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Using polygenic risk scores to dissect heterogeneity between major depressive disorder subtypes

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ABSTRACT:

Major depressive disorder (MDD) is a common and highly heterogeneous psychiatric disorder but little is known about the genetic characterization of this heterogeneity. Understanding the genetic etiology of MDD can be challenging as large sample sizes are needed for gene discovery but this is often achieved with a trade-off in the depth phenotyping. The Australian Genetics of Depression Study is the largest stand-alone depression cohort with both genetic data and in-depth phenotyping and comprises a total of 15,792 participants of European ancestry, 92% of which, met diagnostic criteria for MDD. We leveraged the unique nature of this cohort to investigate genetic heterogeneity across various clinical subtypes of MDD using polygenic risk scores (PRS). We show that a PRS for depression explains 5.7% of variance in MDD liability in our sample and find strong support for genetic heterogeneity in depression with differential associations of multiple psychiatric and comorbid traits with age of onset, longitudinal course and various clinical subtypes of MDD. Until now, this degree of detailed phenotyping in such a large sample of MDD cases has not been possible. In this study, we provide support for differential pathways to illness models that recognize both the overlap with other common psychiatric disorders, as well as pathophysiological differences.