in cognitively unimpaired individuals was associated with higher rates of progression to MCI or dementia over the following 5 years compared with their Aβ PET-positive/tau PET-negative and Aβ PET-negative/tau PET-negative counterparts. These results highlight the potential clinical relevance of Aβ PET and tau PET positivity in the absence of symptoms.

In AD dementia, the frequency curve of tau PET positivity closely matched that of Braak stages V and VI derived in the neuropathology cohort (Figure 1C), further supporting that a positive tau PET scan reflects advanced tau pathology in AD.[13] The decrease in frequency with age is likely attributable to 2 factors: (1) with advancing age, neuropathological changes other than AD pathology are more likely to result in an AD-like clinical syndrome[45,46]; and (2) with advancing age, the likelihood

## Figure 3. Clinical Outcomes of Tau Positron Emission Tomography (PET)–Positive Individuals




A and B, Kaplan-Meier–based estimates of the absolute risk of clinical progression to MCI or dementia in cognitively unimpaired vs symptomatic individuals according to different Aβ PET/tau PET biomarker profiles. C and D, Kaplan-Meier–based estimates of the absolute risk of increasing CDR-G score, by group. Crosses in A-D indicate censoring. E and F, Mean trajectories of the CDR-SB score (range, 0-18, higher scores = worse clinical symptoms) in cognitively unimpaired vs symptomatic individuals, according to Aβ PET/tau PET profiles. Modeled trajectories are conditional on age (70 years). Panel insets show covariate-adjusted cause-specific hazard ratios (HRs), using the respective Aβ PET−/tau PET− profile as reference.

Table 2. Absolute Risk of Clinical Progression, by Aβ PET/Tau PET Profile[a]

| Outcome | Absolute risk, % (95% CI)[b] | | |
|---|---|---|---|
| | Aβ−/tau− | Aβ+/tau− | Aβ+/tau+ |
| Progression to MCI or dementia over the next 5 y among cognitively unimpaired | 6.4 (4.7 to 8.2) | 16.6 (12.5 to 21.8) | 57.4 (45.4 to 70.8) |
| Progression to dementia over the next 5 y among MCI | 15.3 (9.5 to 22.2) | 30.4 (15.9 to 47.8) | 69.9 (59.3 to 81.2) |
| Progressing CDR-G score over the next 5 y among cognitively unimpaired | 7.8 (6.0 to 9.6) | 20.0 (16.5 to 23.7) | 56.1 (48.2 to 64.2) |
| Progressing CDR-G score over the next 5 y among MCI | 11.1 (5.9 to 17.0) | 15.2 (6.6 to 24.9) | 60.6 (49.2 to 72.6) |
| Progressing CDR-G score over the next 3 y among AD dementia | 33.9 (15.5 to 55.7) | 32.4 (20.6 to 44.9) | 67.2 (60.8 to 73.6) |

Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; CDR-G, Clinical Dementia Rating Global score; MCI, mild cognitive impairment; PET, positron emission tomography.

[a] Aβ± and tau± represent Aβ PET and tau PET status (positive/negative), respectively.

[b] Shown are the estimated absolute risks of clinical progression (ie, the probability of clinical progression accounting for the competing risk of death during follow-up; see eMethods 1.7 in Supplement 1 for details) to different outcomes among initially cognitively unimpaired individuals, as well as patients with MCI or AD dementia with different Aβ PET/tau PET biomarker profiles. 95% Confidence intervals were estimated using bootstrap.

of developing comorbid Aβ pathology increases.[6] These 2 phenomena lead to a higher frequency of elderly individuals with an AD-like clinical syndrome primarily caused by a non-AD condition, in whom comorbid Aβ pathology is present.[47,48]

An Aβ PET-positive/tau PET-positive profile was associated with increased incidence of clinically relevant outcomes in both participants with MCI and early AD dementia (Figure 3). These results suggest that tau PET positivity is a reliable indicator of AD pathology being a dominant contributor to clinical symptoms. However, interpretation of tau PET findings must consider that positivity can also occur in Aβ-negative patients. The reasons behind tau PET positivity in the absence of Aβ remain unclear, although explanations include flortaucipir F 18 binding to AD-like tau aggregates present in tangle-dominant forms of dementia,[49] binding to targets other than tau, and false-positive Aβ PET and/or tau PET scans. It is also important to note that tau PET radiotracers other than flortaucipir F 18 may have different off-target binding profiles,[50] and the frequency of positivity in Aβ-negative conditions with these radiotracers may differ from the estimates derived in this study.

Between 10% and 30% of the participants with a clinical diagnosis of dementia with Lewy bodies, behavioral variant frontotemporal dementia, semantic or nonfluent variant primary progressive aphasia, or corticobasal syndrome exhibited an Aβ PET-positive/tau PET-positive profile (eFigure 4 in Supplement 1). While Aβ positivity alone should not be used to infer that AD pathology is a primary contributor to symptoms in non-AD disorders,[43] the relevance of concurrent Aβ and tau PET positivity in these patients remains uncertain. Future studies are needed to clarify the relevance of this profile in these non-AD conditions.

Tau PET positivity was more frequent in cognitively impaired females, consistent with prior reports of sex-related increases in tau PET signal.[51] This pattern was not observed in cognitively unimpaired individuals, possibly due to subthreshold or regionally restricted differences. Similarly, higher tau PET positivity rates among APOE ε4 carriers align with previously observed tau PET signal elevations associated with this genotype.[52]

### Limitations

This study has several limitations. First, pooling data from independent studies may have introduced biases due to differences in study design. However, complementary analyses showed limited cohort-related variability, with relatively small between-cohort differences (eFigures 8 and 10 and eTable 24 in Supplement 1).

Second, cognitively unimpaired individuals were primarily recruited from research cohorts that are not representative of the general population, which may have introduced bias in the estimated frequency of tau PET positivity. However, comparisons with estimates derived solely from the Mayo Clinic Study of Aging—a population-based cohort—revealed only minimal differences (eFigure 11 in Supplement 1), suggesting that any potential bias is likely limited.

Third, absolute risk estimates were informed by incorporating 2019 US mortality rates into the estimates and may differ in populations with varying life expectancies. Fourth, despite being the largest tau PET study using clinically approved methods, the sample sizes for Aβ PET-negative/tau PET-positive individuals, other neurodegenerative disorders, and those aged older than 90 years were relatively small and should be interpreted with caution.

Fifth, tau PET quantification or alternative visual read methods might detect early tau deposition (eg, isolated mesial temporal signal) that is not captured by flortaucipir F 18's visual interpretation, which may also be linked to higher clinical progression risk.[16] Sixth, this study only included flortaucipir F 18 PET scans, as second-generation tau tracers currently lack a standardized, neuropathologically validated, and clinically approved definition of tau PET positivity. Seventh, many cohorts did not collect race or ethnicity data, preventing a robust analysis of the influence of these factors on tau PET positivity and clinical outcomes. Additionally, the majority of participants were White and thus the generalizability of these findings to more diverse populations remains to be confirmed.

## Conclusions

Tau PET positivity is detectable in a small but nonnegligible proportion of individuals in the preclinical stages of AD, with increasing frequency in symptomatic stages of the disease. The combination of a positive tau PET scan with a positive Aβ PET

scan was associated with an increased risk of clinically relevant outcomes across the entire AD spectrum. These findings highlight the potential role of tau PET for staging AD-related neuropathologic changes.

## ARTICLE INFORMATION

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