

**ENVIRONMENTAL-RISK (E-RISK) LONGITUDINAL TWIN STUDY
CONCEPT PAPER FORM**

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Provisional Paper Title: Longitudinal associations between ADHD and affective disorders from childhood to young adulthood

Date: January 2018

Objective of the study and its significance:

Attention deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood. It is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning and development (Diagnostic and Statistical Manual of Mental Disorders, 5th edition; [DSM-5]; American Psychiatric Association, 2013). Its estimated prevalence in childhood is 3.4% according to a recent meta-analysis (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Childhood ADHD is a familial disorder, with a relative risk of 5-9 in first-degree relatives of probands with ADHD. It is a highly heritable condition in childhood with genetic factors explaining 60-90% of the variance (Faraone & Mick, 2010; Kuntsi et al., 2004; Larsson et al., 2013; Posthuma & Polderman, 2013; Thapar et al., 2013; Thapar & Cooper, 2016). In the last few years, a growing body of research indicated that ADHD can occur throughout the life span, and once considered only a childhood disorder, it is now recognized to also persist or emerge in adulthood (Agnew-Blais, Polanczyk, Danese, Wertz, Moffitt, & Arseneault, 2016; Caye, et al., 2016; Moffitt et al., 2015). The estimated prevalence of ADHD in adulthood ranges between 2.5% and 5% (Fayyad et al., 2007; Franke et al., 2012; Kessler et al., 2006; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). The heritability in adulthood is lower than in childhood, accounting for approximately 30-41% of the variance of adult ADHD (Agnew-Blais et al., 2016; Franke et al., 2012).

ADHD typically presents itself with a broad range of comorbid psychiatric disorders including affective disorders, such as anxiety and depression. Children with ADHD have a threefold increased risk of anxiety disorders and a fourfold increased risk of depressive disorders (Yoshimasu et al., 2012). Approximately 12–50% of children and adolescents with ADHD exhibit internalizing problems, such as anxiety or depression (Angold, Costello, & Erkanli, 1999; Chen et al., 2015; Gillberg et al., 2004; Bauermeister et al., 2007). The association between ADHD and affective disorders remains with aging. Odds ratios of 1.5–5.5 for anxiety disorders and of 2.7–7.5 for mood disorders, were found among adults with ADHD (Kessler et al., 2006; Michielsen, Comijs, Semeijn, Beekman, Deeg, & Kooij, 2013). The co-occurrence of ADHD and affective disorders has been associated with greater social impairment, poorer academic functioning and more psychiatric problems, as well as with suicide, and higher levels of substance use later in life (Biederman et al., 2008; Blackman, Ostrander, & Herman, 2005; Daviss, 2008; Rydell, Taylor, & Larsson, 2017).

All previous studies have looked only at the concurrent associations between ADHD and affective disorders (Chen et al., 2015; Cole et al., 2009; Michelini, Eley, Gregory, & McAdams, 2015; Rydell et al., 2017; Spatola et al., 2007). Despite the established co-occurrence of ADHD and affective disorders, no study has examined the developmental associations between them. There is a need to examine whether ADHD symptoms lead to affective disorders or whether affective disorders lead to ADHD. Furthermore, only few studies have explored whether the two dimensions of ADHD (inattention and

hyperactivity/impulsivity) differentially associated with affective disorders. A recent twin study by Michelini et al. (2015) found that the associations between anxiety and attention-deficit/hyperactivity dimensions are likely to be primarily due to an association between anxiety and attention problems, rather than between anxiety and hyperactivity/impulsivity. Anxiety is characterised by enhanced levels of attention towards threat stimuli (Beck & Clark, 1997), which leads to reduced attentional resources for other stimuli (Cisler & Koster, 2010). Therefore, anxious people experience attention problems as a consequence of their attention biases towards threat stimuli, which may produce enhanced inattention to everyday activities (Michelini et al., 2015) and can overlap with inattention symptoms of ADHD.

There is a growing body of evidence regarding the genetic and environmental contribution to the overlap between ADHD and affective disorders. Previous twin studies demonstrated evidence supporting modest to high (27%-77%) common genetic influence underlying symptoms of ADHD and affective disorders (Chen et al., 2015; Cole et al., 2009; Michelini et al., 2015; Rydell et al., 2017; Spatola et al., 2007). Findings regarding environmental influences are mixed, whereas some studies found that shared environmental influences explain part of the overlap between ADHD and affective disorders (Chen et al., 2015; Rydell et al., 2017), others found non-shared environmental influences (Cole et al., 2009; Michelini et al., 2015; Spatola et al., 2007). No study has examined the contribution of common genetic and environmental influences to the developmental associations between ADHD and affective disorders.

This study will investigate the associations between ADHD and affective disorders in childhood up to early adolescence. First, we will examine the concurrent and longitudinal associations between ADHD symptoms and emotional problems in childhood (ages 5,7,10 and 12). More specifically, we will test whether ADHD symptoms lead to emotional problems or whether emotional problems lead to ADHD. We will test whether these associations are specific to the inattention domain of ADHD rather than the hyperactivity/impulsivity domain. Second, we will investigate the contribution of common genetic and environmental influences to the developmental associations between ADHD and emotional problems in childhood and in early adolescence, using twin modelling. Furthermore, as previous studies found that the concurrent association between ADHD and affective disorders is partly explained by environmental factors (Chen et al., 2015; Cole et al., 2009; Michelini et al., 2015; Rydell et al., 2017), we will further examine the contribution of specific environmental factor to this association.

Based on a previous study from the E-Risk (Wertz et al., 2015), which examined the association between externalizing problems in childhood and internalizing problems in preadolescence, we will look at negative experiences (bullying victimization, maternal dissatisfaction and academic difficulties) as possible mediators. As children with externalizing problems, children with ADHD are at risk of experiencing negative situation because of their behaviour: they are victimized by their peers (Holmberg & Hjern, 2008; Hoza et al., 2005), experience academic difficulties (Barbarese, Katusic, Colligan, Weaver, & Jacobsen, 2007) and have conflictual relationships with their parents (Deault, 2010; Lifford, Harold, & Thapar, 2008). Children who go through such experiences are more likely to develop internalizing problems. Therefore, we assume that these factors will explain in part why children with ADHD develop emotional problems as they grow older.

As mentioned earlier, ADHD can occur throughout the life span, and also persist or emerge in adulthood (Agnew-Blais et al., 2016; Caye, et al., 2016; Moffitt et al., 2015). Moreover, stability in symptoms and diagnoses of anxiety and depression is also evident throughout the lifespan (Beesdo-Baum & Knappe, 2012; Nivard et al., 2015). Therefore, we will examine the longitudinal associations between ADHD diagnosis with anxiety and depression from early adolescence to young adulthood. We will test whether ADHD in early adolescence leads to anxiety and depression in young adulthood or whether anxiety and depression in early adolescence predict ADHD in young adulthood. Then, we will test whether having a co-twin with ADHD in early adolescence increases risks of having anxiety and depression in young adulthood, or vice-versa.

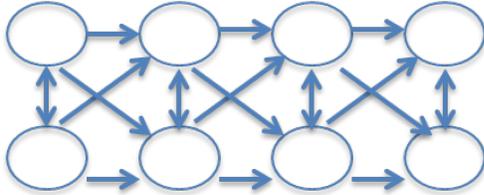
The main objectives of this study will be:

- (1) To examine the associations between ADHD symptoms and emotional problems in childhood
 - (a) To examine the associations between ADHD sub-scales (inattention and hyperactivity/impulsivity) and emotional problems in childhood
- (2) To investigate the contribution of common genetic and environmental influences to the developmental associations between ADHD and emotional problems in childhood

- (3) To test whether markers of failure can explain the associations between ADHD and emotional problems in childhood
- (4) To examine the association between ADHD diagnosis with anxiety and depression from early adolescence to young adulthood
- (5) To explore whether having a co-twin with ADHD in early adolescence increases risks of having anxiety or depression in young adulthood, or vice-versa

Statistical analyses:

- (1) We will use structural equation modelling (SEM) procedures to examine the concurrent and longitudinal associations between ADHD symptoms and emotional problems in childhood (ages 5,7,10 and 12). We will test a full cross-lagged model with the autoregressive effects and both ADHD and emotional problems predicting each other at a later time point. We will conduct the analyses controlling for sex and SES.



- (a) We will test these associations using ADHD symptom sub-scales (inattention and hyperactivity/impulsivity) separately.
- (2) We will use twin methodology to test the relative influence of genes and the environment on the developmental associations between age-5 ADHD symptoms and age-12 emotional problems. An initial examination of the relative contributions of genetic and environmental factors will be based on twin correlations assessing twin similarity for a trait between twins in a pair. Then, we will fit Cholesky decomposition to further estimate the influences on covariation between ADHD symptoms and emotional problems in childhood.
- (3) We will use linear regression models to examine the effect of the mediating variables (at age-10) on the association between age-5 ADHD symptoms and age-12 emotional problems.
- (4) We will use structural equation modelling (SEM) procedures to examine the longitudinal associations between ADHD diagnosis with anxiety and depression from age 12 to age 18.
- (5) We will use twin correlations to explore whether having a co-twin with ADHD at age 12 increases risks of having anxiety or depression at age 18, or vice-versa.

Variables Needed at Which Ages (names and labels):

Study:

Age 5

Usual Identifiers

- TOTEMOE5 - Total Mum & Teacher Emotional Scale (Ex Somatic) - Elder twin
- TOTEMOY5 - Total Mum & Teacher Emotional Scale (Ex Somatic) - Younger twin
- inemt5 - 'Inattention symptom count (M & T average) - P5 – E-Twin
- inymt5 - 'Inattention symptom count (M & T average) - P5 – Y-Twin
- hyemt5 - 'Hyperactive/Impulsive symptom count (M & T average) - P5 – E-Twin
- hyymt5 - 'Hyperactive/Impulsive symptom count (M & T average) - P5 – Y-Twin
- tadhdemt5 - 'Total Inattentive/Hyperactive/Impulsive symptom count (M & T average) - P5 – E-Twin
- tadhymt5 - 'Total Inattentive/Hyperactive/Impulsive symptom count (M & T average) - P5 – Y-Twin
- ADHDD3E5 - ADHD diagnosis - New Criteria - P5 – Elder
- ADHDD3Y5 - ADHD diagnosis - New Criteria - P5 - Younger

Age 7

TOTEMOE7 - Total Mum & Teacher Emotional Scale (Ex Somatic) - Elder twin
TOTEMOY7 - Total Mum & Teacher Emotional Scale (Ex Somatic) - Younger twin
Inemt7 - 'Inattention symptom count (M & T average) – P7 – E-Twin
Inymt7 - 'Inattention symptom count (M & T average) – P7 – Y-Twin
Hyemt7 - 'Hyperactive/Impulsive symptom count (M & T average) – P7 – E-Twin
Hyymt7 - 'Hyperactive/Impulsive symptom count (M & T average) – P7 – Y-Twin
Tadhemt7 - 'Total Inattentive/Hyperactive/Impulsive symptom count (M & T average) – P7 – E-Twin
Tadhymt7 - 'Total Inattentive/Hyperactive/Impulsive symptom count (M & T average) – P7 – Y-Twin
ADHDD3E7 - ADHD diagnosis - New Criteria – P7 – Elder
ADHDD3Y7 - ADHD diagnosis - New Criteria – P7 - Younger

Age 10

TOTEMOE10 - Total Mum & Teacher Emotional Scale (Ex Somatic) - Elder twin
TOTEMOY10 - Total Mum & Teacher Emotional Scale (Ex Somatic) - Younger twin
Inemt10 - 'Inattention symptom count (M & T average) – P10 – E-Twin
Inymt10 - 'Inattention symptom count (M & T average) – P10 – Y-Twin
Hyemt10 - 'Hyperactive/Impulsive symptom count (M & T average) – P10 – E-Twin
Hyymt10 - 'Hyperactive/Impulsive symptom count (M & T average) – P10 – Y-Twin
Tadhemt10 - 'Total Inattentive/Hyperactive/Impulsive symptom count (M & T average) – P10 - E-Twin
Tadhymt10 - 'Total Inattentive/Hyperactive/Impulsive symptom count (M & T average) – P10 – Y-Twin
ADHDD3E10 - ADHD diagnosis - New Criteria – P10– Elder
ADHDD3Y10 - ADHD diagnosis - New Criteria – P10 – Younger
BLA10E10 - Bullied at age 10 - Elder Twin
BLA10Y10 - Bullied at age 10 - Younger Twin
DISSE10 - Dissatisfaction/Negativity towards elder twin
DISSY10 - Dissatisfaction/Negativity towards younger twin
EDUCPRFE10 - School performance (English & Maths average) - P10 – Elder
EDUCPRFY10 - School performance (English & Maths average) - P10 - Younger

Age 12

TOTEMOE12 - Total Mum & Teacher Emotional Scale (Ex Somatic) - Elder twin
TOTEMOY12 - Total Mum & Teacher Emotional Scale (Ex Somatic) - Younger twin
MASCE12 - Anxiety Scale - MASC – Elder
MASCY12 - Anxiety Scale - MASC – Younger
CDIE12 - Depression Scale - CDI – Elder
CDIY12 - Depression Scale - CDI - Younger
Inemt12 - 'Inattention symptom count (M & T average) – P12 – E-Twin
Inymt12 - 'Inattention symptom count (M & T average) – P12 – Y-Twin
Hyemt12 - 'Hyperactive/Impulsive symptom count (M & T average) – P12 – E-Twin
Hyymt12 - 'Hyperactive/Impulsive symptom count (M & T average) – P12 – Y-Twin
Tadhemt12 - 'Total Inattentive/Hyperactive/Impulsive symptom count (M & T average) – P12 - E-Twin
Tadhymt12 - 'Total Inattentive/Hyperactive/Impulsive symptom count (M & T average) – P12 – Y-Twin
ADHDD3E12 - ADHD diagnosis - New Criteria – P12– Elder
ADHDD3Y12 - ADHD diagnosis - New Criteria – P12 - Younger
ADHDANYE512 Any ADHD dx [incl meds] - P5-12 - Elder
ADHDANYY512 Any ADHD dx [incl meds] - P5-12 - Younger
ADHDCNTE512 Number of ADHD dx [incl meds] - P5-12 - Elder
ADHDCNTY512 Number of ADHD dx [incl meds] - P5-12 – Younger
inemt512 'Inattention symptom count - (M & T average) - thru age 12 – E-Twin
inymt512 'Inattention symptom count - (M & T average) - thru age 12 – Y-Twin
hyemt512 'Hyperactive/Impulsive symptom count - (M & T average) - thru age 12 – E-Twin
hyymt512 'Hyperactive/Impulsive symptom count - (M & T average) - thru age 12 – Y-Twin
tadhemt512 'Total Inattentive/Hyperactive/Impulsive symptom count - (M & T average) - thru age 12 – E-Twin
tadhymt512 'Total Inattentive/Hyperactive/Impulsive symptom count - (M & T average) - thru age 12 – Y-Twin

Age 18

DXGADE18 - Gen Anxiety Disorder, dsm4_based - P18 - Elder
 DXGADY18 - Gen Anxiety Disorder, dsm4_based - P18 - Younger
 DXMDEE18 - Major depressive episode, dsm4 - P18 - Elder
 DXMDEY18 - Major depressive episode, dsm4 - P18 - Younger
 DXADHD5X_18E DSM-5 ADHD Dx (based on >=5 Symp) [incl 4 NEET & meds] - P18 - ET
 DXADHD5X_18Y DSM-5 ADHD Dx (based on >=5 Symp) [incl 4 NEET & meds] - P18 - YT
 SR_INSUM18E # DSM-5 Inattn Symp, Max=9, 18, E-Twin
 SR_INSUM18Y # DSM-5 Inattn Symp, Max=9, 18, Y-Twin
 SR_HYSUM18E # DSM-5 Hyper/Imp Symp, Max=9, 18, E-Twin
 SR_HYSUM18Y # DSM-5 Hyper/Imp Symp, Max=9, 18, Y-Twin
 SR_SYMTOT18E # DSM-5 Inattn/Hyper/Imp Symp, Max=18, 18, E-Twin
 SR_SYMTOT18Y # DSM-5 Inattn/Hyper/Imp Symp, Max=18, 18, Y-Twin
 inf_adhd18e # Any informant ADHD symptoms, Max = 8, 18 E-Twin
 inf_adhd18y # Any informant ADHD symptoms, Max = 8, 18 Y-Twin
 par_adhd18e # Parent informant ADHD symptoms, Max = 8, 18 E-Twin
 par_adhd18y # Parent informant ADHD symptoms, Max = 8, 18 Y-Twin
 twin_adhd18e # Co-Twin informant ADHD symptoms, Max = 8, 18 E-Twin
 twin_adhd18y # Co-Twin informant ADHD symptoms, Max = 8, 18 Y-Twin
 adhd4cate18 - ADHD group status (thru age 18) – Elder
 adhd4caty18 - ADHD group status (thru age 18) - Younger

Informant - anxiety?

Informant - depression?

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Data Security Agreement

Provisional Paper Title	Longitudinal associations between ADHD and affective disorders from childhood to young adulthood
Proposing Author	Adi Stern
Today's Date	January 2018

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- _____ I am current on Human Subjects Training (CITI (www.citiprogram.org) or training in human subject protection through my post or courses.
- AS My project is covered by Duke or King's IRB OR I have /will obtain IRB approval from my home institution.
- AS I will treat all data as "restricted" and store in a secure fashion.
- AS I will not share the data with anyone, including students or other collaborators not specifically listed on this concept paper.
- AS I will not post data online or submit the data file to a journal for them to post. Some journals are now requesting the data file as part of the manuscript submission process. The E-Risk Study cannot be shared because the Study Members have not given informed consent for unrestricted open access. Speak to Terrie or Avshalom for strategies for dealing with data sharing requests from Journals.
- AS Before submitting my paper to a journal, I will submit my draft manuscript and scripts for data checking, and my draft manuscript for co-author mock review, allowing three weeks.
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