

Exploring Indirect Genetic Links Between Psychiatric Traits, Frailty, and Alzheimer’s Disease

Jessica L Miller^{ab}, Jonny P Flint^{ac}, Md Rezanur Rahman^a, David D Ward^a, Michelle K Lupton^{ab}.
a. QIMR Berghofer Medical Research Institute, QLD, Australia. b. Faculty of Medicine, The University of Queensland, QLD, Australia. c. University of Exeter, Exeter, England

Psychiatric traits such as anxiety, major depressive disorder (MDD), post-traumatic stress disorder (PTSD) and conditions that arise from adverse childhood experiences by way of childhood maltreatment (ChildMal) are consistently associated with accelerated cognitive decline and poorer outcomes in Alzheimer’s Disease (AD). However, large scale genomic studies suggest modest direct genetic overlap between these psychiatric conditions and AD, creating a discrepancy between genetic evidence and clinical observations.

Additionally, acceleration of frailty (declining physiological and mental reserve) has been shown to begin approximately nine years prior to the clinical onset of AD, aligning with prodromal stages and emergence of early biomarkers. Frailty has been linked to increased dementia risk and adverse aging outcomes, and shares overlapping pathological features with psychiatric traits. For example, Frailty, PTSD, and depression have each been implicated in accelerated brain aging, which is associated with cognitive decline and may reflect heightened vulnerability to neurodegenerative processes relevant to AD.

This suggests frailty may act as an intermediary linking psychiatric traits to dementia risk, helping reconcile clinical, epidemiological, and genetic findings. The present study applies Genomic Structural Equation Modelling (Genomic SEM) to investigate shared genetic liability across anxiety, MDD, PTSD, and Childhood Maltreatment, and examines frailty as a mediator between psychiatric vulnerability and AD risk.

Methods

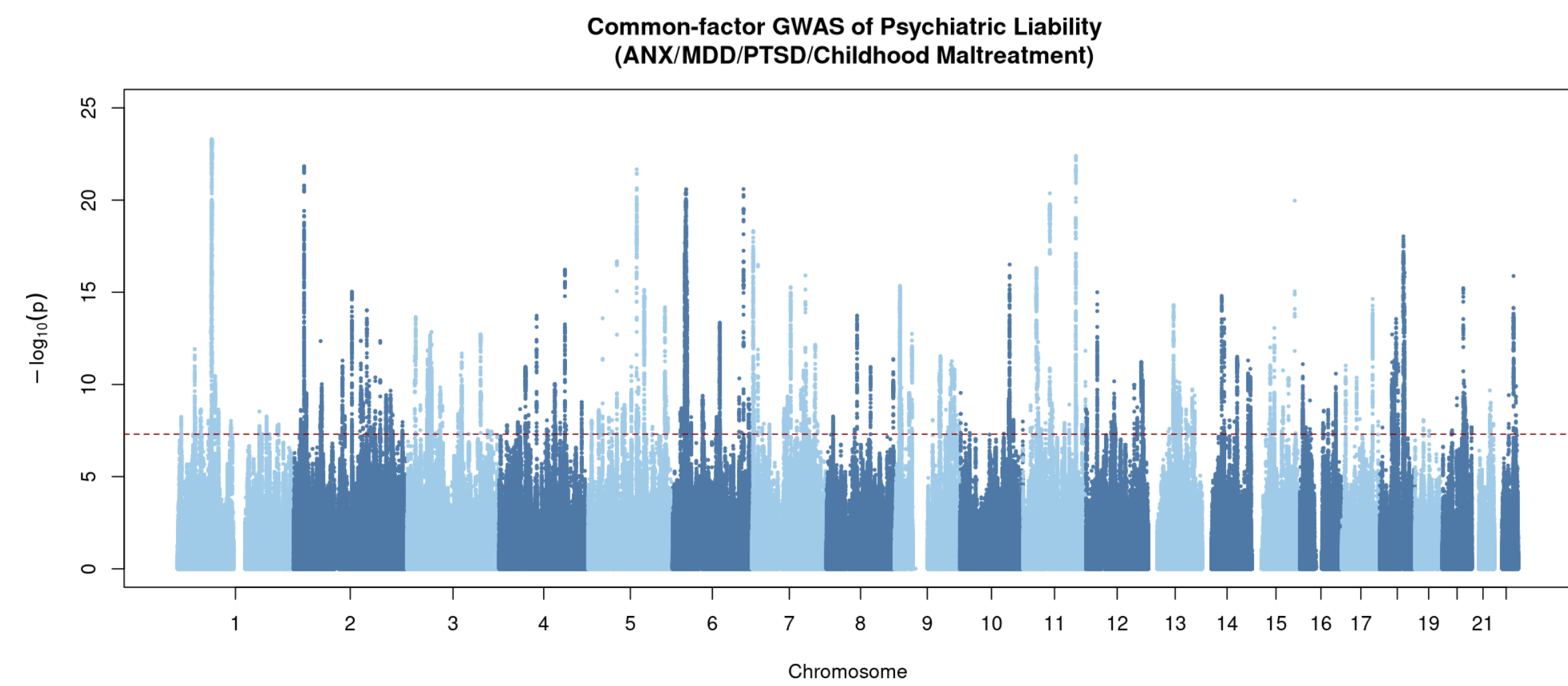
- We analysed genome-wide association study (GWAS) summary statistics for anxiety disorders, MDD, and PTSD, along with principal components derived from a measure of childhood maltreatment¹⁻⁴. We also included GWAS summary statistics for generalised frailty (GF) and AD⁵⁻⁶.
- Genetic covariance among psychiatric traits, frailty and AD was estimated using multivariable linkage disequilibrium score regression (LDSC).

Common-Factor Genome-Wide Association Study

- A single psychiatric-latent factor capturing shared genetic liability across anxiety, MDD, PTSD, and Childhood Maltreatment was estimated using Common Factor GWAS functions in R-package Genomic SEM. Model parameters were estimated using diagonally weighted least squares (DWLS). Factor loadings and residual variances were examined to ensure adequate model fit and identification.
- SNP-level associations with the psychiatric-latent factor were estimated using common-factor GWAS within the Genomic SEM framework. To ensure numerical stability during genome-wide estimation, SNP effects were estimated using an unweighted least squares (ULS) estimator, while DWLS was retained for the latent factor model.

Genetic Mediation Analysis

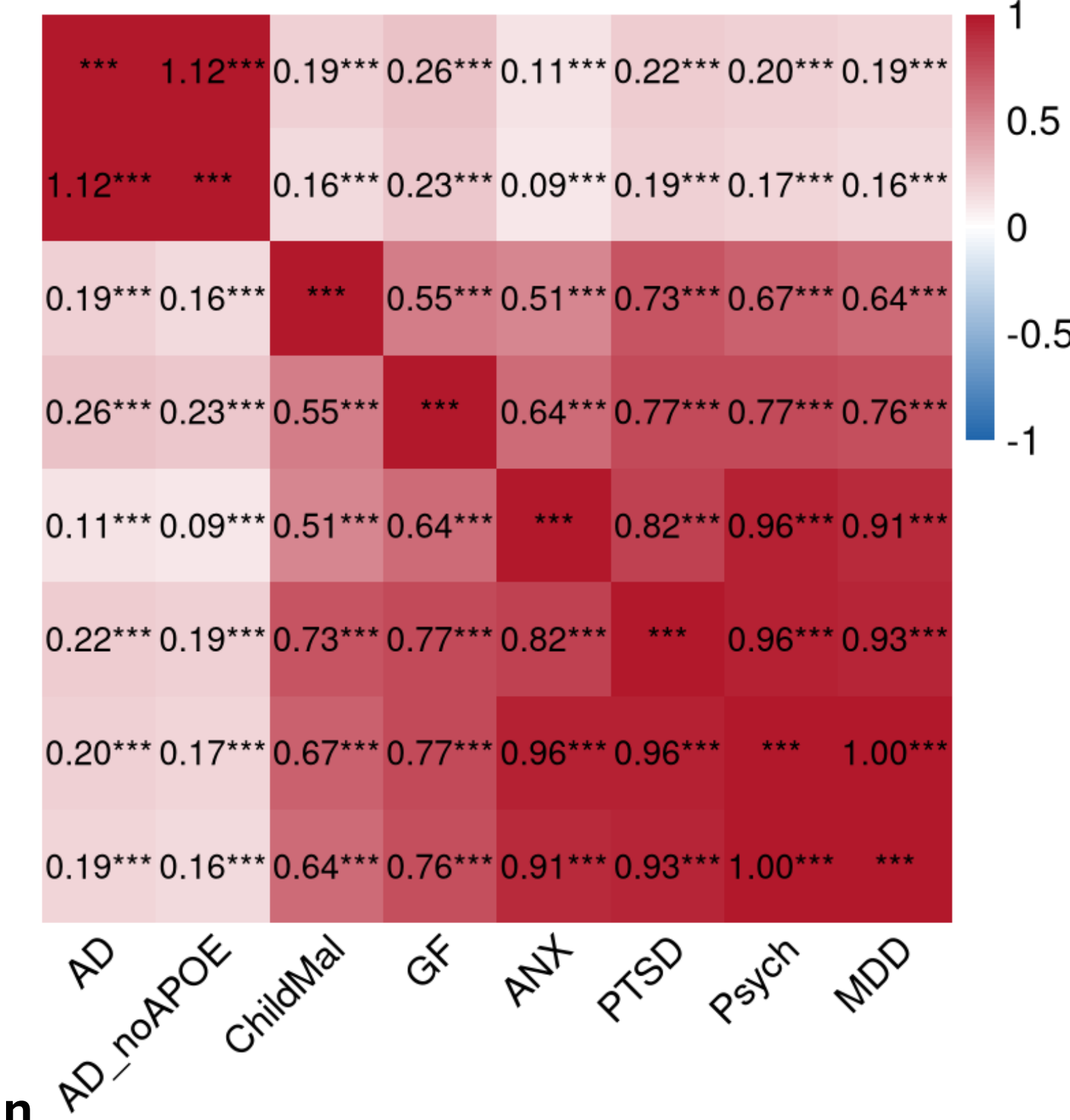
- Genetic mediation models were estimated using Genomic SEM to examine whether genetic liability to frailty mediated the association between psychiatric liability and AD. Models were estimated using DWLS and specified paths included psychiatric-liability → frailty → AD, along with a direct psychiatric → AD path. The model was run for both AD with and without the APOE region to determine if APOE may be a key driver of the examined relationships.



Results

- Common Factor:** All four indicators (anxiety, MDD, PTSD, and Childhood Maltreatment) loaded significantly onto a single latent factor (Psych Factor) representing shared psychiatric genetic liability. The factor demonstrated substantial SNP-heritability on the liability scale.
- Common-Factor GWAS:** The GWAS revealed diffuse polygenic signal across the genome, with no discrete loci dominating the association pattern. This profile was consistent with highly polygenic shared liability rather than locus-specific effects.
- Bivariate Genetic Associations:** The psychiatric factor showed a modest but highly significant genetic correlation with AD, which remained after excluding the APOE region ($r_g \approx 0.20$; ≈ 0.17 without APOE; $p < .001$).
- Genetic Mediation by Frailty:** In genetic mediation models excluding the APOE region:
 - Psychiatric–liability strongly predicted frailty ($\beta \approx 0.77$, $p < 10^{-80}$)
 - Frailty showed a modest association with AD ($\beta \approx 0.24$, $p \approx 0.07$).
 - The direct psychiatric → AD path was negligible ($\beta \approx -0.01$, $p \approx 0.90$), indicating the relationship is primarily mediated ¹ through frailty.
- The indirect effect via frailty ($\beta \approx 0.19$, $p \approx 0.08$) accounted for essentially the entire total effect, with the proportion mediated slightly exceeding the total (i.e., over 100%) due to a small negative direct effect.
- Results were highly similar in models including APOE, with slightly stronger relative mediation observed after APOE exclusion (see figure right)

Genetic Correlations

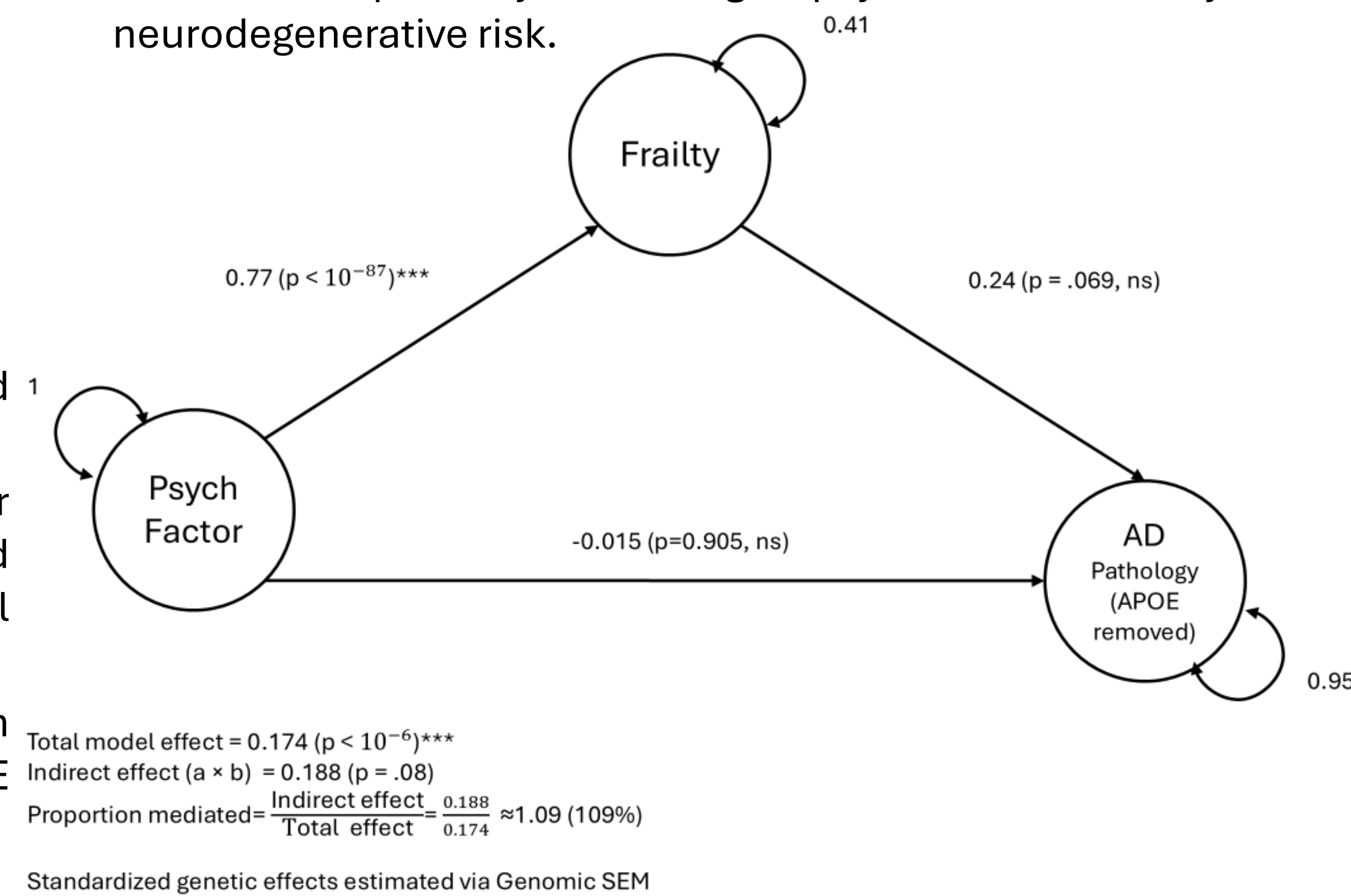


Discussion

Shared psychiatric–liability is strongly associated with genetic liability to frailty, and frailty largely accounts for the observed genetic association between psychiatric–liability and AD. The absence of a direct psychiatric disorder → AD genetic path after accounting for frailty supports an indirect mechanism consistent with systemic vulnerability rather than direct neurodegenerative risk.

The diffuse signal observed in the common-factor GWAS highlights the highly polygenic nature of shared psychiatric liability and aligns with the mediation findings, suggesting that aggregated psychiatric genetic risk acts through downstream integrative phenotypes (e.g., frailty). Limitations include restricted ancestry and limited power to detect small downstream effects for AD.

Future work will extend this framework by modelling frailty as a multi-component construct to capture specific biological and functional pathways linking psychiatric liability to neurodegenerative risk.



Data Sources:

1. Strom et al., medRxiv, 2024 (Anxiety)
2. Adams et al., Cell, 2025 (MDD)
3. Nievergelt et al., Nat Genet, 2024 (PTSD)
4. Chen et al., Mol Psychiatry, 2025 (Childhood Maltreatment)
5. Foote et al., Nat Genet, 2025 (Frailty)
6. Jansen et al., Nat Genet, 2019 (Alzheimer’s Disease)

Contact: Jessica Miller. Email: jessica.miller@qimrb.edu.au