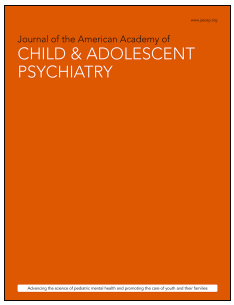

Registered Report: Clinical and cognitive mediators underlying subsequent depression in individuals with ADHD: a developmental approach

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Study Preregistration: Clinical and Cognitive Mediators Underlying Subsequent Depression in Individuals With Attention-Deficit/Hyperactivity Disorder: A Developmental Approach

RH = ADHD and Depression: Clinical and Cognitive Mediators

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Gemma Hammerton, Jon Heron, and Kate Tilling are statistical experts in mediation and missing data.

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Disclosure: Eglė Padaigaitė-Gulbinienė, Gemma Hammerton, Jon Heron, Olga Eyre, Giorgia Michelini, Alexandra Wilson-Newman, Clara S. Garavini, Thalia C. Eley, Anita Thapar, and Lucy Riglin have reported no biomedical financial interests or potential conflicts of interest.

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STUDY SYNOPSIS

Introduction Summary

Individuals with attention deficit hyperactivity disorder (ADHD) are about 5.5 times more likely to develop depression[1] and this comorbidity is associated with greater impairment than either disorder alone. While there is evidence that ADHD may play a causal role in the development of depression,[2,3] the underlying mechanisms remain poorly understood. Several clinical and cognitive mechanisms have been proposed: 1) clinical antecedents of depression, such as irritability and anxiety, often observed in individuals with ADHD;[4,5] 2) cognitive-affective functions (response inhibition, working memory, sustained attention, and emotion recognition) impaired in individuals with ADHD and, to a lesser extent, in depressed individuals;[6,7] or 3) negative thought patterns underlying vulnerability to depression also observed in individuals with ADHD (external locus of control and negative cognitive styles).[8] Nevertheless, few longitudinal studies have tested these as potential mediators between ADHD and subsequent depression. Existing studies are primarily cross-sectional, limited by small sample sizes, and have not examined developmental stage-specific effects. Therefore, we will explore the mediating role of clinical, cognitive-affective, and negative thought patterns and whether their role varies by developmental stage and sex. We will examine all mediators simultaneously, the relative contribution of 3 categories of mediators, and the associations between ADHD and each hypothesised mediator/factor. We hypothesise that: 1) ADHD will be more strongly associated with irritability and emotion recognition in childhood than adolescence and young adulthood; 2) The association between ADHD and anxiety will be consistent across development; 3) ADHD will be more strongly associated with response inhibition, working memory, sustained attention, external locus of control and negative cognitive style in adolescence and young adulthood compared to childhood.

Method Summary

Analyses will be performed in the primary sample (the Avon Longitudinal Study of Parents and Children (ALSPAC); total N = 14,541) and replicated in the Twins Early Development Study (TEDS; total N = 16,810 twins). Ethical approvals for both studies were obtained from the ALSPAC Law and Ethics and Local Research Ethics and The King's College London Ethics Committees.

In both cohorts, ADHD will be assessed using the hyperactivity/inattention subscale of the Strengths and Difficulties Questionnaire (SDQ), while depression will be assessed using the short Mood and Feelings Questionnaire (sMFQ). Irritability will be assessed using 3 items from the Oppositional Defiant Disorder (ODD) section of the Development and Well-Being Assessment (DAWBA) in ALSPAC and 1 item from the SDQ conduct subscale in TEDS. Anxiety will be assessed using the generalised anxiety subscale from DAWBA and Screen for Adult Anxiety Related Disorders (SCAARED) in ALSPAC, the Anxiety-Related Behaviours Questionnaire (ARBQ) and Generalised Anxiety Disorder Dimensional Scale (GAD-D) in TEDS. Cognitive-affective functions will be examined in ALSPAC only. Emotion recognition will be assessed using the Diagnostic Analysis of Non-Verbal Accuracy (DANVA) and Emotion Recognition (ERT) tasks, while response inhibition - the Stop-Signal Task (SST). Working memory will be assessed using the Counting Span (CST) and N-Back (NBT) tasks. Sustained attention will be assessed using Sky Search Dual (SSDT) and Sustained Attention to Response (SART) tasks. Locus of control will be assessed using children's Nowicki-Strickland Internal External Control Scale (CNSIE), while negative cognitive styles will be assessed using the Cognitive Styles Questionnaire Short Form (CSQ-SF).

Mediation will be assessed using a counterfactual approach, which assumes no unmeasured confounding and allows the incorporation of exposure-mediator interactions.[9] We will estimate pure natural direct effects (PNDE), total natural indirect effects (TNIE), and proportion-mediated. First, the total proportion-mediated will be estimated by including all mediators (see **Figure 1**). Then, the effects of individual categories of mediators (i.e. clinical, cognitive-affective, and negative thought patterns) will be examined. We will also examine if potential mechanisms may vary by developmental stage or sex. A directed acyclic graph (DAG) will inform the choice of which variables to include in a model to adjust for potential confounders. Missing data will be imputed based on the missing data patterns and predictors of missingness.

Significance Summary

Emerging evidence suggests that ADHD may have a causal impact on depression,[2,3] but little is known about the mechanisms that could explain why many individuals with ADHD

develop consequent depression. This study will identify clinical and cognitive mechanisms potentially underlying the development of depression in children and young people with ADHD and whether their role varies across developmental periods or sex. Previous research suggests that standard psychological interventions for depression may be less effective in children and young people with ADHD.[10] Therefore, findings from this study have the potential to pinpoint those most at risk and help to identify targets for depression interventions tailored for individuals with ADHD.

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Figure 1: Time of Assessments for Attention-Deficit/Hyperactivity Disorder, Hypothesised Mediators and Depressive Symptoms in Childhood, Adolescence, and Young Adulthood in Both Cohorts

Note: ALSPAC = The Avon Longitudinal Study of Parents and Children; TEDS = the Twins Early Development Study; DAWBA = the Development and Well-Being Assessment; DANVA = the Diagnostic Analysis of Non-Verbal Accuracy; SST = the Stop-Signal Task; CST = the Counting Span Task; SSDT = Sky Search Dual Task; CNSIE = the children's Nowicki-Strickland Internal External Control Scale; NBT = the N-Back task; CSQ-SF = the Cognitive Styles Questionnaire Short Form; SCAARED = the Screen for Adult Anxiety Related Disorders; ERT = the Emotion Recognition Task; SART = the Sustained Attention to Response Task; SDQ = the Strengths and Difficulties Questionnaire; sMFQ = the short Mood and Feelings Questionnaire; ARBQ = the Anxiety-Related Behaviours Questionnaire; GAD-10 = the Generalised Anxiety Disorder Assessment; y = years.