Title: Identifying novel types of irritability using a developmental genetic approach

Lucy Riglin, PhD[1]

Olga Eyre, MRCPsych[1]

Ajay K Thapar, MRCGP, PhD[1]

Argyris Stringaris, MD, PhD[2]

Ellen Leibenluft, MD[2]

Daniel Pine, MD[2]

Kate Tilling, PhD[3]

George Davey Smith, MD, DSc [3]

Michael C O'Donovan, FRCPsych, PhD[1]

Anita Thapar, FRCPsych, PhD[1*]

[1]Division of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, UK

[2] Emotion and Development Branch, National Institute of Mental Health, Bethesda, MD, USA

[3]MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK

[*]Corresponding author. Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Hadyn Ellis Building, Maindy Road, Cathays, Cardiff CF24 4HQ. Tel: +442920688325. Email: thapar@cardiff.ac.uk

Main text word count: 4117

Previous presentation: Some of the findings from this study was presented at the Inaugural Professor Sir Michael Rutter Lecture given by Anita Thapar on July 3rd 2018. This work has been uploaded to bioRxiv, doi: 10.1101/433342.

Disclosures and acknowledgments.

All authors report no competing interests.

We acknowledge the members of the Psychiatric Genomics Consortium for the publicly available data used as the discovery samples in this article. We thank the research participants and employees of 23andMe, Inc. for their contribution to this study. We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (102215/2/13/2) and the University of Bristol provide core support for ALSPAC. GWAS data was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. We thank Alexander Richards and Richard Anney for preparing the quality controlled genome-wide association study summary statistics. This study was supported by the Wellcome Trust (204895/Z/16/Z).

Abstract.

Objective. Irritability is a common reason for referral to services, strongly associated with impairment and negative outcomes, but is a nosological and treatment challenge. A major issue is how irritability should be conceptualized. This study used a developmental approach to test the hypothesis that there are several forms of irritability, including a 'neurodevelopmental/ADHD-like' type with onset in childhood and a 'depression/mood' type with onset in adolescence. *Method*. Data were analyzed in the Avon Longitudinal Study of Parents and Children, a prospective UK population-based cohort. Irritability trajectory-classes were estimated for 7924 individuals with data at multiple time-points across childhood and adolescence (4 possible time-points from approximately ages 7 to 15 years). Psychiatric diagnoses were assessed at approximately ages 7 and 15 years. Psychiatric genetic risk was indexed by polygenic risk scores (PRS) for attention-deficit/hyperactivity disorder (ADHD) and depression derived using large genome-wide association study results. *Results*. Five irritability trajectory classes were identified: low (81.2%), decreasing (5.6%), increasing (5.5%), late-childhood limited (5.2%) and high-persistent (2.4%). The early-onset, high-persistent trajectory was associated with male preponderance, childhood ADHD (OR=108.64 (57.45-204.41), p<0.001) and ADHD PRS (OR=1.31 (1.09-1.58), p=0.005); the adolescent-onset, increasing trajectory was associated with female preponderance, adolescent depression (OR=5.14 (2.47-10.73), p<0.001) and depression PRS (OR=1.20, (1.05-1.38), p=0.009). Both trajectory classes were associated with adolescent depression diagnosis and ADHD PRS. *Conclusions*. The developmental context of irritability may be important in its conceptualization: early-onset persistent irritability maybe more 'neurodevelopmental/ADHD-like' and later-onset irritability more 'depression/mood-like'. This has implications for treatment as well as nosology.

Keywords. ALSPAC; irritability; longitudinal; trajectories; genetic; polygenic risk scores

Identifying novel types of irritability using a developmental genetic approach

Irritability – a heightened propensity to anger, relative to peers – is a common reason for referral to mental health services, is strongly associated with impairment and long-term adverse outcomes (1-6), yet remains a nosological and treatment challenge (1, 2). Currently, it is treated as a homogenous construct, but it is a core or accompanying feature of several psychiatric disorders and such differential associations suggest that subtyping may be necessary. This study set out to examine the possibility that there are multiple forms of irritability, including a 'neurodevelopmental' type with onset in childhood and a 'depression/mood' type with onset in adolescence.

Childhood irritability has typically been considered a feature of Oppositional Defiant Disorder (ODD) (7) - in the forthcoming ICD-11 it is likely to be considered a specifier of ODD. However irritability has been shown to be distinct from other ODD dimensions (headstrong, hurtful) in that it shows phenotypic and genetic associations with unipolar depression (5, 8). The DSM-5 has categorized severe, chronic childhood irritability as Disruptive Mood Dysregulation Disorder (DMDD) and grouped it with the mood disorders (9). ICD-11 and DSM-5 also include irritability as a diagnostic symptom of depression in children and adolescents (for dysthymic disorder specifically in ICD-11).

Yet irritability – and, more broadly, emotional dysregulation – is an especially common feature of attention-deficit/hyperactivity disorder (ADHD), which is grouped as a neurodevelopmental disorder under DSM-5. Irritability prevalence rates of 91% have been reported in children with the disorder (10). Evidence of clinical overlap between irritability and ADHD (11, 12), genetic overlap with ADHD, as well as features such as its manifestation in early development and male preponderance also have led recently to the suggestion that irritability should perhaps be conceptualized as a neurodevelopmental/ADHD-like problem, rather than a mood problem (12).

Two differentiating factors between neurodevelopmental and mood problems are developmental course and sex preponderance. Neurodevelopmental problems typically onset early, decline across childhood/adolescence and are more common in males, while mood problems tend to onset in adolescence and are more common in females (13). A developmental approach may therefore help towards better establishing whether irritability it is more appropriately conceptualized as a mood or neurodevelopmental problem.

One possibility is that irritability is a heterogeneous construct; there may be different "types" of irritability, including a neurodevelopmental/ADHD-like irritability and a mood/depression-like irritability. Consistent with this premise, a recent population-based, cross-sectional investigation of irritability symptoms observed different developmental patterns for males and females: irritability was more common in boys during childhood (and levels tended to decrease with age) while irritability was more common in girls in adolescence (levels tended to increase with age) (12). These findings are consistent with there being two "types" of irritability; one that onsets early and is more common in boys (a pattern typical of neurodevelopmental problems) and another "type" that starts in adolescence and is more common in girls (a pattern typical of mood problems). To our knowledge age-at-onset in childhood compared to adolescence has not previously been investigated as a possible source of heterogeneity in irritability.

The aim of this study was to take advantage of a longitudinal population-based cohort and use a developmental approach to test the hypothesis that there are at least two forms of irritability: one 'neurodevelopmental/ADHD-like' type with onset in childhood and one 'depression/mood' type with onset in adolescence. Specifically, we used a latent growth modelling approach to test the following hypotheses suggested by this formulation of irritability: (a) an irritability trajectory defined by an early age-at-onset would be associated with male sex, ADHD genetic liability as indexed by ADHD genetic risk scores (polygenic risk scores: PRS) and a higher rate of diagnosis of ADHD in childhood, and (b) an irritability trajectory defined by an age-at-onset

around early-mid adolescence would be associated with female sex, depression genetic liability as indexed by depression genetic risk scores, and a diagnosis of depression in adolescence.

Method

Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a well-established prospective, longitudinal birth cohort study. The enrolled core sample consisted of 14,541 mothers living in Avon, England, who had expected delivery dates of between 1st April 1991 and 31st December 1992. Of these pregnancies 13,988 children were alive at 1 year. When the oldest children were approximately 7 years of age, the sample was augmented with eligible cases who had not joined the study originally, resulting in enrollment of 713 additional children. The resulting total sample size of children alive at 1 year was N=14,701. Genotype data were available for 8,365 children following quality control. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Full details of the study, measures and sample can be found elsewhere (14, 15). Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). Where families included multiple births, we included the oldest sibling.
Analyses were conducted including participants with at least two time-points of irritability data (see below) (N=7924): further details of sample sizes for available data are shown in Supplementary Figure 1.

Irritability

In-line with previous work (7) irritability was defined using parent-reported data from the oppositional defiant disorder (ODD) section of the Development and Well-Being Assessment (DAWBA)(16) - a structured research diagnostic interview - at ages 7 years 7 months, 10 years

8 months, 13 years 10 months and 15 years 6 months. For the first 3 assessments, the parent version of the DAWBA was sent to mothers in a package of postal measures. For the final assessment, mothers independently completed the same version of the DAWBA in the ALSPAC clinic. Irritability in the last six months was measured by three items (severe temper tantrums, touchy and easily annoyed, angry and resentful) rated on a 3-point scale (no more than others; a little more than others; a lot more than other) and summed to give a total score (0-6). Distributions and descriptive statistics are shown in Supplementary Table 1.

Diagnoses

The DAWBA (16) was also used to assess ADHD, ODD (which included the irritability items), conduct disorder (CD), general anxiety disorder (GAD) and depression. In childhood (age 7 years 7 months) parent-reports were used. In adolescence (15 years 6 months) parent-reports were used to assess ADHD, ODD and CD; self-reports were used to assess GAD and depression. DSM-IV diagnoses were generated using computer generated diagnoses (17); no diagnoses were mutually exclusive.

Genetic liability

Polygenic risk scores (PRS) were used to capture common variant genetic liability for two disorders - depression and Attention Deficit Hyperactivity Disorder (ADHD). For each disorder, PRS were generated as the weighted mean number of disorder risk alleles in approximate linkage equilibrium (r-square<0.1), derived from imputed autosomal SNPs using PRSice (18) (N=5559 of those included in this study: see Supplementary Figure 1). Sensitivity analyses were conducted using inverse probability weighting (19) to assess the impact of missing data (see Supplementary Material). Risk alleles were defined as those associated with case-status from the latest genome-wide association studies of depression (135,458 cases and 344,901 controls) (20) and ADHD (19,099 cases and 34,194 controls) (21). The depression GWAS sample consisted of adults with depression although affected individuals had varying ages-at-onset (e.g.

22). Individuals in the ADHD GWAS sample all had ADHD that by definition has onset in childhood. Primary analyses defined risk alleles as those associated at a threshold of $p<0.05$; associations across a range of p-thresholds are shown in Supplementary Figure 2. Scores were standardized using Z-score transformation. Genotyping details as well as full methods for generating the PRS are presented in the Supplementary Material.

Analyses

Growth mixture modelling (GMM) was conducted to identify developmental trajectories of irritability across ages 7 to 15 years in Mplus (23). GMM aims to group individuals into categories (trajectories) based on patterns of change across multiple time-points, with individuals within each category assumed to have the same growth curve (24). Thus, differing levels of irritability are captured based on observed differences (i.e. data-driven) rather than based on cut-points, in-line with evidence supporting liability to psychiatric problems being continuously distributed (25). Starting with a single *k*-class solution, *k*+1 solutions are fitted until the optimum solution is reached. Models were run using a robust maximum likelihood parameter estimator (MLR) and full information maximum likelihood (FIML) estimation (26). As recommended, the optimal number of categories was determined by interpretability as well as model fit indices (see Supplementary Material)(24). Following identification of the irritability trajectories, to test associations with PRS, sex and diagnoses and to estimate/compare prevalence rates, analyses were conducted in Mplus, using a bias-free three step approach which accounts for measurement error in class assignment (27); multinomial odds ratios are reported. Inverse probability weighting (19) was used to assess the impact of missing genetic data, which weights observations based on measures assessed in pregnancy that were predictive of variables in the analysis and/or inclusion in the subsample with genetic data (see Supplementary Material). Sensitivity analyses were conducted including sex as a covariate.

Results

Irritability trajectories

We identified a five-class solution (see Supplementary Material), characterized by distinct irritability trajectory classes: low (81.2%), decreasing (5.6%), increasing (5.5%), late-childhood limited (5.2%) and high-persistent (2.4%), shown in Figure 1.

A male preponderance was observed for the decreasing, late-childhood limited and high-persistent trajectory classes (55.7%, 55.7% and 63.7% male respectively) and a female preponderance for the increasing trajectory class (40.5% male). Accordingly, male sex was associated with an increased likelihood of being in the decreasing (OR=1.27(1.01-1.59), p=0.038), late-childhood limited (OR=1.37 (1.09-1.73), p=0.007) or high-persistent classes (OR=1.76 (1.30-2.40), p<0.001) and a decreased likelihood of being in the increasing trajectory (OR=0.68 (0.54-0.87), p=0.002) compared to the low trajectory class (49.8% male).

Genetic risk

Associations between irritability trajectory classes and ADHD PRS and depression PRS are shown in Table 1. Mean PRS for each of the trajectory classes are shown in Figure 2. Compared to the low trajectory class, ADHD PRS were associated with an increased likelihood of being in both the high-persistent (OR=1.31 (95% CI 1.09-1.58), p=0.005) and increasing (OR=1.28 (95% CI 1.11-1.48), p=0.001) trajectory classes, with a similar risk of being in either trajectory (high-persistent vs. increasing OR=1.02 (95% CI 0.81-1.29), p=0.854).

Depression PRS were associated with an elevated likelihood of being in the increasing trajectory class compared to the low trajectory class (OR=1.20 (95% CI 1.05-1.38), p=0.009), although evidence for an elevated likelihood of being in the increasing trajectory class compared to the high-persistent trajectory class was weaker (OR=1.20 (95% CI 0.96-1.52), p=0.116).

Multivariable analyses including both PRS in the same model revealed the same pattern of results (see Table 1 vs. Supplementary Table 3) as did sensitivity analyses using inverse probability weighting to assess the impact of missing genetic data (Supplementary Table 4).

Diagnoses

Estimated prevalence rates of ADHD, depression, GAD, ODD and CD in childhood and adolescence are shown in Tables 2 and 3. Rates of all diagnoses varied across the irritability trajectory classes, with the exception that there was not strong evidence of variation in adolescent GAD across classes. At both developmental stages, rates of all diagnoses were generally highest in the high-persistent trajectory and were particularly high for ODD.

Childhood ADHD. Childhood ADHD was associated with an increased likelihood of being in the decreasing (OR=30.97 (15.47-61.98), p<0.001) increasing (OR=5.89 (1.96-17.73), p=0.002), late-childhood limited (OR=20.39 (9.78-42.52) p<0.001) and the high-persistent (OR=108.64 (57.45-204.41), p<0.001) compared to the low trajectory class.

Comparing these four irritability trajectories, childhood ADHD was associated with a decreased likelihood of being in the increasing trajectory class (compared to decreasing OR=0.19 (0.07-0.52), p=0.001; late-childhood limited OR=0.29 (0.10-0.84), p=0.023; high-persistent OR=0.05 (0.02-0.15), p<0.001) and with the greatest likelihood associated with the high-persistent classes (compared to decreasing OR=3.50 (2.09-5.87), p<0.001; late-childhood limited OR=5.33 (2.92-9.73), p<0.001).

Adolescent depression. Compared to the low trajectory class, an increased likelihood of adolescent depression was found for the increasing (OR=5.14 (2.47-10.73), p<0.001) and high-persistent (OR=7.18 (3.10-16.61), p<0.001) trajectory classes (decreasing class OR=2.32 (0.88-6.12), p=0.088; late-childhood limited class OR=1.95 (0.63-6.04), p=0.250). Likelihood of

adolescent depression was similar for the high-persistent compared to the increasing trajectory class (OR=1.40 (0.51-3.84), p=0.516).

Sensitivity analyses

Controlling for sex revealed the same pattern of results for both PRS and diagnoses (Supplementary Tables 5 and 6); mean PRS and estimated prevalence rates for diagnoses by sex are shown in Supplementary Figures 3 and 4).

Discussion

This study aimed to investigate developmental trajectories of irritability across childhood and adolescence to test the hypothesis that there are different forms of 'neurodevelopmental' and 'depression/mood' irritability. Specifically we hypothesized that a 'neurodevelopmental/ADHD-like' irritability trajectory would be defined by an early age-at-onset, a male preponderance and would be associated with an increased genetic liability to ADHD and ADHD diagnosis in childhood, whereas a 'depression/mood' irritability trajectory would be defined by a later age-at-onset, a female preponderance, and would be associated with increased genetic liability to depression and depression diagnosis in adolescence.

We identified five distinct developmental trajectory classes of irritability across childhood and adolescence. Four classes were characterized by elevated levels of irritability during at least some of this developmental period. Two irritability trajectory classes were early-onset: one was defined by symptoms that decreased over time and the other by high symptoms that persisted (5.6% and 2.4% of the sample respectively). These two groups show very similar developmental patterns to ADHD; with some individuals showing persistence over time and others remitting. An additional unexpected trajectory with irritability onset in late childhood was defined by an increase in symptoms at around age 10 years and a subsequent decrease at around age 13 years (5.2% of the sample). That is the age of high school transition in the UK as

well as the onset of puberty for many but we can only speculate as to the underlying mechanisms for this class as this group has not been previously described. The final trajectory was defined by increasing symptoms that showed a later onset, around adolescence (5.5% of the sample).

In line with our first hypothesis, the two irritability trajectories with early-onset (decreasing and high-persistent) were both associated with male sex and ADHD diagnosis in childhood, as was the late-childhood onset (late-childhood limited) class. The high-persistent trajectory was also associated with increased ADHD genetic risk scores - although the childhood-onset trajectories that did not have persistent symptoms (decreasing and late-childhood limited) were not. This is similar to findings on the developmental patterns of ADHD symptoms, that those with persistent compared to childhood-limited symptoms of ADHD have an increased genetic liability to ADHD (28). An association between irritability and ADHD PRS has been observed previously in the total sample as well as a clinical sample and accords with an earlier twin study that observed shared genetic links between ADHD and emotional lability (11, 12). Interestingly, the later-onset (increasing) irritability trajectory was also associated with ADHD PRS – although rates of childhood ADHD diagnosis were low. It may be that the phenotypic expression of ADHD genetic liability in this predominantly female group manifests as mood problems (see 29), although further work would be needed to investigate this. Our findings therefore support the suggestion of a neurodevelopmental/ADHD-like 'type' of irritability, which onsets early, has a male preponderance and is associated with ADHD.

In line with our second hypothesis, the trajectory with irritability onset in adolescence (the increasing trajectory class) was associated with female sex. This 'depression/mood-type' irritability trajectory class was also associated with depression genetic risk scores and depression diagnosis in adolescence. This class was also associated with ADHD genetic risk scores. Although twin work had indicated genetic overlap between irritability and depression, previous analyses of this same sample had failed to observe association between irritability

with depression genetic risk scores (8, 30). This raised questions about the primary classification of severe irritability as a mood problem. Indeed it appears that ICD-11 is going to take a different approach to DSM-5 and conceptualize irritability as a specifier of ODD, and not include severe irritability / disruptive mood dysregulation disorder as a mood disorder (the approach taken by DSM-5). ICD-11 does however now include irritability as an alternative symptom to depressed mood for dysthymic disorder for children and adolescents (a similar approach to that used by DSM-5 for depression). Our findings suggest that the association between irritability and depression genetic risk scores may be specific to a type of irritability that onsets during adolescence.

Regardless of whether the DSM-5 or ICD-11 stance to dealing with severe irritability is most valid, neither have taken a developmental approach. Our findings suggest that development matters. This view is not new (see 31) and has been applied to other phenotypes including anti-social behavior (32) but perhaps has been forgotten because it poses substantial challenges to clinicians and researchers. A transdiagnostic conceptualization of irritability such as that used by R-DoC, or the "p-factor" framework (33), could provide a helpful research framework for conceptualizing irritability dimensionally across multiple levels. Our study suggests that if such a framework were to be implemented, it should be developmentally informed, taking into account age (and age-at-onset).

In terms of how the trajectory classes relate to psychiatric diagnoses, diagnostic rates are relatively low because this is a population-based cohort; nevertheless, there are some notable observations. Interestingly, while the high-persistent 'neurodevelopmental/ADHD-like' irritability trajectory class was not associated with depression PRS, this class showed a similar risk of adolescent depression as the increasing 'depression/mood-like' irritability trajectory. Thus both trajectory classes are associated with risk of depression in adolescence, although the mechanisms of this associations are likely different, for example increased risk for depression in the early-onset irritability type may be driven by environmental factors, such as increased life

events associated with irritability, rather than genetic risk for depression - although further work into this would be needed. It is established that child neurodevelopmental disorders such as ADHD, as well as oppositional defiant disorder and conduct problems, are risk factors for later depression so it is perhaps unsurprising that the 'neurodevelopmental' irritability trajectory is also associated with depression, although emerging research suggests that the presence of irritability in those with ADHD confers additional risk of depression (34).

Consistent with previous work (2) we found elevated rates of other psychiatric disorders in those with elevated irritability. Rates of ODD were particularly high in the elevated irritability trajectory classes and followed a similar developmental pattern to irritability levels. This is unsurprising given that irritability is a core component of ODD, indeed irritability was defined by terms from the ODD section of the DAWBA instrument. However a large proportion (39-99%) of individuals in the elevated irritability trajectory classes did not have ODD, suggesting that irritability in those without ODD is also important and adds to the idea that irritability is transdiagnostic. Interestingly, despite previous work findings associations between irritability and anxiety as well as depression (2), we did not find strong evidence that the rates of GAD in adolescence differed between those in each of the irritability trajectory classes. Previous research on links between irritability and depression has often included anxiety symptoms in the same measure (30), or found the same pattern of results for depression and anxiety (6). Our findings suggest specificity to depression in adolescence.

One explanation for the apparent existence of different irritability "types" is that irritability is simply a feature of different underlying diagnoses (e.g. depression and ADHD). However the low rates of those diagnoses in the population-based trajectory classes (see Tables 2 and 3) suggest this is not the case (e.g. only a small minority of those in the increasing irritability trajectory class had a diagnosis of depression) and associations with PRS were similar when excluding those with diagnoses (Supplementary Table 7). Also, sex differences for the early-onset, persistent and increasing irritability trajectory classes were not as pronounced as typically

reported for depression and ADHD (35). These observations suggest that the different irritability "types" are not simply a feature of different underlying diagnoses (ADHD and depression).

Our findings should be considered in light of some limitations. First, ALSPAC is a longitudinal birth cohort study that suffers from non-random attrition and those with increased genetic liability to disorder and with higher levels of psychopathology are more likely to drop out of the study (36, 37). However, our trajectory analyses used full information maximum likelihood (FIML) estimation (26) so that complete data on irritability were not required. Moreover, inverse probability weighted (IPW) analyses suggested that missingness of genetic data did not have a large effect on our findings. It is possible that associations between depression PRS and (increasing) irritability were inflated by some of the cases in the depression GWAS having (adolescent-onset) irritability as a symptom. Also, while PRS are useful indicators of genetic liability, ADHD and depression PRS currently explain a minority of common variant liability to the disorder (20, 21). Our analyses were therefore underpowered to detect associations between PRS and irritability trajectories: our analyses had 80% power to detect odds ratios of 1.35 for the increasing trajectory and 1.60 for the high-persistent trajectory (38). Thus while the effect sizes we observed are in-line with similar types of analyses reported elsewhere (39), PRS regarded as indicators of genetic liability rather than as predictors of psychopathology. We deliberately elected to use depression PRS derived from adult samples that reflect 'typical' depression. Pre-pubertal/childhood depression is rare and considered to be atypical not only in age of onset but also in terms of other features (e.g. 40). The associations that we observe between adolescent-onset irritability and depression PRS are therefore consistent with previous work showing associations between irritability and adolescent/adult depression.

We did not include covariates in our analyses of ADHD and MDD diagnoses as we were interested in describing observed associations: this means that we cannot infer any causal associations between irritability and diagnoses. Different methods such as Mendelian

randomization (MR) would be needed to investigate such research questions (41). Finally, our aim was to use a developmental approach to investigate nosology. However diagnostic and subgroup overlap is the rule in Psychiatry and this study was no exception. Our 'neurodevelopmental/ADHD-like' and 'depression/mood-like' irritability classes were both associated with ADHD and depression diagnoses and ADHD genetic risk scores. We observed different patterns for these classes rather than identifying completely distinct groups. Finally, there are difficulties in determining the optimum number of classes using growth mixture modelling. Given this is the first study to our knowledge to investigate irritability trajectories across childhood and adolescence, we emphasize that further research is needed in this area that includes testing the replicability of these trajectories in different samples.

In conclusion, our study identified different developmental trajectories of irritability including one with characteristics typical of neurodevelopmental/ADHD-like problems - early-onset, male preponderance and clinical and genetic links with ADHD - and one with characteristics typical of depression/mood problems - later-onset, female preponderance and clinical and genetic links with depression. Both groups were associated with risk of adolescent depression; both were associated with ADHD genetic risk scores. Overall the findings suggest that the developmental context of irritability may be important in its conceptualization; that has implications for treatment as well as nosology (2).

References

1. Leibenluft E. Irritability in children: what we know and what we need to learn. World Psychiatry. 2017;16(1):100-1.
2. Stringaris A, Vidal-Ribas P, Brotman MA, Leibenluft E. Practitioner Review: Definition, recognition, and treatment challenges of irritability in young people. J Child Psychol Psychiatry. 2018;59(7):721-39.
3. Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. Am J Psychiatry. 2009;166(9):1048-54.
4. Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry. 2006;60(9):991-7.
5. Stringaris A, Goodman R. Longitudinal Outcome of Youth Oppositionality: Irritable, Headstrong, and Hurtful Behaviors Have Distinctive Predictions. J Am Acad Child Adolesc Psychiatry. 2009;48(4):404-12.
6. Vidal-Ribas P, Brotman MA, Valdivieso I, Leibenluft E, Stringaris A. The Status of Irritability in Psychiatry: A Conceptual and Quantitative Review. J Am Acad Child Adolesc Psychiatry. 2016;55(7):556-70.
7. Stringaris A, Goodman R. Three dimensions of oppositionality in youth. J Child Psychol Psychiatry. 2009;50(3):216-23.
8. Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: phenotypic associations and genetic links with depressed mood. Am J Psychiatry. 2012;169(1):47-54.
9. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry. 2011;168(2):129-42.
10. Eyre O, Langley K, Stringaris A, Leibenluft E, Collishaw S, Thapar A. Irritability in ADHD: Associations with depression liability. J Affect Disord. 2017;215:281-7.
11. Merwood A, Chen W, Rijsdijk F, Skirrow C, Larsson H, Thapar A, et al. Genetic Associations Between the Symptoms of Attention-Deficit/Hyperactivity Disorder and Emotional Lability in Child and Adolescent Twins. J Am Acad Child Adolesc Psychiatry. 2014;53(2):209-20.
12. Riglin L, Eyre O, Cooper M, Collishaw S, Martin J, Langley K, et al. Investigating the genetic underpinnings of early-life irritability. Translational psychiatry. 2017;7(9):e1241.
13. Pine DS, Fox NA. Childhood antecedents and risk for adult mental disorders. Annu Rev Psychol. 2015;66:459-85.
14. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. International journal of epidemiology. 2013;42(1):111-27.
15. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, et al. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. International journal of epidemiology. 2013;42(1):97-110.
16. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry. 2000;41(5):645-55.
17. Goodman A, Heiervang E, Collishaw S, Goodman R. The 'DAWBA bands' as an ordered-categorical measure of child mental health: description and validation in British and Norwegian samples. Soc Psychiatry Psychiatr Epidemiol. 2011;46(6):521-32.
18. Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. Bioinformatics. 2015;31(9):1466-8.
19. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res. 2013;22(3):278-95.
20. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50(5):668-81.

21. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nature Genetics. 2019;51:63-75.
22. Power RA, Tansey KE, Buttenschon HN, Cohen-Woods S, Bigdeli T, Hall LS, et al. Genome-wide Association for Major Depression Through Age at Onset Stratification: Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Biol Psychiat. 2017;81(4):325-35.
23. Muthén LK, Muthén BO. MPlus User's Guide. 7th. ed. Los Angeles, CA. 2012.
24. Muthen B, Muthen LK. Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. Alcohol Clin Exp Res. 2000;24(6):882-91.
25. Martin J, Taylor MJ, Lichtenstein P. Assessing the evidence for shared genetic risks across psychiatric disorders and traits. Psychol Med. 2018;48(11):1759-74.
26. Muthén LK, Muthén BO. Mplus User's Guide. Seventh ed. Los Angeles, CA: Muthén & Muthén; 1998-2012.
27. Asparouhov T, Muthen B. Auxiliary Variables in Mixture Modeling: Three-Step Approaches Using Mplus. Struct Equ Modeling. 2014;21(3):329-41.
28. Riglin L, Collishaw S, Thapar AK, Dalsgaard S, Langley K, Smith GD, et al. Association of Genetic Risk Variants With Attention-Deficit/Hyperactivity Disorder Trajectories in the General Population. JAMA Psychiatry. 2016;73(12):1285-92.
29. Martin J, Taylor MJ, Rydell M, Riglin L, Eyre O, Lu Y, et al. Sex-specific manifestation of genetic risk for attention deficit hyperactivity disorder in the general population. J Child Psychol Psychiatry. 2018;59(8):908-16.
30. Savage J, Verhulst B, Copeland W, Althoff RR, Lichtenstein P, Roberson-Nay R. A genetically informed study of the longitudinal relation between irritability and anxious/depressed symptoms. J Am Acad Child Adolesc Psychiatry. 2015;54(5):377-84.
31. Rutter M. Epidemiological approaches to developmental psychopathology. Arch Gen Psychiatry. 1988;45(5):486-95.
32. Moffitt TE. Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. Psychol Rev. 1993;100(4):674-701.
33. Caspi A, Moffitt TE. All for One and One for All: Mental Disorders in One Dimension. Am J Psychiatry. 2018;175(9):831-44.
34. Eyre O, Langley K, Stringaris A, Leibenluft E, Collishaw S, Thapar A. Irritability in ADHD: associations with depression liability. Manuscript submitted for publication. 2018.
35. Rutter M, Caspi A, Moffitt TE. Using sex differences in psychopathology to study causal mechanisms: unifying issues and research strategies. Journal of Child Psychology and Psychiatry. 2003;44(8):1092-115.
36. Wolke D, Waylen A, Samara M, Steer C, Goodman R, Ford T, et al. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. Br J Psychiatry. 2009;195(3):249-56.
37. Martin J, Tilling K, Hubbard L, Stergiakouli E, Thapar A, Davey Smith G, et al. Association of Genetic Risk for Schizophrenia With Nonparticipation Over Time in a Population-Based Cohort Study. Am J Epidemiol. 2016;183(12):1149-58.
38. Dudbridge F. Power and predictive accuracy of polygenic risk scores. PLoS Genet. 2013;9(3):e1003348.
39. Rice F, Riglin L, Thapar AK, et al. Characterizing developmental trajectories and the role of neuropsychiatric genetic risk variants in early-onset depression. JAMA Psychiatry. 2019;76(3):306-13.
40. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. Lancet. 2012;379(9820):1056-67.
41. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. International journal of epidemiology. 2004;33(1):30-42.

Table 1. Association between ADHD and depression genetic risk scores and irritability trajectories

	ADHD PRS			Depression PRS		
	OR	95% CI	p	OR	95% CI	p
Childhood-onset irritability						
Decreasing	1.06	(0.92, 1.22)	0.425	1.12	(0.97, 1.29)	0.126
Late-childhood limited	1.14	(0.99, 1.32)	0.071	0.93	(0.82, 1.06)	0.266
High-persistent	1.31	(1.09, 1.58)	0.005	1.00	(0.82, 1.21)	0.992
Adolescent-onset irritability						
Increasing	1.28	(1.11, 1.48)	0.001	1.20	(1.05, 1.38)	0.009

Low trajectory as reference. ADHD=attention-deficit/hyperactivity disorder, PRS = polygenic risk score

Table 2. Estimated prevalence of diagnoses in childhood across irritability trajectories

	ADHD (N=7043)	Depression (N=6947)	GAD (N=7029)	ODD (N=7034)	CD (N=6979)
Low	0.3% (0.1)	0.1% (0.1)	0.0% (0.0)	0.1% (0.1)	0.0% (0.0)
Childhood onset irritability					
Decreasing	9.3% (1.6)	5.7% (1.2)	1.1% (0.6)	28.3% (2.5)	4.0% (1.1)
Late-childhood limited	6.3% (1.4)	0.7% (0.5)	0.5% (0.4)	5.9% (1.5)	1.0% (0.6)
High-persistent	26.4% (3.4)	4.2% (1.6)	3.6% (1.4)	51.0% (3.9)	11.7% (2.5)
Adolescent onset irritability					
Increasing	1.9% (0.9)	0.0% (0.0)	0.0% (0.0)	0.6% (0.7)	0.2% (0.3)
$\chi^2(4)$	122.64 p<0.001	45.68 p<0.001	14.92 p=0.005	342.50 p<0.001	43.22 p<0.001

Standard errors in parentheses. ADHD=attention-deficit/hyperactivity disorder, GAD=generalised anxiety disorder, ODD=oppositional defiant disorder, CD=conduct disorder

Table 3. Estimated prevalence of diagnoses in adolescence across irritability trajectories

	ADHD (N=4500)	Depression (N=4900)	GAD (N=4896)	ODD (N=4490)	CD (N=4489)
Low	0.2% (0.1)	1.1% (0.1)	0.4% (0.1)	0.1% (0.1)	0.1% (0.1)
Childhood onset irritability					
Decreasing	1.7% (0.9)	2.5% (1.1)	0.8% (0.6)	2.1% (1.2)	1.1% (0.8)
Late-childhood limited	0.6% (0.8)	2.1% (1.1)	0.8% (0.7)	1.1% (1.5)	0.7% (1.0)
High-persistent	14.2% (3.4)	7.3% (2.6)	3.1% (1.8)	60.9% (5.1)	17.4% (3.8)
Adolescent onset irritability					
Increasing	7.3% (1.9)	5.3% (1.6)	2.9% (1.2)	46.0% (3.9)	17.0% (2.7)
$\chi^2(4)$	43.83 p<0.001	15.34 p<0.001	7.51 p=0.111	325.23 p<0.001	76.93 p<0.001

Standard errors in parentheses. ADHD=attention-deficit/hyperactivity disorder, GAD=generalised anxiety disorder, ODD=oppositional defiant disorder, CD=conduct disorder

Figure 1. Irritability trajectories by class

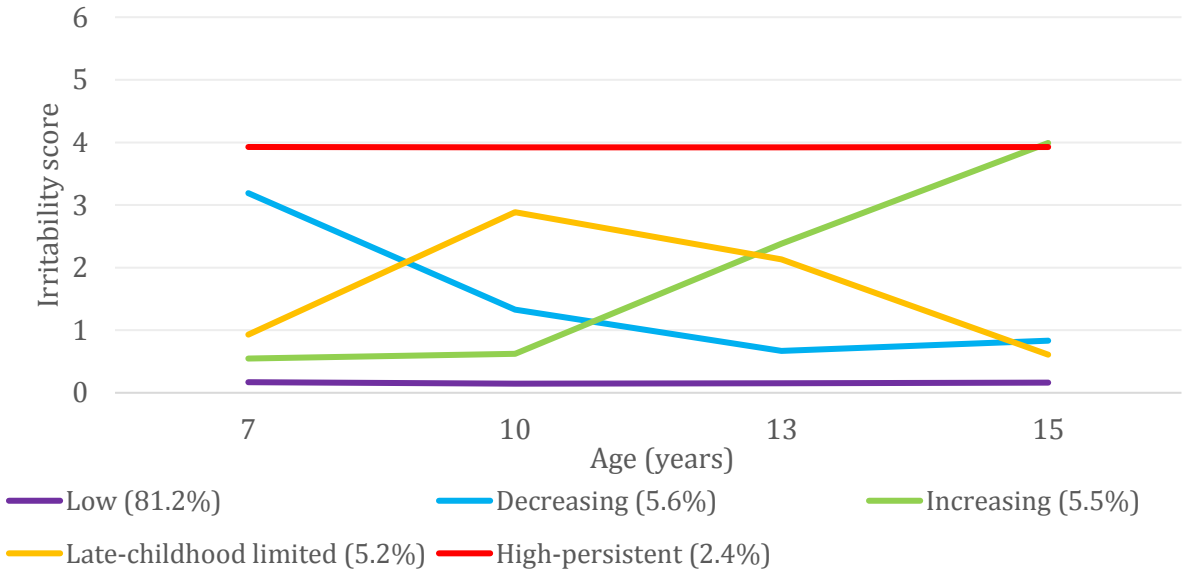
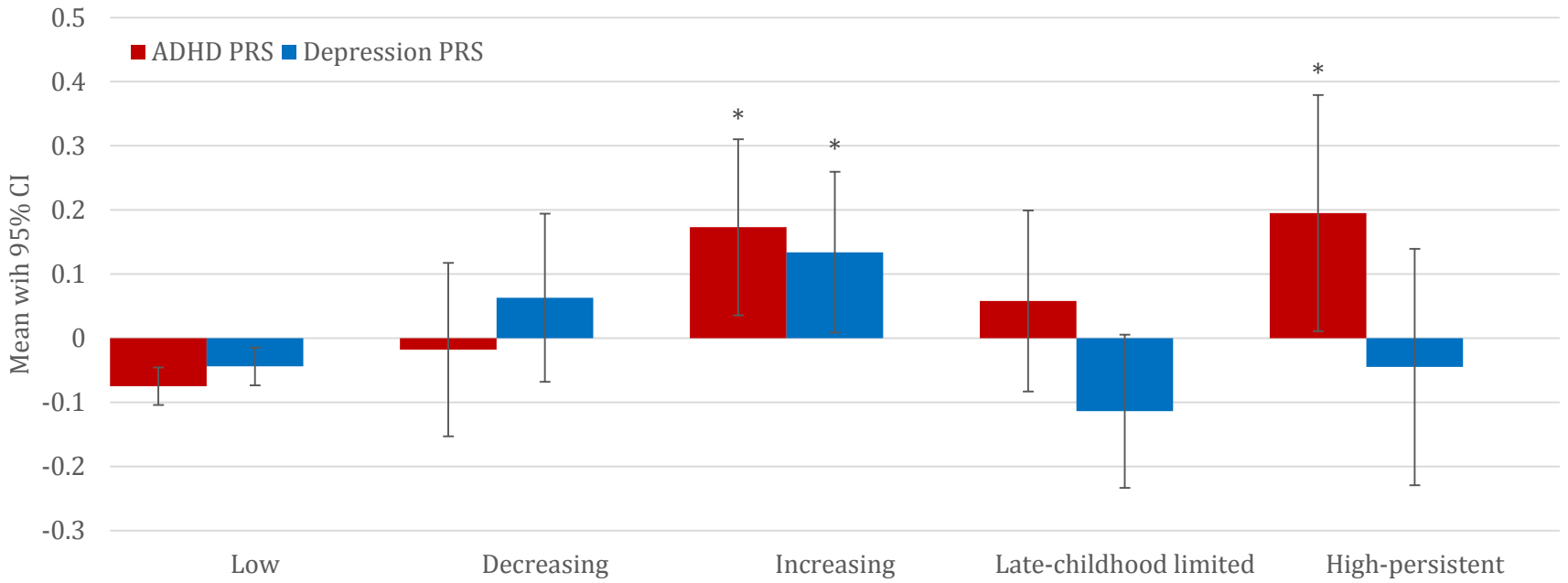


Figure 2. Mean ADHD and depression genetic risk score by irritability trajectories, with 95% confidence intervals



*Different from low at p<0.05

Supplementary Material

Generating polygenic risk scores

In total 9912 ALSPAC children were genotyped using the Illumina HumanHap500-quad genotyping array. Individuals were excluded on the basis of gender mismatches; minimal or excessive heterozygosity, disproportionate levels of individual missingness (>3%), insufficient sample replication (IBD <0.8), non-European ancestry (assessed by multidimensional scaling analysis and compared with Hapmap II) and cryptic relatedness (IBD > 0.1). SNPs were excluded based on minor allele frequency (<1%), call rate (<95%) or evidence for violations of Hardy-Weinberg equilibrium (P < 5E-7). Imputation was conducted by the ALSPAC team using Impute V2.2.2 against the 1000 genomes reference panel (Phase 1, Version 3: all polymorphic SNPs excluding singletons), using all 2186 reference haplotypes (including non-Europeans). SNPs were subsequently filtered based on minor allele frequency (<1%) and imputation quality (INFO<0.8). Following quality control and limiting individuals to one child per family, genetic data were available for N=7975.

Genome-wide association study (GWAS) summary statistics used to generate PRS were filtered to remove SNPs that were palindromic, insertions/deletions, non-autosomal, INFO score <0.8, missing in N>1 study and duplicates (https://github.com/ricanney). Depression results for 23andme (75,607 cases and 231,747 controls) (1) and the other samples included in the latest depression GWAS (2) (PGC29, deCODE, Generation Scotland, GERA, iPSYCH, and UK Biobank) were meta-analyzed in METAL. PRS were generated in ALSPAC using PRSice (3); SNPs were clumped with an R^2 threshold of 0.1 and a distance threshold of 1000kb and excluding the extended major histocompatibility complex (MHC; chromosome 6: 26-33Mb) due to the high linkage disequilibrium (LD) within this region.

Selecting the number of trajectories

To select the number of classes for the two growth mixture models (GMMs), we initially modelled a single k-class solution, modelling subsequent k+1 solutions until the optimum solution was reached. Residual variances were fixed across measurement points. Each model was run with 5000 random starting values and 500 optimizations (STARTS = 5000 500 in Mplus) (4) and included both linear and quadratic change. Fit statistics are presented in Supplementary Table 2. Both the intercept and quadratic variance was fixed to zero because for models with more than two classes these explained the variation in the intercept and quadratic (i.e. was close to zero). Model fit significantly improved, as indicated by the fall in loglikelihood

value, sample size adjusted Bayesian information criterion as well as the Bootstrapped Likelihood Ratio Test, from the one to six class solutions. However, the six class two small classes (≤2%). Current guidance (5) suggests that if fit indices are similar (size adjusted Bayesian information criterion being the preferred index), unless there are strong theoretical reasons for preferring a particular solution, the more parsimonious solution i.e. with fewer classes is preferred. Because this is the first study to our knowledge to investigate irritability trajectories across childhood and adolescence, there is no clear theoretical guidance on how many or what shaped trajectories are to be expected. The five class solution was therefore selected and this also showed high classification accuracy (entropy = 0.94).

Inverse probability weighting

Inverse probability weighting (IPW) was used to assess the impact of missing genetic data and has been recommended over alternative methods such as multiple imputation in situations where whole blocks of data are missing for a large proportion of individuals (6). As described elsewhere (7), weights were derived from a logistic regression analysis of missing genetic data for those in the 'core' ALSPAC sample (N = 7495/13793) for a set of measures assessed in pregnancy: child gender, maternal age and child birth weight. The analyses were rerun using IPW to address any potential bias caused by only a subsample having genetic data and revealed a similar pattern of results (see Supplementary Table 5).

References

1. Hyde CL, Nagle MW, Tian C, Chen X, Paciga SA, Wendland JR, et al. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat Genet. 2016;48(9):1031-6.
2. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50(5):668-81.
3. Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. Bioinformatics. 2015;31(9):1466-8.
4. Muthén LK, Muthén BO. Mplus User's Guide. Seventh ed. Los Angeles, CA: Muthén & Muthén; 1998-2012.
5. Wickrama KK, Lee TK, O'Neal CW, Lorenz FO. Higher-order growth curves and mixture modeling with Mplus: A practical guide: Routledge; 2016.
6. Seaman SR, White IR, Copas AJ, Li L. Combining multiple imputation and inverse-probability weighting. Biometrics. 2012;68(1):129-37.
7. Riglin L, Thapar AK, Leppert B, Martin J, Richards A, Anney R, et al. The contribution of psychiatric risk alleles to a general liability to psychopathology in early life. bioRxiv. 2018;doi:10.1101/409540.

Supplementary Table 1. Irritability measure descriptive statistics

		Cumulative frequency (%)							Average	
		0	0-1	0-2	0-3	0-4	0-5	0-6	Mean	(SD)
Age 7 years 7 months	(N=6975)	76.36	87.17	93.72	97.12	98.39	99.20	100	0.48	(1.06)
Age 10 years 8 months	(N=7180)	75.84	86.31	93.30	96.85	97.97	98.86	100	0.51	(1.12)
Age 13 years 10 months	(N=6646)	78.33	87.30	93.73	97.14	98.09	98.92	100	0.46	(1.09)
Age 15 years 6 months	(N=4415)	76.81	86.14	92.46	96.44	97.40	98.53	100	0.52	(1.18)

Supplementary Table 2. Model fit indices for irritability growth mixture models

	LL	Free parameters	BIC	ssaBIC	Smallest class	Entropy	VLMR-LRT p value	BLRT p value
1 class	-37494.52	5	75033.93	75018.04	100%			
2 classes	-33448.78	9	66978.35	66949.75	8%	0.96	<0.0001	<0.0001
3 classes	-32326.50	13	64769.70	64728.39	6%	0.96	0.0599	<0.0001
4 classes	-30994.71	17	62142.04	62088.02	3%	0.95	0.0009	<0.0001
5 classes*	-30023.11	21	60234.75	60168.02	2%	0.94	0.0001	<0.0001
6 classes**	-29399.46	24	59014.39	58938.12	2%	0.94	0.0004***	<0.0001***

LL=Loglikelihood; BIC= Bayesian Information Criteria; ssa= sample size adjusted; VLMR-LRT=Vuong-Lo-Mendell-Rubin Likelihood Ratio Rest; BLRT=Bootstrapped Likelihood Ratio Rest. *Final model. **Slope variance also fixed to zero variance because the slope variance was close to zero (i.e. classes explained the variation in the slope). ***Compared to a 5 class model where slope variance was also fixed to zero.

Supplementary Table 3. Multivariate associations between genetic risk and trajectories

	ADHD PRS			Depression PRS		
	OR	95% CI	p	OR	95% CI	p
Childhood-onset irritability						
Decreasing	1.05	(0.91, 1.20)	0.524	1.11	(0.96, 1.28)	0.147
Late-childhood limited	1.15	(1.00, 1.33)	0.053	0.92	(0.81, 1.04)	0.173
High-persistent	1.32	(1.09, 1.60)	0.005	0.97	(0.79, 1.17)	0.726
Adolescent-onset irritability						
Increasing	1.26	(1.09, 1.45)	0.002	1.17	(1.01, 1.34)	0.032

Low trajectory as reference. ADHD=attention-deficit/hyperactivity disorder, PRS = polygenic risk score

Supplementary Table 4. Associations between genetic risk and trajectories using IPW

	Original result			Core sample			Core sample: IPW		
ADHD PRS	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Decreasing	1.06	(0.92, 1.22)	0.425	1.09	(0.95-1.26)	0.221	1.10	(0.95-1.28)	0.201
Late-childhood limited	1.14	(0.99, 1.32)	0.071	1.14	(0.98-1.32)	0.079	1.13	(0.98-1.31)	0.093
High-persistent	1.31	(1.09, 1.58)	0.005	1.30	(1.08-1.57)	0.006	1.29	(1.07-1.56)	0.007
Increasing	1.28	(1.11, 1.48)	0.001	1.28	(1.11-1.49)	0.001	1.31	(1.13-1.53)	<0.001
	Original result			Core sample			Core sample: IPW		
Depression PRS	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Decreasing	1.12	(0.97, 1.29)	0.126	1.14	(0.99-1.31)	0.075	1.16	(1.00-1.34)	0.043
Late-childhood limited	0.93	(0.82, 1.06)	0.266	0.93	(0.82-1.06)	0.298	0.94	(0.83-1.07)	0.382
High-persistent	1.00	(0.82, 1.21)	0.992	1.03	(0.85-1.24)	0.763	1.03	(0.85-1.25)	0.732
Increasing	1.20	(1.05, 1.38)	0.009	1.21	(1.051.40)	0.009	1.24	(1.07-1.44)	0.004

Low trajectory as reference. IPW= inverse probability weighting. ADHD=attention-deficit/hyperactivity disorder, PRS = polygenic risk score

Supplementary Table 5. Association between ADHD and depression genetic risk scores and irritability trajectories, controlling for gender

	ADHD PRS			Depression PRS		
	OR	95% CI	p	OR	95% CI	p
Childhood-onset irritability						
Decreasing	1.06	(0.92, 1.22)	0.401	1.14	(0.99, 1.32)	0.121
Late-childhood limited	1.14	(0.99, 1.32)	0.068	0.93	(0.82, 1.06)	0.281
High-persistent	1.32	(1.09, 1.59)	0.004	1.01	(0.83, 1.22)	0.958
Adolescent-onset irritability						
Increasing	1.28	(1.11, 1.48)	0.001	1.20	(1.05, 1.38)	0.009

Low trajectory as reference. ADHD=attention-deficit/hyperactivity disorder, PRS = polygenic risk score

Supplementary Table 6. Association between childhood ADHD and adolescent depression diagnoses and irritability trajectories, controlling for gender

	Childhood ADHD			Adolescent depression		
	OR	95% CI	p	OR	95% CI	p
Childhood-onset irritability						
Decreasing	29.70	(14.81-59.55)	<0.001	2.41	(0.92-6.34)	0.074
Late-childhood limited	19.13	(9.21-39.73)	<0.001	2.01	(0.66-6.17)	0.220
High-persistent	101.09	(53.05-192.64)	<0.001	7.68	(3.27-18.00)	<0.001
Adolescent-onset irritability						
Increasing	6.40	(2.05-20.04)	0.001	4.73	(2.26-9.90)	<0.001

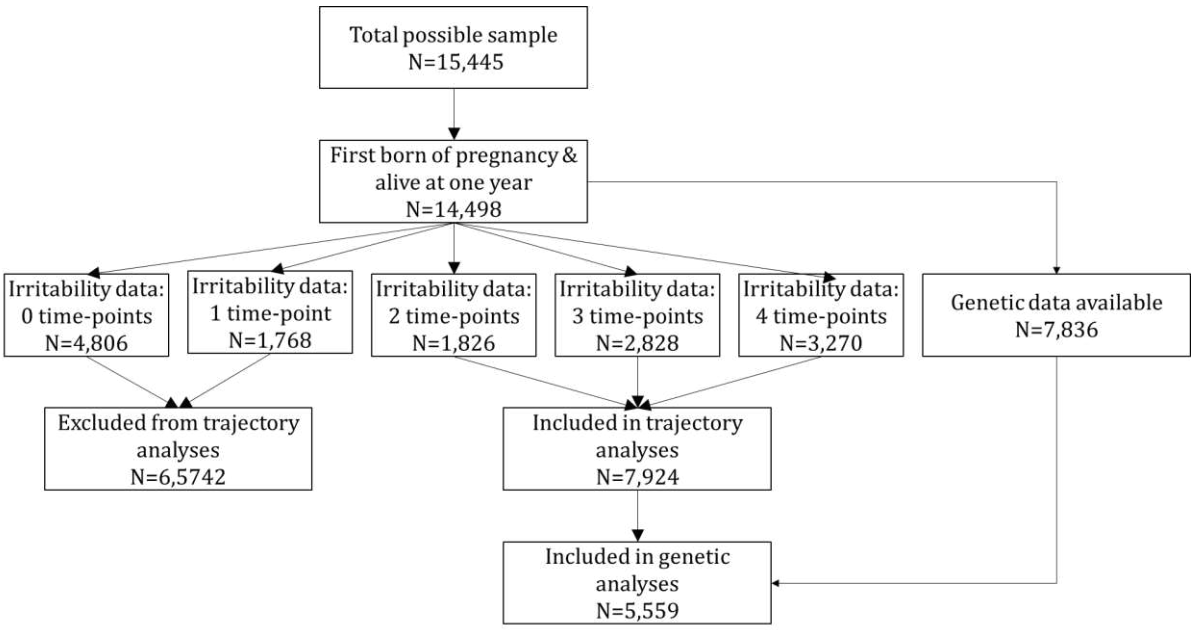
Low trajectory as reference. ADHD=attention-deficit/hyperactivity disorder. OR for childhood ADHD = likelihood of being in irritability trajectory class for ADHD diagnosis vs. no ADHD diagnosis; gender predicting irritability trajectory class. OR for adolescent depression = likelihood of having adolescent depression for given irritability trajectory class vs low irritability trajectory class; gender predicting depression.

Supplementary Table 7. Association between ADHD and depression genetic risk scores and irritability trajectories, excluding diagnoses

	Full sample (N=5559)			Excluding childhood ADHD (N=4892)		
ADHD PRS	OR	95% CI	p	OR	95% CI	p
Decreasing	1.06	(0.92, 1.22)	0.425	1.08	(0.92-1.25)	0.324
Late-childhood limited	1.14	(0.99, 1.32)	0.071	1.11	(0.95-1.29)	0.208
High-persistent	1.31	(1.09, 1.58)	0.005	1.31	(1.04-1.64)	0.021
Increasing	1.28	(1.11, 1.48)	0.001	1.21	(1.03-1.42)	0.021
	Full sample (N=5559)			Excluding adolescent depression (N=3718)		
Depression PRS	OR	95% CI	p	OR	95% CI	p
Decreasing	1.12	(0.97, 1.29)	0.126	1.13	(0.95-1.34)	0.160
Late-childhood limited	0.93	(0.82, 1.06)	0.266	0.88	(0.76-1.02)	0.089
High-persistent	1.00	(0.82, 1.21)	0.992	1.06	(0.81-1.40)	0.659
Increasing	1.20	(1.05, 1.38)	0.009	1.16	(0.97-1.39)	0.109

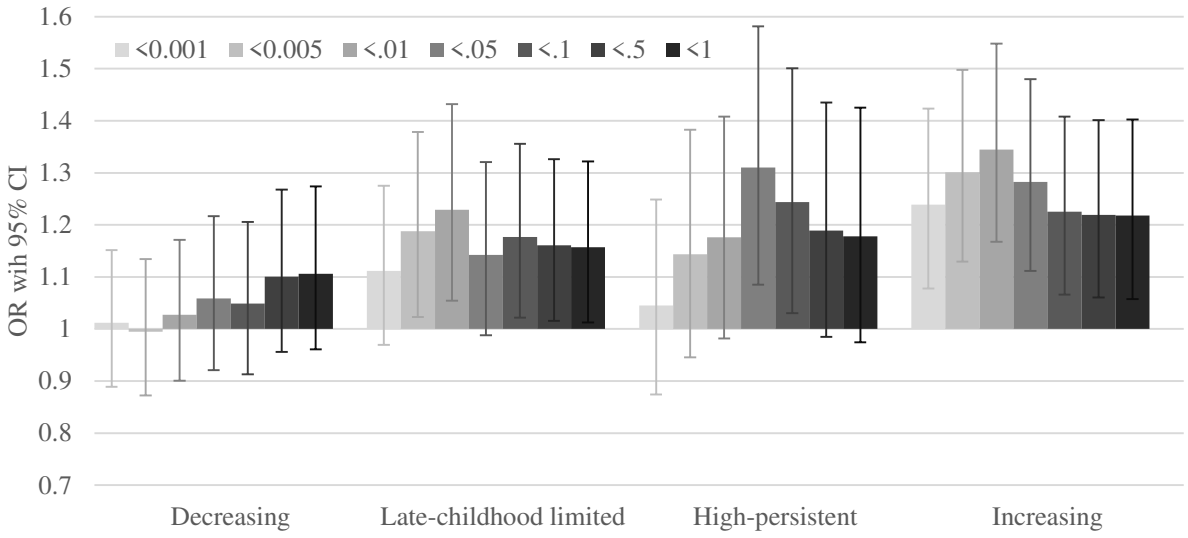
Low trajectory as reference. ADHD=attention-deficit/hyperactivity disorder, PRS = polygenic risk score

Supplementary Figure 1. Participation rates

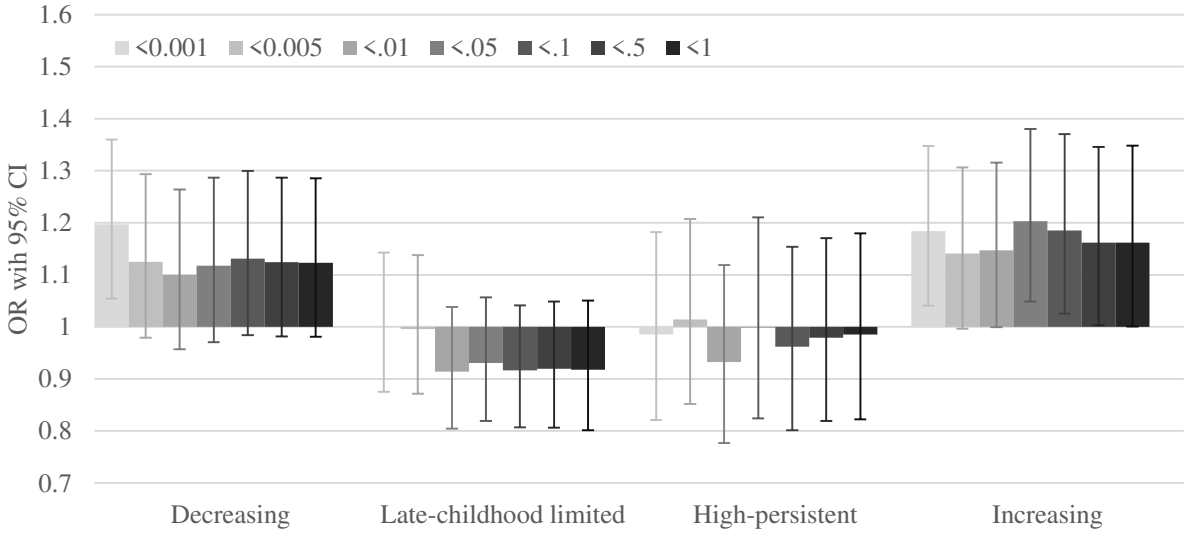


Supplementary Figure 2. Polygenic risk score associations using a range of p-value thresholds from the discovery sample

a) Attention-deficit/hyperactivity disorder polygenic risk scores

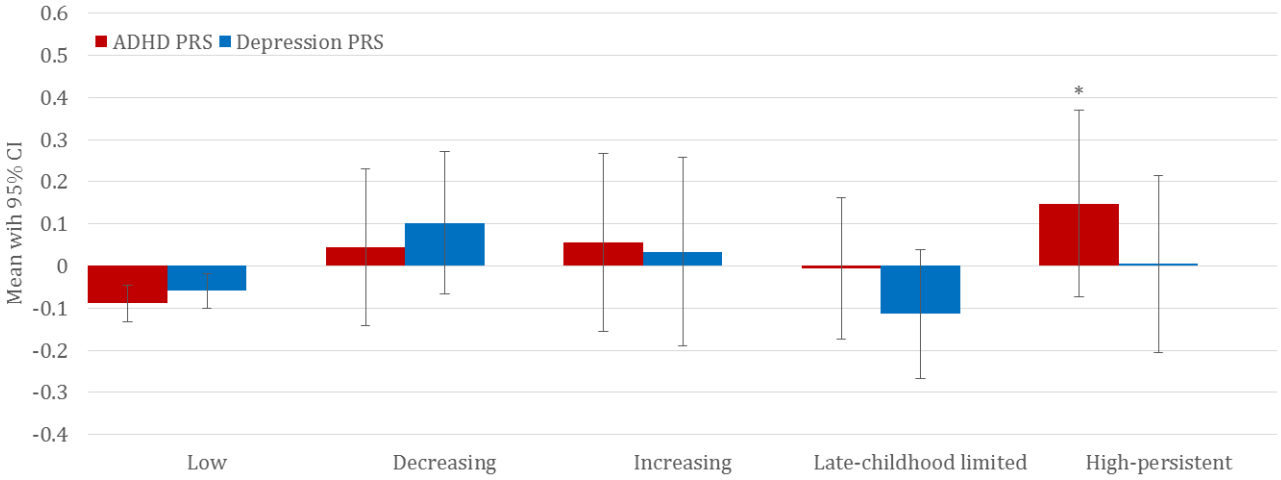


b) Depression polygenic risk scores

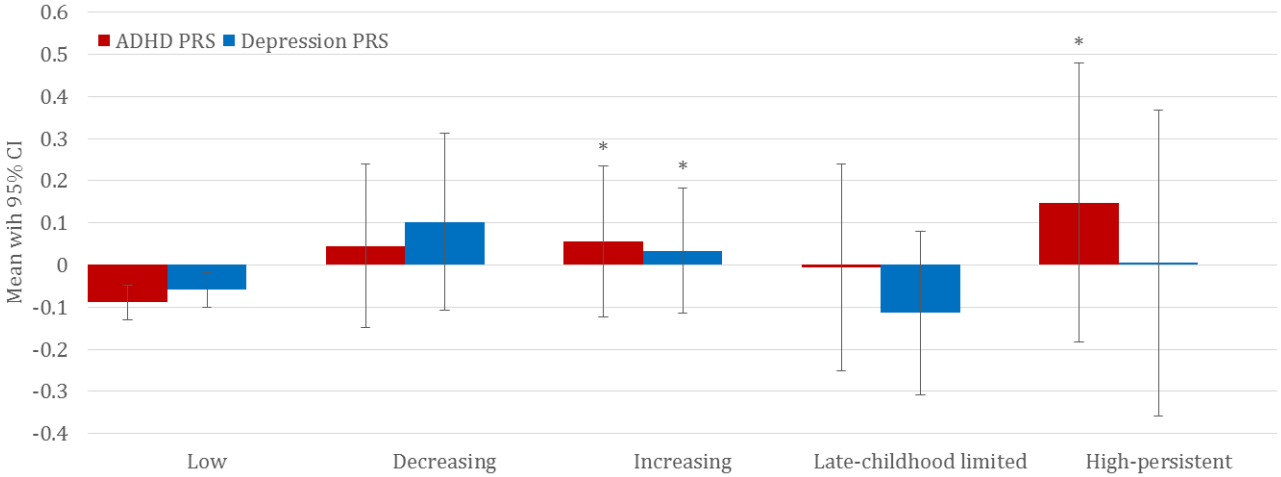


Supplementary Figure 3. Mean ADHD and depression genetic risk score by irritability trajectories, with 95% confidence intervals

a) boys

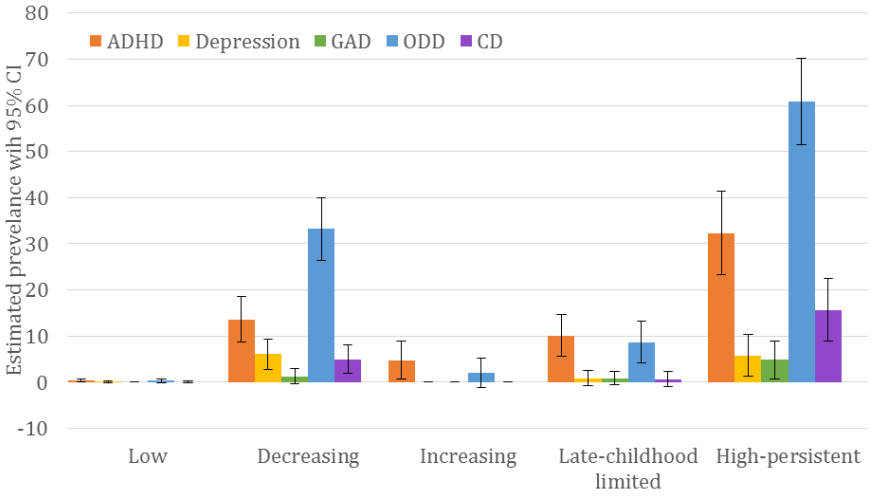


b) girls

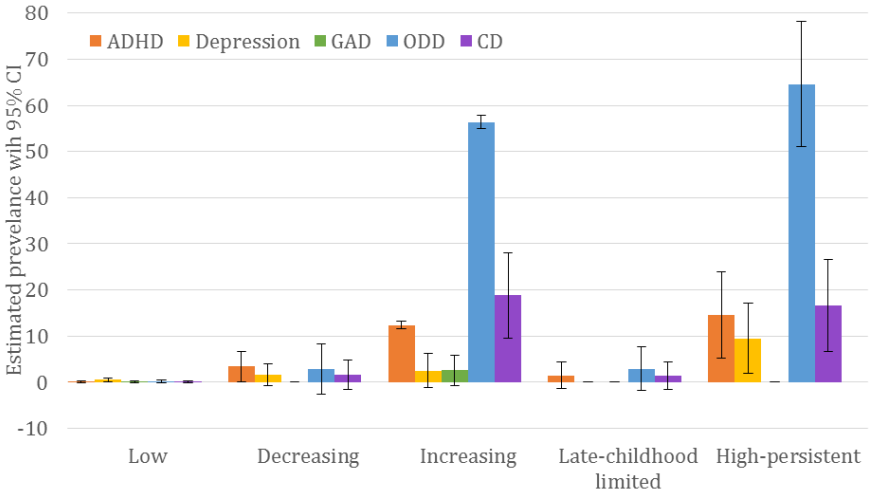


Supplementary Figure 4. Estimated prevalence of diagnoses by irritability trajectories, with 95% confidence intervals

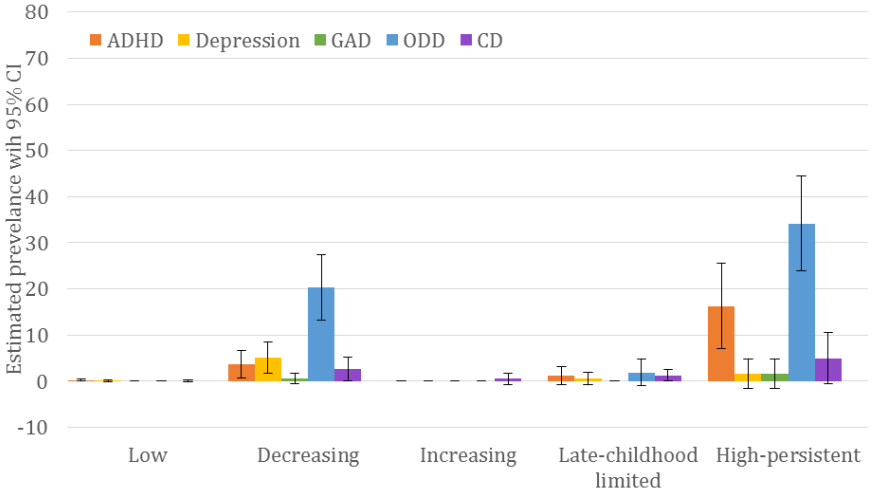
a) Boys: childhood



b) Boys: Adolescence



c) Girls: childhood



d) Girls: Adolescence