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Investigating the associations between neurodevelopmental and psychiatric genetic liability and adverse social and functional outcomes across childhood, adolescence and young-adulthood

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Neurodevelopmental and psychiatric conditions often originate in youth and can lead to adverse social and functional outcomes. It is unclear whether these associations are driven by genetic liability to these conditions, with possible developmental differences. We examined multivariable associations between polygenic scores (PGS) for attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), schizophrenia, bipolar disorder, depression, anxiety and three outcomes: peer problems, educational attainment/employment and suicidality, in childhood, adolescence and young-adulthood. Data were analysed from the Avon Longitudinal Study of Parents and Children; outcomes at ages 10–13, 16 and 24–25 years. ADHD PGS was associated with peer problems (OR = 1.13, $p = 0.020$; OR = 1.21, $p < 0.0001$; OR = 1.14, $p = 0.010$) and lower educational attainment/employment in childhood, adolescence and young-adulthood (OR = 1.40, $p < 0.0001$; OR = 1.62, $p < 0.0001$; OR = 1.29, $p = 0.005$ respectively) and suicidality in childhood (OR = 1.13, $p = 0.030$). ASD PGS was associated with peer problems and suicidality in childhood (OR = 1.24, $p < 0.0001$; OR = 1.24, $p < 0.0001$) and greater educational attainment in childhood and adolescence (OR = 0.88, $p = 0.004$; OR = 0.77, $p = 0.007$). Depression PGS was associated with peer problems in childhood and young-adulthood (OR = 1.18, $p = 0.003$; OR = 1.21, $p < 0.0001$), and poorer educational attainment/employment and suicidality in adolescence (OR = 1.39, $p = 0.004$; OR = 1.28, $p < 0.0001$) and young-adulthood (OR = 1.26, $p = 0.017$; OR = 1.42, $p < 0.0001$). We did not find strong evidence of associations for schizophrenia, bipolar disorder or anxiety PGS. These findings suggest that genetic liability to neurodevelopmental and psychiatric conditions are associated with a range of social/functional outcomes, although the strength and direction of association vary by PGS, outcome and development stage. This highlights the importance of examining genetic liability to multiple conditions simultaneously and of a developmental perspective.

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INTRODUCTION

Neurodevelopmental and psychiatric conditions often originate early in development [1] and are strongly associated with a range of adverse social and functional outcomes [2, 3]. Substantial evidence indicates that common neurodevelopmental and psychiatric conditions such as attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and schizophrenia as well as bipolar disorder, depression, and anxiety share some symptoms and comorbidities are common [4–6]. Adverse outcomes associated with these conditions encompass social and functional domains [7–9], including impairments in social relationships, education and employment, as well as suicidal behaviour (suicidality) [10–14]. Importantly, referrals to mental health services are often driven not solely by the symptoms of the condition but by the broader challenges associated with these outcomes. While evidence for phenotypic associations between

neurodevelopmental and psychiatric conditions and these negative outcomes is clear [7–14], it is unclear whether these associations are driven by genetic liability to these conditions.

Family and twin studies have consistently demonstrated a significant heritable component to neurodevelopmental and psychiatric disorders [15–18]. Social and functional outcomes have also been found to be heritable, including peer relationships [19], educational and employment [20] and suicidality [21]. Twin studies have also indicated genetic overlap between educational attainment and both neurodevelopmental conditions and emotional problems [22, 23], and between peer problems and emotional problems [24]. However, these studies typically investigate conditions in isolation. Research in molecular genetics has also found evidence of associations between genetic liability to neurodevelopmental and psychiatric conditions, indexed by polygenic scores (PGS) and social and functional outcomes, but

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the evidence base varies considerably depending on the specific condition, the outcome assessed, and the developmental stage examined (childhood, adolescence or young-adulthood).

Research examining genetic liability to neurodevelopmental conditions – which onset early in development – such as ADHD and ASD, have shown associations with a range of social and functional outcomes spanning childhood, adolescence and young-adulthood [25–30]. For example, both ADHD and ASD PGS have shown evidence of associations with suicidality in a childhood high-risk population sample [29] and with peer problems in childhood and adolescence in a general population sample [19, 25]. ADHD PGS has also shown associations with poor educational attainment in childhood and adolescence [30–32] and with unemployment in young-adulthood [33, 34], whereas evidence did not support strong associations between ASD PGS and educational attainment in childhood [32] nor unemployment in young-adulthood [34], with limited research conducted in adolescence. Previous research has not identified strong evidence of an association between either ADHD or ASD PGS and suicidality in adulthood [34, 35].

While schizophrenia is not formally classified as a neurodevelopmental disorder and typically does not onset until adolescence or young-adulthood, it is widely considered as neurodevelopmental in origins [36, 37]. Consistent with this, and akin to ASD and ADHD PGS, schizophrenia PGS has also been found to be associated with suicidality in childhood [29] and peer problems in adolescence [38]. However, unlike ADHD PGS, there is little evidence of associations with suicidality or unemployment in adulthood [34]. While schizophrenia PGS has been linked to related constructs such as loneliness in adulthood [39], specific associations with peer problems in young-adulthood have not been examined. Unlike schizophrenia, bipolar disorder is classified as a mood disorder [36] and is not considered neurodevelopmental, given the relative lack of associated early life impairments [40]. Nonetheless, these conditions have considerable genetic overlap, with a genetic correlation of 0.68 [41, 42]. Genetic liability for both conditions is associated with greater educational attainment across development [42, 43] as well as increased lifetime risk of suicide attempts [28]. Unlike schizophrenia PGS, there is not strong evidence of an association between bipolar disorder PGS and peer problems or unemployment [44].

Depression and anxiety are emotional disorders, with a typical onset in adolescence or young-adulthood [45]. They are moderately genetically correlated ($rg = 0.91$) [45], but have a lower heritability than neurodevelopmental conditions, with SNP-based estimates of around 10% [1, 46] compared to 19% for neurodevelopmental conditions [4]. Depression PGS has been associated with peer problems in adolescence and young-adulthood [25, 26] and with suicidality across development [29, 34, 47, 48]. Both depression and anxiety PGS are associated with unemployment in adulthood [15], but there is a lack of literature on associations with educational attainment in earlier in development. Unlike depression, associations between anxiety PGS and suicidality in adulthood are inconsistent [49] and there is limited research into associations with other outcomes in childhood and adolescence.

Thus, the research presented above suggests that genetic liability to neurodevelopmental and psychiatric conditions is associated with social and functional outcomes, but that associations vary for different conditions. Research examining associations across different developmental periods – which appears to be one source of heterogeneity – is limited. Existing research suggests that liability to neurodevelopmental conditions may be associated with outcomes across development. In contrast liability to depression and anxiety may not present associations with outcomes until adolescence, except for depression liability and suicidality, which may present earlier. Finally, liability to bipolar disorder does not appear to present until young-adulthood,

although this may be earlier for educational attainment. Research examining multiple PGS together is also limited, which is important given the genetic overlap between conditions [4, 5, 50].

Therefore, the aims of this study were to investigate associations between PGS for six neurodevelopmental/psychiatric conditions—ADHD, ASD, schizophrenia, bipolar disorder, depression and anxiety—and social and functional outcomes measured across childhood, adolescence, and young-adulthood: i) peer problems, ii) suicidality and iii) educational attainment and employment. These outcomes capture distinct but complementary domains of wellbeing and functioning in young people. Peer relationships reflect social integration and interpersonal functioning, which are central developmental tasks during adolescence and key components of overall wellbeing [51]. Suicidality represents a critical indicator of severe distress and compromised wellbeing. Educational attainment indexes cognitive and functional development, and is a key marker of future life chances, including employment and socioeconomic position [52]. Further, all are phenotypically associated with various neurodevelopmental and psychiatric conditions across development [10–14].

We hypothesised that neurodevelopmental PGS (ADHD, ASD and schizophrenia) would be associated with all outcomes across development. For mood/emotional PGS (bipolar disorder, depression and anxiety) we hypothesised that the presence of associations would depend on the developmental period. We hypothesised that depression PGS would be associated with suicidality at all ages, but with peer problems and educational attainment/employment in adolescence and young-adulthood only. For anxiety PGS, we hypothesised the presence of associations with suicidality, peer problems and educational attainment/employment in adolescence and young-adulthood. Finally, for bipolar disorder PGS, we hypothesised the presence of associations with suicidality and peer problems in young-adulthood, and with educational attainment/employment in adolescence and young-adulthood. Hypotheses are depicted in Fig. 1.

METHODS

Participants

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective population-based cohort study. This study recruited pregnant women residing in Avon, UK with expected due dates between 1st April 1991 and 31st December 1992. Initially 14,541 pregnancies were enrolled with 13,988 children alive at 1 year of age. After further recruitment, the total sample size using any data collected after 7 years old is 15,447 pregnancies of which 14,901 children were alive at 1 year of age. There were 338 women of the initial 14,541 pregnancies who had already enrolled with a previous pregnancy, making 14,203 unique mothers. After another phase of recruitment, there was a total of 14,833 women as of September 2021. For a full description of the cohort see references [53–55]. For participants over the age of 22 years, study data were collected and managed using REDcap (Research Electronic Data Capture, [56]), hosted at the University of Bristol. The study website contains details of all data available through a fully searchable data dictionary and variable search tool (<http://www.bristol.ac.uk/alspac/researchers/our-data/>). A flow diagram summarizing sample selection is shown in Supplementary Figure S1.

Genetic data and polygenic scores

Blood samples for DNA extraction were collected at birth or during study clinics between ages 3 and 7. Genotyping was done via the Illumina HumanHap550 quad platform and imputed using the Haplotype Reference Consortium panel. For details of genetic QC see Supplementary Material.

After QC, 8,591 unrelated individuals remained. PGS were calculated using PGS-CS [57] and derived based on the largest and most recent genome-wide association studies (GWAS) for the 6 neurodevelopmental/psychiatric conditions: 1) ADHD (38,691 cases and 186,843 controls) [58], 2) ASD (18,381 cases and 27,969 controls) [59], 3) schizophrenia (76,755 cases and 243,649 controls) [60] 4) bipolar disorder (41,917 cases and 371,549

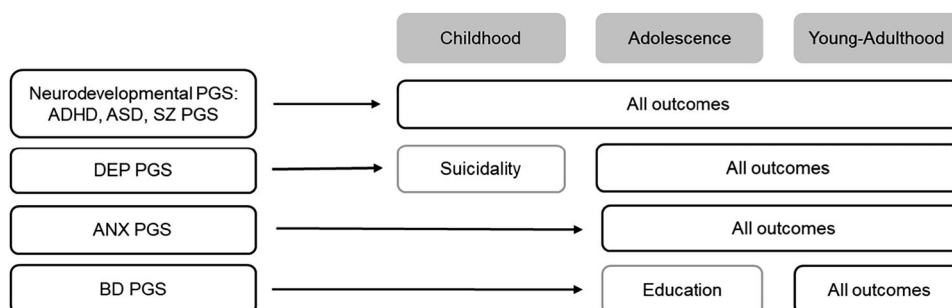


Fig. 1 Hypothesised associations between polygenic scores and social/functional outcomes. Abbreviations – ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; SZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; ANX, anxiety; PGS, polygenic score.

controls [41] 5) depression (688,808 cases and 4,364,225 controls) [46] and 6) anxiety (25,453 cases and 58,113 controls) [61]. All GWAS included participants spanning childhood to and adulthood, except anxiety which only included adults. Most participants in the ADHD and ASD GWAS were children, and most of those in the schizophrenia, bipolar and depression GWAS were adults. Each PGS was residualised against ten ancestry-specific principal components and standardised to aid interpretation.

Outcomes

Peer problems. The peer problem subscale of the Strengths and Difficulties questionnaire (SDQ) [62] was parent-reported at ages 10 and 16 and self-reported at 25 years old. This consists of 5 items: i) solitary and plays alone, ii) has at least one good friend, iii) generally liked by other children, iv) picked on or bullied by others, and v) gets on better with adults than with other children. Items are scored as 0 (not true), 1 (somewhat true) and 2 (certainly true) to give a total score of 10. A standard cut-off score of ≥ 4 [63] was used to index the presence of peer problems.

Educational attainment and employment. To assess educational attainment in childhood, we used parent-reporting of the child's Key Stage 3 SAT (Standard Assessment Tests) levels for Maths and English when offspring were around 13/14 years old. The Key Stage 3 SATs are national curriculum tests sat by UK pupils in year 9 (age 13/14, 3rd year of secondary school). SATs levels ranged from 3 to 8; as per UK government guidelines, children are expected to achieve a level 5 or above [64]. Thus, to dichotomise this variable, a level of ≥ 5 was considered as higher educational attainment and < 5 defined as lower educational attainment.

For adolescent educational attainment, a self-reported retrospective questionnaire on GCSE grades obtained at 16 years old was reported at age 18. GCSEs are exams taken at the end of secondary school (year 11, age 15/16), where students are examined on an average of 8 subjects. At the time of these questionnaires, GCSE grades range from A* to G. In accordance with UK government benchmark measures [65, 66], those who did not achieve grades between A*-C in all the subjects they were studying were defined as lower educational attainment and those who achieved grades within A*-C for all subjects as higher educational attainment.

In young-adulthood, participants self-reported whether they were currently engaged in any education, employment or training at age 25. In accordance with the UK Office of National Statistics, participants who were not in employment (full-time/part-time/occasional or self-employed), doing an apprenticeship or any other government supported training or work experience scheme or full-time education were defined as being NEET (not in education, employment or training) which also included those doing voluntary work, those who were a part or full-time carer or those who were unable to work due to sickness or disability [67].

Suicidality. Suicidality or risk of suicide encompassed questionnaires describing suicidal thoughts, ideation and suicide attempts. For primary analyses, suicidality was defined as a lifetime report at age 11, whereas at ages 16 and 24, suicidality was present only if they had experienced suicidal thoughts within a year of completing the questionnaire. An answer of 'yes' to any suicidality item was defined as the presence of suicidality, as defined previously [68].

At age 11, suicidality was assessed using the Childhood Interview for DSM-IV Borderline Personality Disorder (CI-BPD) [69]. This is a semi-

structured interview including a suicidal behaviours section of four binary (yes/no) items: i) 'told someone you will kill yourself', ii) 'thought about killing yourself', iii) 'made plans to kill yourself' and iv) 'actually tried to kill yourself'.

At age 16 years, suicidality was measured using a self-reported questionnaire on deliberate self-harm. The questions within this section were based on the Child and Adolescent Self-harm in Europe (CASE) study [70]. We defined suicidality as answering 'yes' to both the following questions and reporting these actions within a year of survey completion: 'have you ever hurt yourself on purpose in any way?' and 'on any of the occasions where you have hurt yourself, have you ever seriously wanted to kill yourself?'. In addition, individuals answering 'yes' to 'have you ever felt that life was not worth living?' in the past year since survey completion were also classified as experiencing suicidality.

At age 24 years, suicidality was measured using the computerised Interview Schedule-Revised (CIS-R) questionnaire which is a self-reported interview that determines diagnoses for depression and anxiety disorder, based on ICD-10 criteria [71, 72]. Within this questionnaire were the following items: i) 'ever self-harmed with suicidal intent', ii) 'ever attempted suicide', iii) 'ever had suicidal thoughts' and iv) 'when was the last time you had these thoughts?'.

Analyses. All analyses were conducted using stataSE (version 18). We first present descriptive statistics showing the prevalence of each outcome at each age in the sample. We then performed multivariable logistic regression models of each outcome at each age (9 models), including all PGS simultaneously. We assessed multicollinearity using variance inflation factors (VIF): these are presented, along with correlations between the PGS, in Table S1-2. Outcomes were dichotomised to ease interpretation of results. One unit increase in odds ratio is equivalent to a one unit increase in PGS standard deviation.

We used multiple imputation to account for missing data in our sample (those with genetic data), using the Stata package 'ICE'. All outcomes were included in the imputation model, alongside the same phenotype at different ages (e.g. SDQ peer problems at ages 10 and 16 were used to predict SDQ peer problems at age 25, and suicidality at ages 11 and 16 were used to predict suicidality at age 24). Further auxiliary variables used to predict missingness in ALSPAC were also included in all models (socioeconomic status, multiple birth status, maternal age). 200 imputed data sets were created and results from regression analyses were pooled across all datasets. All other settings remained as the default option. Results using imputed data are presented in the main text, with analysis using unimputed data (listwise deletion) presented as sensitivity analysis.

Sensitivity analyses were also conducted using parent-reported SDQ peer problems data at age 25 and lifetime self-reports of suicidality at ages 16 and 24. We also performed univariable analysis examining the association of each PGS on each outcome.

We used Benjamini-Hochberg false discovery rate (FDR) method to account for multiple comparisons [73]. *P*-values for each PGS were corrected across the 9 multivariable models (across 9 outcomes). Both original *p*-values and corrected FDR *q*-values are presented in text and tables. As our primary analyses were hypothesis driven, multivariable and our outcomes non-independent, interpretation focusses on results prior to correcting for multiple testing; we refer to $p < 0.05$ as strong evidence of association.

Stata syntax for all analyses is provided in Supplementary materials.

Table 1. Proportion of sample with each outcome.

Outcome	Developmental period	Age (years)	Measure	Proportion present (total <i>N</i> = 8,591)
Peer Problems	Childhood	10	SDQ	8.8% (<i>N</i> = 756)
	Adolescence	16	SDQ	9.1% (<i>N</i> = 785)
	Young Adulthood	25	SDQ	18.5% (<i>N</i> = 1,586)
Suicidality	Childhood	11	CI-BPD	8.2% (<i>N</i> = 708)
	Adolescence	16	CASE	24.3% (<i>N</i> = 2,087)
	Young Adulthood	24	CIS-R	15.0% (<i>N</i> = 1,289)
Educational/employment	Childhood	13/14	KS3 SATs	17.5% (<i>N</i> = 1,505)
	Adolescence	16	GCSEs	7.5% (<i>N</i> = 648)
	Young Adulthood	25	NEET	6.8% (<i>N</i> = 586)

KS3 SATs, Key stage 3 Standard Assessment Tests [64]; SDQ, strengths and difficulties questionnaire [62, 63]; CI-BPD, Childhood Interview for DSM-IV Borderline Personality Disorder [69]; GCSEs, General Certificate of Secondary Education [65, 66]; CASE, Child and Adolescent Self-harm in Europe study [70]; NEET, Not in Education, Employment or Training [67]; CIS-R, computerised Interview Schedule- Revised [71, 72].

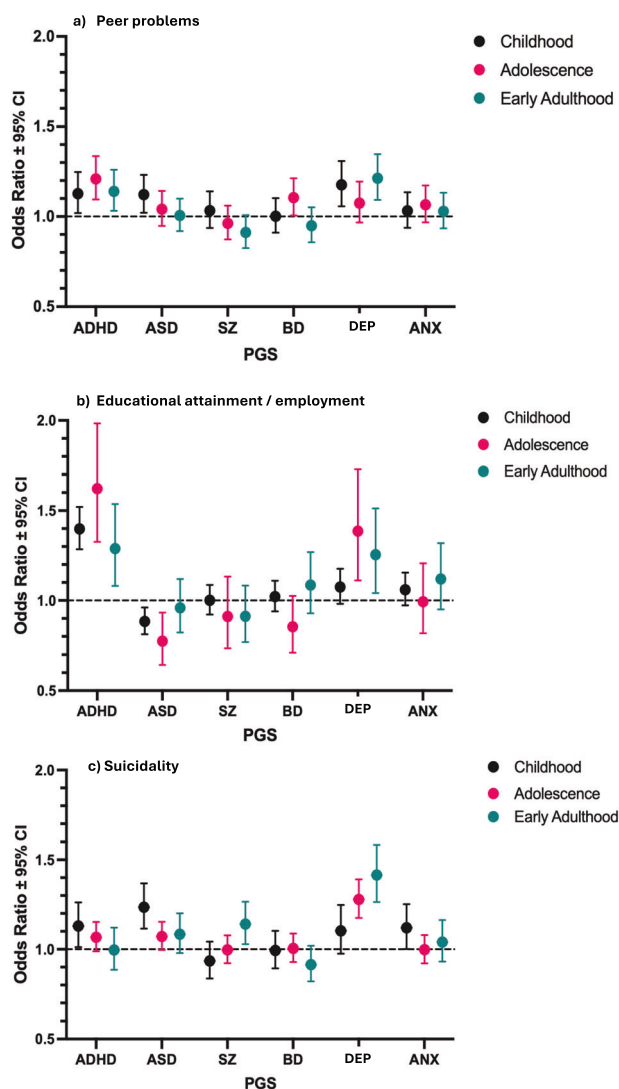


Fig. 2 Associations between polygenic scores (PGS) and social and functional outcomes across development. **a** Peer problems **b** Educational attainment / employment **c** Suicidality. Abbreviations: 95% CI, 95% confidence interval; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; SZ, schizophrenia; BD, bipolar disorder; MDD, depression; ANX, anxiety. Dashed line indicates OR = 1 (null association).

RESULTS

There was no evidence of problematic multicollinearity among predictors ($VIF < 1.5$), see Table S2. The proportion of the sample with each outcome is shown in Table 1.

In the imputed sample ($N = 8,591$), rates of peer problems increased across development (8.8% in childhood, 9.1% in adolescence and 18.5% in young-adulthood). Suicidality was highest in adolescence (24.3%), followed by young-adulthood (15.0%) and lowest in childhood (8.2%). For educational attainment, in childhood 17.5% of participants did not achieve a KS3 SAT grade 5 or above in both maths and English. In adolescence 7.5% did not achieve all GCSEs within A*-C. In young-adulthood 6.8% were not in education, employment or training.

Association between neurodevelopmental/psychiatric PGS with social and functional outcomes

A summary of identified associations between PGS with social and functional outcomes is shown in Supplementary Figure S2.

Peer problems. Figure 2a and Table S3 show multivariable associations between PGS and peer problems across development. ADHD PGS were associated with peer problems in childhood ($OR = 1.13$, 95% CI [1.02–1.25], $p = 0.020$, $q = 0.030$), adolescence ($OR = 1.21$ [1.02–1.34], $p < 0.0001$, $q < 0.0005$) and young-adulthood ($OR = 1.14$ [1.03–1.26], $p = 0.010$, $q = 0.018$), whereas we only found strong evidence of associations between ASD PGS and peer problems in childhood ($OR = 1.12$ [1.02–1.23], $p = 0.017$, $q = 0.038$). Depression PGS were associated with peer problems in childhood ($OR = 1.18$ [1.06–1.31], $p = 0.003$, $q = 0.007$) and young-adulthood ($OR = 1.21$ [1.09–1.35], $p < 0.0001$, $q < 0.0005$). There was also evidence of association between bipolar disorder PGS and peer problems in adolescence although this did not withstand correction for multiple testing ($OR = 1.10$ [1.00–1.21], $p = 0.038$, $q = 0.342$). There was not strong evidence of association between schizophrenia or anxiety PGS and peer problems at any developmental stage.

Educational attainment/ employment. As shown in Fig. 2b and Table S4, ADHD PGS were associated with poor educational attainment in childhood ($OR = 1.40$ [1.29–1.52], $p < 0.0001$, $q < 0.0005$) and adolescence ($OR = 1.62$ [1.33–1.98], $p < 0.0001$, $q < 0.0005$) as well as NEET in young-adulthood ($OR = 1.29$ [1.08–1.54], $p = 0.005$, $q = 0.011$). The opposite relationship was seen for ASD PGS, which was associated with greater educational attainment in childhood ($OR = 0.88$ [0.81–0.96], $p = 0.004$, $q = 0.018$) and adolescence ($OR = 0.77$ [0.64–0.93], $p = 0.007$, $q = 0.021$). Depression PGS were associated with poor educational attainment in adolescence ($OR = 1.39$ [1.11–1.73], $p = 0.004$,

$q = 0.007$) and NEET in young-adulthood ($OR = 1.26$ [1.04–1.51], $p = 0.017$, $q = 0.026$). There was not strong evidence of an association with educational attainment or employment for schizophrenia PGS, bipolar disorder PGS or anxiety PGS at any age.

Suicidality. As shown in Fig. 2c and Table S5, both ADHD PGS ($OR = 1.13$ [1.01–1.26], $p = 0.030$, $q = 0.039$) and ASD PGS ($OR = 1.24$ [1.12–1.37], $p < 0.0001$, $q < 0.0005$) were associated with suicidality in childhood. Depression PGS was associated with suicidality in adolescence ($OR = 1.28$ [1.18–1.39], $p < 0.0001$, $q < 0.0005$) and young-adulthood ($OR = 1.42$ [1.26–1.58], $p < 0.0001$, $q < 0.0005$). There was also evidence of associations between anxiety PGS and suicidality in childhood ($OR = 1.12$ [1.00–1.25], $p = 0.047$, $q = 0.423$) and between schizophrenia PGS and suicidality in young-adulthood ($OR = 1.14$ [1.029–1.266], $p = 0.013$, $q = 0.117$), however these associations did not survive correction for multiple testing. There was not strong evidence of association with suicidality and bipolar disorder PGS at any developmental stage.

Sensitivity analyses

Analyses using parent-reported peer problems in young-adulthood (Table S6) showed a consistent pattern of results as the primary self-reported analyses. Analyses investigating lifetime suicidality in adolescence were consistent with those in the primary analyses (suicidality within one year of assessment, see Table S7). However, in young-adulthood, unlike in primary analyses, there was not strong evidence of association between lifetime suicidality and schizophrenia PGS ($OR = 1.06$, 95% $CI = 0.98$ – 1.15 , $p = 0.161$), but there was evidence of association for ASD PGS ($OR = 1.11$, 95% $CI = 1.02$ – 1.20 , $p = 0.013$), see Table S8.

Analyses using listwise deletion were consistent with primary analyses using imputed data (Tables S9–11).

Finally, the results of univariate analyses between each PGS with each outcome was largely consistent with the primary analyses (Tables S12–14). These found that ADHD and ASD PGS were associated with peer problems and suicidality across development, and depression and anxiety PGS were associated with all outcomes across development. Unlike in the multivariable analyses, univariable analyses did not provide strong evidence of an association between ASD PGS and educational attainment.

DISCUSSION

This study used data from a longitudinal birth cohort to examine associations between PGS for six neurodevelopmental/psychiatric conditions (ADHD, ASD, schizophrenia, bipolar disorder, depression and anxiety) and adverse outcomes (peer problems, educational attainment/employment and suicidality) across childhood, adolescence and young-adulthood. ADHD PGS were associated with outcomes across development, while ASD PGS were associated more with outcomes in childhood, and depression PGS with outcomes in adolescence and young-adulthood. We did not find strong evidence of associations for schizophrenia, bipolar disorder and anxiety PGS. Findings in relation to the hypotheses are discussed below.

Consistent with the first neurodevelopmental hypothesis, ADHD PGS were associated with peer problems and lower educational attainment/unemployment across development as well as suicidality in childhood. Evidence of an association between ADHD PGS and peer problems in childhood and adolescence is supported by previous findings [25]; we extend these findings by identifying an association in young-adulthood. Possible explanations for this association include genetic overlap between ADHD and peer problems and evocative gene-environment correlation. Previous research has found peer problems to be heritable [19]; it may be that the same genetic factors which increase liability to ADHD also

increase liability to peer problems directly, or that this association is via the behavioural manifestations of ADHD genetic liability, evoking negative responses from peers [74]. There was not strong evidence of an association between ADHD PGS and suicidality in adolescence and young-adulthood, which corroborates findings from a previous study [34]. A potential explanation for this is that ADHD PGS show greater associations with cognitive traits, like educational attainment, in young-adulthood than psychological traits, like suicidality [75].

Inconsistent with our neurodevelopmental hypothesis, we did not find consistent evidence of an association for ASD PGS across development, but with peer problems and suicidality in childhood only. Previous research suggests that childhood peer problems associated with ASD PGS remain elevated and developmentally stable, indicating that an association would likely persist across development [19]. Indeed, previous works found evidence of an association between ASD PGS and peer problems during adolescence [19]; however, this analysis was based on univariable analyses, which may have also captured associations with genetic liability for other genetically correlated conditions. A similar pattern was observed in the present study, where univariable, but not multivariable, analyses identified an association between ASD PGS and peer problems in adolescence as well as childhood. Our results contrast with previous work in ALSPAC which did not find strong evidence of association between ASD PGS and peer problems in childhood, which may have arisen from using a different approach to PGS generation [25]. This suggests that previous associations between ASD PGS and peer problems after childhood may have been driven by genetic correlation with other conditions, such as ADHD [76].

Additionally, due to genetic overlap between ADHD and ASD, and the phenotypic associations with lower educational attainment [77] it was hypothesised that both ADHD and ASD PGS would be associated with poorer educational attainment/NEET across development. However, while multivariable analyses showed association between ASD PGS and *greater* educational attainment in childhood and adolescence. Univariable analyses, which did not covary for other PGS (including ADHD PGS), did not show strong evidence of association between ASD PGS and educational attainment. These findings are consistent with previous genetic studies using different methods to investigate differentiating genetic architecture for ASD and ADHD [75, 78]. They suggest that the shared genetic liability to ADHD and ASD, and genetic liability specific to ADHD, are associated with lower educational attainment, whereas genetic liability specific to ASD is associated with higher educational attainment [75]. One explanation is that those recruited to the ASD GWAS from which our PGS were derived were particularly well-educated autistic individuals (selection bias). Alternatively, common variants associated with autism that are not shared with ADHD may also be associated with traits that increase the likelihood of higher educational attainment. This is consistent with suggestions that some non-cognitive phenotypic characteristics of ASD, such as hyper-systemizing and attention to detail, may have beneficial effects on educational attainment [79]. Our findings, like others, highlight the importance of multivariable approaches to studying the genetic liability of multiple conditions together, rather than in isolation and underscores the complexity of the genetic liability for each condition with intricate genetic underpinnings that require careful interpretation.

We also hypothesised that schizophrenia PGS would be associated with outcomes across development, due to the neurodevelopmental nature of the condition. Yet our findings support association with suicidality in young-adulthood only (which did not withstand correction for multiple testing). This is inconsistent with previous findings of associations with suicidality in both childhood [29] and adulthood [80]. One difference between studies is the specific phenotype examined: while our

measure encompassed suicidal thoughts, ideation and suicide attempts, previous work found associations specifically with suicide attempt in childhood and adulthood [29, 80]. In contrast, other research investigating association with a range of suicidality measures, including suicide attempt, did not observe associations with schizophrenia PGS in childhood [44]. These findings thus provide some evidence that schizophrenia PGS may be associated with a range of suicidality outcomes in young-adulthood, but that earlier associations may be more specific to suicide attempt. Studies that are not sensitive to the developmental context may therefore miss these specific associations, which emphasises the significance of the developmental approach. Inconsistent with our hypothesis, we did not find strong evidence of associations between schizophrenia PGS and peer problems or educational attainment/employment at any developmental stage.

Consistent with our depression hypothesis, depression PGS were associated with poor educational attainment/unemployment and suicidality in adolescence and young-adulthood. Unexpectedly, we did not find strong evidence of an association between depression PGS and suicidality in childhood in multivariable analyses, although evidence of association was present for univariable analyses. One explanation is that manifestations of genetic liability specific to depression, like depression itself, do not typically onset until after adolescence, and the associations we, and others [29], observe in univariable analyses are driven by genetic correlation between depression and neurodevelopmental traits [59, 76]. However, we did find evidence of associations between depression PGS and peer problems in childhood, as well as young-adulthood, like a previous study examining univariable associations in the same cohort [25].

Unlike for depression PGS, in multivariable analyses we did not find strong evidence of an association between anxiety PGS and peer problems, suicidality or educational attainment/unemployment in childhood, adolescence or young-adulthood. These results support a previous study [81] which also did not find strong evidence of association between anxiety PGS and adult suicidality. However, in this current study, univariable analyses did show associations for anxiety PGS with all three outcomes, across developmental stages. Taken together with the multivariable analyses, these findings highlight genetic overlap between anxiety and other neuropsychiatric conditions and suggest that it may be the shared effects of these that drive associations for anxiety PGS seen in univariable analyses. Again, this underscores the importance of studying genetic liability to multiple conditions together.

Finally, findings for bipolar disorder PGS were not consistent with our hypotheses (based on phenotypic associations and previous molecular genetic studies [28, 43, 82] that bipolar disorder PGS would be associated with greater educational attainment/unemployment in adolescence and young-adulthood, as well as peer problems and suicidality in young-adulthood. Strong evidence was not found in support of any of these, except for an association with peer problems in adolescence, which did not withstand correction for multiple testing. As with depression, one potential explanation is that bipolar-specific genetic liability manifestations may not typically onset until after young-adulthood.

Strengths and limitations

This study has several important strengths. The longitudinal design allowed us to examine outcomes assessed prospectively across three developmental periods. Further, the use of both multivariable and univariable models to examine genetic liability means that that we could assess the impact of genetic liability specific to individual neurodevelopmental/psychiatric disorders on outcomes of interest. Additionally, a general population sample reduces the sampling bias often seen in clinical samples. Since genetic liability to these conditions is continuous, population

samples better capture associations between varying genetic risk and adverse outcomes, improving generalisability.

The results of this study should be viewed considering methodological limitations. Firstly, except for the SDQ peer problems subscale, outcome measures varied across development. These somewhat limit comparability of suicidality and educational attainment across ages. Like educational attainment/NEET, suicidality was assessed using a different measure at each age and included items which may relate to self-harm without suicidal intent at age 16, likely capturing a broader phenotype. Our outcomes were also assessed at slightly different ages in childhood, with peer problems and suicidality assessed at ages 10/11 but educational attainment at ages 13–14. While we only found strong evidence of associations with childhood education for ADHD and ASD PGS, further studies could investigate associations with education outcomes at younger ages. To improve validity, future longitudinal studies should use consistent measures where possible to distinguish true developmental changes from measurement variation. However, this may not always be feasible, as some tools may not be appropriate for all age groups. Moreover, while we examined different developmental periods, we did not directly compare effect sizes across ages and confidence intervals overlapped. Thus, developmental differences should be interpreted with caution. Similarly, we used cross-sectional analyses, limiting our ability to assess changes over time and therefore, cannot infer how neurodevelopmental/psychiatric PGS may relate to developmental trajectories of educational attainment, suicidality and peer problems. It is possible that neurodevelopmental/psychiatric PGS are more closely linked to changes in adverse outcomes rather than their absolute levels at a single point in time. To explore this further, future research could benefit from trajectory-based methods, to identify developmental patterns.

Finally, whilst the GWAS used for each condition generally include participants from developmental periods spanning childhood to adulthood [41, 58–61], the anxiety GWAS included only adults [61], although research suggests that genetic correlation between childhood and adult anxiety is high [83]. Nevertheless, future work could investigate whether the associations we investigated differ when using PGS derived from GWAS based on different developmental periods. Furthermore, polygenic scores (PGS) capture only the additive effects of common genetic variants associated with each condition. As a result, they do not account for genetic liability arising from rarer mutations, such as copy number variants, which may also be relevant to the outcomes of interest. Finally, our power to detect associations varied across PGS, and may explain some of the null findings for anxiety and autism PGS.

CONCLUSIONS

This study provides novel insights into how genetic liability to neurodevelopmental/psychiatric conditions relates to adverse social and functional outcomes across development. We found variation in the strength and direction of associations across conditions, outcomes and development stage. Our results showed that ADHD and depression PGS were linked to all examined outcomes, suggesting broad and potentially negative influences of genetic liability to these conditions. However, while ADHD PGS showed association with peer problems and educational attainment/employment across development and with suicidality in childhood, depression PGS were associated with education/employment and suicidality from adolescence. ASD PGS showed associations with peer problems and suicidality in childhood, as well as with greater educational attainment in childhood and adolescence. We did not find strong evidence of associations for schizophrenia, bipolar disorder or anxiety PGS. Our findings highlight the importance of examining genetic liability to multiple

neurodevelopmental/psychiatric conditions simultaneous and of a developmental perspective.

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AUTHOR CONTRIBUTIONS

BF conceptualised the study and conducted the literature review. BF, LR and AS developed the methodology and study design. CD and AS cleaned and prepared the data, and BF and AS conducted the data analysis. All authors contributed to interpreting the data. BF wrote the original draft, with CD, LR and AS reviewing and editing. LR and AS provided project supervision, acting as joint senior authors. All authors approved the final version of the manuscript.

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ETHICAL APPROVAL

Ethical approval for this study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). 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.

COMPETING INTERESTS

The authors declare no competing interest.

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