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## **Genome-wide cross-disorder analysis of ADHD and cannabis use disorder and cannabis use**

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Individuals with ADHD have a 10-time increased risk of comorbid substance use disorder compared to individuals without ADHD. Especially cannabis use disorder (CUD) is a prevalent comorbid condition in ADHD, and ADHD has significant positive genetic correlation ( $r_g$ ) with both CUD and cannabis use (CU). The genetic architecture of CUD and CU only partly overlap but it is not known to what extent the part of the genetic architecture of CUD and CU that overlaps with ADHD differ from one another.

We present preliminary results from a cross-disorder GWAS study of ADHD+CUD and ADHD+CU. We performed cross-disorder GWAS meta-analyses of ADHDxCUD, and ADHDxCU, using data from GWAS of ADHD (38,691 cases, 186,843 controls), CUD (14,080 cases, 343,726 controls) and CU (162,082 individuals).

We identified 10 genome-wide significant loci for ADHDxCUD and 13 loci for ADHDxCU. Mapping risk variants to genes identified 134 ADHDxCUD genes and 24 ADHDxCU genes. ADHDxCUD genes were significantly upregulated across brain development compared to ADHD+CU genes ( $P=6.98e-79$ ). We found significant stronger negative  $r_g$  between e.g. ADHDxCUD and educational attainment ( $r_g=-0.60$ ) compared  $r_g$  of ADHDxCU and educational attainment ( $r_g=-0.20$ ), a significant stronger positive  $r_g$  of ADHDxCU with autism ( $r_g=0.53$ ) compared to ADHDxCUD and autism ( $r_g=0.37$ ), and same level of  $r_g$  with smoking initiation ( $r_g$  around 0.77).

Our results suggest that the shared genetic component of ADHD with CUD and CU, respectively, differ from one another, and that the component shared with CUD has a substantially stronger negative impact on cognitive performance compared to the component shared with CU.