Alzheimer’s disease (AD) is as a continuum entailing a preclinical phase, where individuals are cognitively unimpaired but amyloid-β (Aβ) and tau pathology have begun, followed by a clinical phase (including mild cognitive impairment and dementia). In the preclinical Alzheimer stage, Aβ and tau progressively accumulate over 2 decades or more. On top of these, multiple other pathophysiological processes are altered, including astroglial and microglial activation, synaptic dysfunction, vascular dysfunction and the presence of co-pathology.

The measurement of the core cerebrospinal fluid (CSF) biomarkers (i.e. Aβ42, t-tau and p-tau) and Aβ and tau PET enables the very accurate diagnosis of AD in patients with cognitive symptoms. These excellent biomarkers also allow the detection of preclinical Alzheimer, when pathological brain changes emerge in the absence of evident clinical symptoms. Yet, it should be emphasised that preclinical Alzheimer is not a uniform or unvarying stage, but it is a long process during which Aβ gradually accumulates until overt Aβ plaque deposition is present. Even before Aβ plaques are formed, and Aβ PET becomes positive, there is a transitional stage preceding the threshold of Aβ positivity that has received several names, such as intermediate levels, emerging pathology, early preclinical, pre-preclinical or low Aβ burden.3 While the field moves towards intervention trials in earlier disease stages, there is the unmet need to develop sensitive and robust biomarkers that stage the progression within preclinical Alzheimer (from early to late preclinical Alzheimer).

The pattern of phosphorylation of p-tau changes across the course of the disease4 and, hence, the sequential changes in the different p-tau epitopes are good candidates to delineate the different phases within preclinical Alzheimer. CSF p-tau181 is the most widely used p-tau biomarker, particularly in the clinical setting, but new data indicate that other p-tau epitopes phosphorylated at other sites, namely p-tau217 and p-tau231, may be at least as useful as p-tau181. Indeed, CSF p-tau217 may outperform CSF p-tau181 to detect preclinical and clinical AD,5 and CSF p-tau231 increases early in the Alzheimer’s continuum, when only subtle Aβ changes are detected.6 Another p-tau epitope, CSF p-tau235, is significantly increased at the later phase of preclinical Alzheimer.7 It needs to be investigated to what extent each of the p-tau epitopes provide different information on the disease and what they may be more useful for, both in clinical practice and in research settings.

In this line, in eBioMedicine, Ashton & Benedet et al. investigated CSF p-tau181, p-tau217 and p-tau231 across the Alzheimer’s continuum, from the preclinical to the dementia stage, in the Translational Biomarkers in Aging and Dementia (TRIAD) cohort. They demonstrate that all p-tau epitopes are significantly increased in asymptomatic and symptomatic individuals with underlying AD pathology (as defined by Aβ and tau PET), and discriminate them from individuals without AD pathology. Yet, there are remarkable differences between the three p-tau epitopes. Both CSF p-tau217 and p-tau231 showed a stronger association with both Aβ and tau PET than CSF p-tau181. Moreover, CSF p-tau217 had the highest fold-change increases in symptomatic stages of the disease, while CSF p-tau231 better captured the earliest Aβ changes in the preclinical stage. A key result of this study is that CSF p-tau231 is already significantly increased before overt Aβ pathology. In cognitively unimpaired individuals, CSF p-tau231 was significantly associated with Aβ PET retention in brain areas that are typically affected early in the AD process, such as the medial orbitofrontal, precuneus and posterior cingulate cortices. Finally, the modelling of the CSF p-tau biomarkers as a function of Aβ PET Centiloids (CL) showed that CSF p-tau231 was the first biomarker to surpass abnormal levels (as defined by 2 standard deviations), at approximately 37-38 CL, while CSF p-tau181 and p-tau217 reached those abnormal levels at higher Aβ burdens.

Based on these findings, it would seem that CSF p-tau231 responds to early Aβ dyshomeostasis, even

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preceding Aβ and also tau aggregation and deposition. In the context of the ATN classification, it may be discussed whether CSF p-tau231 should be considered as part of the “T” (tau pathology) or the “A” (Aβ pathology). Albeit counterintuitive, the early increase of CSF p-tau231 argues in favour of the latter. This is consistent with the evidence of active secretion of p-tau in response to Aβ.9

Thus, we now have a range of p-tau biomarkers that, although similar and highly correlated among them, have subtle differences in their indication of Aβ and tau pathology across the disease continuum. This has clear consequences for the design of both observational and interventional studies at different stages of the Alzheimer’s continuum, particularly in the long preclinical stage. The choice of focusing a prevention trial at earlier or later stages of preclinical Alzheimer or, in other words, different baseline levels of Aβ burden, may change depending on the mechanisms being targeted. Some considerations on this choice are the specific drug being tested and whether combination trials are considered (e.g. anti-amyloid and anti-tau drugs), the expected length of follow-up to detect changes in the main outcome, or the age range of the participants. In this context, CSF p-tau231 may be the biomarker of choice for identifying individuals in the very earliest stages of the Alzheimer’s continuum with subtle Aβ changes. In later stages of preclinical AD (when there are clear signs of Aβ and tau pathology as assessed by PET), all CSF p-tau biomarkers show excellent performance but, once patients transition to the symptomatic stage, CSF p-tau217 renders the best results. In conclusion, different p-tau epitopes change in the CSF during the course of AD and may be useful to indicate different stages of the disease. Current and rapid developments point out that these findings in CSF will also be translated to blood,10 which - if confirmed - will greatly facilitate prevention trials in AD.

Declaration of interests
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References
1. Mila-Alomá M, Salvadó G, Shekari M, et al. Comparative analysis of different definitions of amyloid-B positivity to detect early downstream pathophysiological alterations in preclinical Alzheimer. J Prev Alzheimer’s Dis. 2020;7:1–10. https://doi.org/10.14283/jpad.2020.51.
2. Aisen PS, Bateman RJ, Carrillo M, et al. Platform trials to expedite drug development in Alzheimer’s disease: a report from the EU/US CTAD task force. J Prev Alzheimer’s Dis. 2021;8:306–312. https://doi.org/10.14283/jpad.2021.21.
3. Farrell ME, Jiang S, Schultz AP, et al. Defining the lowest threshold for amyloid-PET to predict future cognitive decline and amyloid accumulation. Neurology. 2021;96:e619–e631. https://doi.org/10.1212/WNL.0000000000001214.
4. Barthelemy NR, Li Y, Joseph-Mathurin N, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer’s disease. Nat Med. 2020;26:498–507. https://doi.org/10.1038/s41591-020-0781-z.
5. Janelidze S, Stromrud E, Smith R, et al. Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer’s disease. Nat Commun. 2020;11:1683. https://doi.org/10.1038/s41467-020-15436-0.
6. Suárez-Calvet M, Karikari TK, Ashton NJ, et al. Novel tau biomarkers phosphorylated at Thr181, Thr217 or Thr231 rise in the initial stages of the preclinical Alzheimer’s continuum when only subtle changes in Aβ pathology are detected. EMBO Mol Med. 2020;12:e12921. https://doi.org/10.15252/emmm.202012921.
7. Lantero-Rodriguez J, Snellman A, Benedet AL, et al. P-tau235: a novel biomarker for staging preclinical Alzheimer’s disease. EMBO Mol Med. 2021:15. https://doi.org/10.15252/emmm.202115098.
8. Ashton NJ, Benedet AL, Pascoal TA, et al. Cerebrospinal fluid p-tau231 as an early indicator of emerging pathology in Alzheimer’s disease. eBioMedicine. 2020;76. https://doi.org/10.1016/j.ebiom.2020.103836.
9. Sato C, Barthelemy NR, Mawuenyega KG, et al. Tau kinetics in neurons and the human central nervous system. Neuron. 2018;97:1284–1298. https://doi.org/10.1016/j.neuron.2018.02.015.
10. Ashton NJ, Pascoal TA, Karikari TK, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer’s disease pathology. Acta Neuropathol. 2021. https://doi.org/10.1007/s00401-021-02275-6.