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Polygenic risks for joint developmental trajectories of internalizing and externalizing problems: findings from the ALSPAC cohort

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Background: Joint developmental trajectories of internalizing and externalizing problems show considerable heterogeneity; however, this can be parsed into a small number of meaningful subgroups. Doing so offered insights into risk factors that lead to different patterns of internalizing/externalizing trajectories. However, despite both domains of problems showing strong heritability, no study has yet considered genetic risks as predictors of joint internalizing/externalizing problem trajectories. **Methods:** Using parallel process latent class growth analysis, we estimated joint developmental trajectories of internalizing and externalizing difficulties assessed across ages 4 to 16 using the Strengths and Difficulties Questionnaire. Multinomial logistic regression was used to evaluate a range of demographic, perinatal, maternal mental health, and child and maternal polygenic predictors of group membership. Participants included 11,049 children taking part in the Avon Longitudinal Study of Parents and Children. Polygenic data were available for 7,127 children and 6,836 mothers. **Results:** A 5-class model was judged optimal: *Unaffected, Moderate Externalizing Symptoms, High Externalizing Symptoms, Moderate Internalizing and Externalizing Symptoms* and *High Internalizing and Externalizing Symptoms*. Male sex, lower maternal age, maternal mental health problems, maternal smoking during pregnancy, higher child polygenic risk scores for ADHD and lower polygenic scores for IQ distinguished affected classes from the unaffected class. **Conclusions:** While affected classes could be relatively well separated from the unaffected class, phenotypic and polygenic predictors were limited in their ability to distinguish between different affected classes. Results thus add to existing evidence that internalizing and externalizing problems have mostly shared risk factors. **Keywords:** Joint mental health trajectories; internalizing; externalizing; polygenic risk; ALSPAC.

Introduction

Developmental mental health trajectories in childhood and adolescence are complex, correlated across disorders and characterized by considerable heterogeneity (Murray, Eisner, Eisner, Nagin, & Ribeaud, 2020; Patalay, Moulton, Goodman, & Ploubidis, 2017). This developmental heterogeneity can be summarized in terms of a small number of developmental subtypes to help illuminate aetiology, mechanisms and consequences of specific patterns of mental health development. This is typically done in relation to one disorder at a time for instance, for conduct problems (e.g. Barker & Maughan, 2009), ADHD (e.g. Riglin et al., 2016) or depression (Rice et al., 2019). Internalizing and externalizing difficulties commonly co-occur, with up to 45% of children and adolescents showing clinical levels of internalizing symptoms also suffering from high levels of externalizing symptoms and vice versa (Patalay et al., 2017). These domains also have correlated developmental trajectories such that children following a particular trajectory of internalizing problems likely follow a similar trajectory for externalizing difficulties (Nivard et al., 2017). Whether such subgroups of joint internalizing and externalizing problems can be identified and differentiated on the basis of genetic and phenotypic risks, such as maternal age or prematurity, is what we test in the current study. This novel approach can illuminate their co-occurrence, providing new insights into when and why internalizing and externalizing problems occur together and in isolation.

Using methods such as parallel process latent class analysis or growth mixture modelling, a few studies have investigated the joint development of internalizing and externalizing difficulties, categorizing them into potentially meaningful subgroups (e.g. Murray, Eisner, et al., 2020; Patalay et al., 2017). Patalay et al. (2017) analysed the joint trajectories of emotional and behavioural problems in 3- to 11-year-old children from the UK Millennium Cohort Study, identifying five distinct classes characterized as 'low symptoms', 'moderate behavioural', 'moderate emotional', 'high emotional and moderate

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behavioural' and 'high behavioural and moderate emotional'. Predictors considered as potential differentiators of subtypes only distinguished well between high and low symptom groups but not between subtypes with similar symptom levels but with different predominant symptoms (i.e. 'high emotional and moderate behavioural' vs 'moderate emotional and high behavioural'). Murray, Eisner, et al. (2020) estimated the joint trajectories of internalizing and externalizing difficulties and ADHD symptoms across ages 7–15, finding that risk factors mostly distinguished unaffected from affected groups but were again limited in their ability to differentiate between affected trajectory groups with different predominant symptoms.

Identifying developmental subtypes of symptom trajectories is only beneficial if these subtypes also represent meaningful clinical groups that, for example, differ in their aetiology and thus might respond differently to treatment. Whereas demographic, perinatal, child dispositional, and family and broader social environmental predictors of joint internalizing/externalizing developmental trajectories have been studied, the role of genetic predisposition to mental health problems has only been indirectly considered through parental history of psychiatric illness. Yet, the heritability for both internalizing and externalizing difficulties is estimated to be above 30% (Nikstat & Riemann, 2020) and for externalizing difficulties as high as 80% (Hicks, Krueger, Iacono, McGue, & Patrick, 2004). The genetic architecture of internalizing and externalizing difficulties is complex with hundreds to thousands of genes contributing to their heritability and individual risk alleles typically only having very small effects. Thus, composite measures, such as polygenic risk scores (PRS), are usually more useful indicators of genetic risk than single genetic risk variants (Ronald, 2020). PRS measure an individual's genetic risk by summing up all trait-associated alleles weighted by association study allele effect size. PRS for mental health disorders and cognitive abilities predict internalizing and externalizing symptoms in clinical as well as general populations (Jansen et al., 2018). To date, only a few studies have considered PRS to disentangle the aetiology of different subtypes of mental health trajectories (Agnew-Blais et al., 2021). Rice et al. (2019) investigated the associations of PRS for major depressive disorder, schizophrenia and ADHD with developmental trajectories of depression, finding that a later-adolescence–onset class was associated with higher PRS for major depressive disorder, whereas an early-adolescence–onset class was associated with higher PRS for schizophrenia and ADHD. Riglin et al. (2016) explored polygenic antecedents of ADHD symptom subtype trajectories in the general population. They found that higher PRS for ADHD distinguished individuals with persistent ADHD symptom trajectories from individuals following other ADHD trajectories. These studies provide initial evidence that PRS might be useful in differentiating subgroups of individuals following distinct mental health trajectories. In addition, PRS for some mental health problems are more strongly related to co-occurring presentation of disorders than problems occurring in isolation; thus, PRS might be particularly relevant in the aetiology of joint trajectories (Hamshere et al., 2013).

The extent to which polygenic scores capture purely genetic effects or whether gene-environment correlations drive the effects identified by PRS (since a child's PRS profile is directly related to their parent's genome) should also be considered. Any direct environmental links from parent to child are likely to be confounded by shared genetics while direct effects of the child's genotype could still be mediated through the parental genome, for instance through parental genetic effects on the intrauterine and rearing environments. This effect of 'genetic nurture' might have effects over and above the transmission of alleles that might be independently associated with certain risks (Taylor & Polderman, 2020). The effect of genetic nurture on children's development has not been widely investigated, but some preliminary evidence suggests that up to 14% of variance in childhood depressive symptoms can be explained through genetic nurture (Cheesman et al., 2020), hence, highlighting the need for also considering parental genetic effects when investigating children's socio-emotional development.

The aims of the current study are twofold: first, using Parallel Process Latent Class Growth Analysis (PP-LCGA), we examine whether joint developmental trajectories of internalizing and externalizing difficulties across childhood and adolescence (ages 4–16) can be classified into meaningful subtypes of symptom trajectories in a large UK-based longitudinal birth cohort ($N = 11{,}049$). Second, we investigate whether a number of candidate predictors differentiate children who belong to an affected class from those who belong to an unaffected class, with a focus on PRS for mental health problems. We included PRS for the child and for the mother, the latter as a measure of genetic nurture. We additionally consider demographic risk factors, perinatal risk factors and maternal mental health as these have previously been shown to differentiate between symptom classes. We include polygenic scores for intelligence and years of schooling as genetic indicators of cognitive abilities.

Methods

Participants

Participants were part of the Avon Longitudinal Study of Parents and Children (ALSPAC), a longitudinal birth cohort study. Pregnant women resident in Avon, UK, with expected dates of delivery 1 April 1991 to 31 December 1992 were invited to take part in the study. The initial number of pregnancies enrolled is 14,541 (for these at least one

questionnaire has been returned or a 'Children in Focus' clinic had been attended by 19/07/99). Of these initial pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age (Boyd et al., 2013; Fraser et al., 2013). The study website contains details of available data through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). For families with multiple births, we only included the oldest child in order to guard against biases due to overlapping genotypes and to allow for the inclusion of as many time points as possible. The current study included all children who had data on the Strengths and Difficulties Questionnaire, the study's outcome measure, at least at one time-point (N = 11,049). Polygenic data were available for 7,127 children and 6,836 mothers.

Ethical considerations

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). For further information, see http://www.bristol.ac.uk/alspac/researchers/research-ethics.

Measures

Internalizing and externalizing difficulties. Data on internalizing and externalizing difficulties were collected when children were median-aged 4, 7, 8, 9, 11, 13 and 16, using parent-reported Strengths and Difficulties Questionnaires (SDQ) (Goodman, 1997). The SDQ is a behavioural screening tool measuring children's socio-emotional development in five domains of psychosocial functioning: prosocial behaviour, emotional problems, peer problems, conduct problems and hyperactivity/inattention. Each domain is assessed using five items scored on a 3-point Likert scale ('not true', 'somewhat true', 'certainly true'). Internalizing difficulties are calculated by summing up responses to peer and emotional problems (range 0–20), whereas externalizing difficulties are calculated as the sum score of conduct problems and hyperactivity/inattention items (range 0–20). Higher scores represent more difficulties. Psychometric analyses of the SDQ have found support for structural, discriminative and convergent validity (Kersten et al., 2016) as well as configural, metric and scalar gender and longitudinal invariance over ages 5–14 (Murray, Speyer, et al., 2020). The SDQ has been shown to have good predictive validity for psychiatric disorders (Goodman, Renfrew, & Mullick, 2000).

Phenotypic predictors. Phenotypic predictors included *child's sex, maternal age at birth, maternal education, area-based deprivation, prematurity, maternal prenatal smoking, ever breastfed, maternal prenatal depression, maternal postnatal depression* and *maternal history of psychiatric illness*. For details regarding assessment and coding of phenotypic predictors, see Appendix S1.

Polygenic predictors. Polygenic risk scores (PRS) were calculated for the following mental health problems: *Autism Spectrum Disorder* (ASD), *Attention Deficit and Hyperactivity Disorder* (ADHD), *Conduct Disorder, Anxiety Disorder, Major Depressive Disorder* (MDD) and *Schizophrenia*. In addition, polygenic scores (PS) for *Intelligence* (IQ) and *Years of Schooling* were included as genetic indicators of cognitive abilities. PRS were calculated for mothers and children (insufficient genotyped fathers were available). For details regarding the calculation of PRS, the discovery samples that PRS were based on and selected p-value thresholds for each of the included PRS, see Appendix S2.

Statistical analysis

Parallel process latent class growth analysis. To identify meaningful subtypes of joint externalizing and internalizing difficulties trajectories, a Parallel Process Latent Class Growth Analysis (PP-LCGA) was fitted using Mplus 8.5 (Muthén & Muthén, 2018). PP-LCGA estimates latent classes based on growth factors from parallel estimated growth curves. In contrast to growth mixture modelling, LCGA does not assume that these classes represent 'true' subtypes but rather assumes that these subtypes are a convenient summary of a continuous distribution and therefore do not allow for within class variation. This is reflected in the model by fixing factor variances, and by extension, covariances to zero (Nagin & Odgers, 2010). Growth for internalizing and externalizing difficulties was defined by intercepts and linear and quadratic slopes since previous research has found that children and adolescents' mental health trajectories follow a curvilinear trend (Murray, Eisner, et al., 2020). Models with one to eight classes were estimated and compared using Lo-Mendell-Rubin (LMR) tests, Akaike information criterion (AIC), Bayesian information criterion (BIC), sample size adjusted BIC (saBIC), model entropy and smallest class size. To select the optimal number of classes, the LMR test was used as the main selection criterion with other criteria reported to provide supplementary information to help arbitrate if the LMR test yielded ambiguous results. The LMR test quantifies whether a k-class model performs better than a $k-1$ class model and was assessed at $\alpha < .001$. Lower values on AIC, BIC and saBIC indicate better model fit and higher model entropy values indicate better distinguishability of classes (though the latter is not recommended for use in model selection; Henson, Reise, & Kim, 2007). The decision to stop at eight classes was made a priori to ensure that smaller classes would have large enough sample sizes to allow for further analysis. Models were fit using a robust maximum likelihood estimator with full information maximum likelihood estimation thus used to handle missing data (Enders, 2001).

Prediction of class membership. Upon selection of the optimal latent class model, following the three-step approach which accounts for class membership uncertainty (Asparouhov & Muthén, 2014), multiple multinomial logistic regression with the largest group as reference group was used to examine the associations between class membership and all candidate predictors at once. The analysis was adjusted for the first five principal components of ancestry. Missing predictor data were dealt with using multiple imputation (n = 20) with chained equations following the 'H0' approach which, using a Bayes estimator and incorporates the main analysis model in the imputation model. Since a substantial number of children did not have complete data for child and maternal polygenic (risk) scores, a sensitivity analysis with only children with complete polygenic data was carried out for the prediction step (N = 5,008).

Results

Parallel process latent class growth analysis

Results of the PP-LCGA showed that a 5-class model best described parallel trajectories of internalizing and externalizing difficulties. The LMR test indicated that a 5-class model was significantly better than a 4-class model while adding a 6th class did not

improve model fit. Classes were reasonably well separated (entropy = 0.773), hence, allowing for further analyses. For model fit indices of all estimated models and classification probabilities as well as growth parameters for the different classes in the 5-class model, see Table S1–S3. As visualized in Figure 1, the chosen model included the following classes: *Unaffected* (40.6%), *Moderate Externalizing Symptoms* (29.8%), *High Externalizing Symptoms* (11.4%), *Moderate Internalizing and Externalizing Symptoms* (13.3%) and *High Internalizing and Externalizing Symptoms* (4.86%).

Prediction of class membership

Full results of the multinomial logistic regression of class membership for phenotypic and polygenic predictors with the *Unaffected* class as reference group summarized in Figure 2 and presented in the Table S4. Sex was a strong predictor, with children in the *High Internalizing and Externalizing Symptoms*, the *Moderate Externalizing Symptoms* and the *High Externalizing Symptoms* classes being more likely to be male compared to the *Unaffected* class. Lower maternal age was also found to increase the chance of falling into the *High Internalizing and Externalizing Symptoms*, the *Moderate Externalizing Symptoms* and the *High Externalizing Symptoms* classes, whereas living in a more deprived area was only associated with a higher likelihood of being in the *High Internalizing and Externalizing Symptoms* class. Perinatal factors did not distinguish well between classes with only maternal smoking during pregnancy being a significant class membership predictor. In particular, children born to mothers who smoked during pregnancy were more likely to be in the *High Internalizing and Externalizing Symptoms*, the *High Externalizing Symptoms* and the *Moderate Externalizing Symptoms* classes. Compared to the *Unaffected* class, children in all other classes were more likely to have a mother who suffered from pre- or postnatal depression. Having a mother with a history of psychiatric illness further increased the chances of being in the *High Internalizing and Externalizing Symptoms*, the *Moderate Externalizing and Internalizing Symptoms* and the *High Externalizing Symptoms* classes. Higher PRS for ADHD and Schizophrenia as well as lower PS for IQ were found to increase the likelihood of being in the *High Internalizing and Externalizing Symptoms* class. Higher PRS for ADHD as well as lower PS for IQ and years of schooling, increased the chances of being in the *Moderate Externalizing Symptoms* and the *High Externalizing Symptoms* classes. Maternal PRS were not associated with class membership. Since it is possible that some of the included phenotypic risk factors, such as breastfeeding or maternal mental health problems, lie on the pathway from maternal

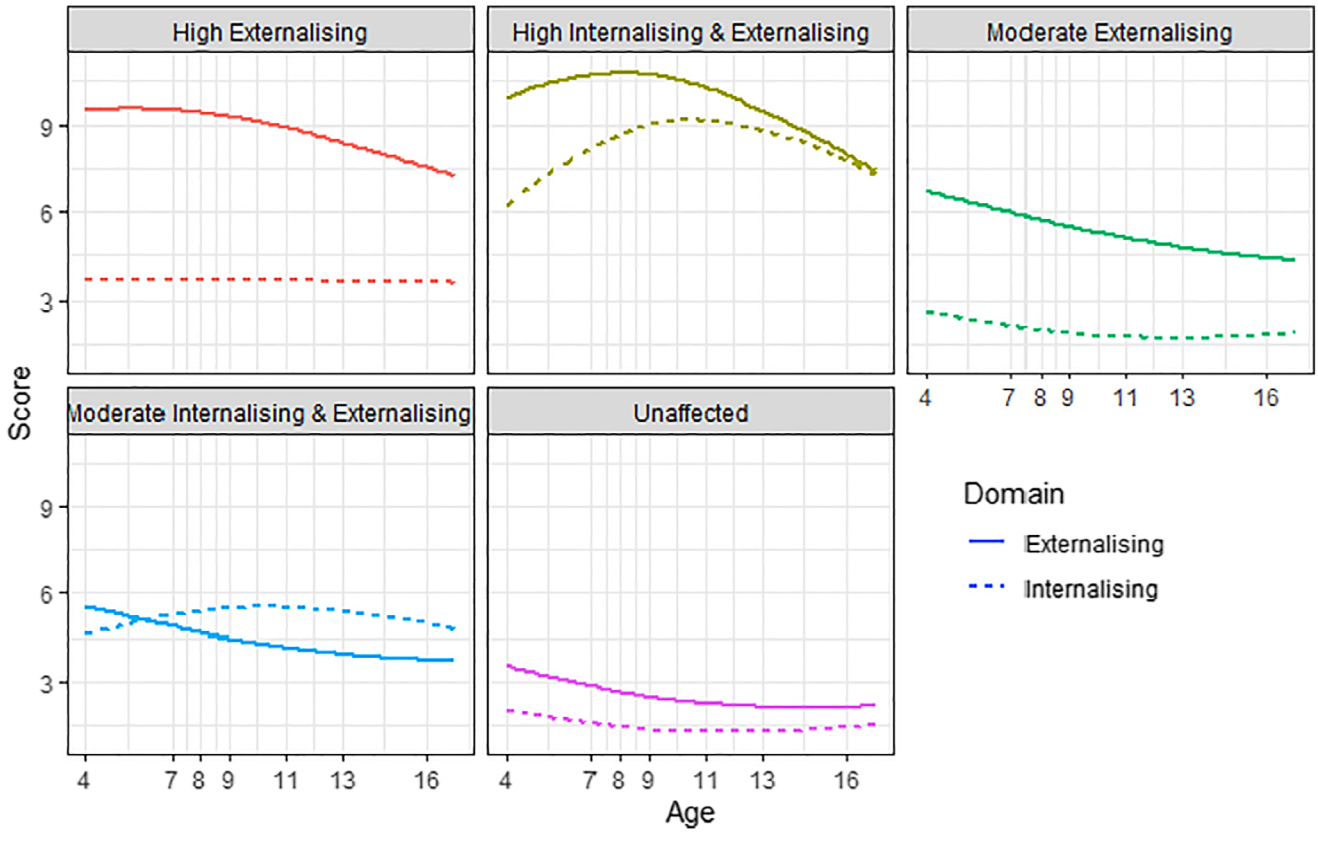

Figure 1 Trajectories of Internalizing and Externalizing Difficulties for the selected 5-class model

PRS to children's internalizing and externalizing problems, we additionally estimated a model that did not include any environmental risk factors. This model still indicated that maternal PRS were not associated with class membership (see Table S5), thus making it unlikely that there could be a potential mediation pathway from maternal PRS through environmental risk factors.

The multinomial regression model was also fit with the *High Internalizing and Externalizing Symptoms* class and the *High Externalizing Symptoms class* as the reference group in order to investigate whether any of the candidate predictors separated the most affected classes from the other affected classes (see Table S4). In these comparisons, worse maternal mental health emerged as the strongest indicator of class membership, increasing the likelihood of belonging to the *High Internalizing and Externalizing Symptoms* class. The sensitivity analysis only including children with complete polygenic data yielded very similar results to the main analysis (see Table S6).

Discussion

Parallel-process latent class growth analysis indicated that internalizing and externalizing trajectories across childhood and adolescence can be summarized in terms of five distinct groups: *Unaffected, Moderate Externalizing Symptoms*, *High Externalizing Symptoms*, *Moderate Internalizing and Externalizing Symptoms* and *High Internalizing and Externalizing Symptoms*; with most children *Unaffected* (40.6%). A number of predictors differentiated membership in all other groups compared to the unaffected group, including male sex, lower

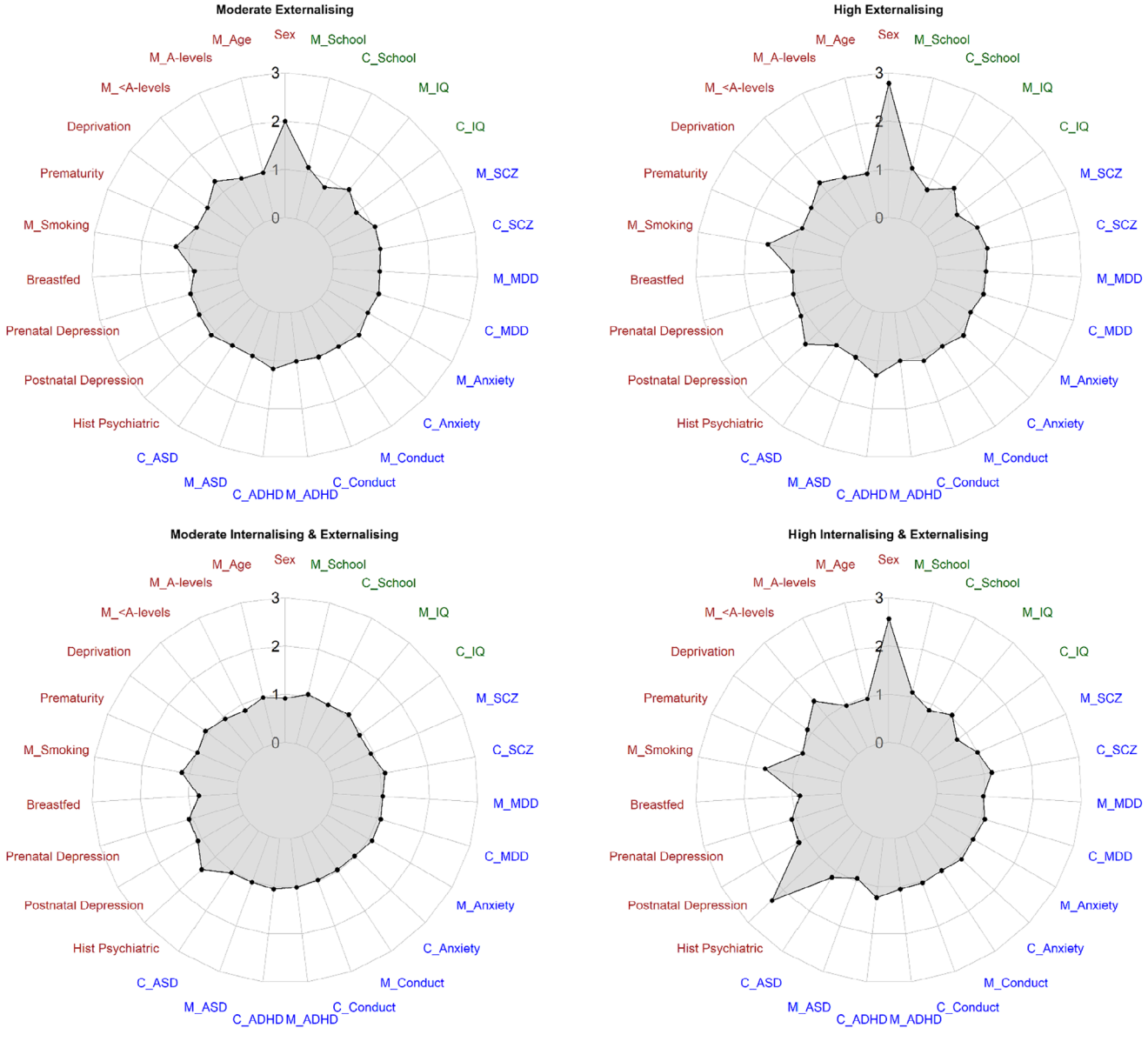

Figure 2 Predictor profiles for all classes with the *Unaffected* class as reference group. Estimates represent odds ratio. C = child, M = maternal. Risk factors in red represent phenotypic factors, risk factors in green represent polygenic scores for cognitive abilities and risk factors in blue represent polygenic risk scores for mental health problems

maternal age, maternal mental health problems, maternal smoking during pregnancy, higher polygenic risk scores for ADHD as well as lower polygenic scores for IQ, while pure externalizing trajectories were further differentiated from the unaffected class through lower polygenic scores for years of schooling. Maternal mental health problems emerged as the strongest distinguishing factors between the most affected co-occurring issues class (*High Internalizing and Externalizing Symptoms*) and the other classes. Genetic nurture, via mothers, did not predict class membership.

The joint trajectories were largely characterized by steady levels of internalizing difficulties and slightly decreasing levels of externalizing difficulties during adolescence. Two co-occurring issues trajectories emerged, one with moderate symptom levels of internalizing and externalizing problems and one with high symptom levels in both domains. Internalizing symptoms in the co-occurring issues trajectory classes were characterized by a slight increase in symptoms before adolescence. This increase is in line with research showing that the median age of onset for internalizing disorders such as anxiety is around age 11 (Kessler et al., 2005). We identified two pure externalizing difficulties trajectories, one at moderate levels and one at high levels, which were not present in previous analyses taking similar approaches. Patalay et al. (2017) who investigated the joint trajectories of emotional and behavioural difficulties in a similar UK-based population, found that externalizing difficulties were always accompanied by internalizing difficulties, either at higher or lower severity but never at the same severity. We found that internalizing and externalizing problems either occurred at approximately the same level of severity, or externalizing difficulties occurred in isolation. Murray, Eisner, et al. (2020) did not identify a pure externalizing group and also found a pure internalizing trajectory group, but like us, they did identify trajectories that were characterized by similar levels of both externalizing and internalizing difficulties in Swiss youths. Our study covered a wider age range of 4–16 years, whereas Patalay et al. only investigated trajectories from ages 3 to 11, and Murray et al. included ages 7–15. This will have affected our trajectory parameters and, thus, the identification of classes; further research is needed to replicate our findings in a similar age group.

Examining whether individuals in the affected classes had a different set of risk profiles than individuals in the unaffected class, our findings of phenotypic predictors were in line with existing literature (Patalay et al., 2017). Sex, maternal age, maternal smoking during pregnancy and maternal mental health problems were all found to be relatively strong distinguishing factors. We further found that some child polygenic scores distinguished between trajectory groups. In particular, higher PRS for ADHD and as well as lower PS for IQ emerged as a distinguishing factor between affected classes and the unaffected class. The two co-occurring issues trajectories were characterized by a similar set of risk factors but were distinguished by the severity of these risk factors. While children in both co-occurring issues classes had lower PS for IQ compared to the unaffected class, lower PS for IQ also made it more likely to be in the high co-occurring issues class compared to the moderate co-occurring issues symptom class. This pattern was also true for younger maternal age and maternal mental health problems. Comparing the pure externalizing trajectories with the co-occurring issues trajectories no strong distinguishing factors emerged, with only PRS for schizophrenia significantly distinguishing between the high co-occurring issues and the moderate externalizing symptoms class. This is in line with previous literature hypothesizing that psychotic disorders are the most severe manifestation of a general risk for psychopathology (Stochl et al., 2015). However, both pure externalizing trajectories were characterized by lower PS for years of schooling compared to the unaffected class, suggesting that genetic factors underlying noncognitive education-related traits such as self-efficacy or conscientiousness may be particularly important in relation to the development of externalizing difficulties.

While some of the PRS and PS distinguished between different trajectory groups, overall our findings indicated that, similarly to phenotypic risks, genetic risks mainly separate affected from unaffected classes, thus supporting the hypothesis that most mental health difficulties share common aetiological factors (Caspi & Moffitt, 2018). Several recent studies have found evidence in line with this 'p-factor' model of psychopathology with many phenotypic risk factors for specific mental health problems having been shown to be significantly associated with the p-factor (Deutz et al., 2020). There is also evidence for a p-factor at the genetic level, with most mental health disorders having been found to share genetic risks (Brikell et al., 2020). Hence, genes involved in mental health disorders potentially operate through pleiotropic mechanisms, consequently enhancing the risk for developing any or multiple mental health problems rather than one specific disorder. This is in line with the generalist genes hypothesis, which suggests that there is a general genetic risk for all mental health disorders with environmental factors determining specific manifestations (Marceau & Neiderhiser, 2020). However, the environmental risk factors considered in the current study did not differentiate trajectories well either; thus, future studies into which factors might distinguish trajectories are needed, including tests of interactions between polygenic scores and environmental factors.

That PRS for ADHD emerged as a distinguishing factor between affected and unaffected trajectories is

also in line with previous research that has consistently identified ADHD PRS to be associated with internalizing and externalizing problems (Brikell et al., 2020), whereas evidence for association of PRS of other mental health problems with internalizing and externalizing problems has so far been more mixed (Riglin et al., 2020). Interestingly, while polygenic scores for IQ differentiated all affected classes from the unaffected class, years of schooling only distinguished the pure externalizing trajectories from the unaffected class. This is consistent with previous research finding stronger links for an association of polygenic scores for educational attainment with externalizing problems than with internalizing problems (Ensink et al., 2020). One potential explanation for this finding is that, in the pure externalizing symptoms class, externalizing behaviours could be more of an overt reaction to struggles in keeping up with school, caused by differences in traits that have been associated with staying in school such as conscientiousness, rather than the result of a more general genetic liability to mental health problems that manifests itself in multiple domains. This is in line with findings that academic underachievement often precedes externalizing problems (Zimmermann, Schütte, Taskinen, & Köller, 2013). Finally, we did not identify any significant effects of maternal polygenic scores; thus, we found no evidence for an effect of genetic nurture on joint developmental trajectories of internalizing and externalizing problems. It could, however, be that this effect is of a magnitude such that larger samples are needed to detect any effects; hence, future larger studies need to be conducted to confirm these null findings ideally using Bayesian approaches.

Strengths and limitations

The key strength of this study is that we were able to investigate the role of genetic risks for joint developmental trajectories of internalizing and externalizing difficulties in addition to phenotypic risks over the whole period of childhood and adolescence in a well-powered sample. We could also explore the role of genetic nurture in joint developmental trajectories. With regard to limitations, ALSPAC is a longitudinal cohort with non-random attrition; children with more behavioural difficulties are more likely to drop-out (Wolke et al., 2009), which likely underestimates our effect sizes. Due to insufficient numbers, we could not examine the effect of paternal non-transmitted alleles and hence had a weaker measure of genetic nurture (Bates et al., 2018). Also, some of the PRS were based on GWAS with little power as they only included limited numbers of cases (particularly Conduct and Anxiety Disorder). These PRS may not be as informative as, for example, PRS for ADHD which were based on a better-powered GWAS. In addition, the ADHD GWAS was based on a sample that included a large number of children while most of the other GWAS were based on adult samples. Considering that the importance of genetic effects may vary across development, this may also explain why ADHD PRS were a particularly strong predictor of children's internalizing and externalizing problems. Replications of this study using PRS solely based on well-powered GWAS that ideally also include children would therefore be highly valuable and could potentially lead to different results. Further, PRS-threshold selection was based on class membership prediction within the same dataset rather than on predictions within an independent dataset. This may have inflated results of the multinomial logistic regression (Choi, Mak, & O'Reilly, 2020). Finally, LCGA requires modelling choices (e.g. stopping criterion for number of classes, estimation of within-group variances) that can affect class estimation and therefore class identification.

Conclusion

Affected subgroups from joint trajectory modelling of internalizing and externalizing difficulties could be separated from the unaffected class by polygenic risk scores for ADHD and polygenic scores for IQ, and by various phenotypic predictors. However, these risk factors were limited in differentiating specific affected trajectory types. Future work focusing on the interaction of genetic and environmental predictors, or on a larger range of predictors may uncover aetiological factors related to these developmental trajectories.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Phenotypic predictors.
Appendix S2. Polygenic predictors.
Table S1. Model fit indices for the parallel process-latent class growth analysis.
Table S2. Classification probabilities for the selected 5-class model.
Table S3. Growth parameters for the selected 5-class model.
Table S4. Regression parameters with different classes as reference group.
Table S5. Regression parameters for analysis excluding environmental risk factors with the *Unaffected* class as reference group.
Table S6. Regression parameters with the *Unaffected* class as reference group (using complete cases on child and maternal polygenic scores, $N = 5008$).

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Key points

- Previous research indicated that internalizing and externalizing developmental trajectories can be summarized into distinct subgroups, giving unique insights into risk factors that lead to different patterns of internalizing/externalizing trajectories.
- Even though heritability estimates are very high, the role of genetic predisposition in joint internalizing/externalizing trajectories has not been explored yet.
- Our findings indicated that higher child polygenic risk scores for ADHD, lower polygenic scores for IQ and a number of phenotypic predictors distinguished affected from the unaffected group, but were limited in distinguishing between different affected groups.
- Importantly, our results show that developmental patterns of mental health difficulties mostly share common genetic and other etiological factors.
- Future work needs to focus on gene-by-environment interaction and a broader range of predictors.

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