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**TITLE:** Sex differences in psychiatric polygenic risk in children with ADHD

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**ABSTRACT:**

Attention deficit hyperactivity disorder (ADHD) is more commonly diagnosed in males than females. It is frequently comorbid with and shares genetic risks with anxiety and depression, which are more common in females in the general population. We tested for sex differences in polygenic risk scores (PRS) for anxiety and depression in children with ADHD and examined possible sex differences in the association between anxiety and depression PRS with anxiety and depression symptoms in the context of ADHD. Exploratory analyses tested for sex differences in PRS for other psychiatric disorders.

Children with ADHD were recruited from clinics and symptoms of anxiety (separation, social and generalised) and depression were assessed using a standardised diagnostic interview. We derived PRS based on large genetic studies of anxiety, major depressive disorders, ADHD, autism, bipolar disorder, and schizophrenia.

In 885 children with ADHD (14% female), we found no sex differences in comorbid anxiety and depression symptoms or anxiety/depression PRS. Exploratory analyses suggested higher PRS for bipolar disorder in females [OR(CIs)=1.23(1.00–1.51)] and this was replicated using an independent ADHD sample [OR(CIs)=1.09(1.00–1.19)]. Anxiety PRS were associated with social [OR(CIs)=1.54(1.14–2.09)] and generalised anxiety

symptoms [OR(CIs)=1.46(1.11–1.92)] in males but not females, with significant sex-by-PRS interactions. Depression PRS were not associated with depression symptoms.

The results support the presence of sex differences in children with ADHD, indicating that the genetic link between ADHD and bipolar disorder may be stronger in females and that the aetiology of comorbid anxiety problems may differ in males and females with ADHD.

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