Concept Paper

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

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

1 – MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK
2 – MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK

Author's Email: beate.leppert@bristol.ac.uk, RiglinL@cardiff.ac.uk

P.I. Sponsor: Temi Moffitt (with Prof. Anita Thapar, Cardiff)

Today's Date: 11.03.2019

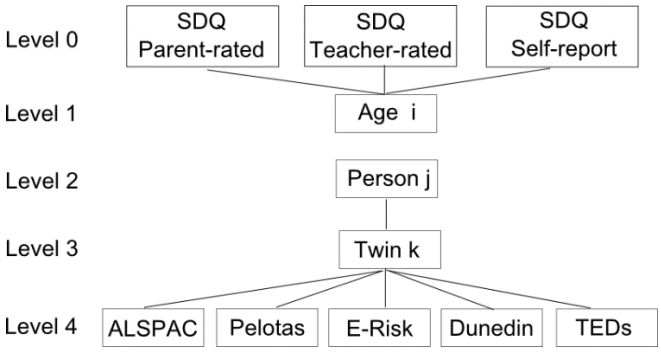
Objective of the study:

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.

Data analysis methods:

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:

ADHD trait measures / diagnosis:

Age 5:
ADHD trait measure (Rutter checklist, parent and teacher rated)

Age 7:
ADHD trait measure (Rutter checklist, parent and teacher rated)

Age 9:
ADHD trait measure (Rutter checklist, parent and teacher rated)

Age 11:
ADHD trait measure (Rutter checklist, parent and teacher rated)
ADHD diagnosis

ADHD self-rated trait measures (DISC)

Age 13:
ADHD trait measure (Rutter checklist, parent and teacher rated)
ADHD diagnosis
ADHD self-rated trait measures (DISC)

Age 15:
ADHD trait measure (Rutter checklist, parent rated)
ADHD diagnosis
ADHD self-rated trait measures (DISC)

Age 38:
ADHD items under consideration for DSM-5 in 2012
ADHD diagnosis

Age 45:
ADHD items under consideration for DSM-5 in 2012
ADHD diagnosis

General:
Any measures of ADHD taken twice (repeated) at the same assessment (including subsample), to assess measurement error

(age at each measure)

Supplementary data to assess comparability across cohorts (including patterns of missingness and confounding) :

Phase 0 (Perinatal data):

- Birthweight
- Gestational age
- Ethnicity
- Child sex
- Maternal and paternal age at delivery
- Number of Previous Deliveries
- Maternal and paternal educational attainment (Socio-Economic Status)
- (Smoking during pregnancy)
- Parity

Other supplementary data at any age: {Note, the ones in italics are not feasible for Dunedin)

- *Other known diagnosis of psychiatric or other major disorder in the child or parents*
- *Any complete data, e.g. from linked records or records at start of study*
- Child height (at any age – to assess comparability across samples)

- Child weight (at any age – to assess comparability across samples)
- Child educational attainment
- *Child employment status*

Significance of the Study (for theory, research methods or clinical practice):

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.

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.