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Genetic susceptibility for major depressive disorder associates with trajectories of depressive symptoms across childhood and adolescence

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Background: Early-onset depression during childhood and adolescence is associated with a worse course of illness and outcome than adult onset. However, the genetic factors that influence risk for early-onset depression remain mostly unknown. Using data collected over 13 years, we examined whether polygenic risk scores (PRS) that capture genetic risk for depression were associated with depressive symptom trajectories assessed from childhood to adolescence. **Methods:** Data came from the Avon Longitudinal Study of Parents and Children, a prospective, longitudinal birth cohort (analytic sample = 7,308 youth). We analyzed the relationship between genetic susceptibility to depression and three time-dependent measures of depressive symptoms trajectories spanning 4–16.5 years of age (class, onset, and cumulative burden). Trajectories were constructed using a growth mixture model with structured residuals. PRS were generated from the summary statistics of a genome-wide association study of depression risk using data from the Psychiatric Genomics Consortium, UK Biobank, and 23andMe, Inc. We used MAGMA to identify gene-level associations with these measures. **Results:** Youth were classified into six classes of depressive symptom trajectories: *high/renitent* (27.9% of youth), *high/reversing* (9.1%), *childhood decrease* (7.3%), *late childhood peak* (3.3%), *adolescent spike* (2.5%), and *minimal symptoms* (49.9%). PRS discriminated between youth in the late childhood peak, high/reversing, and high/renitent classes compared to the minimal symptoms and childhood decrease classes. No significant associations were detected at the gene level. **Conclusions:** This study highlights differences in polygenic loading for depressive symptoms across childhood and adolescence, particularly among youths with high symptoms in early adolescence, regardless of age-independent patterns. **Keywords:** Depression trajectories; longitudinal; polygenic risk scores; development; ALSPAC.

Introduction

Major depressive disorder (MDD) is one of the most common, costly, and disabling mental disorders, with lifetime prevalence estimated at 11.7% among adolescents (Merikangas et al., 2010) and 16.6% among adults in the United States (Kessler et al., 2005). Although depression can emerge at any point in the life course, nearly one third of those who have depression report a first onset before age 21 (Zisook et al., 2007). These early-onset cases of depression, compared with later onset, have been associated with worse illness course and outcomes in adulthood, including increased risk for adult depression and later physical and mental health comorbidities (McLaughlin et al., 2012). However, depression is complex and developmentally heterogenous. Individuals with depression not only have different ages of first onset, but also show varying patterns of persistence once the disorder begins. Although prior cross-sectional studies have modeled this heterogeneity to identify more homogenous subgroups of depression, such studies are limited because depressive symptoms were assessed at a single point in time (Nandi, Beard, & Galea, 2009).

More recent longitudinal studies have sought to model this time-dependent heterogeneity in depressive symptoms (and internalizing symptoms more broadly) by classifying individuals into subgroups based on their symptom *trajectories* over time. These studies have prospectively and repeatedly assessed depressive symptoms across an average of 3–6 years of development (Ellis et al., 2017). Most studies have characterized between three and six primary trajectory classes, which include people with consistently low symptoms, chronically high symptoms, or decreases/increases in symptoms during childhood and adolescence. Importantly, this body of work has shown that subtyping depression by developmental trajectory can help identify the factors that shape the course of depressive symptoms over time.

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Genetic mechanisms in particular may explain part of the heterogeneity in depressive symptoms across development (Cai, Choi, & Fried, 2020). Genome-wide association studies (GWAS) suggest that common genetic variation accounts for approximately 9% of the variance in the heritability of adult depression (Howard et al., 2019; Wray et al., 2018). Studies in children have also shown some links between genetic variation and depressive phenotypes, with a recent study finding associations between one genetic locus and depressive symptoms at age 13 in the ALSPAC cohort (Sallis et al., 2017). However, most GWAS have focused on presence versus absence of lifetime depression and/or cross-sectional measures, which do not account for depression heterogeneity (Lee et al., 2013). Thus, additional studies using longitudinal data are needed to enhance our understanding of the genetic predictors of depressive symptoms across time, especially because prior work has shown that estimates of depression heritability may change over time (Bergen, Gardner, & Kendler, 2007; Nivard et al., 2015).

In addition to longitudinal data, polygenic risk scores (PRS), which capture the additive effect of multiple alleles using summary statistics from GWAS, have been used recently to examine genetic liability to depression. PRS have been used to assess the aggregate impact of genetic contributions on depressive phenotypes at various ages. For example, PRS of depression have recently been associated with self- or maternal-reported childhood psychopathologies, such as internalizing symptoms from age 7 to 16 (Akingbuwa et al., 2020), emotional problem trajectories from age 4 to 17 (Riglin et al., 2018), clinically measured depressive symptoms between age 7 and 18 (Halldorsdottir et al., 2019), as well as self-reported adolescent depressive symptom trajectories from age 10 to 22 (Kwong et al., 2019; Rice et al., 2018). Although these studies have provided important new insights into the genetic underpinnings of depression, they collectively have two main limitations. First, most studies focus on narrower age ranges and few include children younger than 7 years old. Thus, there has been limited attention to the earliest manifestations of depressive symptoms, which is a shortcoming because some symptoms can emerge as early as preschool (Whalen, Sylvester, & Luby, 2017). Accounting for the complete age span when symptoms emerge and occur is needed to capture the full course of depressive symptoms during development and to identify the factors that drive and shape symptom trajectories across the life course. Second, because longitudinal studies have focused almost exclusively on age-related changes in symptoms, genetic links to age-independent patterns, such as changes in symptom length and recurrence frequency across time, are poorly understood. For example, young people may have characteristic patterns of responding to positive and/or negative life events that can influence the chronicity and recurrence of any given depressive episode (Hawrilenko, Masyn, Cerutti, & Dunn, 2020). Efforts to disentangle biological and environmental sources of this interindividual variability in depressive symptom patterns are needed.

To address these gaps and determine how polygenic factors shape depressive symptom trajectories, we examined the genetic contributions to depressive symptoms across a 13-year period (from age 4 to 16.5). To our knowledge, this is the longest time span examined for depressive (or internalizing) symptoms across childhood and adolescence. Recognizing that developmental heterogeneity encompasses not only symptom trajectories across time, but also the age at onset and burden of symptoms, we modeled the developmental patterns of depressive symptoms using three measures. First, we assessed classes of depressive symptom trajectories, constructed using a new form of growth mixture modeling that includes structured residuals to account for symptom changes over time (GMM-SR; Hawrilenko et al., 2020). Second, we modeled the onset of depressive symptoms at age 4, coinciding with the earliest time period reported in prior studies (Whalen et al., 2017). Third, we examined the cumulative burden of depressive symptoms, reflecting the overall level of depressive symptoms across childhood and adolescence. We assessed both polygenic and gene-specific mechanisms on these three measures in two ways. We first tested whether our measures were associated with polygenic risk for depression, using summary statistics generated from recent large-scale GWAS of depression (Howard et al., 2019). We then performed the first genome-wide, gene-level analysis of longitudinal depressive phenotypes to determine whether specific genes were implicated in these associations.

Materials and methods

Cohort and analytic sample

Data came from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large population-based birth cohort out of Avon, England, of children followed from before birth through early adulthood (Boyd et al., 2013; Fraser et al., 2013) (Appendix S2). The current study's analytic sample consisted of 7,308 children who met the following inclusion criteria: singleton births with genotype data and at least one measure of depressive symptoms completed between 4 and 16.5 years of age (Figure S1). Compared to the total original ALSPAC sample, youths in our analytic sample were more likely to be white, have slightly higher birth weights, and have mothers who were older, married, and had higher employment, higher education, and fewer previous pregnancies (Table S1).

Genotyping, quality control, and imputation

Nine thousand nine hundred and twelve youths in the full ALSPAC cohort were genotyped on the Illumina HumanHap550-Quad genotyping platform (Illumina Inc., San Diego, CA). After quality control, 500,527 directly genotyped SNPs and 8,082 youths remained, of whom 7,308 (90.4%) were

included in our analyses, based on the exclusion criteria above (Figure S1; Appendix S2).

Depressive symptom measures

Depressive symptom scores were derived from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) and the Short Mood and Feelings Questionnaire (SMFQ; Angold, Costello, Messer, & Pickles, 1995), both of which were completed by caregivers via mail. Briefly, depressive symptoms were measured with two of the five SDQ subscales, *child emotional problems* and *peer difficulties,* as well as with the SMFQ in adolescents. Using multiple measures helped ensure that the most developmentally relevant depressive symptoms were tapped at each age (Graham, Taylor, Olchowski, & Cumsille, 2006). The SDQ subscales captured 'internalizing symptoms' at seven timepoints: ages 4, 7, 8, 9.5, 11.5, 13, and 16.5 (Goodman, 2001), while the SMFQ assessed depressive symptoms in adolescents at three timepoints: ages 11.5, 13, and 16.5 (Angold et al., 1995). We used confirmatory factor analysis to combine information across all questionnaire items into a single factor score representing the latent cause of their shared variability, which we interpreted as *depressive symptoms* (Table S2; Appendix S2) (Hawrilenko et al., 2020; Kline, 2015). Full details of the measurement invariance analyses can be found in the technical supplement for Hawrilenko et al. (2020). Factor score estimates of this latent score were used in the subsequent growth mixture models (Curran et al., 2018).

Depressive symptom trajectories

In a previous analysis, Hawrilenko and colleagues used a novel form of growth mixture modeling with structured residuals (GMM-SR) in MPlus (version 8.0) to classify youths into distinct subgroups using their patterns of depressive symptoms (Hawrilenko et al., 2020; Muthén & Muthén, 2017). The GMM-SR partitions individual variability in depressive symptoms over time into (a) an average level, (b) age-dependent trajectories, and (c) group-specific, time-anchored patterns of change. The latter were modeled through the structured residual, which captured the difference between the observed depression score and the score predicted by the age-dependent trajectory at any timepoint. Thus, the residual represented the influence of unmodeled events, adding an autoregressive structure to how these unmodeled events related over time. Positive values represented the degree to which a deviation from average symptom levels perpetuated across time (renitent responding), whereas negative values represented the tendency for symptoms to fluctuate above and below an average level (reversing responding). Importantly, the GMM-SR allowed us to analyze not only depressive symptom levels as a function of age (age-dependent patterns), but also how symptom levels responded to change from unmodeled life events (everything except age) within and between youths over time.

To characterize depressive symptoms across childhood and adolescence, we analyzed three time-dependent measures of depressive symptoms trajectories: (a) trajectory classes; (b) onset of symptoms; and (c) cumulative burden of symptoms. The methods used to construct these variables are described below.

Depressive symptom trajectory classes

Based on work by Hawrilenko et al. (2020), we characterized six overarching classes of depressive symptom trajectories within our analytic sample (Figure 1): (a) *minimal symptoms* (stable and low symptoms across development), (b) *adolescent spike* (low childhood symptoms spiking to high levels in adolescence), (c) *late childhood peak* (symptoms increasing through middle childhood and decreasing over adolescence), (d) *childhood decrease* (high symptoms decreasing across childhood), (e) *high/reversing* (high symptoms with sharp oscillations between ages), and (f) *high/renitent* (high symptoms with few oscillations between ages). The model-estimated proportion of youths assigned to each trajectory class was 49.9% minimal symptoms, 2.5% adolescent spike, 3.3% late childhood peak, 7.3% childhood decrease, 9.1% high/reversing, and 27.9% high/renitent. Demographics for individuals in each class can be found in Table S3.

Onset of depressive symptoms

Second, we measured the earliest possible onset of depressive symptoms, captured by the intercept of each youth's depressive symptom trajectory at age 4. This intercept corresponded to baseline depressive symptoms latent score at age 4 for each individual (values ranged from 0.20 to 1.56, mean = 0.75; Table S4), where lower values represented less depressive symptoms. Given that clinically relevant depressive symptoms can emerge at preschool age (i.e., around age 4), early manifestations of depression may be more genetically driven and reflect stronger pre-existing biological vulnerabilities than symptoms that emerge at later ages (Luby, 2010; Whalen et al., 2017).

Cumulative burden of depressive symptoms

Third, we measured cumulative burden of depressive symptoms using the area under the curve (AUC) of the depressive symptom trajectory (Mills et al., 2018). We calculated the AUC as the integral of the function describing depressive symptom trajectories, estimated using individual growth factors (intercept, slope, quadratic, cubic, and quartic terms). Thus, youths with higher depressive symptoms over developmental time displayed higher a cumulative burden of symptoms (AUC values ranged from 0.28 to 2.53, mean = 1.13; Table S4). Of note, this measure was highly correlated with the onset of depressive symptoms (r = .909), suggesting that the two measures likely tap similar dimensions of depressive symptom trajectories.

Analyses

We performed our analysis in two main stages. All analyses were adjusted for sex and the top 10 principal components to account for population stratification.

Polygenic risk score (PRS) analysis

We constructed PRS for depression using the latest summary statistics from the Psychiatric Genomics Consortium GWAS of MDD, wave 2 (PGC-MDD2; 43,204 cases; 95,680 controls), UK Biobank (127,552 cases; 233,763 controls), and 23andMe (75,607 cases; 231,747 controls) in PLINK v.1.07 (Howard et al., 2019; Purcell et al., 2007) (Appendix S2). To assess polygenic influences on depressive symptom trajectory classes, we included PRS scores as predictors of class membership in MPlus, using the two-step method to account for classification uncertainty (Bakk & Kuha, 2018). The first step estimated the unconditional six-class GMM-SR in the current analytic sample. In the second step, the growth model parameters (e.g., intercepts, slope terms, autoregressive terms) were

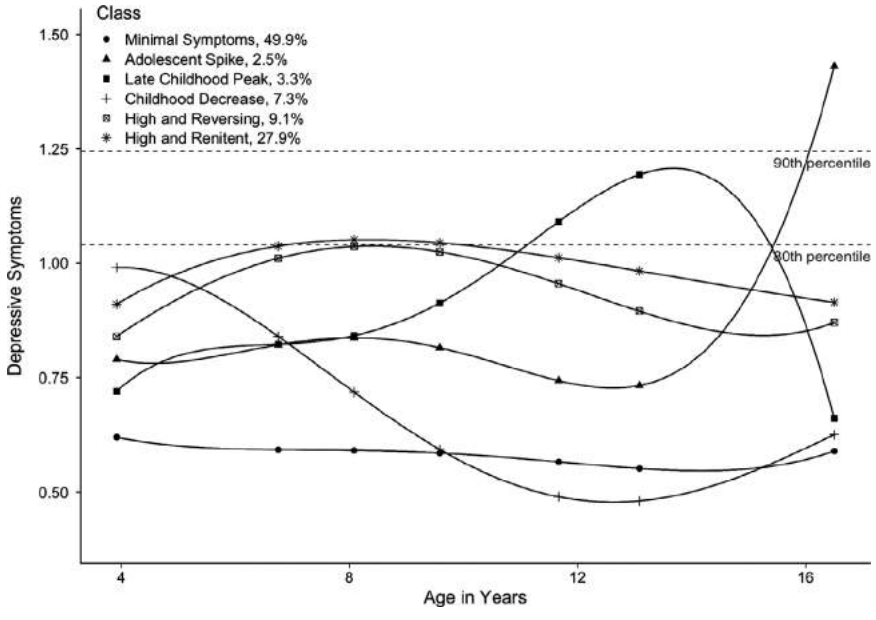

Figure 1 Six classes were characterized using latent score analysis across ages 4–16.5 in 7,308 youths of the ALSPAC cohort. The latent scores were a composite score that captured depressive symptoms measured from the SDQ and SMFQ. Youth with higher scores had more depressive symptoms at that specific age. The percent of individuals assigned to each trajectory class was based on the model-estimated proportions. These were slightly different from the modal class proportions used in the MAGMA analysis, as they took into account the second and third place class assignments for each individual

fixed at the estimates found in step 1, while class thresholds and covariate effects were freely estimated. We standardized PRS as z-scores so that all reported odds ratios (OR) could be interpreted as the effect of moving up or down one standard deviation of PRS on the odds of class membership. We first used the Wald omnibus test to assess the relationship between PRS and depressive symptom trajectories. Multinomial logistic regressions were then used to contrast the model-estimated probability of assignment between different classes (Hawrilenko et al., 2020). Since the trajectories represent different groups of youths, these pairwise comparisons allowed us to understand the specific patterns of depressive symptoms differentiated by PRS. Parallel to the class-based analysis, we tested the relationship between PRS and depressive symptom onset or cumulative burden using linear regressions in R (version 3.6.1). We adjusted all PRS analyses for multiple comparisons using a false discovery rate (FDR) threshold of 5% (Benjamini & Hochberg, 1995).

Gene-level analyses

To assess specific genetic influences on trajectory features, we performed genome-wide, gene-level associations with our three outcome measures using regression analyses in MAGMA (version 1.06)(de Leeuw, Mooij, Heskes, & Posthuma, 2015). For our gene-based analysis of trajectory classes, we focused on the two largest and most conceptually different classes, *minimal symptoms* and *high/renitent*. Because no tools currently exist to account for measurement error/classification uncertainty inherent to GMM in genome-wide analyses, we used modal class assignment to generate a case/control subset of youths in these two classes (Appendix S2). Although this approach may lead to liberal estimates of standard errors by not accounting for the uncertainty associated with GMM, point estimates remained unbiased (Vermunt, 2017). Briefly, each youth received a probability of assignment to each class, summing to 100%, and were assigned to the class in which they had the highest probability (i.e., modal class). The average probability of assigned class across all individuals was 76% (*standard deviation* = 18%; Figure S2). Using this approach, 4,416 youths were classified as *minimal symptoms* (controls) and 1,895 youths were classified as *high/renitent* (cases). Sensitivity analyses using a higher probability threshold or continuous class probabilities for the high/renitent class can be found in Appendix S2.

Our analyses of depressive symptom onset and cumulative burden used the continuous variables described earlier across all youths ($N = 7{,}308$). A significance threshold of $p < 2.93\text{e-}6$ was set to account for multiple testing of 17,044 genes; a nominal significance threshold was set at $p < 1\text{e-}4$.

Sensitivity analysis of maternal PRS

Given that depressed mothers may be more likely to rate their children as depressed, we performed a sensitivity analysis to determine if our results were biased by the use of maternal reports for youths' depressive symptoms. To this end, we included maternal PRS for depression as predictors of child

depressive symptom trajectories in 5,301 mother–child pairs (Appendix S2). Since mother and youth PRS were strongly correlated (r = .52), we expected a decrease in youth PRS effects when controlling for maternal PRS.

Results

PRS were associated with depressive symptom trajectory classes

Our initial analysis revealed a significant relationship between PRS for depression and depressive symptom trajectories (χ^2 = 45.8, p < 1e-4; Figure S3), showing that the probability of class membership varied across PRS (Figure 2, Figure S4). To understand which specific patterns within trajectories drove these results, we examined pairwise contrasts between each pair of trajectories for a total of 15 contrasts (Table 1; Figure S5). Four contrasts showed statistically significant differences following multiple-test correction (FDR < 0.05). Specifically, one standard deviation increase in PRS was associated with increased odds of assignment to the late childhood peak (OR = 1.30, 95% CI: 1.10–1.54), high/reversing (OR = 1.23, 95% CI: 1.07–1.41), or high/renitent classes (OR = 1.28, 95% CI: 1.17–1.38), as compared to the minimal symptoms class. Similarly, each one-unit increase in the standardized PRS was associated with increased odds of being assigned to the high/renitent class compared to the childhood decrease class (OR = 1.22, 95% CI: 1.05–1.42). When accounting for maternal PRS, these effects decreased an average of 34% (range: 28%–45%) in statistically significant contrasts (Table S5; Appendix S2).

PRS were associated with depressive symptom onset and cumulative burden

We next assessed whether PRS might influence features of depressive symptom trajectories beyond class alone. We found that higher PRS were associated with higher onset depressive symptoms (p = 2.1e-10, β = .018) and higher overall cumulative burden of depressive symptoms (p = 4.1e-16, β = .042) across all youths.

Gene-based analyses revealed nominal associations with depressive symptom trajectory class, onset, and cumulative burden

Finally, we attempted to identify specific genes associated with our three outcome measures. No genes reached statistical significance at the genome-wide level (p < 2.93e-6) when comparing youths in the high/renitent class to those in the minimal symptoms class, or when modeling onset and cumulative burden of depressive symptoms (Figures S6, S7, S8, S9; Table S6). However, seven different genes were nominally associated with depressive symptom features (GABRA4, LRR1, SIX5, DMPK, DKK1, SMDT1, DWMD). Of note, SIX5 and DMPK were nominally associated with both onset and cumulative burden of depressive symptoms.

Discussion

In this study, we examined the role of genetic contributions in shaping developmental patterns of depressive symptoms trajectories (class, onset, and cumulative burden) across a 13-year age range that spanned childhood and adolescence. Using the

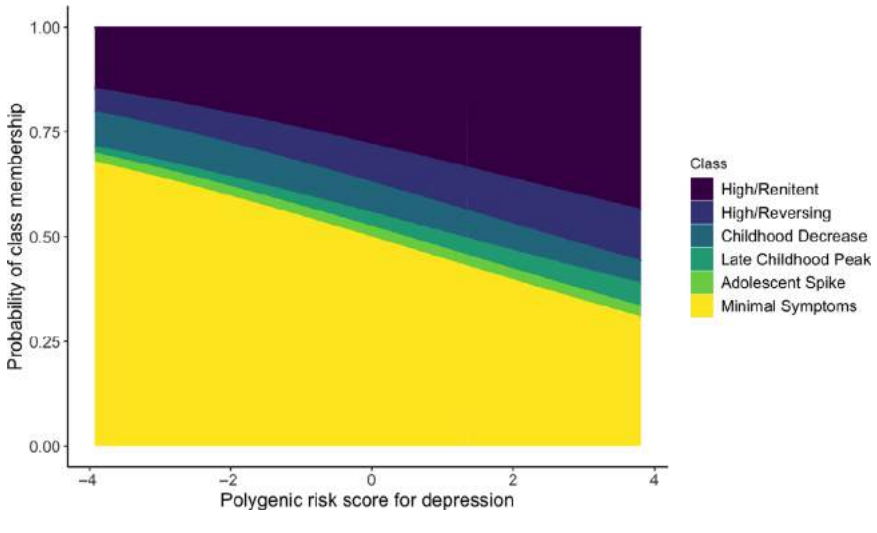

Figure 2 The probability of assignment to depressive symptom trajectory classes was skewed with PRS. The probability of class membership was calculated from the multinomial logistic regressions of estimated class probability. Negative PRS indicated lower genetic risk for depression, whereas positive PRS indicated higher risk. All classes showed differences in probability of assignment based on PRS, except the adolescent spike class [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1 Odds of reference class assignment for each one standard deviation difference in standardized PRS

		Reference category				
		Minimal symptoms	Adolescent spike	Late childhood peak	Childhood decrease	High/ reversing
Alternative Category	Minimal symptoms					
	Adolescent spike	1.14 (0.94, 1.38)				
	Late childhood peak	1.30 (1.1, 1.54)*	1.14 (0.89, 1.46)			
	Childhood decrease	1.04 (0.90, 1.21)	0.92 (0.73, 1.15)	0.80 (0.65, 0.99)		
	High/ reversing	1.23 (1.07, 1.41)*	1.08 (0.86, 1.35)	0.95 (0.77, 1.17)	1.18 (0.98, 1.42)	
	High/ renitent	1.28 (1.17, 1.38)*	1.12 (0.92, 1.36)	0.98 (0.82, 1.18)	1.22 (1.05, 1.42)*	1.04 (0.89, 1.22)

*Statistically significant at FDR < .05.

GMM-SR, we characterized six independent depressive symptom trajectories, which provided additional insight into the specific patterns of depressive symptoms that may be driven by genetic or environmental factors (Hawrilenko et al., 2020). Using trajectory classes, onset, and cumulative burden of depressive symptoms, we showed that polygenic influences may shape depressive symptom trajectories across development.

Similar to previous studies, our results showed that genetic liability may best discriminate between generally high versus low patterns of depressive symptoms during development (Kwong et al., 2019; Rice et al., 2018). However, our results extended beyond this known relationship, showing for the first time that these associations hold true irrespective of age-associated patterns of responding (i.e., renitent and reverse responding). As age-associated patterns of responding capture how youths respond to life events, fluctuations in depressive symptoms between timepoints may reflect coping mechanisms that are environmentally driven or learned, rather than genetic (Waugh & Koster, 2015).

Our results also further refined the time period when PRS may influence high depressive symptoms, showing that increased genetic risk for depression may manifest through elevated depressive symptoms during late childhood to early adolescence (approximately age 10–15). This result was in line with previous work that showed an association between PRS of depression and early-adolescent onset depressive symptom trajectories (Rice et al., 2018). As such, early adolescence may be a period when symptoms linked to genetic liability for depression are more likely to emerge.

Of note, the childhood decrease class has not been previously described in the depression genetics literature. This class was closer to the minimal symptoms class in terms of genetic influences, which may reflect maternal or other environmental influences. Indeed, Hawrilenko et al. (2020) reported that higher maternal psychopathology and education distinguish the childhood decrease class from the minimal symptoms class. The contrast between the childhood decrease and high/renitent classes also showed one of the largest decreases in effect size when maternal PRS for depression was included in the analysis (Appendix S2). Thus, the childhood decrease class may represent youths who are at lower risk for depression, but whose early-life depressive symptoms are driven by early-life events not captured by the depression PRS. Since genetics are stable throughout the life course, it is possible that genetic vulnerability or resilience to depression could manifest throughout childhood and adolescence and that while depressive symptom trajectories vary, individual risk for depression later in life may remain the same. Previous work has also shown that the impact of genetics on depression (i.e., heritability) increases over time, suggesting that some youths may self-select environments that reinforce their genetic susceptibility to depression (Bergen et al., 2007).

The only depressive symptom trajectory not associated with PRS was the adolescent spike class. Although the small size of this class may have affected our ability to detect significant associations, we detected associations between PRS and other classes of moderate size. As such, membership to this class may be primarily driven by environmental factors or sex-specific mechanisms, as shown by Hawrilenko et al. (2020). Indeed, the adolescent spike class showed an inflection point consistent with periods related to both internal (i.e., puberty) and external factors previously associated with depression, such as social environment, academic testing, and the like (Graber, Lewinsohn, Seeley, & Brooks-Gunn, 1997). However, these results are in contrast to previous work showing that depression PRS is associated with trajectories that arise later in adolescence or early adulthood (Kwong et al., 2019; Rice et al., 2018). These findings highlight the importance of multiple timepoints and broader developmental periods when assessing the factors

influencing depressive symptoms, as shorter time periods may not have captured these distinct patterns of developmental heterogeneity. Future studies with access to data extending into adulthood may be able to further refine these trajectories and determine whether they do indeed reflect depressive symptom trajectories that continue into adulthood.

Beyond the polygenic influences of depression, we found no significant associations between individual genes and depressive symptom trajectories. Although the lack of associations may, in part, be due to small sample size, the genes identified at more relaxed *p*-value thresholds may reflect pathways impacting the manifestation of symptoms during development. For instance, GABRA4, a member of the GABAergic pathway, was nominally significant in the analyses of youths in the high/renitent and minimal symptoms classes. As this pathway has been previously associated with depression, our results could potentially point to a role in shaping developmental profiles of depression (Luscher, Shen, & Sahir, 2011). In contrast to our PRS results, our lack of significant gene-level associations may also emphasize the polygenicity of depression, where its characteristics cannot be attributed to specific genes. Nevertheless, more comprehensive genome-wide analyses, such as gene sets or pathway analyses, in larger samples may extend these findings by providing insight into the specific pathways shaping patterns of depressive symptoms across development.

Finally, previous work using these trajectories has shown that maternal psychopathology, abuse, and neighborhood-level disadvantage may increase the risk of belonging to all classes other than the minimal symptoms group (Hawrilenko et al., 2020). Given that depressive symptoms are highly correlated with environmental factors in this sample, the high variation in depressive symptom onset, cumulative burden, and overall trajectory may be attributed to factors not captured by genetics alone (Hawrilenko et al., 2020; Smoller et al., 2019). Genetic and environmental factors may also interact to drive depressive symptom trajectories, leading to the more complex phenotypes observed in our study.

Limitations

There are some limitations to the present study. Aside from the relatively small sample size of this cohort for genetic analyses, this longitudinal sample is subject to attrition and self-selection over time and is composed of mainly European-ancestry youths, reducing the generalizability of our findings to other populations (Boyd et al., 2013). Depressive symptom scores were generated from maternal reports only, which may introduce inconsistencies over time or bias in reporting through residual maternal depression. However, when controlling for maternal depression PRS in our analyses, we only observed a small decrease in the effects of child PRS on depressive symptoms trajectories (Appendix S2). These results suggested that maternal polygenic risk was not as strong a predictor as the child's own polygenic risk, despite child depressive symptoms being reported by their mothers. The PRS were also primarily generated from studies of depression in European adults, limiting the interpretability of findings in non-European populations (Howard et al., 2019). In addition, PRS built on summary statistics from adults may not be entirely reflective of genetic influences on depressive symptoms during early life. Nevertheless, as childhood and adult depression are highly correlated, our results likely captured a subset of youths that display increased genetic predisposition to lifetime depression. Finally, PRS only explain a very small portion of the variance in depression (1%–2%), which limits their ability to fully explain the genetic mechanisms influencing depressive symptom trajectories and may reduce their application to clinical settings (Martin, Daly, Robinson, Hyman, & Neale, 2019).

Conclusions

Overall, our findings point to PRS as potential detectable early risk factors for depressive phenotypes during childhood and adolescence, particularly in youth with higher depressive symptoms during early adolescence, provide new insights into how polygenic influences may shape depressive symptom trajectories. These findings may ultimately lead to the identification of genetic factors that shape age of depression onset and overall disease course, providing early targets to guide depression prevention efforts.

Supporting information

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

Appendix S1. Members of the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium.
Appendix S2. Supplemental methods.
Table S1. Summary of the analytical subsample from the ALSPAC cohort.
Table S2. Means, standard deviations, and correlations for study variables.
Table S3. Child and mother characteristics stratified by latent class.
Table S4. Growth parameters for the unconditional six-class growth mixture model with structured residuals.
Table S5. Sensitivity analysis examining difference in PRS effects when controlling for mother's PRS score.
Table S6. Summary of gene-based hits using MAGMA.
Figure S1. Flowchart of ALSPAC sample selection.

Figure S2. Probability of class assignment for individuals within their assigned latent class.
Figure S3. The PRS with pT < 0.1 was the 'best fit' polygenic risk score.
Figure S4. Model estimated proportions of individuals in each latent class.
Figure S5. Polygenic risk scores identified differences in membership to classes of depressive symptom trajectories.
Figure S6. Quantile-quantile (QQ) plots of gene-level genome-wide associations showed good model fit of the MAGMA analysis.
Figure S7. Depressive symptom developmental features showed nominal gene-level associations.
Figure S8. MAGMA analysis of the probability of assignment to the high/renitent class.
Figure S9. MAGMA analysis of youths in the high/renitent versus minimal symptoms class.

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Key points

- The genetic factors that influence early-onset depression and depressive symptoms over developmental time remain mostly unknown.
- PRS for depression can discriminate between high and low patterns of depressive symptoms during development, particularly during early adolescence.
- PRS may be detectable risk factors for early-onset depressive phenotypes, particularly in youth with higher depressive symptoms.
- Further research is needed to understand the environmental and biological mechanisms driving depressive symptom trajectories.

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Supporting Information – Genetic susceptibility for major depressive disorder associates with trajectories of depressive symptoms across childhood and adolescence – by Lussier *et al.*

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Conor V Dolan 9
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Isaac S Kohane 64, 65, 66
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Zoltán Kutalik 68, 69
Yihan Li 67
Penelope A Lind 29
Donald J MacIntyre 70, 71
Dean F MacKinnon 50
Robert M Maier 2
Wolfgang Maier 72
Jonathan Marchini 73
Hamdi Mbarek 9
Patrick McGrath 74
Peter McGuffin 28
Sarah E Medland 29
Divya Mehta 2, 75
Christel M Middeldorp 9, 76, 77
Evelin Mihailov 78
Yuri Milaneschi 19
Lili Milani 78
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Grant W Montgomery 1
Sara Mostafavi 79, 80
Niamh Mullins 28
Matthias Nauck 81, 82
Bernard Ng 80
Michel G Nivard 9
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Paul F O'Reilly 28
Hogni Oskarsson 84
Michael J Owen 60
Jodie N Painter 29
Carsten Bøcker Pedersen 11, 12, 13
Marianne Giørtz Pedersen 11, 12, 13
Roseann E Peterson 17, 85
Erik Pettersson 22
Wouter J Peyrot 19
Giorgio Pistis 27
Danielle Posthuma 86, 87
Jorge A Quiroz 88
Per Qvist 8, 13, 24
John P Rice 89
Brien P. Riley 17
Margarita Rivera 28, 90
Saira Saeed Mirza 36
Robert Schoevers 91
Eva C Schulte 92, 93
Ling Shen 62
Jianxin Shi 94
Stanley I Shyn 95
Engilbert Sigurdsson 96
Grant C B Sinnamon 97
Johannes H Smit 19
Daniel J Smith 98
Hreinn Stefansson 99
Stacy Steinberg 99
Fabian Streit 45
Jana Strohmaier 45
Katherine E Tansey 100
Henning Teismann 101
Alexander Teumer 102
Wesley Thompson 13, 54, 103, 104
Pippa A Thomson 105
Thorgeir E Thorgeirsson 99
Matthew Traylor 106

Jens Treutlein 45
Vassily Trubetskoy 4
Andrés G Uitterlinden 107
Daniel Umbricht 108
Sandra Van der Auwera 109
Albert M van Hemert 110
Alexander Viktorin 22
Peter M Visscher 1, 2
Yunpeng Wang 13, 54, 104
Bradley T. Webb 111
Shantel Marie Weinsheimer 13, 54
Jürgen Wellmann 101
Gonneke Willemsen 9
Stephanie H Witt 45
Yang Wu 1
Hualin S Xi 112
Jian Yang 2, 113
Futao Zhang 1
Volker Arolt 114
Bernhard T Baune 115, 116, 117
Klaus Berger 101
Dorret I Boomsma 9
Sven Cichon 35, 47, 118, 119
Udo Dannlowski 114
EJC de Geus 9, 120
J Raymond DePaulo 50
Enrico Domenici 121
Katharina Domschke 122, 123
Tõnu Esko 5, 78
Hans J Grabe 109
Steven P Hamilton 124
Caroline Hayward 125
Andrew C Heath 89
Kenneth S Kendler 17
Stefan Kloiber 59, 126, 127
Glyn Lewis 128
Qingqin S Li 129
Susanne Lucae 59
Pamela AF Madden 89
Patrik K Magnusson 22
Nicholas G Martin 29
Andrew M McIntosh 10, 34
Andres Metspalu 78, 130
Ole Mors 13, 131
Preben Bo Mortensen 11, 12, 13, 24
Bertram Müller-Myhsok 15, 132, 133
Merete Nordentoft 13, 134
Markus M Nöthen 35
Michael C O'Donovan 60
Sara A Paciga 135
Nancy L Pedersen 22
Brenda WJH Penninx 19
Roy H Perlis 38, 136
David J Porteous 105
James B Potash 137
Martin Preisig 27
Marcella Rietschel 45
Catherine Schaefer 62
Thomas G Schulze 45, 93, 138, 139, 140
Jordan W Smoller 38, 39, 40
Kari Stefansson 99, 141
Henning Tiemeier 36, 142, 143
Rudolf Uher 144
Henry Völzke 102
Myrna M Weissman 74, 145
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Appendix S2. Supplemental methods.

Cohort description

Data came from the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective, longitudinal birth cohort of children born to mothers who were living in the county of Avon England (120 miles west of London) with estimated delivery dates between April 1991 and December 1992 ALSPAC was designed to identify the determinants of health across the lifespan, with an emphasis on genetic and environmental factors. The initial number of pregnancies enrolled is 14,541 (for these at least one questionnaire has been returned or a

"Children in Focus" clinic had been attended by 19/07/99). Of these initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years old, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally, resulting in an additional 913 children being enrolled. As such, the total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies, resulting in 15,589 fetuses. Of these 14,901 were alive at 1 year of age. The ALSPAC website contains details of all the data that is available through a fully searchable data dictionary and variable search tool: www.bristol.ac.uk/alspac/researchers/our-data/. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committee. 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.

Genotyping, quality control, and imputation

We performed standard quality control measures to exclude youths on the basis of gender mismatch, minimal or excessive heterozygosity, individual genotyping call rates < 97%, insufficient sample replication (IBD<0.8), cryptic relatedness (IBD>0.1), and non-European ancestry (assessed using multidimensional scaling analysis and compared to HapMap II, release 22). For the current analyses, we further excluded 21 youths who self-reported as non-whites. We excluded genotyped SNPs based on the following criteria: minor allele frequency <1%; missing rate >5%; and significant deviation from Hardy-Weinberg Equilibrium (p<1e-7). We conducted imputation using Impute V2.2.2 against the 1000 genomes reference panel (Phase 1,

version 3), with 2,186 reference haplotypes including non-Europeans (Abecasis et al., 2012; Marchini, Howie, Myers, McVean, & Donnelly, 2007).

Confirmatory factor analysis of the growth mixture modeling with structured residuals

As noted in the main text, we used confirmatory factor analysis to combine information across all questionnaire items into a single factor score estimate representing the latent cause of their shared variability, which we interpreted as *depressive* symptoms (Hawrilenko, Masyn, Cerutti, & Dunn, 2020; Kline, 2015). Preliminary measurement invariance analyses revealed that some items changed over time due to non-depression-related factors, suggesting scalar non-invariance. We accounted for this scalar non-invariance by combining items into parcels (meaning, the averaged subsets of items) with internally consistent patterns of scalar non-invariance; we also released scalar constraints on the non-invariant waves, allowing the non-invariant parcels to contribute to factor score information within each wave, but not to changes in factor scores across waves (Little, Cunningham, Shahar, & Widaman, 2002). Standardized factor loadings were moderate to strong for items representing emotional difficulties (range: 0.61 to 0.81) and in the moderate range for peer difficulties (range: 0.39 to 0.55). Full details of the measurement invariance analyses can be found in the technical supplement for Hawrilenko and colleagues, 2020 (*Child Development*).

Polygenic risk score (PRS) generation and selection

Prior to score construction, we performed additional genomic quality control procedures by removing imputed SNPs with imputation quality metric score <0.8, MAF <1%, call rate <95%, and HWE p<1e-6. SNPs were then pruned for linkage disequilibrium using p-value informed

clump-based pruning in PLINK v1.90 (r^2=0.25 within a 250kb window). We created the PRS in PLINK v.1.07, using methods described by Purcell et al., where the PRS for each youth was the sum of the risk alleles (0, 1, or 2) for each SNP at a given p-value threshold weighted by the logarithm of its odds ratio (OR) for MDD in the PGC GWAS (Purcell et al., 2007). Using Pthe summary statistics from Howard et al., 2019 (PGC-MDD2, UK Biobank, 23andme) as the discovery sample and the ALSPAC cohort as the training sample, we selected independent subsets of SNPs from GWAS summary data at 10 GWAS significance thresholds (p_T), 0.0001, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1. We standardized all PRS prior to analysis so that all reported ORs could be interpreted as a one standard deviation increase in the score. As the PRS with p_T<0.1 explained the most phenotypic variance in the analytic sample compared to the other scores (Wald omnibus value = 45.8; Chi-squared p-value < 1e-4; **Figure S6**), we focused on the results from this 'best model fit' score.

Modal class assignment in the MAGMA analysis

Modal class assignments were used in the gene-level MAGMA analysis, as to our knowledge, no existing software tools currently exist to account for measurement error/classification uncertainty inherent to GMM in genome-wide analyses. To this end, participants were assigned to latent classes based on posterior probabilities of their membership in each latent class, calculated from their observed data and the latent class model parameters. Each youth had probabilities summing to 100%, reflecting their probability of assignment to each of the 6 latent classes. To assign a modal class to each individual, we selected the latent class with the highest probability. Using this approach, the average modal class probability (i.e., the highest probability class for each individual) across all individuals was 76% (SD = 18%; **Figure S2**). With this approach, the

number of youths assigned to each trajectory class was estimated as follows: 4,146 minimal symptoms (56.7%), 182 adolescent spike (2.5%), 222 late childhood peak (3%), 440 childhood decrease (6%), 423 high/reversing (5.8%), and 1,895 high/renitent (25.9%). Although modal-class assignment may lead to lower standard errors to or overly-optimistic inferential tests, point estimates remained unbiased (Vermunt, 2017). We also note that modal class proportions are slightly different from the model-estimated proportions reported in Figure 1, as they do not take into account the "second place" and "third place" class assignments for each individual (Hawrilenko et al., 2020).

Sensitivity analyses of class assignment in the MAGMA analyses

We performed additional analyses in MAGMA using trajectories classes. First, we performed a case/control analysis on individuals in the high/renitent and minimal symptoms class who had a modal class probability equal to or greater than 80%. This threshold resulted in 786 youths in the high/renitent class and 2,258 youths in the minimal symptoms class (Figure S9). Second, we performed an analysis on continuous probabilities for the high/renitent class across all individuals (0-100%) (Figure S8).

Author contributions

A.A.L. analyzed the data, compiled the results, and wrote the manuscript. M.H. performed the analyses in MPlus. M.W. generated the polygenic risk scores. K.C. and J.C. helped with writing and interpretation of findings. Y.Z. helped with data analysis of the ALSPAC cohort. E.C.D. helped write the manuscript and compile the results. All authors provided critical feedback at all stages of the manuscript.

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Table S1. Summary of the analytical subsample from the ALSPAC cohort.

	Original Sample (N=15445) n (%)	**Analytic Sample (N=7,308)** n (%)	**Original vs. Analytic** $\chi 2$ p-value
Sex			
Males	7542 (51.3)	3707 (50.7)	0.151
Females	7152 (48.7)	3601 (49.3)	
Race			
Non-white	611 (5.1)	0 (0)	<0.001
White	11488 (94.9)	6639 (100.0)	
Age of Mother at Child's Birth			
Ages 15-19	650 (4.6)	142 (2.0)	<0.001
Ages 20-35	12363 (88.4)	6281 (89.8)	
Age 36+	968 (6.9)	575 (8.2)	
Parental Social Class			
Professional	1419 (9.6)	942 (12.9)	<0.001
Managerial and technical	4288 (29.0)	2583 (35.3)	
Skilled, non-manual	2623 (17.8)	1456 (19.9)	
Skilled, manual	909 (6.2)	438 (6.0)	
Semi-skilled, manual	270 (1.8)	125 (1.7)	
Unskilled, manual/other	5254 (35.6)	1764 (24.1)	
Number of previous pregnancies			
0	5800 (44.7)	3045 (44.9)	<0.001
1	4550 (35.0)	2480 (36.6)	
2	1860 (14.3)	921 (13.6)	
3+	772 (5.9)	330 (4.9)	
Birth weight (g)			
< 3000	3649 (24.8)	1572 (21.5)	<0.001
3000 - 3499	4924 (33.5)	2446 (33.5)	
3500 - 3999	4382 (29.8)	2338 (32.0)	
>= 4000	1735 (11.8)	952 (13.0)	
Maternal Education			
less than O-level	3735 (30.0)	1575 (23.3)	<0.001
O-level	4303 (34.6)	2366 (35.1)	
A-level	2795 (22.5)	1724 (25.5)	
Degree or Above	1603 (12.9)	1084 (16.1)	
Maternal Marital Status			
Never Married	2522 (19.2)	950 (13.9)	<0.001
Widowed/Divorced/Separated	787 (6.0)	364 (5.3)	
Married	9838 (74.8)	5529 (80.8)	

Table S2. Means, standard deviations, and correlations for study variables.

Variable	n (% non-missing)	M	SD	Min/Max	1	2	3	4	5	6	7
1. Dep. 3.9 years	6054 (82.8)	0.75	0.30	0.13/1.88	---	---	---	---	---	---	---
2. Dep. 6.8 years	5644 (77.2)	0.76	0.35	0.05/1.99	0.79	---	---	---	---	---	---
3. Dep.8.1 years	5414 (74.1)	0.83	0.36	0.07/2.05	0.71	0.90	---	---	---	---	---
4. Dep.9.6 years	5632 (77.1)	0.75	0.38	0.00/2.00	0.63	0.83	0.87	---	---	---	---
5. Dep.11.7 years	5275 (72.2)	0.73	0.39	0.06/2.17	0.54	0.75	0.78	0.83	---	---	---
6. Dep.13.1 years	5099 (69.8)	0.73	0.40	0.04/2.20	0.54	0.73	0.74	0.79	0.85	---	---
7. Dep. 16.5 years	4167 (57.0)	0.74	0.40	0.02/2.24	0.51	0.65	0.69	0.68	0.72	0.77	---
8. Child PRS	7308 (100.0)*	0.00	1.00	-4.24/3.48	0.06	0.09	0.09	0.09	0.10	0.10	0.10

Note. M = Mean. SD = Standard Deviation. Dep = Depression. PRS = Polygenic Risk Score. Participants were included in the count of non-missing if they had at least one complete parcel of the SDQ or SMFQ. *Child PRS was non-missing by definition, as all participants with missing PRS were excluded.

Table S3. Child and mother characteristics stratified by latent class.

	Overall	Minimal Symptoms	Adolescent Spike	Late Childhood Peak	Childhood Decrease	High and Reversing	High and Renitent	χ2 p-value
n	7308	4146	182	222	440	423	1895	
Mother's age at birth (%)								

Ages 15-19	142 (2.0)	71 (1.8)	1 (0.6)	4 (1.8)	10 (2.3)	7 (1.7)	49 (2.7)	0.73
Ages 20-35	6281 (89.8)	3568 (89.9)	160 (90.4)	194 (89.4)	389 (89.4)	365 (90.1)	1605 (89.5)	
Age 36+	575 (8.2)	332 (8.4)	16 (9.0)	19 (8.8)	36 (8.3)	33 (8.1)	139 (7.8)	
Marital status (%)								
Never Married	950 (13.9)	516 (13.3)	15 (8.6)	18 (8.5)	58 (13.6)	59 (14.9)	284 (16.3)	0.02
Widowed/ Divorced/ Separated	364 (5.3)	203 (5.2)	7 (4.0)	9 (4.2)	19 (4.4)	27 (6.8)	99 (5.7)	
Married	5529 (80.8)	3167 (81.5)	152 (87.4)	186 (87.3)	350 (82.0)	310 (78.3)	1364 (78.1)	
Parent SES (%)								
Professional	942 (12.9)	561 (13.5)	21 (11.5)	33 (14.9)	63 (14.3)	61 (14.4)	203 (10.7)	0.035
Managerial and technical	2583 (35.3)	1456 (35.1)	75 (41.2)	91 (41.0)	156 (35.5)	155 (36.6)	650 (34.3)	
Skilled, non-manual	1456 (19.9)	823 (19.9)	47 (25.8)	44 (19.8)	91 (20.7)	82 (19.4)	369 (19.5)	
Skilled, manual	438 (6.0)	245 (5.9)	1 (0.5)	13 (5.9)	27 (6.1)	25 (5.9)	127 (6.7)	
Semi-skilled, manual	125 (1.7)	69 (1.7)	2 (1.1)	3 (1.4)	8 (1.8)	4 (0.9)	39 (2.1)	
Unskilled, manual/other	1764 (24.1)	992 (23.9)	36 (19.8)	38 (17.1)	95 (21.6)	96 (22.7)	507 (26.8)	
Mother's education (%)								
Less than O-level	1575 (23.3)	873 (22.8)	27 (15.4)	43 (19.9)	94 (22.0)	85 (21.4)	453 (26.4)	0.01
O-level	2366 (35.1)	1360 (35.6)	63 (36.0)	66 (30.6)	147 (34.4)	131 (33.0)	599 (35.0)	
A-level	1724 (25.5)	1000 (26.2)	54 (30.9)	62 (28.7)	102 (23.9)	104 (26.2)	402 (23.5)	
Degree or above	1084 (16.1)	588 (15.4)	31 (17.7)	45 (20.8)	84 (19.7)	77 (19.4)	259 (15.1)	
Child sex (%)								
Female	3601 (49.3)	1976 (47.7)	120 (65.9)	111 (50.0)	188 (42.7)	231 (54.6)	975 (51.5)	<0.001
Male	3707 (50.7)	4145 (52.3)	62 (34.1)	111 (50.0)	252 (57.3)	192 (45.4)	920 (48.5)	
Previous pregnancies (%)								
0	3045 (44.9)	1631 (42.5)	81 (47.1)	100 (46.7)	199 (46.8)	191 (48.6)	843 (48.7)	0.006
1	2480 (36.6)	1481 (38.6)	59 (34.3)	79 (36.9)	151 (35.5)	128 (32.6)	582 (33.6)	
2	921 (13.6)	538 (14.0)	29 (16.9)	31 (14.5)	58 (13.6)	50 (12.7)	215 (12.4)	
3+	330 (4.9)	191 (5.0)	3 (1.7)	4 (1.9)	17 (4.0)	24 (6.1)	91 (5.3)	
Birthweight								

< 3000	1572 (21.5)	850 (20.5)	39 (21.4)	48 (21.6)	78 (17.7)	102 (24.1)	455 (24.0)	0.063
3000 - 3499	2446 (33.5)	1382 (33.3)	61 (33.5)	76 (34.2)	170 (38.6)	135 (31.9)	622 (32.8)	
3500 - 3999	2338 (32.0)	1355 (32.7)	57 (31.3)	58 (26.1)	142 (32.3)	127 (30.0)	599 (31.6)	
>= 4000	952 (13.0)	559 (13.5)	25 (13.7)	40 (18.0)	50 (11.4)	59 (13.9)	219 (11.6)	

Note. Participant characteristics were determined by assigning each individual to their most likely latent class. SES = Socioeconomic status. PRS = Polygenic risk score.

Table S4. Growth parameters for the unconditional six-class growth mixture model with structured residuals.

	Latent Class					
	Minimal Symptoms	Adolescent Spike	Late Childhood Peak	Childhood Decrease	High and Reversing	High and Renitent
Parameter	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)

Means						
Intercept	0.61 (0.008)	0.78 (0.03)	0.68 (0.03)	1.03 (0.03)	0.84 (0.05)	0.91 (0.02)
Slope	-0.23 (0.04)	-0.28 (0.19)	0.90 (0.19)	0.09 (0.18)	0.62 (0.17)	0.68 (0.06)
Quadratic	0.59 (0.12)	1.81 (0.97)	-3.30 (0.80)	-2.39 (0.48)	-0.22 (0.84)	-0.89 (0.23)
Cubic	-0.70 (0.14)	-3.01 (1.20)	4.82 (0.80)	2.45 (0.48)	-0.74 (1.03)	0.39 (0.25)
Quartic	0.26 (0.05)	1.41 (0.43)	-2.01 (0.34)	-0.69 (0.16)	0.41 (0.36)	-0.06 (0.09)
Structured Residual	0.43 (0.04)	0.42 (0.17)	-0.49 (0.05)	0.15 (0.09)	-0.41 (0.03)	0.87 (0.01)
Area under the curve	0.87 (0.004)	1.27 (0.03)	1.34 (0.02)	1.09 (0.01)	1.44 (0.02)	1.61 (0.006)
Variances*						
Intercept	0.042 (0.002)	0.042 (0.002)	0.042 (0.002)	0.042 (0.002)	0.042 (0.002)	0.042 (0.002)
Linear Slope	0.013 (0.001)	0.013 (0.001)	0.013 (0.001)	0.013 (0.001)	0.013 (0.001)	0.013 (0.001)

Note. *Linear time was coded as months divided by 100 and higher order time transformations were based off of that. Variances were constrained equal across latent classes. Quadratic and higher order variances were constrained to zero within each class.

Table S5. Sensitivity analysis examining difference in PRS effects when controlling for mother's PRS score.

Comparison		**Child PRS Only (N = 5311)** Child Effects		**Model Includes Mother PRS Scores (N = 5311)** Child Effects		Mother Effects		**Difference Between Models**	
Reference Category	Alternative Category	Log Odds	SE	Log Odds	SE	Log Odds	SE	Change in child log odds (raw)	Change in child log odds (%)
Minimal Symptoms	Adolescent Spike	0.14	0.11	0.13	0.12	0.03	0.10	-0.02	-10%
Minimal Symptoms	**Late Childhood Peak**	**0.21#**	**0.10**	**0.15**	**0.12**	**0.12**	**0.13**	**-0.06**	**-30%**
Minimal Symptoms	Childhood Decrease	0.08	0.08	0.07	0.09	0.02	0.09	-0.01	-14%
Minimal Symptoms	**High and Reversing**	**0.22***	**0.08**	**0.16**	**0.10**	**0.12**	**0.08**	**-0.06**	**-28%**
Minimal Symptoms	**High and Renitent**	**0.24***	**0.05**	**0.16***	**0.06**	**0.16**	**0.06**	**-0.08**	**-35%**
Adolescent Spike	Late Childhood Peak	0.07	0.15	0.02	0.16	0.09	0.16	-0.05	-70%
Adolescent Spike	Childhood Decrease	-0.06	0.13	-0.06	0.15	-0.01	0.13	0.00	-6%
Adolescent Spike	High and Reversing	0.07	0.13	0.03	0.15	0.09	0.12	-0.05	-62%
Adolescent Spike	High and Renitent	0.10	0.12	0.03	0.13	0.13	0.11	-0.07	-69%
Late Childhood Peak	Childhood Decrease	-0.13	0.12	-0.08	0.14	-0.11	0.14	0.05	-39%
Late Childhood Peak	High and Reversing	0.01	0.13	0.01	0.14	-0.01	0.14	0.00	0%
Late Childhood Peak	High and Renitent	0.03	0.11	0.01	0.13	0.04	0.13	-0.02	-69%
Childhood	High and	0.14	0.11	0.09	0.12	0.10	0.11	-0.05	-36%

Decrease	Reversing								
Childhood Decrease	**High and Renitent**	**0.16***	**0.08**	**0.09**	**0.10**	**0.14**	**0.09**	**-0.07**	**-45%**
High and Reversing	High and Renitent	0.03	0.09	0.00	0.11	0.04	0.09	-0.02	-96%

Note. Comparisons that were statistically significant in the original analysis are bolded for ease of interpretation. Log odds are shown rather than odds ratios because the model is linear in terms of log odds, which facilitates comparisons between parameters in percentage terms. The N is smaller than the N for the original model because 1997 participants with child genetic data did not also have mother genetic data, and they were listwise deleted to facilitate direct comparisons in changes across models. **FDR<0.05;* *#p<0.05, but FDR>0.05.*

Table S6. Summary of gene-based hits using MAGMA.

Gene	Chr	Start	Stop	# of SNPs	R^2	P-value	Association
GABRA4	4	46920917	46996424	218	0.0069	$6.84e^{-5}$	HR vs MS
LRR1	14	50065415	50081390	43	0.0045	$4.71e^{-5}$	HR vs MS
SIX5	19	46268043	46272497	3	0.0029	$9.16e^{-6}$	AUC
DMPK	19	46272975	46285815	17	0.0030	$4.97e^{-5}$	AUC
DKK1	10	54074041	54077417	5	0.0023	$9.23e^{-5}$	AUC
SIX5	19	46268043	46272497	3	0.0033	$5.56e^{-6}$	Intercept
DMPK	19	46272975	46285815	17	0.0042	$1.05e^{-5}$	Intercept
SMDT1	22	42475695	42480288	6	0.0033	$2.31e^{-5}$	Intercept
DMWD	19	46286264	46296060	17	0.0041	$9.79e^{-5}$	Intercept

*HR = high/renitent class; MS = minimal symptoms class; AUC = cumulative burden of depressive symptoms; intercept = onset of depressive symptoms

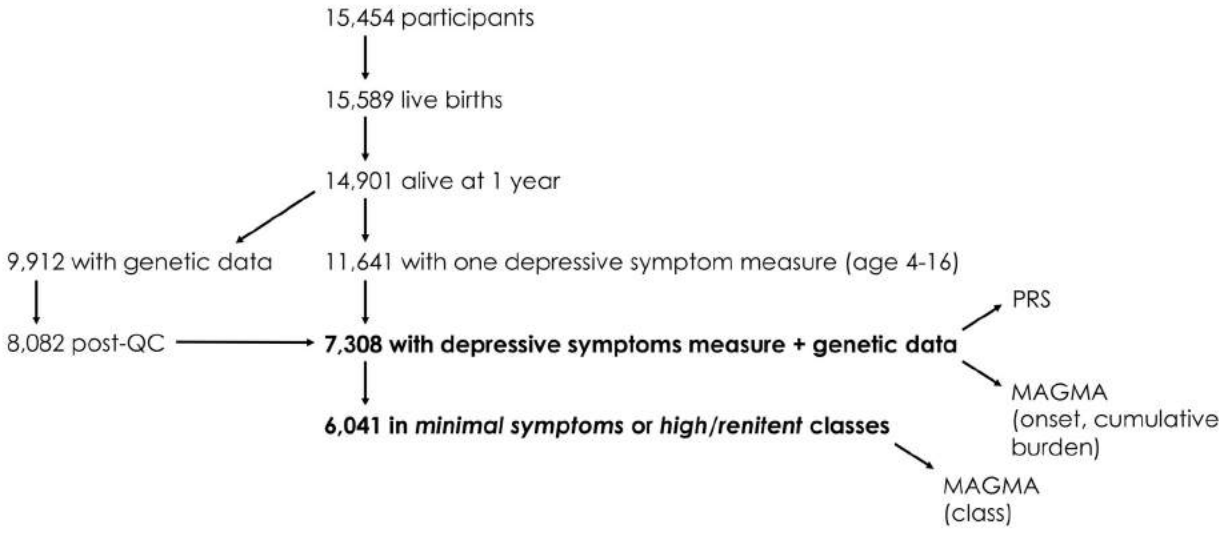


Figure S1. Flowchart of ALSPAC sample selection.

Of the eligible participants after 1 year (14,901), two subsamples were selected: those with genetic data (9,912) and those with at least one measure of depressive symptoms from age 4-16 (11,641). Following quality control measures, the genetic subsample was reduced to 8,082 individuals. The overlap between these two samples was 7,308 individuals, which we defined as the analytical sample for the polygenic risk score (PRS) analyses of depressive symptom trajectories, as well as gene-level associations with depressive symptom onset and cumulative burden using MAGMA. The analytical sample was further subset to 6,041 individuals for the trajectory class-based MAGMA analysis, which focused solely on youths classified as high/renitent or minimal symptoms for the depressive symptom trajectories.

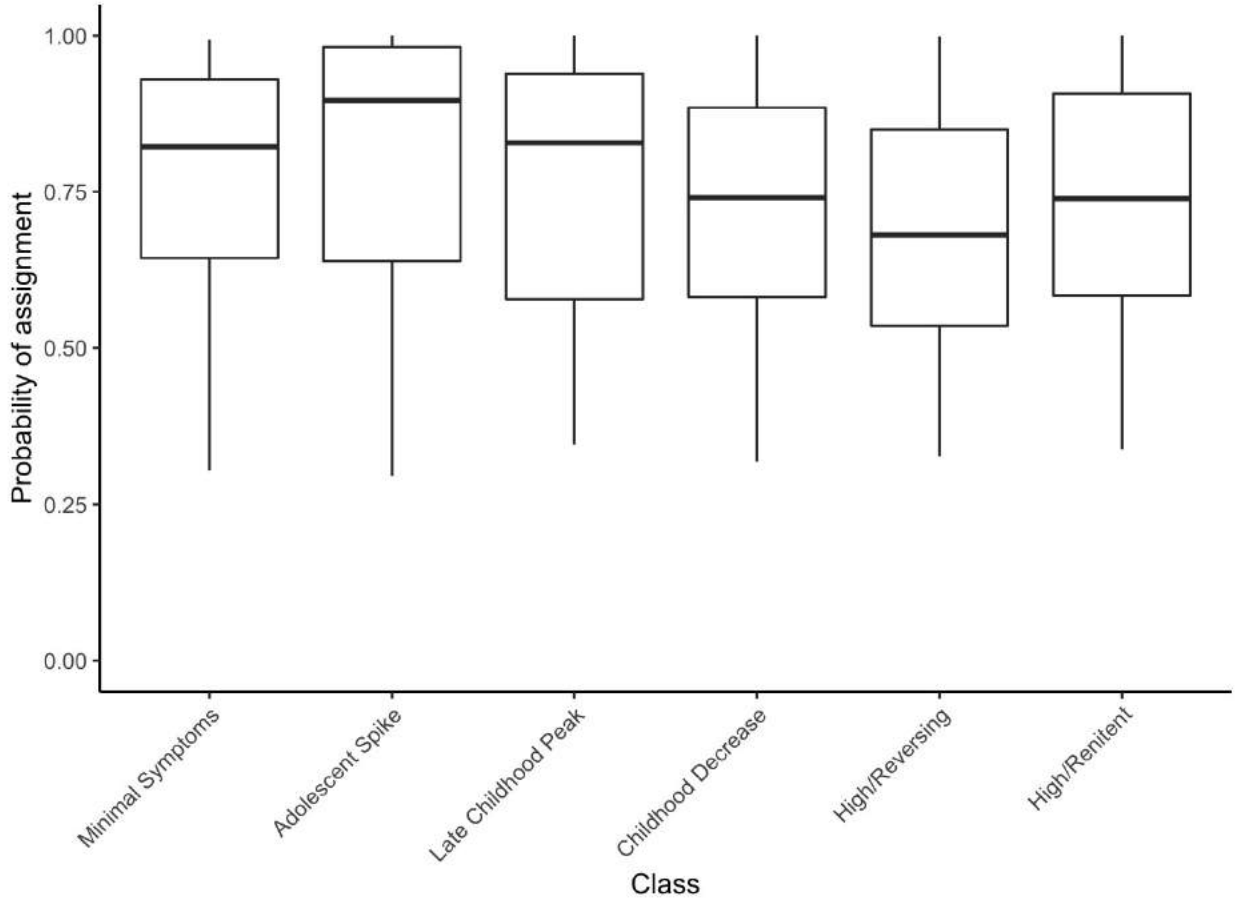


Figure S2. Probability of class assignment for individuals within their assigned latent class. Each individual was assigned to the trajectory class reflecting their highest probability of assignment across all classes (which ranged from 0-100). Within each class, the probability of highest assignment ranged from 0.3 to 1. The percentage of youths assigned to each trajectory class was estimated as follows: 4,146 minimal symptoms (56.7%), 182 adolescent spike (2.5%), 222 late childhood peak (3%), 440 childhood decrease (6%), 423 high/reversing (5.8%), and 1,895 high/renitent (25.9%).

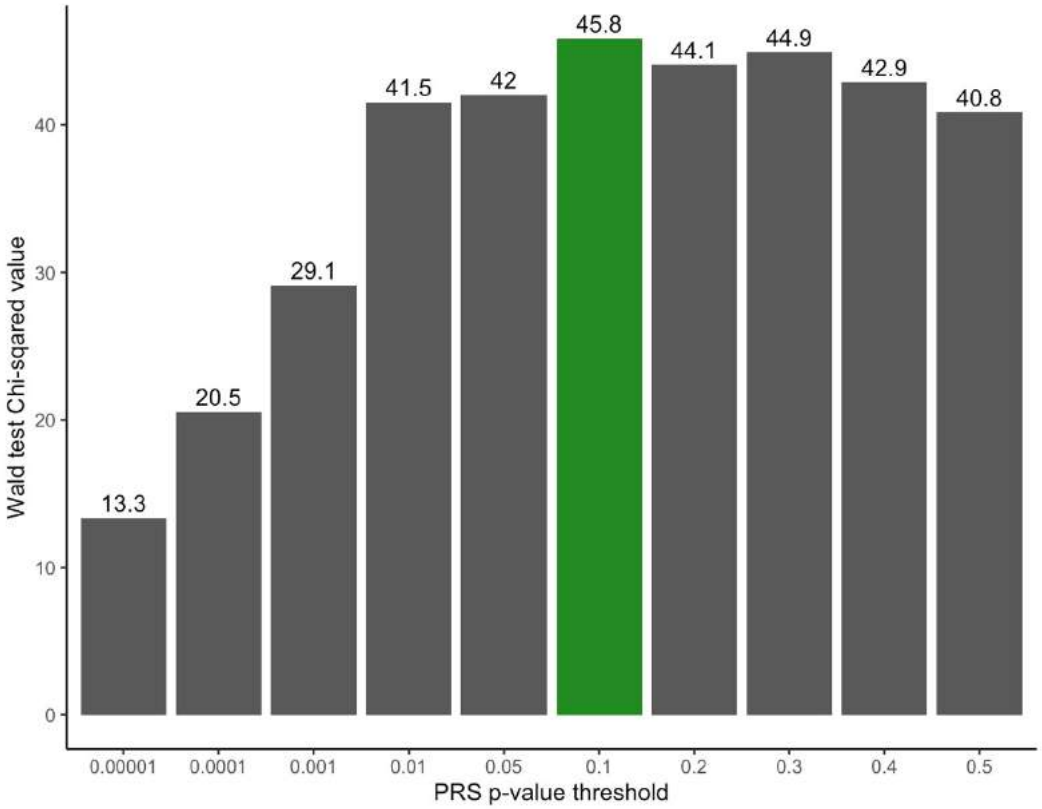


Figure S3. The PRS with pT<0.1 was the 'best fit' polygenic risk score.

Using the Wald omnibus test of parameter constraints, we show that the polygenic risk score (PRS) generated with the p-value threshold of p<0.1 (green) explained the most variance in the depression trajectories.

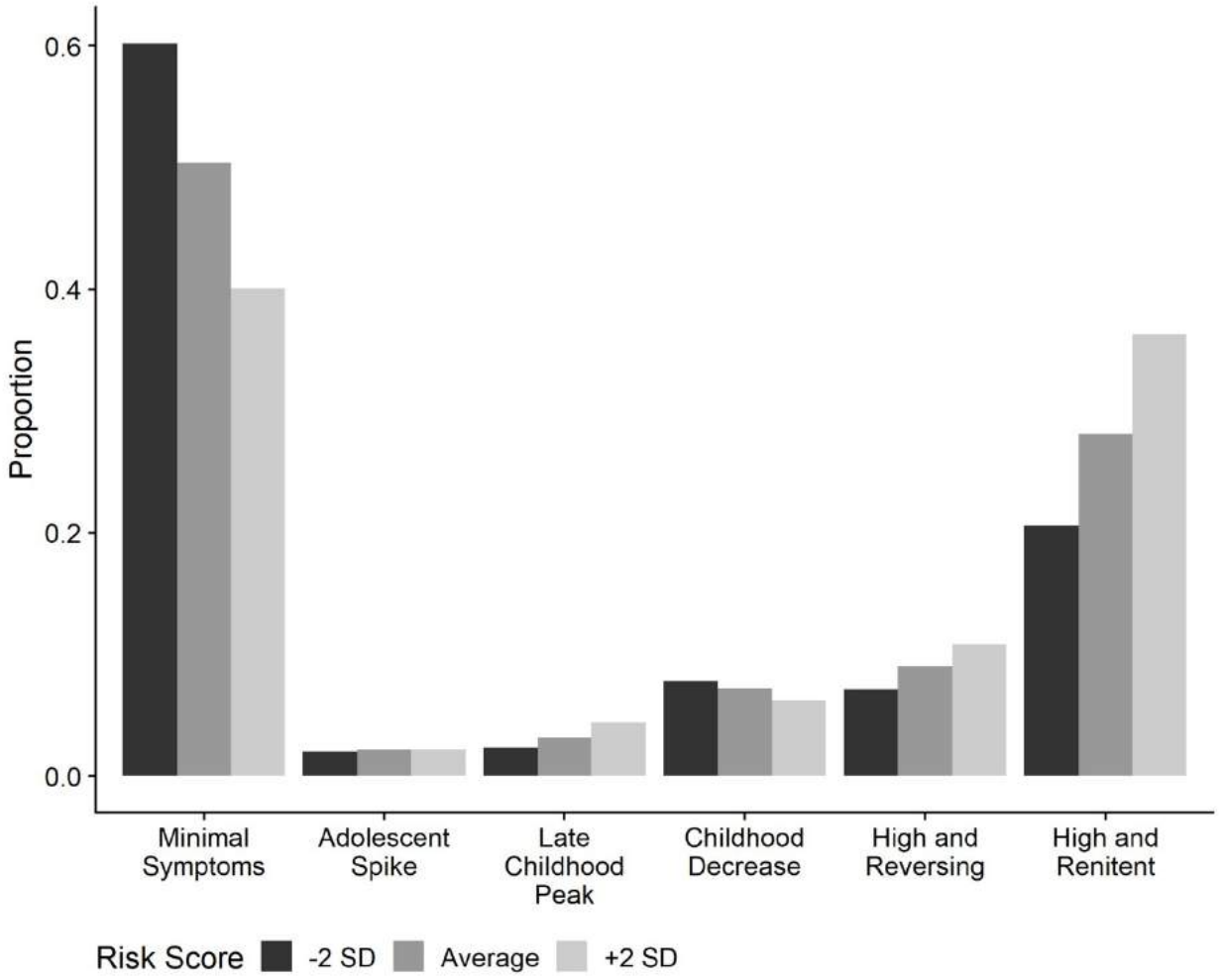


Figure S4. Model estimated proportions of individuals in each latent class.

The model-estimated proportion of individuals in each latent class are shown across low (-2 SD) average and high (+2 standard deviation) polygenic risk scores. For example, about 60% of participants with a risk score 2 standard deviations below the average would be expected to be in the Minimal Symptoms class, whereas only 40% of participants with a risk score 2 standard deviations above average would be expected to be in the Minimal Symptoms class.

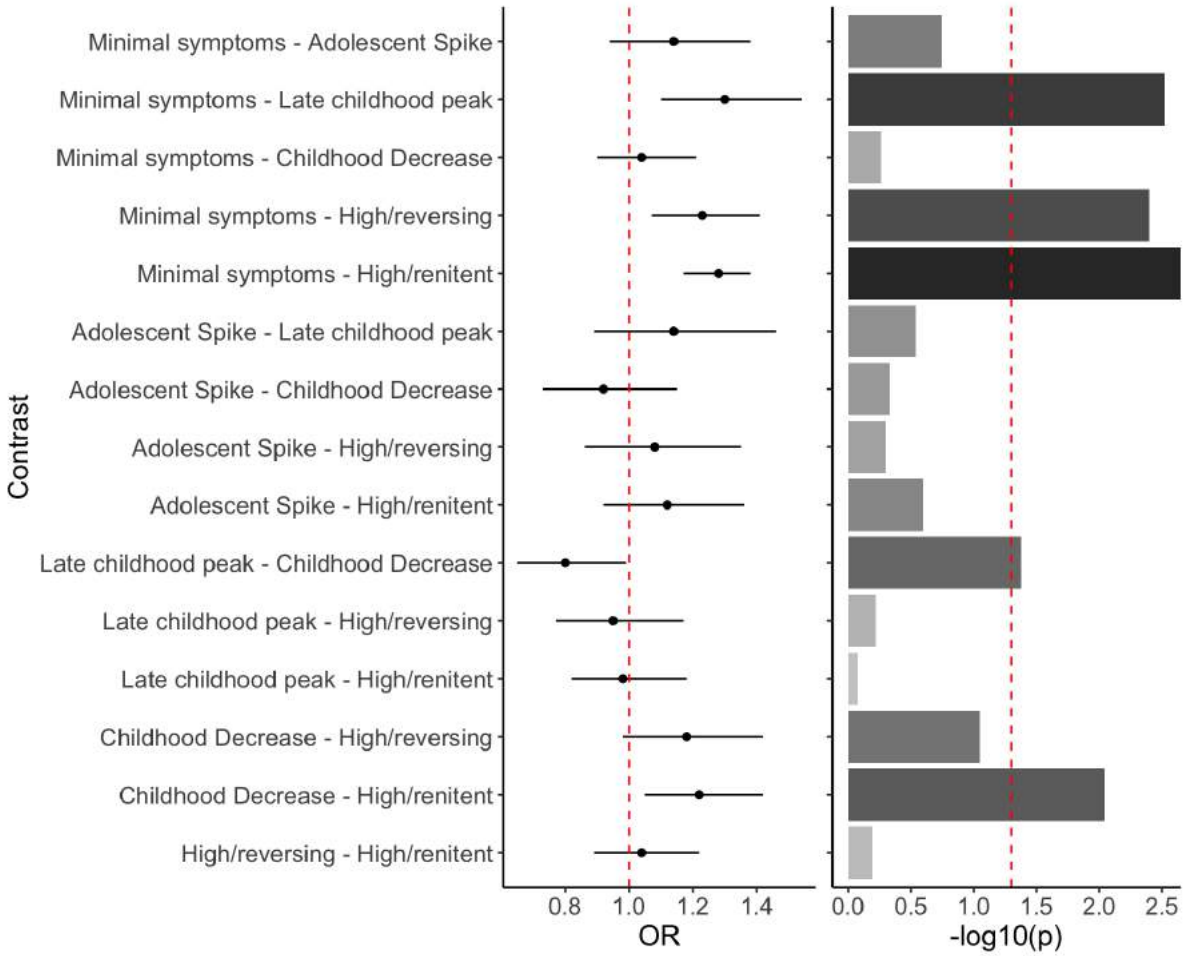


Figure S5. Polygenic risk scores identified differences in membership to classes of depressive symptom trajectories.

Odds ratios (OR) were calculated to determine the odds of membership of each class versus the referent given a one unit increase in polygenic risk score (PRS). While five contrasts were significant ($p<0.05$), only four remained significant after multiple test correction at an FDR<0.05 (high/stable vs minimal symptoms; high/stable vs childhood decrease; high/unstable vs minimal symptoms).

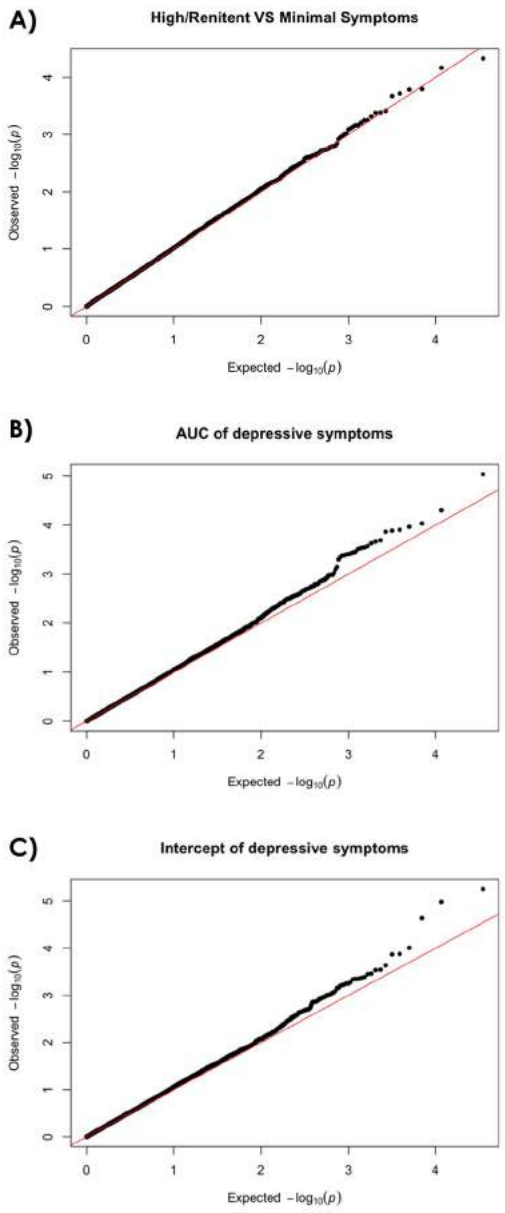


Figure S6. Quantile-quantile (QQ) plots of gene-level genome-wide associations show good model fit of the MAGMA analysis.

A) The QQ plot of the high/stable (HS) and minimal symptoms (MS) classes of depressive symptoms trajectories showed good model fit, with a slight downward skew. **B)** The QQ plot of depressive symptom persistence across age 4-16, defined as the area under the curve (AUC) of the trajectory was slightly skewed upward, but showed good model fit. **C)** The QQ plot of

depressive symptom onset, defined by the intercept of the trajectory, was also slightly skewed upward and showed good model fit.

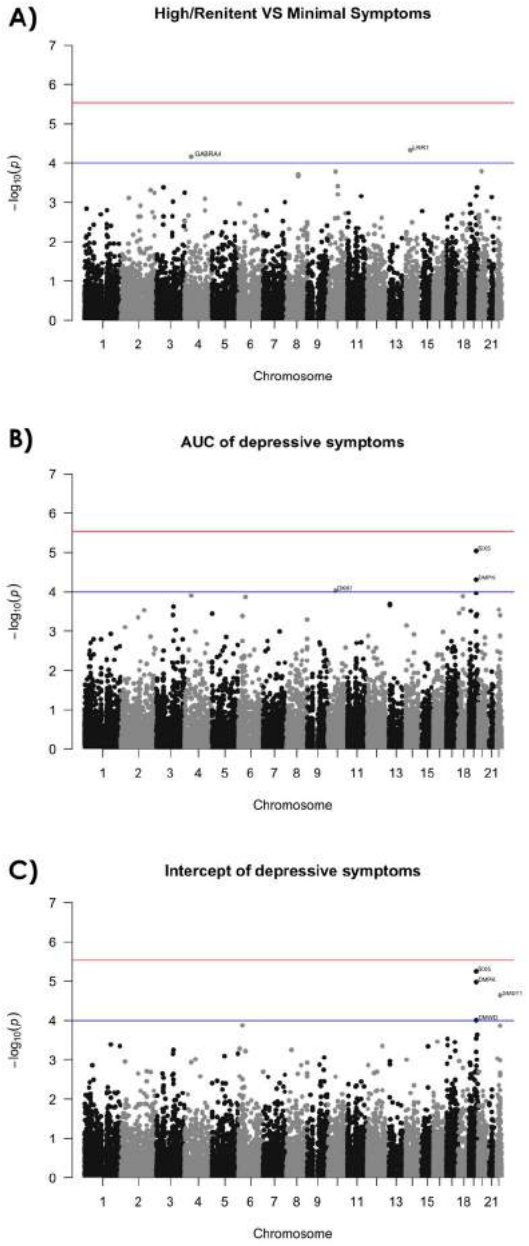
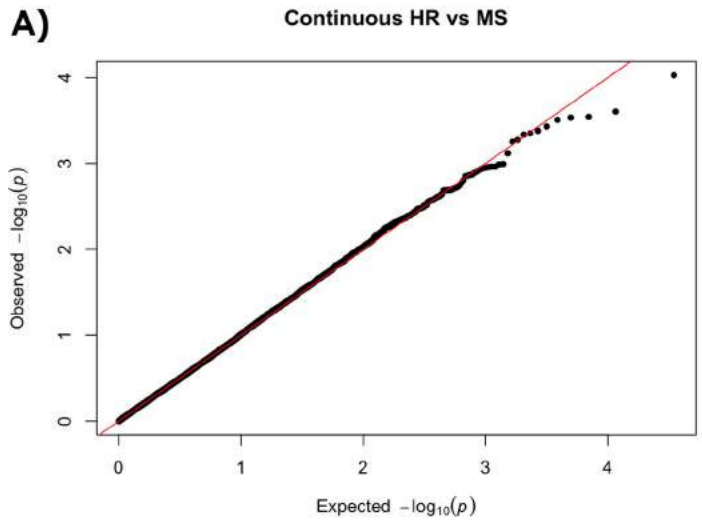
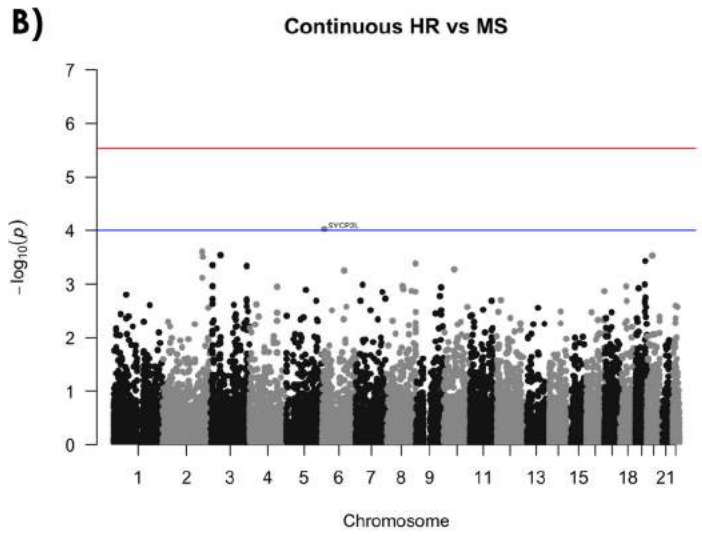


Figure S7. Depressive symptom developmental features showed nominal gene-level associations.

A) The contrast of high/renitent (HR) and minimal symptoms (MS) classes showed two nominal associations (GABRA4, LRR1). **B)** Depressive symptom cumulative burden (AUC) showed

three nominal associations (SIX5, DPMK, DKK1). **C)** Depressive symptom onset (intercept) showed four nominal associations (SIX5, DPKM, SMDT1, DMWD). Genome-wide significance was set at 2.93e-6 (red) and the nominal threshold was set at 1e-4 (blue).



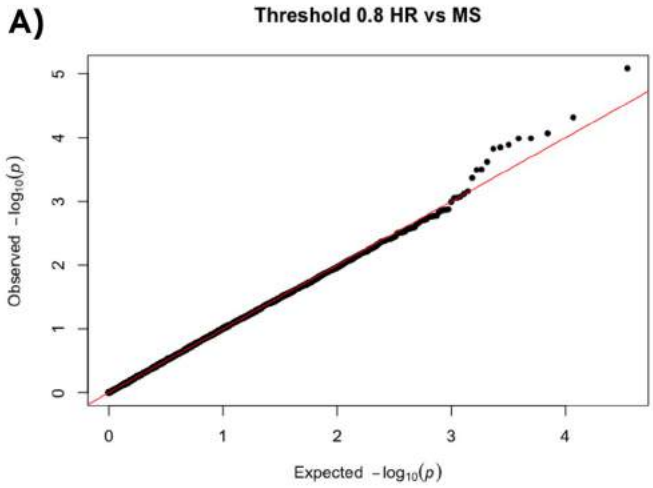


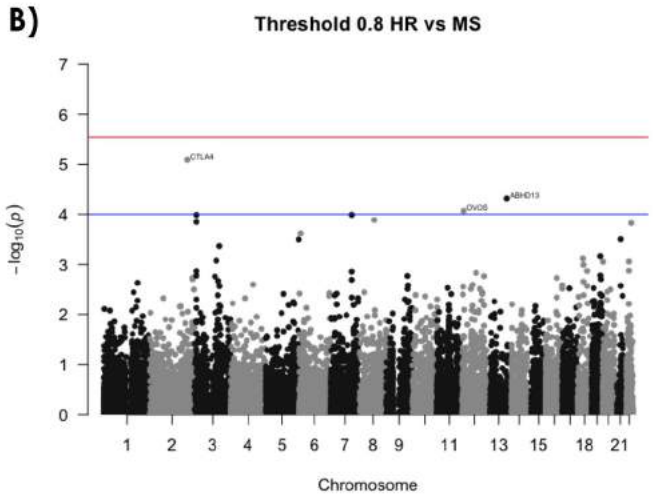
C)

Gene	Chr	Start	Stop	# of SNPs	R^2	P-value
SYCP2L	6	10887064	10974542	220	0.0072	$9.37e^{-5}$

Figure S8. MAGMA analysis of the probability of assignment to the high/renitent class.

MAGMA was performed using all 7,308 individuals and their probability of being assigned to the high/renitent class was used to identify gene-level associations. No genes reached the genome-wide significance threshold (p<2.93e-7; red line in B), but one gene reached the nominal threshold of p<1e4 (blue line in B; results shown in C).





C)

Gene	Chr	Start	Stop	# of SNPs	R^2	P-value
CTLA4	2	204732511	204738683	5	0.0086	$8.17e^{-6}$
OVOS	12	9613794	9725776	14	0.0092	$8.58e^{-5}$
ABHD13	13	108870763	108886603	38	0.0097	$4.82e^{-5}$

Figure S9. MAGMA analysis of youths in the high/renitent vs minimal symptoms class.

MAGMA was performed using youths in the high/renitent (HR) or minimal symptoms (MS) classes that had 80% probability of class assignment (2258 MS vs 786 HR). No genes reached the genome-wide significance threshold ($p<2.93e-7$; red line in B), but three genes reached the nominal threshold of $p<1e4$ (blue line in B; results shown in C).