

1. Background

- We know up to 40% of dementia cases could be prevented through addressing modifiable risk factors¹
- We also know Alzheimer’s disease (AD) is preceded by up to decades of silent pathological change²
- 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 state⁵
- ISLAND participants were invited to complete a set of surveys online: a questionnaire on dementia risk factor adherence, demographic surveys⁵
- 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

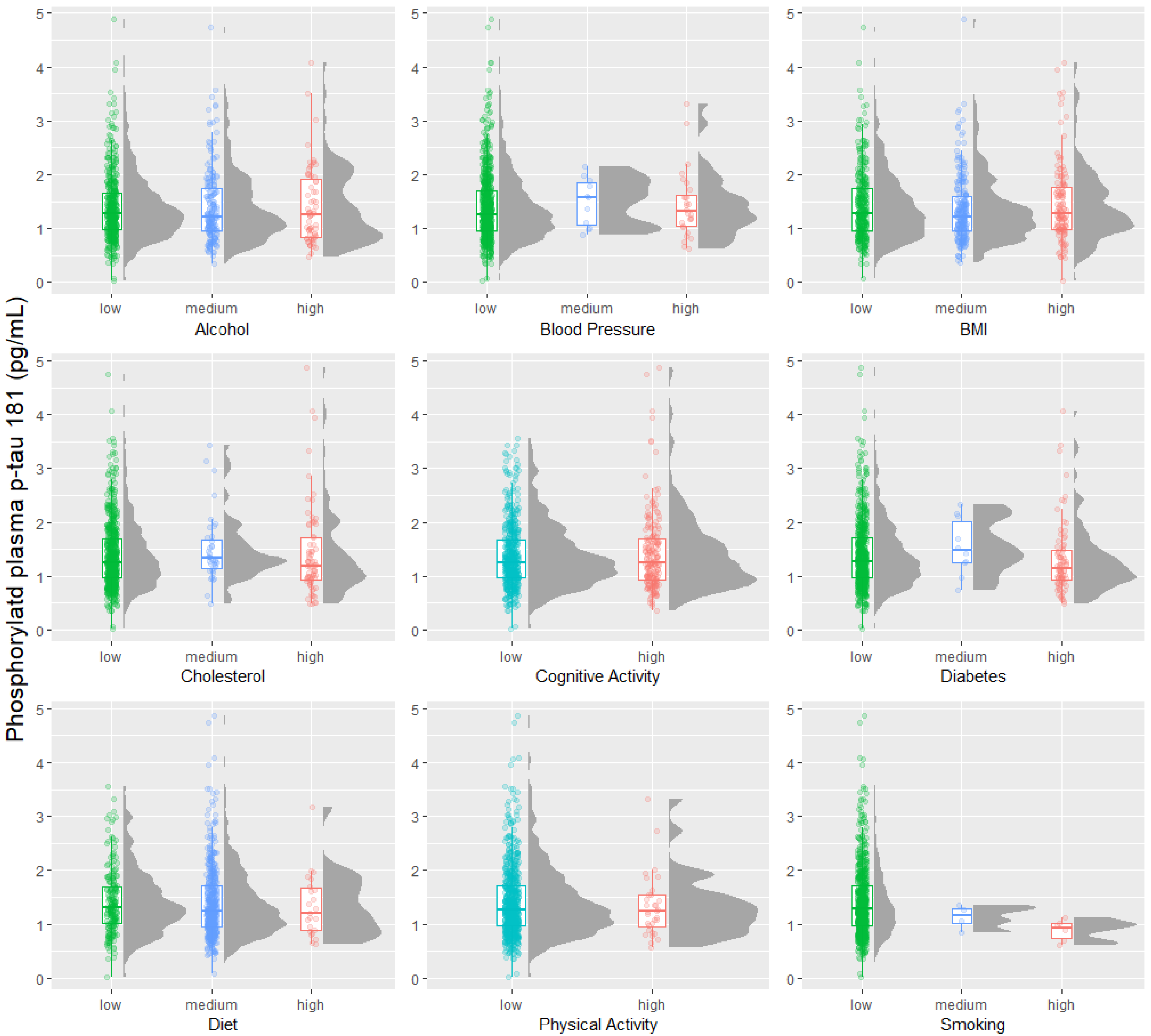


Figure 1: Modifiable risk factors and plasma concentrations of p-tau 181 (pg/mL)

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-Schminich 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.

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