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Performance of a polygenic risk score for depression in a deeply phenotyped sample

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Depression is a prevalent and costly disorder that leads to impaired functioning and poor health outcomes. Moreover, depression is highly comorbid with other psychiatric and medical disorders. Improved understanding of genetic liability may aid in prevention and treatment efforts. However, this effort is impeded by the heterogeneity of psychiatric disorders. While large, electronic health record (EHR)-based biobanks have provided insight into the genetic architecture of depression, deeply phenotyped samples can provided additional information about the shared genetic etiology underlying this comorbidity. We calculated polygenic risk scores for major depressive disorder (PRS-MDD) and subsequently conducted a phenome wide association study (PheWAS) in European-ancestry individuals from the Yale-Penn sample (YP). The YP dataset is a cross-sectional sample (N>17,000) enriched for individuals who use substances. The in-depth interview produces data on demographics, environment, medical disorders, and psychiatric and substance use diagnoses. As expected, PRS-MDD was significantly associated with multiple depression related phenotypes, including total number of MDD symptoms (b=0.39, $p=1.75x10^{-14}$), loss of interest (OR=1.24, $p=1.24x10^{-13}$), and depressed/irritable mood (OR=1.2, $p=2.3x10^{-10}$). Interestingly, there were significant associations with 16 alcohol-related phenotypes, including seeking treatment for alcohol (OR=1.19, $p=4.27x10^{-9}$) and number of AUD criteria met (b=0.3, $p=4.6x10^{-8}$). Other significant associations include tobacco dependence, skipping school, number of PTSD criteria met, cocaine withdrawal, and self-reported health status. Results showed many cross-trait associations across various domains, indicating broad genetic liability. The wealth of phenotypic data in the YP sample, beyond what is typically available in an EHR, informs our understanding of the pleiotropic pathways underlying depression.