Title: Investigating the developmental impacts of schizophrenia risk alleles and childhood peer victimization on early-onset mental health trajectories

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Abstract.

Objective. Twin studies suggest that genetic factors contribute to continuity in mental health problems and environmental factors are the major contributor to developmental change. We investigated the influence of psychiatric risk alleles on early-onset mental health trajectories and whether these were subsequently modified by exposure to childhood victimization. *Method.* The sample was a prospective UK population-based cohort, the Avon Longitudinal Study of Parents and Children. Developmental trajectories in childhood (approximately ages 4 to 8 years) and adolescence (approximately ages 12 to 17 years) were estimated for emotional problems. Psychiatric risk alleles were indexed by polygenic risk scores (PRS) for schizophrenia using genome-wide association study results from the Psychiatric Genomics Consortium. Chronic peer victimization in late childhood (ages 8.5 and 10.5 years) was assessed as an index of environmental exposure. Individuals with sufficient data on emotional problems, PRS and victimization were included in the main analyses: N=3988. *Results.* Higher schizophrenia PRS were associated with a trajectory of early-onset increasing emotional problems (OR=1.18 (1.02-1.36)) compared to a trajectory of low-stable emotional problems. Subsequent exposure to victimization increased the likelihood of transitioning from a low-stable emotional problems trajectory during childhood (before exposure) to an increasing trajectory in adolescence (after exposure) (OR=2.59 (1.48-4.53)). *Conclusions.* While the early development of emotional problems was associated with genetic risk (schizophrenia risk alleles), the subsequent course of emotional problems for those who might otherwise have remained on a more favorable trajectory was altered by exposure to peer victimization, which is a potentially modifiable environmental exposure.

Investigating the developmental impacts of schizophrenia risk alleles and childhood peer victimization on early-onset mental health trajectories

Most psychiatric disorders, regardless of when first manifest, originate in childhood (1). However early childhood problems are not associated with later mental health outcomes for all - there is change as well as continuity across development (1). Twin studies consistently show that continuity in mental health problems across time is highly heritable (2, 3). This suggests that genetic factors make an important contribution to developmental trajectories. However twin studies show that environmental factors are a major contributor to change (3, 4). Identifying potentially malleable environmental factors that may alter the developmental course of heritable mental health problems is an important step towards guiding prevention strategies.

Molecular genetic studies have revealed that while the genetic architecture of psychiatric disorders is complex, it is now possible to assign to individuals a biologically valid indicator of common variant genetic liability for that phenotype (polygenic risk score, PRS) (5). To date, genetic findings in schizophrenia have led the field of PRS research, largely reflecting the relatively high power of genome wide association studies of that disorder (6). PRS derived from schizophrenia risk alleles predicts increased liability not only to that disorder but also other adult psychiatric disorders, for example major depression, and to mental health and neurodevelopmental traits in childhood (7, 8). Associations between schizophrenia PRS and anxiety/emotional problems have now been observed across the lifespan - in childhood, adolescence and adult life (8-11). These cross-sectional observations suggest that schizophrenia risk alleles may contribute to the trajectories of emotional problems from an early age, although this has not yet been tested directly. However,

genetics alone cannot explain the developmental course of emotional problems (1). Psychosocial stressors also contribute risk; some are particularly prevalent in childhood (12). An example is chronic childhood peer victimization, a common social stressor in childhood that contributes to subsequent emotional problems in childhood and later adult life (13-18). Being bullied has been found to be associated with childhood emotional symptoms even when allowing for genetic confounding (15, 16, 18). Investigating genetic and environmental risk factors together is important to gain understanding of how these factors simultaneously affect the longitudinal course of mental health problems.

In this paper, we use a large prospective, population-based cohort, ALSPAC, that underwent the same repeated mental health assessments from ages 4 to 17 years, to test specific hypotheses concerning the association of schizophrenia PRS and childhood victimization with emotional problem trajectories. We postulated first that schizophrenia risk alleles (PRS) contribute to early-onset emotional problems that remain on an unfavorable trajectory. Second, that chronic peer victimization in late childhood would modify early trajectories by increasing the likelihood of transitioning from a low symptom trajectory in childhood (before exposure) to an elevated trajectory in adolescence (after exposure). We also explored the impact of the presence/absence of victimization for those already on an elevated trajectory in early childhood.

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 (19, 20). 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.

Emotional problems

Emotional problems were assessed using the parent-rated 5-item emotional problems subscale (range 0-10) of the Strengths and Difficulties Questionnaire (SDQ) (21) that includes primarily anxiety items (often complains of headaches; many worries; often unhappy, downhearted; nervous or clingy in new situations; many fears, easily scared). 'Childhood' data were collected at ages 47, 81 and 97 months (approximately age 4 to 8 years) and 'adolescent' data were collected at ages 140, 157 and 198 months (approximately age 12 to 17 years).

Polygenic risk scores

Schizophrenia polygenic risk scores (PRS) were generated as the weighted mean number of disorder risk alleles in approximate linkage equilibrium (r-square<0.25), derived from dosage data of 1,813,169 imputed autosomal SNPs using standard procedures (7). Risk alleles were defined as those associated with case-status in the Psychiatric Genomics Consortium (PGC) analyses of schizophrenia (35,476 cases and 46,839 controls) at a threshold of p<0.05 as this maximally captures phenotypic variance (6). Associations across a range of p-thresholds are shown in Figure SF1 in the online data supplement. Genotyping details, as well as full methods for generating the PRS can be found elsewhere (8).

Peer victimization

Peer victimization was assessed by interviews with the children using a 9-item modified version of the bullying and friendship interview schedule (13, 22) that asked about different types of overt and relational victimization experienced in the past six months. Data were collected at ages 8.5 and 10.5 years (after the 'childhood' and before the 'adolescent' emotional problems assessments). Individuals who reported having been victim to any of the items "frequently" or "very frequently" (several times a month/week) at both ages were classified as having been exposed to (chronic) peer victimization (11.6% of the sample). Those who reported being victims "seldom" or "never" for all items at either age were categorized as not having been exposed to (chronic) peer victimization.

Statistical analysis

Analyses were conducted in several steps – depicted in Figure 1 and the final model in Figure 2. We modelled emotional problem trajectories by fitting Growth Mixture

Models (GMM) separately for (a) the three childhood time-points, (b) the three adolescent time-points. Separate models for childhood and adolescence were fit to enable investigation of trajectory change before and after exposure to victimization. GMM groups individuals into trajectory classes (categories) based on patterns of growth (change) (23). Grouping individuals enabled us to investigate whether exposure to victimization was associated with transitioning from low emotional problems in childhood to having problems in adolescence. A latent class approach enabled us to identify unmeasured probabilistic subgroups (classes) based on the developmental patterns (trajectories) from repeated measures of observed variables (emotional problems). Starting with a single k-class solution, $k+1$ solutions were fitted until the optimum solution was reached. GMM solutions were selected based on fit indices (see online data supplement).

Once trajectory classes had been defined, we assessed whether schizophrenia PRS predicted childhood and adolescent trajectory classes. We also checked for associations between schizophrenia PRS and child-reports of victimization.

Next, we examined transitions between childhood and adolescent emotional problem classes (i.e. before and after exposure to victimization). These were modelled by latent transition analysis using a bias-adjusted 3-step approach, which accounts for measurement error in class assignment (24). Measurement invariance between the childhood and adolescent trajectories was not assumed, given possible differences in longitudinal patterns (25).

We tested whether schizophrenia PRS and victimization were associated with change/transition in emotional problem trajectory class (from before exposure to victimization in childhood to after exposure in adolescence) (26). Testing association

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with transition combines the direct effect of schizophrenia PRS and victimization on adolescent trajectory classes and the moderating effect of schizophrenia PRS and victimization on the association between the childhood and adolescence classes.

Sensitivity analyses were conducted (a) including potential confounders, (b) excluding individuals who (according to an earlier parent-report measure) were exposed to prior peer victimization (before the self-reported victimization assessment at age 8.5 years), and (c) assessing the impact of missing data (see below). Full details of the sensitivity analyses are given in the online data supplement.

All analyses were conducted in Mplus using a maximum likelihood parameter estimator for which standard errors are robust to non-normality (MLR) (27). Binary/multinomial logistic regressions were used as appropriate and associations are presented as odds ratios. Multinomial logistic regression technically estimates multinomial odds ratios (or relative risk ratios); however, we refer to effects as odds ratios (usually used for two exhaustive categories) throughout the results section for clarity.

Missing data

Details of the available sample sizes at each step of analysis are shown in shown in Figure SF2 in the online data supplement. The starting sample size included individuals with data on emotional problems for at least two of the three relevant time-points in either childhood (N=8425) or adolescence (N=7018). These individuals were included in the GMMs that were used to derive the emotional problems classes; GMM were conducted in Mplus using full information maximum likelihood estimation (FIML) (27). GMM data in both childhood and adolescence were available

for N=6146, of whom 75% had genetic data and 83% had victimization data: 65% had both genetic and victimization data and thus formed our 'main sample' (N=3988). Inverse probability weighting (28) was used to assess the impact of missing data, whereby observations were weighted based on measures assessed in pregnancy that were predictive of variables in the analysis and/or inclusion in the main sample (see online data supplement).

Results

Modelling emotional problem developmental trajectories

Descriptive statistics including gender differences are shown in Table ST1 in the online data supplement. As shown in Figure 3, in both childhood (N=8425) and adolescence (N=7018), we observed three emotional problem trajectory classes: low (79.2% in childhood, 83.3% in adolescence), decreasing (11.0% in childhood, 7.6% in adolescence) and increasing (9.8% in childhood, 9.1% in adolescence). Subsequent analyses of trajectories focus on the (less favorable) increasing class compared to the (most favorable) low emotional problems class.

There was strong evidence for an association between childhood and adolescent emotional problem trajectory classes, although confidence interval were wide: compared to the low class in childhood, a much higher proportion of the individuals in the childhood increasing class were also in the increasing class in adolescence (OR=17.07 (10.30-28.30), p<0.001). All transition probabilities for the latent transition analysis are shown in Figure SF3 in the online data supplement.

Schizophrenia PRS and emotional problem developmental trajectories

Higher schizophrenia PRS were associated with an elevated likelihood of being in the increasing emotional problem trajectory class in childhood (OR=1.18 (1.02-1.36), p=0.030). Despite the adolescent trajectory classes being strongly associated with prior childhood trajectories, schizophrenia PRS still showed some independent association with emotional problem trajectories in adolescence (OR=1.17 (1.00-1.36), p=0.050), when compared to the low class.

Self-reported victimization exposure

Victimization exposure in late childhood was predicted by earlier, childhood emotional problems - the increasing childhood trajectory class (OR=1.79 (1.21-2.66), p=0.004). However schizophrenia PRS were not associated with exposure to child-reported chronic victimization (OR=0.95 (0.86-1.04), p=0.292).

Schizophrenia PRS and victimization: associations with trajectory changes

Schizophrenia PRS were not associated with transitioning from the low childhood trajectory class to the increasing trajectory class in adolescence (OR=1.04 (0.81-1.34), p=0.758).

Chronic peer victimization however was associated with transition from the low trajectory class in childhood (before exposure) to the increasing trajectory class in adolescence (after exposure; OR=2.59 (1.48-4.53) p=0.001). This association held when schizophrenia PRS were included in the model (OR=2.57 (1.46-4.52), p=0.001).

Post-hoc analyses suggested that for those (already) in the childhood increasing trajectory class, victimization did not alter the trajectory in adolescence as it was not associated with transitions for this trajectory class (overall Wald $\chi^2(2)=3.61$, p=0.165: adolescent increasing vs. low OR=2.51 (0.54-11.68); decreasing vs. low OR=4.26 (0.94-19.39)).

Sensitivity analyses

Including sex, social class and maternal depression, home ownership, education and marital status as covariates revealed a similar pattern of results (see Table TF3 in the online data supplement).

Excluding individuals who were exposed to prior peer victimization (maternal reports at ages 4-8 years) also revealed a similar pattern of results, with the exception that the association between victimization and transitioning from the low to increasing class was reduced (OR=1.90 (0.90-4.00), p=0.093; see online data supplement). Thus, the observed association between chronic peer victimization and transitioning from a low to increasing class may be driven by individuals exposed to particularly chronic victimization (i.e. which occurred in early childhood as well as at ages 8.5 and 10.5 years).

Finally, using inverse probability weighting to assess the impact of missing data did not change the interpretation of results (see online data supplement).

Discussion

This study aimed to investigate the contribution of schizophrenia risk alleles to developmental trajectories of emotional problems across childhood and adolescence in the general population. We also set out to assess whether early developmental trajectories could be shifted by an environmental stressor - peer victimization. Specifically, we tested the hypotheses that schizophrenia risk alleles, indexed by PRS, would be associated with an elevated trajectory of early-onset emotional problems that persisted through adolescence, and that exposure to chronic peer victimization would alter the subsequent developmental course of trajectories. Our findings suggest that schizophrenia risk alleles contribute to an increasing trajectory of emotional problems in early childhood and adolescence. Later environmental risk exposure - in this case chronic peer victimization – contributes to change over time. The findings suggest there are at-least two routes into an increasing trajectory of emotional problems during adolescence. The first is via genetically influenced childhood-onset emotional problems - which show strong continuity to adolescent emotional problems - and the second is via exposure to peer victimization, which alters the developmental course of individuals who are initially on a low risk trajectory to a less favorable trajectory.

The results from this study supported our first hypothesis that schizophrenia PRS contribute to a developmental trajectory of increasing emotional problems that begin early in childhood. However, the PRS did not explain the transition between childhood and adolescent trajectories and developmental trajectories during adolescence were most strongly predicted by earlier childhood trajectories. This suggests that PRS impacts during adolescence are predominantly explained via association with earlier childhood trajectories; they do not contribute substantially to *changes* in emotional problem trajectories. This is consistent with cross-sectional

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genetics research, including in this sample, that has shown associations between schizophrenia PRS and emotional problems in childhood, adolescence and adulthood (8-11) and with twin studies, which infer genetic contribution to continuity in mental health problems (2). Taken together these observations suggest that interventions aimed at improving developmental trajectories for those at elevated genetic risk of mental health problems likely need to begin very early in life-in the pre-school years.

The findings also suggest that exposure to chronic peer victimization in late childhood further shapes the developmental course of emotional problems. Specifically, exposure to victimization during childhood that was not predicted by schizophrenia PRS altered subsequent adolescent trajectories. We observed an increased likelihood of individuals transitioning from a consistently low emotional problem trajectory in childhood (before victimization exposure) to a trajectory of increasing emotional problems in adolescence (after exposure). Twin studies have repeatedly highlighted environmental factors as important contributors to change in mental health over time (4), and chronic childhood peer victimization is considered as a robust risk factor for emotional problems and depression even when using genetically-sensitive twin designs (13, 14).

We also observed that exposure to subsequent chronic victimization was associated with prior increasing emotional problems in childhood. Psychopathology is known to increase the likelihood of exposure to environmental risk factors including victimization (29). However, post-hoc analyses found that victimization was not associated with *change* in emotional problems for those who were on the less favorable trajectory of (increasing) emotional problems in childhood. This suggests

that while experiencing chronic victimization is associated with developing new emotional problems in adolescence, it may not drive the persistence of very early-onset chronic difficulties – i.e. eliminating peer victimization may not prevent ongoing problems for those who are already on a trajectory of increasing emotional problems, although further work testing this hypothesis is required. Nevertheless, in-line with previous research (30), the findings suggest that these children with early-onset emotional problems may benefit from monitoring of peer relations. An interesting direction for future research would be to investigate whether protective environmental factors can alter the course of early emotional problems trajectories away from later emotional problems (31).

This study has a number of strengths, including the integration of molecular genetic and epidemiological approaches to investigate the impact of both genetic and environmental risks on developmental trajectories. However, our findings should be considered in light of some limitations. First, ALSPAC is a longitudinal birth cohort study that suffers from non-random attrition, whereby individuals with higher levels of psychopathology and PRS are less likely to be retained in the study (32, 33). Analyses using inverse probability weighting to assess the impact of missing data did not change the interpretation of results, suggesting this has not made a major impact on our results. Despite a large sample for analysis (N=3988), sample size may have impacted our ability to detect other trajectory classes, for example those with persistently high problems, which may be reflected in our wide confidence intervals when testing for associations with the different trajectories. This could also have been the result of running separate models for childhood and adolescence, although other studies that have examined trajectories of emotional problems across childhood/adolescence have also not identified a 'persistent' trajectory (34). As only

three time-points for each of the growth models were available, we were also only able to model linear change in emotional problems – other patterns may better reflect developmental changes. We also used a parent-report questionnaire measure to assess emotional problems, which may not generalize to diagnoses, although the SDQ is a well-validated measure (21) and our classes were associated with depression diagnosis at age 18 years (see online data supplement). Moreover, using the same measure and informant is a strength for assessing developmental trajectories as otherwise change could be explained by measurement differences. In addition, schizophrenia PRS currently explains a minority of common variant liability to the disorder (6) and the effect sizes we observed are typical for this kind of work (9). For example – adopting an approach previously used to quantify effects (35), individuals in the top 2.5% for schizophrenia PRS would have a roughly 36% increased odds of having increasing, compared to low, emotional problems in childhood. Thus, PRS should be regarded as indicators of genetic liability rather than as predictors. We did not find schizophrenia PRS was associated with child-reported victimization. However we cannot completely rule out the possibility of genetic confounding; findings might differ depending on who is reporting the victimization (here we use child reports, rather than parent reports), the severity of bullying, and also other types of genetic variants could still contribute to links between victimization and emotional problems.

Finally, our analyses and hypotheses were shaped by previous work (16) and because of the availability in ALSPAC of three emotional symptoms assessments prior to exposure to victimization and three assessments after exposure. However our methods could be used in other cohorts to address developmental questions relevant to other environmental exposures, such as life events (36) and for additional

psychiatric outcomes (18). Future work investigating how genetic risk variants work together with environmental risk - and protective – factors, on a range of psychiatric outcomes will be needed, although rigorous methods are needed to know which environmental risk factors are likely causal (37, 38).

We found that a higher burden of schizophrenia risk alleles is associated with a developmental trajectory of increasing emotional problems that begins in early childhood. Exposure to chronic peer victimization in late childhood alters emotional problem trajectories, whereby individuals in a stable-low state across childhood transition to a trajectory of increasing emotional problems in adolescence.

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Figure 1. Analysis steps

A) Defining emotional problems

i) Childhood GMM

ii) Adolescent GMM

iii) LTA

B) Genetic risk

i) Childhood

ii) Adolescence

iii) Transition to adolescence

C) Victimization

i) PRS

ii) Prior emotional problems
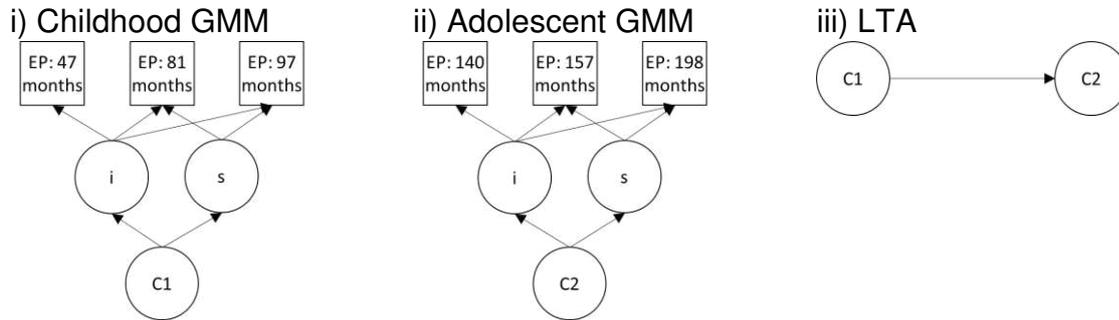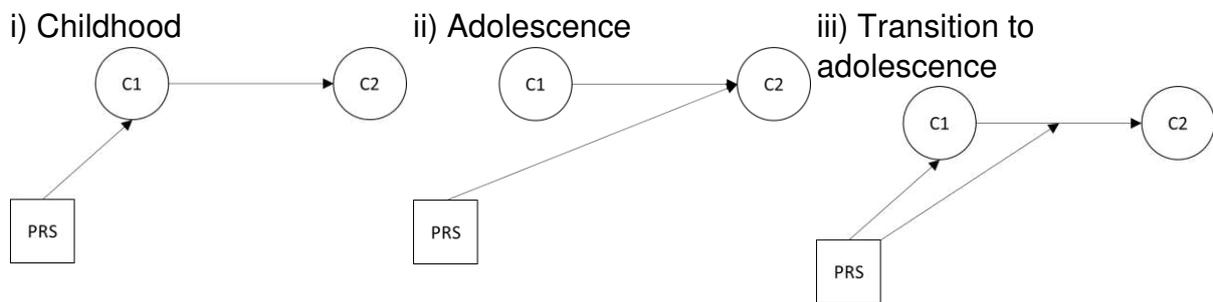
iii) Transition to adolescence
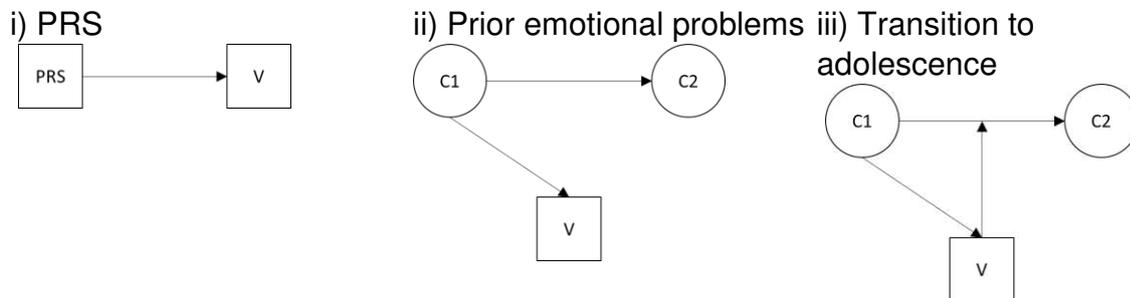
GMM=growth mixture model, LTA=latent transition analysis, EP=emotional problems, i=intercept, s=slope, C1=class 1 (childhood), C2=class 2 (adolescence) PRS = schizophrenia polygenic risk scores, V=victimization

Figure 2. Final model: associations between PRS, victimization and transition between childhood and adolescent emotional problems classes
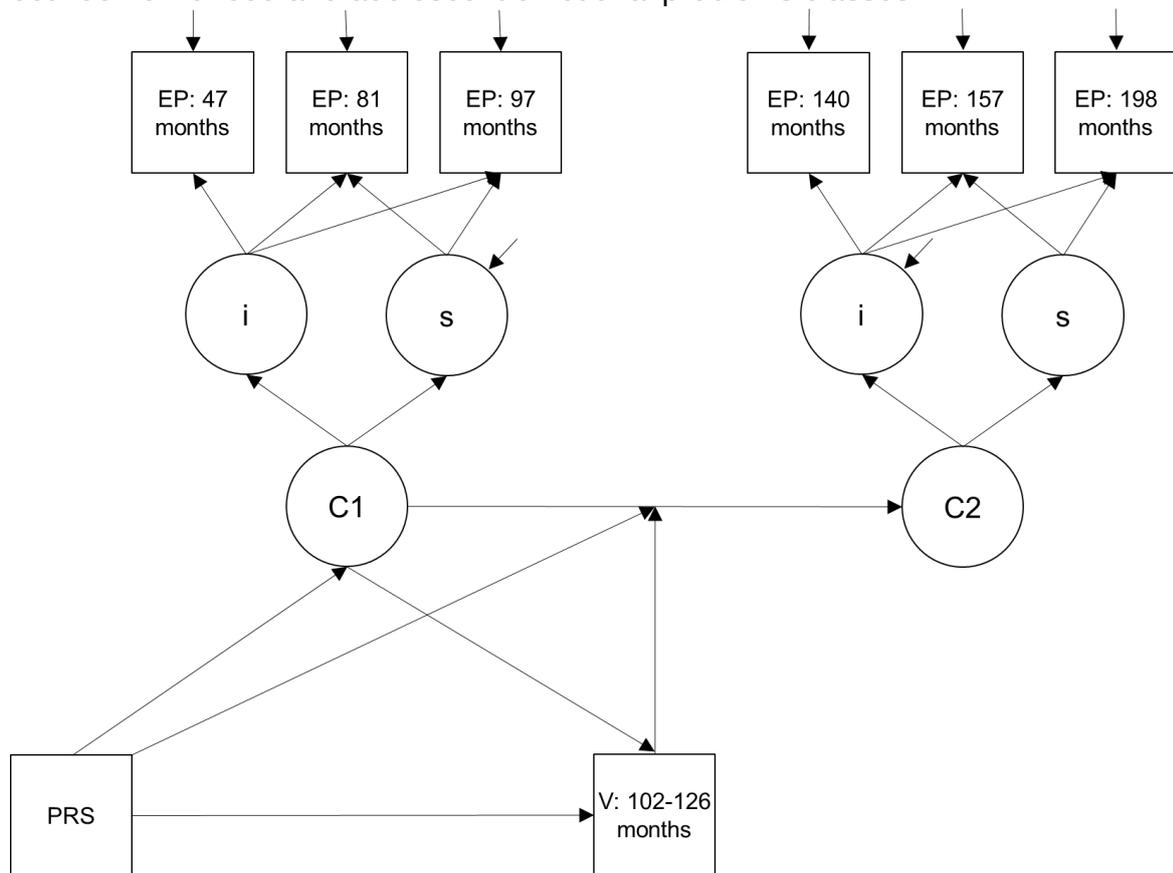
EP=emotional problems, PRS=polygenic risk score, V=victimization, i=intercept, s=slope, C1=class 1 (childhood), C2=class 2 (adolescence).

Figure 3. Emotional problem class by age

a) Childhood

Low (79.2%) — Decreasing (11.0%) — Increasing (9.8%)

b) Adolescence

Low (83.3%) — Decreasing (7.6%) — Increasing (9.1%)
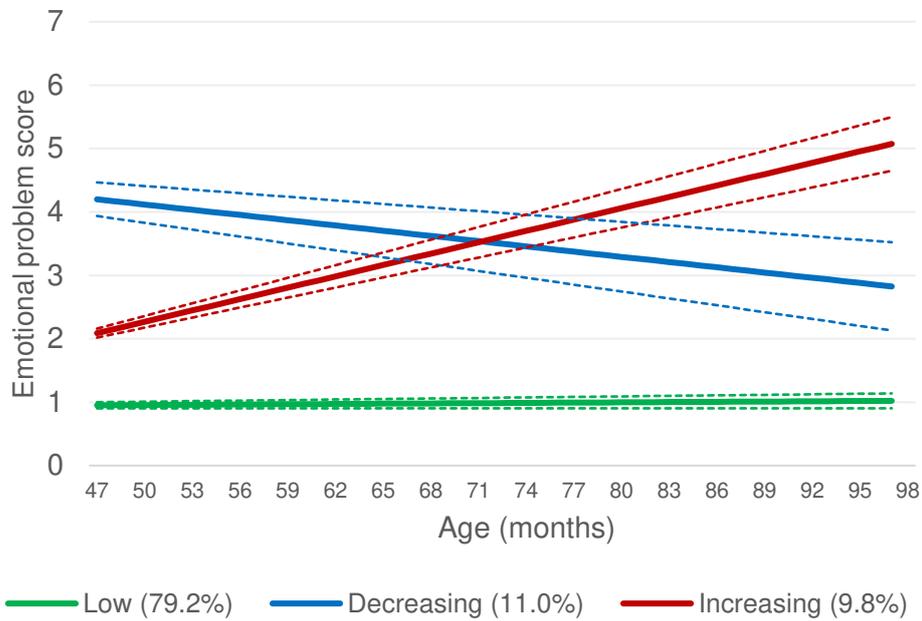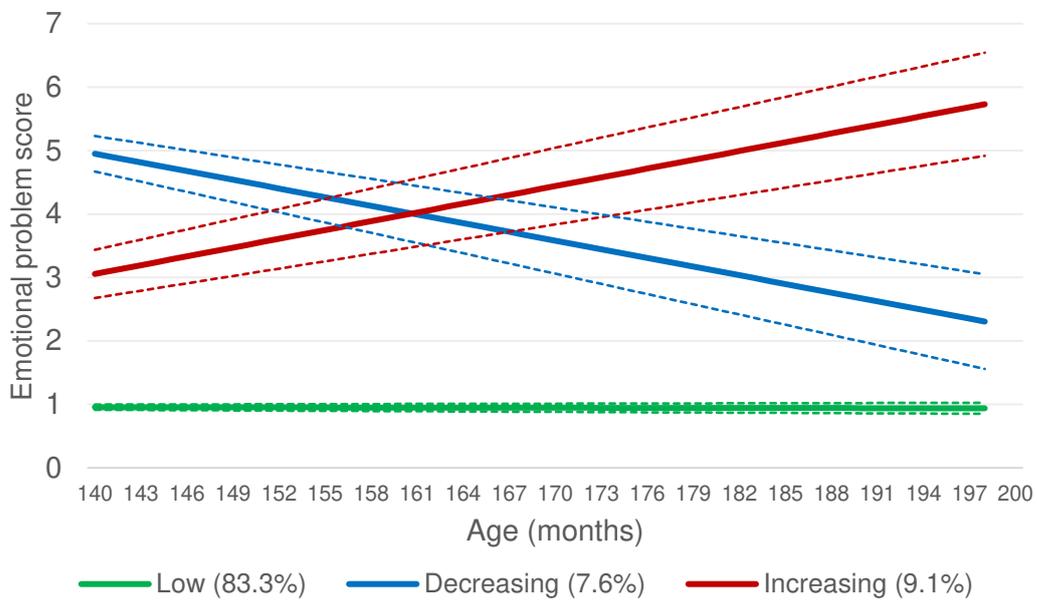
Mean trajectories with 95% confidence intervals for each class

Supplementary Material

Selecting the number of classes

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 for repeated measures of emotional problems were fixed to equality over time. Each model was run with 4000 random starting values and 400 optimisations (STARTS = 4000 400 in Mplus) (1). As only three time-points were available for both the childhood and adolescent GMMs, change was modelled as linear. Fit statistics for the GMMs are presented in Table ST2. For childhood models, intercept variance was fixed to zero because for models with more than 2-classes the classes explained the variation in the intercept (i.e. the intercept variance was close to zero). Similarly, for adolescent models slope variance was fixed to zero because for models with more than 2-classes, the classes explained the variation in the slope (i.e. the slope variance was close to zero). For both the childhood and adolescence GMMs, model fit improved from 1- to 4-class solutions, as indicated by the sample size adjusted Bayesian information criterion (ssaBIC), Vuong-Lo-Mendell-Rubin Likelihood Ratio Rest (VLMR-LRT) and bootstrap likelihood ratio test (BLRT). However, both the childhood and adolescent 4-class solution included a small class (<5%), which was likely to lead to estimation problems / model instability in subsequent analyses. The 3-class solutions in both childhood and adolescence were therefore selected (entropy = 0.844 and 0.877 respectively).

To determine whether the classes were theoretically meaningful, we first interpreted the trajectories in light of the suggested cut-points for the emotional problems measure (scores ≥5 considered abnormal/high and those =4 borderline/slightly raised) (2) and then assessed differences in 'validators' of class membership.

We assessed early temperament and later depressive disorder in early adulthood as class 'validators'. Early temperament was measured at age 3 years using the parent-rated EAS Temperament Survey five-item emotionality subscale (3) (cries easily; tends to be somewhat emotional; often fusses and cries; gets upset easily; reacts intensely when upset) (individual item range 1-5). Depressive disorder was assessed at age 17.5 years using the Computerised Interview Schedule – Revised (CIS-R) (4) to generate depression diagnoses according to ICD10-F32 criteria.

Early temperament was associated with both the childhood and adolescent emotional problem classes (Wald $\chi^2(2)$=483.58, p<0.001 and Wald $\chi^2(2)$=142.73, p<0.001 respectively). For the childhood classes, higher early emotionality was associated with increased likelihood of being in both the decreasing (OR=1.26 (1.23-1.28)) and increasing classes (OR=1.16 (1.13-1.18)) compared to both the low class. It was also associated with the decreasing compared to the increasing class (OR=1.09 (1.05-1.12)). For the adolescent classes, higher early emotionality was again associated with both the decreasing (OR=1.13 (1.10-1.16)) and increasing classes (OR=1.11 (1.09-1.14)) compared to the low class. Early temperament did not differentiate the decreasing and increasing adolescent classes (OR=1.01 (0.98-1.05)). Both the childhood emotional problem classes and the adolescent emotional problem classes were associated with depressive disorder in early adulthood (Wald $\chi^2(2)$=8.49, p=0.014 and Wald $\chi^2(2)$=52.22, p<0.0001 respectively). Specifically, membership in the increasing childhood class (OR=1.89 (1.23-2.90), but not the decreasing class (OR=0.93 (0.53-1.63), was associated with an increased likelihood of MDD (major depressive disorder) compared to the low class. Membership in the increasing childhood class was not associated with an increased likelihood of MDD compared to the decreasing class (OR=2.04 (0.97-4.28)). In adolescence, the increasing class was associated with MDD compared to the low class (OR=3.87 (2.67-5.61)) but the decreasing class was not (OR=1.41 (0.78-2.55)). The increasing class was also associated with MDD compared to the decreasing class (OR=2.75 (1.37-5.52)).

Including covariates

The potential confounders of child sex, social class and maternal depression, home ownership, education and marital status were assessed. Social class was assessed as the average household income band, including social benefits, each week on a ten-point scale when the child was 134 months old. In-line with previous definitions, low income was categorised as the bottom quintile (5). Maternal severe depression, home ownership, education (O level or higher vs. below O level) and marital status (married vs. not married) were assessed my maternal report, assessed in pregnancy. Including these covariates revealed a similar pattern of results (see Supplementary Table ST3).

Excluding individuals exposed to prior peer-victimization

Sensitivity analyses were conducted excluding individuals who - according to an earlier parent-report measure - were exposed to peer victimization prior to the self-reported victimization assessment at age 8.5 years. Prior peer victimisation was assessed using a single item of the Strengths and Difficulties Questionnaire (SDQ) (2) peer problems subscale "picked on or bullied by other children" in childhood (ages 47, 81 and 97 months). Children were coded as having been exposed to prior victimization if parents rated this to have been "certainly true" at any of the three ages (N=129: 3.8%) and not having been exposed to prior victimization if parents rated this as "not true" or "somewhat true" at all three time-points (N=3296). Excluding individuals who were exposed to (parent-reported) prior victimization prior to the (self-reported) victimization assessment at age 8.5 years revealed a similar pattern of results, with the exception that the impact of victimization on transitioning from the low to the increasing trajectory was reduced (Supplementary Table ST3).

Inverse probability weighting

Inverse probability weighting (IPW) was used to address missing data. IPW has been recommended over alternative methods for dealing with missing data (such as multiple

imputation) in situations where whole blocks of data are missing for a large proportion of individuals (6). Weights were derived from a logistic regression analysis between a set of measures assessed in pregnancy (child sex, maternal severe depression and maternal financial difficulties (difficulties affording food, clothing, heating, accommodation and things for the baby)) that were independently predictive of variables in the analysis and/or inclusion in the main sample (N = 3988 / 9297). Minimal missing data on indicators used to derive weights were singly imputed as the modal or mean value (all indicators had <9% of values missing). The Hosmer-Lemeshow test was used assess the fit of the missingness model, with results showing no indication of poor fit (Hosmer-Lemeshow $\chi^2(6)=6.210$, p=0.400). Weights ranged from 2.13 to 3.83. The analyses were rerun using IPW to address any potential bias caused by participant dropout. Using IPW revealed a similar pattern of results (see Supplementary Table ST3).

References.

1.   Muthén LK, Muthén BO. Mplus User's Guide. Seventh ed. Los Angeles, CA: Muthén & Muthén; 1998-2012.
2.   Goodman R. The Strengths and Difficulties Questionnaire: A research note. Journal of Child Psychology and Psychiatry. 1997;38(5):581-6.
3.   Buss AH, Plomin R. Temperament: Early Developing Personality Traits. Hillsdale, NJ: Lawrence Erlbaum; 1984.
4.   Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. Psychol Med. 1992;22(02):465-86.
5.   Langton EG, Collishaw S, Goodman R, Pickles A, Maughan B. An emerging income differential for adolescent emotional problems. Journal of Child Psychology and Psychiatry. 2011;52(10):1081-8.
6.   Seaman SR, White IR, Copas AJ, Li L. Combining Multiple Imputation and Inverse-Probability Weighting. Biometrics. 2012;68(1):129-37.

ST1: Descriptive statistics for emotional problems

Age	N	Mean (SE)	Female mean (SE)	Male mean (SE)	Mean gender difference (SE)	
47 months	8083	1.44 (0.02)	1.46 (0.02)	1.41 (0.02)	0.06 (0.03)	p=0.095
81 months	7954	1.50 (0.02)	1.57 (0.03)	1.42 (0.03)	0.15 (0.04)	p<0.001
91 months	7191	1.65 (0.02)	1.71 (0.03)	1.60 (0.03)	0.11 (0.04)	p=0.008
140 months	6427	1.45 (0.02)	1.60 (0.03)	1.29 (0.03)	0.31 (0.04)	p<0.001
157 months	7018	1.44 (0.02)	1.66 (0.03)	1.58 (0.03)	0.45 (0.04)	p<0.001
198 months	5563	1.49 (0.02)	1.87 (0.04)	1.08 (0.03)	0.78 (0.05)	p<0.001

Possible N=8425 in childhood (ages 47, 81 and 91 months) and N=7018 in adolescnece (ages 140, 157 and 198 months).

ST2: Fit Information for the Growth Mixture Models

| Number of classes	LL	Number of free parameters	ssaBIC	VLMR-LRT p-value	BLRT p-value	Entropy	Smallest class
Childhood[*]							
1	-43505.261	4	87033.967	-	-	-	N=8425 (100%)
2	-41532.872	7	83106.772	<0.0001	<0.0001	0.827	N=1496 (18%)
3	-41121.069	10	82300.750	0.0017	<0.0001	0.844	N=826 (10%)
4	-40668.793	13	81413.780	<0.0001	<0.0001	0.829	N=309 (4%)
Adolescence[**]							
1	-35181.780	4	70386.273	-	-	-	N=7018 (100%)
2	-34230.458	7	68500.666	<0.0001	<0.0001	0.888	N=887 (13%)
3	-33676.819	10	67410.423	<0.0001	<0.0001	0.877	N=446 (6%)
4	-33307.880	13	66689.580	0.0001	<0.0001	0.856	N=248 (4%)

[*]Intercept variance was constrained to zero [**]Slope variance was constrained to zero. LL=Loglikelihood; ssaBIC= sample size adjusted Bayesian Information Criteria; VLMR-LRT=Vuong-Lo-Mendell-Rubin Likelihood Ratio Rest; BLRT= Bootstrapped Likelihood Ratio Rest. Smallest class based on the estimated model, rounded to nearest person/percent.

ST3: Sensitivity analyses

	Original results (N=3988)			Including covariates (N=3118)			Excluding prior victims (N=3296)			Using IPW (N=3988)		
	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p
Schizophrenia PRS and increasing emotional problem class[*]												
Childhood	1.18	(1.02-1.36)	0.030	1.18	(1.00-1.40)	0.048	1.17	(0.97-1.40)	0.094	1.18	(1.02-1.36)	0.026
Adolescence	1.17	(1.00-1.36)	0.050	1.21	(1.01-1.46)	0.040	1.21	(1.01-1.44)	0.043	1.17	(1.00-1.37)	0.052
Transitioning from low childhood to increasing adolescent class[**]												
Schizophrenia PRS	1.04	(0.81-1.34)	0.758	1.13	(0.87-1.48)	0.349	1.12	(0.83-1.51)	0.466	1.06	(0.82-1.37)	0.668
Chronic victimisation	2.59	(1.48-4.53)	0.001	2.54	(1.26-5.11)	0.009	1.90	(0.90-4.00)	0.093	2.53	(1.44-4.45)	0.001

IPW= inverse probability weighting. [*]Low as the reference class, covariates predicting childhood and adolescent class [**]Covariates predicting victimisation and adolescent class

SF1. Associations for schizophrenia polygenic risk using a range of p-value thresholds from the discovery sample
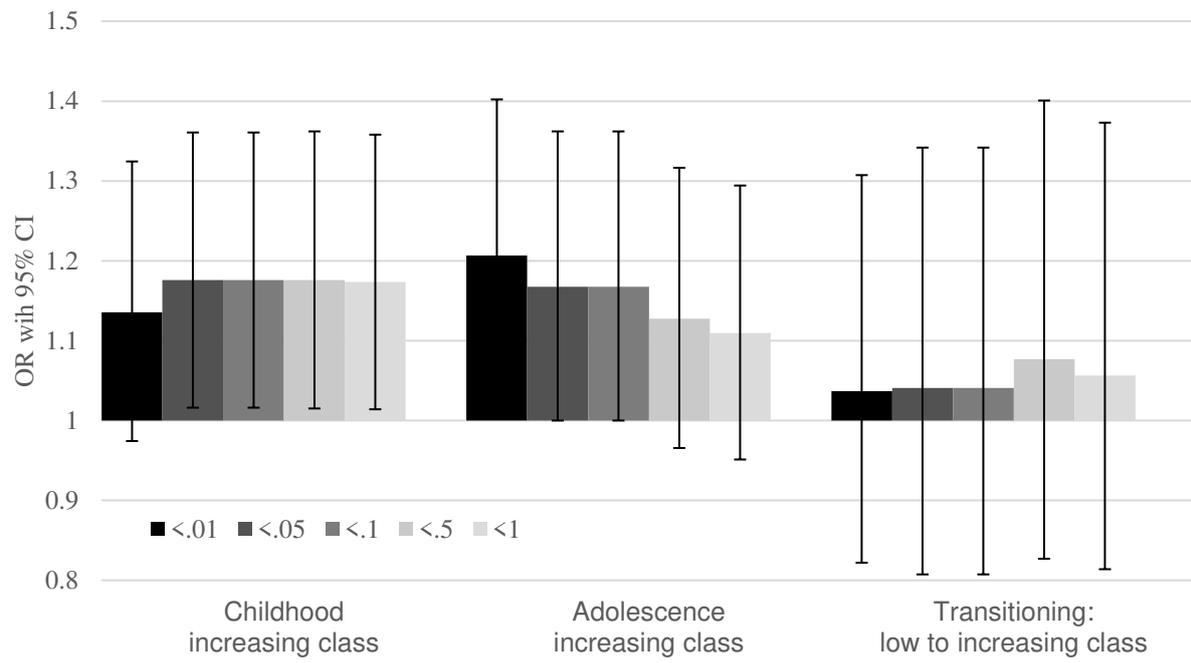
SF2. Participation rates and missing data

Data available

Childhood EP data
(at least 2 time points)
N=8425

Adolescent EP data
(at least 2 time points)
N=7018

Growth mixture models

Childhood & adolescent
EP data
N=6146

Genetic data
N=4585

Victimisation data
N=5073

Genetic & victimisation
data
N=3988

Main sample
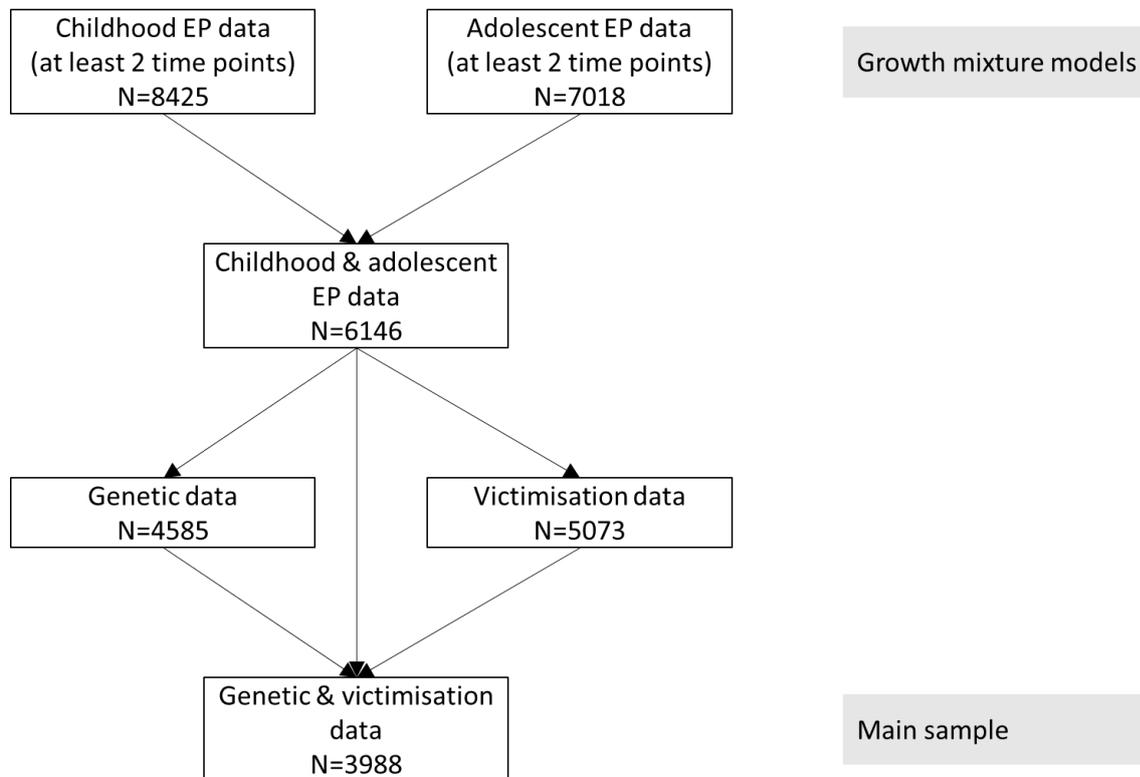
EP=emotional problems

SF3: The probabilities of transitioning from each of the childhood trajectory classes to each of the adolescent classes