

## **Does depression in old age reflect prodromal dementia? A polygenic risk score approach**

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The extent to which depression in old age reflects prodromal dementia remains controversial. A genetic investigation could provide further clarification to the depression-dementia association.

This project utilized the polygenic risk score (PRS) approach to compare the contribution of genetic risk for depression and dementia to depression assessed in (1) a population-based sample of older individuals and (2) dementia cases prior to dementia diagnosis.

Data were drawn from Screening Across the Lifespan of Twins study (SALT)(genetic data  $n = 10,000$ ), with probable depression assessed in 1998–2002 (CESD; cut-off 9 of 32; mean time prior to dementia = 13.7y), and subsequent dementia diagnoses ( $n = 700$ ) from national health registries. PRSs were computed based on the most recent GWAS on Major Depression (MD) and Alzheimer's Disease (AD). The associations between PRS, depression and dementia were tested using logistic regression, and variance explained calculated from Nagelkerke  $R^2$ .

The PRS<sub>MD</sub>  $p$ -value threshold 0.05 and PRS<sub>AD</sub>  $10^{-5}$  explained the most variance in depression (0.3%) and dementia (2.5%), respectively. PRS<sub>AD</sub> did not contribute to depression in the total sample. In those who later developed dementia, however, PRS<sub>AD</sub> explained more variance in depression than did PRS<sub>MD</sub> (0.32% vs. 0.19%). In addition, the PRS<sub>AD</sub> was a stronger predictor of subsequent dementia among those with depression (OR = 11.9 for the highest vs. lowest PRS<sub>AD</sub> decile) than among those without depression (OR = 4.6 for the highest vs. lowest PRS<sub>AD</sub> decile).

These results suggest that depression prior to dementia is genetically more strongly associated with dementia than major depression, implying that depression in old age may indicate prodromal dementia.