The Development of Mental Health Difficulties in Young People with and without Developmental Language Disorder: A Gene-Environment Interplay Study Using Polygenic Scores

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Abstract

Purpose: Young people with developmental language disorder (DLD) have poorer mental health than those without DLD. However, not all young people with DLD are equally affected; some have more mental health difficulties than others. What explains these differences remains unclear.

Method: Data from a community cohort study, the Avon Longitudinal Study of Parents and Children, was analysed to investigate genetic and environmental influences on the development of mental health difficulties at five time points from childhood (7 years) to adolescence (16 years) in 6,387 young people (8.7% with DLD). Regression and latent class models were fitted to the data.

Results: Polygenic scores, indices of genetic risk, for common psychiatric disorders (major depressive disorder, anxiety disorder, and attention deficit hyperactivity disorder) predicted mental health difficulties in both groups (with and without DLD). The presence of DLD, in some instances, amplified mental health difficulties for those with high genetic risk for common psychiatric disorders. Sub-groups of children with similar developmental trajectories of mental health difficulties were identified. Young people with DLD were more likely than those without DLD to follow mental health sub-groups characterised by consistently high levels of difficulties during development. Polygenic scores, socioeconomic status, and the early home environment distinguished sub-groups with low mental health difficulties from those characterised by high levels of difficulties, but these effects did not differ based on DLD status.

Conclusion. These findings suggest that, for the most part, both genetic and environmental risk affect the development of mental health difficulties in a cumulative way for young people with DLD (and those without). Some analysis did, however, suggest that genetic risk for common

psychiatric disorders might manifest more strongly in those with DLD compared to those without DLD.

Introduction

Background

Symptoms of psychiatric disorders are common during childhood and adolescence. Indeed, almost half of all lifetime psychiatric disorders have their onset before the age of 14 years (Kessler et al., 2005). Children with developmental language disorder (DLD) are disproportionately affected, with prevalence rates approximately double that of children with typically developing language (Yew & O'Kearney, 2013). Such adverse outcomes are not, however, inevitable. Some children with DLD have very few mental health difficulties whilst others have persistent problems throughout childhood and into adolescence. What explains these individual differences in the developmental trajectories of mental health remains unclear. In the current study, we sought to address this gap in knowledge by investigating some genetic and environmental influences on the developmental trajectories of mental health difficulties from childhood to adolescence in young people with and without DLD.

Developmental Language Disorder (DLD)

DLD is a common childhood onset condition affecting between 5-8% of school aged children (Norbury et al., 2016). It is characterised by impairments in understanding (receptive) and using (expressive) oral language relative to others of a similar age. Children with DLD do not have sensory impairments (e.g., deafness), they are not autistic, and they do not necessarily have low IQ. The term DLD is a relatively new term introduced as a result of a wide-ranging

consensus exercise (Bishop et al., 2017). Previously, the term 'specific language impairment (SLI)' was used, and still is by some researchers (e.g., Rice et al., 2020), to describe children with language impairments whose non-verbal IQ is in the normal range (Tomblin et al., 1997). Therefore, all children with specific language impairment can be referred to as having DLD but not all children with DLD can be referred to as having specific language impairment. Evidence from genetic (Bishop, 1994) and behavioural studies (Norbury et al., 2016) suggests that specific language impairment is not necessarily distinct from non-specific language impairment. Therefore, in the current study, we use the term DLD to refer to previous studies of specific language impairment and DLD.

Mental Health Difficulties

Mental health difficulties can be thought of as symptoms of psychiatric disorders. These are defined as a health condition involving changes in thinking, emotion, or behaviour, which is associated with impairments in everyday functioning (American Psychiatric Association, 2013). Experiencing symptoms of psychiatric disorders is common. To some extent, it is a normal part of being human. Such symptoms become problematic when they are persistent and lead to impaired functioning in everyday activities. During childhood and adolescence mental health difficulties commonly manifest as emotional (e.g., symptoms of depression and anxiety) and behavioural problems (e.g., inattention and hyperactivity). It has been suggested that they can be explained by a shared overarching factor (i.e., the psychopathology factor, Patalay et al., 2018), meaning that they may be different outward manifestations of a common underlying tendency for psychological distress (Sallis et al., 2019). This is also supported by the fact that there is considerable co-occurrence of different types of difficulties; for example, experiencing one type of difficulty (e.g., emotional problems) during childhood is a risk factor for experiencing a

different type of difficulty (e.g., behavioural problems) later in childhood and adolescence (Finsaas et al., 2018), which is known as heterotypic continuity. Therefore, mental health difficulties refer to a broad range of symptoms with many co-occurrences of different types.

Developmental Language Disorder and Mental Health

As a group, children and adolescents with DLD are more likely to have poorer mental health compared to those without DLD. This includes diagnosable psychiatric disorders (Cantwell & Baker, 1987) as well as symptoms of psychiatric disorders (Yew & O'Kearney, 2013). Such mental health difficulties often begin in childhood (Eadie et al., 2018), continue into adolescence (Botting et al., 2016b) and persist into young adulthood (Botting et al., 2016a). There is, however, considerable variability in the mental health difficulties experienced by young people with DLD. In a clinical sample of young people with DLD, who were followed from age 7 to 14 years, nine in ten experienced some emotional problems between childhood and adolescence (Conti-Ramsden et al., 2019) and two in three experienced conduct problems or symptoms of hyperactivity (Pickles et al., 2016). There is also considerable co-occurrence of different types of difficulties. Half of young people with DLD who had conduct problems also had attention problems/hyperactivity (Pickles et al., 2016) and two in five who had emotional problems also experienced peer problems (Conti-Ramsden et al., 2019). The timing of difficulties was also varied; some experienced difficulties that began in childhood but were resolved by adolescence, others had adolescent-onset difficulties and others had persistent difficulties through childhood and adolescence (Conti-Ramsden et al., 2019; Pickles et al., 2016). These findings suggest that there are considerable within-group differences in a) whether young people with DLD experience mental health difficulties, b) which combination of difficulties they experience, and c) the timing and onset of mental health difficulties.

Theoretically, young people with DLD might be more likely to experience mental health difficulties compared to those without DLD for a number of reasons. First, it may be that having DLD leads to mental health difficulties because oral language ability is important to recognise and label emotions (Hobson et al., 2019). Children with DLD may be impaired in their ability to recognise emotions (Griffiths et al., 2020) and therefore may not recognise mental health difficulties and, subsequently, may not have the necessary oral language skills to seek out support. Even if they do recognise their mental health difficulties and seek support, commonly used therapies for mental health difficulties require the use of oral language (e.g., cognitive behavioural therapy) and may not be effective. Therefore, having DLD may lead to higher initial prevalence and longer term persistence of mental health difficulties.

Research on individual differences in the trajectories of mental health difficulties in children and adolescents with DLD is limited. Often past research has focused on clinical samples, which is problematic because such populations are prone to referral bias. This means that only those with the most severe needs, or with a specific language profile, are identified and receive support (Bishop & Hayiou-Thomas, 2008). DLD often goes unidentified and so many young people with DLD do not have a formal diagnosis. Some studies of DLD have included general population samples, but these have typically focussed on one type of mental health difficulty (e.g., St Clair et al., 2019). Additionally, past work has not considered how trajectories of mental health difficulties during childhood and adolescence compare between those with and without DLD (see St Clair et al., 2019 for an exception). This does not allow for the investigation of whether the developmental trajectories of mental health difficulties differ between groups of young people with and without DLD and whether support needs to be targeted differently at young people with DLD. We addressed these limitations in the present study by investigating a

range of mental health difficulties in young people with and without DLD from a community sample who were followed from childhood to adolescence.

Individual Differences in Mental Health of Young People with DLD

What predicts within-group differences in mental health difficulties for children and adolescents with DLD remains unclear. Much of the previous work has focussed on social and behavioural correlates of mental health difficulties. For example, children and adolescents with DLD who are bullied, experience peer problems, or adopt maladaptive emotional regulation strategies are at increased risk of experiencing emotional difficulties (Forrest et al., 2018; Kilpatrick et al., 2019; St Clair et al., 2019). Conversely, those with higher levels of prosociality (helping, caring, or sharing behaviours), play, and emotional awareness tend to experience fewer emotional and behavioural difficulties (Bakopoulou & Dockrell, 2016; Samson et al., 2020; Toseeb et al., 2020; Toseeb et al., 2017; Toseeb & St Clair, 2020). The early home environment and socioeconomic status are also important factors. Specifically, children with DLD who experience a positive early language and communication environment in the first two years of life or come from high socioeconomic households experience fewer behavioural difficulties in middle childhood (Toseeb et al., 2020). Whilst informative, the focus on social and behavioural correlates, without consideration of genetics, is problematic because mental health difficulties are influenced by the interplay of genetic and environmental factors (Allegrini et al., 2020).

Behavioural Genetics

Behavioural genetic methods can be used to investigate genetic and environmental influences on mental health difficulties. Such methods include twin, family, and molecular genetic designs. Twin studies take advantage of the fact that monozygotic twins share 100% of their DNA whilst dizygotic twins share approximately 50% of theirs and allow for the distinction

between shared and non-shared environment. Therefore, if pairs of monozygotic twins are more similar to each other in their levels of mental health difficulties than dizygotic twins, it suggests that such difficulties are influenced by genetic factors. As would be expected, mental health difficulties during childhood are found to be substantially influenced by genetic factors and these influences grow stronger through development (Allegrini et al., 2020). Whilst twin studies are informative in terms of estimating the proportion of variance explained by genetic and environmental factors, they do not identify which genetic variants or specific environmental exposures influence difficulties and how these interact with each other.

To identify more specific genetic risk, molecular genetic studies investigate the effects of common genetic variants, such as single nucleotide polymorphisms (SNPs), on outcomes. Genetic effects are complex, involving many interacting SNPs, each with a small effect size. These are commonly investigated using genome-wide association studies (GWAS), which test for associations between SNPs and outcomes of interest. The additive effect of all available SNPs on an outcome of interest can be captured in a single polygenic score. This provides an index of the genetic propensity for a given outcome, consisting of only those variants found to be associated with the outcome. Therefore, twin studies can be used to estimate the population-based proportion of variance in mental health difficulties attributable to genetic and environmental influences, and polygenic methods can be used to estimate an individual-level index of genetic propensity, which can be used to further investigate gene-environment interplay in the links between mental health difficulties and DLD.

There has been rapid progress in the development of polygenic scores for common psychiatric disorders. Samples of hundreds of thousands of individuals have been used to identify associated SNPs which have in turn been used to develop polygenic scores for common

psychiatric and neurodevelopmental disorders such as major depressive disorder, anxiety, and attention hyperactivity disorder (Demontis et al., 2019; Howard et al., 2019; Purves et al., 2020). A key finding from psychiatric genetics research is that genetic influences are general rather than specific. That is, polygenic scores for one mental health condition are likely to be predictive of other mental health conditions too, given that common psychiatric disorders share genetic aetiology (Brikell et al., 2020). Such general effects can also go beyond clinical boundaries; seemingly unrelated conditions seem to share genetic aetiology (Hagenaars et al., 2016). Therefore, there has been considerable progress in linking specific genetic influences to mental health difficulties.

Genetic Influences on Mental Health Difficulties in DLD

The research on genetic influences on mental health difficulties in children and adolescents with DLD is lacking; we are aware of only three studies. The first adopted a molecular genetics approach and found that a polygenic score for expressive language ability predicted non-specific mental health difficulties (Newbury et al., 2019). This was an encouraging preliminary finding, demonstrating a shared genetic aetiology between language and mental health difficulties but was limited by its focus on a handful of candidate genetic variants, which, in a recent genome-wide study, were not found to be strong risk loci (Eising et al., 2021). The second study used a family design to determine the extent to which language and emotional difficulties can be explained by common genetic and/or shared environmental influences (Helland et al., 2020). This study found that common familial influences explained most of the co-occurrence between language and emotional difficulties. However, the design of the study meant that genetic effects could not be distinguished from shared environmental effects (e.g. aspects of the shared home environment). In the third study, the twin method was used to

investigate genetic influences on mental health difficulties in children with DLD (Toseeb et al., 2022). These researchers found that DLD and emotional problems share a common genetic aetiology, that is, genetic influences on DLD overlap with those on emotional problems. They also found that genetic influences on emotional problems were stronger in children with DLD compared to those without DLD, suggesting that having DLD may exacerbate genetic risk for mental health difficulties. What remains unclear is how genetic risk for mental health difficulties in children with DLD is moderated by (varies with) specific environmental influences.

The Current Study

In the current study, we addressed these gaps in knowledge by combining data on genetic and environmental factors to investigate developmental trajectories of mental health difficulties in young people with and without DLD. Specifically, we were interested in investigating whether DLD moderates the effect of genetic liability for mental health difficulties (Research Question 1, RQ1). Evidence from a twin study suggests that the presence of DLD exacerbates genetic risk for mental health difficulties (Toseeb et al., 2022). Therefore, we expected DLD to moderate the association between mental health difficulties and the genetic liability for common psychiatric disorders, as indexed by polygenic scores. We also sought to map the developmental trajectories of mental health difficulties from childhood to adolescence in young people with and without DLD (Research Question 2, RQ2). Previous work in clinical samples of young people with DLD suggests considerable heterogeneity in the developmental trajectories of mental health difficulties from childhood to adolescence (Conti-Ramsden et al., 2019; Pickles et al., 2016). Similarly, in general population samples, there is considerable heterogeneity in development (St Clair et al., 2019). Therefore, in the current investigation, we expected there to be sub-groups of young people with differing patterns of development from childhood to adolescence. We also

expected that those with DLD would be disproportionately represented in sub-groups with the persistently high mental health difficulties. Finally, we investigated the extent to which genetic and specific environmental effects impact on the developmental trajectories of mental health difficulties identified in RQ2 (Research Question 3, RQ3). We know that the power of polygenic scores to predict mental health difficulties is low compared to environmental risk factors (e.g., socioeconomic status and home environment). Therefore, we expected that after controlling for environmental risk factors, the power of polygenic scores to predict individual differences in developmental trajectories of mental health differences would be attenuated.

Method

Ethical Approvals

The study was a secondary analysis of existing data from the Avon Longitudinal Study of Parents and Children (ALSPAC). Ethical approval for data collection was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees (Health Authority). 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). Full details of ethics processes can be accessed on the ALSPAC webpage (http://www.bristol.ac.uk/alspac/researchers/research-ethics/). No further ethical approval was sought for the secondary analysis of existing data from the ALSPAC cohort; this is in line with the recommendations of Education Ethics Committee at the University of York.

Sample

Pregnant women resident in Avon, UK with expected dates of delivery between 1st April 1991 and 31st December 1992 were invited to take part in the study. The initial number of

pregnancies enrolled was 14,541, of which 13,988 children were alive at 1 year of age. Parents and children provided biological samples, questionnaire data and took part in direct assessments. Full details of the cohort are reported elsewhere (Boyd et al., 2013; Fraser et al., 2013). The study website contains details of all the data available and provides a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

Inclusion and Exclusion Criteria

From the overall ALSPAC sample, individuals were excluded if they met one of the following criteria: did not attend a speech and language assessment at age 8 years; performance IQ below 60; was autistic or had hearing loss; not possible to determine DLD status; or mental health data not available for at least one time point. For families who had multiple children in the study cohort, the second child was excluded from the analysis to control for within-family confounding. This resulted in a maximum sample size of 6,387 children (50% boys); the actual sample size varied depending on the available data for each set of analysis.

Identifying Children Developmental Language Disorder

DLD status was determined when the child was aged 8-9 years using data from a battery of language assessments. We replicated an approach adopted by previous work in the ALSPAC sample (Newbury et al., 2019; Scerri et al., 2011; Toseeb et al., 2020). A child was identified as having DLD if they met at least two of the following four criteria:

a) Pragmatic language more than 1 SD below standardised mean. When the child was 9 years old, parents completed the Children's Communication Checklist (Bishop, 1998). Responses to questions on five subscales were summed to create an overall pragmatic language score. The subscales were: inappropriate initiation, coherence, stereotyped

conversation, use of conversational context, and conversational rapport. Scores ranged

from 86 to 162. Higher scores indicated better pragmatic language.

b) Nonword repetition more than 1 SD below the standardised mean. An adapted version of

the Nonword Repetition Test (Gathercole et al., 1994) was used to obtain a measure of

nonword repetition when the child was 8 years old. The child was instructed to listen and

repeat out loud each of the three-, four-, and five-syllable nonwords presented. Responses

were binary (0 = *incorrect*, 1 = *correct*) and summed to create a score ranging from 0 to

12, with higher scores indicating better nonword memory.

c) Receptive language more than 1 SD below the standardised mean. The Weschler

Objective Language Dimensions (Rust, 1996) was used to measure receptive language.

Only one of the two subsets was used in the analysis reported here. The child was shown

a picture and listened to a paragraph about the picture. They then answered questions

about what they had heard. The child was asked 16 questions. Responses were coded on a

binary scale (0 = *incorrect*, 1 = *correct*), yielding a summed score of between 0 and 16.

Higher scores indicated better receptive language.

d) Positive response to "child has ever had speech/language therapy". When the child was 8

years old, parents were asked whether their child has ever had speech and language

therapy (0=*no,* 1=*yes).*

A total of 557 children met the criteria for DLD, translating to a prevalence estimate of

8.7%, which is broadly in line with expectations (Norbury et al., 2016).

Genotyping and Quality control

Children within the ALSPAC sample were genotyped using the Illumina HumanHap550

quad chip at the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory

Corporation of America, Burlington, NC, US. Standard quality control was conducted on the raw genotype data excluding individuals based on gender mismatches; minimal or excessive heterozygosity; disproportionate levels of individual missingness (>3%) and insufficient sample replication (IBD < 0.8). Multidimensional scaling analysis was conducted to assess population stratification and compared with HapMap II (release 22) European descent (CEU), Han Chinese, Japanese and Yoruba reference populations. All individuals with non-European ancestry were removed.

Single nucleotide polymorphisms (SNPs) with minor allele frequencies (MAF) of < 1%, a call rate of < 95% or those that violated Hardy-Weinberg equilibrium ($P < 5\text{x}10\text{-}7$) were removed. Cryptic relatedness was assessed as proportion of identity by descent (IBD > 0.1). Related individuals that passed all other quality control thresholds were retained during subsequent phasing and imputation.

Imputation was performed using Impute v3 and the HRC 1.1 imputation reference panel. Further quality control was then applied excluding any imputed SNPs with MAF <0.01, imputation INFO scores <0.8, call rates of <95%, and any violation from Hardy-Weinberg equilibrium ($P < 5\text{x}10\text{-}7$). Initially, there were 38,898,739 SNPs. Following quality control processes, a total of 6,774,469 genotyped and imputed SNPs remained for analysis.

Measures

Mental Health Difficulties

The parent-reported Strengths and Difficulties questionnaire (SDQ: Goodman, 1997) was used to screen for mental health difficulties when the child was 7, 9, 11, 13, and 16 years old. In line with the general psychopathology factor (Patalay et al., 2018), we considered symptoms of emotional and behavioural disorders as mental health difficulties. Three subscales of the SDQ

were used: emotional problems (e.g., "often unhappy, downhearted"); conduct problems (e.g., "often has temper tantrums or hot tempers"); and hyperactivity (e.g., "constantly fidgeting or squirming"). Parents responded on a three-point scale (0=*not true,*1=*somewhat true, 2=certainly true*). Each subscale consisted of five questions so sum scores ranged from 0 to 10, with higher scores representing more difficulties. The SDQ has good reliability and is invariant between ages 7 and 16 years in the ALSPAC sample (Speyer et al., 2022). Therefore, it is suitable for the investigation of developmental change in mental health difficulties from childhood to adolescence.

Early Language and Communication Environment

Parents were asked to report on their child's early language and communication environment (ELCE) when the child was 18 and 24 months old. We used a measure described in previous work (Roulstone et al., 2011; Toseeb et al., 2020). Although the measure does not directly assess language and communication in the home, it reflects the kinds of activities that might be helpful for the development of language and communication skills. There were five sub-scales: mother–child direct teaching (e.g., mum teaches songs), mother–child activities (e.g., frequency mum has physical play with child), other–child interactions (e.g., child sung to), resources (e.g., number of toy vehicles child has at home) and other activities (e.g., frequency child taken to park). Scores on the five sub-scales were standardised and then summed to create a single variable with higher scores indicating a more positive ELCE.

Socioeconomic Status

A composite measure of socioeconomic status was used in line with previous work (Roulstone et al., 2011; Toseeb et al., 2020). The measures were administered at 8 and 32 weeks of gestation. Parents were asked about paternal occupation (0 = *manual*, 1 = *non-manual*),

maternal education (0 = *lower than A Level*, 1 = *A Level or higher*), house tenure (0 = *not owned*, 1 = *owned*), home overcrowding (0 = *more than one person per room*, 1 = *less than one person per room*), and financial difficulties (0 = *financial difficulties reported*, 1 = *no financial difficulties reported*). These binary variables were then summed to create a socioeconomic status score ranging from 0 to 5. Higher scores indicated higher socioeconomic status.

Polygenic Scores (PGSs)

Three sets of PGSs were created in PRSice 2.0 (Choi & O'Reilly, 2019) using GWAS summary statistics: major depressive disorder (MDD, Howard et al., 2019); anxiety disorder (AD, Purves et al., 2020), and attention deficit hyperactivity disorder (ADHD, Demontis et al., 2019). PGSs were only created for individuals with genetic data available and for whom DLD status could be determined (N=5,176). All summary statistics were subject to standard quality control procedures. Principal components were included as covariates when creating all PGSs to control for population stratification and variants with imputation INFO scores < 0.8 or minor allele frequency (MAF) <0.01 were excluded.

Statistical Analysis

Preregistration

The analyses reported here were pre-registered on the open science framework (https://osf.io/8u4tv/). Any deviations from this analysis plan are clearly highlighted in the relevant part of this statistical analysis section.

Research Question 1

To determine whether the presence of DLD moderates genetic risk for mental health difficulties, 12 multi-level regression models were fitted to the data from participants for whom PGSs were generated (N=5,176). See supplementary materials for further details on how PGS

thresholds were determined. Given that PGSs best predict risk at the extreme ends of the distribution, the PGS variables were converted into tertiles and used to derive a binary PGS variable comprising the extreme categories of the PGS tertiles (0=*lowest tertile for PGS*, 1=*highest tertile for PGS*). In all models, the fixed effects were the linear effect of time (age 7, 9, 11, 13, 16 years), sex (0=*female*, 1=*male*), DLD (0=*without DLD*, 1= *with DLD*), binary PGS (varied dependent on model), and a PGSxDLD interaction. Anonymised participant number and linear time were included as random effects. For models 1-4, the outcome variable was emotional problems and the PGSs were MDD (model 1), AD (model 2), ADHD (model 3), and the combined PGS (model 4). To generate the combined PGS, the three PGSs were standardised and summed, which is in line with previous work (Schoeler et al., 2019). These models were then repeated for conduct problems (models 5-8) and hyperactivity (models 9-12) as separate outcomes.

Research Question 2

Latent class growth curve models, using Poisson regression, were fitted to SDQ subscales in Mplus 7.0 (Muthén & Muthén, 2012). This was done to identify potential sub-groups within the sample who share similar patterns of emotional problems, conduct problems, and hyperactivity (in separate models). To maximise power, the models were fitted to the full sample (N=6,387) even if genetic data was not available. The fit of two to six groups was assessed using the Akaike Information Criterion (AIC) and the sample size adjusted Bayesian Information Criterion (BIC). Better fitting models were indicated by lower values. Entropy measures were also used to assess how accurately the children were classified into the chosen model, with higher values (range 0–1) indicating better classification. The Lo-Mendel Rubin (LRT) adjusted likelihood test identified the best model, with non-significance indicating the previous model as

the most appropriate fit for the data. Interpretability was a key driving factor in choosing the optimal number of classes to carry forward to the next set of analyses. Given the achieved sample size of children with DLD, models where the smallest class was smaller than 10% of the sample were not carried forward as this would mean the subsequent analysis would be underpowered.

Research Question 3

To investigate whether genetic and environmental indices of risk differentiate developmental trajectories of mental health difficulties identified in the above analysis, and whether these effects are different in those with and without DLD, a number of multinomial logistic regression models were fitted to the data. Again, these analyses only included individuals with genetic data (N=5,176). We deviated from the planned analyses because it would mean running models with four main effects, a covariate, and three two-way interactions. Given the achieved sample size for the DLD group and the size of the sub-groups, this would mean potentially running underpowered and over-fitted models. Therefore, we only fitted models with the combined PGSs (to maximise power) with four main effects: DLD, socioeconomic status (SES), early language and communication environment (ELCE), combined PGS; a co-variate: sex, and one interaction effect per model. For models 1-3, the outcome variable was emotional problems sub-groups and the interaction effect was ELCE x combined PGS (model 1), SES x combined PGS (model 2), and DLD x combined PGS (model 3). This was then repeated for conduct problems sub-groups (models 4-6) and hyperactivity sub-groups (models 7-9) as separate outcomes.

Results

Descriptive statistics for the sample are shown in Table 1.

[Table 1 at back]

DLD as a Moderator of Genetic Risk for Mental Health Difficulties

To investigate whether DLD moderates genetic risk for mental health difficulties (Research Question 1), a series of multi-level regression models were fitted. As shown in Table 2, boys scored higher on conduct problems and hyperactivity and girls scored higher on emotional problems (effects of sex). Additionally, there was a significant decrease in emotional problems, conduct problems, and hyperactivity as children got older (effects of time). The confidence intervals were, however, close to zero for the emotional problems models. As would be expected, young people with DLD consistently fared worse on emotional problems, conduct problems, and hyperactivity compared to those without DLD (effect of DLD).

[Table 2 at back]

Young people (irrespective of DLD status) in the highest MDD, AD, ADHD, and combined PGSs tertile consistently fared worse for emotional problems, conduct problems, and hyperactivity compared those in the lowest tertile (effect of PGS). The only exception was model 3; young people in the highest tertile for ADHD PGS did not have more emotional problems compared to those in the lowest ADHD PGS tertile, although, again, the confidence intervals were close to zero. That is, those with the highest genetic risk for mental health difficulties (the top 1/3) had more mental health difficulties compared to those with the lowest genetic risk for mental health difficulties (the bottom 1/3). For both emotional and conduct problems, the strongest PGS was the combined PGS, whereas for hyperactivity, the strongest PGS was the ADHD PGS.

To determine whether DLD moderates genetic risk for mental health difficulties, interaction effects between PGSs and DLD were tested (again, see Table 2). Despite not reaching statistical significance, the coefficients for the interactions between the MDD PGS and DLD were

consistently the largest across all outcomes (except conduct problems whereby the combined PGS was the strongest). The confidence intervals (models 1, 5, and 9) were wide and included zero suggesting that there may have been interaction effects that we were underpowered to detect. There was only one significant interaction effect (model 8), which again had wide confidence intervals but did not cross zero. As shown in Figure 1, the difference in conduct problems between those with and without DLD was greater in the high combined PGS group (β=.47, 95%CI=.33,.61, p=<.001) compared to the low combined PGS group (β=.25, 95%CI=.11,.39, p=<.001). That is, the magnitude of the group difference in conduct problems (i.e., in those with and without DLD) increases as genetic risk increases. This suggests young people with highest genetic risk for mental health difficulties are more susceptible to the effects of DLD on conduct problems compared to those with the lowest risk or that the risk for conduct problems is highest among young people with DLD who also have a high genetic risk for mental health difficulties. Therefore, DLD moderates the effect of genetic risk for mental health difficulties on conduct problems, in those at greatest genetic risk.

[Figure 1 at back]

This set of analyses (i.e., the models in Table 2) was repeated with PGS as a continuous variable rather than binary variable. This approach maximised sample size (by including the middle 1/3) and therefore increased power. These additional models (Table S2 and Figures S7-S9 Supplementary Materials) produced broadly similar results in terms of the pattern of main effects and the interaction effects.

Heterogeneity in the Development of Mental Health Difficulties

To investigate whether there are sub-groups of young people who share similar patterns of emotional problems, conduct problems, and hyperactivity from childhood to adolescence

(Research Question 2), a series of latent class growth curve models were fitted (see Table 3 and Tables S3-S5 in Supplementary Materials). The chosen sub-groups for each of the type of difficulties is shown in Figure 2 and the descriptive statistics at each time point are shown in Table 3. For emotional problems, the four-group solution was chosen. The groups were characterised by emotional problems that were stable low (37%), decreasing within normal range (29%), increasing within normal range (16%), and consistently raised (18%) from childhood to adolescence. For both conduct problems and hyperactivity, the three-group solutions were chosen. For all conduct and hyperactivity sub-groups, problems remained stable from childhood to adolescence. The groups were stable low (conduct problems 13%, hyperactivity 20%), stable within normal range (conduct problems 53%, hyperactivity 51%), and consistently raised (conduct problems 13%, hyperactivity 20%). Therefore, there was heterogeneity in the development of emotional problems, conduct problems, and hyperactivity from childhood to adolescence.

[Table 3 at back]

[Figure 2 at back]

As an additional set of exploratory analyses, we tested whether it is the same children who were in the consistently raised or stable low sub-groups and whether these proportions differed based on DLD status. The proportion of young people with DLD who experienced consistently raised problems across all three types of mental health difficulty was higher compared to those without DLD (9% vs 3%, odds ratio 3.08, 95% CI 2.21, 4.30). Conversely, the proportion of young people with DLD who experienced stable low problems across all three types of mental health difficulty was lower compared to those without DLD (4% vs 10%, odds ratio .34, 95% CI .22, .54). This suggests that proportion of young people with DLD who concurrently experience multiple types of mental health difficulties is much higher than young people without DLD.

Genetic and Environmental Influences on the Trajectories of Mental Health Difficulties

Finally, we investigated genetic and environment influences in relation to the sub-groups of emotional problems, conduct problems, and hyperactivity during childhood and adolescence in young people with and without DLD (Research Question 3).

Environmental and Child-Level Predictors

Across all the different types of difficulties (emotional, conduct, and hyperactivity), ELCE and SES distinguished those in the stable low groups from those in the consistently raised groups (Tables 4-6). When comparing the stable low groups to the other groups, ELCE and SES also distinguished those in the stable within normal range groups for conduct problems and hyperactivity. For emotional problems, the effects of ELCE and SES were inconsistent when comparing the stable low sub-group to the decreasing and increasing sub-groups.

Young people with DLD were disproportionately represented in the sub-groups characterised by higher levels of difficulties. For emotional problems, they were more likely to be in the increasing within the normal range and the consistently raised groups compared to the stable low groups. For conduct problems and hyperactivity, young people with DLD were more likely than those without DLD to be in the stable within normal range and consistently raised groups compared to the stable low groups.

Polygenic Scores

The combined PGS, the only one that was tested, distinguished the stable low sub-groups from other groups for a range of difficulties (Tables 4-6). For all types of difficulties (emotional problems, conduct problems, and hyperactivity), young people in the stable low groups had lower PGSs compared to those in the consistently high groups. For conduct problems and hyperactivity, those in the stable low groups also had lower PGSs compared to those in the stable within the

normal range groups. For emotional problems, there was a trend that PGS were higher in the decreasing and increasing groups, the relative risk ratios were above 1, but the confidence intervals were wide suggesting that the analysis was potentially underpowered. None of the interaction effects in any of the models were significant. This suggests that PGSs predict trajectories of mental health difficulties in young people with and without DLD even after controlling for the early home environment and socioeconomic status but the analyses were likely underpowered to detect gene-environment interactions.

[Table 4 at back]

[Table 5 at back]

[Table 6 at back]

This set of analyses (i.e., the models in Tables 4-6) was repeated with PGS as a continuous variable rather than binary variable to maximise sample size and increase power. These additional models (Table S6-S8) produced very similar results in terms of the pattern of main effects and the interaction effects.

Discussion

In this study, we investigated genetic and environmental influences on the development of mental health difficulties from childhood to adolescence in a community sample of young people with and without DLD. We found that a) polygenic scores for common psychiatric disorders predict mental health difficulties during childhood and adolescence in young people with and without DLD, b) to some extent, the presence of DLD may amplify mental health difficulties for those with high genetic risk for common psychiatric disorders, c) young people with DLD are more likely than those without DLD to follow mental health trajectories characterised by consistently high levels of difficulties during development, and d) early

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environmental influences (i.e., early language and communication environment and socioeconomic status) are important for the developmental trajectories of mental health difficulties for young people with and without DLD, even after controlling for genetic effects. Our findings make a unique contribution to the literature as we demonstrate genetic and environmental influences on mental health difficulties from childhood to adolescence appear to be similar for young people with and without DLD, for the most part. We present additional evidence on how the presence of DLD may interact with genetic risk for psychiatric disorders to explain heterogeneity in the development of mental health difficulties during childhood and adolescence. In the subsequent sections, we discuss these findings with reference to previous research and their implications for young people with DLD.

Genetic Influences on Mental Health Difficulties in DLD

To the best of our knowledge, this was the first study to demonstrate the role of common genetic variants in explaining individual differences in mental health difficulties in young people with and without DLD. We extended previous work in two ways. First, we used a polygenic approach to assess the effect of genetic variants associated with specific psychiatric disorders in young people with DLD. This builds on previous work by Toseeb et al. (2022) who used the twin method to demonstrate heritability of mental health difficulties in young people with and without DLD. The twin method can demonstrate *whether* genetic influences confer susceptibility for mental health difficulties at the level of the population whereas the molecular genetics approach, like the one used here, can help identify those with greatest genetic risk. Second, we build on previous work by Newbury et al. (2019), who only focussed on a handful of candidate genes. Here, we used genome-wide data to demonstrate genetic influences on mental health difficulties. This is important because mental health difficulties are complex traits, meaning that

they are influenced by common variants across the genome rather than a specific gene (Demontis et al., 2019; Howard et al., 2019; Purves et al., 2020). Therefore, our findings demonstrate that common genetic variants, which have previously been used to explain psychiatric disorders in the general population, similarly explain risk for mental health difficulties in young people with and without DLD.

We found indicative evidence for potential differential genetic effects for young people with DLD. Whilst, on the whole, young people with DLD experienced more mental health difficulties compared to those without DLD, the magnitude of risk was greatest for young people with DLD who also had the highest genetic risk for psychiatric disorders. That is, having high genetic risk for psychiatric disorders was more detrimental for young people with DLD than it was for those without DLD. Additionally, whilst only one of these interaction effects reached the conventional level of "statistical significance" (conduct problems), the interactions with the genetic risk for depression (MDD PGS) were of a similar magnitude, but not statistically significant. Thus, a high genetic risk for depression may differentially increase the likelihood of mental health difficulties (emotional and conduct problems and hyperactivity in the present study) among young people with DLD compared to young people without DLD and/or young people with DLD who have a low genetic risk for depression. Previous work provides confidence in our speculative interpretation of the findings. Toseeb et al. (2022) also found that DLD may exacerbate genetic risk for mental health difficulties (specifically emotional problems). They used a different sample and a different method of analysis, but similarly, their analysis was likely underpowered. If replicated in sufficiently powered samples (e.g., thousands rather than hundreds of cases), together these findings suggest that DLD may moderate genetic

risk for psychiatric disorders on mental health difficulties, more so in those at the highest level of genetic risk.

Heterogeneity in the Development of Mental Health Difficulties

Our work demonstrates that there is considerable heterogeneity in the development of mental health difficulties during childhood and adolescence for young people with DLD. Young people with DLD are more likely to follow developmental trajectories characterised by higher levels of mental health difficulties compared to those without DLD. These findings build on previous work in three ways. First, previous work investigating such heterogeneity has focussed on clinical samples of young people with DLD (e.g., Conti-Ramsden et al., 2019; Pickles et al., 2016). This is problematic because many young people with DLD go unnoticed and so the focus on clinically referred sample only represents those with a specific profile of DLD; for example those with speech production difficulties (Zhang & Tomblin, 2000). Our focus on a community sample demonstrates that similar levels of heterogeneity exist outside of clinical referred DLD samples. Second, previous work on the heterogeneity of mental health difficulties in DLD populations has focussed on one type of mental health difficulty (e.g., St Clair et al., 2019). Our findings demonstrate that there is considerable heterogeneity in the development of various types of mental health difficulties in young people with DLD. Third, we demonstrate that, whilst heterogeneity in the developmental trajectories of mental health difficulties is also common for young people without DLD, those with DLD are more likely to follow developmental trajectories characterised by higher levels and more persistent difficulties. These findings suggest that from childhood to adolescence, young people with DLD are disproportionately affected by a range of mental health difficulties compared to those without DLD.

A positive message from our analysis is that, during childhood and adolescence, mental health difficulties are not inevitable for young people with DLD. Whilst this has been shown in clinical samples, we demonstrate this for the first time in a community sample. Specifically, approximately two in five young people with DLD (43%) *do not* experience mental health difficulties that are likely to be of clinical concern (i.e., all those that were not in the consistently raised sub-group for at least one area of mental health difficulty). The majority of these experienced conduct problems and hyperactivity while a minority experienced emotional problems. Whilst the proportion of those *not* affected by likely clinical levels of mental health difficulties is much higher in those without DLD (67%), it emphasises the message that, whilst mental health difficulties are an area of concern for children and adolescents with DLD, they are not inevitable.

Predictors of Developmental Trajectories of Mental Health Difficulties

We attempted to explain this heterogeneity in the development of mental health difficulties using indices of genetic and early environmental risk, and interplay between them, in both young people with and without DLD. We found that genetic risk for psychiatric disorders, socioeconomic status, and the early language and communication environment *all* distinguished trajectories of mental health difficulties. As expected, those with high genetic risk, low socioeconomic status, poor early language and communication environment, or DLD were disproportionately represented in trajectories characterised by high levels of difficulties (i.e., sub-groups other than "stable low"). Surprisingly, we found no evidence of gene-environment interplay between genetic risk and either socioeconomic status, early language and communication environment, or DLD on trajectories of mental health difficulties from childhood to adolescence. Our work demonstrates that indices of genetic risk for common psychiatric

disorders, socioeconomic status, and the early language and communication environment can be used to distinguish those with low levels of mental health difficulties (i.e., the stable low groups) from those with high levels of mental health difficulties (i.e., consistently raised) and that these effects are not different for young people with and without DLD. This suggests that, if causal, *both* genetic *and* environmental factors make unique contributions to the onset and development of mental health difficulties in young people with and without DLD.

These findings potentially have implications for the provision of support for young people with and without DLD. If causality can be established, they suggest that early interventions aimed at promoting a positive early language and communication environment, and boosting socioeconomic status, are likely to have positive knock-on effects on the mental health of all children and adolescents, irrespective of whether they have DLD. An additional point to consider is that the effect of a positive early language and communication environment is independent of socioeconomic status. Therefore, even in low resource settings, interventions aimed at boosting the early language and communication environment are likely to be beneficial for subsequent mental health difficulties.

Strengths and Limitations

Our study has a number of strengths and limitations. The strengths were that we had a large sample of young people with DLD, which allowed us to comprehensively investigate a number of predictors in the statistical models, although admittedly some of the analyses are likely to have been underpowered. As a field, we need to do more to harmonise genetic datasets and pool samples of young people with DLD (e.g., GenLang Consortium; genlang.org) to increase power through larger sample sizes while maintaining specificity of the phenotype. We also made use of a community sample, which meant that we were not limited to clinically

referred samples. Additionally, we made use of genome-wide genetic data for the first time in a sample of young people with DLD in relation to mental health difficulties. A number of limitations should be borne in mind when interpreting the findings. Firstly, whilst our study employed a longitudinal design, we tested associations and not causal pathways. Therefore, in order to conclude that a positive early language and communication environment and high socioeconomic status *leads* to positive mental health outcomes, further work needs to be done using causal statistical methods and causal designs. Secondly, the measure of mental health difficulties was parent-reported. Whilst parents are good at reporting some symptoms of mental health difficulties (e.g., conduct problems and hyperactivity) as these manifest externally, they may not be accurate at reporting other types of symptoms, which usually manifest internally (i.e., feelings of low mood). Additionally, parent-reports of the child's mental health difficulties might be influenced by their own levels of mental health difficulties. For example, parents with high levels of mental health difficulties might report more difficulties in their child compared to parents with low mental health difficulties or indeed might be better equipped to recognise difficulties in their child. Future work should triangulate measures of mental health difficulties from multiple sources such as self-report, parent-report, and direct assessments of the child by trained researchers, and also control for parents' mental health.

Conclusions

In this community-based sample, we found that there are considerable individual differences in the developmental trajectories of emotional problems, conduct problems, and hyperactivity in young people with and without DLD. Those with DLD were more likely than those without DLD to follow trajectories characterised by higher levels of difficulties but these were not inevitable. A substantial minority of children and adolescents with DLD did not

experience raised difficulties that were likely to be of clinical concern. Such individual differences were explained by both genetic and environmental influences. That is, children with low genetic risk for common psychiatric disorders, those who experienced positive early language and communication environment, or came from high socioeconomic households were more likely to follow developmental trajectories characterised by low levels of mental health difficulties. Additionally, whilst polygenic scores for common psychiatric disorders predicted mental health difficulties in young people with and without DLD, we found some evidence that DLD differentially exacerbates genetic risk, specifically in those with the highest levels of genetic risk. These findings emphasise the need to control for genetic effects in DLD research but also underline the importance of the early home environment for subsequent mental health difficulties in young people with and without DLD.

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Data Availability Statement

The datasets generated analysed for the current study are available by to researchers who follow

the Data Access Policy (http://www.bristol.ac.uk/alspac/researchers/access/).

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Supplementary Material

The supplementary material contains details of exploratory analysis used to determine the p-value threshold for the polygenic scores. Details of the model fit statistics for RQ2 and analysis with continous PGS scores for RQ1 and RQ3.

Table 1. *Descriptive Statistics at Each Time Point (Raw Scores)*

	Range	Overall		Without DLD		With DLD	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Early Language and Communication Environment	48-116	5,582	98.95 (6.98)	5,099	99.21 (6.75)	483	96.14 (8.56)
Socioeconomic Status	0-5	6,098	3.15 (1.27)	5,564	3.20 (1.25)	534	2.63 (1.32)
Emotional Problems							
Age 7 years	0-9	5,486	1.50 (1.65)	5,009	1.46 (1.62)	477	1.90 (1.93)
Age 9 years	0-10	5,656	1.47 (1.71)	5,152	1.43 (1.68)	504	1.90 (2.00)
Age 11 years	0-10	5,230	1.43 (1.69)	4,784	1.38 (1.66)	446	1.93 (1.91)
Age 13 years	0-10	5,034	1.38 (1.65)	4,604	1.33 (1.62)	430	1.88 (1.94)
Age 16 years	0-10	4,193	1.46 (1.83)	3,861	1.42 (1.81)	332	1.83 (1.99)
Conduct Problems							
Age 7 years	0-10	5,489	1.56 (1.44)	5,013	1.51 (1.42)	476	2.03 (1.55)
Age 9 years	0-10	5,662	1.24 (1.39)	5,155	1.18 (1.33)	507	1.85 (1.72)
Age 11 years	0-10	5,239	1.19 (1.41)	4,791	1.14 (1.37)	448	1.69 (1.72)
Age 13 years	0-10	5,031	1.21 (1.40)	4,601	1.16 (1.35)	430	1.71 (1.78)
Age 16 years	0-9	4,200	1.02 (1.36)	3,869	1.00 (1.33)	331	1.34 (1.61)
Hyperactivity							
Age 7 years	0-10	5,484	3.24 (2.30)	5,009	3.14 (2.25)	475	4.38 (2.51)
Age 9 years	0-10	5,632	2.75 (2.27)	5,130	2.61 (2.19)	502	4.15 (2.58)
Age 11 years	0-10	5,230	2.68 (2.19)	4,787	2.55 (2.11)	443	4.02 (2.54)
Age 13 years	0-10	5,033	2.82 (2.17)	4,605	2.71 (2.11)	428	3.99 (2.45)
Age 16 years	0-10	4,199	2.50 (2.12)	3,868	2.42 (2.07)	331	3.44 (2.40)

M = mean, SD = standard deviation, DLD = developmental language disorder, N = sample size

Table 2. *Multi-level Regression Models Predicting Mental Health Difficulties*

Outcome Variable	Predictor PGS	Covariate Sex β (95% CI)	P	Covariate Time β (95% CI)	P	Main Effect PGS (Binary) β (95% CI)	P	Main Effect DLD β (95% CI)	P	PGS x DLD Interaction β (95% CI)	P
Emotional Problems	Model 1: MDD	.17 (.11,.22)	<.001	-.01 (-.02,.00)	.043	.11 (.06,.16)	<.001	.21 (.08,.34)	.002	.15 (-.03,.34)	.099
	Model 2: AD	.17 (.12,.22)	<.001	-.01 (-.02,.00)	.085	.09 (.04,.15)	.001	.37 (.24,.50)	<.001	-.06 (-.25,.12)	.494
	Model 3: ADHD	.18 (.13,.23)	<.001	-.01 (-.02,.00)	.033	.05 (-.01,.11)	.083	.31 (.17,.45)	<.001	.00 (-.19,.19)	.978
	Model 4: Combined	.19 (.14,.24)	<.001	-.01 (-.02,.00)	.009	.13 (.07,.18)	<.001	.29 (.15,.43)	<.001	.02 (-.17,.21)	.831
Conduct Problems	Mode 5: MDD	-.11 (-.17,-.06)	<.001	-.07 (-.08,-.06)	<.001	.09 (.04,.15)	.001	.26 (.12,.39)	<.001	.18 (-.02,.37)	.071
	Model 6: AD	-.09 (-.15,-.04)	.001	-.07 (-.08,-.06)	<.001	.11 (.05,.17)	<.001	.34 (.20,.48)	<.001	.16 (-.03,.36)	.098
	Model 7: ADHD	-.12 (-.17,-.07)	<.001	-.07 (-.08,-.06)	<.001	.19 (.14,.25)	<.001	.32 (.18,.47)	<.001	-.03 (-.23,.16)	.735
	Model 8: Combined	-.11 (-.16,-.05)	<.001	-.07 (-.08,-.06)	<.001	.17 (.12,.23)	<.001	.26 (.11,.40)	.001	.22 (.02,.41)	.031
Hyper-activity	Model 9: MDD	-.35 (-.40,-.29)	<.001	-.06 (-.07,-.05)	<.001	.06 (.01,.12)	.029	.48 (.34,.62)	<.001	.18 (-.01,.38)	.070
	Model 10: AD	-.34 (-.40,-.29)	<.001	-.05 (-.06,-.05)	<.001	.08 (.02,.14)	.007	.66 (.52,.79)	<.001	-.05 (-.24,.15)	.648
	Model 11: ADHD	-.32 (-.37,-.26)	<.001	-.05 (-.06,-.04)	<.001	.20 (.14,.26)	<.001	.50 (.35,.65)	<.001	.07 (-.12,.27)	.466
	Model 12: Combined	-.36 (-.42,-.31)	<.001	-.05 (-.06,-.04)	<.001	.18 (.12,.23)	<.001	.53 (.39,.68)	<.001	.07 (-.12,.27)	.472

Note. PGS = Polygenic Score, DLD = developmental language disorder, MDD = major depressive disorder, AD = anxiety disorder,

ADHD = attention deficit hyperactivity disorder.

Table 3. *Descriptive Statistics for Sub-Groups of Emotional Problems, Conduct Problems, and Hyperactivity*

	Without DLD N (%)	With DLD N (%)	Range	Age 7 M (SD)	Age 9 M (SD)	Age 11 M (SD)	Age 13 M (SD)	Age 16 M (SD)
Emotional Problems Sub-Groups								
Stable Low	2,219 (38%)	154 (28%)	0-3	.41 (.64)	.27 (.52)	.23 (.48)	.24 (.48)	.32 (.58)
Decreasing within Normal Range	1,701 (29%)	151 (27%)	0-9	2.14 (1.32)	1.91 (1.27)	1.53 (1.18)	1.16 (1.00)	.63 (.71)
Increasing within Normal Range	903 (15%)	90 (16%)	0-10	.73 (.79)	.86 (.87)	1.33 (1.15)	1.67 (1.24)	2.71 (1.39)
Consistently Raised	1,007 (17%)	162 (29%)	0-10	3.47 (1.86)	3.79 (1.88)	3.82 (1.84)	3.72 (1.80)	3.76 (2.16)
Conduct Problems Sub-Groups								
Stable Low	2,049 (35%)	120 (21%)	0-4	.49 (.71)	.20 (.43)	.15 (.37)	.16 (.38)	.24 (.51)
Stable within Normal Range	3,097 (53%)	309 (55%)	0-10	1.77 (1.13)	1.38 (.98)	1.29 (.96)	1.33 (.96)	1.08 (1.05)
Consistently Raised	684 (12%)	128 (23%)	0-10	3.56 (1.55)	3.48 (1.56)	3.65 (1.53)	3.56 (1.61)	3.16 (1.85)
Hyperactivity Sub-Groups								
Stable Low	1,797 (31%)	67 (12%)	0-8	1.22 (1.10)	.72 (.83)	.71 (.78)	.85 (.88)	.88 (1.00)
Stable within Normal Range	2,988 (51%)	254 (46%)	0-10	3.28 (1.59)	2.77 (1.53)	2.64 (1.30)	2.80 (1.32)	2.52 (1.58)
Consistently Raised	1,042 (18%)	236 (42%)	0-10	6.16 (1.93)	5.75 (1.97)	5.82 (1.88)	5.85 (1.78)	5.13 (2.06)

N= number of individuals, M = mean, SD = standard deviation

Table 4. *Genetic and Environmental Influences on Sub-Groups of Emotional Problems*

	Stable Low	Decreasing within Normal Range		Increasing within Normal Range		Consistently Raised	
		RRR (95% CI)	P	RRR (95% CI)	P	RRR (95% CI)	P
Model 1	**Reference**						
ELCE		.98 (.94,1.03)	.469	1.00 (.95, 1.06)	.851	.94(.90, .99)	.017
SES		.86 (.79, .95)	.003	.93 (.83, 1.05)	.251	.78 (.70, .88)	<.001
DLD		1.38 (.98, 1.94)	.068	1.67 (1.12, 2.48)	.012	1.95 (1.35, 2.81)	<.001
Sex		1.28 (1.07, 1.53)	.006	2.15 (1.73, 2.68)	.000	2.19 (1.77, 2.71)	<.001
PGS		1.13 (.95, 1.35)	.180	1.07 (.86, 1.32)	.561	1.34 (1.08, 1.65)	.007
PGSs x ELCE		1.02 (.97, 1.08)	.440	.95 (.89, 1.02)	.139	1.03 (.97, 1.10)	.337
Model 2	**Reference**						
ELCE		1.00 (.97, 1.03)	.820	.98 (.94, 1.01)	.197	.96 (.93, .99)	.017
SES		.83 (.72, .95)	.008	.94 (.80, 1.11)	.466	.75 (.63, .88)	<.001
DLD		1.38 (.98, 1.94)	.069	1.69 (1.13, 2.51)	.010	1.94 (1.35, 2.80)	<.001
Sex		1.28 (1.08, 1.54)	.006	2.15 (1.73, 2.67)	.000	2.20 (1.78, 2.72)	<.001
PGS		1.12 (.94, 1.34)	.207	1.07 (.86, 1.33)	.543	1.32 (1.07, 1.62)	.011
PGSs x SES		1.08 (.90, 1.30)	.418	.99 (.79, 1.24)	.910	1.09 (.88, 1.36)	.428
Model 3	**Reference**						
ELCE		1.00 (.97, 1.03)	.798	.98 (.94, 1.01)	.194	.96 (.93, .99)	.017
SES		.86 (.79, .95)	.003	.93 (.83, 1.05)	.246	.78 (.70, .88)	<.001
DLD		1.68 (1.04, 2.73)	.036	1.77 (1.00, 3.15)	.051	1.90 (1.09, 3.32)	.024
Sex		1.28 (1.07, 1.54)	.006	2.15 (1.73, 2.67)	.000	2.19 (1.77, 2.71)	<.001
PGS		1.17 (.97, 1.41)	.098	1.08 (.86, 1.35)	.519	1.31 (1.05, 1.63)	.016
PGS x DLD		.67 (.34, 1.32)	.251	.91 (.42, 1.98)	.808	1.01 (.49, 2.09)	.977

RRR = relative risk ratio, CI= confidence intervals, ELCE = early language and communication environment, SES = socioeconomic status, PGS = polygenic score, DLD = developmental language

Table 5. *Genetic and Environmental Influences on Sub-Groups of Conduct Problems*

	Stable Low	Stable within Normal Range		Consistently Raised	
		RRR (95% CI)	P	RRR (95% CI)	P
Model 4	**Reference**				
ELCE		.97 (.93, 1.00)	.087	.93 (.88, .99)	.018
SES		.89 (.82, .97)	.007	.70 (.62, .79)	<.001
DLD		1.85 (1.32, 2.60)	<.001	2.76 (1.83, 4.15)	<.001
Sex		.95 (.81, 1.11)	.526	.72 (.57, .92)	.008
PGS		1.40 (1.19, 1.64)	<.001	1.6 (1.26, 2.04)	<.001
PGS x ELCE		.99 (.94, 1.04)	.728	.99 (.92, 1.06)	.752
Model 5	**Reference**				
ELCE		.96 (.94, .99)	.008	.93 (.89, .96)	<.001
SES		.91 (.81, 1.02)	.115	.76 (.63, .91)	.004
DLD		1.85 (1.32, 2.60)	<.001	2.76 (1.83, 4.15)	<.001
Sex		.95 (.81, 1.11)	.517	.72 (.57, .91)	.007
PGS		1.41 (1.20, 1.65)	<.001	1.59 (1.25, 2.03)	<.001
PGS x SES		.95 (.81, 1.13)	.590	.86 (.67, 1.10)	.231
Model 6	**Reference**				
ELCE		.96 (.94, .99)	.008	.93 (.89, .97)	<.001
SES		.89 (.82, .97)	.007	.70 (.62, .79)	<.001
DLD		1.78 (1.13, 2.82)	.014	2.27 (1.24, 4.12)	.007
Sex		.95 (.81, 1.11)	.521	.72 (.57, .92)	.007
PGS		1.39 (1.18, 1.63)	<.001	1.54 (1.19, 1.98)	.001
PGS x DLD		1.10 (.56, 2.17)	.773	1.44 (.63, 3.26)	.386

RRR = relative risk ratio, CI= confidence intervals, ELCE = early language and communication environment, SES = socioeconomic status, PGS = polygenic score, DLD = developmental language disorder

Table 6. *Genetic and Environmental Influences on Sub-Groups of Hyperactivity*

|	Stable Low	Stable within Normal Range		Consistently Raised	
		RRR (95% CI)	P	RRR (95% CI)	P
Model 7	Reference				
ELCE		.94 (.91, .98)	.004	.88 (.84, .93)	<.001
SES		.86 (.78, .94)	.001	.71 (.63, .80)	<.001
DLD		2.25 (1.46, 3.46)	<.001	4.85 (3.08, 7.65)	<.001
Sex		.54 (.45, .64)	<.001	.25 (.20, .32)	<.001
PGS		1.51 (1.27, 1.80)	<.001	1.88 (1.50, 2.35)	<.001
PGS x ELCE		.98 (.92, 1.04)	.476	1.01 (.94, 1.08)	.822
Model 8	Reference				
ELCE		.93 (.91, .96)	<.001	.89 (.86, .92)	<.001
SES		.87 (.77, .99)	.032	.78 (.65, .92)	.004
DLD		2.25 (1.46, 3.47)	<.001	4.85 (3.07, 7.64)	<.001
Sex		.54 (.45, .64)	<.001	.25 (.20, .32)	<.001
PGS		1.52 (1.28, 1.81)	<.001	1.85 (1.47, 2.31)	<.001
PGS x SES		.97 (.81, 1.17)	.756	.85 (.67, 1.08)	.182
Model 9	Reference				
ELCE		.93 (.91, .96)	<.001	.89 (.86, .92)	<.001
SES		.86 (.78, .94)	.001	.71 (.63, .80)	<.001
DLD		3.00 (1.62, 5.54)	<.001	5.16 (2.65, 10.04)	<.001
Sex		.54 (.45, .64)	<.001	.25 (.20, .32)	<.001
PGS		1.55 (1.30, 1.84)	<.001	1.80 (1.43, 2.28)	<.001
PGS x DLD		.55 (.23, 1.31)	.180	.83 (.34, 2.07)	.696

RRR = relative risk ratio, CI= confidence intervals, ELCE = early language and communication environment, SES = socioeconomic status, PGS = polygenic score, DLD = developmental language disorder.

Supplementary Material

Exploratory Analysis

To select the appropriate polygenic scores (PGS) at specific p-value thresholds for inclusion in downstream analysis, exploratory analysis was conducted. This analysis examined associations between polygenic scores for major depressive disorder (MDD), anxiety disorder (AD), attention deficit hyperactivity disorder (ADHD) and emotional problems, conduct problems, and hyperactivity, as well as Developmental Language Disorder (DLD). Initially, associations with difficulties at each of the time points was assessed in separate models and then these associations were tested in multi-level models accounting for clustering based on age. Associations were assessed at several p-value thresholds ranging from 0.01 to 1 using multiple linear regression models (**Figure S1**).

Figure S1. Illustrating associations between (a) AD, (b) MDD, and (c) ADHD polygenic scores and the SDQ subscales (hyperactivity, emotional problems and conduct problems) at eight p-value thresholds (pt) at each of the five timepoints (ages 7,9,11,13,16). Nominally significant findings are indicated with a single asterisk (*), with a double asterisk (**) highlighting a finding that was significant follow multiple testing corrections.
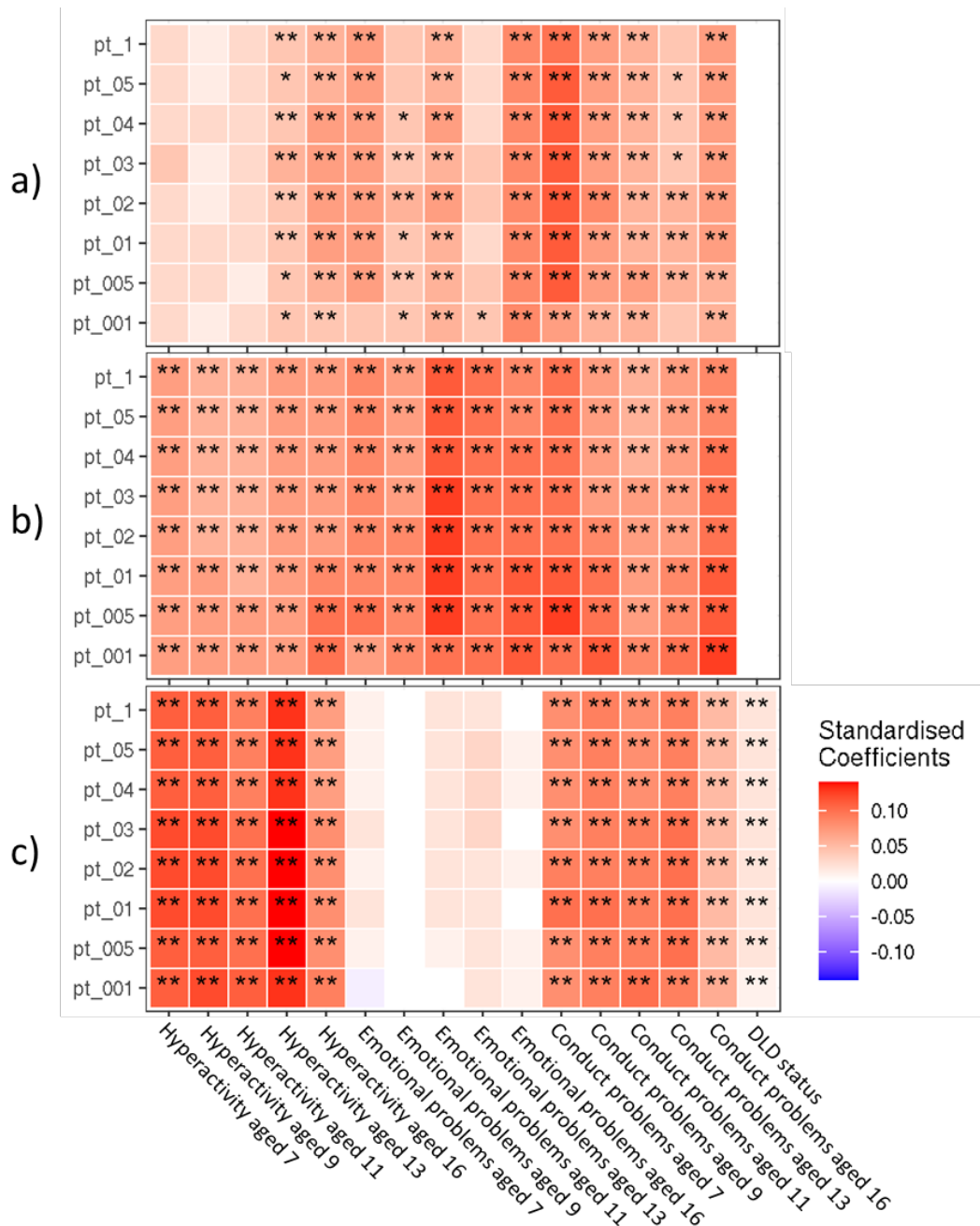
Anxiety Disorder

Findings relating to the associations between the AD PGS and the SDQ subscales under assessment, whilst highlighting multiple significant associations, also demonstrated inconsistencies in associations across timepoints and p-value thresholds. For instance, the first three timepoints (ages 7, 9, 11) showed no significant associations at any p-value threshold. However, associations were then shown to increase at timepoint four (age 13), highlighting three nominally significant finding and five that remained significant following multiple testing corrections. Associations then became consistently significant across all thresholds following multiple testing corrections at timepoint 5 (age 16). This

increase in association, from earlier to later timepoints may imply that the effect of genetic risk for AD on hyperactivity increases over time.

Inconsistencies were also evident for associations between the AD PGS and emotional problems. Whilst timepoint one (age 7) highlighted significant associations following multiple testing corrections at all but one threshold (0.01), associations were then shown to drop at timepoint two (age 9) with associations at only three thresholds (0.3, 0.2, 0.05) surviving multiple testing corrections. Timepoint three (age 11) then saw significant associations at all p-value thresholds, with all associations surviving corrections for multiple testing. Significant associations all but disappeared at timepoint four (age 13) except for one nominally significant association at the lowest p-value threshold (0.01) before returning at timepoint five (age 16) with increased significance and effect.

Associations between the AD PGS and conduct problems demonstrated a far more consistent pattern of association, with the first three time points (ages 7, 9, 11) highlighting significant associations following multiple testing corrections at all p-value thresholds. This consistent pattern of association then dissipated at timepoint four (age 13) with only three thresholds showing significant effects following corrections for multiple testing (0.2, 0.1, 0.05). Significant associations at all thresholds then returned at timepoint five (age 16) with all associations remaining significant following multiple testing corrections.

Despite the inconsistency in significant associations, all results demonstrated a consistent positive direction of effect suggesting that genetic risk for AD is associated with increases in levels of hyperactivity, emotional problems and conduct problems. However, this was not the case regarding the DLD status as there were no associations, significant or otherwise, between the AD PGS and DLD status at any timepoint or p-value threshold.

Major Depressive Disorder

Results regarding the MDD PGS demonstrated strong and consistent significant associations with all three SDQ subscales. These associations were significant at all timepoints and thresholds. All finding were found to have a consistent positive direction of effect and were significant following corrections for multiple testing. This suggests that genetic risk for depression is associated with increased hyperactivity, emotional problems and conduct problems alike. As with the findings regarding the AD PGS there was no associations, significant or otherwise observed between genetic risk for depression and DLD status at any timepoint or threshold.

Attention Deficit Hyperactivity Disorder

Results relating to the associations between the ADHD PGS and the SDQ subscales, whilst not consistently significant across all subscales, did reveal a specific pattern of associations, with the subscales hyperactivity and conduct problems showing consistently significant positive associations with genetic risk for ADHD. Conversely, no significant associations, nominally or otherwise, were observed regarding the ADHD PGS and emotional problems suggesting that genetic risk for ADHD is not significantly associated with emotional problems. However, unlike the findings regarding both the MDD and AD PGS, the ADHD PGS demonstrated consistently significant positive associations, at all p-value thresholds, with DLD status. Furthermore, despite effect sizes being small, all association survived correction for multiple testing. This therefore suggests that genetic variant implicated in ADHD are also associated with a positive DLD status within the current sample.

Accounting for Time-Ordered Natures of Data

To further assess these effects, linear mixed effects models were constructed examining associations between the three polygenic scores at the same eight p-value thresholds and each of the SDQ subscales across all timepoints. This approach maximizes the effective power of the sample to

assess the consistency and robustness of the previous associations. All models included the fixed effects of age and sex and the random effect age. Results of these analyses are illustrated below in **Figure S2**.

Figure S2. Heatmap illustrating findings from the mixed effects models examining the associations between AD, MDD, and ADHD polygenic scores and the SDQ subscales (hyperactivity, emotional problems and conduct problems) at eight p-value thresholds, and across all timepoints. Nominally significant findings are indicated with a single asterisk (*), with a double asterisk (**) highlighting a finding that was significant follow multiple testing corrections.
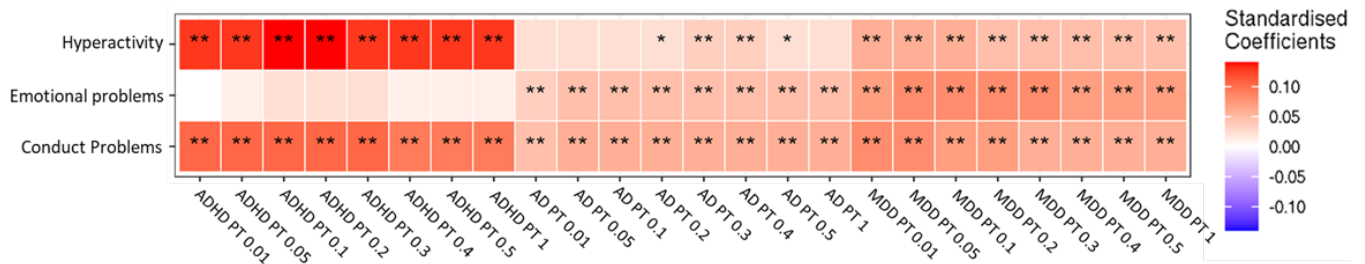
Findings from the linear mixed effects models demonstrate that the lack of association seen in **Figure S1** between the ADHD PGS and emotional problems was a robust finding, further confirming that genetic risk for ADHD is not significantly associated with emotional problems within the current sample. Furthermore, results also confirmed strong positive associations, at all thresholds following multiple testing corrections, between the ADHD PGS and both hyperactivity and conduct problems.

It was also revealed that whilst the association between genetic risk for anxiety and hyperactivity may increase over time, as suggested in the previous analysis, it also appears that the significance of this positive effect is limited to specific p-value thresholds. This is unlikely to be the result of a lack of power as the mixed effects approach used increases statistical power by assessing associations across all timepoints. However, it may suggest that the SNPs included at these specific thresholds are those driving the association, and that the reduction or inclusion of further unassociated SNPs are impacting on this relationship. Elsewhere, the AD PGS was shown to be significantly association with increases in emotional problems and conduct problems, all of which survived correction for multiple testing. This likely suggests that the inconsistencies seen between timepoints in the previous analysis were the result of a drop in power at specific timepoint due to missing SDQ data.

Lastly, and in line with the previous results from the regression analysis at each timepoint, the MDD PGS was found to be significant following multiple testing corrections at all thresholds across each of the SDQ subscales.

Taken together, findings highlight 0.3 and 0.4 as representing the most consistently significant p-value thresholds across each PGS, and the only to remain significant across each of the SDQ measures, with the exception of the ADHD PGS on emotional problems.

Variance Explained

Informed by the previous analyses, variance in the SDQ subscales explained by each PGS at the most consistently significant p-value thresholds (0.3 and 0.4) were assessed at each time point. Results of these assessments are illustrated in the bar charts below (**Figure S3**).
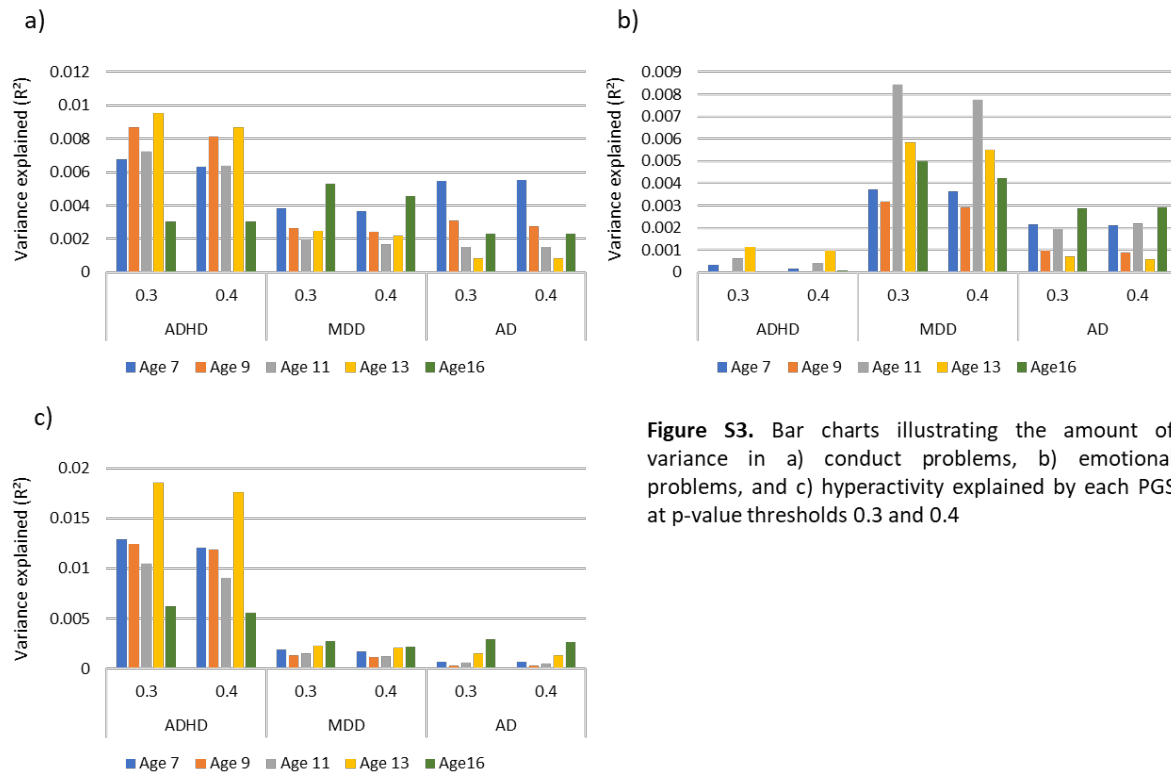
a)

b)

c)

Figure S3. Bar charts illustrating the amount of variance in a) conduct problems, b) emotional problems, and c) hyperactivity explained by each PGS at p-value thresholds 0.3 and 0.4

Results revealed that a p-value threshold of 0.3 more consistently explained the most variance in each of the SDQ subscales compared to 0.4, although the differences were small. Variance explained across the three SDQ subscales by the each PGS at the 0.3 p-value threshold ranged from 0.07% to 0.5% for the AD PRS, 0.2% to 0.8% for the MDD PRS and <.001% to 1.9% for the ADHD PRS. Informed by these findings, and to reduce the multiple testing burden whilst also maximising power, the 0.3 p-value threshold of each PGS was used in further downstream analysis.

Polygenic Scores

PGSs were calculated using the 0.3 p-value threshold. The descriptive statistics for these PGSs are shown in Table S1 and the distribution of PGS is shown in Figures S4 and S5.

Table S1. Descriptive statistics of MDD, AD, and ADHD genome-wide polygenic scores (PT 0.3).

PGS (PT 0.3)	SNPs	n	Unstandardized mean (SD)	Standardized mean (SD)	Skewness	Kurtosis
MDD	139934	5395	-6.6×10^{-4} (1.9×10^{-5})	-5.03×10^{-17} (1)	-.034	3.031
AD	146154	5395	2×10^{-5} (5.6×10^{-5})	-2.17×10^{-17} (1)	-.003	3.122
ADHD	101631	5395	-4.2×10^{-4} (8×10^{-5})	-2.9×10^{-16} (1)	-.019	3.016

* **SNPS** = number of variants included. **n** = number of individuals in the ALSPAC dataset with genetic data. **SD** = standard deviation

Figure S4. Histograms displaying the distributions of the unstandardized AD, MDD, and ADHD PRS for all individuals within the ALSPAC dataset. The distribution was assessed at a p-value thresholds of 0.3.

Figure S5. Histograms displaying the distributions of the standardized AD, MDD, and ADHD PRS for all individuals within the ALSPAC dataset. The distribution was assessed at a p-value thresholds of 0.3.
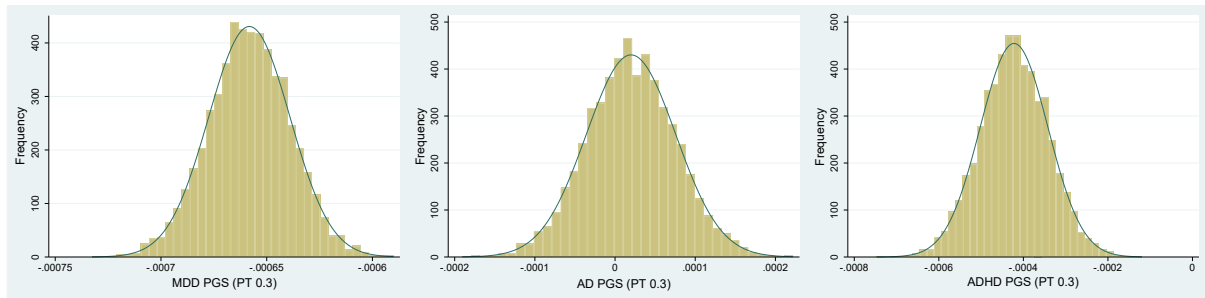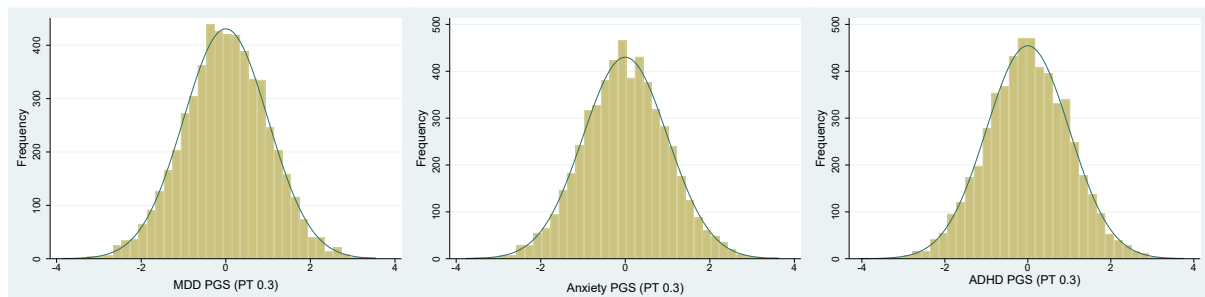
Table S2. Full results from mixed effects models with continuous PGS including main effects and co-variates.

Outcome Variable	Predictor PGS	Covariate Sex			Covariate Time			Main Effect PGS (Continuous)			Main Effect DLD			PGS x DLD Interaction		
		β	95% CI	P	β	95% CI	P	β	95% CI	P	β	95% CI	P	β	95% CI	P
Emotional Problems	Model 1: MDD	.18	(.13,.22)	**<.001**	-.01	(-.02,-.00)	.007	.06	.04,.08	**<.001**	.32	.24,.39	**<.001**	.06	-.02,.14	.113
	Model 2: AD	.18	(.14,.22)	**<.001**	-.01	(-.02,-.00)	.007	.04	.02,.06	**<.001**	.32	.24,.39	**<.001**	-.02	-.10,.05	.554
	Model 3: ADHD	.18	(.14,.22)	**<.001**	-.01	(-.02,-.00)	.007	.01	-.01,.03	.293	.31	.23,.39	**<.001**	.01	-.07,.08	.895
	Model 4: Combined	.18	(.13,.22)	**<.001**	-.01	(-.02,-.00)	.008	.03	.02,.04	**<.001**	.31	.23,.38	**<.001**	.01	-.03,.05	.681
Conduct Problems	Model 5: MDD	-.10	(-.15,-.06)	**<.001**	-.07	(-.08,-.06)	**<.001**	.05	.02,.07	**<.001**	.38	.30,.45	**<.001**	.08	.00.17	**.048**
	Model 6: AD	-.10	(-.15,-.06)	**<.001**	-.07	(-.08,-.06)	**<.001**	.05	.02,.07	**<.001**	.37	.30,.45	**<.001**	.09	.01,.16	**.029**
	Model 7: ADHD	-.11	(-.15,-.06)	**<.001**	-.07	(-.08,-.06)	**<.001**	.08	.06,.11	**<.001**	.36	.28,.44	**<.001**	0	-.08,.08	.960
	Model 8: Combined	-.11	(-.15,-.06)	**<.001**	-.07	(-.08,-.06)	**<.001**	.04	.03,.06	**<.001**	.36	.28,.44	**<.001**	.04	.00,.08	**.049**
Hyperactivity	Model 9: MDD	-.33	(-.37,-.28)	**<.001**	-.05	(-.06,-.05)	**<.001**	.04	.01,.06	**.002**	.59	.51,.67	**<.001**	.06	-.02,.15	.132

Model 10: AD	-.32	(-.37,-.28)	**<.001**	-.05	(-.06,-.05)	**<.001**	.03	.00,.05	**.039**	.59	.51,.67	**<.001**	0	-.08,.08	.959
Model 11: ADHD	-.33	(-.37,-.28)	**<.001**	-.05	(-.06,-.05)	**<.001**	.10	.08,.13	**<.001**	.56	.48,.64	**<.001**	.03	-.05,.11	.498
Model 12: Combined	-.33	(-.37,-.28)	**<.001**	-.05	(-.06,-.05)	**<.001**	.04	.03,.05	**<.001**	.57	.49,.65	**<.001**	.02	-.02,.06	.327

Figure S7 MDD PGS Interaction Effects. High MDD PGS slope: β=.44, 95%CI=.32,.55, p=<.001, Low MDD PGS slope: β=.31, 95%CI=.20,.42, p=<.001
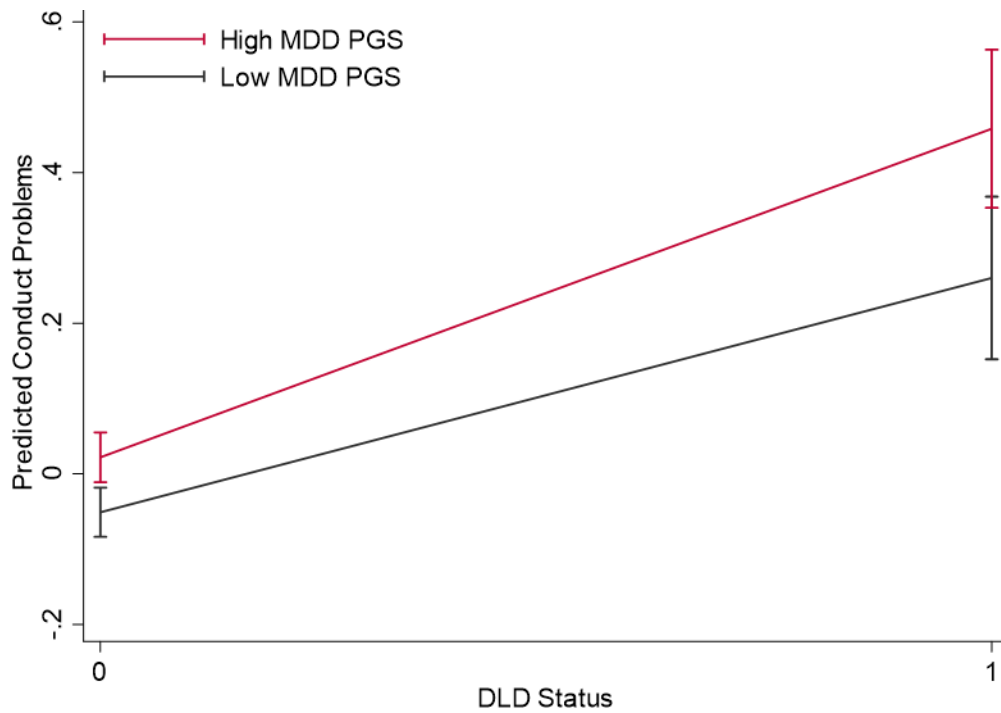
Figure S8. AD PGS Interaction Effects. High anxiety PGS slope: β=.46, 95%CI=.34,.57 p=<.001. Low anxiety PGS slope: β=.30, 95%CI=.19,.41, p=<.001

Figure S9. Combined PGS Interaction Effects. High combined PGS slope: β=.44, 95%CI=.33,.55, p=<.001. Low combined PGS slope: β=.29, 95%CI=.18,.40, p=<.001
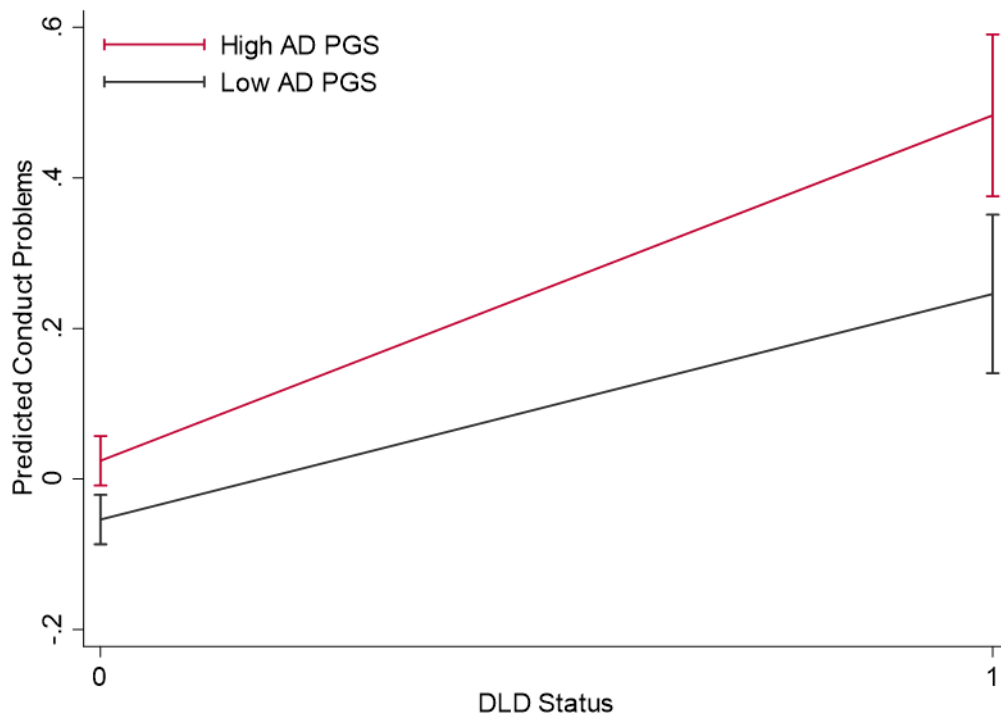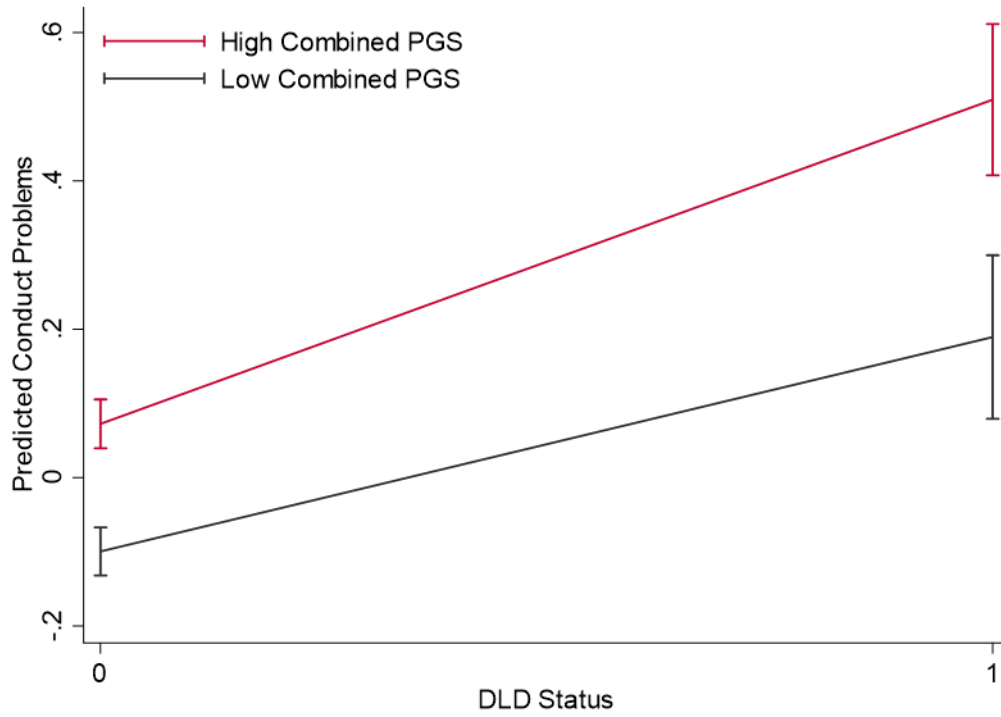
Summary of Latent Sub-Groups

Table S3.

Emotional Problems

Number of Groups	AIC	ssa-BIC	Entropy	Smallest Class	LRT
2	79998.946	80024.036	.760	37%	<.001
3	78255.568	78294.995	.683	18%	<.001
4	**77984.264**	**78038.028**	**.581**	**16%**	**<.001**
5	77748.364	77816.465	.563	5%	.028
6	77655.531	77737.969	.521	6%	.019

Table S4.

Conduct Problems

Number of Groups	AIC	ssa-BIC	Entropy	Smallest Class	LRT
2	72191.221	72216.311	.702	42%	<.001
3	**70839.056**	**70878.483**	**.669**	**13%**	**<.001**
4	70622.626	70676.390	.612	5%	.003
5	70567.771	70635.872	.636	1%	<.001
6	70576.358	70658.797	.663	0%	.939

Table S5.

Hyperactivity

Number of Groups	AIC	ssa-BIC	Entropy	Smallest Class	LRT
2	99348.996	99374.082	.765	49%	<.001
3	**97352.178**	**97391.599**	**.698**	**20%**	**<.001**
4	96901.571	96955.328	.683	7%	<.001
5	96798.613	96866.705	.644	3%	<.001
6	96788.661	96871.089	.584	3%	.298

	Stable Low	Decreasing within Normal Range		Increasing within Normal Range		Consistently Raised	
		RRR (95% CI)	P	RRR (95% CI)	P	RRR (95% CI)	P
Model 1	**Reference**						
ELCE		.99 (.97,1.02)	.645	.99 (.96,1.02)	.358	.95 (.92,.98)	<.001
SES		.91 (.84,.99)	.021	.95 (.87,1.04)	.292	.83 (.76,.91)	<.001
DLD		1.33 (1.00,1.77)	.047	1.53 (1.10,2.13)	.011	2.22 (1.65,2.97)	<.001
Sex		1.22 (1.05,1.41)	.008	2.21 (1.85,2.64)	<.001	2.13 (1.79,2.54)	<.001
PGS		1.03 (.99,1.07)	.103	1.03 (.98,1.07)	.229	1.08 (1.03,1.13)	.001
PGSs x ELCE		1.00 (.99,1.02)	.508	.98 (.97,1.00)	.012	1.01 (.99,1.02)	.449
Model 2	**Reference**						
ELCE		.99 (.97,1.02)	.665	.98 (.96,1.01)	.272	.95 (.93,.98)	.001
SES		.91 (.84,.99)	.021	.95 (.87,1.05)	.305	.83 (.76,.91)	<.001
DLD		1.33 (1.00,1.77)	.048	1.55 (1.12,2.15)	.009	2.21 (1.65,2.96)	<.001
Sex		1.22 (1.05,1.41)	.008	2.20 (1.84,2.63)	<.001	2.13 (1.79,2.54)	<.001
PGS		1.03 (.99,1.07)	.123	1.03 (.98,1.07)	.232	1.07 (1.03,1.12)	.001
PGSs x SES		1.01 (.97,1.05)	.721	1.00 (.96,1.05)	.945	1.02 (.98,1.07)	.333
Model 3	**Reference**						
ELCE		.99 (.97,1.02)	.640	.98 (.95,1.01)	.265	.95 (.93,.98)	.001
SES		.91 (.84,.99)	.021	.95 (.87,1.04)	.298	.83 (.76,.91)	<.001

DLD	1.33 (1.00,1.77)	.048	1.56 (1.12,2.16)	.008	2.19 (1.63,2.94)	<.001
Sex	1.22 (1.06,1.41)	.007	2.20 (1.84,2.63)	<.001	2.13 (1.79,2.54)	<.001
PGS	1.04 (1.00,1.08)	.044	1.03 (.99,1.08)	.172	1.07 (1.03,1.12)	.002
PGS x DLD	.89 (.78,1.03)	.111	.94 (.80,1.11)	.470	.98 (.85,1.13)	.813

Table S6.

Genetic

and

Environmental Influences on Sub-Groups of Emotional Problems (Continuous Combined PGS)

RRR = relative risk ratio, CI= confidence intervals, ELCE = early language and communication environment, SES = socioeconomic status, PGS = polygenic score, DLD = developmental language disorder

Table S7. *Genetic and Environmental Influences on Sub-Groups of Conduct Problems (Continuous Combined PGS)*

	Stable Low	Stable within Normal Range		Consistently Raised	
		RRR (95% CI)	P	RRR (95% CI)	P
Model 4	**Reference**				
ELCE		.96 (.94, .98)	<.001	.91 (.88, .94)	<.001
SES		.89 (.83, .96)	.002	.73 (.66, .81)	<.001
DLD		1.55 (1.19, 2.02)	.001	2.4 (1.74, 3.33)	<.001
Sex		.95 (.83, 1.08)	.397	.70 (.57, .85)	<.001
PGS		1.09 (1.05, 1.12)	<.001	1.14 (1.08, 1.19)	<.001
PGS x ELCE		1.00 (.99, 1.01)	.949	1.00 (.98, 1.01)	.699
Model 5	**Reference**				
ELCE		.96 (.94, .98)	<.001	.91 (.88, .94)	<.001
SES		.89 (.83, .96)	.001	.73 (.66, .81)	<.001
DLD		1.55 (1.19, 2.02)	.001	2.41 (1.74, 3.33)	<.001
Sex		.95 (.83, 1.08)	.397	.70 (.57, .85)	<.001
PGS		1.09 (1.06, 1.13)	<.001	1.14 (1.08, 1.20)	<.001
PGS x SES		.98 (.95, 1.02)	.332	.96 (.92, 1.01)	.159
Model 6	**Reference**				
ELCE		.96 (.94, .98)	<.001	.91 (.88, .94)	<.001

	RRR (95% CI)	p	RRR (95% CI)	p
SES	.89 (.83, .96)	.002	.73 (.66, .81)	<.001
DLD	1.55 (1.19, 2.02)	.001	2.35 (1.69, 3.27)	<.001
Sex	.95 (.83, 1.08)	.398	.70 (.57, .85)	<.001
PGS	1.09 (1.05, 1.13)	<.001	1.13 (1.07, 1.19)	<.001
PGS x DLD	.98 (.86, 1.12)	.789	1.06 (.90, 1.25)	.464

RRR = relative risk ratio, CI= confidence intervals, ELCE = early language and communication environment, SES = socioeconomic status, PGS = polygenic score, DLD = developmental language disorder

Table S8. *Genetic and Environmental Influences on Sub-Groups of Hyperactivity (Continuous Combined PGS)*

	Stable Low	Stable within Normal Range		Consistently Raised	
		RRR (95% CI)	P	RRR (95% CI)	P
Model 7	Reference				
ELCE		.94 (.92, .96)	<.001	.89 (.87, .92)	<.001
SES		.84 (.78, .91)	<.001	.73 (.66, .80)	<.001
DLD		2.14 (1.52, 3.00)	<.001	4.69 (3.28, 6.69)	<.001
Sex		.58 (.50, .66)	<.001	.29 (.24, .35)	<.001
PGS		1.08 (1.04, 1.12)	<.001	1.15 (1.10, 1.21)	<.001
PGS x ELCE		1.00 (.99, 1.01)	.910	1.00 (.99, 1.02)	.737
Model 8	Reference				
ELCE		.94 (.92, .96)	<.001	.94 (.92, .96)	<.001
SES		.84 (.78, .91)	<.001	.84 (.78, .91)	<.001
DLD		2.14 (1.53, 3.00)	<.001	2.14 (1.52, 3.00)	<.001
Sex		.58 (.50, .66)	<.001	.58 (.50, .66)	<.001
PGS		1.08 (1.04, 1.12)	<.001	1.08 (1.04, 1.12)	<.001
PGS x SES		.99 (.96, 1.03)	.712	1.00 (.99, 1.01)	.910
Model 9	Reference				
ELCE		.94 (.92, .96)	<.001	.89 (.87, .92)	<.001

SES	.84 (.78, .91)	<.001	.73 (.66, .80)	<.001
DLD	2.12 (1.51, 2.97)	<.001	4.57 (3.20, 6.53)	<.001
Sex	.58 (.50, .66)	<.001	.29 (.24, .35)	<.001
PGS	1.08 (1.05, 1.12)	<.001	1.14 (1.09, 1.20)	<.001
PGS x DLD	.91 (.77, 1.08)	.291	1.00 (.83, 1.19)	.986

RRR = relative risk ratio, CI= confidence intervals, ELCE = early language and communication environment, SES = socioeconomic status, PGS = polygenic score, DLD = developmental language disorder