

Tau PET positivity in individuals with and without cognitive impairment varies with age, amyloid- β status, *APOE* genotype and sex

Received: 22 August 2024

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Accepted: 9 May 2025

Published online: 16 July 2025

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Tau positron emission tomography (PET) imaging allows in vivo detection of tau proteinopathy in Alzheimer's disease, which is associated with neurodegeneration and cognitive decline. Understanding how demographic, clinical and genetic factors relate to tau PET positivity will facilitate its use for clinical practice and research. Here we conducted an analysis of 42 cohorts worldwide ($N = 12,048$), including 7,394 cognitively unimpaired (CU) participants, 2,177 participants with mild cognitive impairment (MCI) and 2,477 participants with dementia. We found that from age 60 years to 80 years, tau PET positivity in a temporal composite region increased from 1.1% to 4.4% among CU amyloid- β ($A\beta$)-negative participants and from 17.4% to 22.2% among CU $A\beta$ -positive participants. Across the same age span, tau PET positivity decreased from 68.0% to 52.9% in participants with MCI and from 91.5% to 74.6% in participants with dementia. Age, $A\beta$ status, *APOE* $\epsilon 4$ carriership and female sex were all associated with a higher prevalence of tau PET positivity across groups. *APOE* $\epsilon 4$ carriership in CU individuals lowered the age at onset of both $A\beta$ positivity and tau positivity by decades. Finally, we replicated these associations in an independent autopsy dataset ($N = 5,072$ from 3 cohorts).

Alzheimer's disease (AD) is the most common cause of dementia, with a worldwide prevalence of ~32 million in 2023, which is expected to double by 2060 because of increased life expectancy¹. AD is neuropathologically characterized by the aggregation of amyloid- β ($A\beta$) proteins into extracellular plaques and of tau proteins into intracellular neurofibrillary tangles. Since the 2000s ($A\beta$)² and 2010s (tau)³, both proteinopathies can be visualized and quantified in the living human brain using positron emission tomography (PET). This has led to pivotal insights into the progression of AD over time. For example, amyloid-PET studies have consistently shown that $A\beta$ proteinopathy is an early event in the AD pathophysiological process and typically emerges decades before symptom onset⁴. As such, many elderly cognitively unimpaired (CU) individuals exhibit considerable $A\beta$ proteinopathy without manifest cognitive deficits (that is, at age 70 years, PET-assessed $A\beta$ positivity is ~23%, which increases to ~48% when carrying at least one *APOE* $\epsilon 4$ allele)^{5,6}. Consequently, the temporal association between

$A\beta$ proteinopathy and cognitive decline is moderate^{7,8}. Also, major reductions of $A\beta$ proteinopathy achieved by monoclonal antibody therapy have led to statistically significant but modest clinical benefits in symptomatic AD^{9,10}. In contrast, the presence and amount of tau proteinopathy are strongly associated with neurodegeneration, cognitive impairment, rate of clinical progression and treatment response to amyloid-lowering therapies^{11,12}. Even in CU individuals, the presence of tau proteinopathy as measured by PET profoundly increases the risk of short-term clinical progression^{13,14}.

Based on the recognition of tau proteinopathy as a key manifestation of AD, tau PET tracers are increasingly used in both the clinic and trials¹⁵ and are now incorporated into the core diagnostic criteria for AD^{16,17}. One tau PET tracer (that is, [¹⁸F]florbetapir/Tauvid) has received approval from the US Food and Drug Administration for clinical use to support a clinical diagnosis of AD¹⁸, because it (and other tau PET tracers) can accurately distinguish between AD dementia and most other

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Table 1 | Participant characteristics

	CU	MCI	Dementia ^a
<i>n</i>	7,394	2,177	2,477
Age, years	68.7±11.1	71.3±8.8	69.9±9.0
Sex, <i>n</i> women (%)	4,136 (55.9)	980 (45.0)	1,255 (50.9)
APOE ε4 status, <i>n</i> carrier (%)	2,322 (35.9)	879 (47.5)	1,096 (57.0)
Aβ status, <i>n</i> positive (%)	2,218 (30.9)	1,258 (59.3)	1,730 (76.8)
Aβ modality, <i>n</i> PET (%)	6,584 (95.3)	1,892 (90.3)	1,651 (73.3)
Education, years	14.7±3.7	13.5±4.3	13.1±4.2
MMSE	28.7±1.7	26.7±2.4	20.9±6.0
Race/Ethnicity, <i>n</i> self-report (% of total)			
Non-Hispanic white	3,744 (80.5)	879 (80.8)	603 (72.1)
Asian	276 (5.9)	131 (12.0)	187 (22.4)
Black/African American	286 (6.2)	47 (4.3)	26 (3.1)
Hispanic	317 (6.8)	27 (2.5)	14 (1.7)
American Indian or Alaskan Native	9 (0.2)	0 (0.0)	2 (0.2)
Hawaiian/Pacific Islander	1 (0.0)	0 (0.0)	0 (0.0)
More than one	13 (0.3)	3 (0.3)	3 (0.4)
Other	4 (0.1)	1 (0.1)	1 (0.1)
Tau PET tracer, <i>n</i> (%)			
[¹⁸ F]flortaucipir	4,118 (55.7)	1,125 (51.7)	1,237 (49.9)
[¹⁸ F]MK6240	2,066 (27.9)	587 (27.0)	503 (20.3)
[¹⁸ F]RO948	1,111 (15.0)	434 (19.9)	439 (17.7)
[¹⁸ F]PI2620	99 (1.3)	31 (1.4)	298 (12.0)

Shown are mean±s.d. unless specified otherwise. Sex was missing for 10 participants (0.1%), APOE ε4 status for 1,796 participants (14.9%), Aβ status for 489 participants (4.1%), Aβ modality for 789 participants (6.5%), education for 1,114 participants (9.3%), Mini-Mental State Examination (MMSE) for 792 participants (6.6%) and race for 5,593 participants (46.4%). Aβ modality refers to the method used to determine Aβ status, which could include either PET or cerebrospinal fluid markers. ^aPatients with a syndromic dementia diagnosis met diagnostic criteria for AD-type dementia (*n*=1,804) or non-AD neurodegenerative disorders including FTD (*n*=162), PSP (*n*=141), CBS (*n*=101), DLB (*n*=76), PDD (*n*=39), VaD (*n*=32) or dementia-not otherwise specified (*n*=122).

(non-AD) neurodegenerative disorders^{19,20}. Furthermore, several tau PET tracers have been implemented into clinical trials for participant selection, stratification and/or as a secondary or exploratory outcome measure. This includes application in anti-tau trials^{21,22}, but also in anti-Aβ trials³¹⁰. To optimize the future use of tau PET in clinical settings, accurate prevalence estimates of tau PET positivity and understanding of how demographic, clinical and genetic factors are associated with these prevalence estimates are essential. This will help clinicians and trialists to interpret the clinical importance of tau PET results and inform clinical trial design. Most tau PET studies conducted to date are single-center studies with insufficient sample sizes for providing reliable prevalence estimates of tau PET positivity, especially when these samples are stratified to explore the effects of individual risk factors for AD-type dementia such as age, sex and APOE genotype.

In the present study, we conducted a large-scale, multicenter analysis of 42 cohorts worldwide (*N* = 12,048). The present study aimed to estimate the prevalence of tau proteinopathy as measured by PET in CU participants and in individuals with mild cognitive impairment (MCI) or dementia. We investigated whether and how Aβ positivity, age, sex and APOE genotype are associated with tau PET-positivity prevalence estimates. We also compared the estimated tau PET-positivity prevalence against gold standard assessment of tau pathology, that is, the prevalence of neocortical tau proteinopathy in an independent postmortem dataset (*n* = 5,072).

Results

We included 12,048 participants with tau PET from 42 cohorts worldwide, of whom 7,394 were CU participants (mean age: 68.7 ± 11.1 years, 55.9% women, 30.9% Aβ positive), 2,177 with MCI (mean age: 71.3 ± 8.8, 45.0% women, 59.3% Aβ positive) and 2,477 with dementia (mean age: 69.9 ± 9.0, 50.9% women, 76.8% Aβ positive; Table 1). Participant characteristics stratified by Aβ status are presented in Supplementary Table 1. In addition, we included 5,072 participants from 3 independent autopsy cohorts (1,026 CU, 661 MCI and 3,385 dementia; Extended Data Table 1). Throughout the text, the term ‘tau positivity’ refers to a positive (abnormal) tau PET scan based on suprathreshold (cohort-specific threshold of mean + 2 s.d. in Aβ-negative CU individuals who were aged ≥50 years) tracer uptake in a previously established AD-specific region of interest (ROI), covering medial and lateral parts of the temporal cortex^{4,19}, or the presence of Braak stage V–VI for neurofibrillary tangle pathology on neuropathological examination (that is, ‘B3’ according to the AD neuropathological scoring system²³). In secondary analyses, we assessed tau PET positivity in alternative ROIs (entorhinal cortex and a whole-brain ROI), using alternative thresholds (mean + 1 s.d. and mean + 1.5 s.d.) and alternative methods of threshold definition (Gaussian mixture modeling; see Methods for further details). The term ‘prevalence’ refers to the frequency of tau PET positivity in the current dataset.

Tau positivity according to diagnosis and Aβ status

The observed prevalence of tau PET positivity in the temporal cortex was 7.6% (558 of 7,394) in CU individuals, 36.8% (801 of 2,177) in participants with MCI and 64.4% (1,595 of 2,477) in participants with all-cause dementia (Extended Data Fig. 1a). When stratifying for Aβ status and syndrome diagnosis, the prevalence of tau positivity in the temporal cortex was 2.1% (102 of 4,968) in Aβ-negative CU participants versus 20.0% (443 of 2,218) in Aβ-positive CU participants, 6.4% (55 of 863) in Aβ-negative participants with MCI versus 58.1% (731 of 1,258) in Aβ-positive participants with MCI and 10.0% (52 of 522) in participants with Aβ-negative dementia versus 83.5% (1,445 of 1,730) in participants with Aβ-positive dementia (Extended Data Fig. 1b,c). When stratifying for Aβ status and clinical dementia diagnosis, the prevalence of tau positivity in the temporal cortex was 23.7% (36 of 152) and 88.5% (1,366 of 1,544) for Aβ-negative versus Aβ-positive participants with AD-type dementia, 7.4% (9 of 121) and 13.0% (3 of 23) for Aβ-negative versus Aβ-positive participants with frontotemporal dementia (FTD), 1.4% (1 of 71) and 11.8% (2 of 17) for Aβ-negative versus Aβ-positive participants with progressive supranuclear palsy (PSP), 2.9% (2 of 69) and 27.8% (5 of 18) for Aβ-negative versus Aβ-positive participants with corticobasal syndrome (CBS), 3.3% (1 of 30) and 41.0% (16 of 39) for Aβ-negative versus Aβ-positive participants with dementia with Lewy bodies (DLB), 7.1% (1 of 14) and 33.3% (1 of 3) for Aβ-negative versus Aβ-positive participants with Parkinson’s disease dementia (PDD), 4.6% (1 of 22) and 0.0% (0 of 9) for Aβ-negative versus Aβ-positive participants with vascular dementia (VaD) and 2.3% (1 of 43) and 67.5% (52 of 77) for Aβ-negative versus Aβ-positive participants with dementia-not otherwise specified (Extended Data Fig. 1b,c). The observed prevalence of tau positivity in the entorhinal cortex and a whole-brain ROI by (syndrome and clinical) diagnosis and Aβ status is presented in Supplementary Figs. 1 and 2, respectively.

Tau positivity according to age and Aβ status

Logistic generalized estimating equation (GEE) models showed significant interactions between age and biomarker-defined Aβ status on tau positivity in the temporal cortex in CU participants and those with MCI and dementia (β , the estimated regression coefficient, = −0.06 for CU, β = −0.09 for MCI and β = −0.09 for dementia, all P < 0.001; Fig. 1a,c). From age 60 years to 80 years, the estimated prevalence of tau positivity in the temporal cortex increased from 1.1% (95% confidence interval (CI) 0.7–1.4%) to 4.4% (95% CI 3.2–5.6%) among Aβ-negative CU

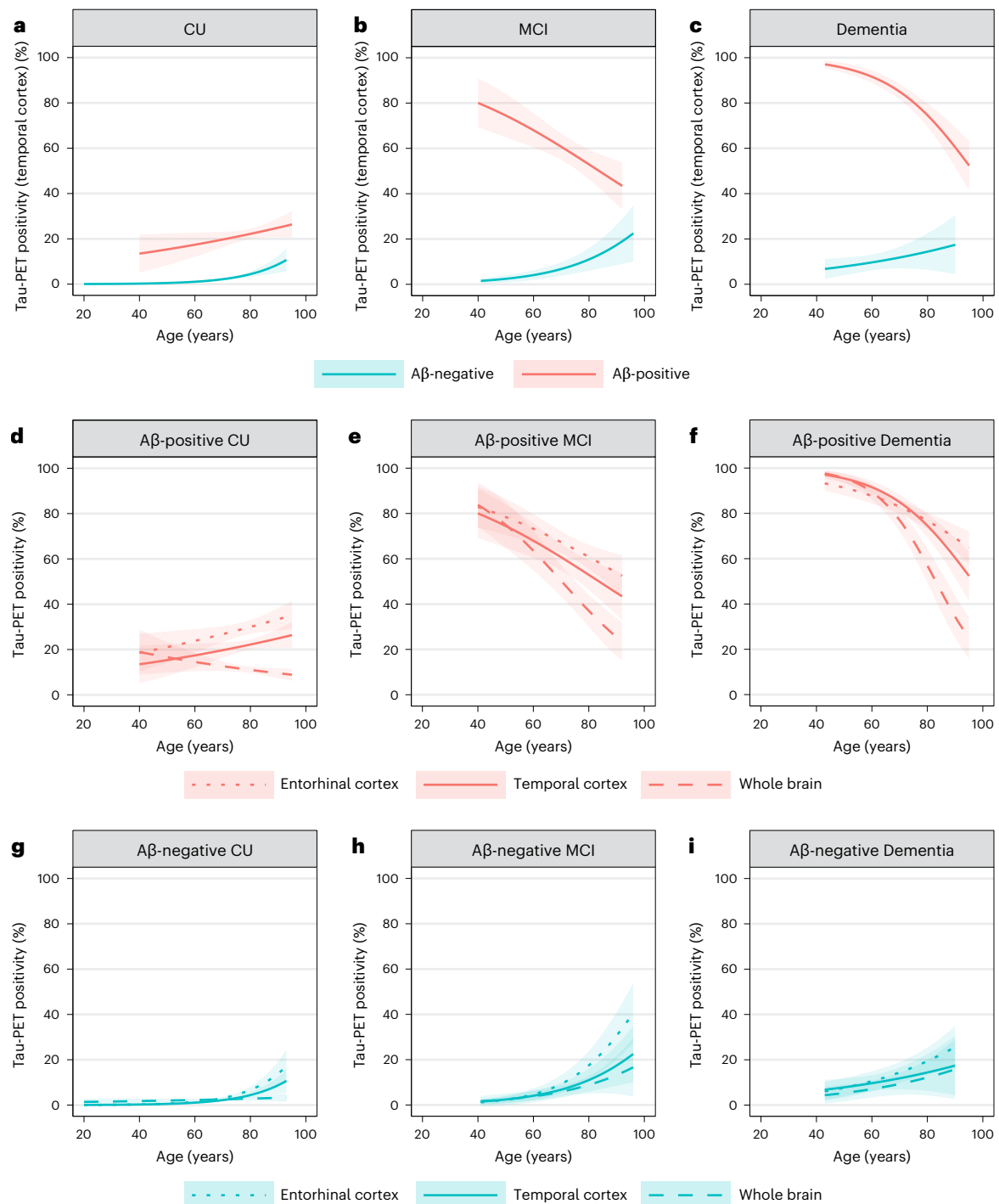


Fig. 1 | Prevalence estimates of tau PET positivity according to age, A β and cognitive status. **a–i**, Tau PET positivity in CU (**a,d,g**), MCI (**b,e,h**) and dementia (**c,f,i**) modeled using age, A β status and an interaction between age and A β status as determinants. Models were stratified by syndrome diagnosis. Tau PET positivity was assessed in the temporal cortex (**a–i**) as well as in the entorhinal cortex and whole brain (**d–i**). The figure includes 7,186 CU, 2,121 MCI and 2,252

dementia participants for tau PET positivity in the temporal cortex and whole-brain region and 7,174 CU, 2,117 MCI and 2,234 dementia participants for tau PET positivity in the entorhinal cortex. The y axes reflect estimated probabilities of tau PET positivity (prevalence estimates) generated from GEEs. Shaded areas indicate the 95% CIs.

participants, and from 17.4% (95% CI 12.1–22.8%) to 22.2% (95% CI 19.9–24.5%) among A β -positive CU participants (Fig. 1a and Table 2). Among A β -negative participants with MCI and dementia, from age 60 years to 80 years, the estimated prevalence of tau positivity increased from 4.1% (95% CI 1.9–6.2%) to 11.0% (95% CI 6.0–16.0%) in MCI and from 9.7% (95% CI 6.1–13.2%) to 14.4% (95% CI 6.3–22.5%) in dementia (Fig. 1b,c and Table 2). In contrast, among A β -positive participants with MCI

and dementia, from age 60 years to 80 years, the estimated prevalence of tau positivity decreased from 68.0% (95% CI 60.4–75.6%) to 52.9% (95% CI 46.3–59.5%) in MCI and from 91.5% (95% CI 88.8–94.3%) to 74.6% (95% CI 69.4–79.7%) in dementia (Fig. 1b,c, Table 2 and Supplementary Table 2). Next, we separately assessed tau positivity in two additional ROIs, that is, the entorhinal cortex and the whole-brain ROI. Across all groups, we observed that, at the same age, the prevalence

Table 2 | Prevalence estimates of tau PET positivity in the temporal cortex according to age, A β and cognitive status

Age, years	CU, % (95% CI)			MCI, % (95% CI)			Dementia, % (95% CI)		
	Total	A β negative	A β positive	Total	A β negative	A β positive	Total	A β negative	A β positive
50	2.4 (1.6–3.1)	0.5 (0.2–0.8)	15.3 (8.3–22.4)	32.0 (24.2–39.7)	2.4 (0.8–4.1)	74.5 (64.9–84.1)	74.5 (65.2–83.9)	7.8 (4.0–11.7)	95.4 (93.3–97.6)
55	3.2 (2.3–4.1)	0.7 (0.4–1.1)	16.3 (10.1–22.6)	33.7 (26.7–40.6)	3.2 (1.3–5.0)	71.3 (62.7–80.0)	73.0 (64.4–81.6)	8.7 (5.1–12.3)	93.8 (91.3–96.2)
60	4.2 (3.2–5.2)	1.1 (0.7–1.4)	17.4 (12.1–22.8)	35.4 (29.1–41.8)	4.1 (1.9–6.2)	68.0 (60.4–75.6)	71.4 (63.6–79.3)	9.7 (6.1–13.2)	91.5 (88.8–94.3)
65	5.6 (4.5–6.7)	1.5 (1.1–1.9)	18.5 (14.1–22.9)	37.2 (31.3–43.1)	5.3 (2.7–7.8)	64.4 (57.9–71.0)	69.8 (62.7–76.9)	10.7 (6.8–14.6)	88.7 (85.6–91.7)
70	7.4 (6.2–8.7)	2.2 (1.7–2.7)	19.7 (16.3–23.1)	39.0 (33.2–44.8)	6.8 (3.7–9.8)	60.7 (54.8–66.6)	68.1 (61.5–74.7)	11.8 (7.0–16.6)	84.9 (81.5–88.4)
75	9.8 (8.4–11.2)	3.1 (2.4–3.8)	20.9 (18.4–23.5)	40.9 (34.9–46.9)	8.6 (4.8–12.5)	56.9 (51.0–62.7)	66.4 (60.1–72.6)	13.1 (6.8–19.3)	80.3 (76.2–84.3)
80	12.8 (11.1–14.4)	4.4 (3.2–5.6)	22.2 (19.9–24.5)	42.8 (36.2–49.4)	11.0 (6.0–16.0)	52.9 (46.3–59.5)	64.6 (58.3–70.9)	14.4 (6.3–22.5)	74.6 (69.4–79.7)
85	16.5 (14.4–18.7)	6.2 (4.0–8.4)	23.5 (20.6–26.4)	44.7 (37.2–52.2)	13.9 (7.2–20.6)	48.9 (40.9–56.9)	62.8 (56.1–69.5)	15.8 (5.4–26.2)	67.9 (61.0–74.7)
90	21.1 (18.1–24.1)	8.7 (5.0–12.5)	24.9 (20.7–29.1)	46.6 (38.1–55.1)	17.4 (8.5–26.3)	45.0 (35.3–54.6)	60.9 (53.4–68.4)	17.4 (4.3–30.5)	60.4 (51.5–69.3)

The prevalence estimates of tau positivity in the temporal cortex were generated from logistic GEE models stratified by syndrome diagnosis. Prevalence estimates in the total group were modeled using age as a determinant. Prevalence estimates according to A β status were modeled using age, A β status and an interaction between age and A β status. The analyses presented in this table are based on 7,394 CU participants (68.7 \pm 11.1 years, 55.9% women), of whom 7,186 had A β status available (68.7 \pm 11.1 years, 56.0% women), 2,177 participants with MCI (71.3 \pm 8.8 years, 45.0% women), of whom 2,121 had A β status available (71.4 \pm 8.8 years, 44.8% women) and 2,477 participants with dementia (69.9 \pm 9.0 years, 50.9% women), of whom 2,252 had A β status available (69.9 \pm 9.0 years, 51.2% women).

of tau positivity was highest for the entorhinal cortex, followed by the temporal cortex and then the whole-brain ROI (Fig. 1d,i and Extended Data Tables 2 and 3). For example, in A β -positive CU participants aged 80 years, the estimated prevalence of tau positivity was 30.0% (95% CI 26.9–33.0%) for the entorhinal cortex, 22.2% (95% CI 19.9–24.5%) for the temporal cortex and 11.0% (95% CI 9.5–12.5%) for the whole-brain ROI. An additional analysis, including individuals with clinically diagnosed AD-type dementia, yielded very similar results compared with the analysis in the all-cause dementia group (Extended Data Fig. 2 and Extended Data Table 4). The proportion of tau positivity across ROIs for early onset (age at PET < 66 years) versus late-onset (age at PET > 65 years) AD is provided in Supplementary Fig. 3 and Supplementary Table 2.

The same analyses presented above but now using cohort-specific thresholds of mean + 1 s.d. and 1.5 s.d. in A β -negative CU individuals yielded largely similar results (Extended Data Fig. 3), as well as analyses in which tau PET thresholds derived from tracer-specific Gaussian mixture modeling (instead of a cohort-specific mean + 2 s.d. in the A β -negative CU individual threshold used in the primary analyses; Supplementary Fig. 4). The observed tau PET-positivity prevalence by age, diagnosis and A β status is presented in Supplementary Table 3, to allow comparison against the estimated prevalence presented in Table 2.

Tau positivity by age and APOE ϵ 4 status in CU individuals

In CU individuals, APOE ϵ 4 status (APOE ϵ 4⁺ versus APOE ϵ 4[−], β = 1.04, P < 0.001; Fig. 2a and Extended Data Table 5) and the number of APOE ϵ 4 alleles (APOE ϵ 4 homozygous versus APOE ϵ 4 noncarrier, β = 2.06, P < 0.001, APOE ϵ 4 heterozygous versus APOE ϵ 4 noncarrier, β = 0.94, P < 0.001 and APOE ϵ 4 homozygous versus APOE ϵ 4 heterozygous, β = 1.12, P < 0.001; Fig. 2b and Supplementary Table 4) were associated with a higher estimated prevalence of tau positivity in the temporal cortex. At the median age of 71 years, the prevalence estimates of tau positivity in the temporal cortex were higher in APOE ϵ 4/ ϵ 4 compared with all other genotypes (mean difference ϵ 4/ ϵ 4 versus ϵ 2/ ϵ 3: 24.1% (95% CI 15.5–32.6%); ϵ 4/ ϵ 4 versus ϵ 2/ ϵ 4: 20.9% (95% CI 10.6–31.2%); ϵ 4/ ϵ 4 versus ϵ 3/ ϵ 3: 23.7% (95% CI 15.3–32.2%); and ϵ 4/ ϵ 4 versus ϵ 3/ ϵ 4: 16.8% (95% CI 9.4–24.2%); all P < 0.001) and higher in ϵ 3/ ϵ 4 compared with ϵ 2/ ϵ 3 and ϵ 3/ ϵ 3 genotypes (mean difference ϵ 3/ ϵ 4 versus ϵ 2/ ϵ 3: 7.3% (95% CI 3.1–11.5%), P < 0.001; ϵ 3/ ϵ 4 versus ϵ 3/ ϵ 3: 6.9% (95% CI 2.8–11.0%); P < 0.001; Fig. 2c and Supplementary Table 5). No significant differences were found between the other genotypes and none of the 22 CU participants with an ϵ 2/ ϵ 2 genotype were tau positive in any of the ROIs.

A β and tau positivity by age and APOE ϵ 4 in CU individuals

Next, we aimed to estimate the timing of biomarker positivity for both A β and tau pathology as a function of age and APOE status or genotype in CU individuals to capture the earliest stages of AD pathophysiology. Figure 2d,e and Extended Data Table 6 illustrate that an increasing APOE ϵ 4 dose is associated with both A β and tau positivity occurring at a substantially younger age. The estimated age for 10% A β -positivity prevalence is 40.5 years in APOE ϵ 4/ ϵ 4 carriers, 49.0 years in APOE ϵ 3/ ϵ 4 carriers and 56.5 years in APOE ϵ 4 noncarriers. The estimated age for 10% tau-positivity prevalence in the entorhinal cortex is 44.5 years in APOE ϵ 4/ ϵ 4 carriers, 63.5 years in APOE ϵ 3/ ϵ 4 carriers and 77.5 years in APOE ϵ 4 noncarriers (Fig. 2d). The estimated age for 10% tau-positivity prevalence in the temporal cortex is 54.5 years in APOE ϵ 4/ ϵ 4 carriers, 69.0 years in APOE ϵ 3/ ϵ 4 carriers and 81.0 years in APOE ϵ 4 noncarriers (Fig. 2e). These results imply that, at a group level, APOE ϵ 4/ ϵ 4 CU individuals become tau positive in the entorhinal cortex at a younger age than APOE ϵ 4 noncarriers become A β positive (Fig. 2d), whereas the prevalence curves for tau positivity in the temporal cortex in APOE ϵ 4/ ϵ 4 carriers versus A β positivity in APOE ϵ 4 noncarriers largely overlap (Fig. 2e).

A β and tau positivity by age and sex in CU individuals

In CU individuals, female sex was associated with a higher estimated prevalence of A β positivity (β = 0.13, P = 0.005), tau positivity in the entorhinal cortex (β = 0.41; P < 0.001) and tau positivity in the temporal cortex (β = 0.27, P < 0.001; Fig. 2f,g) compared with male sex. The estimated age for 10% A β -positivity prevalence is 48.5 years for women and 50.0 years for men, the estimated age for 10% tau positivity in the entorhinal cortex is 67.5 years for women and 73.5 years for men (Fig. 2f) and the estimated age for 10% tau positivity in the temporal cortex is 73.0 years for women and 77.5 years for men (Fig. 2g and Extended Data Table 7). These results imply that, at a group level, CU women become A β positive and tau positive at a younger age than CU men.

Tau positivity by age, APOE ϵ 4 status and A β status

Given that the age effect on tau positivity was strongly modulated by A β status (for example, positive associations in A β -negative individuals with MCI or dementia versus negative associations in A β -positive individuals with MCI or dementia), we next modeled age, A β status and APOE ϵ 4 status simultaneously. In models adjusting for age and A β pathology, APOE ϵ 4 carriership was associated with a higher prevalence of tau positivity in the temporal cortex in all diagnostic groups (β = 0.55 for CU, β = 0.64 for MCI and β = 0.59 for dementia; all P < 0.001; Fig. 3a,c and Supplementary Table 6). For example, at the median age of 71 years, the prevalence estimates of tau positivity in the temporal

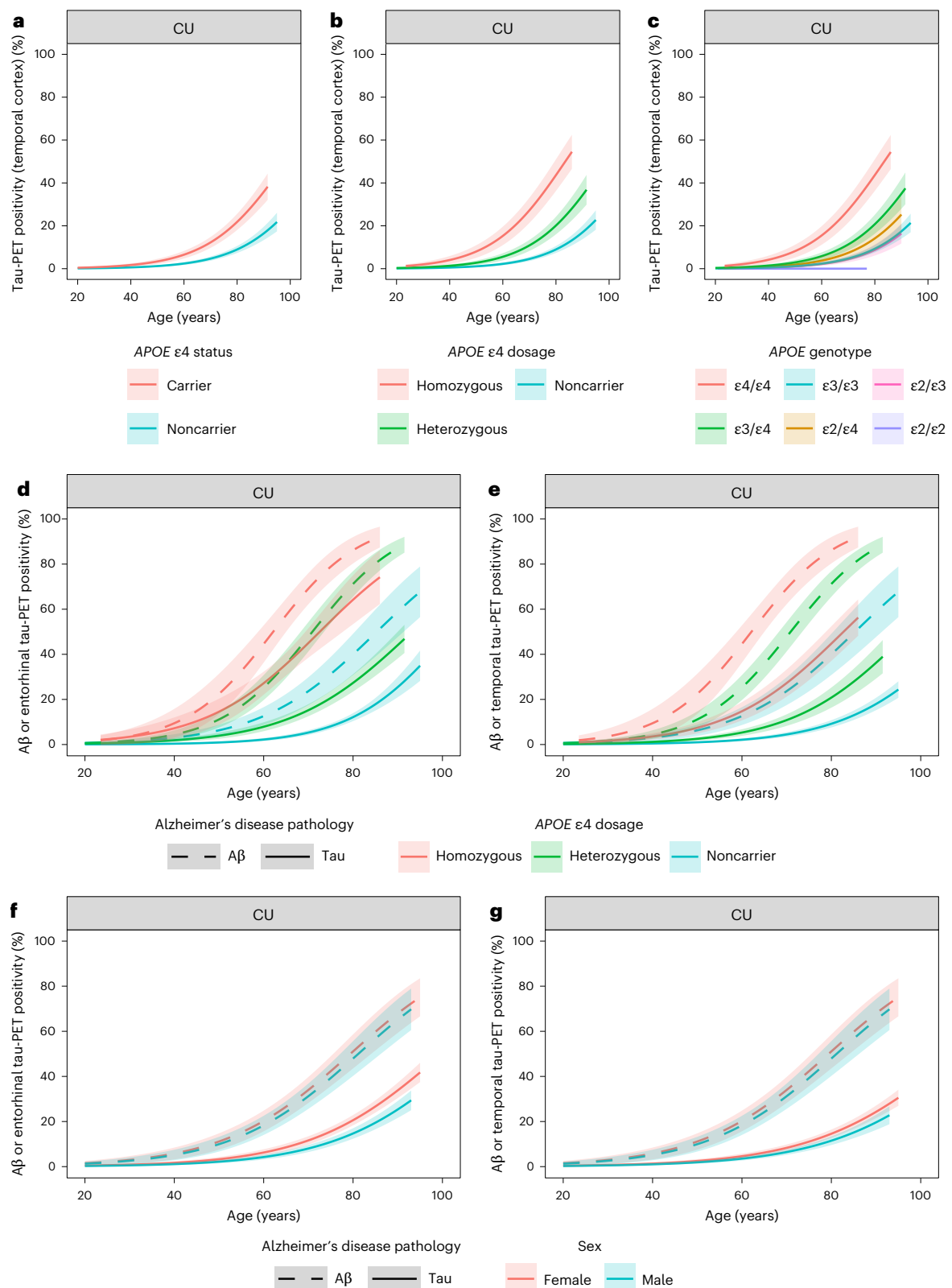


Fig. 2 | Prevalence estimates of tau PET and A β positivity by age, APOE and sex in CU individuals. a–c. The models including age and APOE $\epsilon 4$ status (a, $n = 6,476$), APOE $\epsilon 4$ dosage (b, $n = 6,288$) or APOE genotype (c, $n = 5,963$). **d,e.** The models including age and APOE $\epsilon 4$ dosage, with an additional interaction term between age and APOE $\epsilon 4$ dosage in the model estimating the prevalence of A β positivity ($n = 6,184$). **f,g.** The models including age and sex ($n = 7,173$). For the models presented in **d–g**, we included only individuals who had both A β status and entorhinal tau PET status and/or temporal cortex tau PET status available. Separate models were performed for estimating the prevalence of A β positivity

and tau positivity. Note that **d** and **f** depict A β positivity or tau PET positivity in the entorhinal cortex, whereas **e** and **g** depict A β positivity or tau PET positivity in the temporal cortex. In **a–c**, the y axes reflect estimated probabilities of tau PET positivity (prevalence estimates) generated from GEEs. In **d–g**, the y axes reflect estimated probabilities of A β positivity or tau PET positivity (prevalence estimates) generated from GEEs. Shaded areas indicate the 95% CIs. In **c**, none of the participants with APOE $\epsilon 2/\epsilon 2$ were tau positive, hence no 95% CI was provided for this group.

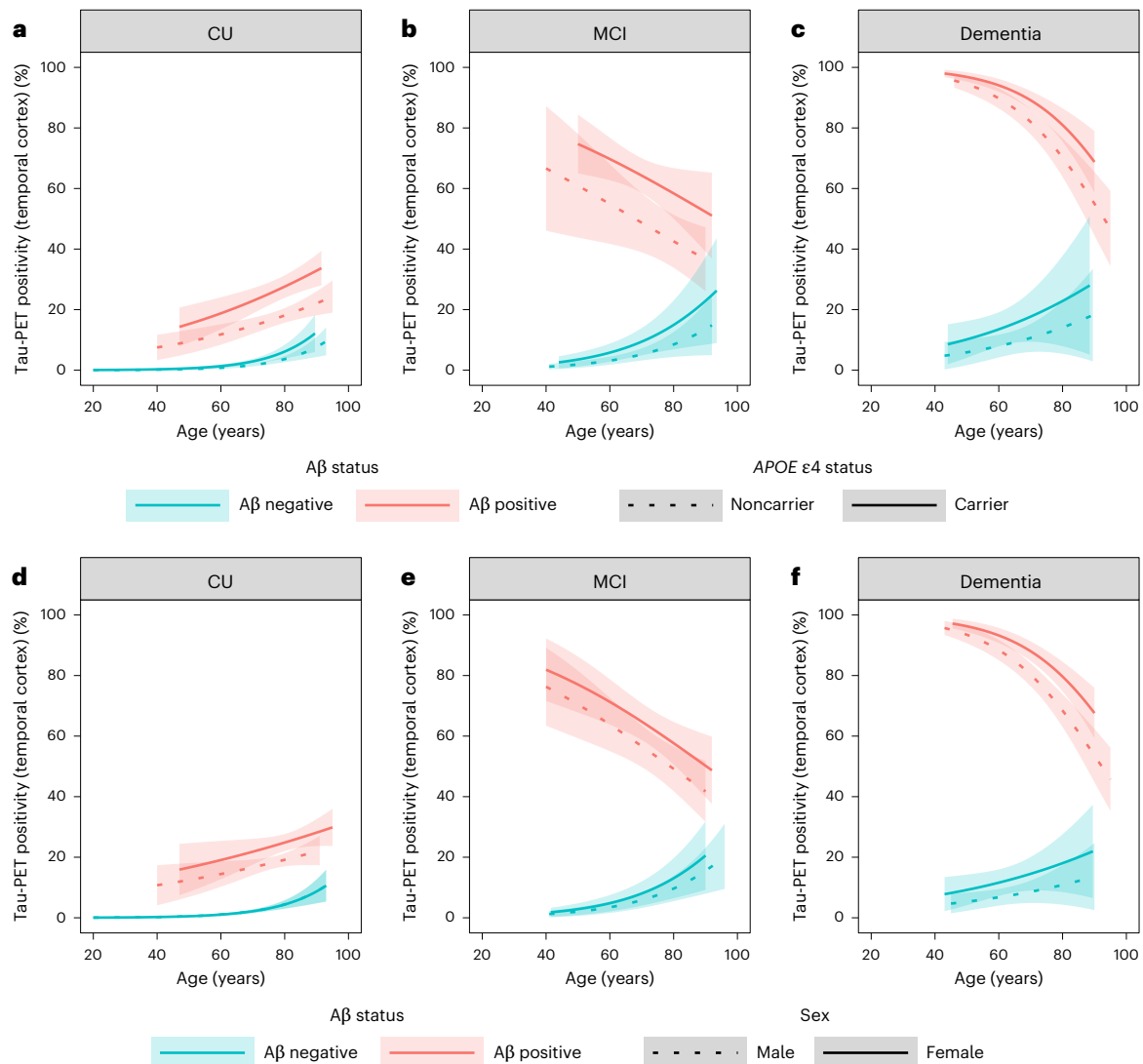


Fig. 3 | Tau PET positivity in association with age, A β status, APOE ϵ 4 status and sex. **a–c**, Models including age, A β status, APOE ϵ 4 status and an interaction between age and A β status for CU (**a**), MCI (**b**) and dementia (**c**). **d,e**, Models including age, A β status, sex and interaction terms between age and A β status (**d**) and between sex and A β status (**e**). **f**, Models including age, A β status, sex and an interaction term between age and A β status. Models were stratified

for CU (**a** ($n = 6,384$) and **d** ($n = 7,185$)), MCI (**b** ($n = 1,823$) and **e** ($n = 2,121$)) and dementia (**c** ($n = 1,869$) and **f** ($n = 2,252$)) participants. The y axes reflect estimated probabilities of tau PET positivity in the temporal cortex (prevalence estimates) from GEEs. Shaded areas indicate the 95% CIs. Note that in **d**, the estimated probabilities and 95% CIs for the A β -negative men and A β -negative women are fully overlapping.

cortex were higher in A β -positive APOE ϵ 4 carriers compared with A β -positive APOE ϵ 4 noncarriers in CU individuals (mean difference 8.4% (95% CI 3.0–13.8%), $P < 0.001$), individuals with MCI (mean difference 15.6% (95% CI 4.7–26.5%), $P = 0.001$) and those with dementia (mean difference 7.5% (95% CI 3.1–11.9%), $P < 0.001$).

Tau positivity according to age, sex and A β status

In line with the previous section, we simultaneously modeled age, A β status and sex as predictors of tau positivity. There was a significant interaction between sex and A β status on the prevalence of tau positivity in the temporal cortex for CU ($\beta = 0.34$, $P = 0.02$) participants, indicating that, in the presence of A β pathology, CU women showed a higher prevalence of tau positivity than men (Fig. 3d,e and Supplementary Table 7). The interaction between sex and A β status on the prevalence of tau positivity was not significant in the MCI and dementia groups, but there were significant main effects of sex on tau positivity in the MCI ($\beta = 0.34$, $P < 0.001$) and dementia ($\beta = 0.59$, $P < 0.001$) groups (Fig. 3f and Supplementary Table 7). At the median age of 71 years,

the prevalence estimates of tau positivity in the temporal cortex were higher in A β -positive women compared with A β -positive CU men (mean difference 5.2% (95% CI 1.7–8.8%), $P = 0.001$), MCI (mean difference 8.2% (95% CI 2.1–14.3%), $P = 0.003$) and dementia (mean difference 8.1% (95% CI 4.6–11.6%), $P < 0.001$).

Tau positivity using tau PET versus postmortem examination

Although neuropathological studies have shown that the vast majority of older individuals harbor some degree of tau tangle pathology in the temporal cortex, antemortem tau PET versus postmortem comparisons indicated that tau PET scans typically become positive when tau tangle pathology is observed in the Braak V–VI regions^{18,24–28}. Although prevalence estimates of tau positivity were generally higher when assessed using tau PET (temporal cortex) compared with neuropathology, we found comparable effects of age and A β status on tau positivity in autopsy versus PET datasets (Fig. 4). In line with the tau PET results, from age 60 years to age 80 years the estimated prevalence of neuropathologically defined Braak stages V–VI increased from 0.0% (95% CI

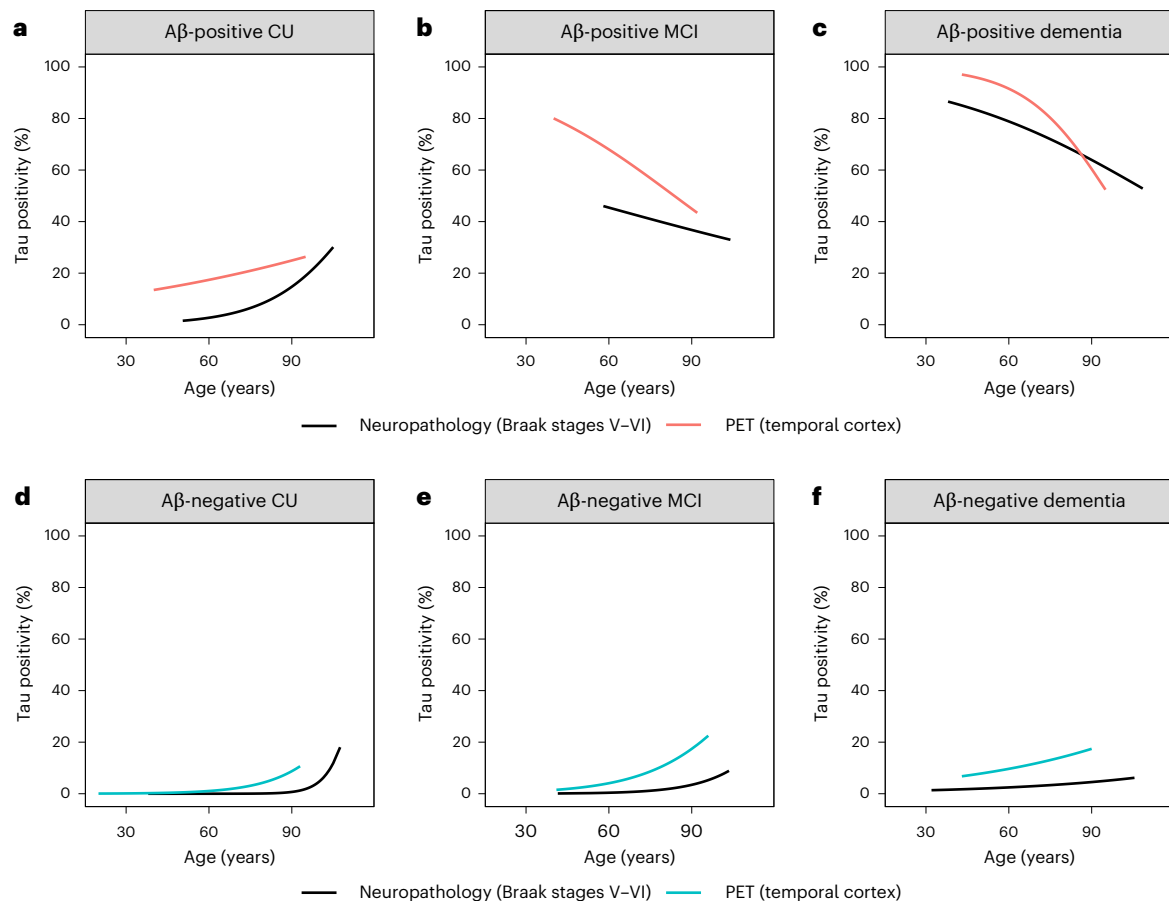


Fig. 4 | Prevalence of tau positivity on PET (temporal cortex) versus neuropathological examination (Braak V–VI). **a–f**, Tau positivity on PET or neuropathology in Aβ-positive (**a**) and Aβ-negative (**d**) CU individuals and Aβ-positive (**b**) and Aβ-negative (**e**) participants with MCI and Aβ-positive (**c**) and Aβ-negative dementia (**f**), modeled using age, Aβ status and an interaction between age and Aβ status as determinants. The models were stratified by

syndrome diagnosis. The y axes reflect estimated probabilities of tau positivity on PET (temporal cortex) or neuropathology (Braak V–VI) (prevalence estimates) generated from GEEs. Prevalence estimates for PET are based on 7,186 CU, 2,121 MCI and 2,252 dementia participants. Prevalence estimates for neuropathology are based on 1,026 CU, 661 MCI and 3,385 dementia participants.

0.0–0.0%) to 0.1% (95% CI 0.0–0.3%) among Aβ-negative CU participants and from 2.6% (95% CI 0.0–7.9%) to 8.6% (95% CI 0.2–16.9%) among Aβ-positive CU participants (Fig. 4a,d and Supplementary Table 8). Among Aβ-negative participants with MCI and dementia, from age 60 years to 80 years, the estimated prevalence of Braak stages V–VI increased from 0.4% (95% CI 0.1–0.6%) to 1.7% (95% CI 1.3–2.1%) in MCI and from 2.4% (95% CI 0.0–9.5%) to 3.7% (95% CI 0.0–8.5%) in dementia (Fig. 4e,f and Supplementary Table 8). In contrast, among Aβ-positive participants with MCI and dementia, from age 60 years to 80 years, the estimated prevalence of Braak stages V–VI decreased from 45.6% (95% CI 0.0–98.0%) to 39.6% (95% CI 13.4–65.8%) in MCI and from 78.9% (95% CI 71.2–86.5%) to 69.4% (95% CI 61.1–77.8%) in dementia (Fig. 4b,c and Supplementary Table 8). A sensitivity analysis comparing tau positivity in neuropathologically defined Braak stages V–VI with tau PET positivity in a whole-brain ROI showed comparable results, although in Aβ-positive CU, the prevalence of tau PET positivity decreased with advancing age as opposed to postmortem Braak V–VI regions and tau PET positivity in the temporal cortex (Fig. 4a and Supplementary Fig. 5).

Discussion

This large multicenter study aimed to estimate the prevalence of tau pathology as measured by PET as a function of Aβ status, age, *APOE* genotype and sex in CU individuals, individuals with MCI and individuals with dementia. Age and Aβ status showed the strongest associations with tau positivity. We found that age was positively associated with

tau positivity in CU (irrespective of Aβ status) and showed a negative relationship with tau positivity in Aβ-positive individuals with MCI and Aβ-positive individuals with all-cause dementia. *APOE* ε4 carrier-ship and female sex were associated with a higher prevalence of tau positivity across diagnostic groups. *APOE* ε4 carrier-ship in CU individuals was associated with a lower age at onset of both Aβ positivity and tau positivity by decades in a dose-dependent fashion. Finally, the observed associations between age and Aβ status with tau pathology, as measured by PET, were validated in an independent autopsy dataset. Altogether, our study provides robust prevalence estimates of tau PET positivity across syndrome diagnoses and biomarker profiles, which can aid the interpretation of tau PET in the clinic and inform prevention studies and clinical trial designs.

One of the key findings of the present study is that carrying an *APOE* ε4 allele was associated with a lower age at onset of both Aβ positivity and tau positivity in CU individuals by decades in a dose-dependent fashion^{5,6,29}. This shift is so pronounced that individuals with the *APOE* ε4/ε4 genotype exhibit tau PET positivity in the entorhinal cortex at a younger average age than *APOE* ε4 noncarriers become Aβ positive. To exemplify, the estimated ages at which 10% of CU *APOE* ε4/ε4 individuals show Aβ positivity (global) versus tau positivity (entorhinal cortex and temporal cortex) are 41, 45 and 55 years, respectively. In contrast, these estimated ages are 57, 78 and 81 years, respectively, for CU *APOE* ε4 noncarriers. Another key correlate of tau positivity in CU was Aβ status, because only 2.1% of Aβ-negative CU individuals were tau PET

positive in the temporal cortex, whereas the prevalence was ~10-fold higher in A β -positive CU individuals. Also, the prevalence of entorhinal tau positivity was higher compared with the temporal tau positivity, which is in line with established neuropathological and PET-based staging schemes proposing this topography of tau progression^{27,30,31}. Collectively, these data support a model where A β pathology triggers the spread of tau pathology from the medial temporal lobe to the neocortex, which is a critical harbinger of neurodegeneration and cognitive impairment in the near future^{32,33}.

Age was also strongly associated with an increased prevalence of tau positivity in the entorhinal cortex and the temporal cortex in CU individuals, even among individuals who were A β negative. The latter can be explained by A β -independent tau accumulation (for example, primary age-related tauopathy (PART)), off-target binding of tau PET tracers (for example, to monoamine oxidase B, neuromelanin, iron accumulation and/or microhemorrhages, which all become more pronounced with advancing age), increased false-negative A β status and/or false-positive tau PET scans, partial volume effects resulting from atrophy or an atypical neurobiological phenotype (for example, a tau-first subtype)^{34–39}. Among A β -positive CU individuals, contrary to entorhinal and temporal cortex tau positivity, tau positivity in the whole-brain ROI decreased in older age. This observation might be explained by a survival effect or a potentially increased susceptibility, in older participants, to the downstream neurotoxic effects of widespread tau pathology, for example, through less efficient compensatory neuronal mechanisms with age⁴⁰. This reduced resilience might render older individuals more vulnerable to developing cognitive symptoms when tau aggregates are present in the neocortex, resulting in progression from CU to MCI or dementia at lower global levels of tau pathology. Consequently, a decrease of whole-brain tau positivity is observed in the CU group at older age. Longitudinal studies are essential to formally test the above proposed hypotheses.

At symptomatic AD stages (that is, A β -positive MCI and dementia), age was negatively associated with the prevalence of tau positivity in the entorhinal cortex, temporal cortex and whole-brain ROI. This finding is consistent with previous observations from both neuropathological and tau PET studies and this pattern has also been firmly established for A β pathology^{29,41,42}. This observation can be explained in at least four distinct but not mutually exclusive ways. First, older individuals are more prone to co-occurring neuropathology like α -synuclein, TDP-43 or vascular injury⁴³. According to the 'double-hit' hypothesis, even at lower (subthreshold) levels of tau pathology, this cumulative pathological burden may be sufficient to cause an MCI or dementia syndrome. Second, related to the above, decreased resilience to tau pathology with advanced age may lead to cognitive impairment at lower levels of tau pathological burden⁴⁴. Third, individuals with advanced AD pathology in addition to substantial comorbid pathology are probably too cognitively impaired to participate in research studies and were thus potentially not included in our analyses. Fourth, misfolded tau proteins may spread or amplify faster in younger individuals with higher degrees of functional connectivity⁴⁵. Also, younger individuals may be more susceptible to early deposition of tau pathology in hub network regions, which further accelerates the rate of tau accumulation⁴⁶.

In CU individuals, we observed a lower age at onset for women relative to men for tau positivity in the entorhinal cortex and, more subtly, for A β positivity and tau positivity in the temporal cortex. Furthermore, in the CU group, we found that female sex was associated with a higher prevalence of temporal cortex tau positivity in the presence of A β pathology. This observation is in line with previous literature showing that clinical as well as biological AD are more common in women than in men: women exhibit a greater tau burden (particularly in the entorhinal cortex) at similar levels of A β pathology and A β -positive women show faster tau accumulation over time compared with A β -positive men^{45,47,48}. Mechanisms relating to biological sex or social implications of gender could contribute to this difference, including (premature or

early) menopause, late initiation of hormone therapy, differences in depression rates and educational attainment, as well as sex-specific innate and adaptive immune responses, synapse biology, mitochondrial functioning, neurotrophic factors and epigenetic alterations^{49,50}.

An indirect comparison between tau positivity defined using PET in the temporal cortex versus neuropathological Braak stages V–VI showed similar associations with age and A β status across syndrome diagnostic groups. As a potential consequence of selecting advanced Braak stages as the primary neuropathological outcome measure in our study, the PET-based prevalence estimates were generally higher, particularly for A β -negative participants. This was still the case when we assessed a whole-brain ROI versus postmortem Braak stages V–VI. This may be related to differences in how the two modalities measure A β and tau pathology (for example, varying sensitivity and detection thresholds), differences in participants enrolled in PET versus autopsy studies or modality-specific measurement errors (for example, off-target binding in PET). There have been relatively few direct antemortem PET versus postmortem neuropathology comparison studies to date. Most of these showed a good correlation between tau PET signal and neuropathological Braak stages, and this correlation is further strengthened when, rather than the rather crude Braak staging, a more quantitative measure of postmortem tau pathology was used, such as the percentage of tissue stained by AT8 immunohistochemistry^{18,25,51}. More multimodal studies are needed to better understand the overlap and differences between tau pathology as detected by PET versus at neuropathological examination, preferably assessed in the same individuals.

The main strength of this work is the large sample size ($N = 12,048$ for the PET sample and an additional $n = 5,072$ for postmortem validation) which allowed sufficient statistical power to provide robust prevalence estimates of tau PET positivity as a function of A β pathology and other individual risk factors for AD-type dementia such as age, *APOE* genotype and sex. Several limitations need to be considered when interpreting the present study. First, even though we include a global sample, generalizability is still limited because participants were, overall, highly educated (~14 years), mainly non-Hispanic white (79.5% of individuals had available data on race or ethnicity) and there were relatively few individuals aged >80 years, although this age range represents the largest segment of individuals with dementia in the community. Furthermore, data on race and/or ethnicity were available in only 54.6% of participants, which, combined with the overrepresentation of non-Hispanic white individuals, did not provide sufficient statistical power for conducting stratified analyses. Second, we pooled data from many cohorts. Although we used study-specific thresholds in the primary analyses and accounted for study effects within our statistical models, this may still have resulted in reduced internal validity as a result of differences in study designs. Third, owing to the absence of histopathological data in participants with tau PET (this was compared only in independent datasets), the present study lacked a gold standard. Fourth, we pooled data from four tau PET tracers that share similar properties but also show differences in tracer kinetics, selectivity and affinity, as well as differences in the degree and type of off-target binding patterns. Efforts are ongoing to harmonize tau PET data across tracers along common scales such as CenTauR⁵² or unit (that is, equivalent to the Centiloid approach for amyloid-PET⁵³), which will improve future multicenter studies and trials that include tau PET. Fifth, there is no broad consensus on the most optimal way of operationalizing tau PET positivity quantitatively⁵⁴. We acknowledge that several of our methodological decisions have impacted the reported prevalence estimates. In line with previous work¹⁹ we focused on AD-specific regions, which has potentially resulted in an underestimation of tau PET positivity in primary tauopathies characterized by differential tau patterns⁵⁵. Also, we used the mean + 2 s.d. in A β -negative CU individuals aged >50 years as a threshold, whereas more liberal (for example, mean + 1.5 s.d.) or conservative (for example, mean + 2.5 s.d.) approaches could be considered for detecting early stage versus later-stage tau pathology⁵⁶,

respectively. Cohort-specific selection of reference regions, brain atlases and processing methods also all influence tau PET quantification. We have partially addressed these potential confounding factors by adjusting all statistical analyses for cohort and validating the main results using an alternative threshold method (that is, Gaussian mixture modeling or lower thresholds). However, some residual variability and imprecision probably remain. Sixth, although, to our knowledge, this is one of the largest tau PET studies to date, the sample size for some specific subgroup analyses was relatively small and resulted in wide CIs. In particular, the prevalence estimates associated with age and *APOE* genotype in MCI and dementia at the lower and higher age extremes should be interpreted with caution.

In conclusion, among people with and without cognitive impairment, the prevalence of tau pathology as determined by PET imaging was associated with A β status, age, sex and *APOE* genotype. Our findings support the clinical utility of tau PET for differential diagnosis and inform trial designs that utilize tau PET for participant selection and stratification. In terms of future directions, it will be important to (1) compare the tau PET prevalence estimates against biofluid (cerebrospinal fluid or plasma) markers of soluble tau pathology such as p-tau217 or MTBR-243 (refs. 57,58), (2) conduct a similar study with adjusted ROIs in other populations such as primary tauopathies (for example, globus pallidus in PSP⁵⁵) or atypical variants of AD (for example, occipital cortex in posterior cortical atrophy⁴¹), (3) assess genetic effects beyond *APOE* genotype on tau PET prevalence⁵⁹ and (4) repeat the current analyses once approaches of harmonization across different tau PET tracers are more advanced.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41593-025-02000-6>.

References

- Gustavsson, A. et al. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimers Dement.* **19**, 658–670 (2023).
- Klunk, W. E. et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann. Neurol.* **55**, 306–319 (2004).
- Chien, D. T. et al. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *J. Alzheimers Dis.* **34**, 457–468 (2013).
- Jack, C. R. Jr. & Holtzman, D. M. Biomarker modeling of Alzheimer's disease. *Neuron* **80**, 1347–1358 (2013).
- Jansen, W. J. et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA* **313**, 1924–1938 (2015).
- Fortea, J. et al. APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. *Nat. Med.* **30**, 1284–1291 (2024).
- Donohue, M. C. et al. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. *JAMA* **317**, 2305–2316 (2017).
- Nelson, P. T. et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J. Neuropathol. Exp. Neurol.* **71**, 362–381 (2012).
- Sims, J. R. et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA* **330**, 512–527 (2023).
- van Dyck, C. H. et al. Lecanemab in early Alzheimer's disease. *N. Engl. J. Med.* **388**, 9–21 (2023).
- La Joie, R. et al. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Sci. Transl. Med.* **12**, eaau5732 (2020).
- Ossenkoppele, R. et al. 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. *JAMA Neurol.* **78**, 961–971 (2021).
- Ossenkoppele, R. et al. Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. *Nat. Med.* **28**, 2381–2387 (2022).
- Strikwerda-Brown, C. et al. Association of elevated amyloid and tau positron emission tomography signal with near-term development of Alzheimer disease symptoms in older adults without cognitive impairment. *JAMA Neurol.* **79**, 975–985 (2022).
- Ossenkoppele, R., van der Kant, R. & Hansson, O. Tau biomarkers in Alzheimer's disease: towards implementation in clinical practice and trials. *Lancet Neurol.* **21**, 726–734 (2022).
- Jack, C. R. Jr. et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement.* **20**, 5143–5169 (2024).
- Dubois, B. et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol.* **20**, 484–496 (2021).
- Fleisher, A. S. et al. Positron emission tomography imaging with [¹⁸F]flortaucipir and postmortem assessment of Alzheimer disease neuropathologic changes. *JAMA Neurol.* **77**, 829–839 (2020).
- Ossenkoppele, R. et al. Discriminative accuracy of [¹⁸F]flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. *JAMA* **320**, 1151–1162 (2018).
- Pascoal, T. A. et al. 18F-MK-6240 PET for early and late detection of neurofibrillary tangles. *Brain* **143**, 2818–2830 (2020).
- Edwards, A. L. et al. Exploratory tau biomarker results from a multiple ascending-dose study of B1B080 in Alzheimer disease: a randomized clinical trial. *JAMA Neurol.* **80**, 1344–1352 (2023).
- Teng, E. et al. Safety and efficacy of semorinemab in individuals with prodromal to mild Alzheimer disease: a randomized clinical trial. *JAMA Neurol.* **79**, 758–767 (2022).
- Montine, T. J. et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol.* **123**, 1–11 (2012).
- Josephs, K. A. et al. Flortaucipir PET uncovers relationships between tau and amyloid-beta in primary age-related tauopathy and Alzheimer's disease. *Sci. Transl. Med.* **16**, eado8076 (2024).
- Lowe, V. J. et al. Tau-positron emission tomography correlates with neuropathology findings. *Alzheimers Dement.* **16**, 561–571 (2020).
- Soleimani-Meigooni, D. N. et al. 18F-flortaucipir PET to autopsy comparisons in Alzheimer's disease and other neurodegenerative diseases. *Brain* **143**, 3477–3494 (2020).
- Braak, H. & Braak, E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* **82**, 239–259 (1991).
- Tsartsalis, S., Xekardaki, A., Hof, P. R., Kovari, E. & Bouras, C. Early Alzheimer-type lesions in cognitively normal subjects. *Neurobiol. Aging* **62**, 34–44 (2018).
- Ossenkoppele, R. et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA* **313**, 1939–1949 (2015).
- Scholl, M. et al. PET imaging of tau deposition in the aging human brain. *Neuron* **89**, 971–982 (2016).
- Therriault, J. et al. Biomarker modeling of Alzheimer's disease using PET-based Braak staging. *Nat. Aging* **2**, 526–535 (2022).
- Johnson, K. A. et al. Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Ann. Neurol.* **79**, 110–119 (2016).
- Giorgio, J., Adams, J. N., Maass, A., Jagust, W. J. & Breakspear, M. Amyloid induced hyperexcitability in default mode network drives medial temporal hyperactivity and early tau accumulation. *Neuron* **112**, 676–686.e674 (2024).

34. Cray, J. F. et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol.* **128**, 755–766 (2014).
35. Krishnadas, N. et al. Exploring discordant low amyloid beta and high neocortical tau positron emission tomography cases. *Alzheimers Dement.* **14**, e12326 (2022).
36. Baker, S. L., Harrison, T. M., Maass, A., La Joie, R. & Jagust, W. J. Effect of off-target binding on ¹⁸F-flortaucipir variability in healthy controls across the life span. *J. Nucl. Med.* **60**, 1444–1451 (2019).
37. Aksman, L. M. et al. A data-driven study of Alzheimer's disease related amyloid and tau pathology progression. *Brain* **146**, 4935–4948 (2023).
38. Landau, S. M. et al. Individuals with Alzheimer's disease and low tau burden: characteristics and implications. *Alzheimers Dement.* **20**, 2113–2127 (2024).
39. Marquie, M. et al. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. *Ann. Neurol.* **78**, 787–800 (2015).
40. Kirkwood, T. B. Understanding the odd science of aging. *Cell* **120**, 437–447 (2005).
41. Chappelle, M. et al. Demographic, clinical, biomarker, and neuropathological correlates of posterior cortical atrophy: an international cohort study and individual participant data meta-analysis. *Lancet Neurol.* **23**, 168–177 (2024).
42. Beach, T. G. & Malek-Ahmadi, M. Alzheimer's disease neuropathological comorbidities are common in the younger-old. *J. Alzheimers Dis.* **79**, 389–400 (2021).
43. Karanth, S. et al. Prevalence and clinical phenotype of quadruple misfolded proteins in older adults. *JAMA Neurol.* **77**, 1299–1307 (2020).
44. Bocancea, D. I. et al. Determinants of cognitive and brain resilience to tau pathology: a longitudinal analysis. *Brain* **146**, 3719–3734 (2023).
45. Smith, R. et al. The accumulation rate of tau aggregates is higher in females and younger amyloid-positive subjects. *Brain* **143**, 3805–3815 (2020).
46. Frontzkowski, L. et al. Earlier Alzheimer's disease onset is associated with tau pathology in brain hub regions and facilitated tau spreading. *Nat. Commun.* **13**, 4899 (2022).
47. Buckley, R. F. et al. Sex differences in the association of global amyloid and regional tau deposition measured by positron emission tomography in clinically normal older adults. *JAMA Neurol.* **76**, 542–551 (2019).
48. Barnes, L. L. et al. Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch. Gen. Psychiatry* **62**, 685–691 (2005).
49. Ferretti, M. T. et al. Sex and gender differences in Alzheimer's disease: current challenges and implications for clinical practice: position paper of the Dementia and Cognitive Disorders Panel of the European Academy of Neurology. *Eur. J. Neurol.* **27**, 928–943 (2020).
50. Coughlan, G. T. et al. Association of age at menopause and hormone therapy use with tau and beta-amyloid positron emission tomography. *JAMA Neurol.* **80**, 462–473 (2023).
51. Pontecorvo, M. J. et al. Comparison of regional flortaucipir PET with quantitative tau immunohistochemistry in three subjects with Alzheimer's disease pathology: a clinicopathological study. *EJNMMI Res* **10**, 65 (2020).
52. Leuz, A. et al. Harmonizing tau positron emission tomography in Alzheimer's disease: the CenTauR scale and the joint propagation model. *Alzheimers Dement.* **20**, 5833–5848 (2024).
53. Klunk, W. E. et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement.* **11**, 1–15. e11–14 (2015).
54. Weigand, A. J., Maass, A., Eglit, G. L. & Bondi, M. W. What's the cut-point?: A systematic investigation of tau PET thresholding methods. *Alzheimers Res. Ther.* **14**, 49 (2022).
55. Brendel, M. et al. Assessment of 18F-PI-2620 as a biomarker in progressive supranuclear palsy. *JAMA Neurol.* **77**, 1408–1419 (2020).
56. Dore, V. et al. Relationship between amyloid and tau levels and its impact on tau spreading. *Eur. J. Nucl. Med. Mol. Imaging* **48**, 2225–2232 (2021).
57. Horie, K. et al. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. *Nat. Med.* **29**, 1954–1963 (2023).
58. Palmqvist, S. et al. Blood biomarkers to detect Alzheimer disease in primary care and secondary care. *JAMA* **332**, 1245–1257 (2024).
59. Stage, E. et al. Association of the top 20 Alzheimer's disease risk genes with [¹⁸F]flortaucipir PET. *Alzheimers Dement.* **14**, e12308 (2022).

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Mayo Clinic Study on Aging

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Methods

Written informed consent was obtained from all participants or their designated caregiver and all data collection protocols were approved by each cohort's respective institutional ethical review board. Data analysis protocols for this particular study were approved by the Ethics Committee of Lund University, Lund, Sweden, in accordance with the Declaration of Helsinki, and all methods were carried out in accordance with the approved guidelines.

Data collection and operationalization

We searched the MEDLINE and Web of Science databases for tau PET studies published before 15 November 2023. The search terms used were 'PET' and 'tau' in combination with the four most widely used tau PET tracers to date (that is, 'AV1451/flortaucipir/Tauvid', 'MK6240', 'RO948' or 'PI2620'). Based on titles and abstracts we identified 42 unique cohorts that had previously published tau PET data in peer-reviewed journals. These cohorts represented a mix of secondary and tertiary care research studies, population-based studies and the placebo arm of a clinical trial. We approached study contact people to request participant-level data: 38 cohorts accepted and 4 declined; 4 additional cohorts (that is, Barcelona Beta, UCL, Gothenburg University and the Chinese Preclinical Alzheimer's disease Study) provided currently unpublished tau PET data, totaling participant-level data from 42 cohorts for analysis. Tau PET data were shared through transfer of raw PET images to be centrally processed at Lund University in line with previous procedures (16 cohorts, $n = 4,296$)¹⁹ or transfer of spreadsheets containing regional standardized uptake value (SUVR) data (26 cohorts, $n = 7,752$). In addition, data were shared regarding clinical diagnosis (42 cohorts), A β status (41 cohorts), A β modality (39 cohorts), PET (938 cohorts) and/or cerebrospinal fluid (CSF) (10 cohorts), age (42 cohorts), sex (42 cohorts), education (36 cohorts), race or ethnicity (21 cohorts), *APOE* $\epsilon 4$ status (38 cohorts), *APOE* genotype (35 cohorts) and Mini-Mental State Examination (MMSE) score (42 cohorts). Cohort-specific methods for defining A β status are presented in Supplementary Table 9. We excluded participants with missing tau PET SUVR in the temporal cortex ($n = 8$), missing syndrome diagnosis ($n = 234$) and genetic mutations associated with dementia ($n = 8$) and participants with MCI or dementia who were aged <40 years ($n = 7$).

Participants

Informed consent was obtained from all participants or their assigned surrogate decision-makers and the institutional review boards for human research of the participating centers approved all studies. CU individuals performed cognitive testing within normal limits and did not exhibit any major psychiatric disorder⁶⁰. MCI was defined according to published criteria^{61,62}. These criteria include a decline in memory or another cognitive domain reported by the patient, informant or both, that is, objectively verified by neuropsychological testing, in combination with no or minimal impairment in activities of daily living and not meeting criteria for dementia. Patients with a syndromic dementia diagnosis met diagnostic criteria for AD-type dementia⁶³ ($n = 1,804$) or non-AD neurodegenerative disorders including FTD ($n = 162$, that is, behavioral variant FTD and the semantic and nonfluent variants of primary progressive aphasia combined), PSP ($n = 141$), CBS ($n = 101$), DLB ($n = 76$), PDD ($n = 39$), VaD ($n = 32$) and dementia-not otherwise specified (NOS) ($n = 122$). Note that we reported results for 'all-cause dementia' (that is, all types of dementia combined) in the main text, whereas results for the specific dementia types are reported in Extended Data Fig. 1 and Supplementary Information. In addition, we repeated the main analyses presented in Figs. 1 and 3 specifically for individuals clinically diagnosed with AD-type dementia (Extended Data Fig. 2 and Extended Data Table 4). In addition, for an (indirect) comparison between tau-positivity rates derived from tau PET versus neuropathological examination, we included 5,072 participants from 3 autopsy cohorts (that is, the National Alzheimer's Coordinating

Center database (NACC, $n = 1,638$)⁶⁴, the Religious Orders Studies and Rush Memory and Aging Project (ROSMAP, $n = 1,941$)⁶⁵ and the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND)/Brain and Body Donation Program (AZSAND/BBDP, $n = 1,672$)⁶⁶. The combined autopsy dataset consisted of 1,026 CU individuals, 661 individuals with MCI and 3,385 with dementia (Extended Data Table 1). In line with previous work²⁹, participants who met the Consortium to Establish a Registry for Alzheimer's Disease criteria (CERAD)⁶⁷ for definite, probable or possible AD (indicating the presence of moderate-to-frequent neuritic plaques) were considered A β positive. Based on previous results of antemortem tau PET versus postmortem examination in the same individuals, participants in Braak stage V–VI for neurofibrillary tangle pathology were considered tau positive^{18,24–27}. We compared the prevalence of postmortem Braak stage V–VI against tau PET positivity in the temporal cortex (Fig. 4) and a whole-brain ROI (Supplementary Fig. 5). Participants with missing antemortem diagnosis, age, CERAD score or Braak stage were excluded from the autopsy dataset.

Tau PET procedures

[¹⁸F]Flortaucipir was used in most patients ($n = 6,480$, 25 cohorts), followed by [¹⁸F]MK6240 ($n = 3,156$, 11 cohorts), [¹⁸F]RO948 ($n = 1,984$, 3 cohorts) and [¹⁸F]PI2620 ($n = 428$, 4 cohorts). Cohort-specific information on tau PET tracers, scanning procedures and data processing can be found in Supplementary Table 10. For the primary analysis, we focused on a composite temporal meta-ROI (referred to as 'temporal cortex' throughout the text for readability purposes), consisting of the entorhinal cortex, amygdala, parahippocampus, fusiform gyrus and inferior and middle temporal cortices⁶⁸. In addition, we determined tau PET positivity in the entorhinal cortex (missing for $n = 35$) and in a whole-brain ROI (missing for $n = 2$; see Supplementary Table 11 for cohort-specific ROI compositions). Tau PET scans were dichotomized (positive or negative) using quantitative thresholds. For the primary analyses, we defined the cut-off based on cohort-specific thresholds calculated as the mean + 2 s.d. in A β -negative CU individuals aged >50 years from the same cohort (see Supplementary Table 12 for cohort-specific thresholds). In sensitivity analyses, we also showed the results when determining the threshold based on the mean + 1 s.d. and 1.5 s.d. in A β -negative CU individuals aged >50 years from the same cohort (Extended Data Fig. 3). Furthermore, we defined the cut-off based on tracer-specific Gaussian mixture modeling ([¹⁸F]flortaucipir: SUVR = 1.40; [¹⁸F]MK6240: SUVR = 1.43; [¹⁸F]RO948: SUVR = 1.41; [¹⁸F]PI2620: SUVR = 1.41 in the temporal cortex; see Supplementary Table 12 for tracer-specific thresholds for the entorhinal and whole-brain ROIs).

Statistical analysis

Baseline characteristics were compared using analysis of variance (ANOVA) and Fisher's exact tests, where appropriate. GEEs were used to estimate probabilities of tau PET positivity. GEEs were selected because they allowed the modeling of subject-level data from all studies simultaneously while accounting for the clustering of participants within studies. Furthermore, GEEs provided population-averaged estimates (that is, coefficients representing the average effect on tau PET positivity across the dataset population) as opposed to subject-specific estimates, where coefficients represented the effect on tau PET positivity for the average individual in the dataset. We assumed a logit link function for binary outcomes with an exchangeable correlation structure to account for within-study correlations related to, for example, site-specific PET scanners and study populations. All data were visually inspected and data distribution was assumed to be normal, but this was not formally tested. The main analyses were performed stratified for syndrome diagnosis and included A β status (\pm), age, sex and/or *APOE* $\epsilon 4$ status (\pm) as independent variables. Age was entered as a continuous measure centered at the median (that is, 71 years). We tested two-way and three-way interactions between variables and these terms were retained in the model if

they appeared significant by Wald's statistic (indicated in table footnotes and figure legends). We used estimated probabilities and 95% CIs from the GEE analyses in tables and figures. These GEE-estimated probabilities were compared with observed probabilities to determine the goodness of fit between GEE-estimated and actual data and these comparisons are presented in Supplementary Table 3. In addition, we modeled A β positivity and tau PET positivity as a function of age and *APOE* ϵ 4 dose (that is, homozygous versus heterozygous versus noncarrier) and as a function of age and sex, and we compared the estimated tau-positivity prevalence as determined in tau PET versus postmortem datasets. The significance level was set at $\alpha = 0.05$ and the analyses were performed using R v.4.2.1.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

As a result of the multicenter design of the study, individual participant data from each cohort will have to be made available through the principal investigators of the respective cohorts. Generally, anonymized data can be shared by request from qualified academic investigators for the purpose of replicating procedures and results presented in the Article, if the data transfer is in agreement with the data protection regulation at the institution and approved by the local ethics review board.

Code availability

The codes used for data collection in our study were implemented in R v.4.2.1 and can be requested from the corresponding authors (R.O. or O.H.). The codes used for data analysis were implemented in R v.4.2.1 and are available via GitHub at <https://github.com/OssenKoppeLab>.

References

60. Sperling, R. A. et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging—Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* **7**, 280–292 (2011).
61. Petersen, R. C. Mild cognitive impairment as a diagnostic entity. *J. Intern Med* **256**, 183–194 (2004).
62. Albert, M. S. 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. *Alzheimers Dement.* **7**, 270–279 (2011).
63. McKhann, G. M. et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging—Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* **7**, 263–269 (2011).
64. Beekly, D. L. et al. The National Alzheimer's Coordinating Center (NACC) database: an Alzheimer disease database. *Alzheimer Dis. Assoc. Disord.* **18**, 270–277 (2004).
65. Bennett, D. A. et al. Religious orders study and rush memory and aging project. *J. Alzheimers Dis.* **64**, S161–S189 (2018).
66. Beach, T. G. et al. Arizona study of aging and neurodegenerative disorders and brain and body donation program. *Neuropathology* **35**, 354–389 (2015).
67. Mirra, S. S. et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* **41**, 479–486 (1991).
68. Jack, C. R. Jr. et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement.* **13**, 205–216 (2017).

Acknowledgements

The present study was directly supported by the European Research Council (ERC; no. 949570, to R.O.), Stichting Dioraphte, Alzheimer Nederland (nos. WE.03-2024-03 and WE.15-2022-04 to E.C. and WE.03-2024-06 to C.G.) and ZonMW (project no. 10510022110010 to C.G.). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. We thank all participants in the study and their family members for their dedication to research and for allowing us to perform this research. In addition, we would like to acknowledge the valuable contribution of several multicenter studies involved in this project: the Department of Defense Alzheimer's Disease Neuroimaging Initiative (ADNI-DOD; https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf) Australian Imaging, Biomarkers & Lifestyle (AIBL; <https://aibl.org.au/about/our-researchers>) study, the Longitudinal Early-onset Alzheimer's Disease Study (LEADS; <https://leads-study.medicine.iu.edu>) and the A4 study (<https://www.a4studydata.org>). Furthermore, we acknowledge the contributions of researchers and participants of the Harvard Aging Brain Study (HABS; <https://habs.mgh.harvard.edu>), the Berkeley Aging Cohort Study (BACS; <https://jagustlab.neuro.berkeley.edu/bacs>), the Mayo Clinic Study of Aging (MCSA; <https://www.mayo.edu/research/centers-programs/alzheimers-disease-research-center/research-activities/mayo-clinic-study-aging/overview>), the Alzheimer and Families (ALFA; <https://www.barcelonabeta.org/en/alfa-study/about-the-alfa-study>) study, the Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD; <https://openpreventad.loris.ca>) study and the Wisconsin Registry for Alzheimer's Prevention (WRAP; <https://wrap.wisc.edu>). Part of the data used in preparation of this Article was obtained from the ADNI database (<https://adni.loni.usc.edu>). 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. A complete listing of ADNI investigators can be found at https://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/policy/ADNI_Acknowledgement_List%205-29-18.pdf.

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R.O., E.C., C.G. and O.H. designed the study. R.O., E.C. and C.G. had full access to raw data and carried out the statistical analyses. R.O., E.C., C.G. and O.H. wrote the manuscript and had the final responsibility to submit for publication. All other authors contributed demographic, clinical, biomarker and neuroimaging data, contributed to the interpretation of the results and critically reviewed the manuscript.

Funding

Open access funding provided by Lund University.

Competing interests

R.O. received research support from Avid Radiopharmaceuticals, Janssen Research & Development, Roche, Quanterix and Optina Diagnostics. He has given lectures in symposia sponsored by GE Healthcare and serves on advisory boards and/or steering committees for Asceneuron, Biogen and Bristol Myers Squibb. All of the above is paid to his institutions. E.v.d.G. received research support from NWO, ZonMw, Hersenstichting, Alzheimer Nederland, Health-Holland and KWF. J.T. is funded by the Colin J. Adair Charitable Foundation fellowship. Funding for the TRIAD cohort comes from the Weston Brain Institute, Canadian Institutes of Health Research (CIHR) (grant nos. MOP-11-51-31; RFN 152985, 159815 and 162303), Canadian Consortium of Neurodegeneration and Aging (CCNA; grant no. MOP-11-51-31-team 1), the Alzheimer's Association (grant nos. NIRG-12-92090 and NIRP-12-259245), Brain Canada Foundation (CFI, project no. 34874, grant no. 33397), the Fonds de Recherche du Québec—Santé (FRQS; Chercheur Boursier, grant no. 2020-VICO-279314) and the Colin J. Adair Charitable Foundation. A.d.B. received research funding from

Alzheimer Association, Alzheimer Nederland, Stichting Dioraphte, Health Holland, Weston Brain Institute and Selfridges Group Foundation. A.J.S. receives support from multiple National Institutes of Health (NIH) grants. He has also received support from Avid Radiopharmaceuticals, a subsidiary of Eli Lilly (in kind contribution of PET-tracer precursor) and participated in scientific advisory boards (Bayer Oncology, Eisai, Novo Nordisk and Siemens Medical Solutions USA, Inc.) and an Observational Study Monitoring Board (MESA, NIH, National Heart, Lung, and Blood Institute), as well as external advisory committees for multiple National Institute on Aging (NIA) grants. He also serves as Editor-in-Chief of *Brain Imaging and Behavior*, a Springer Nature Journal. J.B.R. is supported by the Medical Research Council (MRC, grant nos. MC_UU_00030/14 and MR/T033371/1) and National Institute for Health and Care Research (NIHR) Cambridge Biomedical Research Centre (grant no. NIHR203312), the PSP Association and the Cambridge Centre for Parkinson-plus. M.M. is supported by Race Against Dementia Alzheimer's Research UK (grant no. ARUK-RADF2021A-010), NIHR Cambridge Biomedical Research Centre (grant no. NIHR203312) and the UK Dementia Research Institute through UK DRI Ltd, principally funded by the MRC. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. J.M.S. acknowledges the support of the NIHR University College London Hospitals Biomedical Research Centre, Wolfson Foundation, Alzheimer's Research UK, Brain Research UK, Weston Brain Institute, MRC, British Heart Foundation, UK Dementia Research Institute and Alzheimer's Association. J.M.S. received research funding and PET tracer from AVID Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly) and Alliance Medical, has consulted for Roche, Eli Lilly, Biogen, AVID, Merck and GE and is Chief Medical Officer for Alzheimer's Research UK. V.G. was funded from the Swiss National Science Foundation (project nos. 320030_169876 and 320030_185028), VELUX Foundation, Schmidheiny Foundation and Fondation Privée of the University Hospitals of Geneva. Research programs of W.M.v.d.F. have been funded by ZonMW, NWO, EU-JPND, EU-IHI, Alzheimer Nederland, Hersenstichting CardioVascular Onderzoek Nederland, Health-Holland, Topsector Life Sciences & Health, stichting Dioraphte, Gieskes-Strijbis fonds, stichting Equilibrio, Edwin Bouw fonds, Noaber foundation, Pieter Houbolt Fonds, Pasman stichting, stichting Alzheimer & Neuropsychiatrie Foundation, Philips, Biogen MA Inc, Novartis-NL, Life-MI, AVID, Roche BV, Fujifilm, Eisai and Combinostics. W.M.v.d.F. holds the Pasman chair and is recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (grant no. 73305095007) and Health-Holland, Topsector Life Sciences & Health (PPP-allowance; grant no. LSHM20106). She is a recipient of TAP-dementia (www.tap-dementia.nl), receiving funding from ZonMw (grant no. 10510032120003) in the context of Onderzoeksprogramma Dementie, part of the Dutch National Dementia Strategy. TAP-dementia receives co-financing from Avid Radiopharmaceuticals, Roche Diagnostics and Amprion. Gieskes-Strijbis Fonds also contributes to TAP-dementia. W.M.v.d.F. has been an invited speaker at Biogen MA Inc, Danone, Eisai, WebMD Neurology (Medscape), Novo Nordisk, Springer Healthcare and European Brain Council. She is a consultant to Oxford Health Policy Forum CIC, Roche, Biogen MA Inc. and Eisai, and participated in advisory boards of Biogen MA Inc., Roche, and Eli Lilly. W.M.v.d.F. is a member of the steering committee of EVOKE/EVOKE+ (Novo Nordisk). All funding is paid to her institution. She is member of the steering committee of PAVE and Think Brain Health. S.K. was financed by grants from the Swedish state under the agreement between the Swedish Government and the county councils, the ALF agreement (grant nos. ALFGBG-965923, ALFGBG-81392 and ALFGBG-771071). The Alzheimerfonden (grant nos. AF-842471, AF-737641, AF-929959 and AF-939825). The Swedish Research Council (grant nos. 2019-02075 and 2019-02075_15) and Stiftelsen Psykiatriska Forskningsfonden. S.P.

has acquired research support (for the institution) from ki elements/ADDF and Avid. In the past 2 years, he has received consultancy or speaker fees from Bioartec, Biogen, Eisai, Lilly and Roche. M.M. provides consultancy unrelated to the current work to Astex Pharmaceuticals. J.T. has served as a consultant for the Neurotorium educational platform and for Alzheon. P.R.-N. has served at scientific advisory boards and/or as a consultant for Roche, Novo Nordisk, Eisai and Cerveau Radiopharmaceuticals. C.C.R. has received research grants from National Health and Medical Research Council (NHMRC), Enigma Australia, Biogen, Eisai and Abbvie. He is on the scientific advisory board for Enigma/Mellieur Technologies and has consulted for Prothena, Eisai, Roche and Biogen Australia. S.C.J. has served in the past 2 years on advisory boards for Enigma Biomedical and ALZPath. K.V.L. has received research grants through KU Leuven from Biogen, BMS, Cerevel, CHDI, Janssen Pharmaceuticals, Lantheus/Cerveau, Lundbeck and Rapport. He is a member of the scientific advisory board for Enigma/Mellieur Technologies. V.G. received research support and speaker fees through her institution from GE Healthcare, Siemens Healthineers, Novo Nordisk, Janssen and Novartis. S.K. has served at scientific advisory boards, speaker and/or consultant for Roche, Eli Lilly, Geras Solutions, Optoceutics, Biogen and Bioartec. S.S., M.P. and I.K. are employees and minor shareholders of Eli Lilly and Co. A.D. received research support from Siemens Healthineers, Life Molecular Imaging, GE Healthcare, AVID Radiopharmaceuticals, Sofie, Eisai, Novartis/AAA and Ariceum Therapeutics. He received speaker or honorary fees and/or contributed to advisory boards for Siemens Healthineers, Sanofi, GE Healthcare, Biogen, Novo Nordisk, Invicro, Novartis/AAA, Bayer Vital, Lilly, Peer View Institute for Medical Education and the International Atomic Energy Agency. He holds stock from Siemens Healthineers, Lantheus Holding, Structured therapeutics, Lilly and a patent for 18F-JK-PSMA-7 (PSMA PET imaging tracer; patent no. EP3765097A1; date of patent: 20 January 2021). He has received national and international grants including DFG grants (nos. SFB 1451 C04 and DR 445/9-1) and serves as Associate Editor of the *Journal of Nuclear Medicine*. L.A. received personal compensation for serving as a consultant for Biogen, Two Labs, Florida Department of Health, Genetech, NIH Biobank, Eli Lilly, GE Healthcare, Eisai and Roche Diagnostics and for serving on a Data Safety and Monitoring Board for IQVIA. L.A. receives research support from the National Institute on Aging, the Alzheimer's Association, Roche Diagnostics, AVID radiopharmaceuticals, Life Molecular Imaging and Eli Lilly. G.B.F. received funding through the Private Foundation of Geneva University Hospitals from: APRA (Association Suisse pour la Recherche sur la Maladie d'Alzheimer), Geneva; Fondation Segré, Geneva; Ivan Pictet, Geneva; Race Against Dementia Foundation, London, UK; Fondation Child Care, Geneva; Fondation Edmond J. Safra, Geneva; Fondation Minkoff, Geneva; Fondazione Agusta, Lugano; McCall Macbain Foundation, Canada; Nicole et René Keller, Geneva; Fondation AETAS, Geneva. He has also received funding through the University of Geneva or Geneva University Hospitals: for IISs from ROCHE Pharmaceuticals OM Pharma EISAI Pharmaceuticals Biogen Pharmaceuticals and Novo Nordisk; and funding for competitive research projects from: H2020, Innovative Medicines Initiative (IMI), IMI2, Swiss National Science Foundation and VELUX Foundation; consulting fees from: Biogen, Diadem and Roche; and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from: Biogen, Roche, Novo Nordisk and GE HealthCare. W.J.J. serves on data monitoring committees for Lilly, holds equity in Optoceutics and Molecular Medicine, receives research support from Biogen and grants from ZonMW, Alzheimer Nederland, St. Rinsum-Ponsen. A.M.B. has received payment for consulting or participation in advisory boards from Cognition Therapeutics, Cognito Therapeutics and CogState. He is a section editor for *Alzheimer's & Dementia*. J.O'B. has acted as a consultant for TauRx, Novo Nordisk, Biogen, Roche, Lilly, GE Healthcare and Okwin

and received grants or academic support from Avid/Lilly, Merck and Alliance Medical. J.A.L. received royalties from Spring for the book *Diabetes in the Brain*, a stipend from Wolters Kluwer as editor of the journal *Alzheimer's Disease and Associated Disorders*, and donated drug and placebo for an NIH-funded clinical trial from EMD Serono. He was a consultant to Merck KGaA in 2022 and to Novo Nordisk in 2024 and 2025. J.D.-G. received research support from GE HealthCare, Roche Diagnostics, Hoffmann—La Roche and Life—MI; participated in symposia sponsored by Biogen, Philips Nederlands, Life-MI and Esteve; acted as a consultant for Roche Diagnostics; and served in the Molecular Neuroimaging Advisory Board of Prothena Biosciences. J.D.-G. is founder, co-owner and member of the Board of Directors of Betascreen SL and is currently a full-time employee of AstraZeneca. W.C.K. has served as a consultant for Cerveau Technologies, Inc. O.H. is an employee of Eli Lilly and Lund University, and he has previously acquired research support (for Lund University) from AVID Radiopharmaceuticals, Biogen, C2N Diagnostics, Eli Lilly, Eisai, Fujirebio, GE Healthcare and Roche. In the past 2 years, he received consultancy or speaker fees from Alzpath, BioArctic, Biogen, Bristol Meyer Squibb, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Siemens. Work at Lund University was supported by the ERC (grant no. ADG-101096455), Alzheimer's Association (grant nos. ZEN24-1069572 and SG-23-1061717), GHR Foundation, Swedish Research Council (grant no. 2022-00775), ERA PerMed (grant no. ERAPERMED2021-184), Knut and Alice Wallenberg foundation (grant no. 2022-0231), Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, Swedish Alzheimer Foundation (grant no. AF-980907), Swedish Brain Foundation (grant no. FO2021-0293), Parkinson Foundation of Sweden (grant no. 1412/22), Cure Alzheimer's fund, Rönström Family Foundation, Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, Skåne University Hospital Foundation (grant no. 2020-0000028), Regionalt Forskningsstöd (grant no. 2022-1259) and Swedish Federal Government under the ALF agreement (grant no. 2022-Projekt0080). The precursor of [^{18}F]flortaucipir was provided by AVID radiopharmaceuticals and the precursor of [^{18}F]RO948 by Roche. The precursor of [^{18}F]flutemetamol was sponsored by GE Healthcare. The MCSA is supported by the National Institute on Aging (grant no. U01 AG006786), GHR and the Alzheimer's Association. G.S. received funding from the European Union's Horizon 2020 Research and Innovation Program under Marie Skłodowska-Curie action (grant no. 101061836), an Alzheimer's Association Research Fellowship (no. AARF-22-972612), the Alzheimerfonden (grant no. AF-980942), Greta och Johan Kocks research grants and travel grants from the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's Disease) at Lund University. The data contributed from Columbia University Irving Medical Center were supported by grant funding from the NIA (grant nos. K23AG052633, R01AG063888, P30AG066462, R01AG055299, RF1AG051556, R01AG050440, R01AG055299, K24AG045334 and R00AG065506). Funding for data from Stanford University was supported by NIA (grant nos. P30AG066515 and R01AG074339 to E.C.M. and K99AG071837 to C.B.Y.) and National Institute of Neurological Disorders and Stroke (grant no. R01NS115114). The data contributed from the Shataut7-IMATAU study (Paris) were supported by French Ministry of Health (grant no. PHRC-2013-0919), CEA, Fondation pour la recherche sur Alzheimer, Institut de Recherches Internationales Servier, France-Alzheimer. The MCSA is supported by the NIA (grant no. U01 AG006786), GHR and the Alzheimer's Association. The data contributed from the Wisconsin Registry for Alzheimer's Prevention were supported by grant funding from the NIA to the University of Wisconsin (grant nos. R01 AG021155 and R01 AG027161 to S.C.J.). Funding for data from Washington University was supported by the NIA (grant nos. R01AG070941 to S.E.S., P30AG066444, P01AG003991 and P01AG026276 to J.C.M.). Blood plasma measurements were

supported by grant nos. RF1AG061900 (to R.J.B.), R56AG061900 (to R.J.B.) and the Tracy Family SILQ Center (to R.J.B.). The data contributed from the PREVENT-AD were supported by public-private partnership funds provided by McGill University, the Fonds de Recherche du Québec—Santé (FRQ-S), an unrestricted research grant from Pfizer Canada, the Levesque Foundation, the Douglas Hospital Research Centre and Foundation, the Government of Canada, the Canada Fund for Innovation, the Canadian Institutes of Health Research, the Alzheimer Society of Canada, the US NIH, the Alzheimer Association and Brain Canada Foundation. Data collection and dissemination of the data presented in this manuscript were supported by the LEADS Consortium (grant nos. R56/U01 AG057195, funded by the NIA, as well as grant no. U24AG021886, Alzheimer's Association, LEADS GENETICS-19-639372, LDRFP-21-818464, Alzheimer's LDRFP-21-824473 and LDRFP-21-828356). NACC is funded by the NIA (grant no. U24 AG072122). NACC data are contributed by the following NIA-funded ADRCs: P30 AG010133, P30 AG062422, P30 AG066462, P30AG066507, P30 AG062421, P30 AG066506, P30AG072977, P30 AG066444, P30 AG066515, P30 AG062677, P30 AG072980, P30 AG072979 and P30 AG066511. The manuscript has been reviewed by the LEADS Publication Committee for scientific content. We acknowledge the invaluable contributions of the participants in LEADS as well as the assistance of the investigators and support staff at each of the participating sites. The ALFA study receives funding from 'la Caixa' Foundation (ID 100010434), under agreement no. LCF/PR/GN17/50300004, the Alzheimer's Association and an international anonymous charity foundation through the TriBEKa Imaging Platform project (TriBEKa-17-519007). Additional support has been received from the Universities and Research Secretariat, Ministry of Business and Knowledge of the Catalan Government under grant no. 2021 SGR 00913. Data were obtained from Australian Imaging Biomarkers and Lifestyle (AIBL) flagship study of aging and the Australian Dementia Network funded by the NHMRC of Australia (grant nos. APP1132604, APP1140853 and APP1152623), a grant from Enigma Australia and support from the Commonwealth Scientific and Industrial Research Organization (CSIRO). The Banner Sun Health Research Institute Brain and Body Donation Program has been supported by the National Institute of Neurological Disorders and Stroke (grant no. U24 NS072026, National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the NIA (grant nos. P30AG019610 and P30AG072980, Arizona Alzheimer's Disease Center), the Arizona Department of Health Services (contract no. 211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contract nos. 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium) and the Michael J. Fox Foundation for Parkinson's Research. The NACC database is funded by the NIA (grant no. U01 AG016976). Data collection and sharing for this project were funded by the ADNI (NIH, grant no. U01 AG024904) and DOD ADNI (Department of Defense award no. W81XWH-12-2-0012). ADNI is funded by the NIA, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Co.; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research provides funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the

NIH (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. ROSMAP is supported by grant nos. P30AG10161, P30AG72975, R01AG15819, R01AG17917, U01AG46152 and U01AG61356. ROSMAP resources can be requested at <https://www.radc.rush.edu> and www.synapse.org. The other authors declare no competing interests.

Additional information

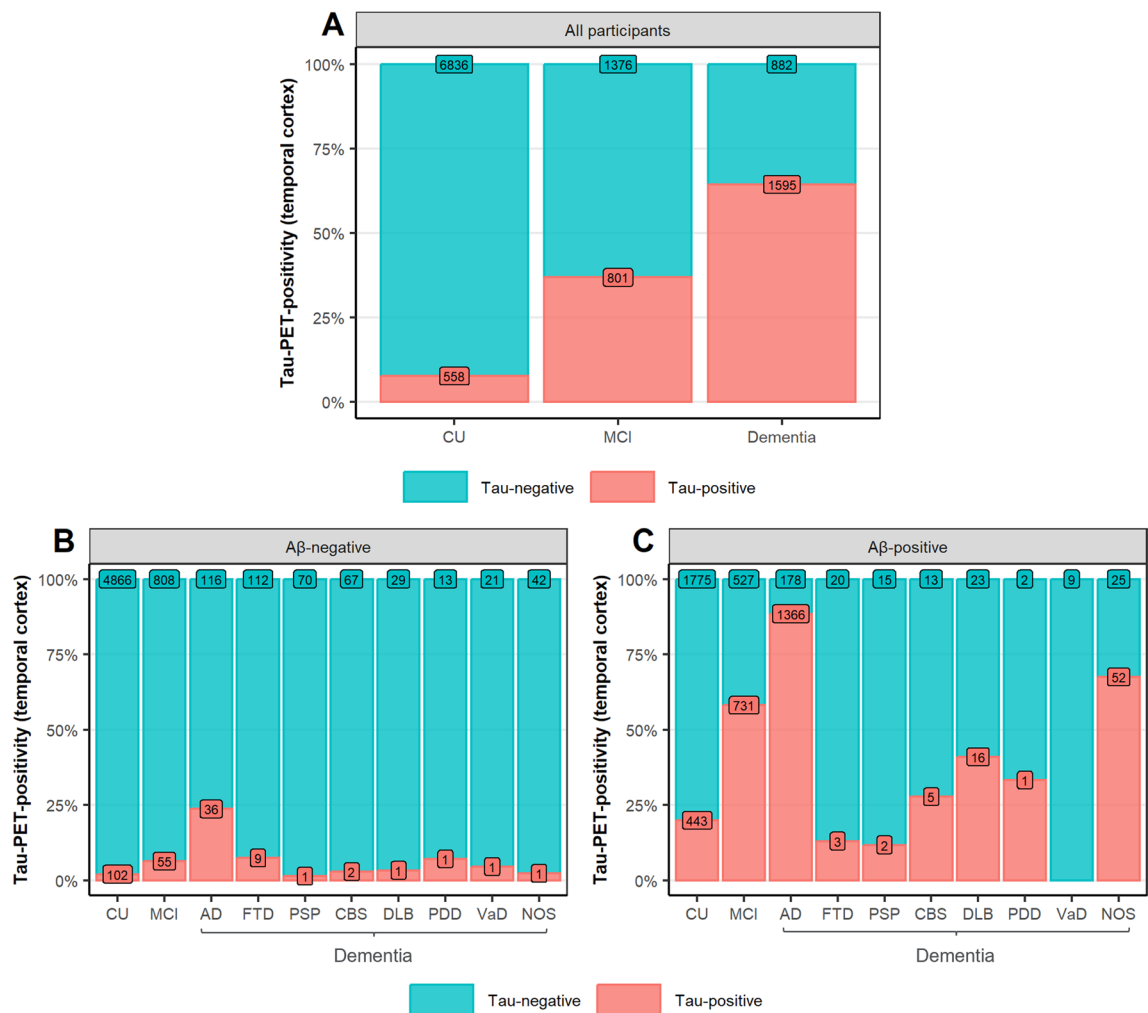
Extended data is available for this paper at <https://doi.org/10.1038/s41593-025-02000-6>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41593-025-02000-6>.

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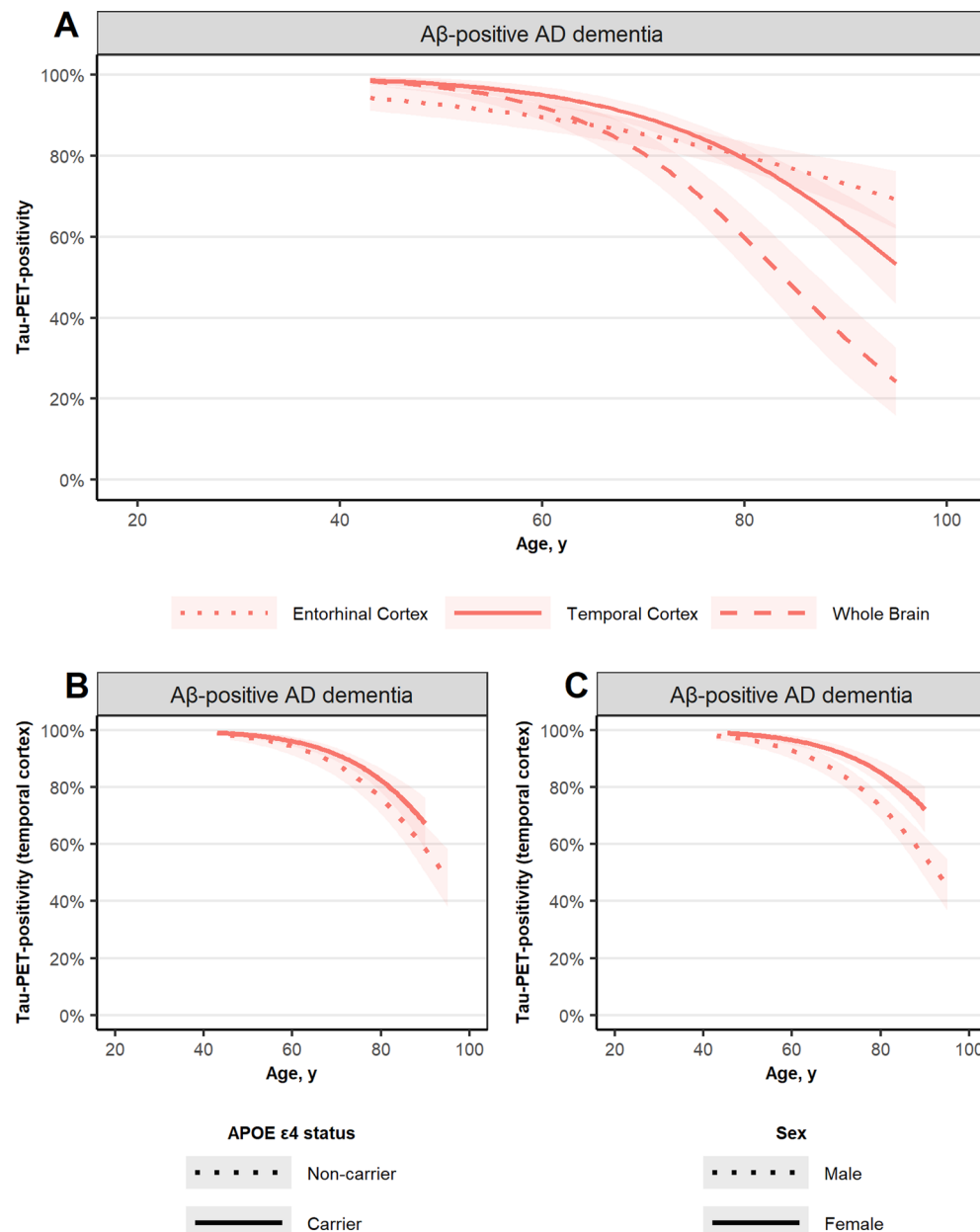
Peer review information *Nature Neuroscience* thanks Julie Ottoy and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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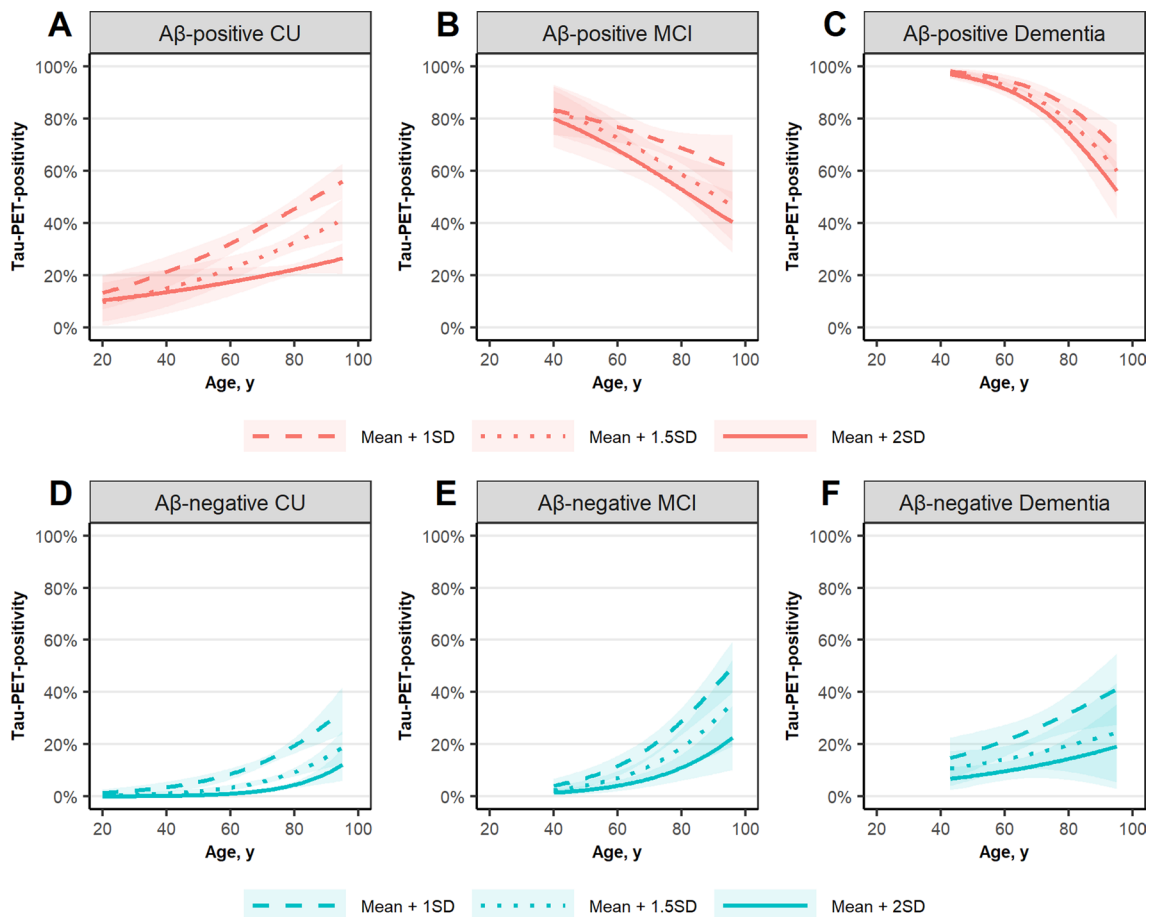
Extended Data Fig. 1 | Observed tau-positivity in the temporal cortex across diagnostic groups. Plots show the observed rates of Tau-PET positivity in the temporal cortex by (syndromic and clinical) diagnosis for all participants (panel **a**, $n = 1,2048$) or stratified by Aβ-status (panels **b** [$n = 6,353$] and **c** [$n = 5,206$]). Aβ = Amyloid-beta; AD = Alzheimer's disease, CBS = Corticobasal

syndrome, DLB = Dementia with Lewy bodies, FTD = Frontotemporal dementia, MCI = Mild cognitive impairment, NOS = Not otherwise specified, PDD = Parkinson's disease dementia, PSP = Progressive supranuclear palsy, VaD = Vascular dementia.



Extended Data Fig. 2 | Prevalence estimates of Tau-PET positivity according to age, $A\beta$, cognitive status and sex in AD-type dementia. Panel **a** resembles Fig. 1f, panel **b** resembles Fig. 3c and panel **c** resembles Fig. 3f, but now in individuals clinically diagnosed with AD-type dementia instead of all-cause dementia. The model presented in panel **a** included age, $A\beta$ -status and an interaction between age and $A\beta$ -status ($n = 1,696$). The model presented in panel **b** included age, $A\beta$ -status, $APOE \epsilon 4$ -status and an interaction between

age and $A\beta$ -status ($n = 1,486$). The model presented in panel **c** included age, $A\beta$ -status, sex and an interaction term between age and $A\beta$ -status ($n = 1,696$). The y-axes reflect estimated probabilities of Tau-PET-positivity (prevalence estimates) from logistic generalized estimating equations. Shading areas indicates the 95% confidence intervals. $A\beta$ = Amyloid-beta; $APOE$ = Apolipoprotein E; PET = Positron emission tomography.



Extended Data Fig. 3 | Prevalence estimates of Tau-PET positivity in the temporal cortex using lower thresholds. The plots depict the prevalence estimates of Tau-PET positivity in the temporal cortex as a function of age, Aβ-status and an interaction between age and Aβ-status in CU (panels **a** and **d**, $n = 7,186$), MCI (panels **b** and **e**, $n = 2,121$) and dementia (panels **c** and **f**, $n = 2,252$). Models were stratified by syndrome diagnoses. Tau-PET-positivity was defined

using three different thresholds for Tau-PET positivity (that is, the mean + 1, 1.5 or 2 s.d. in Aβ-negative CU individuals). The y axes reflect estimated probabilities of tau-PET positivity (prevalence estimates) from logistic GEEs. Shaded areas indicates the 95% confidence intervals. Aβ = Amyloid-beta; CU = Cognitively unimpaired; MCI, mild cognitive impairment; PET = Positron emission tomography.

Extended Data Table 1 | Participant characteristics of the autopsy cohorts

	CU	MCI	Dementia
N	1,026	661	3,385
Age at death, years	85.8 ± 8.5	87.8 ± 8.0	81.7 ± 11.0
Sex, n female (%)	628 (61.2)	373 (56.4)	1,701 (50.3)
<i>APOE</i> ε4, n carrier (%)	187 (19.0)	151 (24.0)	1,408 (44.1)
CERAD, n moderate-to-frequent (%)	473 (46.1)	403 (61.0)	2,628 (77.6)

CERAD, Consortium to Establish a Registry for Alzheimer's Disease criteria.

Extended Data Table 2 | Prevalence estimates of tau-PET positivity in the entorhinal cortex according to age, Aβ and cognitive status

Age, y	CU, % (95% CI)			MCI, % (95% CI)			Dementia, % (95% CI)		
	Total	Aβ-negative	Aβ-positive	Total	Aβ-negative	Aβ-positive	Total	Aβ-negative	Aβ-positive
50	2.9	0.6	21.1	32.8	2.3	78.5	68.0	7.6	91.3
	(2.0-3.9)	(0.2-1.0)	(14.1-28.0)	(25.9-39.7)	(0.7-3.9)	(70.4-86.5)	(58.2-77.8)	(3.3-12.0)	(87.9-94.7)
55	4.0	0.9	22.4	35.4	3.3	76.0	67.7	9.0	89.7
	(2.9-5.1)	(0.5-1.4)	(16.3-28.5)	(29.1-41.8)	(1.3-5.3)	(68.6-83.3)	(59.1-76.4)	(4.6-13.4)	(86.2-93.1)
60	5.4	1.4	23.8	38.2	4.7	73.3	67.5	10.6	87.7
	(4.2-6.7)	(0.8-1.9)	(18.5-29.1)	(32.4-44.0)	(2.2-7.2)	(66.8-79.7)	(59.9-75.0)	(6.2-14.9)	(84.3-91.1)
65	7.3	2.1	25.3	41.0	6.6	70.4	67.2	12.4	85.5
	(5.9-8.8)	(1.5-2.6)	(20.9-29.6)	(35.6-46.5)	(3.5-9.8)	(64.8-76.0)	(60.6-73.8)	(7.9-16.8)	(82.2-88.8)
70	9.9	3.1	26.8	43.9	9.3	67.4	66.9	14.4	82.9
	(8.3-11.4)	(2.5-3.6)	(23.2-30.3)	(38.7-49.2)	(5.3-13.2)	(62.5-72.2)	(61.2-72.7)	(9.8-19.0)	(79.7-86.1)
75	13.2	4.5	28.3	46.9	12.8	64.2	66.7	16.8	80.0
	(11.4-14.9)	(3.8-5.2)	(25.3-31.4)	(41.5-52.2)	(7.8-17.8)	(59.4-68.9)	(61.6-71.8)	(11.7-21.9)	(76.7-83.3)
80	17.3	6.7	30.0	49.8	17.5	60.8	66.4	19.4	76.7
	(15.3-19.4)	(5.3-8.1)	(26.9-33.0)	(44.1-55.5)	(11.1-23.9)	(55.5-66.2)	(61.6-71.2)	(13.4-25.4)	(73.1-80.4)
85	22.5	9.7	31.6	52.8	23.4	57.4	66.1	22.4	73.1
	(19.8-25.2)	(6.8-12.6)	(27.9-35.4)	(46.5-59.0)	(15.2-31.6)	(50.7-64.0)	(61.2-71.0)	(15.0-29.8)	(68.6-77.6)
90	28.6	13.9	33.4	55.7	30.6	53.9	65.9	25.6	69.1
	(25.0-32.3)	(8.5-19.3)	(28.4-38.3)	(48.8-62.7)	(20.2-41.0)	(45.5-62.2)	(60.5-71.2)	(16.3-34.9)	(63.4-74.9)

The prevalence estimates of tau positivity in the entorhinal cortex were generated using logistic GEE models stratified by syndrome diagnosis. Prevalence estimates in the total group were modeled using age as determinant. Prevalence estimates according to Aβ status were modeled using age, Aβ status and an interaction term between age and Aβ status and models were stratified by syndrome diagnosis. The analyses presented in this table are based on 7,381 CU participants (68.7±11.1 years, 56.0% female), of whom 7,174 had Aβ status available (68.7±11.1 years, 56.0% female), 2,173 participants with MCI (71.3±8.8 years, 45.1% female), of whom 2,117 had Aβ status available (71.3±8.8 years, 44.9% female) and 2,459 participants with dementia (69.9±9.0 years, 50.6% female), of whom 2,234 had Aβ status available (69.9±9.0 years, 51.2% female).

Extended Data Table 3 | Prevalence estimates of tau-PET positivity in the whole-brain ROI according to age, A β and cognitive status

Age, y	CU, % (95% CI)			MCI, % (95% CI)			Dementia, % (95% CI)		
	Total	A β -negative	A β -positive	Total	A β -negative	A β -positive	Total	A β -negative	A β -positive
50	3.6	2.0	16.6	32.7	2.5	75.0	77.1	5.3	95.5
	(2.4-4.7)	(1.1-2.8)	(9.8-23.3)	(24.8-40.6)	(0.0-5.1)	(64.8-85.2)	(69.2-84.9)	(1.6-9.0)	(93.5-97.6)
55	4.0	2.1	15.5	32.4	3.1	69.6	73.5	6.1	93.1
	(3.0-5.0)	(1.4-2.8)	(10.2-20.9)	(25.5-39.3)	(0.4-5.8)	(59.9-79.2)	(65.9-81.2)	(2.5-9.8)	(90.4-95.7)
60	4.5	2.2	14.5	32.1	3.8	63.5	69.7	7.1	89.4
	(3.5-5.4)	(1.7-2.8)	(10.4-18.6)	(26.0-38.3)	(1.1-6.5)	(54.8-72.3)	(62.4-77.0)	(3.4-10.8)	(86.1-92.7)
65	5.0	2.4	13.6	31.8	4.7	57.1	65.5	8.1	84.2
	(4.2-5.9)	(1.9-2.8)	(10.5-16.6)	(26.2-37.5)	(2.1-7.4)	(49.3-64.8)	(58.6-72.5)	(4.1-12.2)	(80.1-88.2)
70	5.7	2.5	12.6	31.6	5.8	50.3	61.1	9.3	77.0
	(4.9-6.4)	(2.1-2.9)	(10.5-14.8)	(26.1-37.0)	(3.2-8.5)	(43.4-57.2)	(54.4-67.9)	(4.5-14.1)	(72.1-81.9)
75	6.3	2.7	11.8	31.3	7.2	43.6	56.5	10.7	67.8
	(5.5-7.2)	(2.1-3.3)	(10.2-13.4)	(25.6-36.9)	(4.3-10.1)	(36.9-50.3)	(49.7-63.4)	(4.6-16.7)	(61.7-73.9)
80	7.1	2.8	11.0	31.0	8.9	37.0	51.8	12.2	57.0
	(6.0-8.2)	(2.0-3.7)	(9.5-12.5)	(24.8-37.1)	(5.0-12.7)	(29.9-44.2)	(44.5-59.1)	(4.3-20.1)	(49.5-64.5)
85	7.9	3.0	10.2	30.7	10.8	31.0	47.1	13.9	45.5
	(6.5-9.4)	(1.8-4.2)	(8.5-12.0)	(23.8-37.6)	(5.2-16.5)	(23.2-38.8)	(39.1-55.1)	(3.6-24.2)	(36.7-54.2)
90	8.9	3.2	9.5	30.4	13.2	25.5	42.4	15.8	34.4
	(6.8-10.9)	(1.6-4.8)	(7.3-11.7)	(22.7-38.2)	(4.8-21.6)	(17.1-33.8)	(33.5-51.3)	(2.6-29.0)	(25.0-43.8)

The prevalence estimates of tau positivity in the whole-brain ROI were generated using logistic GEE models stratified by syndrome diagnosis. Prevalence estimates in the total group were modeled using age as determinant. Prevalence estimates according to A β status were modelled using age, A β status and an interaction term between age and A β status, and models were stratified by syndrome diagnosis. The analyses presented in this table are based on 7,394 CU participants (68.7 \pm 11.1 years, 55.9% female), of whom 7,186 had A β status available (68.7 \pm 11.1 years, 56.0% female), 2,177 participants with MCI (71.3 \pm 8.8 years, 45.0% female), of whom 2,121 had A β status available (71.4 \pm 8.8 years, 44.8% female) and 2,475 participants with dementia (69.9 \pm 9.0 years, 50.7% female), of whom 2,252 had A β status available (69.9 \pm 9.0 years, 51.2% female).

Extended Data Table 4 | Prevalence estimates of tau-PET-positivity in amyloid-positive AD-type dementia

Age, y	Alzheimer's disease dementia, % (95% CI)		
	Entorhinal cortex	Temporal cortex	Whole brain
50	92.7	97.7	97.0
	(89.4-96.0)	(96.4-99.1)	(95.3-98.7)
55	91.3	96.7	95.1
	(87.9-94.6)	(94.9-98.4)	(92.7-97.4)
60	89.6	95.1	92.0
	(86.3-93.0)	(93.0-97.1)	(88.8-95.2)
65	87.7	92.8	87.4
	(84.4-91.0)	(90.4-95.2)	(83.3-91.5)
70	85.5	89.6	80.6
	(82.2-88.7)	(86.9-92.2)	(75.5-85.6)
75	82.9	85.1	71.3
	(79.6-86.2)	(82.1-88.2)	(65.2-77.5)
80	80.0	79.3	59.8
	(76.4-83.6)	(75.6-83.0)	(52.5-67.2)
85	76.7	71.9	47.2
	(72.4-81.1)	(66.7-77.0)	(38.8-55.6)
90	73.1	63.0	34.9
	(67.6-78.7)	(55.7-70.4)	(26.1-43.7)

The prevalence estimates of tau-PET positivity in the entorhinal cortex, temporal cortex, and whole brain were generated using logistic GEE models according to age and A β in participants clinically diagnosed with AD-type dementia ($n=1,696$).

Extended Data Table 5 | Age by *APOE* ϵ 4 status in CU individuals

Age, y	% (95% CI)	
	<i>APOE</i> ϵ 4 non-carrier	<i>APOE</i> ϵ 4 carrier
50	1.2 (0.8-1.7)	3.4 (2.2-4.6)
55	1.7 (1.2-2.3)	4.7 (3.2-6.2)
60	2.4 (1.7-3.1)	6.5 (4.8-8.3)
65	3.4 (2.5-4.2)	9.0 (6.9-11.1)
70	4.7 (3.7-5.7)	12.3 (9.7-14.8)
75	6.5 (5.2-7.8)	16.5 (13.4-19.6)
80	9.0 (7.3-10.6)	21.8 (18.0-25.6)
85	12.2 (10.0-14.4)	28.3 (23.6-33.0)
90	16.4 (13.3-19.6)	35.8 (30.0-41.6)

The prevalence estimates of tau positivity in the temporal cortex were generated from logistic GEE models including age and *APOE* ϵ 4 status ($n=6,476$).

Extended Data Table 6 | A β and tau positivity by age and APOE in CU individuals

	A β -positivity	Entorhinal tau-positivity	Temporal cortex tau-positivity
Age at 10% prevalence			
<i>APOE</i> ϵ 4 homozygote	40.5	44.5	54.5
<i>APOE</i> ϵ 4 heterozygote	49.0	63.5	69.0
<i>APOE</i> ϵ 4 non-carrier	56.5	77.5	81.0
Age at 15% prevalence			
<i>APOE</i> ϵ 4 homozygote	45.0	50.5	60.0
<i>APOE</i> ϵ 4 heterozygote	53.5	70.0	75.0
<i>APOE</i> ϵ 4 non-carrier	62.5	82.5	87.0
Age at 20% prevalence			
<i>APOE</i> ϵ 4 homozygote	48.5	55.0	65.0
<i>APOE</i> ϵ 4 heterozygote	57.0	74.5	79.5
<i>APOE</i> ϵ 4 non-carrier	67.0	86.5	91.5

The prevalence estimates of A β and tau positivity were generated using logistic GEE models including age and *APOE* ϵ 4 dosage, and only included individuals that had A β status, entorhinal tau-PET status and temporal cortex tau-PET status available ($n=6,184$). Separate models were performed for estimating the prevalence of A β positivity and tau positivity. Models estimating the prevalence of A β positivity and entorhinal tau positivity additionally included an interaction term between age and *APOE* ϵ 4 dosage.

Extended Data Table 7 | A β and tau positivity by age and sex in CU individuals

	A β -positivity	Entorhinal tau-positivity	Temporal cortex tau-positivity
Age at 10% prevalence			
Women	48.5	67.5	73.0
Men	50.0	73.5	77.5
Age at 15% prevalence			
Women	55.0	74.5	80.5
Men	56.5	80.5	85.0
Age at 20% prevalence			
Women	60.0	79.5	86.0
Men	61.5	85.5	90.5

The prevalence estimates of A β and tau positivity were generated using logistic GEE models including age and sex and models only included individuals that had A β status, entorhinal tau-PET status and temporal cortex tau-PET status available ($n=7,173$). Separate models were performed for estimating the prevalence of A β positivity and tau positivity.

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<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
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Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection implemented in R version 4.2.1 and code can be requested from the corresponding authors

Data analysis implemented in R version 4.2.1 and codes are freely available: <https://github.com/OssenKoppeLab>

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Reporting on race, ethnicity, or other socially relevant groupings	A subset of centers reported self-reported sex and/or ethnicity status and this information is included in table 1
Population characteristics	Included in manuscript, table 1
Recruitment	Recruitment strategies varied by center, information is included in previous publication
Ethics oversight	Data collection oversight by local IRBs data analysis by Ethics Committee of Lund University

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	12048
Data exclusions	No data excluded from participants that met in- and exclusion criteria
Replication	No
Randomization	n.a.
Blinding	n.a.

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n/a	Involved in the study
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<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input type="checkbox"/>	<input checked="" type="checkbox"/> MRI-based neuroimaging

Magnetic resonance imaging

Experimental design

Design type	Processing was performed with various software at participating center (included in supplement)
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Design specifications	see above
Behavioral performance measures	na

Acquisition

Imaging type(s)	Structural
Field strength	Various
Sequence & imaging parameters	Various
Area of acquisition	Cranium
Diffusion MRI	<input type="checkbox"/> Used <input checked="" type="checkbox"/> Not used

Preprocessing

Preprocessing software	Processing was performed with various software at participating center (included in supplement)
Normalization	See above
Normalization template	See above
Noise and artifact removal	See above
Volume censoring	See above

Statistical modeling & inference

Model type and settings	Logistic generalized estimating equation (GEE)
Effect(s) tested	Age, amyloid-status, sex, APOE genotype
Specify type of analysis:	<input type="checkbox"/> Whole brain <input type="checkbox"/> ROI-based <input checked="" type="checkbox"/> Both
Anatomical location(s)	<i>Describe how anatomical locations were determined (e.g. specify whether automated labeling algorithms or probabilistic atlases were used).</i>
Statistic type for inference	Probabilities of Tau pathology
(See Eklund et al. 2016)	
Correction	na

Models & analysis

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Functional and/or effective connectivity
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<input checked="" type="checkbox"/>	<input type="checkbox"/> Multivariate modeling or predictive analysis