Research paper

Investigating the neurodevelopmental correlates of early adolescent-onset emotional problems

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A B S T R A C T

Background: Emotional problems (EPs) increase sharply after mid-adolescence. Earlier EPs are associated with poorer long-term outcomes, and their underlying mechanisms may differ to later-onset EPs. Given an established relationship between ADHD, autism, and later depression, we aimed to examine associations between neurodevelopmental conditions and correlates and early adolescent-onset EPs.
Methods: Adolescents in two UK population cohorts, Avon Longitudinal Study of Parents and Children (ALSPAC) and Millennium Cohort Study (MCS), were included. Individuals scoring >6 on the Strengths and Difficulties Questionnaire (SDQ) emotional problems subscale between ages 11–14 were defined as having early adolescent-onset EP, whilst those scoring >6 for the first time at 16–25 were defined as having later-onset EP. We tested associations between early adolescent-onset EP (total cases = 887, controls = 19,582) and ICD-10/DSM-5 neurodevelopmental conditions and known correlates, including: sex, birth complications, low cognitive ability, special educational needs (SEND), and epilepsy. Analyses were conducted separately in ALSPAC and MCS then meta-analysed.
Results: In the meta-analysis of both cohorts, early adolescent-onset EPs were associated with female sex and greater likelihood of low cognitive ability, SEND, autism, ADHD, and reading difficulties. Compared to later-onset EP, early adolescent-onset EPs were associated with male sex, low cognitive ability, SEND, epilepsy, ASD, ADHD, and reading difficulties.
Limitations: A clinical definition of depression/anxiety was available only in ALSPAC, instead we primarily defined EP via questionnaires, which capture a broader phenotype.
Conclusions: Individuals with early adolescent-onset EP are likely to have a co-occurring neurodevelopmental condition. Clinicians should consider assessing for neurodevelopmental conditions in young adolescents with EPs.

1. Introduction

Depressive and anxiety disorders are among the most common mental health problems worldwide, with a median age at onset of 30 years (Solmi et al., 2022). Emotional disorders of this type are a growing concern due to their rising prevalence in adolescence, and onset of depression in this age group is associated with poorer outcomes (Thapar et al., 2022). Although emotional disorders, especially depression, are viewed and diagnosed as a unitary concept, they are highly heterogeneous and show variability in age at onset, antecedents, chronicity, and treatment response.

Depression incidence typically rises from mid adolescence onwards (Solmi et al., 2022), although some young people develop the condition earlier. Evidence suggests that earlier-onset depression may be different to later-emerging depression, with early studies highlighting potential differences between prepubertal and post-pubertal depression. More recent longitudinal studies suggest this difference may extend to early adolescent-onset depression (before aged 15) compared to later

adolescent and adult-onset (Rice et al., 2019a, 2019b).

These differences include a higher proportion of males in childhood- and early adolescent-onset depression cases, compared to depression overall which is more common in females (Birmaher et al., 1996). Furthermore, childhood- and early adolescent-onset depression is associated with longer and recurrent episodes, a greater likelihood of hospitalization, and greater risk of other mental health problems (Korczak and Goldstein, 2009). Symptom profiles of depression also differ by age at onset, with psychomotor agitation and somatic complaints more common in childhood-onset than adolescent-onset depression (Ryan et al., 1987). Findings on treatment differences are mixed. Tricyclic antidepressants, which are effective in treating adults with depression, appear to show no benefit in treating child and adolescent depression (Hazell and Mirzaie, 2013). However, other interventions, including selective serotonin reuptake inhibitors, do appear effective in treating depression in young people (National Institute for Health and Care Excellence, 2020).

Child and adolescent-onset relative to adult-onset depression also shows a different profile of risk factors and antecedents. Early studies suggest earlier onset depression or affective disturbance (onset by 15 years) is associated with a greater number of obstetric complications, poorer motor skills and later attainment of motor skill milestones, and poorer cognition (Jaffee et al., 2002; van Os et al., 1997), suggestive of a neurodevelopmental aetiology. Additionally, ADHD and schizophrenia genetic liability appear to be more strongly associated with early adolescent-onset emotional problems than later adolescent-onset emotional problems (Riglin et al., 2018; Weavers et al., 2021). Together, these findings raise the possibility that the antecedents and underlying mechanisms for earlier adolescent-onset depression, or more broadly defined emotional disorder, may be different to later adolescent or adult-onset depression. Less is known about the differences between earlier and later onset-anxiety disorders, although the different types of anxiety disorder emerge at different ages (e.g. separation anxiety vs generalised anxiety disorder), and have a greater degree of similarity to each other than depressive disorders across different ages (Rapee et al., 2023).

We aimed to examine associations between broadly defined ICD-10/ DSM-5 neurodevelopmental disorders, and known correlates of these conditions, and early adolescent-onset emotional problems using two large UK population-based cohorts. We define early adolescent-onset as first episode occurring before 15 years of age, consistent with the literature as well as sample data availability (Jaffee et al., 2002; Rice et al., 2019a, 2019b; van Os et al., 1997). We hypothesised that early adolescent-onset emotional problems are associated with a higher burden of neurodevelopmental conditions, including ADHD and autism spectrum disorder (ASD), and known neurodevelopmental disorder correlates, such as preterm birth and special educational needs, compared to i) those who do not have early adolescent-onset emotional disorder and ii) those with later-onset (≥16 years) emotional problems.

2. Method

2.1. Participants

Participants were ascertained from two UK population cohorts: the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Millennium Cohort Study (MCS).

2.1.1. ALSPAC

Pregnant women residing in the Avon area of England with an estimated delivery date between 1st April 1991 and 31st December 1992, were invited to participate in ALSPAC. The core sample consisted of 14,541 pregnancies, and of these pregnancies 13,988 children were alive at 1 year. Following the initial recruitment, an additional 913 children were recruited in three phases. Thus, for data collected after the age of seven, the total sample size is 15,447 pregnancies, resulting in

15,658 foetuses. Of these, 14,901 children were alive at 1 year of age (Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019). At age 25, study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2009). Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool https://www.bristol.ac.uk/alspac/researchers/our-data/. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

2.1.2. Millennium cohort study

Children born in England and Wales between 1st September 2000 and 31st August 2001, or in Scotland and Northern Ireland between 24th November 2000 and 11th January 2002, who were alive at 9 months of age, living in the UK, and eligible to receive child benefit, were able to participate in MCS. At the time, all children living in the UK were eligible to receive child benefit, with the exception of a small group of children, such as asylum seekers. MCS identified residential areas across the UK to recruit from, and intentionally oversampled children living in economically disadvantaged areas and children of ethnic minority backgrounds, in order to adequately represent populations that have been typically under-represented in research. A total of 19,870 children were recruited, and 10,757 participants remained in the sample at age 17. Ethical approval was obtained from the NHS Research Ethics Committee, and parents provided informed consent for their child to participate.

2.2. Exposures (neurodevelopmental phenotypes)

2.2.1. ALSPAC

Details of all individual measures in ALSPAC are provided in Table S1. All items were defined as binary categories. Preterm birth was defined as gestational age < 37 weeks and low birthweight as weight < 2500 g (singleton births only; see analysis section), informed by multiple sources including birth records and parent-report. Low cognitive ability was defined as the lowest-scoring 2.5 %, after age correction, of the Wechsler Intelligence Scale for Children (Wechsler, 1991) at approximately age 8. Special educational needs (SEND) were defined by parent-report at ages 8 or 11. Neurodevelopmental conditions were defined using structured diagnostic interviews and measures that approximated phenotypes included under the umbrella of ICD-10/DSM-5 neurodevelopmental disorders (American Psychiatric Association, 2013; World Health Organisation, 2019), as well as epilepsy, which is considered a neurodevelopmental disorder (Shankar et al., 2020). Epilepsy data defined by parent-report were available between the ages of 18 months and 17 years. ASD-related symptoms were defined as a score > 9 on the parent-reported Social Communication Disorder Checklist (Skuse et al., 2005) at ages 7, 10, 13, or 16. ADHD was defined by the DAWBA (Development and Wellbeing Assessment)(Goodman et al., 2000a) interview with the parent, conducted at ages 7, 10, 13, and 15. Individuals meeting diagnostic criteria at any of the ages were defined as having ADHD, as this definition is comparable to a clinical diagnosis of ADHD. Reading difficulties were assessed at age 7, defined as the lowest scoring 5 % on the Wechsler Objective Reading Dimensions (Rust et al., 1993). Developmental coordination difficulties were defined as the lowest scoring 5 % on the Movement Assessment Battery for Children, measured at age 7 (Eyre et al., 2019; Henderson et al., 2007). Individuals scoring in the lowest 5 % on the Children's Communication Checklist (CCC) at age 9, or on the adult version of the CCC at age 25 were defined as having communication difficulties (Bishop, 1998; Whitehouse and Bishop, 2009).

2.2.2. Millennium cohort study

Details of all individual measures in MCS are provided in Table S2. All variables were defined as binary categories. Preterm birth and low birthweight were defined by parent-report of gestational age < 37 weeks and birthweight <2500 g (singletons only), respectively. To measure cognitive ability, participants completed the picture, pattern, and vocabulary subscales of the British Ability Scales at age 5 (Elliott et al., 1996). Consistent with previous research (Basatemur et al., 2013), we conducted a principal components analysis of these three subscales and standardised the first principal component to create an overall measure of cognitive ability. We then defined low cognitive ability as the lowest scoring 2.5 % of the sample. Parents reported whether their child had been recognized as having SEND at ages 7, 11, or 14. Parent-report was also used to define epilepsy at ages 5, 7, 11, or 17. Parent-report of a clinician diagnosis of autism or Asperger's at age 5, 7, 11, or 14 was used to define ASD. ADHD was defined as a score > 8 on the parent-reported hyperactivity subscale of the SDQ at any of the following ages: 5, 7, 11, 14, or 17 (Goodman et al., 2000b). Children completed the British Ability Scales (Elliott et al., 1996) reading subscale at age 5, which was used to define reading difficulties. Parental ASD was defined by self-report from the parent when cohort members were 14. Older siblings were invited to complete the SDQ when the cohort member was aged 3 and 5. Sibling ADHD, as an index of family history, was defined by the SDQ hyperactivity subscale using the accepted threshold for probable ADHD of >8 (Goodman et al., 2000b).

2.3. Outcomes

In both cohorts, early adolescent-onset emotional problems were assessed using the SDQ emotional problems subscale, which has been validated against ICD diagnoses of major depressive disorder (MDD) and Generalised Anxiety Disorder (GAD) (Armitage et al., 2023; Goodman et al., 2000b). Individuals scoring higher than six (the validated cut-point) on the emotional problems subscale at any point between ages 11 and 14 years were defined as having early adolescent-onset emotional problems. In ALSPAC, we used parent-reported SDQ at ages 12 and 13, whilst in MCS, we used parent-report SDQ at ages 11 and 14.

For older adolescents and young people, individuals scoring >6 on the emotional subscale of the SDQ at age 16 (parent-repot) or 25 (self-report) in ALSPAC, or 17 (self-report) in MCS but not at ages 11–14, were defined as having later adolescent-onset emotional problems. Individuals scoring >6 at a later time point, but who were missing data at all time points between ages 11 and 14 were excluded from the definition of later-onset emotional problems. We chose to only include measurements from age 11 onwards as the SDQ emotional problems subscale has been validated in identifying MDD and GAD in this age group.

In addition, our secondary outcomes were a diagnosis of MDD or GAD in ALSPAC participants, using the DAWBA conducted with the parent. Individuals meeting ICD-10 diagnostic criteria for MDD or Depressive disorder not otherwise specified at ages 10 or 13 were defined as having early adolescent-onset MDD. Individuals who did not meet criteria aged 10–13 but who met ICD-10 criteria for a mild, moderate, or severe depressive episode at age 17 or 24, measured by the Clinical Interview Schedule (CIS-R) (Lewis et al., 1992), were defined as having later-onset MDD. Individuals meeting ICD-10 diagnostic criteria for GAD at ages 10 or 13, identified via the DAWBA, were defined as having early adolescent-onset GAD. Individuals who did not meet ICD-10 GAD criteria at ages 10–13 but met the criteria at ages 17 or 24, measured by the CIS-R, were defined as having later-onset GAD. MDD and GAD diagnoses were not available in MCS.

2.4. Data availability and access

ALSPAC is based at the University of Bristol, and is accessible to bona fide researchers upon application. Researchers can apply for ALSPAC data access on the University of Bristol website: https://www.bristol.ac.uk/alspac/researchers/access/. MCS survey data can be accessed by bona fide researchers through the UK Data Service (doi:https://doi.org/10.5255/UKDA-Series-2,000,031).

3. Analysis

All analysis was undertaken using R (R Core Team, 2022); one twin from each twin pair was excluded from all analyses, and only singleton births were included in the analysis of preterm birth and low birthweight.

3.1. Primary analysis: Early adolescent-onset emotional problems vs remainder of the cohort

Separate univariable logistic regressions were used to test associations between each neurodevelopmental correlate and early adolescent-onset emotional problems, in comparison to the remainder of the sample (i.e. individuals without emotional problems or with later-onset emotional problems), in ALSPAC and MCS. Random-effects models, performed using the R package 'meta' (Balduzzi et al., 2019), were used to meta-analyse findings for phenotypes that were common to ALSPAC and MCS (sex, preterm birth, low birthweight, low cognitive ability, SEND, epilepsy, ADHD, ASD, and reading difficulties). Individuals were included in the primary analysis if they had complete SDQ emotional problems subscale data at age 12 and/or 13 in ALSPAC and age 11 and/or 14 in MCS.

3.2. Secondary analyses: Early adolescent-onset EP vs "later" adolescent EP

To compare early adolescent-onset emotional problems vs "later" youth emotional problems, we used logistic regressions to assess the association between each phenotype and early compared to later-onset emotional problems (i.e. onset at age 11–14 vs. onset at 16–25). In ALSPAC, individuals were included if they had SDQ emotional problems subscale data at i) ages 12 or 13, and ii) ages 16 or 25. Individuals from MCS were included if they had SDQ emotional problems subscale data at i) ages 11 or 14, and ii) age 17. In later adolescence and young adulthood, self-report may be considered a more useful informant of emotional problems (Cohen et al., 2019), thus we define later-onset using self-report items where available, which was at age 25 in ALSPAC and age 17 in MCS. However, as early adolescent-onset was defined by parent-report, we conducted sensitivity checks using parent-reported later-onset emotional problems.

The SDQ captures a broad phenotype encompassing symptoms of both depression and anxiety, and has been validated against a diagnosis of MDD and GAD in the age range of our samples (Armitage et al., 2023). Therefore, to assess whether our findings were specific to MDD, GAD, or both, we repeated the primary analyses using MDD diagnosis as the outcome and separately with GAD diagnosis as the outcome, which were available in ALSPAC only. Individuals with DAWBA data at ages 10 or 13 were included in this analysis, regardless of whether they had suitable SDQ data for the primary analysis. For the comparison between earlier and later-onset MDD and GAD, we compared individuals who met MDD/GAD criteria at age 10–13 to individuals who met criteria for the first time at age 17 or 24.

To investigate potential sex differences, univariable regressions from the primary analysis were repeated, including sex and the phenotype of interest as an interaction term. Finally, as a post-hoc test, as all the neurodevelopmental phenotypes are correlated, we conducted multivariable analyses to explore whether observed associations with early-adolescent onset emotional problems were explained by specific phenotypes.

3.3. Missing data

Multiple imputation was run on the primary analysis sample (i.e., those with early emotional problems data) using the R package 'mice' (Buuren and Buuren and Groothuis-Oudshoorn, 2011) separately in ALSPAC and MCS. In ALSPAC, all items included in the univariable models were included in the imputation, alongside socioeconomic status and multiple birth status. In MCS, all variables analysed in the uni-variable models were included in the imputation, except for sibling ADHD as missingness for this variable is dependent on whether the cohort member has an older sibling. Sample weight at recruitment (derived by MCS for use when handling missing data) (Centre For Longitudinal Studies, 2020), and whether the cohort member was a single or multiple birth were also included in the imputation. Our outcome, early adolescent-onset emotional problems, was not imputed in either cohort. For both cohorts, imputation was run 25 times, with a maximum of 25 iterations per dataset using the predictive mean matching method. All other settings remained as the default option in 'mice'. Univariable regressions were run separately for each imputed dataset, with the effect sizes pooled to give an overall estimate. The main analyses described in the results present complete cases, and MI results are detailed in the supplementary material.

4. Results

4.1. Descriptive data

In ALSPAC, 8104 people had data on emotional problems at ages 12 and/or 13; of these 213 (2.6 %) individuals were classified as having early adolescent-onset emotional problems. 6075 people also had data on emotional problems at ages 16 and/or 25, of whom 483 (8.0 %) were defined as having later-onset emotional problems. 125 out of 8410 (1.5 %) individuals met ICD-10 criteria for MDD before age 14. 584 out of 4774 (12.2 %) individuals met ICD-10 criteria for MDD at age 17 and/or 24, but not before age 14 (i.e. had later-onset MDD). 73 out of 9573 (0.76 %) individuals met ICD-10 criteria for GAD before age 14. 505 out

of 5006 (10.1 %) of individuals met ICD-10 criteria for GAD at age 17–24, but not at age 14. Among the 173 individuals categorised as having early adolescent-onset MDD or GAD, 25 individuals (14.45 %) met criteria for both.

In MCS, 12,365 people had data on emotional problems at age 11 and/or 14. Of these, 674 (5.5 %) individuals were classified as having early adolescent-onset emotional problems. 8886 people also had data on emotional problems at age 17, of whom 1070 (12.0 %) were defined as having later-onset emotional problems.

Table 1 details the number of individuals with each neuro-developmental phenotype examined in ALSPAC and MCS. In ALSPAC, 53.3 % of individuals with early adolescent-onset emotional problems had a probable neurodevelopmental condition (defined as ADHD, ASD, reading difficulties, coordination difficulties, or communication difficulties), compared to 19.4 % of people in ALSPAC without early adolescent-onset emotional problems.

36.2 % of people in MCS with early adolescent-onset emotional problems had a reported neurodevelopmental condition (defined as ADHD, ASD, or reading difficulties), compared to 11.7 % of people in MCS without early adolescent-onset emotional problems.

The percentage of individuals with and without early-adolescent onset emotional problems endorsing 0, 1, 2, or 3 or more of the neurodevelopmental phenotypes are displayed in Fig. S1. All items included in the analysis of each sample, with the exception of sex, were used to derive this measure.

4.2. Primary complete-case analysis: Early adolescent-onset emotional problems vs. those without early adolescent-onset emotional problems

In ALSPAC, which includes more measures of neurodevelopmental phenotypes, early adolescent-onset emotional problems were associated with female sex, SEND, epilepsy, ASD, ADHD, reading difficulties and communication difficulties (Table 2).

In MCS, early adolescent-onset emotional problems were associated with female sex, low cognitive ability, SEND, epilepsy, ASD, ADHD, reading difficulties, sibling ADHD, and parental ASD (Table 2).

Table 1

Frequency (and %) of each phenotype in individuals with and without early adolescent-onset emotional problems. Displayed separately for MCS and ALSPAC.

Item	Group	ALSPAC		MCS	
		No early adolescent-onset emotional problems ($n = 7891$)	Early adolescent-onset emotional problems ($n = 213$)	No early adolescent-onset emotional problems ($n = 11{,}691$)	Early adolescent-onset emotional problems ($n = 674$)
Sex	Male	3959 (50.2 %)	89 (41.8 %)	5961 (51 %)	284 (42.1 %)
	Female	3932 (49.8 %)	124 (58.2 %)	5730 (49 %)	390 (57.9 %)
Preterm birth	No	7128 (95.6 %)	193 (93.7 %)	10,572 (93.4 %)	601 (91.9 %)
	Yes	330 (4.4 %)	13 (6.3 %)	752 (6.6 %)	53 (8.1 %)
Low birthweight	No	7110 (96.5 %)	196 (95.1 %)	10,715 (93.7 %)	614 (92.5 %)
	Yes	259 (3.5 %)	10 (4.9 %)	715 (6.3 %)	50 (7.5 %)
Low cognitive ability	No	5838 (98.0 %)	142 (96.6 %)	10,744 (98.2 %)	598 (95.4 %)
	Yes	119 (2.0 %)	5 (3.4 %)	196 (1.8 %)	29 (4.6 %)
SEND	No	4299 (76.1 %)	84 (57.9 %)	6811 (86.3 %)	313 (60.8 %)
	Yes	1350 (23.9 %)	61 (42.1 %)	1081 (13.7 %)	202 (39.2 %)
Epilepsy	No	7158 (99.3 %)	191 (96.5 %)	7655 (95.7 %)	519 (92.8 %)
	Yes	51 (0.7 %)	7 (3.5 %)	347 (4.3 %)	40 (7.2 %)
ASD	No	6779 (88.6 %)	120 (58.8 %)	7744 (97.1 %)	417 (80.7 %)
	Yes	871 (11.4 %)	84 (41.2 %)	233 (2.9 %)	100 (19.3 %)
ADHD	No	7448 (97 %)	173 (84.8 %)	10,796 (92.4 %)	502 (74.5 %)
	Yes	234 (3 %)	31 (15.2 %)	894 (7.6 %)	172 (25.5 %)
Reading difficulties	No	6069 (96.6 %)	147 (91.3 %)	9915 (95.6 %)	514 (89.5 %)
	Yes	212 (3.4 %)	14 (8.7 %)	453 (4.4 %)	60 (10.5 %)
Coordination difficulties	No	4716 (95.7 %)	117 (92.1 %)	NA	
	Yes	213 (4.3 %)	10 (7.9 %)		
Communication difficulties	No	6326 (92.1 %)	129 (71.7 %)	NA	
	Yes	542 (7.9 %)	51 (28.3 %)		
Sibling ADHD	No	NA		4877 (96.4 %)	273 (93.5 %)
	Yes			182 (3.6 %)	19 (6.5 %)
Parental ASD	No	NA		10,219 (99.1 %)	608 (97.1 %)
	Yes			96 (0.9 %)	18 (2.9 %)

Table 2

The association between each neurodevelopmental phenotype and early adolescent-onset emotional problems, in comparison to the rest of the sample, using individual univariate models in complete-cases. Results are displayed for ALSPAC, MCS, and the meta-analysis between the two cohorts. Columns refer to Odds ratio (OR), 95 % confidence intervals (CI) and *p*-value (P).

Item	ALSPAC				MCS				Meta-analysis			
	OR	Lower CI	Upper CI	P	OR	Lower CI	Upper CI	P	OR	Lower CI	Upper CI	P
Female sex	1.40	1.06	1.85	0.02	1.43	1.22	1.67	8.6E-06	1.42	1.24	1.63	4.3E-07
Preterm birth	1.45	0.82	2.58	0.20	1.24	0.93	1.66	0.15	1.28	0.99	1.66	0.06
Low birthweight	1.40	0.73	2.68	0.31	1.22	0.91	1.64	0.19	1.25	0.95	1.64	0.11
Low cognitive ability	1.73	0.70	4.29	0.24	2.66	1.78	3.96	1.5E-06	2.48	1.72	3.57	1.1E-06
SEND	2.31	1.65	3.23	9.6E-07	4.07	3.37	4.91	2.4E-48	3.12	1.80	5.42	5.3E-05
Epilepsy	5.14	2.30	11.48	6.4E-05	1.70	1.21	2.39	2.2E-03	2.78	0.95	8.17	0.06
ASD	5.45	4.09	7.26	7.1E-31	7.97	6.18	10.28	1.2E-57	6.63	4.57	9.62	2.5E-23
ADHD	5.70	3.81	8.54	2.9E-17	4.14	3.43	4.98	1.4E-50	4.61	3.42	6.21	7.5E-24
Reading difficulties	2.73	1.55	4.80	5.0E-04	2.55	1.92	3.39	8.9E-11	2.59	2.01	3.34	1.9E-13
Coordination difficulties	1.89	0.98	3.66	0.06	NA				NA			
Communication difficulties	4.61	3.30	6.46	4.5E-19	NA				NA			
Sibling ADHD	NA				1.86	1.14	3.04	0.01	NA			
Parental ASD	NA				3.15	1.89	5.25	1.0E-05	NA			

In the meta-analysis of phenotypes common to ALSPAC and MCS, early adolescent-onset emotional problems were associated with female sex, low cognitive ability, SEND, ASD, ADHD and reading difficulties, but not with preterm birth, low birthweight, or epilepsy (Fig. 1 and Table 2).

4.3. Early adolescent-onset emotional problems vs "Later adolescent-onset" emotional problems

Full results of analyses comparing early to later adolescent-onset emotional problems in complete cases are displayed in Table 3 and Fig. 1.

In ALSPAC, early adolescent-onset emotional problems, compared to later-onset emotional problems (age 16–25) were associated with male sex, preterm birth, SEND, epilepsy, ASD, ADHD, reading difficulties, coordination difficulties, and communication difficulties.

In MCS, early adolescent-onset emotional problems, compared to later-onset emotional problems (age 17), were associated with male sex, low cognitive ability, SEND, epilepsy, ASD, ADHD, reading difficulties, and parental ASD.

In a meta-analysis of both cohorts for common measures, early adolescent-onset emotional problems, compared to later-onset emotional problems, were associated with male sex, low cognitive ability, SEND, epilepsy, ASD, ADHD, and reading difficulties, but not with preterm birth or low birthweight.

4.4. Sensitivity analysis

In ALSPAC, the multivariable model containing all neuro-developmental variables showed associations between early adolescent-onset emotional problems and female sex (OR = 3.72 [2.05–6.74], $p = 1.4 \times 10^{-5}$), epilepsy (OR = 7.27 [1.41–37.64], $p = 0.02$), ASD (OR = 5.88 [3.29–10.50], $p = 2.1 \times 10^{-9}$), and communication difficulties (OR
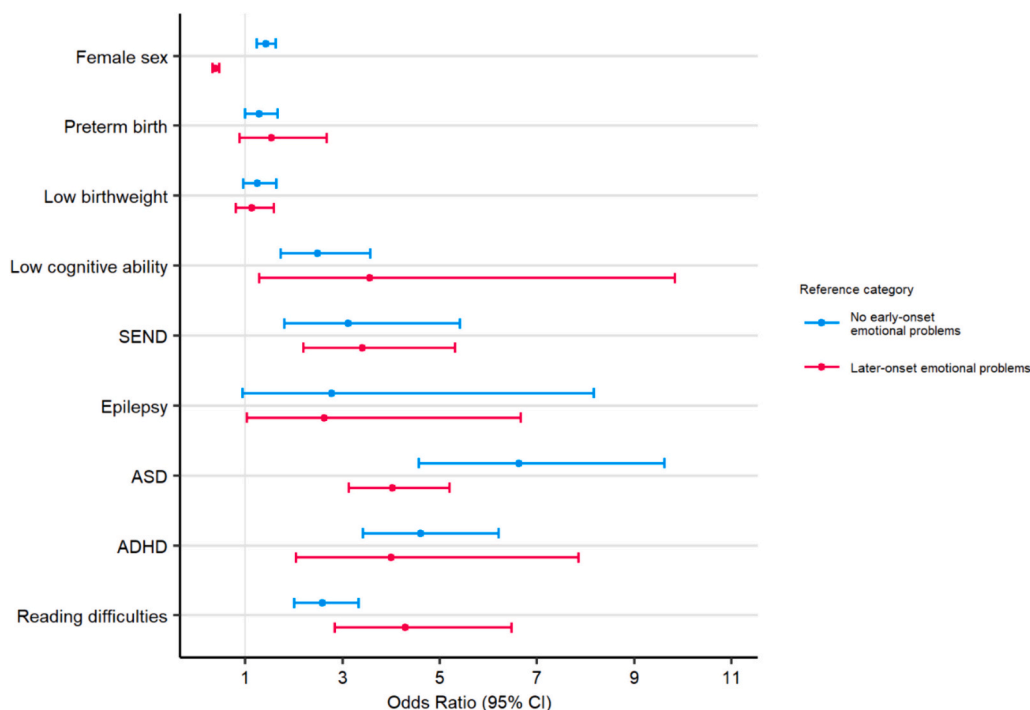

Fig. 1. Results of the meta-analysis of ALSPAC and MCS complete-case analyses. Points indicate odds ratio and error bars indicate 95 % confidence intervals. Blue refers to the primary analysis of early adolescent-onset emotional problems compared to the remainder of the sample. Pink refers to the secondary analysis comparing early adolescent-onset to later-onset emotional problems. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3

The association between each neurodevelopmental phenotype and early adolescent-onset emotional problems, in comparison to individuals with later-onset emotional problems only. Results are displayed for MCS, ALSPAC, and the meta-analysis between the two cohorts.

Item	ALSPAC				MCS				Meta-analysis			
	OR	Lower CI	Upper CI	P	OR	Lower CI	Upper CI	P	OR	Lower CI	Upper CI	P
Female sex	0.34	0.24	0.48	1.6E-09	0.41	0.34	0.51	1.3E-16	0.39	0.33	0.47	2.0E-24
Preterm birth	2.30	1.05	5.05	0.04	1.26	0.87	1.82	0.23	1.53	0.88	2.68	0.13
Low birthweight	1.60	0.70	3.66	0.27	1.05	0.73	1.52	0.79	1.13	0.80	1.58	0.48
Low cognitive ability	1.91	0.60	6.10	0.28	5.47	2.57	11.64	1.0E-05	3.56	1.29	9.83	0.01
SEND	2.64	1.74	4.02	5.9E-06	4.17	3.14	5.52	3.4E-23	3.41	2.19	5.31	5.6E-08
Epilepsy	5.41	1.38	21.15	0.02	1.92	1.19	3.12	0.01	2.63	1.04	6.67	0.04
ASD	2.88	2.01	4.12	8.4E-09	5.71	3.69	8.84	5.1E-15	4.01	2.04	7.85	5.2E-05
ADHD	3.86	2.16	6.90	5.3E-06	4.07	3.07	5.40	2.6E-22	4.03	3.12	5.20	7.4E-27
Reading difficulties	5.40	2.14	13.65	3.6E-04	4.05	2.55	6.42	2.8E-09	4.29	2.84	6.48	4.9E-12
Coordination difficulties	2.50	1.04	6.04	0.04	NA				NA			
Communication difficulties	2.62	1.71	4.02	1.1E-05	NA				NA			
Sibling ADHD	NA				1.74	0.90	3.37	0.10	NA			
Parental ASD	NA				2.32	1.13	4.77	0.02	NA			

$= 2.69$ [1.36–5.29], $p = 4.2 \times 10^{-3}$). In MCS, the multivariable model highlighted associations between early adolescent-onset emotional problems and female sex (OR $= 2.16$ [1.53–3.05], $p = 1.2 \times 10^{-5}$), SEND (OR $= 2.57$ [1.72–3.85], p $= 4.2 \times 10^{-6}$), ASD (OR $= 3.97$ [2.28–6.91], $p = 1.1 \times 10^{-6}$), and ADHD (OR $= 2.90$ [1.90–4.42], $p = 7.5 \times 10^{-7}$).

Sensitivity checks using parent-reported measures to define later-onset emotional problems were broadly consistent with the main findings using self-reported measures (Table S3 and S4).

4.5. Early adolescent-onset major depressive disorder and generalised anxiety disorder

Results were broadly consistent when using the DAWBA to define i)

early adolescent-onset MDD in ALSPAC and ii) early adolescent-onset GAD in ALSPAC, compared to those using the SDQ to define early adolescent-onset emotional problems, displayed in Fig. 2 and Table S5. Results comparing early-adolescent onset MDD and GAD to later-onset MDD and GAD (ages 17–24), respectively, were also consistent with results using the SDQ to define emotional problems across ages (Fig. S2 and Table S6).

4.6. Sex differences

No significant interactions with sex were observed for any of the neurodevelopmental phenotypes.
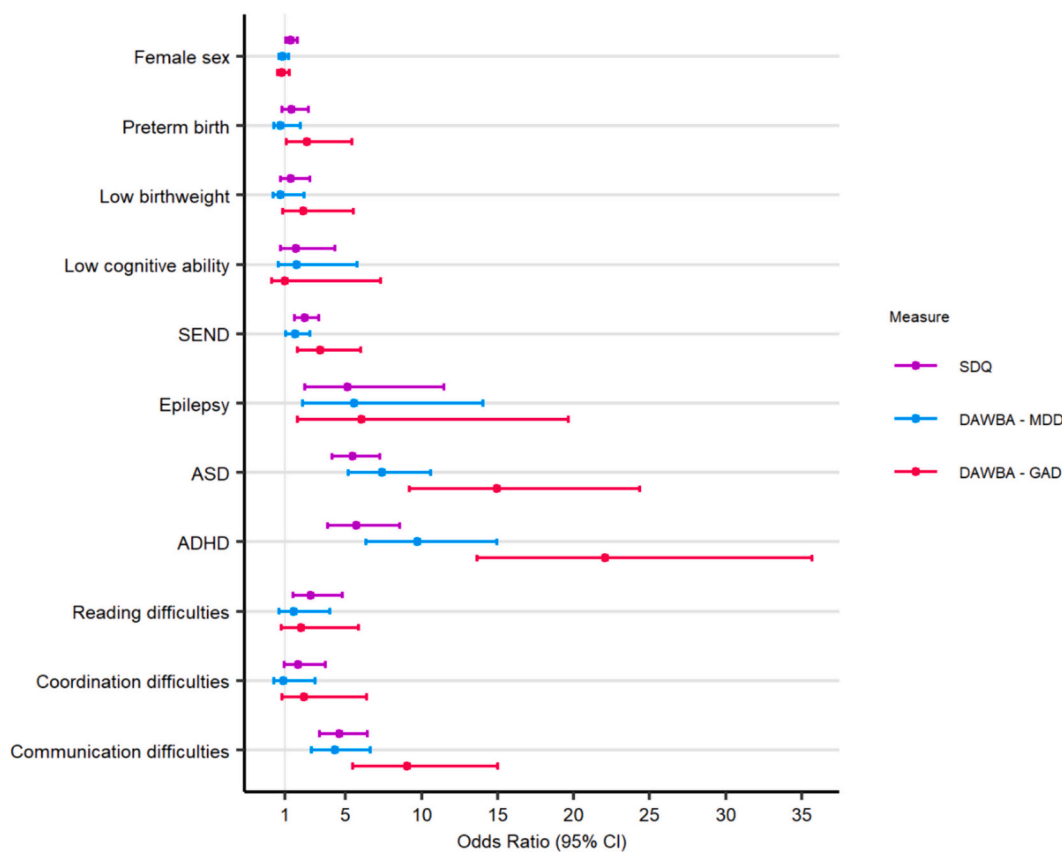

Fig. 2. Odds ratios and 95 % confidence intervals for the association between each neurodevelopmental phenotype and early adolescent-onset emotional problems (purple), early adolescent-onset MDD (blue), and early adolescent-onset GAD (pink) in the ALSPAC cohort, compared to the remainder to the cohort. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.7. Multiple imputation

Results of the multiple imputation in MCS and ALSPAC were consistent with the findings of the complete-case univariable analysis (Tables S7-S9 and Figs. S3-S4).

5. Discussion

In this study, early adolescent-onset emotional problems were associated with a substantially increased likelihood of neurodevelopmental conditions and indices of neurodevelopmental liability, with odds particularly pronounced for ADHD and ASD (OR = 4.61 and 6.63, respectively), when compared to those without early adolescent-onset emotional problems. In the meta-analysis of phenotypes common to ALSPAC and MCS, early adolescent-onset emotional problems were associated with female sex, low cognitive ability, SEND, ASD, ADHD, and reading difficulties, compared to the rest of the sample. We also observed associations between early adolescent-onset emotional problems and neurodevelopmental phenotypes when compared to "later-onset" youth emotional problems at ages 16–25, suggesting neurodevelopmental conditions and liability may represent a specific risk for emotional problems in late childhood/early adolescence, rather than reflecting a difference between youth with and without emotional problems, regardless of age of onset.

For clinicians seeing those with early adolescent-onset emotional problems, including MDD and GAD, our findings highlight the importance of screening for neurodevelopmental conditions. Of those with early adolescent-onset emotional problems in our cohorts, between 36 % and 53 % of children had at least one neurodevelopmental difficulty. Screening for neurodevelopmental difficulties may be especially important as there is evidence to suggest that these conditions, especially ADHD, can be missed in those with depression and anxiety (Bron et al., 2016; Purper-Ouakil et al., 2007). For example, in one UK study of female adults with at least two episodes of MDD, 3 % appeared to have unrecognised ADHD and 13 % a high level of ADHD symptoms. These adults with ADHD had an earlier age at onset of depression than those without ADHD, and ADHD was associated with more severe depressive symptoms, higher recurrence, and increased suicidality and hospitalization (Powell et al., 2021).

For those who are involved in the care of children with neurodevelopmental conditions, our study adds to previous literature highlighting that they are at higher risk of depression (Thapar et al., 2023) and anxiety disorders (White et al., 2009). Previous work in the ALSPAC cohort showed a two-fold increased likelihood of depression in adolescence among individuals with a neurodevelopmental condition (Eyre et al., 2019). Other studies have observed that autistic individuals are four times more likely to experience depression than non-autistic individuals (Hudson et al., 2019) whilst 42–79 % of people with autism experience anxiety disorders (Kent and Simonoff, 2017). Up to 44 % of people with ADHD experience depression (Thapar et al., 2023), and a substantial portion, 31 % in one study, have a co-occurring anxiety disorder (Tsang et al., 2015). We extend these findings to show that other neurodevelopmental conditions, as well as indices of neurodevelopmental liability, are associated with an increased likelihood of early emotional problems, by age 14. Our results thus suggest that practitioners, as well as those working in education, need to be mindful that children and adolescents with neurodevelopmental disorders/liabilities are at higher risk for developing depression/emotional problems and at an earlier age than is typical.

Our findings indicate a potential neurodevelopmental pathway into emotional problems that manifests as onset in childhood or early adolescence. This may explain why previous studies have found childhood-onset depression appears to differ from adolescent- and adult-onset depression in terms of symptom manifestation, correlates, treatment response and outcomes (Doering et al., 2022; Hazell et al., 1995; Jaffee et al., 2002; Rice et al., 2019a, 2019b; Ryan et al., 1987; van Os

et al., 1997). NICE guidelines highlight the importance of considering the child's age when selecting the appropriate treatment for depression (National Institute for Health and Care Excellence, 2019), and comorbid neurodevelopmental conditions may further assist in this decision. However, further work is needed to investigate whether emotional problems accompanied by neurodevelopmental conditions or other correlates of neurodevelopmental liability require different treatment approaches. There are no published medication trials of youth depression or anxiety in those with neurodevelopmental disorders, and psychological therapies may need to be adapted (Thapar et al., 2023). In youth with anxiety disorders, Cognitive Behavioural Therapy (CBT) may be less effective when there is comorbid ADHD, whilst combined CBT and pharmacotherapy appeared equally effective in youth with anxiety disorders with and without ADHD (Halldorsdottir et al., 2015). There is some evidence from a Swedish population sample of 8–46 year olds, that effective treatment of ADHD may reduce risks for depression (Chang et al., 2016). Given early-onset depression is known to have a worse prognosis than later-onset depression (Korczak and Goldstein, 2009), these findings suggest that neurodevelopmental traits/liability may present as a useful index for stratifying depression and anxiety requiring further investigation.

5.1. Sex differences

Whilst depression and anxiety disorders are more common in females (Altemus et al., 2014), neurodevelopmental disorders are more commonly diagnosed in males (Scott et al., 2002). Anxiety disorders appear more common among females with ADHD than males with ADHD (Levy et al., 2005), whilst sex differences in anxiety among individuals with ASD have not been identified (Oswald et al., 2016). There is currently conflicting evidence as to whether depression is more common among females than males with ADHD and ASD. Some studies report depression being more common in females with ADHD than males with ADHD, whilst the prevalence of depression in ASD appears consistent in males and females (Hudson et al., 2019; Thapar et al., 2023). We found that female sex was associated with early adolescent-onset emotional problems when compared to the rest of the sample, but that male sex was associated with early adolescent-onset emotional problems when compared to later adolescent-onset emotional problems. These results suggest that emotional problems with onset between ages 11 and 14 are more common in females than in males, but that this sex ratio bias is less pronounced than is seen in later adolescent-onset emotional problems.

5.2. Strengths and limitations

We utilised two population cohorts to prospectively assess emotional problems and neurodevelopmental phenotypes, providing, to our awareness, the largest sample to study early adolescent-onset emotional disorder. However, this design meant we were unable to use a clinical definition of depression or anxiety, and instead relied on questionnaires, which capture a broader phenotype. However, results from our sensitivity analysis in ALSPAC, using ICD-10 criteria for MDD and GAD, were consistent with the primary results, and in some instances showed stronger associations with neurodevelopmental conditions than observed for early adolescent-onset emotional problems, indicating that our results may be an underestimation of the true effect. As we cover a broad age range, another limitation is that to maintain the same questionnaire across the ages, we relied on parent-reports in early adolescence and self-reports in later-adolescence and early adulthood, as self-report is the preferred informant in this age group. However, our sensitivity analyses using parent-report in late adolescence were consistent with findings using self-report measures.

Longitudinal cohorts are subject to attrition, and study drop-out is associated with elevated depressive symptoms (Rice et al., 2019a, 2019b). To account for bias from missing data, we performed multiple

imputation, finding that results from the imputed data were consistent with the primary findings. However, multiple imputation is only valid if all imputation models are correctly specified and every incomplete variable is missing at random. If drop-out is related to the outcome in an analysis model, both complete case and multiple imputation may be biased.

Another potential limitation is that since some neurodevelopmental difficulties were primarily assessed in childhood and not in late adolescence, association with earlier adolescent-onset emotional problems may be biased due to symptoms being reported at the same ages. Some neurodevelopmental traits are highly stable (e.g., IQ), whilst others, such as ADHD, can change with age. In ALSPAC we were able to include measurements of ADHD from ages 7–15, ASD from 7 to 16, and communication difficulties from 9 to 24, and in MCS ADHD was measured from age 5–17, limiting the impact of earlier assessment of these phenotypes. However, coordination difficulties in ALSPAC, ASD in MCS, and reading difficulties in both cohorts were only assessed during childhood. Nevertheless, these neurodevelopmental conditions typically onset in childhood and have been shown previously to have moderate to high stability across childhood and adolescence (Astrom et al., 2007; Cantell et al., 1994; Johnson et al., 1999; Taylor et al., 2017).

6. Conclusions

Overall, our findings highlight that children with early adolescent-onset emotional problems are considerably more likely to have a neurodevelopmental condition and show indices of neurodevelopmental liability than those without early-onset youth emotional problems. We recommend clinicians assessing and treating individuals with early adolescent-onset emotional problems screen for ASD and ADHD, and other neurodevelopmental difficulties, and also monitor for emotional problems in children already diagnosed with a neurodevelopmental disorder.

CRediT authorship contribution statement

Charlotte A. Dennison: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Amy Shakeshaft:** Writing – review & editing, Resources, Methodology, Data curation. **Olga Eyre:** Writing – review & editing, Resources, Methodology. **Kate Tilling:** Writing – review & editing, Methodology. **Frances Rice:** Writing – review & editing, Funding acquisition, Conceptualization. **Anita Thapar:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

All authors report no conflicts of interest or disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.08.008.

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