Modifiable risk factors for dementia, cognition and plasma phosphorylated tau 181 in a large-scale cohort of Australian older adults

Eddy Roccati[1], Jessica Collins[1], Aidan Bindoff[1], Jane Alty[1,2], Larissa Bartlett[1], Anna King[1], James Vickers[1]

1: Wicking Dementia Research and Education Centre, University of Tasmania 2: Royal Hobart Hospital, Hobart, Tasmania, Australia

eddy.roccati@utas.edu.au - @eddy_roccati - utas.edu.au/wicking

1. Background

- We know up to 40% of dementia cases could be prevented through addressing modifiable risk factors[1]
- We also know Alzheimer's disease (AD) is preceded by up to decades of silent pathological change[2]
- This window of early biological change is a window of opportunity for early detection and intervention
- Blood-based biomarkers offer cost-effective, scalable and minimally invasive ways to measure the impact of an intervention
- Plasma phosphorylated (p-tau) 181 is emerging as a front runner blood-based biomarker for AD
- AD biomarkers are known to be influenced, sometimes differentially, by covariates such as age, sex, ethnicity, apolipoprotein E epsilon 4 (APOE-ε4), renal disease, cardiovascular disease, body mass index (BMI) and hypertension[3,4]
- Several of these covariates are known modifiable risk factors for dementia1 so in order to provide confidence in the interpretation of p-tau 181 in detecting *pre-clinical* AD, we need to understand how both modifiable and non-modifiable risk factors are associated with plasma p-tau 181 in the general population

2. Methods

- Participants recruited from the ISLAND Study Linking Ageing and Neurodegenerative Disease (ISLAND) [5]
- ISLAND is a prospective public health initiative in Tasmania, Australia's southernmost island state[5]
- ISLAND participants were invited to complete a set of surveys online: a questionnaire on dementia risk factor adherence, demographic surveys[5]
- Cognitive tests administered online via the Cambridge Neuropsychological Test Automated Battery (CANTAB); Paired Associates Learning (PAL) and Spatial Working Memory (SWM)
- At four clinics across the state, participants also provided blood samples for measurement of plasma phosphorylated tau 181 (p-tau 181) and genotyping for APOE

3. Results I

- 738 ISLAND participants took part in the study. Almost half of ISLAND participants (49.2%, n = 348) reported a family history of dementia and 26.4% (n = 194) had at least one APOE-ε4 allele
- Participants with a family history of dementia were significantly more likely to possess an ε4 allele. Non-modifiable risk factors were not associated with plasma p-tau 181 after adjustment for covariates
- We found impaired learning (CANTAB PAL) was associated with higher plasma concentrations of phosphorylated p-tau 181
- Increasing age, being female, having less education and possessing the APOE-ε4 allele were significantly associated with worse strategy scores in CANTAB SWM

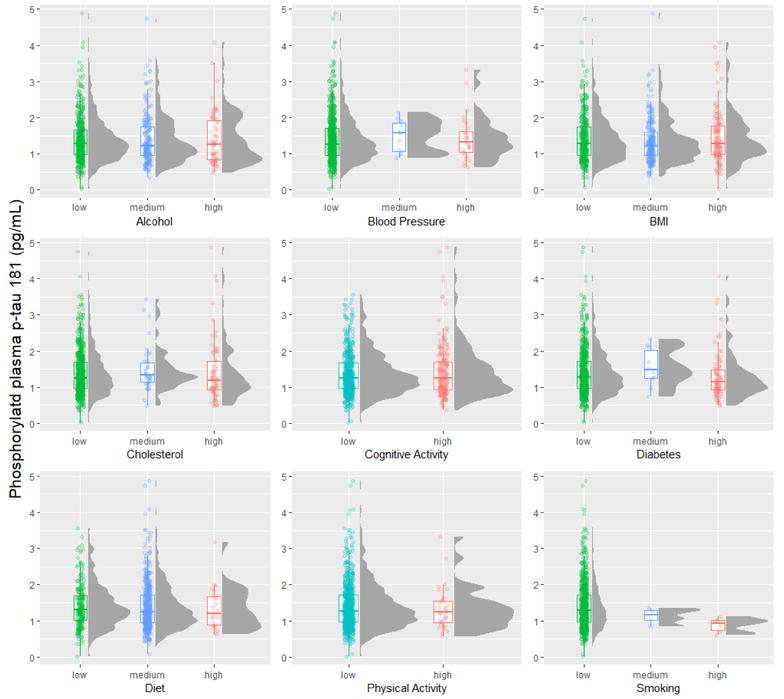

Figure 1: Modifiable risk factors and plasma concentrations of p-tau 181 (pg/mL)

4. Results II

	Total	Female	Male	p-value
N (%)	**738**	**530 (71.8)**	**208 (28.2)**	
Age at baseline (mean [SD])	65.41 (6.89)	65.02 (6.65)	66.40 (7.40)	0.015*
Total school years (mean [SD])	17.36 (3.13)	17.27 (3.07)	17.59 (3.26)	0.319
Employed (%)	277 (38.0)	212 (40.5)	65 (31.6)	0.030*
Family history of dementia (%)	358 (49.2)	267 (51.0)	91 (44.6)	0.145
APOE-ε4 genotype				0.297
e2e2	3 (0.4)	3 (0.6)	0 (0.0)	
e2e3	88 (12.0)	59 (11.2)	29 (14.0)	
e2e4	15 (2.0)	10 (1.9)	5 (2.4)	
e3e3	418 (56.9)	312 (59.1)	106 (51.2)	
e3e4	159 (21.6)	112 (21.2)	47 (22.7)	
e4e4	20 (2.7)	14 (2.7)	6 (2.9)	
CANTAB PAL (mean [SD])	15.87 (13.27)	14.88 (12.44)	18.41 (14.91)	0.001**
CANTAB SWM (mean [SD])	14.45 (4.94)	14.73 (4.73)	13.74 (5.36)	0.015*
Plasma p-tau pg/mL (mean [SD])	1.40 (0.64)	1.34 (0.60)	1.55 (0.72)	0.001**

Table 1: Demographic statistics for included ISLAND participants (n = 738)

5. Conclusions

- In a cognitively healthy cohort recruited from the general population in Tasmania, Australia, we found modifiable risk factors were not associated with plasma levels of p-tau 181, a key biomarker in AD
- Further, given the sex and genetic differences in plasma p-tau 181, we may expect to see sex-specific impacts of modifiable risk on blood-based biomarkers for dementia over time.
- Longitudinal biomarker collection in ISLAND is underway, we will be investigating how positive behaviour change may result in a change in biomarkers for AD, such as plasma p-tau 181

References

1: Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. The Lancet. 2: Jack Jr CR, Bennett DA, Blennow K, et al. NIA-AA Research framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia. 2018. 3: Tariot P. Blood-Based Biomarkers for Alzheimer's Disease: Are We There Yet? JPAD. 2022. 4: Syrjanen J, Campbell M, Algeciras-Schimnich A, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. Alzheimer's & Dementia. 2022. 5: Bartlett L, Doherty K, Farrow M et al. Island Study Linking Aging and Neurodegenerative Disease (ISLAND) Targeting Dementia Risk Reduction: Protocol for a Prospective Web-Based Cohort Study. JMIR research protocols. 2022.

Acknowledgements

- We acknowledge and deeply thank the contributions made by our study participants, the Wicking Centre data managers (Alex Kitsos and Timothy Saunder), Wicking laboratory team (Graeme McCormack), ISLAND Portal web development team (Joshua Eastgate) and the ISLAND Project Team (Helen Douglas, Justine Keay and Adam Kane) are gratefully acknowledged
- This was a sub-study of the ISLAND Project, which is supported by the Medical Research Futures Fund Keeping Tasmanians out of Hospital, the University of Tasmania, St Lukes Health, and the Masonic Centenary Medical Research Foundation.