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Association between Polygenic Risk of Alzheimer's Dementia, Brain MRI and Cognition in UK Biobank

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Abstract : Alzheimer's research UK estimates by 2050, 2 million individuals will be living with Late Onset Alzheimer's disease (LOAD). However, individuals experience considerable cognitive deficits and brain pathology over decades before reaching clinically diagnosable LOAD and studies have utilised gene candidate studies such as genome wide association studies (GWAS) and polygenic risk (PGR) scores to identify high risk individuals and potential pathways. This investigation aims to determine whether high genetic risk of LOAD is associated with worse brain MRI and cognitive performance in healthy older adults within the UK Biobank cohort. Previous studies investigating associations of PGR for LOAD and measures of MRI or cognitive functioning have focused on specific aspects of hippocampal structure, in relatively small sample sizes and with poor 'controlling' for confounders such as smoking. Both the sample size of this study and the discovery GWAS sample are bigger than previous studies to our knowledge. Genetic interaction between loci showing largest effects in GWAS have not been extensively studied and it is known that APOE e4 poses the largest genetic risk of LOAD with potential gene-gene and gene-environment interactions of e4, for this reason we also analyse genetic interactions of PGR with the APOE e4 genotype. High genetic loading based on a polygenic risk score of 21 SNPs for LOAD is associated with worse brain MRI and cognitive outcomes in healthy individuals within the UK Biobank cohort. Summary statistics from Kunkle et al., GWAS meta-analyses (case: n=30,344, control: n=52,427) will be used to create polygenic risk scores based on 21 SNPs and analyses will be carried out in N=37,000 participants in the UK Biobank. This will be the largest study to date investigating PGR of LOAD in relation to MRI. MRI outcome measures include WM tracts, structural volumes. Cognitive function measures include reaction time, pairs matching, trail making, digit symbol substitution and prospective memory. Interaction of the APOE e4 alleles and PGR will be analysed by including APOE status as an interaction term coded as either 0, 1 or 2 e4 alleles. Models will be adjusted partially for adjusted for age, BMI, sex, genotyping chip, smoking, depression and social deprivation. Preliminary results suggest PGR score for LOAD is associated with decreased hippocampal volumes including hippocampal body (standardised beta = -0.04, P = 0.022) and tail (standardised beta = -0.037, P = 0.030), but not with hippocampal head. There were also associations of genetic risk with decreased cognitive performance including fluid intelligence (standardised beta = -0.08, P<0.01) and reaction time (standardised beta = 2.04, P<0.01). No genetic interactions were found between APOE e4 dose and PGR score for MRI or cognitive measures. The generalisability of these results is limited by selection bias within the UK Biobank as participants are less likely to be obese, smoke, be socioeconomically deprived and have fewer self-reported health conditions when compared to the general population. Lack of a unified approach or standardised method for calculating genetic risk scores may also be a limitation of these analyses. Further discussion and results are pending.

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