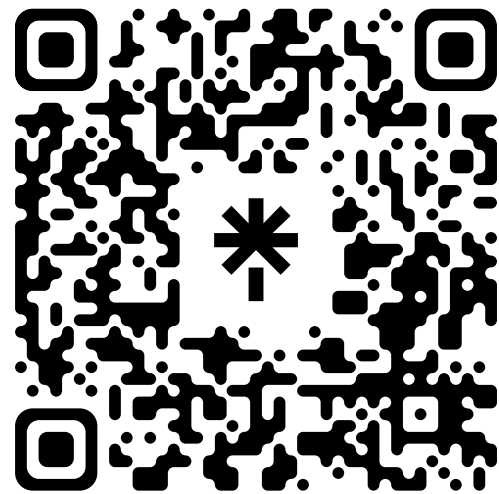
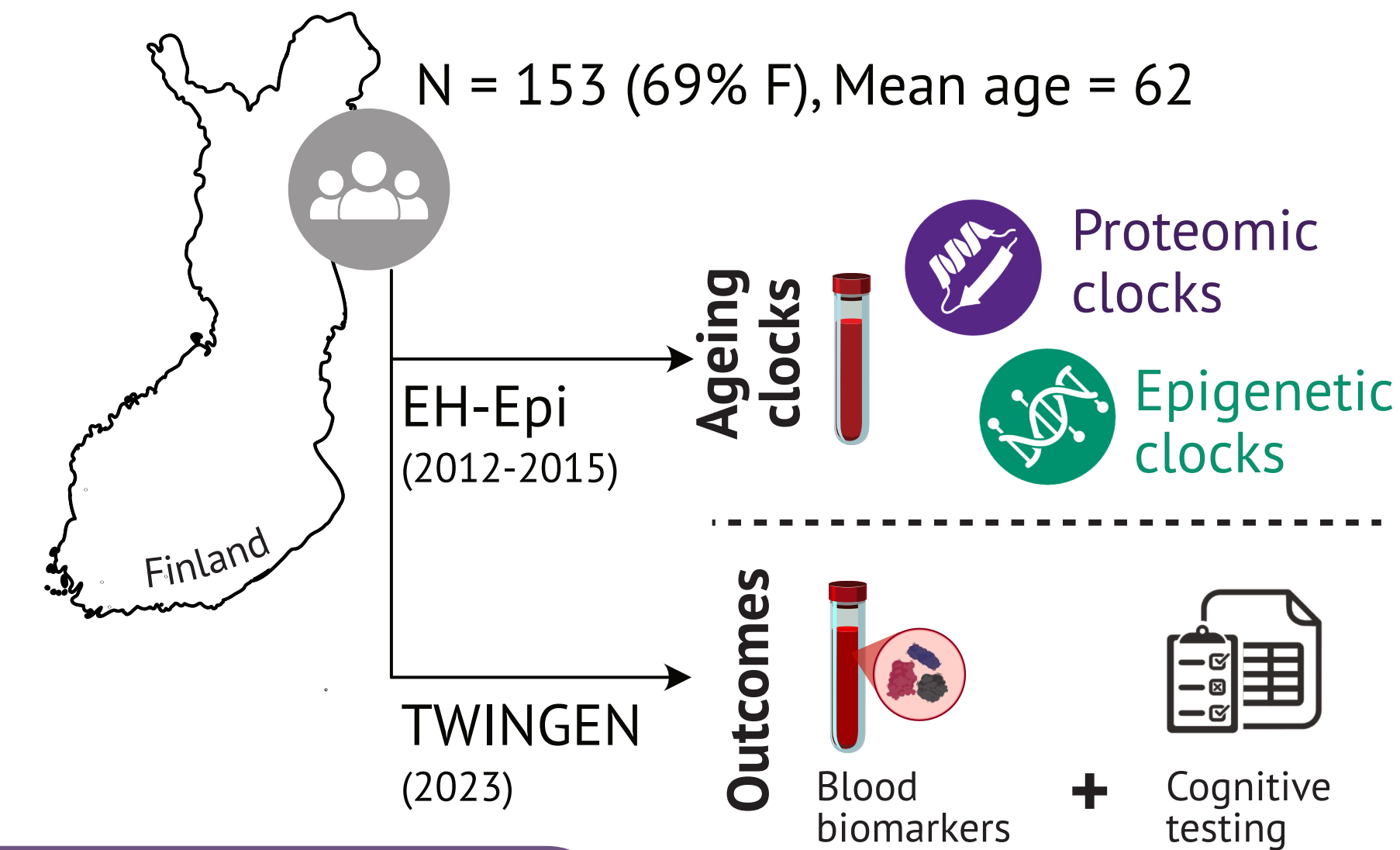


Proteomic ageing associated with neuronal and cognitive health in individuals without a diagnosis of Alzheimer's disease

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BACKGROUND

Disruption of proteostasis driving A β and tau pathologies may show early signs in blood proteomes ^[1].
Proteomic ageing clocks summarize proteomes into biological ageing or morbidity risk estimates ^[2].
These can detect systemic and organ-specific protein changes in blood related to disease ^[3].

Objectives

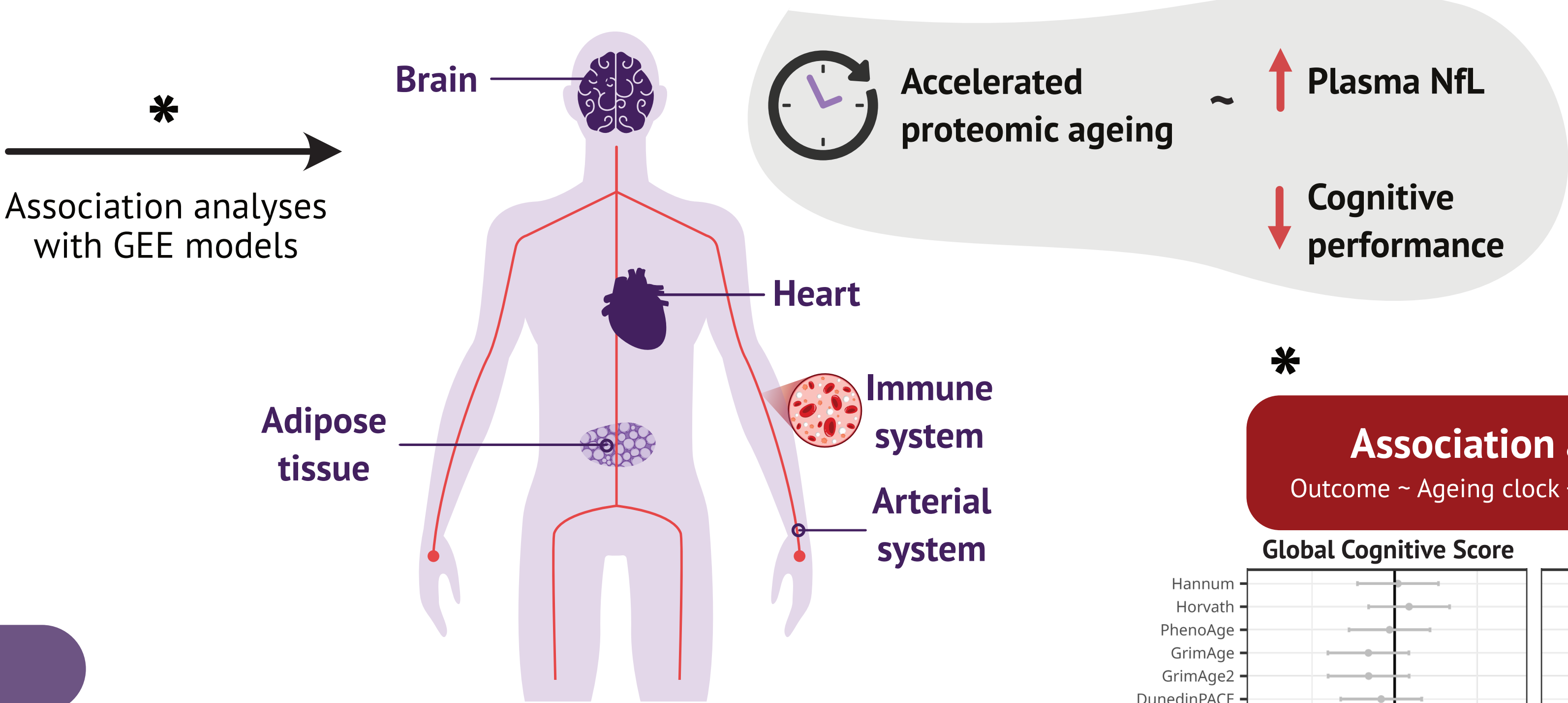
- Evaluate the extend to which proteomic and epigenetic ageing clocks capture variation in Alzheimer's-related phenotypes before clinical manifestation.
- Investigate how common dementia risk factors impact ageing clock-outcome associations.

APPROACH

We used Generalized Estimating Equation models to test associations of ageing clocks with global cognitive scores, tau, neurodegeneration and neuroinflammation biomarkers.
In interaction analyses we tested the potential effect of common dementia risk factors and genetic predisposition to them (*e.g.* diabetes, blood pressure, cholesterol and glucose levels) on the clock-outcome associations.
In multivariable analyses we tested how much information on each outcome proteomic clocks collectively provide over epigenetic clocks.

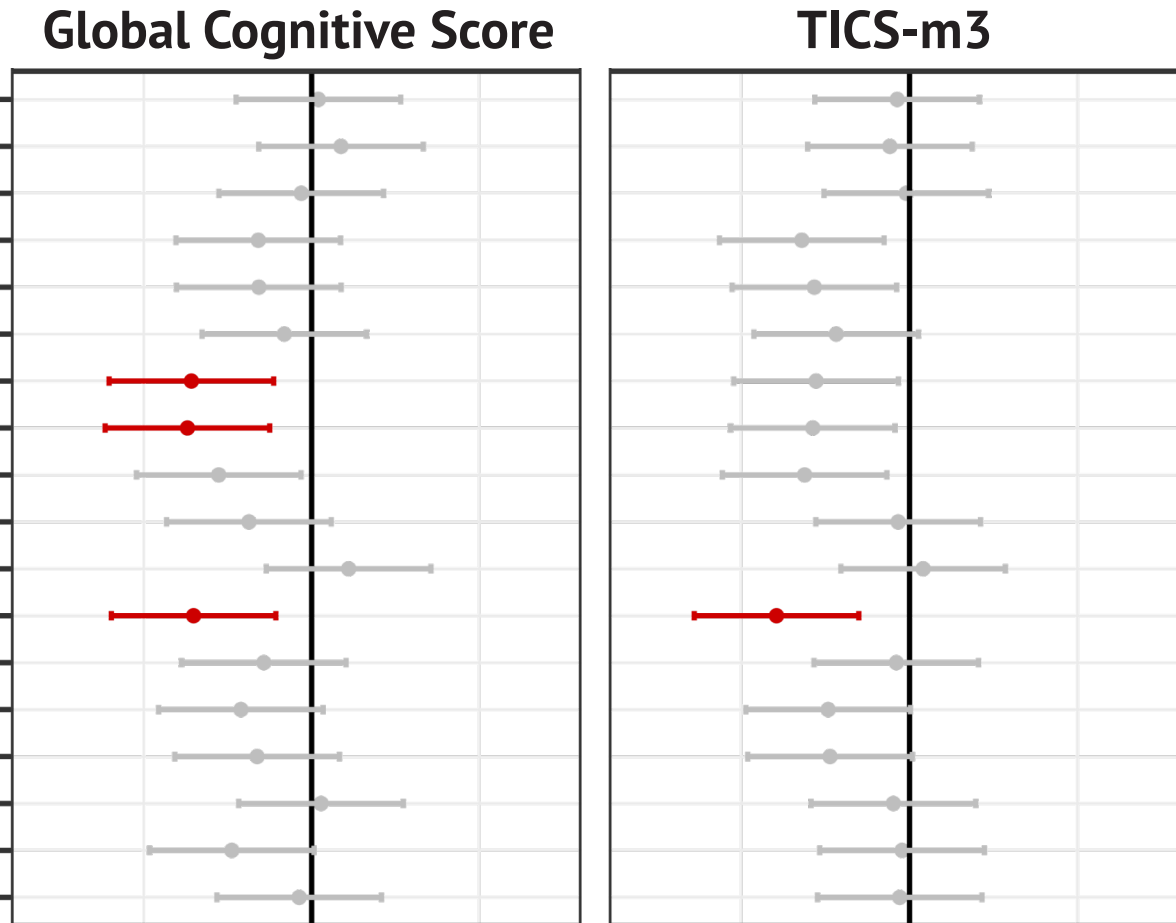
FINDINGS

- Accelerated systemic and brain-specific proteomic ageing were associated with poorer cognition and higher levels of plasma NfL, a neurodegeneration biomarker.
- Interaction analyses suggested weaker brain ageing-cognition associations in individuals with above-average genetic liability for type II diabetes.
- Proteomic clocks collectively explained up to 23% of variance in AD-related phenotypes not captured by epigenetic clocks.



Association analyses

Outcome ~ Ageing clock + sex + age + Δ age



Interaction analyses

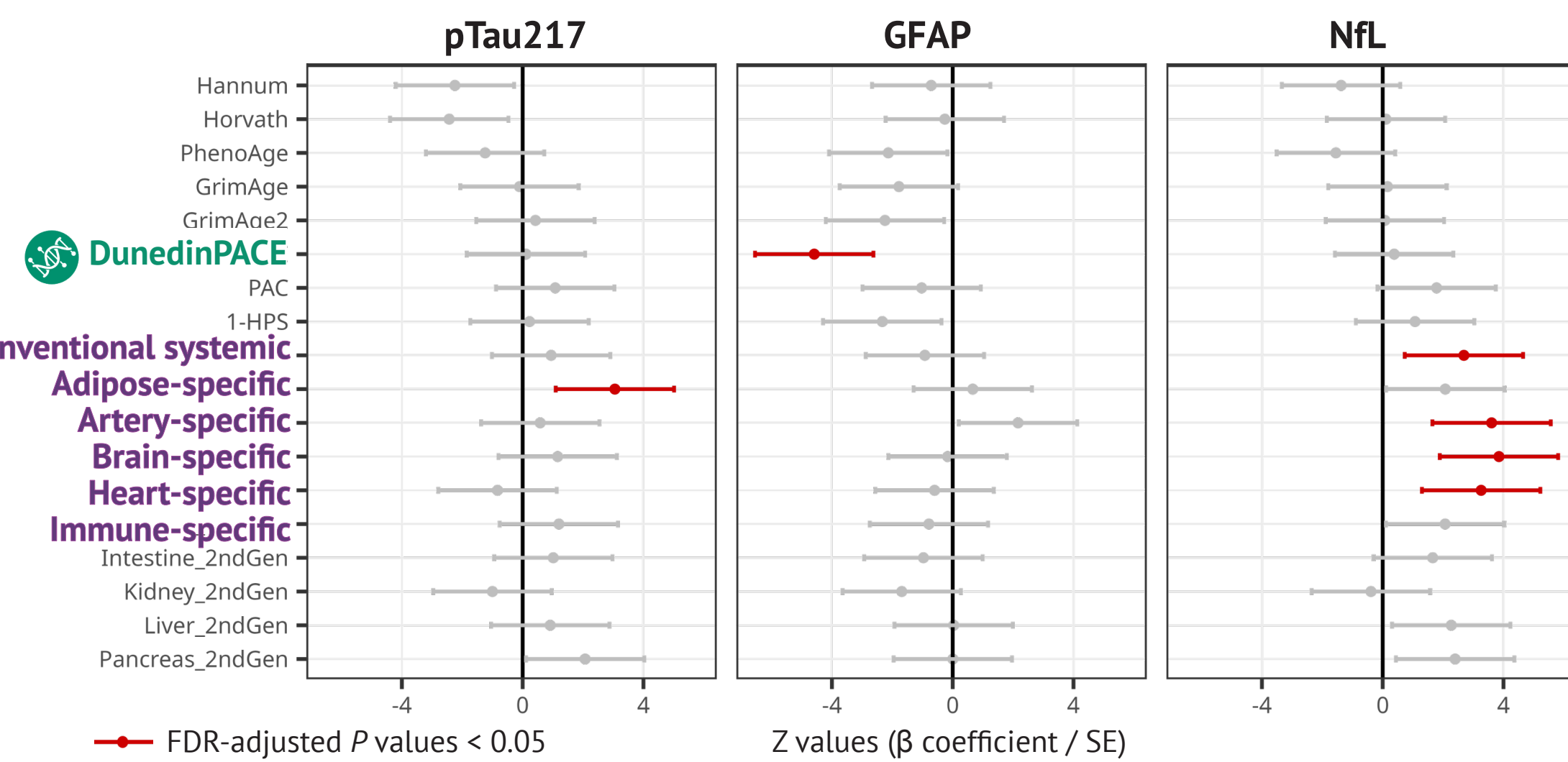
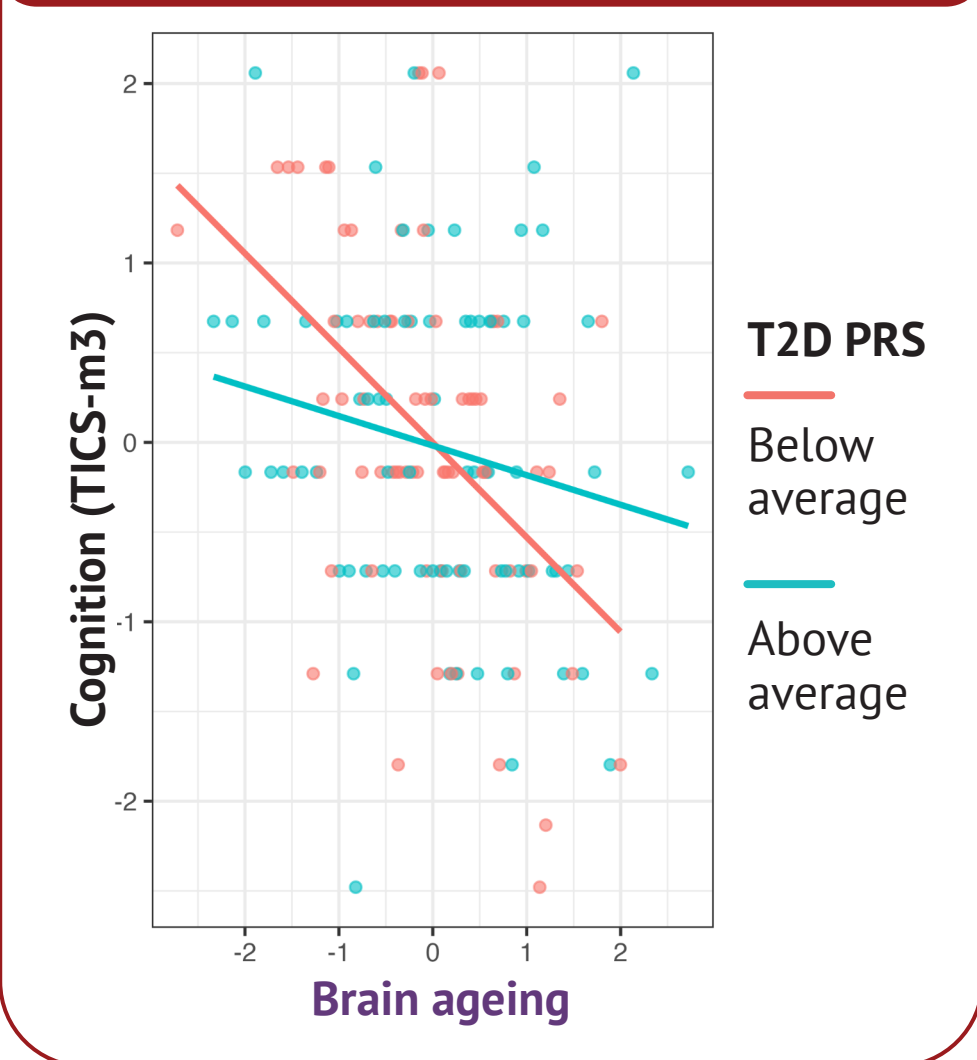


Figure 1. Association analyses: association of epigenetic and proteomic clocks with cognition and Alzheimer's blood biomarkers. **Interaction analyses:** effect of T2D genetic risk on cognition-brain proteomic ageing associations.
Abbreviations: T2D, type II diabetes; PRS, polygenic risk score; TICS-m3, telephone interview for cognitive status - modified version 3; pTau, phosphorylated tau protein; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; FDR, false discovery rate.

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