Title:

Genetic Architectures of Adolescent Depression Trajectories in 2 Longitudinal Population Cohorts

Authors and affiliations:

Poppy Z Grimes, MSc[1*]; Mark J Adams, PhD[1]; Gladi Thng, BSc[1]; Amelia J Edmonson-Stait, BSc[1]; Yi Lu, PhD[2]; Andrew McIntosh, MD[1]; Breda Cullen, PhD[3]; Henrik Larsson, PhD[2,4]; Heather C Whalley, PhD[1,5†]; Alex SF Kwong, PhD[1,6†]

[1]Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, UK

[2]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Sweden

[3]School of Health and Wellbeing, University of Glasgow, UK

[4]School of Medical Sciences, Örebro University, Sweden

[5]Generation Scotland, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, UK

[6]MRC Integrative Epidemiology Unit, University of Bristol, UK

[†]Joint last authorship

*Corresponding author: p.grimes@ed.ac.uk, 7.91 Kennedy Tower, Royal Edinburgh Hospital, Edinburgh, EH10 5HF

Key Points

Question: Could multi-trait polygenic risk scores be used to strengthen genetic prediction of longitudinal depression across adolescence?

Findings: In this longitudinal cohort replication study of 14,112 adolescents, stronger effect sizes of multitrait polygenic risk association with adverse depression trajectories were found compared to unitrait genetic risk.

Meaning: Longitudinal depression has a robust genetic underpinning, and leveraging shared genetic information across multiple psychiatric traits may strengthen prediction models of depression in adolescence.

Abstract

Importance: Adolescent depression is characterised by diverse symptom trajectories over time and has a strong genetic influence. Research has determined genetic overlap between depression and other psychiatric conditions. Investigating the shared genetic architecture of heterogeneous depression trajectories is crucial for understanding disease aetiology, prediction and early intervention.

Objective: To investigate univariate and multivariate genetic risk for adolescent depression trajectories and assess generalisability across ancestries.

Design: Longitudinal growth modelling followed by polygenic risk score (PRS) association testing for individual and multitrait genetic models.

Setting: Two longitudinal cohorts from the US and UK: the Adolescent Brain and Cognitive Development (ABCD, N=11,876) study and the Avon Longitudinal Study of Parents and Children (ALSPAC, N=8787).

Participants: Adolescents with genetic information and depression measures at up to 8 and 4 occasions, respectively.

Main Outcomes and Measures: Trajectories were derived from growth mixture modelling of longitudinal depression symptoms. PRSs were computed for depression, anxiety, neuroticism, bipolar disorder, schizophrenia, attention-deficit/hyperactivity disorder and autism in European ancestry. Genomic structural equation modelling was used to build multi-trait genetic models of psychopathology followed by multitrait PRS. Depression PRSs were computed in African, East Asian and Hispanic ancestries in ABCD only. Association testing was performed between all PRSs and trajectories for both cohorts.

Results: A total sample size of 14,122 adolescents (at baseline: mean [SD] age, 10.5 [0.5] years; 7629 male sex [52%]) from both cohorts were included in this analysis. Distinct depression trajectories (stable low, adolescent persistent, increasing, and decreasing) were replicated in the ALSPAC cohort (6096 participants; 3091 female [51%]) and ABCD cohort (8016 participants; 4274 male [53%]) between ages 10 and 17 years. Most univariate PRSs showed significant uniform associations with persistent trajectories, but fewer were significantly associated with intermediate (increasing and decreasing) trajectories. Multi-trait PRSs – derived from a hierarchical factor model – showed the strongest associations for persistent trajectories (ABCD cohort; OR, 1.46; 95% CI 1.26-1.68; ALSPAC cohort: OR, 1.34; 95% CI, 1.20-1.49), surpassing the effect size of univariate PRS in both cohorts. Multi-trait PRSs were associated with intermediate trajectories but to a lesser extent (ABCD cohort: hierarchical increasing, OR, 1.27; 95% CI, 1.13-1.43; decreasing, OR, 1.23; 95% CI, 1.09-1.40; ALSPAC cohort: hierarchical increasing, OR, 1.16; 95% CI, 1.04-1.28; decreasing, OR, 1.32; 95% CI, 1.18-1.47). Transancestral genetic risk for depression showed no evidence for association with trajectories.

Conclusions and Relevance: Results of this cohort study revealed a high multi-trait genetic loading of persistent symptom trajectories, consistent across traits and cohorts. Variability in univariate genetic association with intermediate trajectories may stem from environmental factors. Multi-trait genetics may strengthen depression prediction models, but more diverse data is needed for generalisability.

Introduction

Adolescence is a crucial period of change in the brain and body, marking the onset of many mental health conditions including depression[1–3]. Depression symptoms markedly increase between 13-18 years[4–6] during which symptom severity is higher compared to that of adult-onset depression[7,8]. Depression is heterogeneous across adolescence due to the complex interplay between biological and environmental factors[8]. Heterogeneity makes stratifying subgroups of depression essential for effective prediction, prevention and treatment targeting[9].

Longitudinal stratification provides a scaffold for identifying specific factors associated with early patterns of depression. Studies have employed latent growth modelling to characterise distinct depression trajectories that capture important intraindividual differences[10–12].

Approximately 90% of studies report 3 or 4 main trajectory groups[11]. These studies typically find a stable low or non-depressed group, a stable high or persistent depressed group, and intermediate groups with positive or negative slopes over time. Slope variation in intermediate groups indicates reduced stability, thought to reflect underpinning by transient environmental rather than fixed biological factors[13]. The highest proportion of individuals are found in the stable low group (>70%), whereas the other groups are more evenly split with the fewest individuals in the stable high group. Risk factors for more adverse trajectories include children of parents with depression [14] and those with higher genetic risk for depression[15,16].

Quantitative genetic and genome-wide association studies have demonstrated the heritability of major depressive disorder (MDD)[9,17–19]. SNP-heritability of early-onset depression was found to be 3-fold higher than late-onset depression[7]. Consistent evidence from cross-sectional and longitudinal research shows that polygenic risk scores (PRSs) of multiple psychiatric

conditions – such as depression/MDD, anxiety, attention-deficit/hyperactivity disorder (ADHD) and schizophrenia – are associated with depression at increasing levels throughout adolescence[15,16,20]. Moreover, increased polygenic risk is associated with more severe and persistent trajectory liability[21].

However, these studies have generally focussed on genetic risk for MDD alone or other individual conditions such as anxiety and schizophrenia[22]. Depression is a complex polygenic trait and shares a high genetic correlation with many psychiatric conditions[23]. Genomic structural equation modelling (GSEM) was recently developed to explore correlated polygenicity amongst traits, including psychopathology[24,25]. GSEM is a dimensional approach that captures shared genetic covariance to determine SNP loadings onto a latent genetic psychopathology factor (p-factor). This approach is akin to the p-factor of phenotypic psychopathology or general intelligence (g-factor)[26]. Genetic p-factor PRSs show increased predictive power compared with single-trait PRSs[24] and multivariate architectures of psychopathological symptoms determine p-factor heritability up to 60% in twin models[27].

The demonstrated association of univariate PRSs with adverse depression trajectories, coupled with the advancements offered by multivariate methods to leverage shared genetic architecture provides the rationale for investigating the combined multitrait genetic risk of stratified longitudinal depression trajectories. This approach may uncover whether genetic susceptibility to correlated traits manifests differently in heterogenous subgroups, thereby providing a more informative forecast for characterising complex depression phenotypes across adolescence and enhanced clinical utility.

Finally, despite the above advancements in statistical genetics and depression research, the underrepresentation of minority ethnic groups, who face elevated depression risks, limits the generalisability of findings across populations[10,11]. We leverage recently available advances in genome-wide studies of major depression across ancestries to include minority groups. Unfortunately, there is insufficient statistical power for other psychiatric conditions.

This study had 3 aims. The first aim was to derive and determine the replicability of depression trajectories across 2 adolescent cohorts. Our second aim was to investigate the association of univariate PRSs for 7 traits and a corresponding multi-trait PRS with patterns of longitudinal depression across cohorts. Lastly, we aimed to test the generalisability of findings for major depression PRSs across under-represented ancestries. Overall, our study sought to characterise the nature and aetiology of multitrait PRSs on depression trajectories to identify how shared genetic risk underpins development across adolescence so that future research can adopt this work and extend it towards the healthcare system.

Methods and Materials

Sample populations

The Adolescent Brain and Cognitive Development (ABCD) study is a longitudinal North American cohort of 11,876 individuals recruited between the ages of 9 and 10 years at baseline[28] accessed through the NDA database (https://nda.nih.gov/abcd/). Self-reported race and ethnicity in the ABCD cohort were as follows: Asian, Black, Hispanic, White and Other (alternative survey option). The Avon Longitudinal Study of Parents and Children (ALSPAC) is a UK-based cohort of 15,645 children born between 1991 and 1992[29,30]. Self-reported race and ethnicity in the ALSPAC cohort was overwhelmingly European White. Both studies

received ethics approval and informed consent; detail and further cohort information is available in **Appendix 1 in Supplement 1**. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Depression measures

In the ABCD study, The Brief Problem Monitoring (BPM) Youth report scale provides a 6-item 3-point Likert subscale of internalising symptoms collected every 6 months[31]. BPM is a self-report validated scale[32,33] with items derived from the more known Child Behaviour Checklist. Eight occasions of BPM were recorded between ages 10.4 and 14.1 years. In the ALSPAC study, the Short Mood and Feeling Questionnaire (SMFQ) comprises an annual collection of 13 items scored on a 3-point Likert scale relating to depressive symptoms[34] and is indicative of clinical depression[35,36]. We used the first 4 occasions between ages 10.6 and 16.7 years to enable quadratic latent factor analysis and for matching cohort age with the ABCD study. For both cohorts, descriptive statistics, questionnaire items and attrition rates are in **Tables S1-S5 in Supplement 1**.

Genome-Wide Association Study Discover Samples

Genome-wide association study (GWAS) summary statistics were obtained for 7 major psychiatric trait conditions in European ancestry: anxiety[37], neuroticism[38], MDD[39], ADHD[40], autism spectrum disorder (ASD)[41], schizophrenia[42] and bipolar II or III[43]. Adequately powered summary statistics for diverse ancestries were available for MDD via 23andMe Inc from the Psychiatric Genomics Consortium in African, American Admixed (Hispanic), East Asian and European[44,45]. Sample size details for discovery cohorts are in **Tables S6-7 in Supplement 1**.

Multivariate Genomic Structural Equation Modelling

We used Genomic Structural Equation Modelling (GenomicSEM) to combine genetic correlations and SNP heritability across GWAS of complex traits using structural equation methods[24]. We used GenomicSEM to conduct multivariate modelling for the 7 genetic traits in European ancestry. In the ABCD cohort, Europeans were identified using k-means clustering following the same approach used previously[46]. The first 2 functions munge the summary statistics and perform linkage-disequilibrium score regression (LDSC) using the HapMap3 (Broad Institute) reference file for allele alignment. We estimated the effective sample size for cohorts where the SNP-specific sum was unavailable.

We initially constructed the common factor model as our baseline. In this model, a single overarching latent factor loads onto all indicators (traits) and explains the shared covariance among indicators. Next, we performed an exploratory factor analysis of traits grouped into 3 hypothesised trait parcels: mood, psychotic and neurodevelopmental. We conducted confirmatory factor analyses and compared cross-model fit parameters for the following model structures: common, correlated, hierarchical and bifactor. Multitrait summary statistics were generated for the latent genetic factors (p-factor or higher-order factors) for comparison using the 1000 genomes phase 3 reference file for SNP variance, information score >0.8 and MAF>0.01. Lastly, the multivariate GWAS function combined summary statistics, LDSC output and the relevant structural equation model structure to retrieve the SNP effects on the latent factors in each model. Further description of the factor models is discussed in **Appendix 7 in Supplement 1**.

PRSs

Full quality control information for the ALSPAC and ABCD studies has been described elsewhere[21,46] but can also be found in **Appendix 3 in Supplement 1**. In the ABCD study, we calculated the top 10 genetic principal components (PCs) with the 1000 genomes reference panel[47]. We trained a random forest on the reference superpopulations using the first 6 PCs to predict the genetic clusters into African, American Admixed (Hispanic), and East Asian ancestries (**Figure S1 in Supplement 1**).

PRSs were computed with PRSice-2 v2.1.11[48] using clumping and thresholding (clump-kb 250kb, clump-r^2 0.1, clump-p 1.0). We generated PRSs for p-value thresholds $5x10^{-8}$, $1x10^{-6}$, $1x10^{-4}$, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5 and 1.0. The best predictive p-value threshold for each PRS was chosen across the phenotype at all time points. Thresholds and SNP counts are in **Tables S8-9 in Supplement 1**.

Trajectory Modelling

We used growth mixture modelling (GMM) to identify subgroups of individuals with different developmental trajectories or classes. GMM is a method for class enumeration that allows for individual variation within class. Classes are iteratively added to the model, assessing fit at each iteration to determine the best model. GMM was performed in MPlus v8.0[49] which utilises maximum-likelihood estimation for parameters. Growth models consisted of intercept, slope and quadratic latent factors. We included individuals with at least 1 depression measure, to maximise available sample size, as these individuals can still contribute to the associations between trajectory groups and the varying PRSs[15]. Missing data are handled using full-information maximum-likelihood (FIML) estimation. Model fit was assessed through a

combination of fit criterion and likelihood ratio tests detailed in **Appendix 5 in Supplement 1**.

Statistical Analyses

Multinomial logistic regression was performed to evaluate the classification of genetic risk scores with each trajectory in both cohorts (significance level of 2-sided P<.05). The stable low class was the reference level and association was determined as the odds ratio (OR) of each class versus the reference with corresponding confidence intervals. Regression analyses were adjusted for sex and the top 6 ancestry principal components. Final associations for European ancestry were for each trajectory with PRSs for 7 univariate traits, 3 correlated factors (mood, psychotic, neurodevelopmental) and 2 latent factors (common, hierarchical). For African, East Asian and Hispanic ancestries, MDD PRS association was tested with classes in the ABCD cohort.

To account for uncertainty in the classification of participants into trajectories we ran the 3-step bias-adjusted model[50]. We examined the impact of attrition by running trajectories for individuals with 50% or more depression measures. We tested trajectory associations adjusting for all PRSs in a multivariable model to determine which contributed most strongly. To determine whether sample size or nosology are impacting the multitrait PRS associations, we performed a leave-one-out (LOO) common factor model for the most informative (MDD) and least informative (ASD) traits. To examine the association between genetic risk and attrition, we tested whether PRSs show consistency in association across questionnaires and whether PRSs were associated with attrition in both cohorts. Although sample sizes for independent ancestries in the ABCD cohort are underpowered, we derived non-European trajectories for

completeness. We performed trajectory associations of self-report ethnicity for comparison with ancestry.

Results

Sample Characteristics

A total sample size of 14,122 adolescents (at baseline: mean [SD] age, 10.5 [0.5] years; 7629 male sex [52%]) from both cohorts were included in this analysis. Participants were selected for availability of genotyped data and at least 1 occasion of depression (phenotype) score. In the ALSPAC cohort, this resulted in 6096 adolescents (3091 female [51%]; 2995 male [49%]) of European ancestry. In the ABCD cohort, there were a total of 8016 adolescents (3739 female [47%]; 4274 male [53%]) including 1715 African, 94 East Asian, 4135 European, and 2072 Hispanic ancestries. Self-reported ethnicity sample sizes for the 8016 individuals from the ABCD cohort are as follows: 85 Asian (1.1%), 1384 Black (17.3%), 1739 Hispanic (21.7%) 4261 White (53.2%), and 547 other (6.8%).

Cross-Cohort Validation of Depression Trajectories

GMM of depressive symptoms and evaluation of model fit parameters identified 4 trajectories in both cohorts (**Figure 1**). Subgroups show highly similar but not identical longitudinal patterns. Cross-cohort trajectory subgroups are stable low (ABCD cohort: 6182 [77.1%]; ALSPAC cohort: 4972 [81.6%]), increasing (ABCD cohort: 632 [7.9%]; ALSPAC cohort: 407 [6.7%]), decreasing (ABCD cohort: 761 [9.5%]; ALSPAC cohort: 351 [5.8%]) and adolescent persistent (ABCD cohort: 441 [5.5%]; ALSPAC cohort: 366 [6.0%]). Results for 1 to 5 class models, fit parameters and class counts are in **Tables S10-13 in Supplement 1**. Phenotypic validations for several risk factors (including diagnosis of depression, poorer sleep, family history of depression, lower socioeconomic status and childhood bullying) showed consistent

and as expected associations across cohorts, thus validating our trajectories (**Table S14 in Supplement 1**).

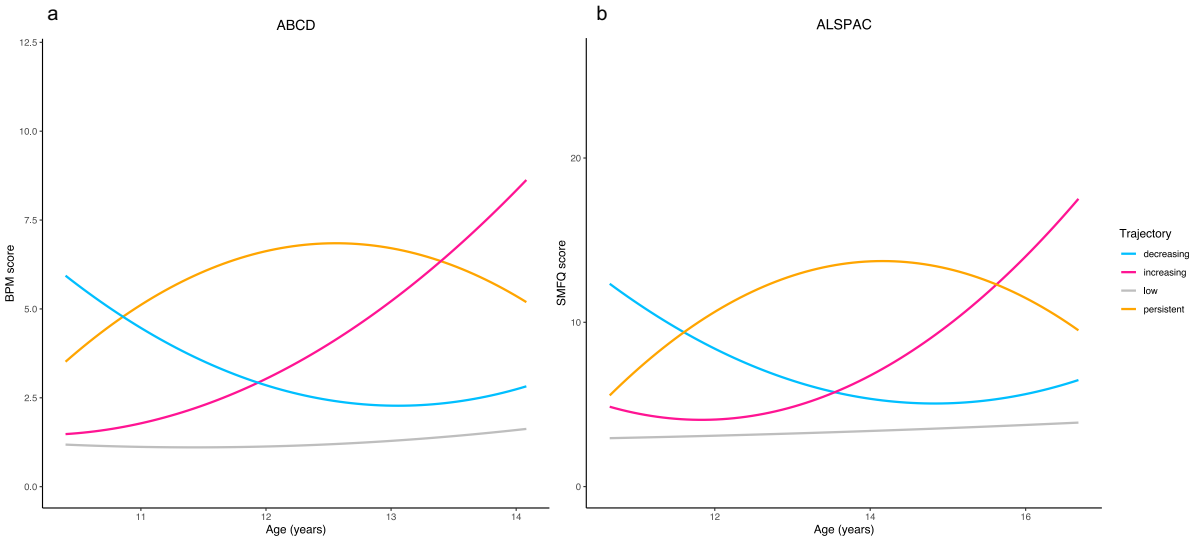

Figure 1. Replication of Depression Trajectories Across Adolescence. *Quadratic growth curves of the Adolescent Brain and Cognitive Development (ABCD) cohort trajectories from 8 measures of Brief Problem Monitoring (BPM) Youth report scale (a) and the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort from 4 measures of the Short Mood and Feeling Questionnaire SMFQ (b). Plotted as estimated sample means.*

Hierarchical Model for Genetic Psychopathology

Exploratory factor analysis of the 7 univariate traits revealed traits grouped into loadings on 3 independent factors (mood, psychotic and neurodevelopmental conditions) as hypothesised (**Figure S2 and Table S15 in Supplement 1**). Confirmatory factor analysis with the multivariable LDSC output returned the hierarchical factor model as the best fit (χ^2 = 86.4, Akaike information criterion [AIC] = 120.4, comparative fit index [CFI] = 0.99, standardised root mean square residual [SRMR] = 0.035) followed by the correlated factor model (χ^2 = 307.2, AIC = 337.2, CFI = 0.96, SRMR = 0.063), and then the common factor model (χ^2 = 1113.4, AIC = 1141.4, CFI = 0.83, SRMR = 0.12) (**Figure 2**). The bifactor model did not converge. Model fit indices, estimates and factor loadings are in **Tables S16-19 in Supplement 1**. For brevity, we only discuss the hierarchical model PRS but present results for all multitrait models in **Table 1, Figure 3** and **Tables S17-19 Supplement 1**.

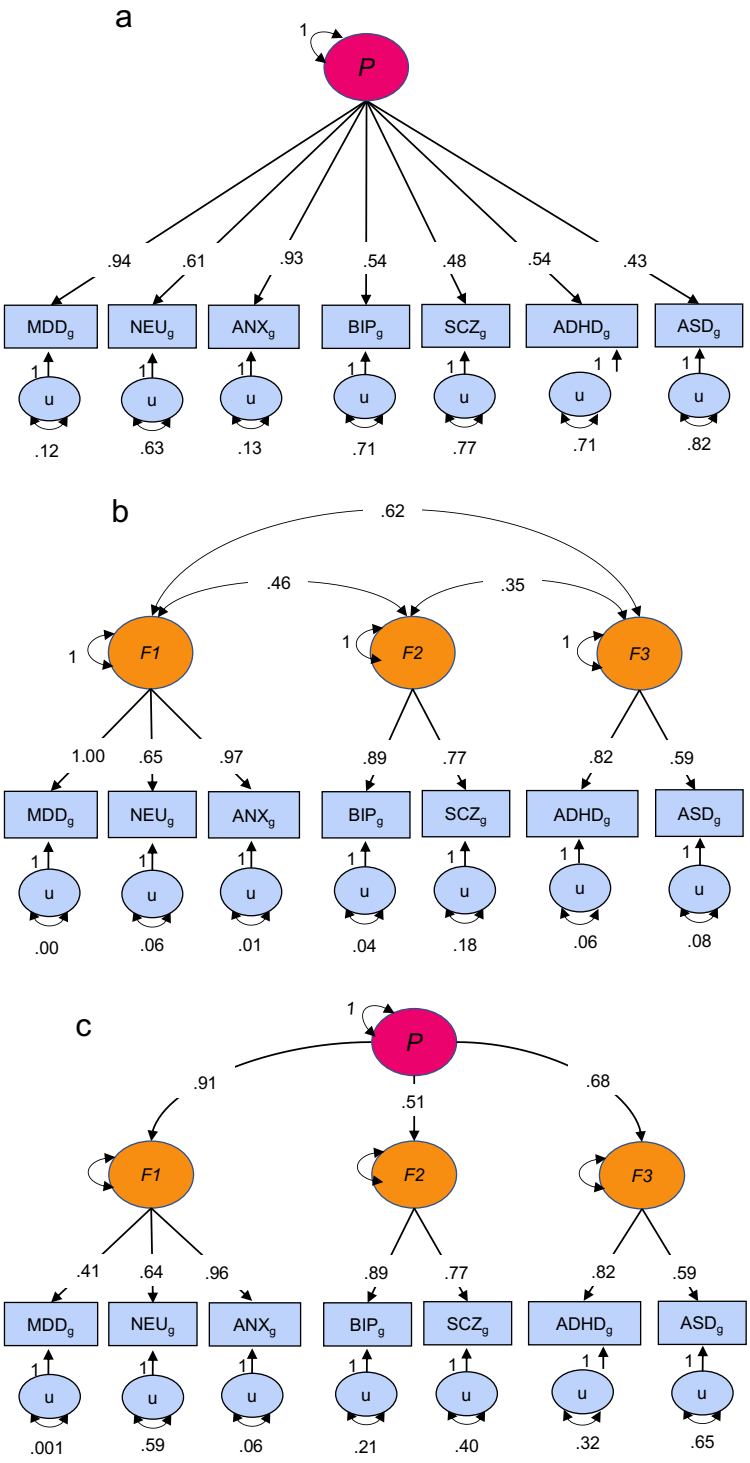

Figure 2. Standardised Multitrait Factor Models. *Standardised estimate results of the common factor model (a), correlated factor model (b), and hierarchical factor model (c). Latent genetic factors are in circles, trait indicators are in rectangles. Straight arrows represent regression pathways. Curved arrows indicate residual (u = unexplained) variances. F1 = mood factor, F2 = psychotic factor, F3 = neurodevelopmental factor.*

Univariate PRS Associations with Depression Trajectories

The adolescent persistent symptom trajectory was associated with PRSs for ADHD, ASD, anxiety, neuroticism and MDD in both cohorts (OR = 1.16-1.40). Schizophrenia was associated with persistent patterns in the ABCD cohort (OR = 1.19) and bipolar disorder with persistent patterns in the ALSPAC cohort (OR = 1.20). The increasing symptom trajectory was associated with PRSs for bipolar disorder, anxiety and MDD in the ABCD cohort (OR = 1.15-1.28) and for ASD, neuroticism and MDD in the ALSPAC cohort (OR = 1.12-1.17). The decreasing symptom trajectory was associated with PRSs for MDD, neuroticism and ADHD in the ABCD cohort (OR = 1.13-1.34) and for ASD, ADHD, neuroticism, anxiety and MDD in the ALSPAC cohort (OR = 1.16-1.34).

No consistent associations were found between MDD PRS for non-European ancestries and depression trajectories in the ABCD cohort (**Figure 4 and Table S20 in Supplement 1**).

Multivariate PRS Associations with Depression Trajectories

Hierarchical model multitrait PRS was strongly associated with all trajectories in both cohorts (**Figure 3**). The strongest association was with the adolescent persistent trajectories in both the ABCD (OR = 1.46, 95% CI 1.26, 1.68) and ALSPAC (OR = 1.34, 95% CI 1.20, 1.49) cohorts surpassing univariate PRS associations. In the ABCD cohort, multitrait hierarchical PRS had similar effect sizes for the increasing (OR = 1.27, 95% CI 1.13, 1.43) and decreasing (OR = 1.23, 95% CI 1.09, 1.40) trajectories. In the ALSPAC cohort, multitrait PRS was associated with the increasing trajectory (OR = 1.16, 95% CI 1.04, 1.28) but more strongly with decreasing (OR = 1.32, 95% CI 1.18, 1.47) trajectory.

Table 1. Association of Univariate and Multivariate Polygenic Risk Scores (PRSs) with Depression Trajectories in European Ancestry

ABCD				
PRS	**OR (95% CI)**			**PT**
	Persistent	**Increasing**	**Decreasing**	
MDD	1.40 (1.22, 1.61)	1.28 (1.14, 1.44)	1.34 (1.18, 1.52)	0.5
NEU	1.33 (1.16, 1.52)	1.09 (0.97, 1.22)	1.13 (1.00, 1.28)	0.2
ANX	1.22 (1.06, 1.40)	1.15 (1.02, 1.29)	1.09 (0.96, 1.23)	0.05
SCZ	1.19 (1.04, 1.37)	1.12 (0.99, 1.26)	1.04 (0.92, 1.18)	0.5
BIP	1.07 (0.93, 1.23)	1.17 (1.04, 1.31)	1.13 (0.99, 1.28)	0.0001
ADHD	1.24 (1.08, 1.43)	0.97 (0.86, 1.08)	1.15 (1.01, 1.30)	0.2
ASD	1.16 (1.02, 1.33)	1.03 (0.92, 1.16)	1.08 (0.96, 1.22)	0.001
MOOD	1.35 (1.55, 1.17)	1.24 (1.40, 1.12)	1.22 (1.38, 1.08)	0.1
PSYCHOTIC	1.19 (1.37, 1.04)	1.17 (1.31, 1.04)	1.07 (1.21, 0.94)	0.05
NEURODEV	1.25 (1.43, 1.09)	0.90 (1.01, 0.80)	1.22 (1.38, 1.08)	0.1
COMMON	1.42 (1.23, 1.63)	1.22 (1.09, 1.37)	1.24 (1.09, 1.40)	0.2
HIERARCHICAL	1.46 (1.26, 1.68)	1.27 (1.13, 1.43)	1.23 (1.09, 1.40)	0.05
ALSPAC				
PRS	**OR (95% CI)**			**PT**
	Persistent	**Increasing**	**Decreasing**	
MDD	1.25 (1.12, 1.39)	1.12 (1.01, 1.24)	1.23 (1.10, 1.37)	0.5
NEU	1.27 (1.14, 1.41)	1.17 (1.05, 1.30)	1.25 (1.12, 1.39)	0.05
ANX	1.18 (1.06, 1.31)	1.00 (0.90, 1.10)	1.16 (1.04, 1.29)	0.1
SCZ	1.10 (0.98, 1.22)	0.99 (0.90, 1.10)	1.02 (0.91, 1.14)	0.0001
BIP	1.20 (1.08, 1.34)	0.98 (0.88, 1.08)	1.05 (0.95, 1.17)	0.5
ADHD	1.18 (1.06, 1.32)	1.07 (0.97, 1.19)	1.34 (1.20, 1.49)	1
ASD	1.17 (1.05, 1.30)	1.16 (1.05, 1.29)	1.24 (1.12, 1.39)	1
MOOD	1.27 (1.42, 1.14)	1.15 (1.27, 1.03)	1.30 (1.45, 1.17)	0.5
PSYCHOTIC	1.17 (1.30, 1.05)	1.03 (1.15, 0.93)	1.02 (1.14, 0.92)	0.05
NEURODEV	1.29 (1.44, 1.16)	1.10 (1.22, 0.99)	1.32 (1.47, 1.18)	0.05
COMMON	1.33 (1.19, 1.48)	1.16 (1.04, 1.28)	1.31 (1.17, 1.46)	0.5
HIERARCHICAL	1.34 (1.20, 1.49)	1.16 (1.04, 1.28)	1.32 (1.18, 1.47)	0.5

Note: OR = odds ratio, CI = confidence interval, PT = P-value of the PRS threshold explaining the most phenotypic variance. MOOD, PSYCHOTIC and NEURODEV correspond to the intermediate grouping factors in the correlated factor model.

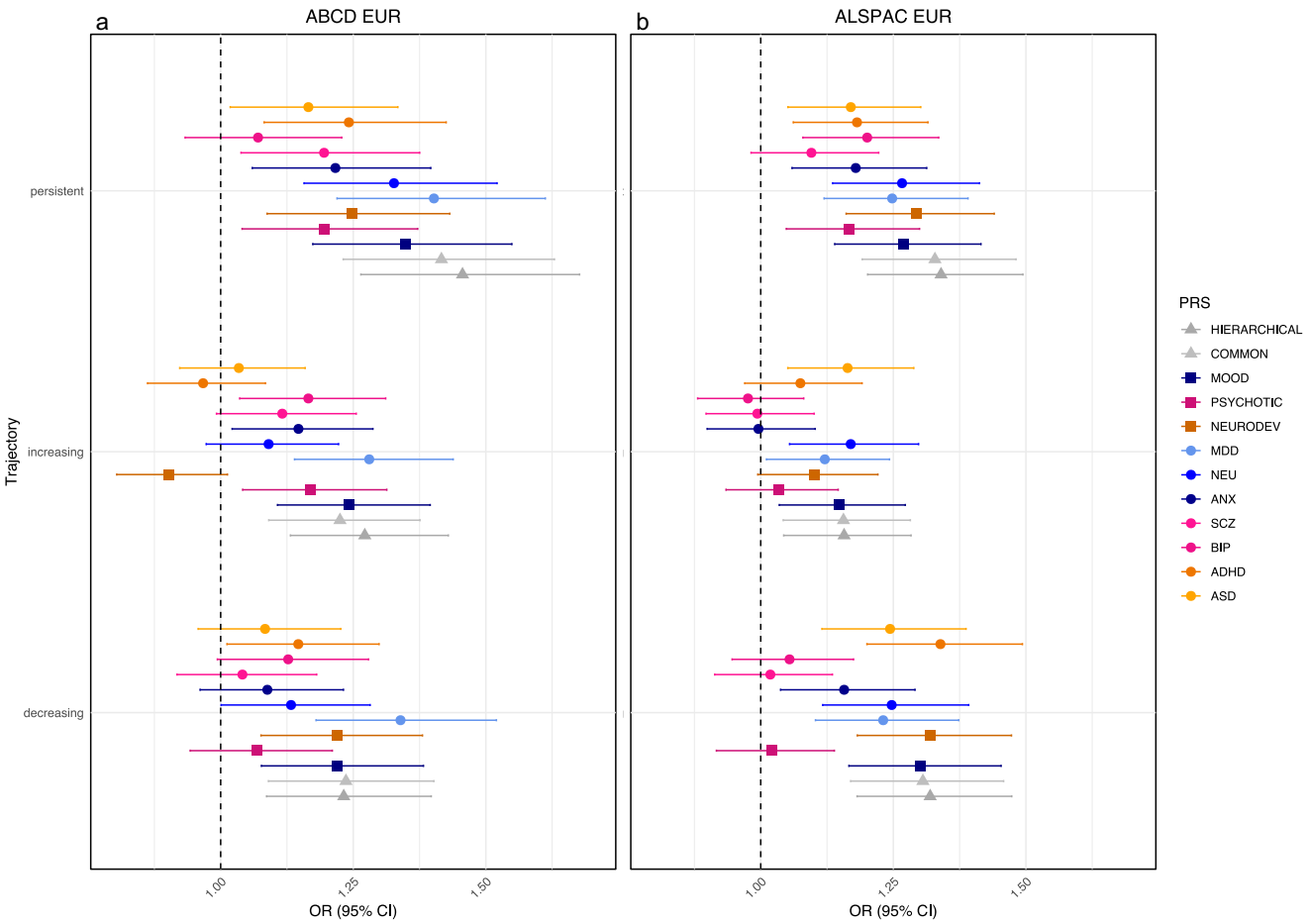

Figure 3. Polygenic Risk Score Associations with Depression Trajectories. *Adolescent Brain and Cognitive Development (ABCD) European ancestry univariate and multivariate p-factor association (a). Avon Longitudinal Study of Parents and Children (ALSPAC) European ancestry univariate and multivariate p-factor association (b). Error bars represent odds ratios (ORs) of each trajectory compared to the low (reference) trajectory with 95% confidence intervals (CI).*

Sensitivity Analyses

The 3-step bias-adjusted models showed consistent results with reported trajectories (**Table S21 in Supplement 1**). In the majority of samples, trajectories were consistent with the 4-class solution for individuals with 50% or more depression measures (**Tables S22-25 in Supplement 1**). As expected, results attenuated in the adjusted multivariable model, likely due to polygenicity, multicollinearity and opposite direction effects (**Table S26 in Supplement 1**). Of note, MDD and neuroticism PRS were consistently associated with adverse trajectories, but there was also some evidence in the ALSPAC cohort that ADHD and ASD PRSs were

associated with the decreasing trajectory. The LOO common factor model showed no divergence from the full model associations (**Figure S3 in Supplement 1**). PRS association with depression score were consistent across time points (**Figure S4-S5 in Supplement 1**). There was some evidence that PRS were associated with questionnaire completion; however this varied substantially across PRSs (**Figure S6-S7 in Supplement 1**). Trajectories differed across non-European ancestries; however, we caution interpretation of trajectory results given limited sample size, low convergence and class counts (**Figure S8 and Tables S27-30 in Supplement 1**). Results for self-reported ethnicity associations with MDD PRS in ABCD are in **Table S31 in Supplement 1**.

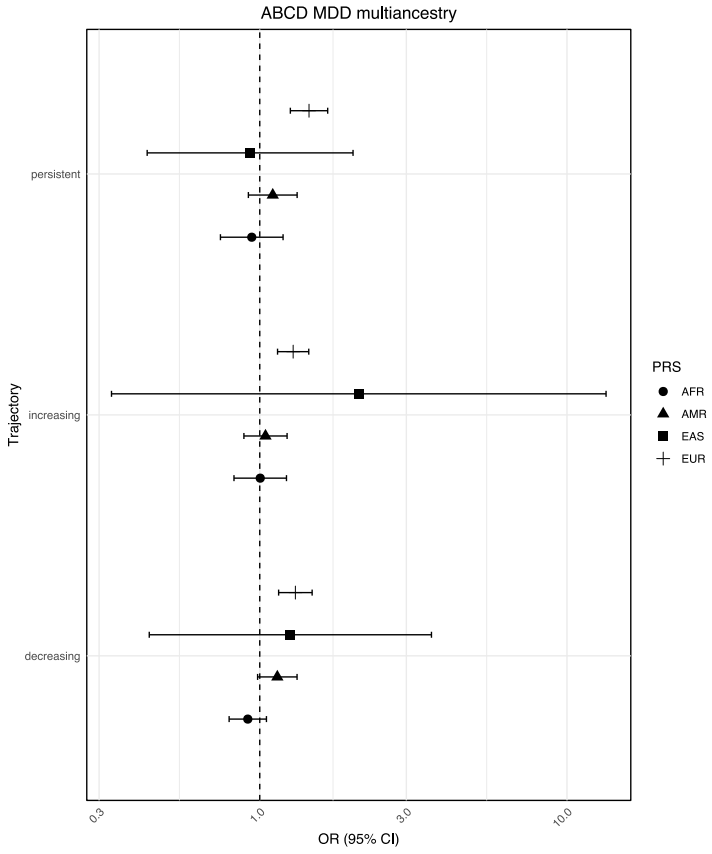

Figure 4. Multiancestry PRS assocations with depression trajectories. *The Adolescent Brain and Cognitive Development (ABCD) multiancestry MDD PRS associations for African, East Asian, Hispanic and European ancestries using 23andMe summary statistics. Error bars represent odds ratios (ORs) of each trajectory compared to the low (reference) trajectory with 95% confidence intervals (CI).*

Discussion

For the first time, we explore how the shared genetic architecture of psychiatric disorders underlies longitudinal patterns of depression across adolescence. In a cross-cohort replication of trajectories, our results suggest that multitrait genetic risk exceeded the association of univariate risk with a more severe adolescent persistent trajectory across psychiatric traits and cohorts. Intermediate patterns of increasing and decreasing symptoms exhibited a less pronounced and consistent association with psychiatric genetic risk, possibly suggesting a greater influence of external environmental factors and cohort differences, as suggested in previous work[15]. We highlighted the lack of psychiatric genetic data for non-European ancestries, which is imperative to prevent health inequalities for prediction modelling in depression and treatment stratification.

Multitrait Genetics of Longitudinal Depression Patterns

In line with previous work utilising GenomicSEM, we found a parcelled structure of genetic psychopathology into factor domains of mood or internalising conditions, psychotic conditions and neurodevelopmental conditions[51–53] with a hierarchical model demonstrating the strongest p-factor loading[25].

The multivariate genetic p-factor showed strong associations across all trajectories, with the adolescent persistent pattern demonstrating the strongest effect sizes. The persistent pattern was also associated with univariate genetic risk for multiple psychiatric conditions in a homogenous fashion. Genetic factors predominantly contribute to the longitudinal stability of depression and anxiety symptoms from childhood to adulthood[13]. Our findings suggest that a high genetic predisposition to any psychopathology could underpin the more stable persistent group.

Intermediate trajectories (increasing and decreasing) were also associated with the multitrait p-factor, although this was less consistently than for the persistent trajectory. The ABCD cohort showed comparable p-factor associations between increasing and decreasing trajectories, whereas associations with the decreasing trajectory in the ALSPAC cohort were considerably higher than for increasing. Of note is the strong association of neurodevelopmental PRS with the decreasing trajectories in both cohorts and the multivariable model associations of ADHD and ASD PRSs in the ALSPAC cohort only (**Table S26 in Supplement 1**). These findings may reflect the early onset of depression for individuals with neurodevelopmental conditions who subsequently recover as neurodivergence is managed or adapted to, particularly in ADHD.

The p-factor involves pleiotropic genes contributing to an overall psychiatric risk[26,54–56] and a *latent intercept factor* that captures baseline stability has been shown as significantly more heritable than depression at any other time point[57]. Our observations indicate that 'p' may be more important at younger ages of depression onset related to comorbidity of neurodevelopmental traits[16,58]. In risk-prediction models, multi-trait genetic information may be useful for supporting the identification of longitudinal risk groups for early intervention in combination with other environmental information. This is supported by transdiagnostic clinical frameworks that exploit shared cross-disorder treatment responses in unified protocols[26,59].

Intermediate trajectories exhibit less pronounced associations across univariate polygenic risk. Environmental factors are more likely to inform variable patterns of depressive symptoms[11], with genetic heritability shown to decrease with age[13]. In the increasing trajectory, environmental risk factors such as low socioeconomic status[60] may be escalating depressive

symptoms towards adulthood. Protective environmental factors could drive a reduction of depressive symptoms over time in the decreasing group. Machine learning methods that combine biological and environmental factors could further characterise the relative contributions that assign an individual to a trajectory.

Achieving Equity in Genetic Association Modelling Through Ancestrally Diverse Data

We found weaker associations for MDD polygenic risk association with longitudinal depression in non-European ancestries, which was not unexpected given the smaller sample sizes. Epidemiological studies show that Asian, Black, and Hispanic adolescents have increased depression symptoms over time compared with White adolescents, impacted by socioeconomic status and stress[61,62]. Racial discrimination is thought to increase depression risk through stress-induced cortisol in the hypothalamic-pituitary-adrenal axis[63] and leads to disproportionate suffering in ethnic minorities. Self-reported associations tended to support this (**Table S31 in Supplement 1**).

Despite the impact of environmental factors, such as discrimination, on the elevated risk of depression in minority groups, we anticipated a genetic risk profile that aligns closely with that of European populations. Our findings highlight a cavity in the acquisition of ancestrally representative genetic data, particularly in genome-wide association studies. Researchers must interpret carefully when generalising findings from European-only ancestries. This is crucial to address when embedding genetic risk-prediction models to prevent the exacerbation of health inequalities. Efforts to sequence and analyse ancestrally diverse genetic data are imperative to design universal models. Importantly, well-phenotyped data from longitudinal cohorts across the globe, particularly non-Western countries, will help improve generalisability of research relating to mental health trajectories.

Limitations

This study demonstrates robustness through cross-validation of 2 large adolescent cohorts with repeated depression measures and genetic data. However, ages did not precisely align between cohorts; the ALSPAC cohort had fewer measures over more years. ALSPAC participants were recruited up to 15 years before the ABCD cohort, implying different generational experiences. Despite sources of heterogeneity across the cohorts – depression measure, measure occasions, generation and age range – we found consistent evidence for genetic underpinnings across both studies suggesting strong evidence of replicable findings. Intrinsic to longitudinal studies, both cohorts experience participant attrition (**Table S5 in Supplement 1**). While utilising FIML in trajectory modelling, this assumes random data missing, which may not hold true. However, we found that trajectories are consistent when restricting to individuals with 50% or more depression measures (**Tables S22-25 in Supplement 1**). We reiterate the low sample sizes for non-European ancestries in the ABCD cohort. For example, only 94 East Asian individuals had genetic and depression data. The availability of more diverse longitudinal cohorts with accompanying genetic data should hope to overcome this in future work.

Conclusions

This study contributes novel evidence highlighting the value of leveraging genetic information across multiple psychopathological traits that correlate with major depression to understand the biological underpinning of depression in a longitudinal context. This is a step toward teasing apart the challenge of genetic-environmental interplay in longitudinal depression aetiology for early intervention. To enhance the comprehensiveness of these findings, it is imperative that we include genetic and longitudinal phenotypic data from diverse ancestries and geographies.

Acknowledgements

This work has made use of the resources provided by the Edinburgh Compute and Data Facility (ECDF, 2023) (http://www.ecdf.ed.ac.uk/).

Data sharing statement

ALSPAC: The ALSPAC study website contains details of all the data that are available through a fully searchable data dictionary at http://www.bristol.ac.uk/alspac/researchers/access/. Permission to use the ALSPAC data is obtained through a proposal system managed by the ALSPAC executive. We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

ABCD: Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children age 9-10 and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/.

ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from https://dx.doi.org/10.15154/8873-zj65. DOIs can be found at https://nda.nih.gov/abcd/. Genetic data: GWAS summary statistics were downloaded from the PGC (https://pgc.unc.edu/for-researchers/download-results/) and iPSYCH (https://ipsych.dk/en/research/downloads) websites.

Funding

This work was funded by a UKRI Medical Research Council grant for the Precision Medicine MRC DTP awarded to PZG (grant number MR/W006804/1). The UK Medical Research Council and Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. GWAS data was generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. AJES was funded by the Wellcome Trust (Grant No. 108890/Z/15/Z). ASFK is supported by a Wellcome Early Career Award (227063/Z/23/Z). This publication is the work of the authors and PZG and ASFK will serve as guarantors for the contents of this paper.

Role of the funding organisations

The funding organisations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of Interest

Henrik Larsson reports receiving grants from Shire Pharmaceuticals; personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; all outside the submitted work. Henrik Larsson is editor-in-chief of JCPP Advances.

Access to data and data analysis

Poppy Grimes had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Data and code availability

All code and analysis scripts are available on GitHub (https://github.com/poppyzenzi).

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