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

Proposing Author: Beate Leppert[1] and Lucy Riglin[2]

Author's affiliation, phone, and e-mail address:

1 – MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK , beate.leppert@bristol.ac.uk
2 – MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK , RiglinL@cardiff.ac.uk

Sponsoring Investigator (if the proposing author is a student, a post-doc or a colleague): Louise Arsenault (with Prof. Anita Thapar, Cardiff)

Proposed co-authors: Kate Tilling, Anita Thapar, Evie Stergiakouli, Louise Arsenault, Robert Plomin, Luis Rohde, Jessica Agnew-Blais, Arthur Caye

Provisional Paper Title: The natural history of neurodevelopmental disorders from childhood to adult life

Date:

Objective of the study and its significance:

Attention Deficit Hyperactivity Disorder (ADHD) is common, onsets in childhood, behaves as a continuous trait and is highly disruptive (Thapar & Cooper, 2016). Although previously considered as a condition limited to childhood, ADHD also affects adults. A growing body of research shows that there is heterogeneity in the developmental course of ADHD. For most children symptoms decline during adolescence but for about 65% of children symptoms remain persistent into adulthood (Faraone, Biederman & Mick, 2006). Intriguingly, recent evidence even suggests that some forms may emerge newly in adolescence (Caye et al., 2016). These findings highlight the need to investigate the natural history of ADHD into adulthood, in unselected population cohorts. We aim to harmonise data across five international population-based cohorts with repeated measures of ADHD and characterise the natural history of ADHD from age 4 to 45 years.

Despite marked developmental change, normative ADHD trajectories have never been described before - unlike physical traits such as blood pressure (Wills et al., 2011). Describing normative patterns that span beyond adolescence and into adulthood is of particular clinical interest, as this is a period when patients move from child to adult services and it is not currently clear what level of ADHD symptoms are developmentally appropriate in adulthood.

We will harmonise a very large dataset of approximately 20,000 participants from five international cohorts to characterise the natural history of ADHD.
This will establish a platform for methods harmonisation and investigating ADHD across international population cohorts.

Statistical analyses:

We will use multi-level modelling (MLM) to estimate individual-specific and average trajectories of ADHD spanning age 4 to 45 years.

We will start by fitting a growth model (two-level MLM) in ALSPAC (the Avon Longitudinal Study of Parents and Children) based on repeated parent-rated continuous trait measures (the Strengths and Difficulties Questionnaire) at 8 time-points spanning ages 4 to 26) (level 1: see Figure) nested in participants (level 2). We will allow for individual variation in both initial levels of ADHD (random intercept) and the longitudinal pattern (random slope) and for differences by sex. Additional ADHD diagnosis derived from the Development and Well Being Assessment will be used to validate the obtained model. We will use structural equation modelling (SEM) to investigate the assumption that there is one underlying pattern of "growth" in SDQ. If evidence against this assumption is found, we will proceed with the best-fitting SEM.

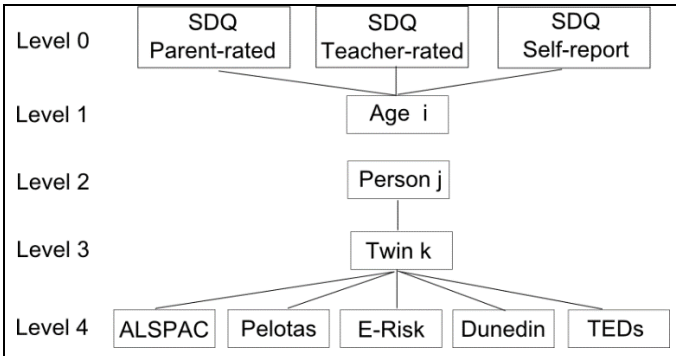
To the best-fitting model (SEM or MLM), we will add teacher- and self-rated ADHD symptoms (SDQ available at ages 7 and 11 years) as a level 0, which themselves will then be nested in age at assessment (level 1). Before incorporating self-rated ADHD symptoms we will conduct an intensive comparison of parent- and self-rated measures in ALSPAC using age 26 data which will inform weights used for different informants. The same approach will be used to derive cohort specific weights.

We will harmonise the five cohorts (ALSPAC, Dunedin Study, E-risk, TEDS and Pelotas) into one dataset including ADHD measures from ages 4 to 45 years. ADHD measures will be standardised within each sample.

We will then fit a model identical in form to the best-fitting ALSPAC model to the combined dataset. We will allow for additional variation between twins (TEDs and E-risk datasets) and cohorts.

We will include all available data in our analyses under the assumption of missing at random (MAR). We will investigate patterns of missing data by investigating associations between missingness and variables with near-complete data (e.g. sex) and assumed confounding factors (e.g. socio-economic factors, education) and assess confounding by comparing differences in longitudinal patterns of ADHD and in patterns of missingness across cohorts.

Analyses will be jointly conducted by Lucy Riglin at Cardiff University and Beate Leppert at the University of Bristol. Kate Tilling will be the statistical guarantor and Anita Thapar will also oversee the project as Principal Investigator of the collaborative grant funding this work.



Variables Needed at Which Ages (names and labels):

Study:
FAMILYID Unique family identifier Primary Family Level ID
ATWINID Twin A ID Primary elder twin ID

Age 5:
ADHD diagnosis and items added to the CBCL-ASEBA (parent- and teacher-rated)

ADHD diagnosis:
ADHDD3E5 ADHD diagnosis—new criteria- P5- elder

Parent-rated items:
PE81M5 Can't concentrate, can't pay attention for long, short attention
PE82M5 Fails to finish things he\she starts
PE83M5 Inattentive or easily distracted
PE86M5 Doesn't pay attention to details
PE87M5 Doesn't notice when people speak to him\her
PE88M5 Doesn't organise him\herself well
PE89M5 Doesn't like activities that require a lot of attention and
PE90M5 Loses things, like toys and clothes
PE91M5 Forgets what he\she is doing
PE84M5 Impulsive or acts without thinking
PE85M5 Interrupts conversations or games
PE96M5 Blurts out answers before the whole question has been asked
PE97M5 Has difficulty waiting for his\her turn
PE92M5 Fidgety or squirmy
PE93M5 Very restless, has difficulty staying seated for long
PE94M5 Cannot settle to anything for more than a few moments, quick
PE95M5 Seems to be "on the go" or acts as if "driven by a motor"
PE64M5 Talks too much

Teacher-rated items:
TRF89E5 Short attention span
TRF90E5 Fails to finish things he\she starts
TRF91E5 Inattentive or easily distracted
TRF94E5 Doesn't pay attention to details
TRF95E5 Doesn't notice when people speak to him\her
TRF96E5 Doesn't organise him\herself well
TRF97E5 Doesn't like activities that require a lot of attention and
TRF98E5 Loses things, like toys and clothes

TRF99E5 Forgets what he\she is doing
TRF92E5 Impulsive or acts without thinking
TRF93E5 Interrupts conversations or games
TRF104E5 Blurts out answers before the whole question has been asked
TRF105E5 Has difficulty waiting for his\her turn
TRF100E5 Fidgety or squirmy
TRF101E5 Very restless, has difficulty staying seated for long
TRF102E5 Cannot settle to anything for more than a few moments
TRF103E5 Seems to be 'on the go' or acts as if 'driven by a motor'
TRF66E5 Talks alot

Age 7:
ADHD diagnosis and items added to the CBCL-ASEBA (parent- and teacher-rated)

ADHD diagnosis
ADHDD3E7 ADHD New Criteria Scale - Elder

Parent-rated items:
PE81M7 Can't concentrate, can't pay attention for long, short attention
PE82M7 Fails to finish things he\she starts
PE83M7 Inattentive or easily distracted
PE86M7 Doesn't pay attention to details
PE87M7 Doesn't notice when people speak to him\her
PE88M7 Doesn't organise him\herself well
PE89M7 Doesn't like activities that require a lot of attention and
PE90M7 Loses things, like toys and clothes
PE91M7 Forgets what he\she is doing
PE84M7 Impulsive or acts without thinking
PE85M7 Interrupts conversations or games
PE96M7 Blurts out answers before the whole question has been asked
PE97M7 Has difficulty waiting for his\her turn
PE92M7 Fidgety or squirmy
PE93M7 Very restless, has difficulty staying seated for long
PE94M7 Cannot settle to anything for more than a few moments, quick
PE95M7 Seems to be "on the go" or acts as if "driven by a motor"
PE64M7 Talks too much.

Teacher-rated items:
TRF89E7 Short attention span
TRF90E7 Fails to finish things he\she starts
TRF91E7 Inattentive or easily distracted
TRF94E7 Doesn't pay attention to details
TRF95E7 Doesn't notice when people speak to him\her
TRF96E7 Doesn't organise him\herself well
TRF97E7 Doesn't like activities that require a lot of attention and
TRF98E7 Loses things, like toys and clothes
TRF99E7 Forgets what he\she is doing
TRF92Y7 Impulsive or acts without thinking
TRF93Y7 Interrupts conversations or games
TRF104Y7 Blurts out answers before the whole question has been asked
TRF105Y7 Has difficulty waiting for his\her turn
TRF100Y7 Fidgety or squirmy
TRF101Y7 Very restless, has difficulty staying seated for long
TRF102Y7 Cannot settle to anything for more than a few moments
TRF103Y7 Seems to be 'on the go' or acts as if 'driven by a motor'

TRF66Y7 Talks alot.

Age 10:
ADHD diagnosis and items added to the CBCL-ASEBA (parent- and teacher-rated)

ADHD diagnosis:
ADHDD3E10 ADHD diagnosis—medicated kids not included
ADHDD3XE10 ADHD diagnosis- New criteria [incl meds]- p10 – elder

Parent-rated items:
PE81M10 Can't concentrate, can't pay attention for long, short
PE82M10 Fails to finish things he\she starts
PE83M10 Inattentive or easily distracted
PE86M10 Doesn't pay attention to details
PE87M10 Doesn't notice when people speak to him\her
PE88M10 Doesn't organise him\herself well
PE89M10 Doesn't like activities that require a lot of attention and
PE90M10 Loses things, like toys and clothes
PE91M10 Forgets what he\she is doing.
PE84M10 Impulsive or acts without thinking
PE85M10 Interrupts conversations or games
PE96M10 Blurts out answers before the whole question has been asked
PE97M10 Has difficulty waiting for his\her turn
PE92M10 Fidgety or squirmy
PE93M10 Very restless, has difficulty staying seated for long
PE94M10 Cannot settle to anything for more than a few moments, quick
PE95M10 Seems to be "on the go" or acts as if "driven by a motor"
PE64M10 Talks too much.

Teacher-rated items:
TRF89E10 Short attention span
TRF90E10 Fails to finish things he\she starts
TRF91E10 Inattentive or easily distracted
TRF94E10 Doesn't pay attention to details
TRF95E10 Doesn't notice when people speak to him\her
TRF96E10 Doesn't organise him\herself well
TRF97E10 Doesn't like activities that require a lot of attention and
TRF98E10 Loses things, like toys and clothes
TRF99E10 Forgets what he\she is doing
PE84M10 Impulsive or acts without thinking
PE85M10 Interrupts conversations or games
PE96M10 Blurts out answers before the whole question has been asked
PE97M10 Has difficulty waiting for his\her turn
PE92M10 Fidgety or squirmy
PE93M10 Very restless, has difficulty staying seated for long
PE94M10 Cannot settle to anything for more than a few moments, quick
PE95M10 Seems to be "on the go" or acts as if "driven by a motor"
*PE64M10 Talks too much

Age 12:
ADHD diagnosis and items added to the CBCL-ASEBA (parent- and teacher-rated)

ADHD diagnosis:
ADHDD3E12 ADHD diagnosis—New criteria—medicated kids not included
ADHDD3XE12 ADHD diagnosis—New criteria [incl meds] P12 – elder

Parent-rated:

```
PE81M12 Can't concentrate, can't pay attention for long, short
PE82M12 Fails to finish things he\she starts
PE83M12 Inattentive or easily distracted
PE86M12 Doesn't pay attention to details
PE87M12 Doesn't notice when people speak to him\her
PE88M12 Doesn't organise him\herself well
PE89M12 Doesn't like activities that require a lot of attention and
PE90M12 Loses things, like toys and clothes
PE91M12 Forgets what he\she is doing.
PE84M12 Impulsive or acts without thinking
PE85M12 Interrupts conversations or games
PE96M12 Blurts out answers before the whole question has been asked
PE97M12 Has difficulty waiting for his\her turn
PE92M12 Fidgety or squirmy
PE93M12 Very restless, has difficulty staying seated for long
PE94M12 Cannot settle to anything for more than a few moments, quick
PE95M12 Seems to be "on the go" or acts as if "driven by a motor"
PE64M12 Talks too much
```

Teacher-rated:

```
TRF89E12 Short attention span
TRF90E12 Fails to finish things he\she starts
TRF91E12 Inattentive or easily distracted
TRF94E12 Doesn't pay attention to details
TRF95E12 Doesn't notice when people speak to him\her
TRF96E12 Doesn't organise him\herself well
TRF97E12 Doesn't like activities that require a lot of attention and
TRF98E12 Loses things, like toys and clothes
TRF99E12 Forgets what he\she is doing.
TRF92E12 Impulsive or acts without thinking
TRF93E12 Interrupts conversations or games
TRF104E12 Blurts out answers before the whole question has been asked
TRF105E12 Has difficulty waiting for his\her turn
TRF100E12 Fidgety or squirmy
TRF101E12 Very restless, has difficulty staying seated for long
TRF102E12 Cannot settle to anything for more than a few moments
TRF103E12 Seems to be 'on the go' or acts as if 'driven by a motor'
TRF66E12 Talks a lot
```

Age 18:

ADHD diagnosis and items under consideration for DSM-5 in 2012 (parent-, self- and ~~teacher-rated~~)

```
DXADHD5X_18E DSM-5 ADHD Dx (>=5 Symp) [incl 4 NEET & meds] - P18 - ET

PAR_ADHD18E # parent informant ADHD symptoms, max=8, 18 E-twin
TWIN_ADHD18E # cotwin informant ADHD symptoms, max=8, 18 E-twin
INF_ADHD18E # Any informant ADHD symptoms, max=8, 18 E-twin
```

Self-reported ADHD items:

```
ADHD1 I'm easily distracted, I get sidetracked easily
ADHD2 I make careless mistakes
ADHD3 I don't listen
ADHD4 I get bored quickly
ADHD5 I misplace my wallet, keys, mobile phone, paperwork. I lose
```

ADHD6 I can't concentrate, my mind wanders
ADHD7 I'm disorganised
ADHD8 I'm forgetful, I forget appointments, forget to do errands,
ADHD9 I tune out when I should focus
ADHD10 I jump into projects without reading the instructions …
ADHD11 I lack self-discipline
ADHD12 I leave projects unfinished
ADHD13 I have difficulty waiting; I'm impatient …
ADHD14 I make "snap" decisions (too fast)
ADHD15 I put off tasks that require lots of effort
ADHD16 I'm impulsive, I act without thinking about what might happen
ADHD17 I have difficulty organising tasks that have many steps
ADHD18 I can't resist temptation
ADHD19 I talk too much
ADHD20 I get uncomfortable sitting still; I need to get up and move …
ADHD21 I don't enjoy doing quiet activities
ADHD22 I'm too loud or noisy
ADHD23 I'm always on the go, in a hurry, as if driven by a motor
ADHD24 I feel fidgety or squirmy
ADHD25 I feel very restless
ADHD26 I blurt out answers before others finish speaking
ADHD27 I interrupt, barge into others' conversations

**tim, they want the individual items, but separately from the mom and the twin—I didn't know how to label them to reflect which informant was reporting
INF60 Impulsive, rushes into things without thinking what might happen
INF67 Is easily distracted, gets sidetracked easily
INF68 Can't concentrate, mind wanders
INF69 Lacks self-discipline
INF70 Makes "snap" decisions (too fast)
INF71 Is uncomfortable sitting still
INF72 Always on the go, in a hurry, fast-paced
INF73 Fidgety, restless

Supplementary data for cohort comparison and identifying patterns of missing data assessed at any age:

Birthweight
BWGRE5 Birth weight (gr) - Elder twin

Gestational age
AGESTAGE Gestation time - weeks

Ethnicity
SETHNIC Ethnicity of twins

Child sex
SAMPSEX Sex of twins: in sample

Maternal and ~~paternal~~ age at delivery
MOTHDOB Mother D.O.B
TWINADOB Elder twin D.O.B

Number of Previous Deliveries
TSOLDML5 Total number of older siblings mum given birth to

Maternal and paternal educational attainment (Socio-Economic Status)
HIEDGM5 Highest educational qualification (grouped—mother)
HIEDPGM5 Highest educational qualification (grouped—partner)
SESWQ35 Social class composite

Smoking during pregnancy
SMKGP Smoking during pregnancy—grouped

Parity
TSMUML5 Total siblings mum given birth to

Other known diagnosis of psychiatric or other major disorder in the child or parents
Tim, as we discussed, this is the same as the one is Jasmin's paper, but it excludes ADHD diagnoses at age 18, so I think it needs to be made. So they don't need the individual dxs below, I'm just listing them to show what went into Jasmin's list:
Other Psychopathology Age 18
DXMDEE18 Major depressive episode, dsm4 - P18 – Elder
DXGADE18 Gen Anxiety Disorder, dsm4_based - P18 – Elder
PTSD Current dx, dsm5 - P18 - Elder
DXALCDEPE18 Alcohol dependent, dsm4_based - P18 – Elder
DXMARJE18 Marijuana dependency, dsm4 - P18 – Elder
CDMODE18 Moderate Conduct Disorder (>=5 count) - P18 - Elder

~~Any complete data, e.g. from linked records or records at start of study~~

Child height (at any age – to assess comparability across samples)
HEIGHT_METERS

Child weight (at any age – to assess comparability across samples)
WEIGHTE18
BMIE18 Body Mass Index - P18 - Elder
PREGE18 Pregnant at visit – P18 – Elder

Child educational attainment
EDUCACHE18 Highest education achievement (based on QCF) – P18 - Elder

Child employment status
NEETE18 NEET: Not in educ, employment or training - P18 - Elder

References cited:

Caye A, Swanson J, Thapar A. et al. (2016). Life span studies of ADHD - Conceptual challenges and predictors of persistence and outcome. *Current Psychiatry Reports, 18*: 111

Faraone SV, Biederman J, Mick E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine, 36*: 159-65.

Thapar A, Cooper M. (2016). Attention deficit hyperactivity disorder. *Lancet, 387*: 1240–50.

Wills AK, Lawlor DA., Matthews FE et al. (2011). Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. *PLoS Medicine, 8*:e1000440.

Data Security Agreement

Provisional Paper Title	The natural history of neurodevelopmental disorders from childhood to adult life
Proposing Author	Beate Leppert and Lucy Riglin
Today's Date	30.04.2019

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

BL_ 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/).

BL_ My project has ethical approval from my institution.

BL_ 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

BL_ My computer is (a) password-protected, (c) configured to lock after 15 minutes of inactivity, (c) has an antivirus client which is updated regularly AND (d) all data is stored on a secure and encrypted server.

BL_ I will treat all data as "restricted" and store in a secure fashion

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

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

BL_ 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.

BL_ 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.

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

BL_ I will delete the data after the project is complete.

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

BL_ **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 the project at the concept paper stage

Signature: .....B. Leppert.....

Data Security Agreement

Provisional Paper Title	The natural history of neurodevelopmental disorders from childhood to adult life
Proposing Author	Beate Leppert and Lucy Riglin
Today's Date	30/04/2019

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

LR 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/).

N/A My project has ethical approval from my institution.

LR 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.

LR When the data stored are ~~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.

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

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

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

LR 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.

LR 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.

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

LR I will delete the data after the project is complete.

N/A **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 never combined or stored with any other E-Risk data (family or town-level data)

LR **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: LRiglin

10

CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author

Proposing Author: Beate Leppert and Lucy Riglin

☐ I have read the E-Risk data-sharing policy guidelines and agree to follow them

Provisional Paper Title: The natural history of neurodevelopmental disorders from childhood to adult life

Potential co-authors: Kate Tilling, Anita Thapar, Evie Stergiakouli, Louise Arsenault, Robert Plomin, Luis Rohde, Jessica Agnew-Blais, Arthur Caye

Potential Journals:

Intended Submission Date (month/year): July 2021

Please keep one copy for your records and return one to Louise (louise.arseneault@kcl.ac.uk)

B. To be completed by potential co-authors:

☐ Approved ☐ Not Approved ☐ Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

☐ Conceptualizing and designing the longitudinal study

☐ Conceptualizing and collecting one or more variables

☐ Data collection

☐ Conceptualizing and designing this specific paper project

☐ Statistical analyses

☐ Writing

☐ Reviewing manuscript drafts

☐ Final approval before submission for publication

☐ Acknowledgment only, I will not be a co-author

Signature: .....