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Polygenic Risk for High Fasting Insulin Predicts Childhood Impulsivity and Adulthood Substance Dependence in Response to Early Adversity

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Co-morbidity between metabolic and psychiatric diseases is well-established but poorly understood, and exposure to early adversity is a common risk factor. We have shown that the genetic background associated with higher fasting insulin moderates the impact of early adversity on childhood impulsivity, an endophenotype known to be linked to the development of substance use disorders (SUDs). We hypothesize that the same polygenic score will predict SUD in adults exposed to early adversity. We calculated polygenic risk scores (PRS) from the fasting insulin genome-wide association study at different thresholds and identified the subset of single nucleotide polymorphisms that best predicted peripheral insulin levels in children from the ALSPAC cohort [N=467; $p_{t\text{-initial}}$=0.24 (10,296 SNPs), $p_{t\text{-refined}}$=0.05 (57 SNPs)]. We calculated the refined PRS (rPRS) in adult participants from the SAGE cohort and investigated its interaction effect with early adversity on SUDs. We found a significant effect of interaction between rPRS and adversity predicting DSM4 dependence on drugs other than marijuana, cocaine, or opiates [N=4024, β=0.077, p=0.019], such that higher PRS [β=0.611, p<0.001] was linked to more SUDs in individuals exposed to more adversity and lower PRS [β=0.458, p<0.001] was linked to less SUDs in individuals exposed to less adversity. Enrichment analysis (MetaCore®) of the rPRS was significant for CNS development processes including D2 receptor signaling, which is a marker of impulsivity in addiction. Our rPRS identifies children at risk for early adversity-induced impulsivity that later develop SUDs, with possible implications for practice.