## DUNEDIN STUDY CONCEPT PAPER FORM

**Provisional Paper Title:** Performance of pTau181 in a middle-aged birth cohort: Associations with cognitive decline, brain structural integrity, and accelerated ageing.

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Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

**Objective of the study:**

Diagnosis of preclinical Alzheimer's disease (AD) is difficult and expensive, with the most commonly used technologies not suitable for population-wide screening. Blood tests measuring biomarkers of preclinical AD appear increasingly appealing as a screening tool as well as vitally important as selection tools and/or surrogate endpoints in clinical trials. However, we need to better understand these biomarkers in the general population, and particularly in middle-aged individuals without dementia, before this biomarker can be progressed to clinical implementation.

Blood-based biomarkers for AD typically reflect the core pathological hallmarks of AD, such as hyperphosphorylated tau (pTau) which forms neurofibrillary tangles.[1,2] Tau phosphorylated at threonine 181 (pTau181) is currently one of the most promising of these biomarkers. Elevated levels of pTau181 are thought to be specific to AD and discriminate from other neurodegenerative disorders,[3–5] and pTau181 levels increase with AD progression.[6,7] High pTau181 levels in plasma have been found to predict progression to AD in cognitively unimpaired individuals[8] and were increased in amyloid β-positive young adults compared to amyloid β-negative young adults,[9] suggesting it may be a potential biomarker for the earliest stages of AD. However, pTau181 has not, to our knowledge, been studied in a middle-aged, general population-based cohort,

and it is not currently known how long before clinical presentation of AD elevated pTau181 levels become apparent.[10] Assessing population-based samples of middle-aged, pre-AD individuals is critical to understanding how and when pTau181 could be useful in identifying risk for AD.

This paper has three objectives:

- Examine the association between pTau181 levels and cognitive decline in middle-age.
- Examine the association between pTau181 levels and neurostructural abnormalities indicative of increased risk for developing AD or related dementias.
- Investigate whether individuals with higher levels of pTau181 are ageing faster than their peers.

**Data analysis methods:**

We will use regression methods to examine associations at age 45 between pTau181 and cognitive decline, brain structure, and pace of biological aging. Sex will be a covariate in all analyses; APOEε4 status will be used as a covariate in sensitivity analysis. Due to the number of analyses with MRI variables, a false discovery rate procedure will be used; for all other analyses, an alpha level of .05 will be used.

First, we will test for an association between pTau181 and cognition in childhood (FSIQ ages 7-11), then with cognition in adulthood (FSIQ and indices at age 45). Then we will test for an association between pTau181 and cognitive decline from childhood to age 45 – firstly, with adult FSIQ and indices as predictors, controlling for childhood IQ, and then by testing for an association with residualised IQ change. In sensitivity analysis we will categorise participants' cognitive decline and test whether those with a greater decline in cognition since childhood display higher levels of pTau181.

We will then test for an association between pTau181 and brainAGE. Posthoc analyses will be conducted to investigate associations between cortical thickness and surface area (at the global and parcel-wise levels), grey matter volume of subcortical structures, and white matter hyperintensities (global). This will help us to determine if specific structural features may be more strongly associated with elevated pTau181 levels.

Finally, we will test for an association between ageing as measured by Pace of Aging (PoA) and/or DNA methylation (DunedinPACE) and pTau181.

**Variables needed at which ages:**

- pTau181 level (Simoa immunoassaying on stored plasma from phase 45)
- APOE ε4 status (from age 26)

- IQ data from age 45 (FSIQ and indices [verbal comprehension, working memory, perceptual reasoning, processing speed])
- FSIQ from ages 7, 9, and 11
- Residualised IQ change (calculated from ages 7, 9, 11, to 45)
- IQ change score (calculated from ages 7, 9, 11, and 45)
- MRI data (all at age 45):
    - brainAGE
    - White matter hyperintensity volume (global)
    - Mean cortical surface area and thickness (global and parcellated)
    - Subcortical structure grey matter volume (10 key subcortical structures)
    - Total brain volume (as covariate in supplementary analysis)
    - Fractional anisotropy (average and tract-wise)
    - White matter volume (global)
    - Total brain volume
- DunedinPACE (age 45)
- Pace of Aging
- Sex

Note: The Otago Health and Disability Ethics Committee has reviewed and approved this research.

**Significance of the Study (for theory, research methods or clinical practice):**
The pathogenesis of AD begins long before symptoms become apparent.[11] This paper will help elucidate whether one of these neuropathological changes, elevated pTau181 levels in plasma, can be detected in middle age, decades before any potential AD diagnosis. In addition, we will examine whether elevated levels of pTau181 are associated with other indicators of higher risk for AD (i.e. neurostructural integrity from MRI and cognitive decline across the lifecourse). These findings could lead to earlier risk assessment and diagnosis of AD, at a point in the disease process when lifestyle and/or pharmaceutical treatments may have the greatest effects, leading to early mitigation and hopefully primary prevention of AD.

Identifying preclinical biomarkers of AD is essential to ensuring effective treatment and mitigation of AD symptoms, as well as facilitating the selection and monitoring of participants in clinical trials for AD treatments. This paper will make a novel contribution to the growing literature on blood-based biomarkers of AD by helping to determine the potential of pTau181 as a blood biomarker of AD in a middle-aged, rather than elderly, population.

Evidence indicates people who are experiencing accelerated neurodegeneration in middle age are also undergoing systemic ageing at a faster rate than their peers,[12,13] in which case a diagnosis of preclinical AD should be accompanied by wrap-around treatment plans that consider other aspects of the individual's health. To investigate

these important questions, we intend to investigate whether higher levels of pTau181 are associated with faster DunedinPACE, a systemic measure of the rate that a person is ageing based on DNA methylation.

Finally, as the Dunedin Study is a population-representative cohort of people who are the same chronological age, data on biomarker levels in the cohort will contribute to the development of reference ranges for pTau181. This is particularly important as levels of pTau181 may alter with age,[14] but this could be a product of increasing likelihood of neuropathy in older people. Examining biomarker levels in a same-aged cohort will provide important information about reference ranges, aiding in the translation of these biomarkers to clinical implementation.[10]

**References:**


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