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REPORT

Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease

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Plasma levels of tau phosphorylated at threonine-217 (p-tau217) is a candidate tool to monitor Alzheimer's disease. We studied 150 cognitively unimpaired participants and 100 patients with mild cognitive impairment in the Swedish BioFINDER study. P-tau217 was measured repeatedly for up to 6 years (median three samples per person, median time from first to last sample, 4.3 years). Preclinical (amyloid-β-positive cognitively unimpaired, $n = 62$) and prodromal (amyloid-β-positive mild cognitive impairment, $n = 49$) Alzheimer's disease had accelerated p-tau217 compared to amyloid-β-negative cognitively unimpaired ($\beta = 0.56$, $P < 0.001$, using linear mixed effects models) and amyloid-β-negative mild cognitive impairment patients ($\beta = 0.67$, $P < 0.001$), respectively. Mild cognitive impairment patients who later converted to Alzheimer's disease dementia ($n = 40$) had accelerated p-tau217 compared to other mild cognitive impairment patients ($\beta = 0.79$, $P < 0.001$). P-tau217 did not change in amyloid-β-negative participants, or in patients with mild cognitive impairment who did not convert to Alzheimer's disease dementia. For 80% power, 109 participants per arm were required to observe a slope reduction in amyloid-β-positive cognitively unimpaired (71 participants per arm in amyloid-β-positive mild cognitive impairment). Longitudinal increases in p-tau217 correlated with longitudinal worsening of cognition and brain atrophy. In summary, plasma p-tau217 increases during early Alzheimer's disease and can be used to monitor disease progression.

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Abbreviations: MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; mPACC = modified Preclinical Alzheimer's Cognitive Composite; NfL = neurofilament light; p-tau = phosphorylated tau

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Introduction

Minimally invasive blood-based biomarkers have the potential to improve clinical management of Alzheimer's disease and design of clinical trials. Promising results have been reported for blood-based biomarkers for core features of Alzheimer's disease, including amyloid-β peptides (Palmqvist *et al.*, 2019*b*; Schindler *et al.*, 2019), neurodegeneration biomarkers (including neurofilament light, NfL) (Mattsson *et al.*, 2017, 2019), and phosphorylated tau (p-tau) (Mielke *et al.*, 2018, Janelidze *et al.*, 2020*a*; Thijssen *et al.*, 2020). Plasma p-tau measures have been validated against CSF p-tau, and PET measurements of tau. Multiple tau phosphorylation epitopes exist, of which p-tau181 and p-tau217 have been studied as biomarkers (Barthélemy *et al.*, 2020). In CSF, p-tau217 performs better than p-tau181, both for diagnosis of Alzheimer's disease, and for correlations with tau PET (Janelidze *et al.*, 2020*b*). We have recently found similar results for plasma p-tau217 when compared to p-tau181 (Palmqvist *et al.*, 2020), but data are lacking on longitudinal plasma p-tau217, and its use for monitoring disease progression. We therefore measured plasma p-tau217 over time in cognitively unimpaired individuals, and in patients with mild cognitive impairment (MCI). We tested if p-tau217 increased over time at the preclinical (amyloid-β+ cognitively unimpaired) and prodromal stages (amyloid-β+ MCI) of Alzheimer's disease, and if the trajectories differed between Alzheimer's disease and other causes of cognitive impairment. For comparison, we included a non-specific marker of neurodegeneration (plasma NfL). We also tested if changes in p-tau217 correlated with changes in cognition or atrophy.

Materials and methods

Participants

Participants were recruited in the prospective Swedish BioFINDER study (www.biofinder.se), including cognitively unimpaired individuals (cognitively healthy controls or individuals with subjective cognitive decline, SCD), and patients with MCI. Details on recruitment, exclusion and inclusion criteria have been presented previously (Mattsson *et al.*, 2016; Ossenkoppele *et al.*, 2018). All subjects underwent lumbar puncture at baseline for CSF sampling. Plasma samples were taken at baseline and every second year for up to 6 years. Clinical assessments for determination of conversion to dementia were done annually (Table 1).

Fluid biomarkers

Plasma p-tau217 was measured using immunoassays at Lilly Research Laboratories (Palmqvist *et al.*, 2019*a*). Plasma NfL was measured using the Quanterix NfL Advantage kit as described before (Mengel *et al.*, 2020). A few outliers were removed for NfL [concentrations > mean + 3 standard deviations (SD), $n = 8$ of 668 data-points]. CSF amyloid-β_{42} and amyloid-β_{40} were measured using Meso Scale Discovery immunoassays (MSD). The CSF amyloid-β_{42}/amyloid-β_{40} ratio (pathological if <0.091) was used to determine amyloid-β-positivity (Janelidze *et al.*, 2016).

Cognitive measures

We used the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) and a cognitive composite (modified Preclinical Alzheimer's Cognitive Composite, mPACC) (Donohue *et al.*, 2014). The mPACC was calculated as the average of five *z*-scores, for tests of memory [the delayed recall test from the cognitive subscale from the Alzheimer's Disease Assessment Scale (ADAS-cog), counted twice in order to preserve the weight on memory from the original PACC (Donohue *et al.*, 2014)], verbal ability (animal fluency), executive function (Trail Making Test B) (Delis *et al.*, 2001), and global cognition (MMSE). Animal fluency was included since category fluency tests may improve detection of early cognitive decline related to amyloid-β pathology (Papp *et al.*, 2017). We restricted the cognitive test data to assessments done within 1 year of plasma sampling.

MRI measures

Anatomical T_1-weighted imaging was performed on a 3 T magnetic resonance scanner (Siemens Tim Trio 3T) producing MP-RAGE images (repetition time = 1.950 ms, echo time = 3.4 ms, 1 mm isotropic voxels, 178 slices) used in the anatomical segmentation and cortical thickness calculations. These were performed using the Freesurfer image analysis pipeline v6.0 (http://surfer.nmr.mgh.harvard.edu/), where each time points' scan was first processed separately. After brain extraction and intensity homogeneity correction, grey and white matter segmentation using intensity gradient and voxel connectivity, cortical modelling allowed parcellation of cerebral cortex into subunits of gyral and sulcal structure. Cortical thickness was measured as the distance from the grey–white matter boundary to corresponding pial surface. Reliable thickness and volume measures were then extracted by entering each subject's processed scans at various time points into FreeSurfer's longitudinal stream (Reuter *et al.*, 2012), creating an unbiased within-subject template over all time points, then used to improve robustness of several processing steps and increase reliability of final results. For the analyses in this paper, we used cortical thickness (adjusted for surface area) from a temporal meta-region of interest (consisting of bilateral entorhinal, fusiform, inferior temporal and middle temporal cortex) and hippocampal volume (averaged between the hemispheres). We restricted the MRI data to scans done within 1 year of plasma sampling.

Statistical analysis

First, we tested longitudinal p-tau217 changes in linear mixed effects (LME) models. We tested the interaction between time and amyloid-β status as a predictor in both cognitively unimpaired and MCI. We also tested the interaction between time and conversion to Alzheimer's disease dementia as a predictor in MCI. Similar models were fitted for NfL. The LME models were adjusted for age and sex and included random intercepts and slopes. Risk for conversion to Alzheimer's disease dementia was also tested in a Cox survival analysis. Second, a power

Table 1 Demographics

	Amyloid-β– CU *n* = 88	Amyloid-β+ CU *n* = 62	Amyloid-β– MCI *n* = 51	Amyloid-β+ MCI *n* = 49
Clinical diagnosis (healthy controls/SCD/MCI)	49/39/0	46/16/0	0/0/51	0/0/49
Age, years	70.7 (4.9)	72.7 (5.2)	69.5 (5.8)	71.0 (5.2)
Sex, M/F	35/53	23/39	38/13	26/23
Education, years	12.2 (3.0)	12.2 (3.7)	11.2 (3.4)	12.1 (3.5)
APOE ε4, –/+	67/21	26/36	38/13	11/38
Baseline p-tau217, ng/l	1.18 (1.64)	1.71 (1.49)	1.80 (1.74)	4.56 (3.11)
Time from first to last p-tau217 sample, years	5.2 (1.5)	4.5 (1.2)	2.7 (1.9)	4.0 (2.0)
Number of plasma p-tau217 measures, 1/2/3/4	4/4/44/36	1/12/39/10	12/22/16/1	7/14/18/10
Baseline NfL, ng/l	12.3 (5.0)	13.9 (5.8)	17.6 (8.5)	16.7 (7.1)
Number of plasma NfL measures, 0/1/2/3/4	0/4/5/44/35	6/2/9/39/6	2/13/20/15/1	7/8/9/15/10
MMSE at baseline, points	29.1 (1.2)	28.9 (1.1)	27.5 (2.0)	26.9 (1.7)
MMSE change/year, points	–0.05 (0.32)	–0.35 (0.65)	–1.00 (1.18)	–1.55 (1.12)
mPACC at baseline, points	0.22 (0.63)	–0.17 (0.81)	–1.21 (0.71)	–1.51 (0.62)
mPACC change/year, points	–0.03 (0.13)	–0.13 (0.25)	–0.24 (0.29)	–0.34 (0.30)
Number of cognitive assessments, 0/1/2/3/4	1/4/3/22/57/1	0/1/1/37/23	2/12/16/12/8/1	0/7/4/11/19/8
Time from first to last cognitive test, years	5.2 (1.1)	4.5 (1.0)	3.5 (1.4)	4.7 (1.3)
Conversion to dementia, none/non-AD dementia[a]/AD dementia	80/8/0	52/2/8	12/35/3[b]	1/11/37
Time-at-risk for dementia, years	5.9 (1.4)	5.1 (1.5)	3.2 (1.8)	3.0 (1.6)
Temporal cortical thickness at baseline, mm	2.59 (0.16)	2.52 (0.20)	2.47 (0.22)	2.45 (0.17)
Temporal cortical thickness change/year, points	–0.013 (0.015)	–0.028 (0.021)	–0.039 (0.042)	–0.065 (0.030)
Hippocampal volume at baseline, mm^3	3363 (447)	3250 (410)	3297 (503)	2899 (413)
Hippocampal volume change/year, points	–38 (28)	–57 (39)	–77 (58)	–94 (34)
Number of MRI scans, 0/1/2/3/4	10/ 2/15/36/25	6/2/12/34/8	15/5/17/12/2	8/4/9/19/9
Time from first to last scan, years	4.5 (1.6)	4.2 (1.5)	3.0 (1.8)	3.9 (1.8)

Continuous data are mean (SD). Time-at-risk for dementia was the overall clinical follow-up, or the time until a dementia diagnosis. The distribution of *APOE* ε4 was balanced between males (53% *APOE* ε4–, 47% *APOE* ε4+) and females (60% *APOE* ε4–, 40% *APOE* ε4+, $P = 0.33$) (chi-square test). AD = Alzheimer's disease; CU = cognitively unimpaired; SCD = subjective cognitive decline.

[a]Amyloid-β– CU: six vascular dementia, one Parkinson's disease dementia/Lewy body dementia, one frontotemporal lobe dementia; Amyloid-β+ CU: one Parkinson's disease dementia/Lewy body dementia, one frontotemporal lobe dementia; Amyloid-β– MCI: 18 vascular dementia, 10 Parkinson's disease dementia/dementia with Lewy bodies, seven frontotemporal lobe dementia, one other dementia; Amyloid-β+ MCI: three vascular dementia, seven Parkinson's disease dementia/Lewy body dementia, one frontotemporal lobe dementia.

[b]Data were missing on dementia conversion in one amyloid-β– MCI patient.

analysis ($n = 500$ bootstrap trials) was performed for p-tau217 in amyloid-β+ cognitively unimpaired and MCI groups, with trial duration assumed to be 48 months for cognitively unimpaired and 18 months for MCI, while follow-up was assumed to occur every 3 months. Third, associations were tested between longitudinal change in p-tau217 and longitudinal measures of cognition and brain structure, in LME models with the interaction between time and plasma p-tau217 slopes as the independent variable, adjusted for age, sex and (for cognitive measures) years of education or (for hippocampal volume) intracranial volume. Statistical analysis was done using R version 4.0.0. Significance was determined at $P < 0.05$ (two-tailed).

Data availability

Anonymized data will be shared by request from a qualified academic investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in agreement with EU legislation on the general data protection regulation and decisions by the Ethical Review Board of Sweden and Region Skåne, which should be regulated in a material transfer agreement.

Results

Longitudinal plasma p-tau217 in different diagnostic groups

See Table 1 for demographics. During the clinical follow-up of all cases, 145 did not develop dementia, 48 developed Alzheimer's disease dementia, and 56 developed other dementias (Table 1). Longitudinal p-tau217 data are shown in Fig. 1. In the cognitively unimpaired, p-tau217 had a trend towards higher levels in amyloid-β+ cognitively unimpaired compared to amyloid-β– cognitively unimpaired at baseline [$\beta = 0.50$ (meaning 0.50 ng/l higher levels in amyloid-β+ cognitively unimpaired), $P = 0.053$], remained stable over time in amyloid-β– cognitively unimpaired ($\beta = 0.11$, $P = 0.30$), and increased significantly over time in amyloid-β+ cognitively unimpaired compared to amyloid-β– cognitively unimpaired (Fig. 1A) [time × amyloid-β-interaction: $\beta = 0.56$ (meaning an acceleration in amyloid-β+ of 0.56 ng/l per year, compared to the rate in amyloid-β– cognitively unimpaired), $P < 0.001$; the increased rate corresponds to

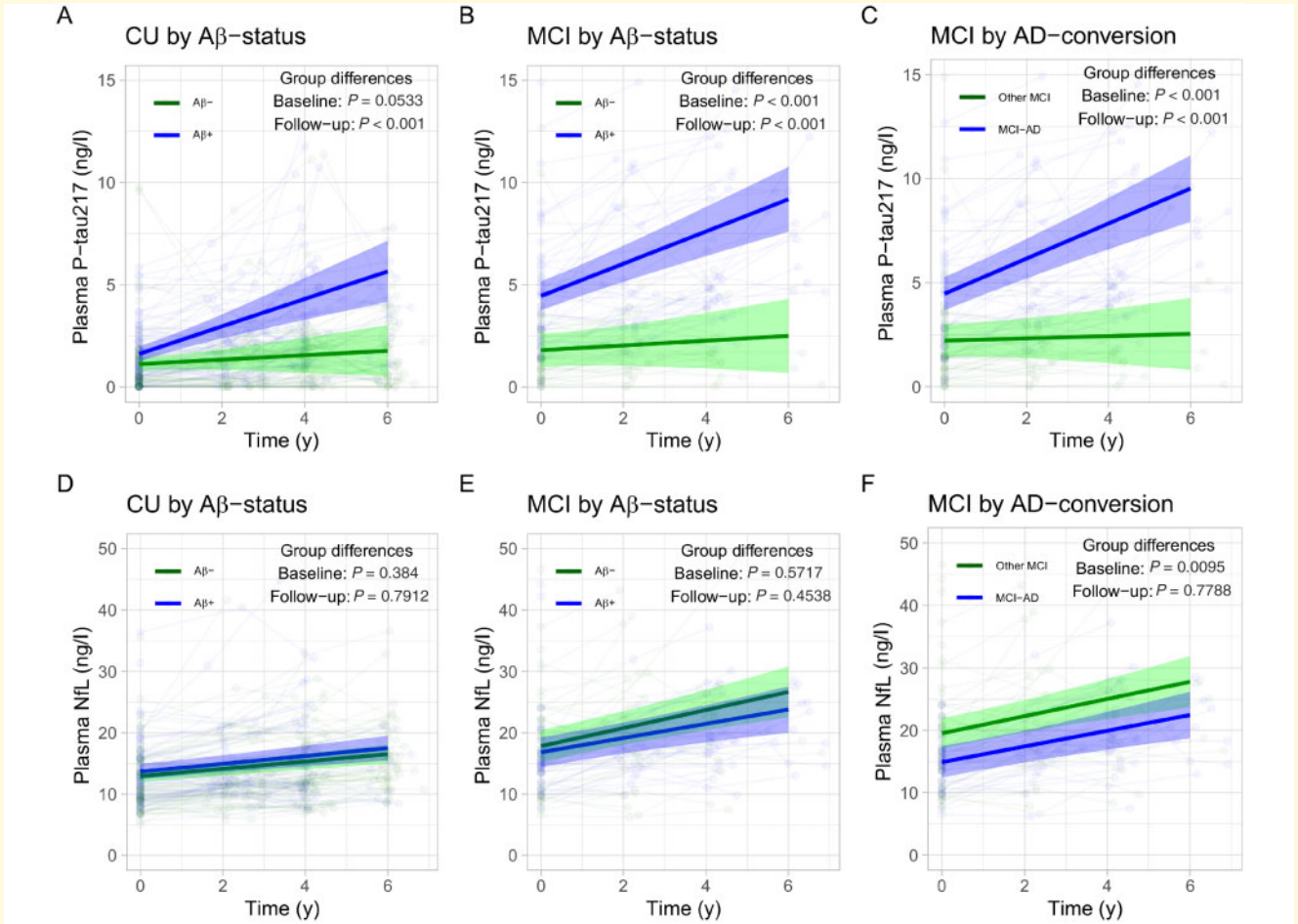

Figure 1 Longitudinal plasma p-tau217 and NfL. Subject-specific biomarker data are shown together with main effects from linear mixed effects models, adjusted for age and sex, for p-tau217 in (**A**) amyloid-β– cognitively unimpaired (CU) versus amyloid-β+ cognitively unimpaired, (**B**) amyloid-β– MCI versus amyloid-β+ MCI, and (**C**) MCI to Alzheimer's disease dementia converters versus the remaining MCI population (i.e. stable MCI or MCI to other dementia converters), and for NfL in (**D**) amyloid-β– cognitively unimpaired versus amyloid-β+ cognitively unimpaired, (**E**) amyloid-β– MCI versus amyloid-β+ MCI, and (**F**) MCI to Alzheimer's disease dementia converters versus the remaining MCI population. Aβ = amyloid-β; AD = Alzheimer's disease; y = years.

32.7% change per year from baseline in amyloid-β+ cognitively unimpaired].

In MCI, p-tau217 was significantly higher in amyloid-β+ MCI at baseline ($\beta = 2.65$, $P < 0.001$). Phosphorylated-tau217 levels remained stable over time in the amyloid-β– MCI group ($\beta = 0.12$, $P = 0.39$), whereas it increased in amyloid-β+ MCI (Fig. 1B) (time × amyloid-β-interaction: $\beta = 0.67$, $P = 0.00032$; the increased rate corresponds to 14.7% change per year from baseline in amyloid-β+ MCI).

P-tau217 was also higher at baseline in MCI patients who subsequently developed Alzheimer's disease dementia (this included three amyloid-β– MCI patients, as the Alzheimer's disease dementia diagnosis was blinded to biomarker results) compared to the remaining MCI group (including both stable MCI and MCI who converted to other dementias) ($\beta = 2.25$, $P < 0.001$). P-tau217 remained stable over time in MCI patients who did not develop Alzheimer's disease dementia ($\beta = 0.053$, $P = 0.68$), but increased significantly over time in MCI to Alzheimer's disease dementia converters (Fig. 1C) (time × conversion interaction: $\beta = 0.79$, $P < 0.0001$). These results for conversion to Alzheimer's disease dementia were corroborated in a Cox survival analysis [hazard ratio (HR) = 1.25 (95% confidence interval, CI: 1.11–1.40), $P < 0.001$]. Similar results were obtained when stable MCI patients were excluded and the comparison was limited to MCI to Alzheimer's disease dementia converters versus those with MCI who converted to other dementias (baseline difference: $\beta = 1.91$, $P = 0.002$; stable over time in non-Alzheimer's disease MCI: $\beta = 0.020$, $P = 0.92$; acceleration in MCI to Alzheimer's disease dementia converters; time × conversion interaction: $\beta = 0.82$, $P = 0.00054$).

Longitudinal plasma neurofilament light in different diagnostic groups

Results for plasma NfL are shown in the lower part of Fig. 1. Among the cognitively unimpaired (Fig. 1D), there was no effect of amyloid-β status at baseline NfL ($P = 0.38$). There was a slight increase over time in NfL in the cognitively unimpaired independent of amyloid-β status (main effect of time in amyloid-β cognitively unimpaired, β = 0.60, $P < 0.001$; no difference depending on amyloid-β status, $P = 0.79$). The findings were similar in MCI (Fig. 1E), with no effect of amyloid-β status at baseline ($P = 0.57$) and a slight increase over time (main effect of time in amyloid-β MCI, β = 1.47, $P < 0.001$; no difference depending on amyloid-β status, $P = 0.45$). MCI patients who did not convert to Alzheimer's disease dementia had higher baseline plasma NfL compared with patients with MCI that converted to Alzheimer's disease dementia (Fig. 1F, β = 4.62, $P = 0.0095$), but there was no difference over time depending on whether they converted to Alzheimer's disease dementia or not ($P = 0.78$). The total number of observations available for plasma NfL was lower than for plasma p-tau217 ($n = 660$ versus $n = 707$). To ensure comparability between the NfL and p-tau217 results, we did a sensitivity analysis for p-tau217 restricted to samples where matching plasma NfL data were available. The results for p-tau217 were similar to the main analysis in this restricted set, both for amyloid-β– cognitively unimpaired versus amyloid-β+ cognitively unimpaired (time × amyloid-β-interaction: β = 0.34, $P < 0.001$), amyloid-β– MCI versus amyloid-β+ MCI (time × amyloid-β-interaction: β = 0.69, $P < 0.001$), and MCI to Alzheimer's disease dementia converters versus the remaining MCI group (time × Alzheimer's disease conversion interaction: β = 0.82, $P < 0.001$).

Power analyses to detect changes in plasma p-tau217

Power analyses showed that 109 participants per arm [interquartile range (IQR: 18, 282) would be required for 80% power to observe a reduction in slope for p-tau217 in amyloid-β+ cognitively unimpaired down to amyloid-β– cognitively unimpaired levels, while 71 participants per arm (IQR: 53, 96) would be required for 80% power to see a reduction in slope in amyloid-β+ MCI down to amyloid-β– MCI levels.

Longitudinal plasma p-tau217 and longitudinal cognition

We next tested associations between longitudinal plasma p-tau217 and longitudinal cognition (Fig. 2). Longitudinal increases in p-tau217 correlated with worsening cognition in both cognitively unimpaired and MCI, and also within the subgroups of amyloid-β+ participants. For each standard deviation higher slope of p-tau217, the decline in MMSE accelerated by β = –0.15 points ($P < 0.001$) in the overall cognitively unimpaired group (Fig. 2A), β = –0.13 points ($P = 0.007$) in the amyloid-β+ cognitively unimpaired group (Fig. 2B), β = –0.35 points ($P < 0.001$) in the overall MCI group (Fig. 2C), and β = –0.21 points ($P = 0.004$) per year in the amyloid-β+ MCI group (Fig. 2D). Corresponding accelerations in mPACC were β = –0.0048 points ($P < 0.001$) in the overall cognitively unimpaired group (Fig. 2E), β = –0.041 points ($P = 0.0245$) in the amyloid-β+ cognitively unimpaired group (Fig. 2F), β = –0.11 points ($P < 0.001$) in the overall MCI group (Fig. 2G), and β = –0.076 points ($P = 0.0074$) in the amyloid-β+ MCI group (Fig. 2H).

Longitudinal plasma p-tau217 and longitudinal atrophy

Finally, we tested associations between longitudinal plasma p-tau217 and longitudinal atrophy (Fig. 3). Longitudinally increased p-tau217 correlated with accelerated atrophy of temporal cortex and hippocampus in the amyloid-β– cognitively unimpaired, amyloid-β+ cognitively unimpaired, and in the overall MCI group. For each standard deviation higher slope of p-tau217 the thinning of temporal cortex accelerated by β = –0.0057 mm ($P < 0.001$) per year in the overall cognitively unimpaired group (Fig. 3A), β = –0.0077 mm ($P < 0.001$) in the amyloid-β+ cognitively unimpaired group (Fig. 3B) and β = –0.0068 mm ($P < 0.001$) in the overall MCI group (Fig. 3C). The association in the amyloid-β+ MCI group was non-significant (Fig. 3D, β = –0.0031 mm, $P = 0.16$). Corresponding accelerations in atrophy of hippocampus were β = –7.56 mm^3 ($P < 0.001$) per year in the overall cognitively unimpaired group (Fig. 3E), β = –11.8 mm^3 ($P < 0.001$) in the amyloid-β+ cognitively unimpaired group (Fig. 3F), and β = –12.0 mm^3 ($P < 0.001$) in the overall MCI group (Fig. 3G). The association in the amyloid-β+ MCI group was not statistically significant (Fig. 3H, β = –0.76 mm^3, $P = 0.72$).

Discussion

Plasma p-tau217 increased over time in the preclinical (amyloid-β+ cognitively unimpaired) and early clinical stages (amyloid-β+ MCI and MCI to Alzheimer's disease converters) of Alzheimer's disease, but remained stable in the control groups, i.e. amyloid-β– cognitively unimpaired, amyloid-β– MCI, and MCI patients who did not convert to Alzheimer's disease dementia. The changes were pronounced, giving high power to detect changes in a clinical trial scenario. Plasma NfL, a marker of neurodegeneration, did not show an Alzheimer's disease-related increase over time in this cohort. The longitudinal changes in plasma p-tau217 correlated to longitudinal changes in cognition and brain atrophy. This was seen for both the overall cognitively unimpaired and MCI groups, as well as in the subgroups of participants with preclinical (for both cognitive and structural measures) and early clinical Alzheimer's disease (for cognitive measures).

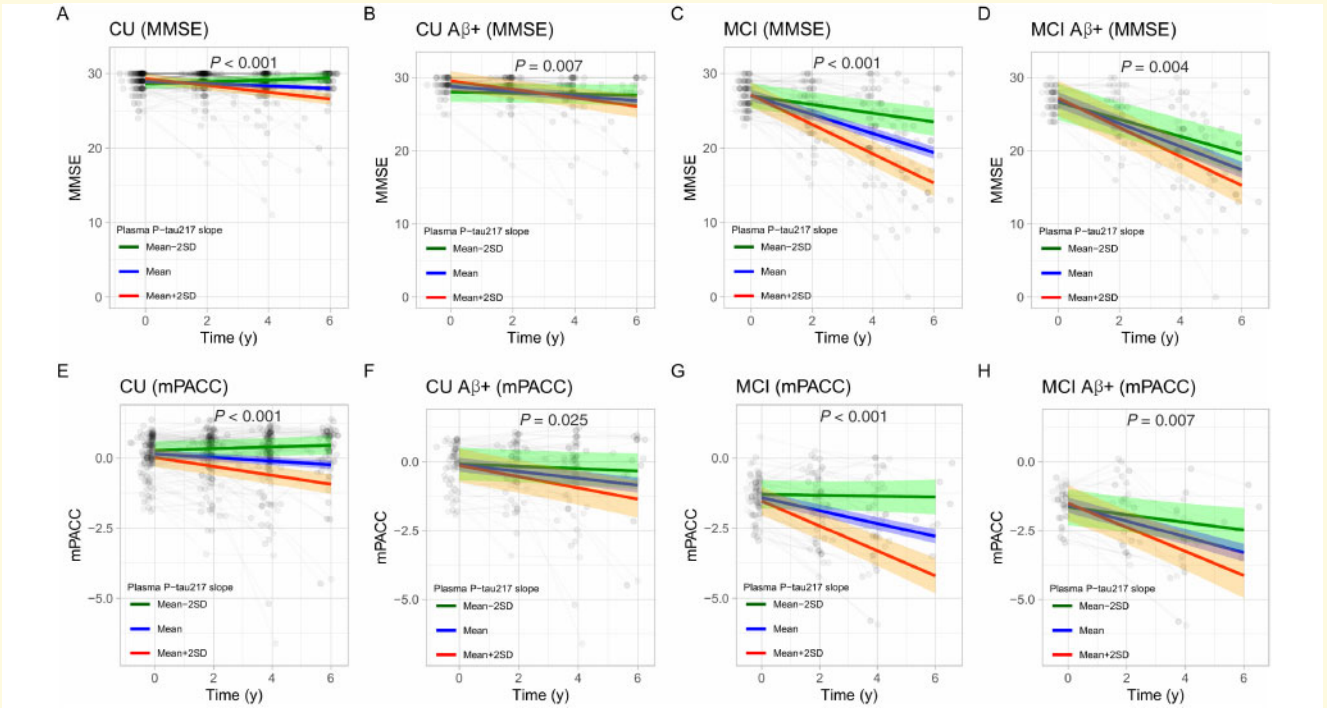

Figure 2 Longitudinal cognition by longitudinal plasma p-tau217. Subject-specific cognitive data are shown for (**A**) MMSE in all cognitively unimpaired (CU), (**B**) amyloid-β+ cognitively unimpaired, (**C**) all MCI, (**D**) amyloid-β+ MCI, €and mPACC in all cognitively unimpaired, (**F**) amyloid-β+ cognitively unimpaired, (**G**) all MCI, and (**H**) amyloid-β+ MCI. The *x*-axes show time from first plasma p-tau217 sample. Model trajectories are shown for different longitudinal plasma p-tau217 slopes (the mean slope and the mean ±2 SD), when adjusted for age, sex and education. Longitudinal p-tau217 correlated to longitudinal cognition in all models (see main text and *P*-values). At the mean p-tau217 slope level, the overall cognitively unimpaired group declined in MMSE and mPACC with β = –0.16 and β = –0.0064, respectively; the amyloid-β+ cognitively unimpaired group declined in MMSE and mPACC with β = –0.32 and β = –0.12, respectively; the overall MCI group declined in MMSE and mPACC with β = –1.28 and β = –0.23, respectively; and the amyloid-β+ MCI group declined in MMSE and mPACC with β = –1.58, and β = –0.29, respectively (all $P < 0.001$). Aβ = amyloid-β.

Taken together, our results demonstrate that plasma p-tau217 is a dynamic biomarker during early Alzheimer's disease, which may be useful to monitor disease progression in clinical practice and in drug development, including to evaluate the effects of novel Alzheimer's disease therapies. The clinically relevant longitudinal changes in plasma p-tau217, which correlate with both cognitive decline and (especially in the preclinical stage of the disease) increased brain atrophy, resemble previous reports of longitudinal changes of p-tau measures in CSF (Donohue *et al.*, 2017; Falcon *et al.*, 2018; Koychev *et al.*, 2020). The fact that these clinically relevant tau-related changes can now be detected in plasma opens new venues of applied research. Already completed clinical trials (e.g. for promising anti-amyloid-β therapies) can be retrospectively tested for effects on plasma p-tau217. Banked longitudinal plasma samples in epidemiological studies can be analysed for p-tau217 to identify factors (e.g. demographic or genetic) that are associated with faster or slower development of tau pathology.

Note that since the individual subgroups were relatively small (e.g. $n = 49$ amyloid-β+ MCI), we may have been underpowered to detect significant correlations between changes in p-tau217 and some other measures (such as associations between changes in p-tau217 and changes in temporal cortex thickness in amyloid-β+ MCI, Fig. 3D).

To conclude, plasma p-tau217 levels accelerate over 6 years in preclinical and prodromal stages of Alzheimer's disease. This can be used for minimally invasive, objective monitoring of disease progression in Alzheimer's disease.

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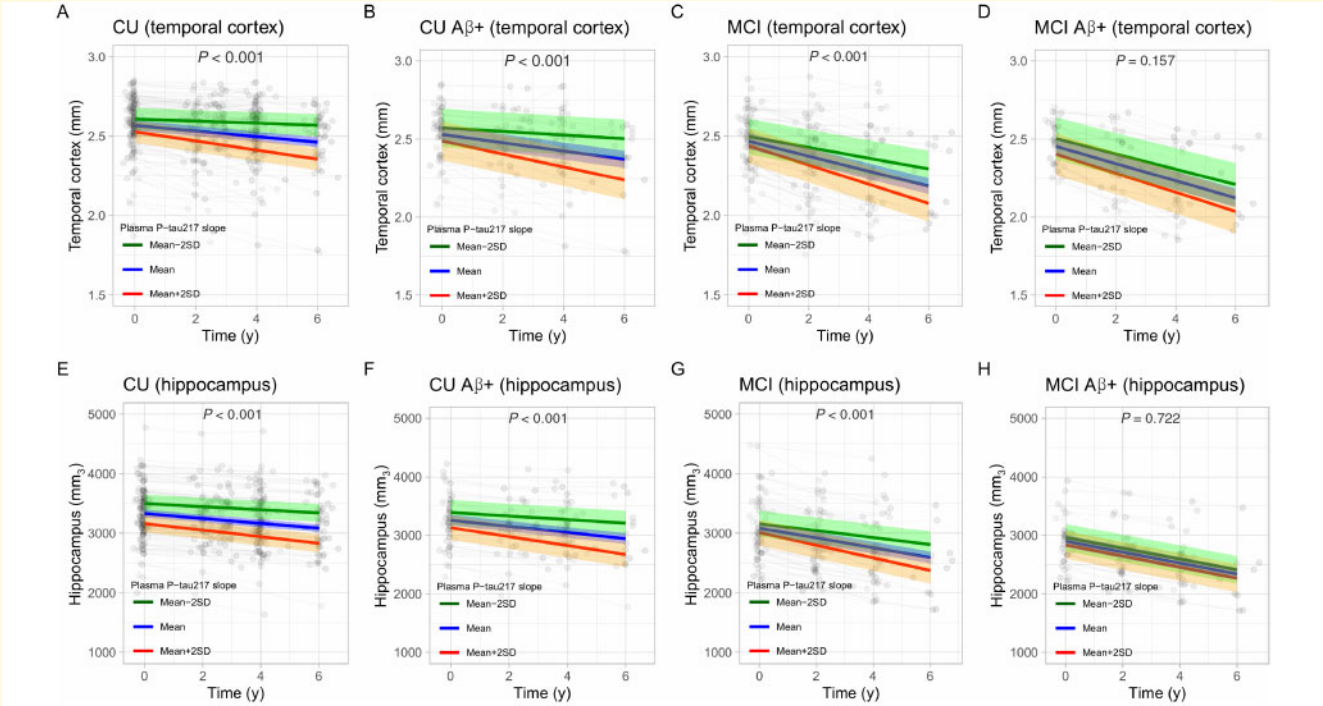

Figure 3 Longitudinal brain structure by longitudinal plasma p-tau217. Subject-specific MRI data are shown for (**A**) temporal cortex thickness in all cognitively unimpaired (CU), (**B**) amyloid-β+ cognitively unimpaired, (**C**) all MCI, (**D**) amyloid-β+ MCI, and (**E**) hippocampal volume in all cognitively unimpaired, (**F**) amyloid-β+ cognitively unimpaired, (**G**) all MCI, and (**H**) amyloid-β+ MCI. The *x*-axes show time from first plasma p-tau217 sample. Model trajectories are shown for different longitudinal plasma p-tau217 slopes (the mean slope and the mean ±2 SD), when adjusted for age, sex and (for hippocampal volume) intracranial volume. Longitudinal p-tau217 correlated to longitudinal atrophy in all models except for in amyloid-β+ MCI (see main text and *P*-values). At the mean p-tau217 slope level, the overall cognitively unimpaired group declined in temporal cortex thickness and hippocampal volume with $\beta = -0.017$ and $\beta = -41.0$, respectively; the amyloid-β+ cognitively unimpaired group declined in temporal cortex thickness and hippocampal volume with $\beta = -0.027$ and $\beta = -53.3$, respectively; the overall MCI group declined in temporal cortex thickness and hippocampal volume with $\beta = -0.047$ and $\beta = -82.2$, respectively; and the amyloid-β+ MCI group declined in temporal cortex thickness and hippocampal volume with $\beta = -0.055$ and $\beta = -93.4$, respectively (all $P < 0.001$).

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Competing interests

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