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## Concatenating plasma p-tau to Alzheimer's disease

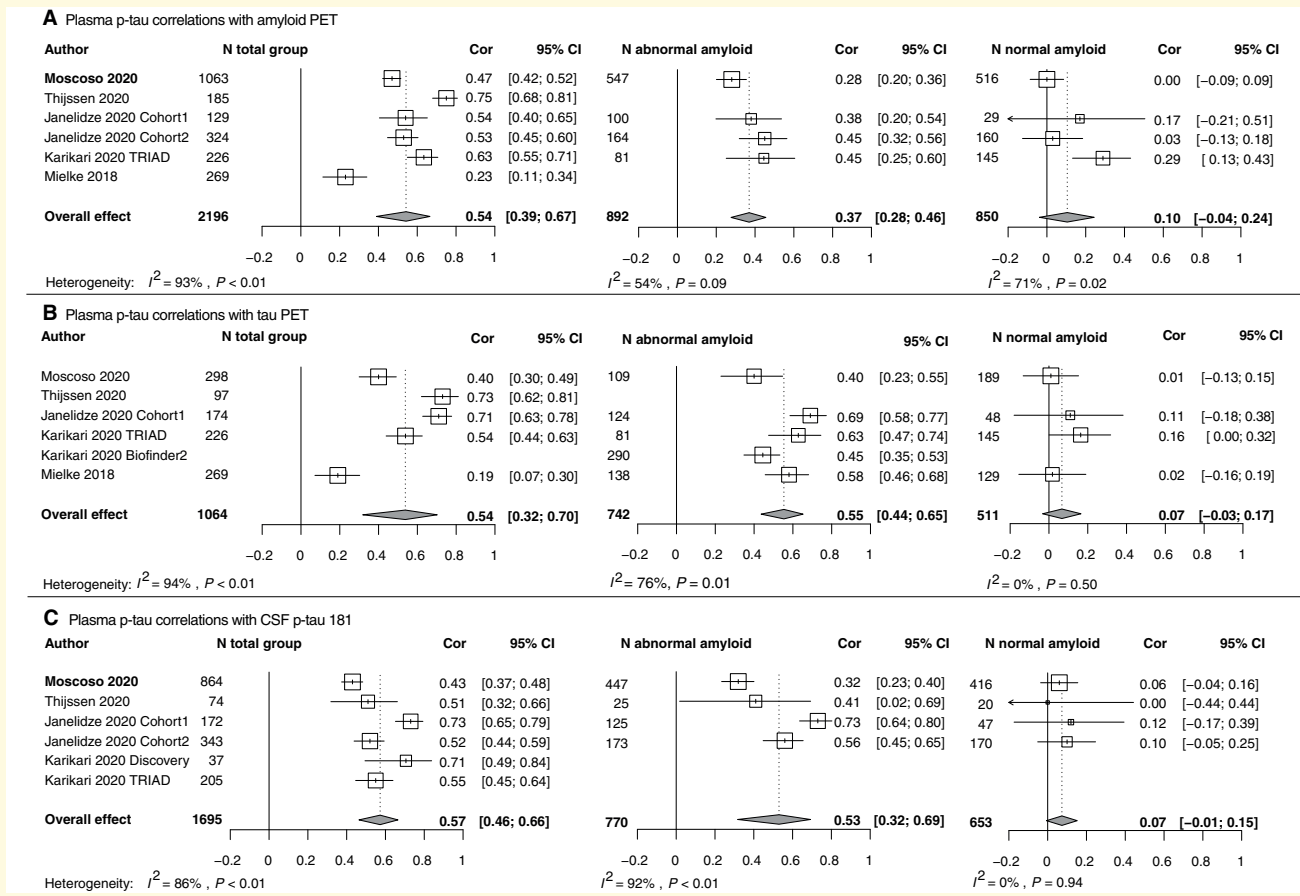
This scientific commentary refers to 'Time course of phosphorylated-tau181 in blood across the Alzheimer's disease spectrum', by Moscoso *et al.* (doi:10.1093/brain/awaa399).

Amyloid plaques and tau tangles are the pathological hallmarks of Alzheimer's disease, and the capacity to detect amyloid and tau on PET and in CSF has greatly improved the disease diagnostic process (Jack *et al.*, 2018). Now amyloid and tau can also be measured in blood, and since blood is easier to obtain than PET images or CSF, this could enable biomarkers to become part of diagnostic work-ups on a much larger scale. One such biomarker is plasma p-tau181, which is proposed to be a specific marker for tau pathology in Alzheimer's disease. Recent studies support its use as a screening tool by showing that its levels are increased in patients with Alzheimer's disease compared to controls or patients with other tauopathies, and correlate with other Alzheimer's disease biomarkers (Mielke *et al.*, 2018; Janelidze *et al.*, 2020; Karikari *et al.*, 2020; Thijssen *et al.*, 2020). But even when markers target the same pathological substrate,

different modalities can pick up different aspects of pathology. For example, CSF measures of amyloid show a higher dynamic range over normal levels, and seem more sensitive than PET to the earliest changes in amyloid concentrations in Alzheimer's disease, whereas PET seems to be better at capturing later changes (Palmqvist *et al.*, 2016). Combining repeated measures from multiple modalities can thus improve our understanding of which aspects of pathophysiology each biomarker captures. Such knowledge is important for trial development, when there is a need to identify individuals in whom primary or secondary interventions would be most effective. Longitudinal biomarker studies are pivotal to our understanding of the natural disease course of Alzheimer's disease, and will enable us to determine when a given biomarker is sensitive to Alzheimer's disease-related changes and could thus be useful as a treatment outcome measure.

Untangling longitudinal changes in p-tau levels across Alzheimer's disease stages was exactly the objective of Moscoso and colleagues, who present their findings on the dynamics of the novel plasma marker p-tau181 in this issue of *Brain* (Moscoso *et al.*, 2021).

They made use of the Alzheimer's Disease Neuroimaging Initiative (ADNI), which has been recruiting and following individuals with normal cognition, mild cognitive impairment (MCI) and dementia since 2004. Some individuals in the ADNI have thus been followed for almost 17 years, which is approaching the hypothesized period of ~20 years that may separate the start of Alzheimer's disease pathophysiology from the onset of clinical symptoms. The ADNI has collected and biobanked biofluid samples, including CSF and blood, and used them to obtain repeated measures of multimodal markers of Alzheimer's disease pathology. This biobank thus provides the opportunity to quickly study and validate new markers for Alzheimer's disease in a large group of individuals with extensive phenotyping. Moscoso *et al.* used one of the new plasma p-tau181 assays on blood samples in an unprecedented sample of 1067 individuals from a single cohort. All individuals had an amyloid PET scan at first visit, a subset had CSF amyloid- $\beta_{1-42}$  and p- and total tau measures, and another subset had tau PET that was acquired 6 years after the first visit.



**Figure 1** Effect size forest plots of reported relationships between plasma p-tau 181 and other biomarkers for amyloid and tau, for total group (left), abnormal amyloid (middle), and normal amyloid (right). (A) Correlations with amyloid PET; (B) correlations with tau PET [note, in Moscoso et al. (2021), tau PET was acquired 6 years after the plasma p-tau measures]; and (C) correlations with CSF p-tau 181. Figure created with the R package ‘meta’ version 4.15-1.

The authors first performed cross-sectional analyses to understand the relationship between plasma p-tau181 levels and CSF and PET measures of amyloid and tau at baseline. Higher plasma p-tau181 concentrations were related to higher amyloid- $\beta$  load on PET, lower concentration of amyloid- $\beta_{1-42}$  in CSF, and higher p-tau levels in CSF. Furthermore, higher plasma p-tau levels at baseline predicted higher tau PET signals 6 years later, suggesting plasma measures pick up very early signs of tangles (although the relationship at baseline remains unknown). All these relationships were only observed in individuals with abnormal amyloid, in line with reports from previous studies in different cohorts (Fig. 1). Together the results suggest that increased levels of p-tau are likely to be a consequence of amyloid plaque aggregation. Across all

studies the strongest correlations were observed with other tau biomarkers, but these too were of only moderate strength. The comparison between plasma and CSF p-tau showed divergence for high CSF p-tau values, where plasma p-tau plateaued. This may suggest that p-tau in blood and CSF reflect distinct aspects of the underlying pathology.

Next, the authors studied changes in plasma p-tau levels over time. The observed average annual increase in cognitively normal individuals with normal amyloid was  $\sim 1.5\%$  compared to baseline. Rates were higher across the Alzheimer’s disease spectrum, with annual increases in plasma p-tau levels of 2.5% in preclinical disease and 3% in Alzheimer’s disease dementia compared to baseline. The investigators then studied how longitudinal changes in p-tau depend on

baseline levels of other biomarkers. Higher baseline levels of amyloid PET and CSF p-tau, and lower levels of CSF amyloid- $\beta_{1-42}$  were related to steeper increases in plasma p-tau181. Furthermore, changes in plasma p-tau181 levels were related to changes in other markers, for example, individuals who showed faster increases in amyloid PET also showed steeper increases in plasma p-tau. These relationships were specific to individuals with abnormal amyloid at baseline. This suggests that the changes in these biomarkers reflect a shared underlying mechanism. Lastly, longitudinal changes in plasma p-tau levels showed stronger correlations with tau PET levels 6 years later than baseline plasma p-tau measures, which supports the possibility that increases in plasma p-tau181 over time reflect the formation of tangles. However, a small subset of

## Glossary

**To concatenate:** To link together things or events in a chain or series, such as tying together individual biomarker trajectories into one overall trajectory spanning the disease course.

~62 (12%) individuals with an initially normal amyloid PET at baseline had high plasma p-tau181 baseline values and rates that were in the same range as those of individuals with abnormal PET. This suggests that high plasma p-tau181 levels may also reflect other aspects of tau metabolism, possibly unrelated to Alzheimer's disease.

Finally, the authors tried to untangle all Alzheimer's disease biomarker trajectories by ordering and concatenating individual biomarker trajectories across 'disease progression time', an approach pioneered by Villemagne and colleagues (Villemagne *et al.*, 2013; Budgeon *et al.*, 2017). Disease progression time is defined as the time it takes for a biomarker to become abnormal starting from the median levels observed for that biomarker in controls with normal amyloid. It is defined for each biomarker separately, and assumes that biomarker levels become increasingly abnormal as the disease progresses. Taking this assumption as a starting point, individuals can then be ordered in their supposed disease trajectory based on the combination of their initial levels and modelled rate of change for that biomarker. In the present study it was estimated that it takes 17.5 years to develop abnormal amyloid PET, which was similar to 19 years estimated previously in ADNI (Budgeon *et al.*, 2017), and somewhat longer than 12 years estimated in another cohort (Villemagne *et al.*, 2013). Plasma and CSF p-tau became abnormal 5 years after amyloid was abnormal. The modelling did not take into account cognitive stage, because it was assumed that disease progression is fully explained by biomarker levels. Impaired cognition is the end result of Alzheimer's disease, and it is unclear which biomarker changes cause decline, since biomarker levels explain only part of the variance in cognition.

High plasma p-tau181 levels, for example, were also observed in cognitively normal controls with normal amyloid, thus these levels do not necessarily reflect impaired cognition. Second, by concatenating short biomarker trajectories across individuals spanning the clinical spectrum it is assumed that all individuals follow the same trajectory. However, there are likely subgroups in the data that could follow different trajectories. For example, 28% of controls were APOE  $\epsilon$ 4 carriers compared to 47% with MCI and 66% with dementia, suggesting that these groups differ at a genetic level, and may thus follow different trajectories. Indeed, in our own study, in which we used actual follow-up time in ADNI, we found that changes in amyloid markers amongst cognitively normal controls seem to be driven by a small group, with the majority of individuals remaining stable over time (Tijms *et al.*, 2018). Cognitively normal individuals whose amyloid levels did become abnormal, took only 4–5 years to reach the thresholds for CSF or PET (Tijms *et al.*, 2018). Thus, modelling disease course by concatenating short trajectories in heterogeneous groups may lead to inaccurate time estimates for biomarkers to become abnormal. Ultimately the true natural disease course of Alzheimer's disease can only be determined in individuals who have been followed for a long enough time period. Even in ADNI, which has been running for 17 years, the repeated biomarker sampling within this timeframe is relatively limited. Therefore, it is critical that longitudinal cohorts such as ADNI continue following their participants with repeated biomarker assessments.

The biological implication of this study is that increases in p-tau are likely to result from amyloid pathology in the majority of individuals, and that changes in p-tau181 occur early but

well after amyloid markers become abnormal. The time window between abnormal amyloid and abnormal plasma p-tau of possibly 6 years, suggests an opportunity for secondary prevention, and the potential for plasma p-tau to serve as an outcome measure to help detect treatment effects.

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## Competing interests

The authors report no competing interests.

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