## Integrating Multi-Omics and Biomarkers for Risk Prediction in Diabetes and Cognitive Health

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Type 2 diabetes (T2D) is a biologically heterogeneous disorder associated with variable risks for cognitive decline and cerebrovascular disease. We integrated multi-omics and biomarker data with clinical features to refine T2D subtyping and enhance prediction of neurovascular outcomes relevant to cognitive health. We analyzed 10,842 adults with T2D from two population-based cohorts with linked genomics, plasma proteomics, metabolomics, and neuroimaging data. Latent molecular factors were derived using a multi-omics factor analysis (MOFA+) framework capturing shared biological variation across omics layers. These factors, together with routinely measured clinical variables, were used to derive reproducible T2D subtypes via consensus clustering. Fine–Gray sub-distribution hazard models estimated risks of incident dementia and stroke accounting for death as a competing event, and Cox models assessed mortality. Linear models compared MRI phenotypes across subtypes, and predictive performance was evaluated using time-dependent C-index, calibration, and decision-curve analyses. Three distinct T2D subtypes emerged: mild metabolic diabetes (MMD), obesity–inflammation diabetes (OID), and vascular-aging diabetes (VAD). Compared with MMD, the VAD subtype showed higher risk of all-cause dementia (sub-distribution hazard ratio [SHR] = 1.79, $p = 3.1\times10^{-5}$), vascular dementia (SHR = 2.04, $p = 1.2\times10^{-3}$), and stroke (SHR = 1.55, $p = 5.0\times10^{-5}$), independent of APOE genotype and T2D polygenic risk. Integrating omics data improved 5-year dementia prediction versus clinical-only models ($\Delta$C-index = +0.08, $p < 0.001$). Multi-omics subtyping delineated biologically distinct T2D phenotypes with differential neurovascular and cognitive trajectories, highlighting vascular, inflammatory, and mitochondrial pathways as key mediators linking diabetes to cognitive health.