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

Proposing Author: Jessica Agnew-Blais

Author's affiliation, phone, and e-mail address: jessica.agnew-blais@kcl.ac.uk

Sponsoring Investigator (if the proposing author is a student, a post-doc or a colleague): Temi Moffitt

Proposed co-authors: Louise Arseneault, Daniel Belsky, Avshalom Caspi, Andrea Danese, Cathryn Lewis, Guilherme Polanczyk, Karen Sugden, Jasmin Wertz, Ben Williams

Provisional Paper Title: Genetic and early environmental risk factors for childhood ADHD symptoms in a population-based cohort

Date: 07 May 2020

Objective of the study and its significance:

Whether a child will develop ADHD symptoms is influenced by a host of genetic and environmental factors, which operate in concert to cause the disorder. The role of genetic factors in ADHD has been informed by a recent genome-wide association study that identified, for the first time, genetic variants significantly associated with ADHD.[1] One way to quantify the overall impact of individual single nucleotide polymorphisms (SNPs) associated with ADHD is using polygenic risk scores (PRS), in which SNPs are combined to create an overall genetic liability score. ADHD PRS have been found to be associated with ADHD symptoms in the general population,[2] conduct disorder among children with ADHD,[3] and IQ and working memory in the general population.[4] However, PRS only explains about 5% of the variance of ADHD case status in independent samples, suggesting that the additive effect of common genetic variants alone does not explain the majority of ADHD.

A wide range of environmental risk factors have been found to be with associated with ADHD, including low socioeconomic status, maternal smoking and psychosocial adversity.[5-7] However whether these environmental exposures are causal influences, or rather reflect gene-environment correlation (Rge, Aim 1) is an open question. Gene-environment correlation occurs when an individual's genotype is associated with their environmental exposure. In the case of environmental exposures and ADHD risk, gene-environment correlation could explain these associations if parental genotype is associated both with childhood genotype (and subsequently, child phenotype), as well as early life environmental risk factors. Evidence for associations between maternal genotype and offspring environment has recently been found for gestational exposures, with maternal ADHD PRS associated with prenatal infection and maternal acetaminophen use during pregnancy.[8] However, this has not been investigated in the context of early childhood environmental household exposures associated with ADHD. In this study, we will investigate Rge with maternal ADHD PRS and adversity in offspring's childhood environment, specifically (1) economic insecurity (food insecurity, economic deprivation) (2) household chaos, and (3) parental instability (parental antisocial behavior and domestic violence) (Hypothetical Table 1).

Next, we will examine how maternal genetic risk, early environmental adverse exposures, and child's own ADHD genetic risk contribute to level of and change in the trajectory of ADHD symptoms across childhood (Aim 2, Hypothetical Table 2). While overall ADHD symptoms tend to decline from early childhood to adolescence, some children are more likely to continue to

exhibit elevated symptoms compared to peers. Previous work in the E-Risk cohort found that ADHD PRS was associated with level of childhood ADHD symptoms, but not with change in ADHD symptoms over time.[10] However, it is not clear how adverse childhood environmental exposures may influence level and change in ADHD symptoms over development, taking into account gene-environment correlation. Gene-environment correlation may completely explain the association between adverse environments and child ADHD symptoms; this kind of process, in which parental genotype influences child phenotype through environmental factors is called genetic nurture. Alternatively, there may be additional risk conferred by an adverse childhood environment, even after accounting for genetic risk. By longitudinally modeling ADHD symptoms across the 4 childhood time points we will be able to examine whether risk factors influence level of, as well as change, in ADHD symptoms from early childhood to adolescence. It is of clinical importance to identify children at increased risk for continued, elevated ADHD symptoms across childhood into adolescence.

To further illustrate the importance of the joint effect of genetic and environmental risk on the trajectory of ADHD symptoms across childhood, we will define different groups based levels of genetic and environmental risk (Aim 3, Hypothetical Figure 1). These groups include: those without household adversity and with low genetic risk, those with high genetic risk but low household adversity, those with low genetic risk and high household adversity, and finally those with both elevated genetic risk and household adversity. These analyses demonstrate the separate and joint effects of risk factors from these different domains.

Research aims:

Gene-environment correlation

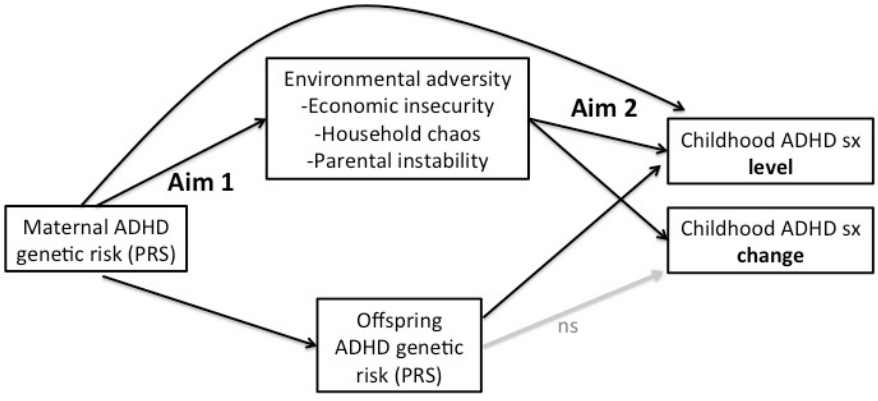
1. To determine whether maternal genetic risk for ADHD (maternal ADHD PRS) is associated with offspring environmental adversity, more specifically childhood economic insecurity, household chaos and parental instability (domestic violence and parental antisocial behaviour).

Gene-environment interplay, genetic nurture, and ADHD symptoms over time

2. To disentangle the associations of genetic and environmental risk factors in relation to level of and change in ADHD symptoms across childhood (from age 5 to age 12).

ADHD symptoms across childhood by risk strata

3. To compare the course of ADHD symptoms across groups of children defined by experience of different levels of ADHD genetic risk and household adversity.



Statistical analyses:

Aim 1. Regression analyses will examine whether maternal ADHD PRS is associated with offspring childhood economic insecurity, household chaos and parental instability.

Aim 2. Level and change in ADHD symptoms across childhood (mother-reported at ages 5, 7, 10 and 12) will be assessed using longitudinal modelling approaches, specifically latent growth curve analyses. Analyses will assess whether childhood adversity is associated with either level and/or change in ADHD symptoms across childhood, adjusting for maternal ADHD PRS. Analyses will also adjust for childhood ADHD PRS (as this will, at least partly, account for confounding by unmeasured paternal genetic risk). In sensitivity analyses, regressions will be repeated using teacher-reported ADHD symptoms from age 5-12.

Aim 3. Risk strata will be created including those at low risk (low genetic and household), genetic risk only, household risk only, and both genetic and household risk. Trajectories between these groups will be compared on both level and slope.

Hypothetical Tables and Figure

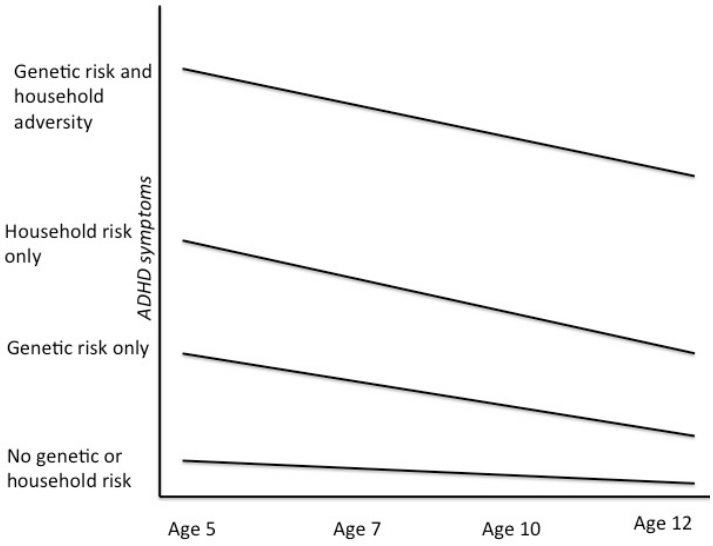
Table 1. Gene-environment correlation: the association of maternal ADHD polygenic risk score with household adversity and offspring ADHD symptoms

	Maternal ADHD PRS	
Household adversity	Beta (95% CI)	P value
Economic insecurity		
Household chaos		
Parental instability		
Childhood ADHD symptoms		
Mother-reported		
Teacher-reported		

Table 2. The association between level and change in ADHD symptoms from age 5 to age 12 with household adversity, further adjusting for maternal and offspring polygenetic risk

	Household adversity		w/ maternal genetic risk		w/ offspring genetic risk	
	Symptom level (intercept)	Symptom change (slope)	Symptom level (intercept)	Symptom change (slope)	Symptom level (intercept)	Symptom change (slope)
	b (95%CI), p	b (95%CI), p	b (95%CI), p	b (95%CI), p	b (95%CI), p	b (95%CI), p
Household adversity						
Economic insecurity	TBD	TBD	TBD	TBD	TBD	TBD
Household chaos	TBD	TBD	TBD	TBD	TBD	TBD
Parental instability	TBD	TBD	TBD	TBD	TBD	TBD
Maternal PRS			TBD	TBD	TBD	TBD
Child ADHD PRS					TBD	TBD

Figure 1. Trajectories of ADHD symptoms across childhood among those with varying levels of genetic and household adversity *[actual trajectories TBD, the below given for illustration purposes]*



Variables Needed at Which Ages (names and labels):

Study:

Age 5:

FAMILYID ID Family
ATWINID ID Twin 1
BTWINID ID Twin 2
SAMPSEX Sex of twins
RORDERP5 Random order variable
SESWQ35 Social Class Composite

ED57M5 Difficult to meet cost of food and other necessities?
EHARDM5 Experience of economic hardship
PARENTASBMN5 parent antisocial scale (mean of aspmm5 & aspfm5)
ANYVIOM5 Any domestic violence (last 5 years)

INEM5 Inattention symptom - 2 Count - Mother - Elder
HYEM5 Hyperactive/Impulsive symptom - 2 Count - Mother – Elder
TADHDEM5 Total ADHD symptom count- 2 Count - Mother – Elder

Age 7:

CHAOSM7—Chaos in the home
FOOD7M7 Food situation- 7 scale
CHAOS10 Chaos in the home

INEM 7 Inattention symptom - 2 Count - Mother - Elder
HYEM7 Hyperactive/Impulsive symptom - 2 Count - Mother – Elder

TADHDEM7 Total ADHD symptom count- 2 Count - Mother – Elder

SESDM7 SES Disadvantage

Age 10:
CHAOSM10 Chaos in the home
TVIOM10 Total partner violence recoded- Sum of scales

INEM10 Inattention symptom - 2 Count - Mother - Elder
HYEM10 Hyperactive/Impulsive symptom - 2 Count - Mother – Elder
TADHDEM10 Total ADHD symptom count- 2 Count - Mother – Elder

FOOD7M10 Food situation – 7 scale

Age 12:
CHAOSSM Chaos scale mother
CHAOSM12 chaos in the home- mum interview
CHAOSC12 chaos in the home—twin interview
CHAOSEC12 Chaos at home (twin computer questionnaire)
ADHDANYE512 Any ADHD dx (incl meds)
ADHDCNTE512 Number of ADHD dx

INEM12 Inattention symptom - 2 Count - Mother - Elder
HYEM12 Hyperactive/Impulsive symptom - 2 Count - Mother – Elder
TADHDEM12 Total ADHD symptom count- 2 Count - Mother – Elder

Mean mother reported ADHD symptoms from age 5-age 12—to be created
Mean teacher reported ADHD symptoms from age 5-age 12—to be created

Age 18:
ADHDPGS_Twins_Feb2020_Clumped
ADHDPGS_Mums_Jan2019 (Clumped version)

References cited:
1. Demontis D, Walters RK, Martin J, Mattheisen M, Alsa TD. Discovery of the first genome-wide significant risk loci for ADHD. Nat Genet. 2019;51:63-75.
2. Groen-Blokhuis MM, Middeldorp CM, Kan KJ, et al. Attention-deficit/hyperactivity disorder polygenic risk scores predict attention poblems in a population-based sample of children. J Am Acad Child Adol Psychiatry. 2014;53:1123-1129.
3. Hamshere ML, Stergiakouli E, Langley K, et al. Shared polygenic contribution between childhood attention-deficit disorder and adult schizophrenia. Br J Psychiatry. 2013;203:107-111.
4. Martin J, Hamshere ML, Stergiakouli E, O'Donovan M, Thapar A. Neurocognitive abilities in the general population and coposite genetic risk scores for attention-deficit hyperactivity disorder. J Child Psychol Psychiatr. 2015;56:648-656.
5. Agnew-Blais JC, Polanczyk GV, Danese A, Wertz J, Moffitt TE, Arseneault L. Persistence, remission and emergence of ADHD in young adulthood: results from a longitudinal, prospective population-based cohort. JAMA Psychiatry. 2016;73:713-720.
6. Langley K, Rice F, van den Bree MB, Thapar A. Maternal smoking dring pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. Minerva Pediatr. 2005;57:359-371.
7. Thapar A, Cooper M, Jefferies R, Stergiakouli E. What causes attention deficit hyperactivity disorder? Arch Dis Child. 2012;97:260-265.
8. Leppert B, Havdahl A, Riglin L, et al. Associations of maternal neurodevelopmental risk alleles with early-life exposures. JAMA Psychiatry. 2019;76:834-842.

Data Security Agreement

Provisional Paper Title	Gene-environment interplay and childhood ADHD symptoms in a population-based cohort
Proposing Author	Jessica Agnew-Blais
Today's Date	20 Apr 2020

Please keep one copy for your records
(Please initial your agreement)

JAB____ I am familiar with the King's College London research ethics guidelines (https://www.kcl.ac.uk/innovation/research/support/ethics/about/index.aspx) and the MRC good research practice guidelines (https://www.mrc.ac.uk/research/policies-and-guidance-for-researchers/good-research-practice/).

_JAB___My project has ethical approval from my institution.

_JAB___I am familiar with the EU General Data Protection Regulation (https://mrc.ukri.org/documents/pdf/gdpr-guidance-note-3-consent-in-research-and-confidentiality/), and will use the data in a manner compliant with its requirements.

_JAB___My computer is (a) encrypted at the hard drive level, (b) password-protected, (c) configured to lock after 15 minutes of inactivity, AND (d) has an antivirus client which is updated regularly.

_JAB___I will treat all data as "restricted" and store in a secure fashion.

_JAB___I will not share the data with anyone, including students or other collaborators not specifically listed on this concept paper.

_JAB___I will not merge data from different files or sources, except where approval has been given by the PI.

__JAB__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 the study PI for strategies for dealing with data sharing requests from Journals.

_JAB___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.

__JAB__I will submit analysis scripts and new variable documentation to project data manager after the manuscript gets accepted for publication.

_JAB___I will delete the data after the project is complete.

__NA__ **For projects using location data:** I will ensure geographical location information, including postcodes or geographical coordinates for the E-Risk study member's homes or schools, is <u>never</u> combined or stored with any other E-Risk data (family or twin-level data)

_JAB___ **For projects using genomic data:** I will only use the SNP and/or 450K data in conjunction with the phenotypes that have been approved for use in this project at the concept paper stage.

Signature: .....Jessica Agnew-Blais.....