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Modeling Cross-Generational Polygenic Risk of Depression in the UK Biobank

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ABSTRACT: Depression is well known to run in families, with studies typically focusing on the influence of genetic transmission or familial environmental factors, which can be confounded (Jami et al., 2021). Renewed interest has grown in estimating and controlling for genetic nurture, the effects of parental genotypes above and beyond those accounted for by genetic transmission. Leveraging recent methodological advancements (Hwang et al., 2020; Tubbs et al., 2021), we infer SNP genotypes of missing parents in 35,975 individuals from the UK Biobank, subsequently calculating offspring, maternal, and paternal polygenic scores for depression (oPGS, mPGS, pPGS). Our current study uses generalized linear mixed models to estimate the joint and interactive effects of these PGS on offspring depression. Controlling for age, sex, and genetic principal components, we find evidence for a statistically significant interaction between oPGS and mPGS ($p = 0.013$), as well as between mPGS and pPGS ($p = 0.005$). These interactions indicate that risk for depression is more strongly influenced by offspring genetic risk when maternal genetic risk is low. Results also suggest that although both parents having a high PGS is associated with greater risk of depression in the offspring, both parents having a low PGS is also predictive of greater offspring depression risk. Follow-up analyses indicate that these effects may be specific to females only, and that they may be partially mediated by childhood abuse or feeling loved as a child. Thus, our analysis supports the presence of context-dependent maternal genetic effects on offspring depression and suggests potential environmental mediators.

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