Weavers, B., Heron, J., Thapar, A. K., Stephens, A., Lennon, J., Bevan Jones, R., Eyre, O., Anney, R. J., Collishaw, S., Thapar, A., & Rice, F. (2021). The antecedents and outcomes of persistent and remitting adolescent depressive symptom trajectories: a longitudinal, population-based English study. *Lancet Psychiatry*, *8*(12), 1053-1061. https://doi.org/10.1016/S2215-0366(21)00281-9

TWhat are the antecedents and outcomes of persistent and remitting adolescent depressive symptom trajectories:- A UK population-based study.

Bryony Weavers [1], Jon Heron [2], Ajay K Thapar [1], Alice Stephens [1], Jessica Lennon [1], Rhys Bevan Jones [1], Olga Eyre [1], Richard JL Anney [1], Stephan Collishaw [1], Anita Thapar [1], Frances Rice [1]*

Bryony Weavers BSc

Jon Heron PhD

Ajay K Thapar PhD

Alice Stephens MSc

Jessica Lennon MSc

Rhys Bevan Jones PhD

Olga Eyre PhD

Richard Anney PhD

Professor Stephan Collishaw PhD

Professor Anita Thapar PhD

Professor Frances Rice PhD

1 Wolfson Centre for Young People's Mental Health, Section of Child and Adolescent Psychiatry, MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK

2 Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, UK

*Correspondence:

Frances Rice, Wolfson Centre for Young People's Mental Health, Section of Child and Adolescent Psychiatry, MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK

Contact: ricef2@cardiff.ac.uk

ORCID 0000-0002-9484-1729

Key words: ALSPAC, depression, adolescence, persist, remit, longitudinal, trajectory

Abstract

Background

Depression first emerges in adolescence and, for many, is a life-long disorder. However, the longer-term clinical course of depression is highly variable. We aimed to examine the adult outcomes of adolescent-onset trajectories of clinically significant depressive symptoms and identify factors differentiating trajectories that persist and desist in adulthood.

Methods

Using data from a UK population-based cohort ALSPAC, we characterized trajectories of depression using repeated measures of symptoms from childhood at age 10·5, across adolescence, to age 25. Adult functional and psychiatric outcomes were assessed at 24 and 25 years. The mean age was 10·6 years (SD=·24) at baseline and 25·8 years (SD=·51) at the final timepoint. Approximately 5% of the children in the ALSPAC sample are non-white. We analysed data from 4234 individuals, 1582 (37%) were male and 2661 (63%) were female and sex was missing for one individual.

Outcomes

We identified four depression trajectory classes: adolescent-persistent depression that onset early in adolescence (7%), adolescent-limited depression that onset later in adolescence and remitted by adult life (14%), adult-increasing depression (25%) and stable-low levels of depression (55%). The persistent adolescent-onset class was associated with extremely poor adult outcomes (functional impairment (62%), suicidal self-harm (27%) and not being in education, employment, or training (16%)). Adolescent-limited depression was associated with transient adolescent stress, but by early adulthood functional impairment and mental health difficulties were similar to the stable-low group. Depression polygenic score OR 1·36 (95% CI=1·04-1·79), adolescent educational attainment OR 0·47 (95% CI=0·30-0·74), and

early adversity OR 2·60 (95% CI=1·42-4·78) which persisted into adulthood OR 1·60 (95% CI=1·38-1·87) distinguished the adolescent-persistent and adolescent-limited groups.

Interpretation

Adolescent-onset depression can show a maladaptive trajectory into adulthood, but some show transient depression. The future course of adolescent depression can be differentiated by age-at-onset during adolescence, adolescent academic attainment, early and persistent adversity and genetic loading. In terms of clinical implications, a detailed social and educational history could be helpful in decisions about the intensity of interventions for young people with clinically elevated depressive symptoms who seek help. The very poor adult outcomes for those whose depressive symptoms start early underscore the importance of overcoming barriers to help seeking and improving access to early evidence-based intervention across a variety of settings.

Funding

Medical Research Council (MR/R004609/1). The Wolfson Centre for Young People's Mental Health. Established with support from the Wolfson Foundation.

Research in context panel

Evidence

Depression is one of the leading causes of disability worldwide and often first emerges in adolescence. There is substantial within variability in the course of early-onset depression: some individuals develop persistent or recurrent depression, and some recover spontaneously. We are not aware of any studies that have sought to compare early-onset persistent and recovering trajectories of depression. We searched PubMed between January 1, 1995 and 1st October 2020 for publications on depression trajectories across childhood, adolescence and the transition to adulthood phases. Search terms were were ("trajectory" OR "trajectories") AND ("depression" OR "depressed" OR "depressive" OR "major depressive disorder" OR "MDD") AND ("longitudinal") AND ("child" OR "childhood") AND ("adolescence" OR "adolescent") AND ("adult" OR "adulthood"). No language restrictions were imposed. Evidence suggested that depression trajectories were heterogenous and could be differentiated based on age of onset and persistence over time. Very few (two) studies examined the adult outcomes of early-onset depression and the few (two) that did focused on a single type of adult outcome. We found no evidence to guide the clinician on what types of adolescent depression are likely to remit versus persist to adulthood.

Added value of this study

Our study is the first that we are aware of to assess what differentiates adolescent-onset depression trajectories that persist and that desist over time. We identified 4 depression trajectory classes that could be differentiated based on age of onset and persistence over time: adolescent-persistent depression, adolescent-limited depression that remitted by adult life, adult-onset depression, and stable low levels of depression. Adolescent-onset depression that persisted over time was associated with very poor adult mental health and occupational outcomes. Adolescent-limited depression was associated with more transient adolescent stress and impairment in adolescent academic attainment, but this group showed adult functioning that was extremely similar to those with stable low depressive symptoms. Adolescent-onset depression can show a maladaptive trajectory into adulthood, but some show transient depression. The future course of adolescent depression can be differentiated by age-at-onset, a history of continuing adversity that begins in childhood, poor educational performance, and genetic loading.

Implications

Depression that begins early in adolescence and persists is associated with poor adult outcomes. Early identification of the most salient risk factors for persistent depression would be a first step in altering this maladaptive trajectory. The clinical implications of these findings are that for younger adolescents (around age 13 years) who present with depressive symptoms, a more intensive strategy than watchful waiting which is recommended by NICE for mild depression, seems warranted. A detailed social and educational history could be clinically helpful in decisions about the intensity of interventions. Finally, results indicate the importance of overcoming barriers to help-seeking for young people with depressive symptoms, particularly when this starts early.

Background

Depression is one of the leading causes of global disability[1]. Its prevalence increases sharply through adolescence, with the peak period of onset occurring in early adulthood[2]. The period spanning adolescence and early adulthood is therefore a crucial, though rarely considered, period for the emergence of depression. Once depression has onset, there is substantial variability in severity and clinical course[3], especially among younger age groups. Prospective community studies report that only 60% of adolescent depression persists into early adulthood which suggests that one-off depressive episodes during adolescence are not uncommon[3,4]. Current UK NICE guidance on treating mild adolescent depression suggests that for some watchful waiting may be indicated[5] as some individuals will show spontaneous remission. However, for clinicians, it can be difficult to distinguish adolescents who will eventually develop persistent depression with poor adult outcomes from those whose depression will spontaneously remit. As depression is common and rates in young people have risen sharply in recent years[6], characterising this variation is important for informing treatment choice and how to allocate finite clinical resources[7].

We sought to characterize depressive symptom trajectories from ages 10 to 25 years and describe their associated adult occupational, educational, and psychopathology outcomes. We further aimed to identify which factors differentiate adolescent-onset depression that persists into adult life from that which desists. Based on previous findings, we expected to identify depression trajectories that differed in terms of age-of-onset[2-4,8-10]. We hypothesised that transient stressors during adolescence would be associated with onset of depression in adolescence that subsequently remits. We hypothesised that adolescent-onset persistent depression would be differentiated by exposure to chronic adversity beginning in childhood (e.g. poverty; adverse childhood experiences), higher genetic liability to depression indexed by neuropsychiatric polygenic scores associated with depression risk and by childhood neurodevelopmental disorders which have been associated with early-onset depression[11-13].

Methods

Study design and participants

Data were from the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing, longitudinal, population-based UK cohort study. ALSPAC enrolled a sample of 14541 pregnant women residing in Avon, England, with expected delivery dates between April 1, 1991, and December 31, 1992. Of these births, 13988 children were alive at one year. In addition, 913 children were enrolled after age seven, giving a total sample of 14901 children alive at 1 year[14-16]. Please note that the study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). For data gathered from participants at 22 years and onwards, study data were collected and managed using REDCap for data collection and management[17,18]. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Consent for biological samples was collected in accordance with the Human Tissue Act (2004). Data on depressive symptoms were available from age 10·5 to age 25 where between 4000 and 7500 participants responded at each assessment point (Supplementary, page 4). To estimate trajectories with accuracy, we required depression data at least once from three 'epochs' over the full 15-year period: childhood/early adolescence (10·5 to 13·5 years), adolescence (16·5 to 18·5 years), and early adulthood (21 to 25 years) N=4234. For twins, we excluded the second-born twin (to avoid non-independent observations). The mean age was 10·6 years (SD=·24) at baseline and 25·8 years (SD=·51) at the final timepoint.

Procedures

Clinically elevated depressive symptom trajectory class was the dependent variable. Childhood antecedent variables (childhood adversity and neurodevelopmental risk),

adolescent stress and academic performance and neuropsychiatric genetic scores variables that were tested for association with trajectory class. Adult outcomes examined were mental health and functional impairment, suicidal self-harm and work or education status.

Self-reported depression symptoms were assessed via questionnaires on 10-occasions using the short Mood and Feelings Questionnaire (sMFQ)[19] at ages 10·5, 12·5, 13·5, 16·5, 17·5, 18·5, 21, 22, 23, and 25 years. The sMFQ is a well validated depression symptom checklist (unpublished data Eyre O, Bevan R, Agha SS, et al) [19] including 13-items about symptoms over the previous two weeks rated on a 3-point scale (0-2, range 0-26). A score of 12 or above is the validated cut-point for clinically elevated symptoms[19] and we used this as our primary outcome to define depression. Major depressive disorder (MDD) episodes were also assessed on four occasions (Supplementary, page 2) though different instruments were used in adolescence and adult life.

Early social adversity was assessed by household income and childhood adverse experiences (ACEs). At child age 11, maternal (or main care-giver) report defined childhood poverty according to household income below 60% of the median for the sample (<£240 per week). An index ACEs summed items assessing physical, or emotional abuse; emotional neglect; parental suicide attempt/addiction; inter-parental violence; parental separation; parental criminal conviction and bullying occurring between child age 9 and 11. These were assessed by maternal-report at child age 11 except for bullying which was assessed by child self-report at age 10. A binary variable of 2 or more ACEs was used as an indicator of severe early adversity (Supplementary, page 2). A variable assessing exposure to *either* of these two early social adversities (poverty or 2+ ACEs) was also calculated.

Childhood neurodevelopmental risk was defined if an individual met criteria (maternal-report) for a diagnosis of ADHD at age 7 or 10, elevated childhood ADHD symptoms at age 10 or elevated autistic traits at age 9 (Supplementary, page 2).

Adolescent academic performance at age 16 was assessed by performance at GCSE (General Certificate of Secondary Education) examinations in national curriculum subjects. Two binary variables were created (no, 0; yes, 1) for GCSE attainment (5 or more achieved, grade A*-C, including English and Maths) and A Level attainment (2 or more passes achieved, grade A*-E), derived through linked data to the National Pupil Database. At age 18, respondents reported on whether they had applied to university (0 no; 1 yes).

Academic stress was defined if, at age 17, young people endorsed: having difficulty keeping up with coursework or studies most of the time or had experienced failure in end of year exams at school. Bullying at age 17 years was defined if a respondent answered ‘quite a lot’ or ‘a lot’ to being directly, relationally, or cyber-bullied in the last six months. Negative family relationships at age 17 were defined if respondents experienced an increase in the number of arguments with parents or felt ‘not very close’ or ‘not close at all’ to their family in the past two months.

Polygenic scores (PGS) sum weighted alleles where weights are based on allelic associations with psychiatric case-control status in a genome-wide association study (GWAS) in a separate sample. We generated PGS for MDD, bipolar disorder, schizophrenia, and ADHD in study individuals as the standardized mean number of disorder risk alleles in approximate linkage equilibrium ($R2<0{\cdot}20$), weighted by GWAS allele effect size, derived from data of imputed autosomal single-nucleotide polymorphisms. We computed each PGS using a range of p-value threshold settings, performed a principal

component analysis (PCA) and used the first principal component in association tests. Simulations show this method provides unbiased estimates (Supplementary, page 2).

Outcomes

The self-reported Strengths and Difficulties Questionnaire (SDQ)[20] which has been validated in populations aged 18 years and above[21] assessed total mental health difficulties at age 25. The impact supplement assessed functional impairment and distress.

Lifetime suicidal self-harm (0 no; 1 yes) was assessed by asking respondents at age 24 *"On any of the occasions you have hurt yourself on purpose, have you ever seriously wanted to kill yourself?"* The question was therefore limited to acts of self-harm with suicidal intent (and did not include suicidal ideation only).

Young people answered 11 self-reported questions about employment and education. Those not in full-time/part-time/irregular work or doing an apprenticeship or self-employed or in full-time education were defined as being not in education, employment or training (NEET) at age 25.

Statistical analysis

We used the sMFQ clinical cut-point to characterise depression trajectories meaning the same measure was used across ages (where depression was defined as clinically relevant depressive symptoms) (n=4234). We used latent class growth analysis (LCGA)[22] in Mplus version 8[23] and considered from one- to six-class solutions. Model selection was informed by model fit indices and interpretability as recommended[24]. Based on the epidemiology of depression, where prevalence typically rises in the early 20s[3,4], we split the time-axis into two developmental phases (10·5-18·5 years and 21-25 years) and constrained change to be linear (on the logit scale) within each of these two periods. The associations between class

membership and both predictor and outcome variables were derived using a manual implementation of the bias-adjusted three-step approach (Supplementary, page 4). LCGA is a model-based approach to clustering which permits a "soft-assignment" of individuals into classes. The probabilistic nature of this methods means it is not possible to think of class-size in terms of a whole number of people, consequently when describing the class-distribution and the relationship between class-membership and other variables we quote percentages. Full Information Maximum Likelihood (FIML), which makes a Missing at Random assumption, permitted partially-incomplete data to be included. This was combined with inverse probability weighting (IPW) to enable the potential for selection-bias to be explored (see Supplementary, page 8).

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication.

Results

Data collection began when the sample was enrolled during pregnancy between April 1, 1991, and December 31, 1992. Analysis took place between 15th February 2019 and 15th June 2021. The analysed sample included 4234 individuals 1582 male, 2651 female (1 missing) which permitted a sex specific analysis. Sex was defined according to maternal report at child age 8 months. As described above individuals with partially incomplete data were included in analyses. Data on ethnicity were not available in our data set but the full ALSPAC cohort shows that approximately 5% (577/12090) of the children are non-white according to maternal reports of maternal and paternal ethnic group[25]. We selected the 4-class model as this provided the best fit to the data and theoretical interpretation

(Supplementary, page 5). Figure 1 shows the 4 trajectory classes: Adolescent-persistent (7%, N≈279); adolescent-limited (14%, N≈592); adult-increasing (25%, N≈1056) and stable-low (55%, N≈2307). The adolescent-persistent class showed early-onset depressive symptoms that persisted into adult life. A very high probability of clinically significant depressive symptoms in adult life was seen in the adolescent-persistent group. All the elevated trajectory groups showed an over-representation of females compared to the low group though this was especially marked in the adolescent-onset persistent group (Table 1). Models run separately for males and females identified similar trajectory classes to the combined models (Supplementary, page 7).

Depression (defined as the probability of clinically significant symptoms on the sMFQ) emerged earlier for the adolescent-persistent group (at age 13·5 years) compared to the adolescent-limited group (at age 17·5 years) (Figure 1). We additionally estimated the number of occasions over the 10 measurement-points where symptoms were above the clinical cut-point in each trajectory class (Figure 1). These illustrate marked variability with the adolescent-persistent class showing 6·5 occasions of elevated symptoms on average and the adolescent-limited class showing 1·5 occasions. Thus, the adolescent-persistent group experienced an overall greater burden of depressive symptomatology in terms of number of occasions symptoms were above the clinical cut-point or an MDD episode was present (Figure 1; Supplementary, page 12).

In terms of adult outcomes, the adolescent-persistent group showed poor functioning across the range of adult outcomes assessed and differed significantly from the adolescent-limited group on these outcomes who, overall, showed good early adult outcomes (Table 1). Rates of suicidal self-harm, (27%), functional impairment (62%), and mental health difficulties

(25%) in adult life were high for this trajectory class. Poor adult occupational outcomes were also observed in the adolescent-persistent group with 16% NEET at age 25.

The adolescent-persistent group had higher rates of early adversity than the adolescent-limited group as indicated by associations with childhood poverty (Table 2) and ACEs which both differentiated the groups (childhood poverty OR, 2·59; *P* =·019; either poverty or multiple ACEs OR, 2·60; *P* =·002). For childhood neurodevelopmental traits, above threshold autistic traits were elevated in the adolescent-persistent group (Table 2) and this differed from the adolescent-limited group (OR, 2·41; *P* =·046). However, childhood ADHD and ADHD symptoms were elevated in both adolescent depression groups. In terms of polygenic scores, compared to the low group, the adolescent-persistent group was associated with higher genetic liability to depression and ADHD as indexed by MDD PGS (OR, 1·49; 95% CI, 1·18, 1·98; *P* = ·001) and ADHD PGS (OR, 1·31; 95% CI, 1·05, 1·63; *P* = ·018) although only MDD PGS differentiated the adolescent-persistent and limited groups (OR, 1·36; 95% CI, 1·04-1·79; *P* = ·024; Table 2).

Both adolescent-onset depression groups were associated with higher levels of adolescent academic and interpersonal stress compared to the low group (Table 2) though this was slightly higher in the adolescent-persistent than adolescent-limited group for a negative family relationship (OR, 1·81; *P* =·017) and bullying (OR, 2·23; *P* =·052). Similarly, both groups performed less well than the low group in terms of academic examinations at GCSE and applying to university though this was more marked in the adolescent-persistent group (GCSEs OR, 0·47; *P* =·001; University OR, 0·49; *P* =·015; Table 2).

We next undertook a number of sensitivity checks to assess whether, as hypothesised, the adolescent-limited group experienced “transient” adolescent stress. We did this by comparing similar stressors earlier in development (childhood academic and interpersonal

stressors) and by examining whether adversity resolved during early adult life for the adolescent-limited group (Table 3). In terms of childhood academic competence, this was higher in the adolescent-limited than the adolescent-persistent group (OR, 0·93; *P* =·041). However, for inter-personal childhood stress (victim of childhood bullying and poor perceived parent-child relationship quality), there were no differences between the adolescent-limited and persistent groups. In terms of the persistence of adversity into adult life, there was evidence that stressful events resolved during early adulthood for the adolescent-limited group compared to the adolescent-persistent group (OR, 1·60; *P* <·001).

Discussion

Using data from age 10 to 25, we characterized trajectories of clinically significant depressive symptoms. We identified 4 trajectories that differed in terms of their age-of-onset and persistence over time: adolescent-persistent (7%), adolescent-limited depression that remitted by adult life (14%) and adult-increasing (25%) depression as well as stable-low levels of depression (55%). Distinguishing adolescents who will eventually develop persistent depression with poor adult outcomes from those with depression that will spontaneously remit is important for informing the choice of intervention and how best to allocate clinical resources[7].

Adolescent-limited and adolescent-persistent depression differed in their age of onset with an earlier age of onset (approximately 13·5 years) for adolescent-onset depression that persisted compared to adolescent-limited depression (approximately 17·5 years). Adolescent-limited depression therefore onset around the age of key school examinations (A levels) and the transition from school to higher education or work - a period of life that can involve upheaval and academic and interpersonal stress for young people. Adolescent-

persistent depression affected a greater proportion of females, consistent with observations that female sex is associated with depression recurrence[4]. As expected, young people with adolescent-onset persistent depression experienced clinically significant depressive symptoms and MDD episodes on a greater number of occasions. Some of the adverse adult outcomes observed in the adolescent-persistent group may therefore be due to the accumulation or sensitization to earlier depression where repeated exposure to depression (or the stressors associated with it) lowers the threshold required to elicit a subsequent depressive mood/episode[26,27].

Adolescent-onset depression which persisted over time was associated with very poor outcomes. In contrast, the adolescent-limited group did not show marked adverse adult outcomes. This is consistent with observations that only a small proportion of those with depression have a form of the condition associated with severe and wide-ranging impairment[8] and that adolescent depressive episodes of brief duration often resolve by early adult life[4]. They also add to growing evidence about the importance of intervening early to prevent the experience of multiple depressive episodes and interventions aiming to shift expected trajectories towards less incapacitating outcomes[28].

We hypothesised that transient stressors limited to adolescence would be associated with onset of depression in adolescence that subsequently remits, whereas early-onset persistent depression would be differentiated by early social adversity[13] that continued over time as well as genetic liability to depression as indexed by neuropsychiatric polygenic scores[11,29]. Both adolescent-onset depression groups showed elevated rates of adolescent stress (academic difficulties, family stress, and victimization) and lower educational attainment during adolescence. Thus, in both groups, depression appeared to interfere with key milestones during adolescence such as academic attainment which may limit young people's

later opportunities. The adolescent-onset persistent group experienced greater early adversity (childhood poverty or adverse childhood experiences) than the adolescent-limited group. Indeed, the adolescent-limited group was notably the only group with elevated depression that did not show a higher rate of childhood adversity than the low group. Childhood autistic traits but not ADHD differentiated the adolescent-onset groups. This was unexpected given that ADHD has previously been associated with early-onset depression, although we note that the childhood-onset depression trajectory observed in the five-class trajectory model was associated with childhood ADHD suggesting that ADHD may be a precursor particularly in those with childhood-onset depressive symptoms (Supplementary, page 7)[11,12]. The adolescent-onset persistent group also had higher genetic loading for PGS that have been associated with early-onset depression[11,29]–specifically MDD and ADHD PGS compared to the stable-low group and a higher MDD PGS than the adolescent-limited group. It is likely that some of the especially poor adult outcomes observed in the adolescent-onset persistent group are due to complex patterns of continuing adversity given that elevated exposure to stressors was observed through childhood, the teenage years and early adulthood in this trajectory class. The increased genetic liability to MDD, as indexed by PGS seen in this group is interesting given that early-onset depression has been found to be more heritable. However, PGS also capture gene-environment correlations and thus environmental mechanisms may still contribute to the poor outcomes seen in this group. Finally, protective factors (e.g. family and peer support) may mitigate risk, particularly in those with adolescent-limited depression.

There are several clinical implications from this work. First, an early age-at-onset is a key influence on the likelihood that adolescent depression will show a persistent trajectory. Thus, for young teenagers with depressive symptoms, encouraging help-seeking is important but based on the current results watchful waiting is unlikely to be a promising clinical strategy for this group. Second, results highlight the importance of transition points between education

and employment/further education as well as between child and adolescent versus adult clinical services which typically happens at age 18. Thus, while young people presenting with depressed mood between the ages of 17 to 18 are more likely to show spontaneous recovery than those with an earlier onset, this age period also coincides with the emergence of depressive symptoms that increase in adulthood (Figure 1). This could have implications for services relevant to young adults including mental health care provision in primary care, higher education, and work-place settings. Moreover, although early adult life is typically considered an especially risky age period, the adolescent-persistent group represented the depressive trajectory class with the poorest outcomes and worst symptoms over time. This observation coupled with the fact that many young people with mental health disorders are overlooked at the transition between child and adolescent and adult services, highlights the importance of ensuring sustained support across the transition period. Most young people with depressive disorder do not access services - the very poor adult outcomes observed in the adolescent-onset persistent group illustrate the importance of overcoming the barriers to help-seeking in young people. Finally, a developmental approach can help distinguish the likely prognosis of young people with depression. The factors distinguishing the persistent and recovering adolescent depression trajectories(age at onset, continuing adversity beginning in childhood, poor educational performance, and genetic loading) suggest that a detailed social and educational history could be clinically helpful in decisions about the intensity of interventions.

Strengths of this study include the repeated assessment of depression from childhood to early adult life using the same instrument and informant. The follow-up into adult life and the broad assessment of adult mental health, occupational status, and functioning are additional strengths outcomes [12,30]. However, the assessments of adversity necessarily differed slightly across childhood, adolescence, and adulthood and we were not able to include some important indicators of childhood adversity (e.g. childhood sexual abuse). Limitations

include non-random loss to follow-up in the ALSPAC cohort [11]. We used several approaches to deal with missing data: full information maximum likelihood in trajectory modelling, sensitivity checks that trajectory classes replicated when requiring fewer completed depression assessments and inverse probability weighting to verify that our sample selection criteria did not affect mean depression scores. We assessed depression using a clinical cut-point on a validated questionnaire meaning results may not apply to clinical disorder. Given the episodic nature of depression, clinically relevant symptoms may also have been missed over the 15-year timeframe. The informant differs for assessment of early antecedents and later outcomes (i.e. carer versus young person) which may influence results. A final limitation is that associations between trajectory classes and predictor variables are not necessarily causal, and the direction of effects may be bi-directional as, for example, in the case of observed associations between depression and academic attainment.

Conclusions

Adolescent depression shows variable adult outcomes. Adolescent depression that persists is characterised by experience of early adversity that continues into adult life, higher genetic loading for depression, and an earlier age of onset. Adolescent-onset depression that remits is associated with more transient adolescent stress that improves by adulthood, and interferes with academic attainment during adolescence, but these adolescent difficulties tend to have remitted by the mid-twenties. This information may be clinically useful for distinguishing young people who will eventually develop persistent or recurrent depression with poor adult outcomes from those with depression that will spontaneously remit.

Acknowledgements

This project was supported by funding from the Medical Research Council (MR/R004609/1) (Rice, AK Thapar, Heron, Collishaw, A Thapar). This publication is the work of the authors and Jon Heron and France Rice will serve as guarantors for the contents of this paper. The Wolfson Centre for Young People's Mental Health was established with support from the Wolfson Foundation. The UK Medical Research Council and Wellcome grant 102215/2/13/2 and the University of Bristol provide core support for Avon Longitudinal Study of Parents and Children (ALSPAC). A comprehensive list of grant funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/researchers/access/).

This data collection for variables included in this research was specifically funded by Wellcome Trust grants 08426812/Z/07/Z and 2048951/Z/16/Z and MRC 092731, which funded data collection on depression and adult outcomes at age 25. Funding for data collection for other primary variables included in the present paper was funded by the Wellcome Trust (076467/Z/05/Z, 102215/Z/13/Z), NIH (PD301198-SC101645), Department for Education and Skills (EOR/SBU/2002/121).

Additional Contributions:

Genome-wide association study data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. We acknowledge the members of the Psychiatric Genomics Consortia for the publicly available data used as the discovery samples in this article. We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

Conflicts of interest: None

Authors contributions:

Study concept, acquisition and design: FR, JH, AKT, AT, SC, BW.~~Rice, Heron, AK Thapar, A Thapar, Collishaw, Weavers.~~

Statistical analysis: BW, JH, AKT, AS, JL, FR~~Weavers, Heron, AK Thapar, Stephens, Lennon~~.

Analysis of genetic data: RJLA.

Drafting of the manuscript: FR, BW, AS, JL.~~Rice, Weavers, Stephens, Lennon~~.

Critical revision of the manuscript for important intellectual content: All authors.

Obtained funding: FR, JH, AKT, SC, AT.~~Rice, Heron, AK Thapar, Collishaw, A Thapar~~.

Had access to the data: BW, JH, AKT, FR, AS, JL, RJLA.

Data sharing statement:

The University of Bristol owns the ALSPAC resource. A data dictionary is available and full instructions can be found at http://www.bristol.ac.uk/alspac/researchers/access/

~~Will individual participant data be available (including data dictionaries)?~~

~~Yes~~

~~What data in particular will be shared?~~

~~The University of Bristol owns the ALSPAC resource. Derived variables (such as newly derived variables coming from secondary analyses) created as part of any research project will be incorporated into the main resource and made available to all researchers.~~

~~What other documents will be available?~~

~~Not available.~~

~~When will data be available (start and end date)?~~

~~Immediately following publication; no end date.~~

~~With whom?~~

~~Investigators whose proposed use of the data has been approved by an independent review committee (the ALSPAC executive) identified for this purpose.~~

~~For what types of analyses?~~

~~To achieve the aims in the approved proposal.~~

~~By what mechanism will data be made available?~~

~~Full instructions can be found at: http://www.bristol.ac.uk/alspac/researchers/access/~~

~~Data requestors will need to sign a data access agreement.~~

References

1 Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2163–96.

2 Rohde P, Lewinsohn PM, Klein DN, Seeley JR, Gau JM. Key Characteristics of Major Depressive Disorder Occurring in Childhood, Adolescence, Emerging Adulthood, Adulthood. *Clin Psychol Sci J Assoc Psychol Sci* **2013;** 1: 41–53.

3 Schubert KO, Clark SR, Van LK, Collinson JL, Baune BT. Depressive symptom trajectories in late adolescence and early adulthood: A systematic review. *Aust NZ J Psychiatry* 2017; **51:** 477–99.

4 Patton GC, Coffey C, Romaniuk H, et al. The prognosis of common mental disorders in adolescents: A 14-year prospective cohort study. *Lancet* 2014; **383:** 1404–11.

5 National Institute for Health and Care Excellence. Depression in children and young people: identification and management. 2019. https://www.nice.org.uk/guidance/ng134. Last accessed 15th June 2021.

6 Collishaw S. Annual Research Review: Secular trends in child and adolescent mental health. *J Child Psychol Psychiatry* 2015; **56:** 370–93.

7 Davey CG, McGorry PD. Early intervention for depression in young people: a blind spot in mental health care. *The Lancet Psychiatry* 2019; **6:** 267–72.

8 Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: Results from the national comorbidity survey replication-adolescent supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry* 2010; **49:** 980–9.

9 Musliner KL, Munk-Olsen T, Eaton WW, Zandi PP. Heterogeneity in long-term trajectories of depressive symptoms: Patterns, predictors and outcomes. *J Affect Disord* 2016; **192:** 199–211.

10 Kwong ASF, López-López JA, Hammerton G, et al. Genetic and Environmental Risk Factors Associated with Trajectories of Depression Symptoms from Adolescence to Young Adulthood. *JAMA Netw Open* 2019DOI:10.1001/jamanetworkopen.2019.6587.

11 Rice F, Riglin L, Thapar AK, et al. Characterizing Developmental Trajectories and the Role of Neuropsychiatric Genetic Risk Variants in Early-Onset Depression. *JAMA Psychiatry* 2019; **76:** 306–13.

12 Eyre O, Hughes RA, Thapar AK, et al. Childhood neurodevelopmental difficulties and risk of adolescent depression: the role of irritability. *J Child Psychol Psychiatry* 2019; **60:** jcpp.13053.

13 Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet.* 2012; **379:** 1056–67.

14 Boyd A, Golding J, Macleod J, et al. Cohort profile: The 'Children of the 90s'-The index offspring of the avon longitudinal study of parents and children. *Int J Epidemiol* 2013; **42:** 111–27.

15 Fraser A, Macdonald-wallis C, Tilling K, et al. Cohort profile: The avon longitudinal study of parents and children: ALSPAC mothers cohort. *Int J Epidemiol* 2013; **42:** 97–110.

16 Northstone K, Lewcock M, Groom A, et al. The Avon Longitudinal Study of Parents

and Children (ALSPAC): an update on the enrolled sample of index children in 2019 [version 1; peer review: 2 approved]. *Wellcome Open Res* 2019; 4. DOI:10.12688/wellcomeopenres.15132.1.

17 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42:** 377–81.

18 Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; **95.** DOI:10.1016/j.jbi.2019.103208.

19 Angold A, Costello EJ, Messer CS, Pickles A, Winder F, Silver D. The Development of a Questionnaire for Use in Epidemiological Studies of Depression in Children and Adolescents. *Int J Methods Psychiatr Res* 1995; **5:** 237–49.

20 Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden *J Child Psychol Psychiatry* 1999; **40:** 791–801.

21 Brann P, Lethbridge MJ, Mildred H. The young adult Strengths and Difficulties Questionnaire (SDQ) in routine clinical practice. *Psychiatry Res* 2018; **264:** 340–5.

22 Muthén B, Muthén LK. Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res* 2000; **24:** 882–91.

23 Muthén LK, Muthén BO. Mplus User's Guide. Eighth Edition. Los Angeles: CA: Muthén & Muthén.

24 http://doc.ukdataservice.ac.uk/doc/6147/mrdoc/pdf/alspac_overview_guide.pdf. Last accessed 6th July 2021.

25 Berlin KS, Parra GR, Williams NA. An introduction to latent variable mixture modeling (Part 2): Longitudinal latent class growth analysis and growth mixture models. *J Pediatr Psychol* 2014; **39:** 188–203.

26 Hammen C. Stress and depression. *Annu Rev Clin Psychol* 2005; **1:** 293–319.

27 Wichers M, Geschwind N, Van Os J, Peeters F. Scars in depression: Is a conceptual shift necessary to solve the puzzle? *Psychol Med* 2010; **40:** 359–65.

28 Arango C, Díaz-Caneja CM, McGorry PD, et al. Preventive strategies for mental health. *The Lancet Psychiatry* 2018; **5:** 591–604.

29 Riglin L, Leppert B, Dardani C, et al. ADHD and depression: Investigating a causal explanation. *Psychol Med* 2020; 1–8. https://doi.org/10.1017/S0033291720000665

30 Fergusson DM, Boden JM, Horwood LJ. Recurrence of major depression in adolescence and early adulthood, and later mental health, educational and economic outcomes. *Br J Psychiatry* 2007; **191:** 335–42.