DOI:
10.1038/s41562-018-0373-9

Document Version
Peer reviewed version

Manuscript title: Genetics of co-developing conduct and emotional problems during childhood and adolescence

Author list: Hannigan[1,2], Laurie J. (PhD); Pingault[1,3], Jean-Baptiste (PhD); Krapohl[1], Eva (PhD); McAdams[1], Tom A. (PhD); Rijsdijk[1], Frühling V. (PhD); Eley[1], Thalia C. (PhD)*

Affiliations:

[1] MRC Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[2] Institute of Health and Wellbeing, University of Glasgow, UK

[3] Division of Psychology and Language Sciences, University College London, London, UK

*corresponding author

Intro para w/c	Main text w/c	# Figures	# Tables	# Supplements
200	4939	3	1	1

Common genetic influences offer a partial explanation for comorbidity between different psychiatric disorders[1–3]. However, the genetics underlying co-*development* – the cross-domain co-occurrence of patterns of change over time – of psychiatric symptoms during childhood and adolescence has not been well explored. Here, we show genetic influence on joint symptom trajectories of parent-reported conduct and emotional problems (overall N = 15,082) across development (4-16 years) using both twin- and genome-wide polygenic score analyses (genotyped N = 2,610). Specifically, we found 7 joint symptom trajectories, including two characterised, respectively, by jointly stable and jointly increasing symptoms of conduct and emotional problems (7.3% of the sample, collectively). Twin modelling analyses revealed substantial genetic influence on trajectories (h^2 estimates range: .41-.78). Furthermore, individuals' risk of being classified in the most symptomatic trajectory classes was significantly predicted by polygenic scores for years-of-education-associated alleles and depressive symptoms-associated alleles. Complementary analyses of child self-reported symptoms across late childhood and early adolescence yielded broadly similar results. Taken together, our results indicate that genetic factors are involved in the co-development of conduct and emotional problems across childhood and adolescence, and that individuals with co-developing symptoms across multiple domains may represent a clinical sub-group characterised by increased levels of genetic risk.

Comorbidity between different forms of psychopathology is a well-documented phenomenon. Clinically, comorbidity is defined as the co-occurrence of different psychiatric disorders across the diagnostic spectrum[4], but it also describes the overlap between psychiatric symptoms at the sub-clinical level within the general population[5,6]. In childhood and adolescence, comorbidity has been called 'the norm rather than the exception'[7]. It has been estimated that up to 40% of adolescents with a psychiatric diagnosis have at least one other clinically-significant psychiatric problem[8]. Furthermore, there is substantial evidence that comorbidity is associated with poorer psychiatric outcomes in adulthood[9,10].

Conduct problems and emotional problems are two common forms of psychopathology in childhood and adolescence[11,12]. They are also frequently comorbid with one another[13–15] . However, symptoms of psychopathology in children and adolescents often wax and wane across development [16,17], and there is evidence that differences in these *patterns* of change over time are predictive – over and above the average level of symptoms experienced – of future wellbeing[18,19]. As a result, when investigating comorbidity in a developmental context, it is necessary to consider not just the contemporaneous co-occurrence of symptoms or problems, but also the extent to which patterns of change in different domains are linked. This can be considered as *co-development*, defined here as the systematic co-occurrence, within groups of individuals, of developmental symptom trajectories in two or more domains. It is most straightforwardly conceptualised as comorbidity given an additional, temporal dimension. Clearly, longitudinal analyses have a particularly crucial role to play in investigating co-development in childhood and adolescence. Often, these involve studying *heterotypic continuity* – the extent to which the earlier presence of one disorder predicts the later emergence of another[20–22]. A 'person-centered' alternative[23], and one that explicitly explores cross-domain relationships among patterns of symptom change, is joint trajectory analysis.

Trajectory-based approaches offer a means of identifying, based on patterns of change and stability of symptoms over time, sub-populations of children who may be at increased risk of later-life problems. Typically, such approaches are used to uncover latent groupings, within a sample, based on individual patterns of change in a given domain. For example, for conduct problems, characteristic symptom trajectories such as early-onset persistent, childhood-limited, and adolescent-onset, have been found across multiple samples[24–27]. These trajectories have been linked to problems at school[28], aspects of the family environment[29,30], and parental mental health[19] and more. Similarly, trajectory-based analyses of emotional problems have revealed associations with several risk factors (e.g., maternal depression and negative control[31], early childhood temperament[32]

and negative outcomes (e.g., peer and family relationships[18], educational attainment[33]. In *joint* trajectory analysis, interpretable sub-groupings of individuals are sought based on the patterns of change in their scores over time, on not one but *two* domains of interest [34]. In this way, the extent of the co-development of symptoms in these domains may be characterised.

Relatively few studies have used joint trajectory approaches to explore the co-development of conduct and emotional problems, or similar traits, across development. Two[35,36] have investigated the co-development of externalizing and internalizing behaviours during childhood. The first found modest-to-moderate positive associations between initial symptom levels and rates of change when children were 2 to 6 years old – though only the initial level of externalizing symptoms was related to change in internalizing, and not vice versa[35]. The second (2-12 years) found that individuals classified in pure externalizing and 'chronic co-occurring' trajectory classes were at especially high risk for experiencing peer-related problems in early adolescence[36]. Three further studies have found similar relationships between symptom trajectories, for similar traits, extending into adolescence [37–39].

Investigating how conduct and emotional problems co-develop throughout childhood and adolescence may help to identify individuals at greatest risk of longer term difficulties. However, to clarify how this long-term risk is mediated, it is also necessary to understand *why* individuals follow the symptom trajectories they do. Common genetic influences have been shown to offer at least a partial explanation for (cross-sectional) comorbidity among psychopathological traits using both behavioural [7] and molecular genetic methods[2,40]. Furthermore, longitudinal studies of behavioural and emotional problems typically find evidence of genetic influence on stability and change across development[41]; and this is true for both conduct[42,43] and emotional problems[44] specifically. Accordingly, genetic factors may also contribute to their *co-development* over time. To our

knowledge, no previous study has investigated the extent of genetic influence upon joint trajectories of conduct and emotional problems across childhood and adolescence.

Estimating genetic influence on symptom trajectories can be done in different ways. Several studies have made use of twin modelling approaches, either examining the aetiology of individual differences in the average level and rate of change in symptoms [42,43,45], or estimating genetic influence on trajectory class membership [46]. However, recent technological and methodological advances mean that approaches using genomic data to estimate genetic influence can also be straightforwardly applied. Indeed, the complementary application of twin-based and genomic methods is one factor that has contributed to the high degree of replicability within the field of behavioural genetics [47].

One increasingly common use of genomic data to estimate genetic influence on complex behaviours is genome-wide polygenic scoring (GPS). This approach aggregates the effects of many common genetic variants associated with a given trait into an individual-specific, single score [48]. This score can then be used as to assess whether variation in a given target behaviour is associated with these variants. Because the score is generated based on variants associated with a specific trait (as identified in a genome-wide association study [GWAS]), the estimate of genetic influence on the target behaviour differs from twin-based estimates, in that it is specific to genetic variants linked to the original GWAS trait. Nonetheless, with many complex traits sharing genetic influences extensively, polygenic scores for one trait are often predictive of variance in a range of other behaviours[49–51]. This means that, as long as well-powered GWAS do not exist for all traits of interest, polygenic scores based on large GWAS of theoretically-relevant traits can be used to provide important proof-of-principle for the direct prediction of behaviour from genomic data. Here, we therefore use polygenic scores based on two of the largest existing GWAS of complex traits relevant to the developmental period under study (years of education and depressive symptoms), alongside

twin analyses, to estimate genetic influence on joint symptom trajectories of conduct and emotional problems.

Here, we aimed to establish whether sub-groups of individuals follow systematically different joint trajectories of symptoms of conduct and emotional problems from childhood into mid- adolescence. Second, using both twin-based and genome-wide polygenic methods, we aimed to estimate the extent to which genetic factors influence individual differences in the co-development of conduct and emotional problems.

Descriptive statistics are presented in **Supplementary Table 1**. Mean levels of both conduct and emotional problems declined slightly across the study period. Results from the baseline Latent Growth Curve Model (LGCM) fitting are presented in **Supplementary Table 2** (and in **Supplementary Table 3** for the child self-report analyses). For parent-reported conduct and emotional problems, models with linear and quadratic terms fit the data best, with acceptable[52] values on all fit indices (RMSEA <= 0.05; CFI/TLI >= 0.95). Non-significant parameters were trimmed from these models for no significant loss of fit.

Restricted Growth Mixture Models (GMMs) were specified using the best-fitting baseline LGCMs and a single categorical latent variable (see **Figure 1**). The results of GMM-fitting for 2 through 11 joint trajectory classes are presented in **Table 1**. A 7-class model was accepted as providing the best fit for our data in the parent report analysis (model-fitting results for the child self-report analysis, which yielded a 4-class model as the best fitting across the 9- to 16- year measurement occasions, are presented in **Supplementary Table 4**). Full details of the model selection process are described in **Supplementary Note 1**.

The joint trajectories of parent-reported conduct and emotional problems identified in the final version of the best-fitting 7-class model are shown in **Figure 2**. Trajectory classes have been re-ordered according to the within-class symptom average at the final wave of measurement (16-yr conduct problems mean + 11-yr emotional problems mean), as an approximation of the level of symptoms individuals classified within them carry forward into adolescence. Thus, class 1, on the far left of **Figure 2**, was the class where the cumulative burden of symptoms across development is lowest. This class contained the majority (54.2%; 8182 individuals) of the sample and can thus be considered a normative class. Classes 2 and 3 both involve stable-low or developmentally-decreasing trajectories of conduct and emotional problems, and are therefore labelled as the 'low/decreasing' symptoms trajectory classes. Together, they accounted for a further 23.8% of the sample (3586 individuals). Classes 4 (9.7%; 1463 individuals) and 5 (5%; 749 individuals) again had, respectively, stable-low and decreasing trajectories of conduct problems, but these ran alongside trajectories of increasing emotional problems. This meant that the overall symptom burden at the end of the modelled growth process was higher than the 'low/decreasing' symptoms classes, but in acknowledgement that the primary source of this burden was, in both cases, emotional problems, these classes will be referred to as 'symptoms of emotional problems only'. The final two classes incorporated 'elevated/increasing' symptom trajectories; with children displaying stable-elevated conduct and stable, moderately elevated emotional problems (class 6), relative to the normative class, and jointly increasing conduct and emotional problems (class 7). In class 6 (3.3%; 498 individuals), conduct problems did begin to decline at the final measurement occasion, meaning that class 7 (4%; 604 individuals) was considered the class with the highest symptom burden continuing into adolescence.

The complementary analysis of child self-reports, covering the final three measurement occasions only, yielded four joint trajectory classes with relatively similar profiles to the groupings described above. These joint trajectories, shown in **Supplementary Figure 1**, were labelled as 'normative'

(71.8% of sample), 'childhood-limited' (8.5%), 'symptoms of emotional problems only' (14.2%), and 'elevated/increasing' symptoms (5.6%).

As expected, odds of classification into the different joint trajectory groups varied by sex. Males were slightly more likely to be classified in the 'elevated/increasing' symptoms classes, and less likely to be in 'symptoms of emotional problems only' classes (see **Supplementary Table 5** for full details).

Genetic analyses were carried out to investigate genetic influence on joint trajectory group membership. First, the results of the twin analyses for parent-report data are presented in **Supplementary Table 6,** and shown graphically in **Supplementary Figure 2**. MZ twins were invariably more often classified similarly to their co-twins than DZ twins in the models, indicating genetic influence upon trajectory class membership. In the twin modelling analyses, significant genetic influence on trajectory class membership was found for all classes. Genetic influence on membership of the normative class (47% variance explained) was lower than 5 of the 6 symptomatic classes, including the elevated/increasing symptoms trajectory classes (78% and 62%) but confidence intervals overlapped. Shared environmental influences were found to be significant only in respect to membership of the normative class (32% variance explained) and one of the two classes characterised by symptoms emotional problems only (class 5; 24%). Non-shared environmental influences were significant and moderate (15-41% variance explained) for all classes.

Results from the twin modelling component of the child self-reports analysis (presented in **Supplementary Figure 3**) were again comparable, with substantial genetic influence on membership of all joint trajectory classes. Shared environmental influences were non-significant in all analyses for the child self-reports, and so were dropped from the final models.

The results of the genome-wide polygenic score analyses of parent-report data are presented in **Supplementary Table 7**, as a series of log odds ratios (ORs) indicating change in an individual's odds of classification into a given class, relative to the normative class, as a function of a 1SD change in their GPS. The education years GPS results revealed significantly decreased probabilities of being in the elevated/increasing symptoms trajectory classes (class 6 OR = 0.72 [0.56–0.92]; class 7 OR=0.64 [0.49–0.83]) relative to the normative class, as a function of increasing polygenic score. This was also true for individuals in one of the 'symptoms of emotional problems only' classes (class 5 OR=0.74 [0.58–0.96]). Taken together, these results indicate that individuals with fewer education-associated alleles are at an increased risk of following these symptomatic joint trajectories. Classes 2-4 also had ORs of less than 1, but confidence intervals for these odds ratios spanned zero. In the depressive symptoms GPS analyses, only probability of classification class 6 (OR = 1.44 [1.13–1.83]), relative to the normative class, was significantly predicted. Log ORs were >1 for all other classes, but confidence intervals indicated these to be non-significant. These trends are visible in the distributions of each of the polygenic scores among each of the 7 joint developmental trajectory classes, which are shown graphically in **Figure 3**.

Finally, results from the polygenic score component of the complementary analyses of child self-reports in late childhood and adolescence were again broadly consistent (see **Supplementary Table 8**). Probability of classification in the 'childhood-limited' (OR = 0.69 [0.58–0.84]) and 'increasing' (OR = 0.69 [0.50–0.94]) joint symptom trajectory groups decreased as a function of increasing education years GPS, while probability of classification in the 'symptoms of emotional problems only' group was associated with the depressive symptoms GPS (OR = 1.18 [1.01–1.37]). The distribution of the polygenic scores among the 4 joint trajectory groups are shown in **Supplementary Figure 4** (education years) and **Supplementary Figure 5** (depressive symptoms).

In a developmental context, comorbidity manifests in not just the overlap between different forms of psychopathology, but also their co-development over time. In this study, we investigated co-development via latent joint trajectories of conduct and emotional problems measured on multiple occasions between the ages of 4 and 16 years. We also estimated the extent to which genetic factors were associated with joint trajectories, using both twin-based and polygenic score analyses.

The phenotypic results of our trajectory modelling are largely consistent with previous work examining developmental patterns of similar traits across childhood and adolescence. Within our joint trajectory model, we saw classes with stable-low, decreasing, moderate, childhood-limited, and increasing conduct problems, which is in line with what has previously been found elsewhere[24–27]. Similarly, we saw stable-low, decreasing, moderate, increasing, and stable high trajectories of emotional problems within the joint trajectory model, which reflects typical developmental patterns of internalizing-type traits[31,18,33,53,54].

Of those previous studies looking at *joint* trajectories of similar phenotypes during a similar period using a GMM approach, all extracted more classes (respectively: 11, 12, 25, and 9/16 [females/males]) than the 7 identified here[36–39]. However, this is largely a methodological artefact. Each of these previous studies estimated an optimum number of trajectories for each phenotype individually (*k*1 and *k*2) and then combined the models to assess conditional probabilities, resulting in *k*1 x *k*2 possible joint trajectory classes. The results of two of these studies indicated that their final models had more-than-optimal numbers of joint classes, with joint classes containing few individuals [38] and non-associated trajectories[37] respectively. In one study[36], the authors trimmed low probability classes from their final model, resulting in an 11- rather than 15- class model from combining the initial 3- and 5-class models – though a top-down approach such as this still may not reveal the most parsimonious model possible. Mindful of the risk for over-extraction of classes using

restricted GMM, we opted to estimate a joint trajectory model directly, using a single latent categorical variable for two parallel growth processes, rather than combining single-variable GMMs.

These methodological differences notwithstanding, we observed broadly similar patterns of symptom co-development to those found in previous studies of similar traits[35–39], with most individuals experiencing approximately parallel symptom trajectories for conduct and emotional problems. This is consistent with a developmental model of comorbidity, wherein the improvement or worsening of symptoms in one domain is linked to similar changes in another[55]. The notable exceptions to this pattern were the two classes of individuals who experienced increasing and/or elevated symptoms of emotional problems alongside low or decreasing symptoms of conduct problems. Similar results have been found before [39]. One possible explanation for this is that the relationship of emotional problems to conduct problems in development is one of necessity-without-sufficiency; that is, conduct problems may be somewhat inherently linked to emotional problems, but not *vice versa*. This is consistent with both evidence of a role for emotional dysregulation in conduct problems[56,57] and with evidence that conduct problems evoke negative feedback from caregivers[58,59], which may in turn lead to higher levels of emotional problems. Understanding the relative importance of processes such as these in underpinning symptom co-development has the potential to help with the targeting of interventions, and this possibility therefore warrants further investigation.

Based on previous findings of genetic influence underpinning comorbidity[2,7,40] and developmental stability[41,43,44] of symptoms of psychopathology, we expected to find genetic influence on joint symptom trajectories of conduct and emotional problems. In the twin analyses, substantial genetic influence was indeed found for all trajectory classes, with moderate to high (range: .41 to .78) heritability for membership of a given joint trajectory class. Genome-wide polygenic score analysis allowed for an alternative means of investigating the role of genes, based on observed individual-

specific genetic variation, rather than genetic variation inferred by known differences in genetic relatedness among identical and non-identical twins. An individual's education years GPS significantly predicted classification in the more symptomatic trajectory groups, relative to the normative class, with this effect approximately linear in relation to the increasing overall symptom severity within the classes. A similar trend was found for individuals' depressive symptoms polygenic scores in relation to their joint symptom trajectories, though only membership of one of the 'elevated/increasing' classes was significantly predicted by this genomic instrument. Moreover, complementary analyses of child self-report data across late childhood and adolescence revealed broadly similar results. Overall, both sets of results are strongly indicative of a genetic basis for the co-development of symptoms of conduct and emotional problems.

Our results, using both behavioural and molecular genetic methods, accord with theoretical accounts of the development of psychopathology that implicate a temporally stable, pleiotropic genetic liability underpinning comorbidity between traits[60–62]. Previous studies have emphasised the potential utility of developmental trajectories as phenotypes for gene-finding studies[44]. Our findings indicate that joint trajectories maybe be particularly suitable candidates for such approaches. Moreover, these results offer proof-of-principle for the use of individual-level polygenic predictors to help differentiate developmental trajectories and sub-populations for whom the risk of later-life psychiatric problems is great. The goal of personalised medicine is that such approaches, in combination with current diagnostic strategies, will have clinical utility in the future[63].

Our study is subject to some limitations. First, complete data were not available for both measures at all measurement occasions. Specifically, we had no measure of parent-reported emotional problems at age 16 to incorporate into the developmental models. This restricted our ability to model adolescent-onset emotional problems, which have been found in previous studies[33,37]. Second, power in liability-threshold modelling is generally more limited than twin models using

continuous data and our power became more limited as the number of individuals in the classes decreased. This widened confidence intervals on estimates and limited our ability to draw conclusions about differences in the aetiology of different trajectory classes. Third, we observed low-level selective attrition on both variables (see **Supplementary Methods 1**), which may have influenced the overall shape of trajectories. Maximum likelihood estimation reduces the impact of selective attrition[64], but this remains a limitation. Finally, within-reporter, cross-domain correlations were relatively low (generally <0.3; see **Supplementary Table 9**). Correlations summarise the symptom overlap at a whole-sample level and are generally uninformative as to the presence or absence of latent sub-groups of individuals with similar patterns of symptom co-development [34]. Thus, while this did not restrict our ability to extract sub-groups based on joint trajectories, it may be indicative of imprecision in the measures, the implications of which are worth considering. For example, one contributing factor may have been slight floor effects resulting from positive skew in the scale data (see **Supplementary Table 1**). As well as attenuating correlations at the whole-sample level, the results of this for our analyses would be to increase the proportion of the sample classified in the normative joint trajectory class, reducing the number of individuals available for classification in the other groups. Thus, a more normally-distributed measure could have resulted in either more symptomatic joint trajectory classes, or more populated symptomatic classes (with increased power for genetic analyses). However, brief questionnaire-based measures such as ours are, for pragmatic reasons, relatively standard in cohorts with the longitudinal structure to support trajectory analyses, and as such this limitation and its implications unlikely to be specific to this study.

Overall, our results demonstrate that, in childhood and adolescence, comorbidity is as much about *co-development* as co-occurrence. We found that, while many individuals showed normative levels of conduct and emotional problems across development, those that had elevated or developmentally-increasing levels of one trait were also more likely to be on similar trajectories for the other. Beyond this, we show that joint symptom trajectories of conduct and emotional problems

are associated with genetic factors – both as inferred by known genetic relationships *and* as measured directly from genotype data. This highlights the potential informativeness and utility of joint trajectories for aetiological studies of developing psychopathology.

Methods

Data for this study were drawn from the Twins Early Development Study (TEDS[65]). All TEDS twins with data available on the main measures at one or more measurement occasion during the study period were included (overall N = 15,082 individuals [4938 DZ twin pairs and 2603 MZ twin pairs] with data available for at least one measurement occasion [52% on $\geq$ 4 occasions, 71% on $\geq$3 occasions, 85% on $\geq$ 2 occasions]), and a genotyped sub-sample was used (N=2,610) for the genome-wide polygenic scores. The TEDS project received ethical approval from the Institute of Psychiatry Ethics Board, and written consent was provided by parents in all participating families. Full details of the study sample, including details of selective attrition, which was observed at a low level for the main study variables during the study period, are presented in **Supplementary Methods 1**.

The main analyses made use of parent-report data, which came from biological mothers in 98.7% cases (as ascertained at the midpoint of the study period). Conduct problems were measured using a 5-item sub-scale of the Strengths and Difficulties Questionnaire (SDQ[66]). Parents rated how true ('Certainly true', 'Sometimes true', 'Not true) a series of statements (e.g., 'Often has temper tantrums or hot tempers') were for their children. Questionnaires were sent in five separate waves of data collection, when children were approximately 4, 7, 9, 11 and 16 years old. Scale scores correlated, on average, at .51 measurement occasions and internal consistencies (ordinal Cronbach's α[67]) ranged from .71 to .83.

Emotional problems were measured using a 5-item sub-scale of the SDQ[66]. This sub-scale included statements such as 'Has many fears, is easily scared', with the same response set as for conduct problems. Emotional problems were measured on four occasions, when children were approximately 4, 7, 9, and 11 years old. In the 4-year measure, one item ('Nervous or clingy…') was missing and was replaced with a proxy item ('Tends to be shy and timid'). Scale scores correlated, on average, at .47 between occasions and internal consistencies (ordinal Cronbach's α[67]) ranged from .69 to .78.

We also conducted all analyses, in parallel, on child self-report versions of the measures, which were available at the 9, 11, and 16 year waves of data collection. Ordinal Cronbach's α [67] ranged from .65 to .76 for the child self-report scales. A matrix of within- and across-reporter correlations for all study variables, at all measurement occasions, is presented in **Supplementary Table 9**. Within measurement occasions, child self-reports of symptoms of conduct and emotional problems correlated, on average, at 0.41 with corresponding parent reports.

To establish baseline models of change in symptoms of conduct and emotional problems over time for use in the joint trajectory modelling, we first ran a series of latent growth models (LGMs) on each phenotype independently. Details of this process are provided in **Supplementary Methods 2**. The best-fitting LGMs formed the basis of the growth mixture models (GMMs) used to estimate joint developmental trajectories. Extending LGMs to GMMs involves the addition of a latent categorical variable, which allows growth parameters from the baseline model to be estimated distinctly for a specified number of latent sub-groups, or 'classes', within the data. The specification of the growth mixture model for joint trajectories of parent-reported symptoms of conduct and emotional problems is illustrated in **Figure 1** (**Supplementary Figure 6** for the child self-report analyses). Further details of GMM-fitting procedure are provided in **Supplementary Methods 3**.

Models were run with an increasing number of classes specified and compared on the following criteria, in order: 1) fit indices (Akaike Information Criterion [AIC],Bayesian Information Criterion [BIC], and entropy); 2) a Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR[68,69]) which compares a *k* class model to a *k-1* class model, wherein a significant (p<0.05) result indicates that the *k* class model offers a better fit[70]; 3) class sizes as a proportion of the overall sample; and 4) theoretical expectations and interpretability of classes.

We used two approaches to estimate genetic influence on joint trajectories. The first applied threshold liability models to twin data in order to estimate genetic, shared, and non-shared environmental influences upon trajectory class membership. A detailed description of this approach is provided in **Supplementary Methods 4**. The second component of the genetic analyses made us of genome-wide polygenic scores (GPS).

GPS analysis is a procedure that involves generating a variable directly from genomic data, to represent an individual's cumulative load of common genetic variants associated with a given trait. This is done by combining information, identified via a genome-wide association study (GWAS) about relationships between specific polymorphisms in the genome and an outcome, into a single weighted score. Widespread pleiotropy among common genetic variants linked to complex behavioural traits[71] means that GPSs can often predict a range of outcomes, beyond the target outcome of the original GWAS. For this reason, and because our main aim is to test the *principle* of predicting patterns of symptom co-development from genomic data, we used a GPS that has previously been shown to be the most predictive for a range of behavioural phenotypes within this [50] and other [51] samples for our primary analysis. This was the education years GPS, based on a recent large (N=293,723) GWAS [72], which aggregates the effects of alleles across the genome associated with years spent in education. Because of the size and power of the GWAS, and given that this score likely reflects genetic 'risk' for a wide range of behaviours and factors that influence time spent in

education, it represents a useful genomic instrument for studies of behaviour across development. We also included a depressive symptoms GPS, from the largest available (N=161,460) GWAS [73] of a trait phenotypically similar to one of our study variables. At the time of analysis, to our knowledge, no comparably well-powered GWAS of conduct problems or aggression exists. Further details about the procedure GPS creation are available in **Supplementary Methods 5**.

After best-fitting growth models were established for the full sample, the specification of these models was retained and the models re-run using only the genotyped sub-sample (N=2,610). In this re-run, GPS was included as a predictor of variance in growth parameters and of trajectory class membership in the model. Given that an individual's education years GPS indicates their 'load' of years-of-education-associated alleles, associations with measures of psychopathology are expected to be negative. The depressive symptoms polygenic score aggregates the effects of alleles associated with depression, so any associations with our study variables are expected to be positive. The prediction of trajectory class membership by GPS is given as a log odds ratio. The results of a power analysis for the logistic regressions that underpin the GPS analyses, presented in **Supplementary Figure 7**, indicated that our sample size (N=2,610) provides >80% power to detect an OR change of $\geq$0.4 for trajectory classes including >2% of the sample.

All stages of the trajectory analysis and the GPS analysis were carried out using the statistical software Mplus version 7.4[74] in conjunction with the MplusAutomation R package[75]. Twin modelling was carried out using OpenMx v2.3.1[76] in R. In all analyses, a full information maximum likelihood approach (FIML) was used to estimate parameter values. This approach performs well in the presence of missing data [77] and minimises the impact of selective attrition [64].

Correspondence

All correspondence and requests for materials should be directed to Prof. Thalia Eley (thalia.eley@kcl.ac.uk) at MRC Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, Denmark Hill London, UK SE5 8AF.

Acknowledgements

We gratefully acknowledge the ongoing contribution of the participants in the Twins Early Development Study (TEDS) and their families. TEDS is supported by a program grant from the UK Medical Research Council (MR/M021475/1 and previously G0901245), with additional support from the US National Institutes of Health (AG046938) and the European Commission (602768; 295366). LJH is supported by a 1 + 3 Ph.D. studentship from the UK Economic and Social Research Council (ESRC). JBP is a fellow of MQ: Transforming Mental Health. EK is supported by the MRC/IoPPN Excellence Award. TAM is supported by a Sir Henry Dale Fellowship, jointly funded by the Wellcome Trust and the Royal Society (107706/Z/15/Z). This study presents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. We would like to thank Robert Plomin for his input and advice.

Author contributions

LJH, TCE, TAM, & FVR conceived of the investigation; LJH, J-BP, & EK discussed analytic strategy; LJH and EK carried out statistical analyses; LJH, TCE, TAM, & FVR worked on interpreting results and refining analyses; LJH wrote the manuscript; all authors critically reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Data availability statement

TEDS data is available to access in line with the TEDS data access policy (http://teds.ac.uk/research/collaborators-and-data/teds-data-access-policy).

Code availability statement

Mplus and OpenMx scripts for data analysis are available, in **Supplementary Methods 6**.

Tables and Figure captions

Model	Entropy	AIC	aBIC	VLMR 2xLLDiff	VLMR p-value
2 Class	0.78	333731.49	333798.14	13064.65	0.00
3 Class	0.80	329375.99	329473.75	4369.50	0.00
4 Class	0.76	326575.42	326704.28	2814.57	0.00
5 Class	0.74	325060.80	325220.76	1528.62	0.00
6 Class	0.75	324066.34	324257.41	1008.46	0.00
7 Class	0.75	323262.89	323485.05	817.46	0.00
7 Class: trimmed	0.74	323726.33	323877.41	.	.
7 Class: trimmed + age & sex as covariates	**0.74**	**322918.64**	**323118.59**	**.**	.
8 Class	0.73	322595.74	322849.01	681.15	0.61
9 Class	0.73	321981.03	322265.41	628.70	0.16
10 Class	0.73	321384.84	321700.32	610.19	0.62
11 Class	0.72	320878.57	321225.15	520.27	0.20

Table 1. | **Model fit statistics for latent growth curve modelling of 2-11 joint developmental trajectories of parent-reported symptoms of conduct and emotional problems**. Entropy values closer to 1 represent increased precision of classification; lower AIC/aBIC values indicate better model fit; non-significant VLMR p-value indicates K-class model offers no significant improvement on fit of K-1 class model

Figure 1. | Joint trajectory latent class growth model for parent-reported symptoms of conduct and emotional problems with intercept and linear/quadratic slopes. C = latent categorical k class variable (where k is a specified number of discrete classes to be estimated); I = intercept; S = linear slope; Q= quadratic slope; [subscript] con = conduct problems; [subscript] emo = emotional problems; Rc = residual variance for conduct problems; Re = residual variance in emotional problems. Slope loadings fixed at values proportionate to mean age at assessment minus mean age at first assessment (e.g., linear values: 0, 0.31, 0.50, 0.73, 1.23). Residuals are fixed to be equal across time (within trait).

Figure 2. | Joint developmental trajectory classes of parent-reported symptoms of conduct and emotional problems from the best-fitting 7-class model (whole sample, N = 15,082). Classes are ordered (from left-to-right) by within-class average symptom burden at the final wave of measurement (16-yr conduct problems mean + 11-yr emotional problems mean); class 1 is referred to in-text as the 'normative' class; classes 2 and 3 are referred to in-text as 'low/decreasing' symptoms classes; classes 4 and 5 are referred to in-text as 'symptoms of emotional problems only' classes; and classes 6 and 7 are referred to in-text as 'elevated/increasing' symptoms classes.

Figure 3. | Distribution of education years (upper panel) and depressive symptoms (lower panel) genome-wide polygenic scores among each of the 7 joint developmental trajectory classes of parent-reported symptoms of conduct and emotional problems (genotyped sub-sample, N = 2,610). Filled circles represent individuals; solid black horizontal lines represent means; narrow grey boxes show 95% confidence intervals around the mean

References

1. Kendler KS, Prescott C a, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry*. 2003;60(9):929-937. doi:10.1001/archpsyc.60.9.929.
2. Lee SH, Ripke S, Neale BM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45(9):984-994. doi:10.1038/ng.2711.
3. Pettersson E, Larsson H, Lichtenstein P. Common psychiatric disorders share the same genetic origin: a multivariate sibling study of the Swedish population. *Mol Psychiatry*. 2015;21(August 2014):1-5. doi:10.1038/mp.2015.116.
4. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617-627. doi:10.1001/archpsyc.62.6.617.
5. Krueger RF, Markon KE. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. *Annu Rev Clin Psychol*. 2006;2:111-133. doi:10.1146/annurev.clinpsy.2.022305.095213.
6. Battaglia M, Przybeck TR, Bellodi L, Cloninger CR. Temperament dimensions explain the comorbidity of psychiatric disorders. *Compr Psychiatry*. 1996;37(4):292-298. doi:10.1016/S0010-440X(96)90008-5.
7. Rhee SH, Lahey BB, Waldman ID. Comorbidity Among Dimensions of Childhood Psychopathology: Converging Evidence From Behavior Genetics. *Child Dev Perspect*. 2015;9(1):26-31. doi:10.1111/cdep.12102.
8. Merikangas KR, He J-P, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication--Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010;49(10):980-989. doi:10.1016/j.jaac.2010.05.017.

9. Lewinsohn PM, Rohde P, Seeley JR. Adolescent psychopathology: III. The clinical consequences of comorbidity. *J Am Acad Child Adolesc Psychiatry*. 1995;34(4):510-519. doi:http://dx.doi.org/10.1097/00004583-199504000-00018.

10. Angold A, Costello EJ, Erkanli A. Comorbidity. *J Child Psychol Psychiatry*. 1999;40(1):55-87. doi:10.1017/S0021963098003448.

11. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry*. 2003;60(8):837-844. doi:10.1001/archpsyc.60.8.837.

12. Merikangas KR, He J-P, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001-2004 NHANES. *Pediatrics*. 2010;125(1):75-81. doi:10.1542/peds.2008-2598.

13. Cunningham NR, Ollendick TH. Comorbidity of Anxiety and Conduct Problems in Children: Implications for Clinical Research and Practice. *Clin Child Fam Psychol Rev*. 2010;13(4):333-347. doi:10.1007/s10567-010-0077-9.

14. Riglin L, Thapar A, Shelton KH, Langley K, Frederickson N, Rice F. Profiling depression in childhood and adolescence: the role of conduct problems. *J Child Psychol Psychiatry*. 2016;57(4):481-490. doi:10.1111/jcpp.12465.

15. Wolff JC, Ollendick TH. The comorbidity of conduct problems and depression in childhood and adolescence. *Clin Child Fam Psychol Rev*. 2006;9(3-4):201-220. doi:10.1007/s10567-006-0011-3.

16. Hofstra MB, van der Ende J, Verhulst FC. Continuity and change of psychopathology from childhood into adulthood: a 14-year follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2000;39(7):850-858. doi:10.1097/00004583-200007000-00013.

17. Costello EJ, Copeland WE, Angold A. Trends in psychopathology across the adolescent years: What changes when children become adolescents, and when adolescents become adults? *J Child Psychol Psychiatry Allied Discip*. 2011;52(10):1015-1025. doi:10.1111/j.1469-

7610.2011.02446.x.

18. Letcher P, Smart D, Sanson A, Toumbourou JW. Psychosocial precursors and correlates of differing internalizing trajectories from 3 to 15 years. *Soc Dev*. 2009;18(3):618-646. doi:10.1111/j.1467-9507.2008.00500.x.

19. Odgers CL, Moffitt TE, Broadbent JM, et al. Female and male antisocial trajectories: from childhood origins to adult outcomes. *Dev Psychopathol*. 2008;20:673-716. doi:10.1017/S0954579408000333.

20. Lahey BB, Zald DH, Hakes JK, Krueger RF, Rathouz PJ. Patterns of Heterotypic Continuity Associated With the Cross-Sectional Correlational Structure of Prevalent Mental Disorders in Adults. *JAMA psychiatry*. 2014;60637(9):1-8. doi:10.1001/jamapsychiatry.2014.359.

21. Reinke WM, Ostrander R. Heterotyic and homotypic continuity: The moderating effects of age and gender. *J Abnorm Child Psychol*. 2008;36(7):1109-1121. doi:10.1007/s10802-008-9236-6.

22. Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry Allied Discip*. 2006;47:276-295. doi:10.1111/j.1469-7610.2006.01614.x.

23. Fanti K. Using a Person-Centered Methodology to Investigate the Co-Occurrence between Psychopathological Problems. *Ann Depress Anxiety*. 2014;1(7):1-5.

24. Barker ED, Maughan B. Differentiating early-onset persistent versus childhood-limited conduct problem youth. *Am J Psychiatry*. 2009;166(August):900-908. doi:10.1176/appi.ajp.2009.08121770.

25. Moffitt TE, Caspi A, Dickson N, Silva P, Stanton W. Childhood-onset versus adolescent-onset antisocial conduct problems in males: Natural history from ages 3 to 18 years. *Dev Psychopathol*. 1996;8(2):399-424. doi:10.1017/S0954579400007161.

26. Maughan B, Pickles A, Rowe R, Costello EJ, Angold A. Developmental Trajectories of Aggressive and Non-Aggressive Conduct Problems. *J Quant Criminol*. 2000;16(2):199-221.

doi:10.1023/a:1007516622688.

27. Bongers IL, Koot HM, van der Ende J, Verhulst FC. Developmental trajectories of externalizing behaviors in childhood and adolescence. *Child Dev*. 2004;75(5):1523-1537. doi:10.1111/j.1467-8624.2004.00755.x.

28. Wildeboer A, Thijssen S, van IJzendoorn MH, et al. Early childhood aggression trajectories: Associations with teacher-reported problem behaviour. *Int J Behav Dev*. 2015. doi:10.1177/0165025414562239.

29. Leve LD, Kim HK, Pears KC. Childhood temperament and family environment as predictors of internalizing and externalizing trajectories from ages 5 to 17. *J Abnorm Child Psychol*. 2005;33(5):505-520. doi:10.1007/s10802-005-6734-7.

30. Shaw DS, Lacourse E, Nagin DS. Developmental trajectories of conduct problems and hyperactivity from ages 2 to 10. *J Child Psychol Psychiatry Allied Discip*. 2005;46(9):931-942. doi:10.1111/j.1469-7610.2004.00390.x.

31. Feng X, Shaw DSD, Silk JJS. Developmental trajectories of anxiety symptoms among boys across early and middle childhood. *J Abnorm Psychol*. 2008;117(1):32-47. doi:10.1037/0021-843X.117.1.32.Developmental.

32. Davis S, Votruba-Drzal E, Silk J. Trajectories of Internalizing Symptoms From Early Childhood to Adolescence: Associations With Temperament and Parenting. *Soc Dev*. 2015:n/a-n/a. doi:10.1111/sode.12105.

33. Dekker MC, Ferdinand RF, van Lang NDJ, Bongers IL, van der Ende J, Verhulst FC. Developmental trajectories of depressive symptoms from early childhood to late adolescence: Gender differences and adult outcome. *J Child Psychol Psychiatry Allied Discip*. 2007;48(7):657-666. doi:10.1111/j.1469-7610.2007.01742.x.

34. Nagin DS, Tremblay RE. Analyzing developmental trajectories of distinct but related behaviors: A group-based method. *Psychol Methods*. 2001;6(1):18-33. doi:10.1037//1082-989X.6.1.18.

35. Gilliom M, Shaw D. Codevelopment of externalizing and internalizing problems in early childhood. *Dev Psychopathol*. 2004;16(2):313-333. doi:10.1017/S0954579404044530.

36. Fanti K, Henrich CC. Trajectories of pure and co-occurring internalizing and externalizing problems from age 2 to age 12: findings from the National Institute of Child Health and Human Development Study of Early Child Care. *Dev Psychol*. 2010;46(5):1159-1175. doi:10.1037/a0020659.

37. Nivard MG, Lubke GH, Dolan C V, et al. Joint developmental trajectories of internalizing and externalizing disorders between childhood and adolescence. *Dev Psychopathol*. 2017;29(3):919-928. doi:10.1017/S0954579416000572.

38. Reinke WM, Eddy JM, Dishion TJ, Reid JB. Joint trajectories of symptoms of disruptive behavior problems and depressive symptoms during early adolescence and adjustment problems during emerging adulthood. *J Abnorm Child Psychol*. 2012;40(7):1123-1136. doi:10.1007/s10802-012-9630-y.

39. Wiesner M, Kim HK. Co-occurring delinquency and depressive symptoms of adolescent boys and girls : A dual trajectory modeling approach Co-Occurring Delinquency and Depressive Symptoms of Adolescent Boys and Girls : A Dual Trajectory Modeling Approach. 2006;(February 2017). doi:10.1037/0012-1649.42.6.1220.

40. Anttila A V, Finucane H, Bras J, et al. Analysis of shared heritability in common disorders of the brain. *bioRxiv*. 2016;Jan:1:048991. doi:10.1101/048991.

41. Hannigan LJ, Walaker N, Waszczuk M, McAdams T, Eley TC. Aetiological influences on stability and change in emotional and behavioural problems across development: a systematic review. *Psychopathol Rev*. 2016;4(1):1-57. doi:10.5127/pr.038315.

42. Lacourse E, Boivin M, Brendgen M, et al. A longitudinal twin study of physical aggression during early childhood: evidence for a developmentally dynamic genome. *Psychol Med*. 2014;44(12):2617-2627. doi:10.1017/S0033291713003218.

43. Pingault J-B, Rijsdijk F, Zheng Y, Plomin R, Viding E. Developmentally dynamic genome:

Evidence of genetic influences on increases and decreases in conduct problems from early childhood to adolescence. *Sci Rep*. 2015;5(May):10053. doi:10.1038/srep10053.

44. Lubke GH, Miller PJ, Verhulst B, et al. A powerful phenotype for gene-finding studies derived from trajectory analyses of symptoms of anxiety and depression between age seven and 18. *Am J Med Genet Part B Neuropsychiatr Genet*. 2016;171(7):948-957. doi:10.1002/ajmg.b.32375.

45. Harden KP, Quinn PD, Tucker-Drob EM. Genetically influenced change in sensation seeking drives the rise of delinquent behavior during adolescence. *Dev Sci*. 2012;15(1):150-163. doi:10.1111/j.1467-7687.2011.01115.x.

46. Fontaine NMG, Rijsdijk F V, McCrory EJP, Viding E. Etiology of different developmental trajectories of callous-unemotional traits. *J Am Acad Child Adolesc Psychiatry*. 2010;49(7):656-664. doi:10.1016/j.jaac.2010.03.014.

47. Plomin R, DeFries JC, Knopik VS, Neiderhiser JM. Top 10 Replicated Findings From Behavioral Genetics. *Perspect Psychol Sci*. 2016;11(1):3-23. doi:10.1177/1745691615617439.

48. Dudbridge F. Power and Predictive Accuracy of Polygenic Risk Scores. *PLoS Genet*. 2013;9(3). doi:10.1371/journal.pgen.1003348.

49. Krapohl E, Patel H, Newhouse S, et al. Multi-polygenic score approach to trait prediction. *Mol Psychiatry*. 2017;(October 2016):1-7. doi:10.1038/mp.2017.163.

50. Krapohl E, Euesden J, Zabaneh D, et al. Phenome-wide analysis of genome-wide polygenic scores. *Mol Psychiatry*. 2016;21(9):1188-1193. doi:10.1038/mp.2015.126.

51. Belsky DW, Moffitt TE, Corcoran DL, et al. The Genetics of Success. *Psychol Sci*. 2016;27(7):957-972. doi:10.1177/0956797616643070.

52. McDonald RP, Ho M-HR. Principles and practice in reporting structural equation analyses. *Psychol Methods*. 2002;7(1):64-82. doi:10.1037/1082-989X.7.1.64.

53. Costello D, Swendsen J, Roes J, Dierker LC. Risk and Protective Factors Associated with Trajectories of Depressed Mood from Adolescence to Early Adulthood. *J Consult Clin Psychol*.

2008;76(2):173-183. doi:10.1037/0022-006X.76.2.173.Risk.

54. Toumbourou JW, Williams I, Letcher P, Sanson A, Smart D. Developmental trajectories of internalising behaviour in the prediction of adolescent depressive symptoms. *Aust J Psychol*. 2011;63(4):214-223. doi:10.1111/j.1742-9536.2011.00023.x.

55. Lahey BB, Loeber R, Burke J, Rathouz PJ, McBurnett K. Waxing and waning in concert: Dynamic comorbidity of conduct disorder with other disruptive and emotional problems over 7 years among clinic-referred boys. *J Abnorm Psychol*. 2002;111(4):556-567. doi:10.1037//0021-843X.111.4.556.

56. Frick PJ, Morris AS. Temperament and Developmental Pathways to Conduct Problems. *J Clin Child Adolesc Psychol*. 2004;33(1):54-68. doi:10.1207/S15374424JCCP3301_6.

57. Dodge KA. Social-Cognitive Mechanisms in the Development of Conduct Disorder and Depression. *Annu Rev Psychol*. 1993;44(1):559-584. doi:10.1146/annurev.ps.44.020193.003015.

58. Burt SA, McGue M, Krueger RF, Iacono WG. How are parent-child conflict and childhood externalizing symptoms related over time? Results from a genetically informative cross-lagged study. *Dev Psychopathol*. 2005;17(1):145-165. doi:10.1017/S095457940505008X.

59. Avinun R, Knafo A. Parenting as a reaction evoked by children's genotype: a meta-analysis of children-as-twins studies. *Personal Soc Psychol Rev*. 2014;18(1):87-102. doi:10.1177/1088868313498308.

60. Caspi A, Houts RM, Belsky DW, et al. The p Factor. *Clin Psychol Sci*. 2014;2(2):119-137. doi:10.1177/2167702613497473.

61. Eley TC. General Genes: A New Theme in Developmental Psychopathology. *Curr Dir Psychol Sci*. 1997;6(4):90-95. doi:10.1111/1467-8721.ep11512831.

62. Lahey BB, Van Hulle C a., Singh AL, Waldman ID, Rathouz PJ. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. *Arch Gen Psychiatry*. 2011;68(2):181-189. doi:10.1001/archgenpsychiatry.2010.192.

63. Visscher PM. Human Complex Trait Genetics in the 21st Century. *Genetics*. 2016;202(2):377-379. doi:10.1534/genetics.115.180513.

64. Enders C, Bandalos D. The Relative Performance of Full Information Maximum Likelihood Estimation for Missing Data in Structural Equation Models. *Struct Equ Model A Multidiscip J*. 2001;8(3):430-457. doi:10.1207/S15328007SEM0803_5.

65. Haworth CM a, Davis OSP, Plomin R. Twins Early Development Study (TEDS): a genetically sensitive investigation of cognitive and behavioral development from childhood to young adulthood. *Twin Res Hum Genet*. 2013;16(1):117-125. doi:10.1017/thg.2012.91.

66. Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry*. 1997;38(5):581-586. doi:10.1111/j.1469-7610.1997.tb01545.x.

67. Gadermann AM, Guhn M, Zumbo BD. Estimating Ordinal Reliability for Likert-Type and Ordinal Item Response Data: A Conceptual, Empirical, and Practical Guide. *Pract Assessment, Res Eval*. 2012;17(3):1-13. doi:http://pareonline.net/getvn.asp?v=17&n=3.

68. Lo Y, Mendell NR, Rubin DB. Testing the number of components in a normal mixture. *Biometrika*. 2001;88(3):767-778. doi:10.1093/biomet/88.3.767.

69. Vuong Q. Likelihood Ratio Tests for Model Selection and Nonnested Hypotheses. *Econometrica*. 1989;57(2):307–333.

70. Ram N, Grimm KJ. Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups. *Int J Behav Dev*. 2009;33(6):565-576. doi:10.1177/0165025409343765.Growth.

71. Sivakumaran S, Agakov F, Theodoratou E, et al. Abundant pleiotropy in human complex diseases and traits. *Am J Hum Genet*. 2011;89(5):607-618. doi:10.1016/j.ajhg.2011.10.004.

72. Okbay A, Beauchamp JP, Fontana MA, et al. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature*. 2016;533(7604):539-542. doi:10.1038/nature17671.

73. Okbay A, Baselmans BML, De Neve JE, et al. Genetic variants associated with subjective well-

being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat Genet*. 2016;48(6):624-633. doi:10.1038/ng.3552.

74. Muthén LK, Muthén BO. *Mplus User's Guide*. Eighth. Los Angeles, CA: Muthén & Muthén; 2017.

75. Hallquist M, Wiley J. MplusAutomation: Automating Mplus Model Estimation and Interpretation. 2014.

76. Neale MC, Hunter MD, Pritikin JN, et al. OpenMx 2.0: Extended Structural Equation and Statistical Modeling. *Psychometrika*. 2015;26(2):99-127. doi:10.1007/s11336-014-9435-8.

77. Jelicić H, Phelps E, Lerner RM. Use of missing data methods in longitudinal studies: the persistence of bad practices in developmental psychology. *Dev Psychol*. 2009;45(4):1195-1199. doi:10.1037/a0015665.