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Polygenic risk for depression, anxiety and neuroticism are associated with the severity and rate of change in depressive symptoms across adolescence

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Background: Adolescence marks a period where depression will commonly onset. Twin studies show that genetic influences play a role in how depression develops and changes across adolescence. Recent genome-wide association studies highlight that common genetic variants – which can be combined into polygenic risk scores (PRS) – are also implicated in depression. However, the role of PRS in adolescent depression and changes in adolescent depression is not yet understood. We aimed to examine associations between PRS for five psychiatric traits and depressive symptoms measured across adolescence using cross-sectional and growth-curve models. The five PRS were as follows: depression (DEP), major depressive disorder (MDD), anxiety (ANX), neuroticism (NEU) and schizophrenia (SCZ). **Methods:** We used data from over 6,000 participants of the Avon Longitudinal Study of Parents and Children (ALSPAC) to examine associations between the five PRS and self-reported depressive symptoms (Short Mood and Feelings Questionnaire) over 9 occasions from 10 to 24 years. The PRS were created from well-powered genome-wide association studies conducted in adult populations. We examined cross-sectional associations between the PRS at each age and then again with longitudinal trajectories of depressive symptoms in a repeated measures framework using multilevel growth-curve analysis to examine the severity and the rate of change. **Results:** There was strong evidence that higher PRS for DEP, MDD and NEU were associated with worse depressive symptoms throughout adolescence and into young adulthood in our cross-sectional analysis, with consistent associations observed across all nine occasions. Growth-curve analyses provided stronger associations (as measured by effect sizes) and additional insights, demonstrating that individuals with higher PRS for DEP, MDD and NEU had steeper trajectories of depressive symptoms across development, all with a greater increasing rate of change during adolescence. Evidence was less consistent for the ANX and SCZ PRS in the cross-sectional analysis, yet there was some evidence for an increasing rate of change in adolescence in the growth-curve analyses with the ANX PRS. **Conclusions:** These results show that common genetic variants as indexed by varying psychiatric PRS show patterns of specificity that influence both the severity and rate of change in depressive symptoms throughout adolescence and then into young adulthood. Longitudinal data that make use of repeated measures designs have the potential to provide greater insights how genetic factors influence the onset and persistence of adolescent depression. **Keywords:** Polygenic risk scores; depressive symptoms; longitudinal; trajectories; ALSPAC; adolescence; development.

Introduction

Depression is a common mental health disorder and predicted to be the highest global burden of disease by 2030 (WHO, 2012). Adolescence marks a period where depressive symptoms increase and major depressive disorder will commonly onset (Kessler, Avenevoli, & Merikangas, 2001; Kessler et al., 2005; Malhi & Mann, 2018; Rohde, Lewinsohn, Klein, Seeley, & Gau, 2013). Adolescent depressive symptoms and major depressive disorder are associated with a number of psychiatric and social impairments in later life and show strong continuity with depression in adult life, thus making it important to prevent and treat (Copeland, Shanahan, Costello, & Angold, 2009; Copeland, Wolke, Shanahan, & Costello, 2015; Fergusson, Boden, & Horwood, 2007; Rutter, Kim-Cohen, & Maughan, 2006).

Depression has a complex and multifactorial aetiology, comprised of both environmental and genetic contributions (Flint & Kendler, 2014; Thapar, Collinshaw, Pine, & Thapar, 2012). Adult twin studies have estimated that the heritability of major depressive disorder is between 31% and 42% (Sullivan, Neale, & Kendler, 2000). Twin studies of adolescent depressive symptoms have estimated similar heritability to adult depression, with a range most likely between 30% and 50%, with lower estimates reported for symptoms during childhood (Glowinksi, Madden, Bucholz, Lynskey, & Heath, 2003; Rice, 2014). However, there is considerable variability in heritability estimates between studies (11–72%) depending on age, sex, informant and measure of assessment (Rice, 2009). Depressive symptomatology typically increases during adolescence, and twin studies have shown that

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genetic contributions influence this developmental change (Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2017). In particular, genetic contributions may increase throughout development (Bergen, Gardner, & Kendler, 2007; Rice, Harold, & Thapar, 2002) although some inconsistent results have also been reported (Nivard et al., 2015). There are strong continuities reported between adolescent and adult depression (Rutter et al., 2006), so inconsistent estimates of heritability for adolescent depressive symptomatology are puzzling and may result from between-study differences in measurement, informant and age. Longitudinal data spanning transitions from early adolescence and young adulthood using the same assessments and respondents over time would aid understanding of the nature of genetic influences on the onset and persistence of symptoms across development.

Recent advances in genome-wide association studies (GWAS) have provided evidence that common genetic variation plays a role in depression (Howard et al., 2018, 2019; Wray et al., 2018) with many genetic variants or single-nucleotide polymorphisms (SNPs) each having a small effect (Mullins & Lewis, 2017). The heritability of depression estimated from SNPs is ~9% in adults (Howard et al., 2019) and ~2% in adolescents (Jami et al., 2020). However, this low SNP heritability in adolescence partly reflects a smaller GWAS sample size used and the varying informants and greater measurement heterogeneity. Polygenic risk scores (PRS), which sum the number of 'risk' SNPs that an individual possesses for a trait weighted by their effect size (Martin, Daly, Robinson, Hyman, & Neale, 2018), can be used as an indicator of an individual's genetic liability to depression. Several studies have used PRS taken from GWAS of psychiatric traits in adult populations to investigate how they associate with depressive symptomatology across development in younger populations (Halldorsdottir et al., 2019; Kwong, López-López, et al., 2019; Rice et al., 2018; Riglin et al., 2018). One study found that a higher PRS for major depressive disorder (MDD) was associated with depression in both clinical and population cohorts of children and adolescents (Halldorsdottir et al., 2019), whilst another found that the influence of an MDD PRS on emotional problems increased with age with weaker effects in childhood which developed in adulthood (Riglin et al., 2018). The same study also found that a higher PRS for schizophrenia was associated with higher emotional problems in childhood. Similar results were observed in a separate study which found that a greater PRS for MDD was associated with both early and later adolescent-onset trajectories of depression, whilst a higher schizophrenia PRS was only associated with an early adolescent-onset trajectory (Rice et al., 2018). Together, these studies highlight that polygenic risk is likely to play a role in the development and maintenance of adolescent depression. Additionally,

other traits such as anxiety and neuroticism are genetically correlated with depression (Luciano et al., 2018; Purves et al., 2020), implying shared genetic aetiology underlying these traits. However, it is still unclear if these genetic factors that show correlations with depression (i.e. anxiety; neuroticism), also uniformly impact on how depression manifests across development. Alternatively, there may be differential effects on developmental depression that are specific to each genetic factor/liability to a trait. Examining how and when PRS for different traits impact on depression developmentally could enhance our understanding of the mechanisms underlying depression and how this varies across developmental stages.

There is evidence that PRS are associated with changes across childhood and adolescence for other traits such as height (Paternoster et al., 2011) and BMI (Khera et al., 2019; Warrington, Howe, et al., 2013). These studies have used a repeated measures framework that estimates trajectories or growth curves to examine genetic associations with changes in a trait. Using a repeated measures framework such as growth-curve modelling may help improve the statistical power of genetic analysis (Lubke et al., 2016). Measurement error and low statistical power are problems in genomic analysis as genetic effects tend to be small in magnitude and require large sample sizes with precision to detect true effects (Hatoum, Rhee, Corley, Hewitt, & Friedman, 2018). Likewise, variation in the reported genetic component for depression may be partially a result of differential phenotypic measurement error at different occasions (Rice, 2014). A longitudinal approach which uses repeated measures may reduce phenotypic measurement error and increase statistical power as there are multiple occasions included in the analysis, rather than just one occasion (Taylor, Simpkin, Haycock, Dudbridge, & Zuccolo, 2016). Indeed, a recent study using an MDD PRS found higher heritability and variance explained by the PRS when utilising a repeated measures framework (Cheesman, 2018). Thus, multiple measurements may obtain a more precise estimate of an individual's 'true' latent trait score as the assessment is repeated over time, and not just on one occasion. Using repeated measurements, it is also possible to reduce the burden for multiple testing that would occur when looking at associations across timings in a growth-curve setting as a number of multiple comparisons are reduced (Warrington, Wu, et al., 2013). Repeated measures analysis, in particular growth-curve modelling, may provide an advantage to traditional cross-sectional analysis and also quantify how and when a trait changes over time, which in this context could help further explain the role of genetic liability in how and when adolescent depression changes over time.

The aim of this study was to examine how genetic liability for five genetically correlated psychiatric

traits (as indexed by PRS) influenced depressive symptoms across adolescence and early adult life using cross-sectional and repeated measures designs. Specifically, we aimed to test how PRS for depression (DEP; aka broad depression), major depressive disorder (MDD), anxiety (ANX), neuroticism (NEU) and schizophrenia (SCZ) were all associated with both the initial level and the rate of change of depressive symptoms over this developmental risk period. We conducted the following analyses: (a) we created five PRS taken from recent GWAS (using clumping and thresholding methods) and examined univariate associations at nine occasions in a UK-based population cohort between the ages of 10 and 24 years old (cross-sectional analysis); (b) we then used growth-curve modelling to construct trajectories of depressive symptoms in the same cohort and examined how the five PRS were associated with the rate of change in depressive symptoms throughout adolescent development; and (c) finally, we examined if higher PRS for each trait were associated with differences in depressive symptoms scores compared to the population average PRS in order to determine when each PRS was most strongly associated with depressive symptomology.

Methods
Sample

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a longitudinal cohort study that recruited pregnant women residing in the former area of Avon, UK, with expected dates of delivery 1st April 1991 to 31st December 1992 (Boyd et al., 2013; Fraser et al., 2013). The initial cohort consisted of 14,062 live births, but has been increased to 14,901 children who were alive after one year with further recruitment (Northstone et al., 2019). Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. 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. A flow diagram highlighting the study sample is given in Figure S1.

Depressive symptoms

Self-reported depressive symptoms were measured on nine occasions between ages 10 and 24 using the Short Mood and Feelings Questionnaire (SMFQ) (Angold, Costello, Messer, & Pickles, 1995). The SMFQ is a 13-item questionnaire that measures the presence of depression symptoms in the previous two weeks and was administered via postal questionnaire or in research clinics. Each item is scored between 0 and 2, resulting in a summed score between 0 and 26. See Table 1 for the means, age range and alpha scores for each SMFQ assessment. The SMFQ correlates highly ($r = .58$) with clinical depression (Thapar & McGuffin, 1998; Turner, Joinson, Peters, Wiles, & Lewis, 2014).

Polygenic risk scores

Five PRS were created with PRSice-2 (Choi & O'Reilly, 2019), using summary statistics from five recent genome-wide

association studies (GWAS): depression (aka broad depression) or DEP (Howard et al., 2019), major depressive disorder or MDD (Wray et al., 2018), anxiety or ANX (Purves et al., 2020), neuroticism or NEU (Luciano et al., 2018), and schizophrenia or SCZ (Schizophrenia Working Group of the Psychiatric Genomics Consortium, Ripke, Walters, & O'Donovan, 2020). ALSPAC was not included in any of these GWAS. All PRS were created by weighting the effect sizes of the single-nucleotide polymorphisms (SNPs) associated with each trait from the initial GWAS at nine p-value thresholds (PT: 5×10^{-08}, 5×10^{-07}, 5×10^{-06}, 5×10^{-05}, .0005, .005, .05, .5 and 1). The number of SNPs included at each of these PRS thresholds is given in Table S1. Each PRS was standardised to have a mean of 0 and a standard deviation of 1; thus, a higher PRS represents higher genetic liability to each trait. We included SNPs that had a MAF of >1% and info score of >80% and excluded SNPs with an R^2 of >0.1 if they were within 250 kb of each other. This was to account for linkage disequilibrium (LD) so that only the most strongly associated SNPs from each region were retained. Complete genotyping information is available in the Supporting Information.

Statistical analysis

For the cross-sectional analyses, regression was performed within PRSice-2 to examine the association between each of the five PRS and depressive symptoms at each of the nine occasions. p-values were corrected using the Benjamini–Yekutieli method for multiple testing (p_{BY}) due to the number of related tests (five PRS × nine PRS thresholds × nine occasions of depressive symptoms [405 tests]). Empirical p-values (with 1,000 permutations) were also calculated to examine within PRS associations between the nine occasions of depressive symptoms at each of the nine PRS thresholds (e.g. DEP PRS × nine PRS thresholds × nine occasions of depressive symptoms). Sex and the first 10 principal components of ancestry were included as covariates.

For the repeated measures analysis, trajectories of depressive symptoms were estimated using multilevel growth-curve modelling (Hedeker & Gibbons, 2006; Raudenbush & Bryk, 2002). Briefly, multilevel growth-curve models create population averaged trajectories with intercept and slope terms. Individual-level trajectories then vary around this population average (i.e. each person can have their own trajectory, with their own intercept and slope that can deviate from the population average). Previous analysis of these data has shown that changes in depressive symptoms over time are nonlinear (Edwards et al., 2014; Kwong, Manley, et al., 2019), with depressive symptoms rising until the age of about 18, then decreasing until around the age of 22, before rising again towards the age of 24. To model these nonlinear trajectories, a multilevel quartic growth-curve polynomial model was chosen. This model contains five key parameters: the intercept, the linear age term, the quadratic age term, the cubic age term and the quartic age term. These age terms allow for nonlinearity in the trajectory and changes in depressive symptoms. Previous research using these data to estimate multilevel growth curves has found higher order polynomials best fitted the data (Kwong, Manley, et al., 2019). We further assessed the fit of this model using information criteria and likelihood ratio tests, consistent with other studies using multilevel growth-curve models (Singer & Willett, 2003) – see Tables S2 and S3, and Figure S2.

To examine how each PRS was associated with changes in depressive symptoms, we included a main effect of each standardised PRS and an interaction of the PRS with each of the fixed-effects age polynomial terms (i.e. linear, quadratic, cubic and quartic age terms). Age was grand-mean centred to 16.53 years (the mean age of all assessments) in order to improve interpretation, since model intercept and intercept variance then broadly correspond to the middle of adolescence

Table 1 Descriptive statistics of the Short Mood and Feelings Questionnaire (SMFQ) for individuals included in this analysis

Occasion (Total *N*)	Mean age	Mean SMFQ	Alpha	% Above SMFQ threshold[a]
1 (*N* = 5,317)	10.63 (0.25)	4.00 (3.49)	.80	5.85
2 (*N* = 4,923)	12.80 (0.23)	3.94 (3.84)	.84	7.11
3 (*N* = 4,492)	13.83 (0.21)	4.92 (4.49)	.86	11.81
4 (*N* = 3,521)	16.68 (0.24)	5.85 (5.63)	.91	17.68
5 (*N* = 3,210)	17.82 (0.37)	6.50 (5.21)	.90	21.05
6 (*N* = 2,387)	18.64 (0.49)	6.73 (5.85)	.91	21.20
7 (*N* = 2,377)	21.94 (0.52)	5.56 (5.46)	.91	17.44
8 (*N* = 2,704)	22.87 (0.51)	6.07 (5.40)	.90	17.64
9 (*N* = 2,737)	23.88 (0.51)	6.84 (5.91)	.91	23.49

Standard deviations are given in (parenthesis).
[a]Scores equal to or above 11 have been proposed as good indicators of depression (Turner et al., 2014). Individuals included in this analysis had data on the SMFQ, genetic data to make the PRS/principal components of ancestry and data on sex. Alpha scores were estimated using Cronbach's alpha.

(Rawana & Morgan, 2014). The intercept and four polynomial age terms were allowed to vary randomly across individuals to capture each individual's unique trajectory (i.e. a random intercept and random slopes model). Each psychiatric PRS was run univariately, and further information regarding model fit and model equations are given in the Supporting Information.

To assess the association between each psychiatric PRS and development of symptoms over time, we created a population average trajectory which was comprised of the mean PRS for the sample, a trajectory associated with lower genetic liability (1 *SD* below mean in PRS) and one trajectory associated with higher genetic liability (1 *SD* above the mean in PRS). We calculated the predicted depressive symptoms scores at each of the following ages: 10.63, 12.80, 13.83, 16.68, 17.82, 18.64, 21.94, 22.87 and 23.88 (to coincide with the mean ages at which the SMFQ was assessed at each of the nine occasions) for the population average, greater liability, and lower liability PRS trajectories. We then compared the predicted depressive symptoms scores at each of these ages between the population average trajectory and the higher genetic risk PRS trajectory (i.e. to compare greater genetic risk for each PRS compared to the population average). Further information on how these were calculated for the trajectories is presented elsewhere (Kwong, Maddalena, Croft, Heron, & Leckie, 2019). Briefly, the depressive symptoms scores were calculated at each age for the two trajectories (i.e. depressive symptom scores at age 12.80 for the population mean and then for the higher PRS [+1*SD*] trajectory). The delta method (which incorporates the estimate, standard errors and confidence intervals) was then used to compare these two scores revealing a predicted difference in scores that are derived estimates from each trajectory – thus utilising the repeated nature of the measures to obtain a more accurate estimate. *p*-values were corrected for using false discovery rate (p_{FDR}). Stata code for our analysis can be found here: https://github.com/kwongsiufung/prs-trajectories. Repeated measures analyses were conducted using Stata 15 (StataCorp, College Station, TX, USA), using the user-written runmlwin command (Leckie & Charlton, 2013), which calls the standalone multilevel modelling package MLwiN v3.01 (www.cmm.bristol.ac.uk/MLwiN/index.shtml). These analyses were adjusted for sex and the first ten principal components of ancestry.

Missing data

Missing data in the trajectories analysis were handled using full information maximum likelihood estimation (FIML) (Curran & Hussong, 2003). Briefly, this assumes that the probability of an individual missing a measure of depressive symptoms does not depend on their underlying depressive symptoms score at that occasion, given their observed depressive symptoms trajectory at other occasions. We included individuals into our analysis if they had at least one measurement of depression symptoms in order to maximise power (Lopez-Lopez et al., 2019). Further information regarding the characteristics of this sample has been described in other work (Kwong, 2019). Previous research on these data has shown that trajectory shapes and characteristics do not vary when comparing individuals with at least one or at least 4 measurements of depressive symptoms (Kwong, Manley, et al., 2019).

Sensitivity analyses

We conducted a variety of sensitivity analyses, as follows. (a) To ensure any benefits of the repeated measures analyses were not due to well-powered GWAS, we ran sensitivity analyses substituting our five psychiatric PRS with two well-powered traits: educational attainment (EA) and height (HEI). We supplemented this by further examining the impact of the five psychiatric PRS on trajectories of height. (b) Given the complexity of our growth curve and the risk over fitting the model, we also estimated a simpler quadratic trajectory with each of the five PRS and calculated the predicted scores for different trajectories in a similar manner to the main analyses. (c) We conducted tests for measurement invariance for depressive symptoms over time (highlighted in Figure S3). (d) We ran analysis exploring the association between the DEP PRS and missing data patterns (shown in Figure S4). Further information regarding these sensitivity analyses can be found in the Supporting Information.

Results
Sample characteristics

Of the original 14,901 children alive after one year, 9,399 had at least one measurement of depressive symptoms and 7,877 had genotype data that passed quality control (see the Supporting Information). For the cross-sectional analysis, data were available for 5,317 individuals with a measurement of depressive symptoms at age 10.63 and genotype data, decreasing to 2,737 at age 23.88 (see Table S4). For the repeated measures analysis, data were available for

6,302 individuals with at least one measurement of depressive symptoms, sex and genotype data.

Cross-sectional associations between polygenic risk scores and depressive symptoms

Figure 1 shows a summary of results from the five psychiatric PRS across all nine ages of depressive symptoms, using the best predictive threshold for each PRS. For the associations between each PRS and depressive symptoms, we present timings that correspond to measures in three key periods early adolescence, late adolescence and early adulthood for brevity. Full estimates and the best predictive PRS for each trait at each age are given in Tables S5–S19. A higher PRS for DEP was associated with higher depressive symptoms across all nine occasions (Tables S5–S7). Effect sizes and the amount of variance explained by the DEP PRS generally increased throughout development with smaller estimates at age 10.63 ($\beta = .208$, 95%CIs = 0.116, 0.301, $R^2 = 0.37\%$, $p_{BY} = .0004$) compared to age 17.82 ($\beta = .583$, 95%CIs = 0.410, 0.757, $R^2 = 1.30\%$, $p_{BY} = 1.55 \times 10^{-08}$) and then age 23.88 ($\beta = .864$, 95%CIs = 0.650, 1.079, $R^2 = 2.21\%$, $p_{BY} = 5.29 \times 10^{-12}$). A similar pattern was observed for the MDD PRS, although the effect sizes and the variance explained were smaller at later ages compared to the DEP PRS (age 10.63: $\beta = .222$, 95%CIs = 0.128, 0.317, $R^2 = 0.40\%$, $p_{BY} = .0002$; age 17.82: $\beta = .405$, 95%CIs = 0.224, 0.587, $R^2 = 0.58\%$, $p_{BY} = .0005$; age 23.88: $\beta = .646$, 95%CIs = 0.430, 0.863, $R^2 = 1.22\%$, $p_{BY} = 5.86 \times 10^{-07}$, Tables S8–S10). Effects were less consistent for the ANX PRS, which showed smaller effect sizes and a lower variance explained compared to the DEP PRS, but still evidence of greater effects over time (age 10.63: $\beta = .128$, 95%CIs = 0.034, 0.222, $R^2 = 0.13\%$, $p_{BY} = .109$; age 17.82: $\beta = .469$, 95%CIs = 0.296, 0.641, $R^2 = 0.85\%$, $p_{BY} = 6.86 \times 10^{-06}$; age 23.88: $\beta = .682$, 95%CIs = 0.470, 0.894, $R^2 = 1.41\%$, $p_{BY} = 7.53 \times 10^{-08}$, Tables S11–S13). The NEU PRS showed comparable associations, effect sizes and variance explained compared to the DEP and MDD PRS at age 10.63 ($\beta = .240$, 95%CIs = 0.147, 0.333, $R^2 = 0.48\%$, $p_{BY} = 2.13 \times 10^{-05}$) and age 17.82 ($\beta = .559$, 95%CIs = 0.385, 0.733, $R^2 = 1.19\%$, $p_{BY} = 7.53 \times 10^{-08}$), but the strongest associations of all the PRS at age 23.88 ($\beta = .919$, 95%CIs = 0.703, 1.135, $R^2 = 2.45\%$, $p_{BY} = 3.52 \times 10^{-13}$, Tables S14–S16). In contrast, the SCZ PRS showed relatively low effect sizes and variance explained compared to the other PRS (age 10.63: $\beta = .112$, 95%CIs = 0.019, 0.205, $R^2 = 0.10\%$, $p_{BY} = .224$; age 17.82: $\beta = .271$, 95% CIs = 0.094, 0.448, $R^2 = 0.27\%$, $p_{BY} = .048$; age 23.88: $\beta = .292$, 95%CIs = 0.073, 0.511, $R^2 = 0.25\%$, $p_{BY} = .127$, see Tables S17–S19).

Associations between polygenic risk scores and trajectories of depressive symptoms and comparisons between population average PRS trajectories and higher PRS trajectories (+1 SD)

The cross-sectional analyses revealed that on average more liberal PRS thresholds (PT: 0.0005 to 1) explained more of the variance in depressive symptoms across ages compared to more stringent PRS thresholds (PT: 5×10^{-08} to 5×10^{-05}, Tables S6, S9, S12, S15 and S18). Consequently, we focused on estimating trajectories with more liberal PRS thresholds for each of the five psychiatric PRS. The best model fit – assessed by lowest deviance – was then used to determine which PRS threshold to compare population average PRS trajectories with higher PRS trajectories (i.e. those with a +1 SD in PRS) for each of the psychiatric PRS traits.

There was evidence that higher psychiatric PRS were associated with greater depressive symptoms scores at the intercept age of 16.53 for the DEP PRS ($\beta = .419$, 95%CIs = 0.286, 0.551, $p = 5.79 \times 10^{-10}$), MDD PRS ($\beta = .426$, 95% CIs = 0.292, 0.559, $p = 4.79 \times 10^{-10}$), ANX PRS ($\beta = .291$, 95%CIs = 0.159, 0.423, $p = 1.0 \times 10^{-05}$), NEU PRS ($\beta = .550$, 95%CIs = 0.419, 0.681, $p = 2.22 \times 10^{-16}$) and SCZ PRS ($\beta = .149$, 95% CIs = 0.016, 0.283, $p = 0.029$). However, only the DEP PRS ($\beta = .062$, 95%CIs = 0.030, 0.094, $p = 0.0001$), MDD PRS ($\beta = .064$, 95%CIs = 0.032, 0.096, $p = 0.0001$) and NEU PRS ($\beta = .041$, 95% CIs = 0.009, 0.072, $p = 0.012$) showed consistent evidence for linear change over time. There was no evidence that any of the psychiatric PRS showed meaningful changes over time for the quadratic, cubic and quartic age terms (Tables S20–S24).

All five psychiatric PRS showed that trajectories were higher for those with greater genetic liability to a trait (+1 SD in PRS) compared to those with the PRS population average (Figure 2). However, only the DEP, MDD, ANX and NEU PRS showed predicted differences in depressive symptoms scores that substantially increased across development (Table 2). There was no consistent evidence that the predicted differences in SCZ PRS increased over time as differences tended to remain small and stable. The predicted depressive symptoms scores at each age and for each trajectory are given in Table S25.

Sensitivity analyses

There was evidence that a higher EA PRS was associated with lower trajectories of depressive symptoms, indexed by multiple rate of change parameters (Table S26). However, this gave inconsistent estimates when comparing the predicted differences in depressive symptoms scores between trajectories for those with greater genetic liability to
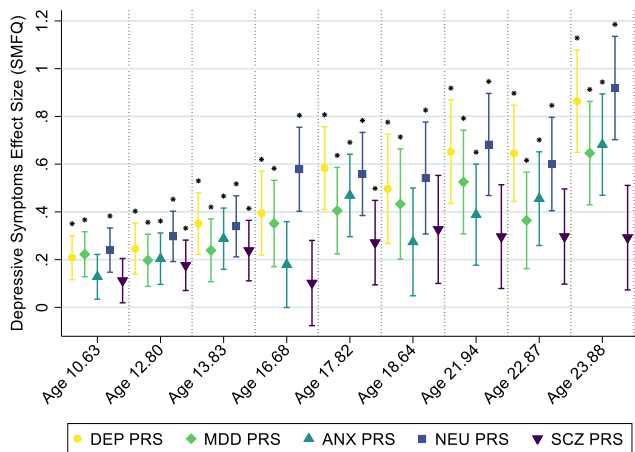
Figure 1 Cross-sectional analysis between the most predictive PRS for each trait and depressive symptoms across adolescence and early adulthood. ANX, anxiety; DEP, depression (broad depression); MDD, major depressive disorder; NEU, neuroticism; PRS, polygenic risk score; SCZ, schizophrenia. SMFQ, Short Mood and Feelings Questionnaire (depressive symptoms). Analyses were adjusted for sex, age and the first ten principal components of ancestry. The most predictive PRS for each trait had *p*-value thresholds (PT) that varied between 5×10^{-08} and 1. These are described in full in Supporting Information.* indicates results were significant after Benjamini–Yekutieli correction to control for the number of related multiple tests (405 related tests)

EA and those with the population average PRS (Table 2). There was no evidence that a greater HEI PRS was associated with trajectories of depressive symptoms or predicted differences in scores between higher genetic liability and the population average (Table 2 and Table S27). The predicted scores for both EA and HEI PRS and their trajectories are given in Table S28 and Figure S5. Furthermore, there was no evidence that any of the psychiatric PRS were associated with trajectories of height (Table S29 and Figure S6), nor any substantive differences when rerunning the analyses with quadratic trajectories of depressive symptoms (Tables S30–S31 and Figure S7). Tests for measurement invariance suggested there was weak measurement invariance between age 10.63 and age 23.88 (difference between models: $x^2 = 355.68$, $df = 12$, $p < .0001$). However, even when taking measurement variance into account, there was still a stronger association between the DEP PRS and depressive symptoms at age 23.88 ($\beta = .146$, 95 CIs = 0.107, 0.185, $p < .001$), compared to age 10.63 ($\beta = .075$, 95 CIs = 0.044, 0.106, $p < .001$) suggesting the association between the DEP PRS and depressive symptoms at age 23.88 reflects a stronger association between the PRS and that depressive symptoms construct, rather than an artefact of measurement variance (Tables S32–S34). Finally, there was evidence that higher PRS for all psychiatric PRS were associated with more missed assessments of depressive symptoms, whereas higher PRS for EA and HEI were associated with less missed assessments (Table S35). Further

information on all analyses is provided in the Supporting Information.

Discussion

In this longitudinal cohort study, we examined multiple cross-sectional analysis at different ages and a growth-curve modelling approach that utilised a repeated measures framework to explore associations between five psychiatric PRS and depressive symptoms across adolescence. In cross-sectional analysis, we found consistent evidence that higher PRS for DEP, MDD and NEU were associated with greater levels of depressive symptoms throughout all of adolescence and early adulthood. There were stronger associations between the PRS and depressive symptoms at older ages that were not explained by measurement invariance. In the growth-curve analysis, we found that higher PRS for DEP, MDD and NEU were strongly associated with steeper trajectories of depressive symptoms. The PRS were associated with trajectories characterised by greater overall depressive symptoms across adolescence, as well as a greater increase in the rate of change of depressive symptoms from early adolescence to early adulthood. There was some evidence that higher ANX PRS were associated with steeper trajectories of depressive symptoms, but these effects were less consistent than the DEP, MDD and NEU PRS. There was less evidence that SCZ PRS were associated with greater levels of depressive symptoms or changes in depressive symptoms across development.

Our results suggest that individuals with higher PRS for DEP, MDD, NEU and to some extent ANX are associated with greater depressive symptoms in adolescence and early adulthood and may influence how depressive symptoms change across adolescence and adulthood. Importantly, we see that higher PRS for these psychiatric traits begin to have higher symptoms scores that emerge between the ages of 12 and 14, suggesting that genetic liability may play a role in the onset of adolescent depression and that this is similar for traits that are genetically correlated and comorbid with depression (i.e. anxiety and neuroticism) – thus implying a shared genetic aetiology may underpin these results. Our results are consistent with research in high-risk family studies (Weissman et al., 2006), and place further emphasis on the idea that depression is not only heritable, but genetic liability may also influence the rate of phenotypic change that is expressed (in this case depressive symptoms across adolescence and young adulthood). Furthermore, the predicted differences between higher genetic risk trajectories and the population average PRS generally increased throughout development, suggesting that higher genetic liability to depression or neuroticism may also influence the maintenance or persistence of worse depressive symptoms across time as well. There was, however, some specificity towards
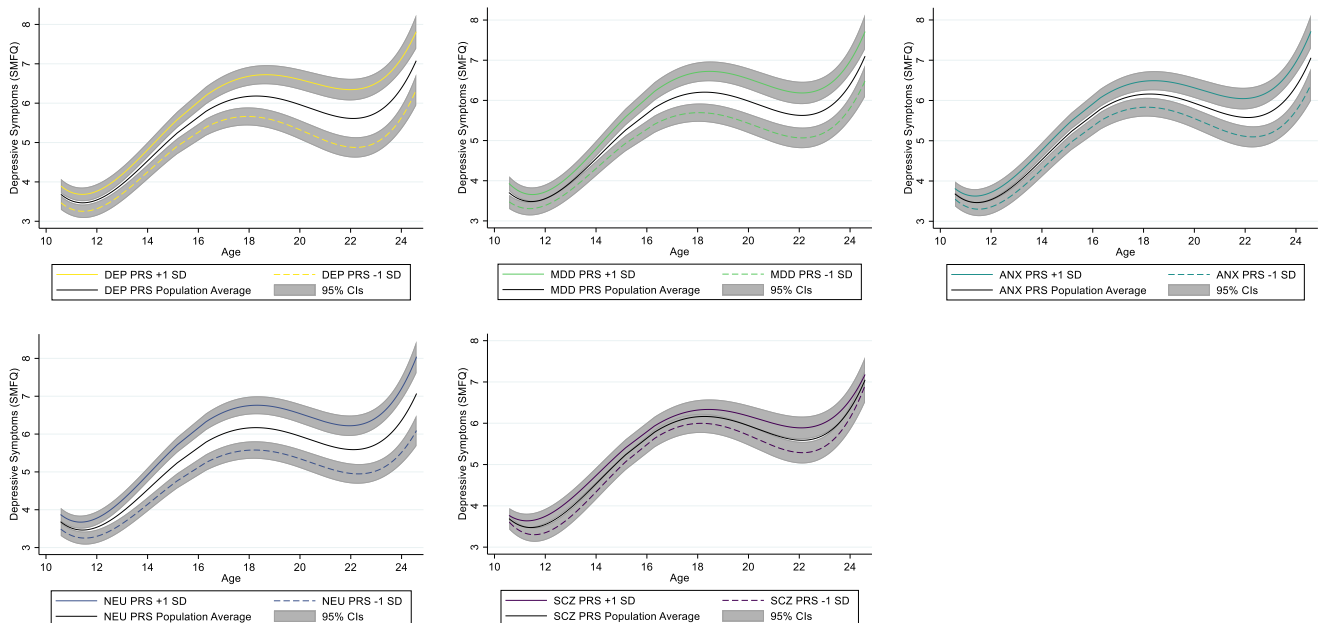
Figure 2 Association between the five psychiatric PRS and trajectories of depressive symptoms. ANX, anxiety; DEP, depression (broad depression); MDD, major depressive disorder; NEU, neuroticism; PRS, polygenic risk score; SCZ, schizophrenina; SMFQ, Short Mood and Feelings Questionnaire (depressive symptoms). Averaged population trajectories of depressive symptoms for greater and less genetic liability (± 1 *SD* PRS) for each of the varying PRS compared the population average of the PRS (black line for all). Analyses were adjusted for sex and the first ten principal components of ancestry

affective disorders, with little evidence for an association with genetic liability for nonaffective domains (i.e. schizophrenia or educational attainment).

Our repeated measures analyses suggested that the DEP, MDD and NEU PRS had stronger associations as age increased and that differences in trajectories could be partially the result of increased genetic liability to specific psychiatric traits across development. This is consistent with longitudinal twin research showing the genetic contribution to depression increases throughout adolescent development (Bergen et al., 2007; Rice et al., 2002) and to some extent research across the life course (Nivard et al., 2015). Together, these results suggest that genetic factors influence how depressive symptoms manifest at different stages of development, but importantly they also demonstrate when depressive symptoms may be more sensitive to genetic or environmental factors. Our results showed the impact of DEP, MDD and NEU PRS on depressive symptoms generally increased with age supporting the idea that the manifestation of the genetic architecture of depression is not stable (Riglin et al., 2018). Further evidence that utilises depression and genetic data measured across childhood, adolescence and later stages of adulthood is required to further enhance our understanding of developmental depression and the role of genetic and environmental influences.

There are several possible explanations as to why genetic liability may influence change over time. First, genetic liability to depression and correlated traits like anxiety and neuroticism may act upon biological and hormonal pathways, especially during adolescence (Paus, Keshavan, & Giedd, 2008). This may result in changes to brain development and hormonal responses that put an individual at greater risk of depression (Blakemore, 2008). Second, gene environment correlation with key environmental risk exposures such as stressful life events may increase with age (Jaffee & Price, 2012; Rice, Harold, & Thapar, 2003; Thapar et al., 2012). This in turn may produce indirect pathways to depression that are a result of increased environmental exposures that occur in later development. Third, differences in genetic liability could be the result of measurement error and statistical noise at the varying occasions, but these may be reduced in repeated measures designs (Lubke et al., 2016). Thus, a repeated measures design that incorporates genetic data may be a more useful model for exploring the temporal association between genetic risk and a complex developing phenotype.

Previous research has shown that PRS can be included into longitudinal models that examine change over time (Khera et al., 2019; Paternoster et al., 2011; Warrington, Howe, et al., 2013). Research has suggested that it is also possible to examine genetic influences on age-related changes in depression (Lubke et al., 2016). We were able to expand upon previous work to examine genetic contributions to varying trajectories of depressive symptoms, but specifically in this study we were able to demonstrate how phenotypic manifestations of genetic liability (as indexed by PRS) vary by age. We demonstrated that genetic influences may be age-

Table 2 Predicted mean differences in depressive symptoms scores at varying ages between trajectories for the mean population PRS and for trajectories for each PRS that were +1 SD (i.e. higher genetic risk)

	DEP (PT = 0.005)	MDD (PT = 0.05)	ANX (PT = 1)	NEU (PT = 0.05)	SCZ (PT = 0.0005)	EA (PT = 1)	HEI (PT = 0.5)
Age 10.63	0.21 (0.12, 0.30); $p_{FDR} = 1.82 \times 10^{-05}$	0.22 (0.13, 0.32); $p_{FDR} = 8.52 \times 10^{-06}$	0.13 (0.04, 0.23); $p_{FDR} = .007$	0.19 (0.10, 0.28); $p_{FDR} = 9.00 \times 10^{-05}$	0.09 (−0.01, 0.18); $p_{FDR} = .087$	0.17 (0.08, 0.27); $p_{FDR} = .0005$	0.06 (−0.03, 0.15); $p_{FDR} = .259$
Age 12.80	0.24 (0.14, 0.34); $p_{FDR} = 3.83 \times 10^{-06}$	0.18 (0.09, 0.28); $p_{FDR} = .0003$	0.21 (0.11, 0.30); $p_{FDR} = 5.56 \times 10^{-05}$	0.30 (0.20, 0.39); $p_{FDR} = 7.30 \times 10^{-09}$	0.21 (0.11, 0.31); $p = 3.82 \times 10^{-05}$	0.09 (−0.01, 0.19); $p_{FDR} = .094$	0.01 (−0.08, 0.11); $p_{FDR} = .801$
Age 13.83	0.28 (0.17, 0.38); $p_{FDR} = 2.42 \times 10^{-07}$	0.24 (0.13, 0.34); $p_{FDR} = 1.18 \times 10^{-05}$	0.23 (0.13, 0.33); $p_{FDR} = 1.18 \times 10^{-05}$	0.38 (0.28, 0.48); $p_{FDR} = 8.82 \times 10^{-13}$	0.20 (0.10, 0.30); $p_{FDR} = .0002$	0.03 (−0.07, 0.13); $p_{FDR} = .579$	0.01 (−0.09, 0.11); $p_{FDR} = .871$
Age 16.68	0.43 (0.29, 0.56); $p_{FDR} = 1.28 \times 10^{-09}$	0.43 (0.30, 0.57); $p_{FDR} = 1.13 \times 10^{-09}$	0.29 (0.16, 0.43); $p_{FDR} = 3.82 \times 10^{-05}$	0.55 (0.42, 0.69); $p_{FDR} = 2.00 \times 10^{-15}$	0.15 (0.01, 0.28); $p_{FDR} = .039$	0.21 (0.07, 0.34); $p_{FDR} = .003$	0.07 (−0.06, 0.21); $p_{FDR} = .326$
Age 17.82	0.50 (0.36, 0.64); $p_{FDR} = 1.53 \times 10^{-11}$	0.50 (0.35, 0.64); $p_{FDR} = 4.20 \times 10^{-11}$	0.32 (0.18, 0.46); $p_{FDR} = 1.70 \times 10^{-05}$	0.59 (0.45, 0.73); $p_{FDR} = 2.00 \times 10^{-15}$	0.16 (0.02, 0.30); $p_{FDR} = .038$	0.23 (0.09, 0.38); $p_{FDR} = .002$	0.07 (−0.07, 0.21); $p_{FDR} = 0.389$
Age 18.64	0.55 (0.41, 0.70); $p_{FDR} = 2.79 \times 10^{-13}$	0.53 (0.38, 0.67); $p_{FDR} = 6.20 \times 10^{-12}$	0.34 (0.20, 0.48); $p_{FDR} = 7.78 \times 10^{-06}$	0.59 (0.45, 0.74); $p_{FDR} = 2.00 \times 10^{-15}$	0.18 (0.03, 0.32); $p_{FDR} = .022$	0.22 (0.08, 0.36); $p_{FDR} = .004$	0.05 (−0.09, 0.19); $p_{FDR} = .537$
Age 21.94	0.73 (0.56, 0.90); $p_{FDR} = 2.79 \times 10^{-13}$	0.56 (0.39, 0.73); $p_{FDR} = 6.20 \times 10^{-12}$	0.47 (0.30, 0.63); $p_{FDR} = 7.78 \times 10^{-06}$	0.63 (0.46, 0.79); $p_{FDR} = 2.00 \times 10^{-15}$	0.30 (0.13, 0.47); $p_{FDR} = .022$	0.06 (−0.11, 0.23); $p_{FDR} = .004$	0.04 (−0.13, 0.20); $p_{FDR} = .537$
Age 22.87	0.75 (0.59, 0.91); $p_{FDR} = 2.00 \times 10^{-15}$	0.56 (0.40, 0.72); $p_{FDR} = 2.54 \times 10^{-10}$	0.52 (0.36, 0.68); $p_{FDR} = 7.72 \times 10^{-08}$	0.69 (0.53, 0.85); $p_{FDR} = 6.04 \times 10^{-13}$	0.29 (0.13, 0.45); $p_{FDR} = .0006$	0.10 (−0.07, 0.26); $p_{FDR} = .537$	0.02 (−0.14, 0.18); $p_{FDR} = .676$
Age 23.88	0.75 (0.57, 0.94); $p_{FDR} = 2.00 \times 10^{-15}$	0.58 (0.39, 0.77); $p_{FDR} = 4.37 \times 10^{-11}$	0.60 (0.41, 0.78); $p_{FDR} = 4.15 \times 10^{-10}$	0.82 (0.64, 1.01); $p_{FDR} = 2.00 \times 10^{-15}$	0.23 (0.04, 0.42); $p_{FDR} = .0006$	0.27 (0.08, 0.46); $p_{FDR} = .286$	0.06 (−0.13, 0.24); $p_{FDR} = .801$
	$p_{FDR} = 1.57 \times 10^{-14}$	$p_{FDR} = 2.99 \times 10^{-09}$	$p_{FDR} = 5.64 \times 10^{-10}$	$p_{FDR} = 2.00 \times 10^{-10}$	$p_{FDR} = .024$	$p_{FDR} = .008$	$p_{FDR} = .599$

Upper and lower 95% confidence intervals for the mean difference between trajectories are given in (parenthesis). p_{FDR} indicates the p-values are corrected for false discovery rate (FDR). The PT and subsequent PRS were selected based upon the best model fit; see Supporting Information for more information and additional sensitivity analyses. Ages coincide with the mean ages from the cross-sectional analysis. All analyses were adjusted for sex and the first ten principal components of ancestry. ANX, anxiety; DEP, depression (broad depression); EA, educational attainment; HEI, height; MDD, major depressive disorder; NEU, neuroticism; PRS, polygenic risk score; PT, p-value threshold for the PRS (i.e. threshold for the number of significant SNPs from the original GWAS included into the PRS); SCZ, schizophrenia.

specific (i.e. may begin to onset at different times) which enhances previous research looking at groups of individuals. Our results highlight a useful approach for a repeat measures framework (such as a growth-curve model) to quantify the extent to which genetics may influence traits over time (by examining rate of change) which goes over and above traditional cross-sectional research.

This study had several strengths. First, we were able to use a large longitudinal population cohort with repeated assessments of depressive symptoms using the same measure and informant across adolescence to adulthood. Many longitudinal studies with this depth of data change measures or informants, yet we were able to utilise the same measures and informants to characterise trajectories of depressive symptoms across key transitional periods of heightened vulnerability to depression. Second, we were then able to expand upon previous research by using a repeated measures model that is a powerful alternative to cross-sectional analysis. By using the correlation between the repeated measurements, it may be possible to reduce measurement error and boost statistical power, evidenced by the stronger associations at varying ages in the growth-curve analysis. Our negative control analysis examining the association between the PRS for height and trajectories of depressive symptoms, and the five psychiatric PRS for trajectories of height support this claim and did not show any evidence for nonspecific genomic predictors influencing unrelated trajectories. There was some evidence that a higher PRS for educational attainment was associated with changes over time, but this led to inconsistent differences across development, which may not be surprising given the genetic correlation with depression (Wray et al., 2018). Third, we were also able to use the same sample across our analysis as the repeated measures model used full-information maximum likelihood (FIML) to account for missing data, which is an advantage of this method compared to the cross-sectional analysis which may require additional methods for handling missing data. Fourth, we able to examine the impact of multiple psychiatric PRS from well-powered GWAS studies. To the best of our knowledge, we show for the first time, a key role for polygenic risk for anxiety and neuroticism in adolescent depressive symptoms. Still, it is important to state here that that anxiety GWAS had a much smaller sample size than the other PRS, which most likely explains the weaker associations.

However, this study had several limitations. First, this study did suffer from attrition as sample sizes varied across ages in the cross-sectional analysis, which may bias our results as missingness is not random. One of the advantages of using the repeat measures model is that we can instead use FIML to account for missing data. This approach also minimises the bias that may be present if each occasion (age wave) represents a different sample. However, even this approach may be biased if the data are missing not at random. For example, genetic risk for depression may predict missing assessments in ALPSAC (Rice et al., 2018; Taylor et al., 2018). This could lead to bias in this study and an underestimation of the true estimate for the trajectories of depressive symptoms and a further underestimation of the genetic contributions to depressive symptoms. We tested this in sensitivity analysis and found that our five psychiatric PRS were associated with the number of times an individual completed the depressive symptoms, whilst higher EA and HEI PRS were associated with more completed assessments. This demonstrates there is likely to be some level of bias between genetic liability to a trait and subsequent attrition. Second, depression is a heterogeneous condition and there may be a genetic difference between sum scores, and specific symptoms of depression (Nagel, Watanabe, Stringer, Posthuma, & van der Sluis, 2018). Depression symptoms may also differ at different ages (Rice et al., 2019). We used the same summary score of depressive symptoms throughout our study, which therefore only captures the sum of depressive symptoms and does not highlight if certain symptoms of depression (i.e. anhedonia, lack of appetite or depressive thoughts) are more related to genetic liability for depressive symptoms. Likewise, tests for measurement invariance indicated that the responses to the depressive symptoms questionnaire may have changed over time, yet the stronger association between the DEP PRS and later occasions was independent of measurement variance. Nevertheless, future research should look to examine how different profiles of depression change across time and how these profiles are independently predicted by genetic risk. Third, our results lack generalisability to all populations as the original GWAS (and subsequently this analysis) was conducted on individuals of European ancestry, and this may have consequences on further clinical applications (Mostafavi, Harpak, Conley, Pritchard, & Przeworski, 2019). However, research is beginning to capture GWAS of non-European populations (Bigdeli et al., 2017), and future studies will be able to examine the impact of genetic liability on adolescent depression in other populations. Finally, whilst our results highlight a potential role for PRS in understanding and examining pathways to depression (particularly as PRS are based on genotypes and are at fixed at birth and therefore less susceptible to reverse causation), the amount of variance in depressive symptoms explained by the PRS was low (never more than 2.45%). Whilst this is similar to the effect sizes reported in previous work (Howard et al., 2019; Luciano et al., 2018; Wray et al., 2018), the clinical implications of these results are not clear and PRS should continue to be used for making group-level, rather than individual-level predictions at this stage (Morris, Davies, & Davey Smith, 2020).

In conclusion, we found evidence that PRS for depression, major depressive disorder and neuroticism were associated with depressive symptoms from ages 10 to 24. These PRS and, to some extent, anxiety were also associated with how depressive symptoms change over time, providing evidence that higher genetic liability to specific mood disorder traits is associated with higher trajectories of depressive symptoms (estimated via a higher intercept and slope). Growth-curve models that use a repeated measures framework may be a useful tool in genetic analysis, providing greater statistical power/measurement precision and the opportunity to examine changes and variation in depression over time. Our results add to the body of evidence that genetics play a role in the onset and maintenance of adolescent depression and highlight the potential importance of this information for examining pathways to depression.

Supporting information

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

Table S35. Association between PRS and the number of completed SMFQs ($n = 7,849$).

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Key Points

- Adolescent depression shows a strong heritable component, but it is unclear how genetic risk scores play a role in the development and maintenance of depression across adolescence and beyond.
- The present study used a longitudinal design to examine the impact of five psychiatric polygenic risk scores on depressive symptoms across nine occasions and then on trajectories of depressive symptoms in over 6,000 individuals. We also sought to test whether using a repeated measures framework could provide additional insights beyond tradition cross-sectional methods.
- We found that individuals with greater genetic risk scores for depression, major depressive disorder and neuroticism were associated with higher depressive symptoms across development and with more severe trajectories of depressive symptoms across adolescence and young adulthood. Evidence was less clear for anxiety and schizophrenia genetic risk scores.
- Our study highlights the role of genetic risk scores in the onset and maintenance of depressive symptoms across development. Repeated measures designs may provide further insight into the relationship between genetics and psychiatric outcomes.

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