

The Relationship Between Depression and Anxiety Polygenic Risk Scores and Cognition: Interactions with Sex and Environment

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Abstract:

Background: Cognitive impairments and sex difference are both common in young adults with major depression and anxiety disorders, although their nature remains partly unclear.

Many environmental factors also increase the risk of depression and anxiety, including social factors such as unemployment and social network, and lifestyle factors such as physical exercise and diet.

Gene–environment interactions (GxEs) whereby a person inherits sensitivity to environmental factors could also play an important role in depression and anxiety.

Polygenic risk score (PRS) methods can be used to examine the effect of multiple disease-risk SNPs in aggregate on phenotypes. To date, few studies have examined the influence of PRS for depression and anxiety on cognition, and rarely have they examined the interaction between polygenic risk and sex/environment.

Methods: We will combine genetic and cognitive data in UK Biobank (334,976 participants) and using the three compound cognitive scores (memory; processing speed and executive & attention) as the primary measure of cognition. We will use linear regression to examine the association between PRS and cognition for MDD and anxiety, adjustment for population ancestry principal components, age and education level, using summary statistics from Wray, 2018 GWAS (depression cases and controls) and the Backman et al. GWAS (Nature, 2021) (anxiety cases and controls). We used linear regression to examine the sex difference and genotype-by-environment interaction. We performed the same analysis in the Maastricht study as a replicate validation (3000 participants).

Expected Results: Males are more likely to have depression/anxiety symptoms than females, and sex difference exist in cognitive performance domains. Depression/anxiety PRS will be negatively associated with cognitive performance in DMS and UK Biobank (UKB) datasets. The association between depression/anxiety PRS and cognitive performance is moderated by environmental factors, age and sex.

Conclusion: This study would improve our understanding of the complex aetiology of mental disorders and related cognitive functioning, might help disentangling the respective

contribution of Gene and Environment risk factors in the clinical expression of MDD and anxiety. Eventually that may have significant clinical implications for guiding diagnosis, treatment, and prevention in a sex-specific and individualized manner.

Keywords: polygenic risk score, genomics, cognition