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***Early Life Adversity and a Sex-Specific Polygenic Risk Score for Altered Fasting Insulin are Associated with Executive Functioning.***

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Insulin is an important homeostatic hormone with implications for childhood growth, development and adult psychopathology. Considering the high prevalence of co-morbidity between altered metabolism and executive function problems (e.g. obesity and ADHD), we hypothesized that 1) the genetic background associated with altered fasting insulin (FI) and ADHD could be shared; 2) if (1) is rejected, it suggests that interactive models between the genetic background associated with altered FI and childhood environment would better predict executive functions. Using conjunctional false discovery rate (FDR), we found no SNPs shared between the FI GWAS and ADHD GWAS. (2) We calculated polygenic risk scores (PRS) from the sex-specific FI GWAS and identified the threshold that best predicted insulin levels in male and female children in the ALSPAC cohort [Nmales = 245, Nfemales = 222; pt-intial-males = 0.35 (41,108 SNPs), pt-intial-females = 0.01 (2751 SNPs)], further refining it to only include SNPs significantly associated with insulin levels [pt-refined-males = 0.05 (32,520 SNPs), pt-refined-females = 0.05 (230 SNPs)]. We calculated the refined PRS (rPRS) at different ages in multiple cohorts and investigated its interaction effect with early adversity on attention deficit assessments, through CBCL Attention Problems Scale and DSM ADHD Scale, in males and females. In MAVAN, there was a significant interaction [N = 74, p = 0.039] in females at the age of 60 months where simple slope analysis informed us that within the low rPRS group, there is a significant [p = 0.005] positive association between postnatal adversity and attention problems. In GUSTO, there was a significant interaction [N = 208, p = 0.026] in males at the age of 4 years where simple slope analysis informed us that within the high rPRS group, there is a significant [p = 0.003] positive association between postnatal adversity and attention problems. In ABCD, there was a significant interaction in males [N = 4012, p = 0.05] at the age of 10 years and in females [N = 1689, p = 0.013] at the age of 11 years where simple slope analysis informed us that within the low and high rPRS groups, there is a significant [plow_PRS_male < 0.01, phigh_PRS_male< 0.01, plow_PRS_female < 0.01, phigh_PRS_female= 0.03] positive association between postnatal adversity and attention problems. The sex differences at different ages observed in these analyses agree with the differences in males' and females' growth trajectories, which are influenced by insulin during development. We conclude that since conjunctional FDR was not feasible and there were no main effects of fasting insulin PRS, the genetic background associated with FI levels is linked with executive function psychopathology, but this effect is sex and environment dependent. The findings reported have implications for age-dependent identification and treatment of psychopathology.

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