Polygenic Risk for Depression is Associated with the Severity and Rate of Change in Depressive Symptoms Across Adolescence

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Abstract

Background:
Adolescence marks a period where depression will commonly onset and previous research using twin studies has suggested that genetic influences play a role in how depression develops and changes across adolescence. Recent genome-wide association studies have also shown that common genetic variants – which can be brought together as polygenic risk scores (PRS) – are also implicated in depression. However, the role of PRS in adolescent depression and changes in adolescent depression is not yet understood. The aim of this study was to examine the association between a PRS for depressive symptoms and depressive symptoms across adolescence and young adulthood, and how polygenic risk is associated with changes in depressive symptoms using two methods: cross-sectional analysis and multilevel growth curve modelling to examine the rate of change over time.

Methods:
Using data from over 6000 participants of the Avon Longitudinal Study of Parents and Children (ALSPAC) we examined associations between genetic liability to depressive symptoms (polygenic risk score (PRS) for depressive symptoms) and self-reported depressive symptoms (short mood and feelings questionnaire over 9 occasions from 10-24 years). We examined cross-sectional associations at each age and trajectories of depressive symptoms in a repeated measures framework using growth curve analysis.

Results:
The PRS was associated with depressive symptoms throughout adolescence and young adulthood in both cross-sectional and growth curve analyses, though associations were stronger in the latter analyses. Growth curve analyses also provided additional insights, demonstrating that individuals with a higher PRS had steeper trajectories of depressive symptoms across adolescence with a greater increasing rate of change.

Conclusions:
In a longitudinal study spanning adolescence to early adult life, these results show that common genetics variants as indexed by a PRS for depressive symptoms influence both the severity of rate of change in adolescent depressive symptoms. Longitudinal data that make use of repeated measures designs have the potential to provide insights into the factors that influence the onset and persistence of adolescent depression.
Introduction

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

Depression has a complex and multifactorial aetiology, comprised of both environmental and genetic contributions (Flint & Kendler, 2014; Thapar, Collinshaw, Pine, & Thapar, 2012). Adult twin studies have estimated that the heritability of major depressive disorder is between 31% - 42% (Sullivan, Neale, & Kendler, 2000), indicating a moderate genetic component of liability to depression. Twin studies of depressive symptoms during adolescence have estimated similar heritability to that of adult depression ~ 40% (Rice, 2014) with lower estimates reported for symptoms during childhood, and considerable variability in heritability estimates between different studies depending on age, informant and measure of assessment (Rice, 2009). Depressive symptomatology typically increases during adolescence and twin studies have also shown that genetic contributions influence this developmental change (Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2017). In particular genetic contributions may increase throughout development (Bergen, Gardner, & Kendler, 2007; Rice, Harold, & Thapar, 2002) although some inconsistent results have also been reported (Nivard et al., 2015). There are strong continuities reported between adolescent and adult depression (Rutter et al., 2006), so the somewhat inconsistent estimates of heritability for adolescent depressive symptomatology are puzzling and are likely due to between study differences in measurement and age of the sample studied. Longitudinal data spanning early adolescence and young adulthood using the same assessments and respondents over time would aid understanding of the nature of genetic influences on onset and persistence of symptoms across development.

Recent advances in genome-wide association studies (GWAS) have provided evidence that polygenic common genetic variation plays a role in depression (Howard et al., 2019; Howard et al.,
2018; Wray et al., 2018) with many genetic variants or single nucleotide polymorphisms (SNPs) each having a small effect (Mullins & Lewis, 2017). Polygenic risk scores (PRS), which sum the number of “risk” variants that an individual possesses for a trait weighted by their effect size (Martin, Daly, Robinson, Hyman, & Neale, 2018), can be used as an indicator of an individual’s genetic liability to depression. Several studies have used depression PRS taken from GWAS of major depressive disorder or depressive symptoms in adult populations to investigate how they influence depressive symptomatology over development in younger populations (Halldorsdottir et al., 2019; Kwong, Lópe-Lópe, et al., 2019; Rice et al., 2018; Riglin et al., 2018). One study found that the influence of an MDD PRS on emotional problems increased with age with weaker effects in childhood which developed in adulthood (Riglin et al., 2018). Two other studies have since used a developmental trajectory approach to identify ‘classes’ of individuals whose depressive symptoms differ across adolescence (Kwong, Lópe-Lópe, et al., 2019; Rice et al., 2018). These studies found evidence of somewhat differing trajectory classes based on age of onset and persistence of symptoms over time that were associated with depression PRS. Another study found that PRS for depression was associated with depression in a clinical and population cohort of children and adolescents (Halldorsdottir et al., 2019). Together, these studies highlight that polygenic risk is likely to play a role in the development and maintenance of adolescent depression and that the role of depression genetic liability may differ according to varying developmental stages.

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

The aim of this study was to examine how genetic liability for depression (as indexed by a PRS for depressive symptoms) influenced depressive symptoms across adolescence and early adult life using cross-sectional and repeated measures designs. Specifically, we aimed to test how a depressive symptoms PRS was associated with both the initial level and the rate of change of depressive symptoms over this developmental risk period for depression. Evidence suggests that depression should be viewed on a continuum (Hankin, Fraley, Lahey, & Waldman, 2005; Wray et al., 2018), as depressive symptoms are strongly associated with depression (Hill, Pettit, Lewinsohn, Seeley, & Klein, 2014; Pine, Cohen, Cohen, & Brook, 1999), and elevated depressive symptoms are associated with a host of adverse outcomes similar to depression (Balazs et al., 2013; Fergusson, Horwood, Ridder, & Beautrais, 2005). We conducted several analyses: 1) we used a PRS taken from a recent GWAS of depressive symptoms (Okbay et al., 2016), and examined associations at nine separate occasions in a UK based population cohort between the ages of 10 and 24 years old (cross-sectional analysis). 2) we then used growth curve modelling to construct trajectories of depressive symptoms in the same cohort and examined how the PRS for depressive symptoms was associated with the rate of change in depressive symptoms throughout adolescent development. 3) finally, we examined if a higher PRS was associated with differences in depressive symptoms scores across this developmental period, in order to determine when the PRS would be having its greatest effect of depressive symptomology.
Methods

Sample

We used data from the Avon Longitudinal Study of parents and Children (ALSPAC), a longitudinal cohort study that recruited pregnant women residing in the former area of Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 (Boyd et al., 2013; Fraser et al., 2013). The initial cohort consisted of 14,062 live births, but has been increased to 14,901 children who were alive after one year with further recruitment (Northstone et al., 2019). Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data.

Depressive Symptoms

Self-reported depressive symptoms were measured on nine occasions between ages 10 and 24 using the short mood and feelings questionnaire (SMFQ) (Angold, Costello, Messer, & Pickles, 1995). See Table 1 for the ages at which the SMFQ was assessed. The SMFQ is a 13-item questionnaire that measures the presence of depression symptoms in the last two weeks and was administered via postal questionnaire or in research clinics. Each item is scored between 0-2, resulting in a summed score between 0-26. The SMFQ correlates highly \( (r = 0.58) \) with clinical depression (Thapar & McGuffin, 1998; Turner, Joinson, Peters, Wiles, & Lewis, 2014).

Polygenic Risk Score for Depressive Symptoms

The PRS for depressive symptoms was created in PRSice (Euesden, Lewis, & O'Reilly, 2015), using summary statistics from a recent genome wide association study (GWAS) of depressive symptoms on 161,460 individuals (Okbay et al., 2016). The PRS was created by weighting the effect sizes of 120,422 single nucleotide polymorphisms (SNPs) associated with depression symptoms from the initial GWAS at eight \( p \)-value thresholds (as \( 5 \times 10^{-08}, 5 \times 10^{-07}, 5 \times 10^{-06}, 5 \times 10^{-05}, 5 \times 10^{-04}, 5 \times 10^{-03}, 5 \times 10^{-02} \) and \( 5 \times 10^{-01} \)). The PRS was standardised to have a mean of 0 and a standard deviation of 1, thus a higher PRS represents higher liability to depression symptoms. We included SNPs that had a MAF of > 1% and info score > 80%) and excluded SNPs with an \( R^2 \) of >0.1, if they...
were within 250Kb of each other. We excluded SNPs located in the extended MHC region (chromosome 6 (26-33Mb)). Further genotyping information is available in the Supplement.

**Statistical Analysis**

For the cross-sectional analysis, linear regression analysis was used to examine the association between depressive symptoms and the PRS at each of the nine occasions. \( P \) values were corrected for false discovery rate (FDR) due to the number of statistical tests (eight PRS thresholds \( \times \) nine depressive symptoms occasions [72 tests]). Bootstrapping, with 1000 iterations was used to calculate confidence intervals for \( R^2 \) (the amount of variance explained by the PRS).

For the repeated measures analysis, trajectories of depressive symptoms were estimated using multilevel growth-curve modelling (Hedeker & Gibbons, 2006; Raudenbush & Bryk, 2002). Briefly, multilevel growth-curve models create population averaged trajectories with intercept and slope terms. Individual level trajectories then vary around this population average (i.e., each person can have their own trajectory, with their own intercept and slope that deviates from the population average). Previous analysis of these data has shown that changes in depressive symptoms over time are non-linear (Edwards et al., 2014; Kwong, Manley, et al., 2019), with depressive symptoms rising until the age of about 18, then decreasing until around the age of 22, before rising again towards the age of 24 – see Table 1. To model these non-linear trajectories, a multilevel quartic growth-curve polynomial model was chosen. This model contains five key parameters: the intercept, the linear age term, the quadratic age term, the cubic age term and the quartic age term. These age terms allow for non-linearity in the trajectory and changes in depressive symptoms. Previous research using this data to estimate multilevel growth curves has found that a quartic polynomial model best fitted the data (Kwong, Maddalena, Croft, Heron, & Leckie, 2019). We assessed the feasibility of this model using information criteria, consistent with other studies using multilevel growth-curve models (Singer & Willett, 2003) – see Supplementary Tables S1 and S2, and Figure S2.

To examine how the PRS was associated with changes in the growth curve model, we included a main effect of the standardised PRS and an interaction of the PRS with each of the fixed-effects age polynomial terms (i.e., the linear, quadratic, cubic and quartic age terms). Age was grand-mean centred to 16.53 years (the mean age of all assessments) in order to improve interpretation, since model intercept and intercept variance then broadly correspond to the middle of adolescence.
(Rawana & Morgan, 2014). The intercept and four polynomial age terms were allowed to vary randomly across individuals to capture each individual’s unique trajectory (i.e., each person had their own intercept and slope). Further information regarding model fit and the model equations can be found in the Supplement.

To assess the association between the depressive symptoms PRS and development of symptoms over time, we created one trajectory associated with low genetic liability (1 SD below mean) and one associated with low genetic liability (1 SD above the mean). We then calculated the predicted depressive symptoms scores at each of the following ages: 10.64, 12.81, 13.83, 16.68, 17.82, 18.64, 21.95, 22.88 and 23.86 (to coincide with the mean ages at which the SMFQ was assessed at each of the nine occasions), for both the greater and lower PRS trajectories. We compared the predicted depressive symptoms scores at each of these ages between greater and lower PRS trajectories. Further information on how these were calculated for the trajectories is presented elsewhere (Kwong, Maddalena, et al., 2019), but briefly the depressive symptoms scores are calculated at each age for the two trajectories (i.e., depressive symptom scores at age 12 for the low PRS and high PRS trajectory). Then using the delta method (which incorporates the estimate, standard errors and confidence intervals), these two scores are then compared to reveal an estimated difference that has measures of certainty and precision.

Finally, to ensure that changes in trajectories were not due to including any genetic predictor into model, we ran a negative control analysis between a PRS for height and trajectories of depressive symptoms and between the depressive symptoms PRS and height trajectories (see Supplement for details and analysis).

All analyses were conducted using Stata 15 (StataCorp, College Station, TX, USA), with trajectories analysis using the user-written runmlwin command (Leckie & Charlton, 2013), which calls the standalone multilevel modelling package MLwiN v3.01 (www.cmm.bristol.ac.uk/MLwiN/index.shtml). All analyses were adjusted for sex, age (only in the cross-sectional analyses, as the longitudinal analyses adjust for age by default) and the first ten principal components of ancestry.

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

Sample Characteristics

Of the original 14,901 participants, 9,399 individuals had at least one measurement of depressive symptoms and 7,877 had genotype data that passed quality control, removal of non-Europeans and related samples. For the cross-sectional analysis, data were available for 5,324 individuals with a measurement of depressive symptoms at age 10 and genotype data. However, sample size decreased to 2,737 individuals with both a depression symptoms measurement at age 24 and genotype data. Descriptive information can be found in Table 1 and a STROBE diagram is given in Supplementary Figure S1. For the repeated measures analysis, data were available for 6,305 individuals with at least one measurement of depressive symptoms and genotype data.

Association Between Depressive Symptoms Polygenic Risk Score and Depressive Symptoms Cross-sectional Analysis

Given that more liberal PRS p-value thresholds have been used when examining the predictive capabilities of PRS for psychiatric traits (Wray et al., 2018), we focused on the more liberal PRS thresholds of 0.005, 0.05 and 0.5. For completeness, full estimates are given for all analyses can be found in Supplement Tables S3-S11.

On average, the PRS with a p-value threshold of 0.005 showed the strongest associations with depressive symptoms across occasions (Supplementary Tables S3-S11). Effect sizes tended to increase throughout adolescence and into young adulthood, as shown in Figure 1 and Table 2. Additional analyses across the three most liberal thresholds (0.005, 0.05 and 0.05) yielded similar results and can be found in Supplementary Figure S3 and Supplementary Table S12.

Association Between Depressive Symptoms Polygenic Risk Score and Trajectories of Depressive Symptoms

We selected the PRS with a p-value threshold of .005 for the trajectory analysis because this PRS threshold showed stronger average effect sizes across the cross-sectional analyses and is a similar threshold to previous studies (see Table S12). Sensitivity analyses were conducted at other thresholds and showed similar results (see Supplementary Tables S13-S15).
A one standard deviation increase in the depressive symptoms PRS was associated with higher depressive symptoms at the intercept age of 16.53 (β = 0.363, 95 CIs = 0.230, 0.496, P = 8.56x10^-08). The depressive symptoms PRS also showed evidence for change over time, with a one standard deviation increase in the PRS strongly associated with a linear change in depressive symptoms (β = 0.048, 95 CIs = 0.016, 0.080, P = 0.003). However, a one standard deviation increase in the PRS showed weak and inconsistent associations with the quadratic, cubic or quartic age terms (see Figure 2 and Table S13).

Comparisons Between Higher and Lower Genetic Risk at Various Ages

Our comparisons between those with higher risk (1 SD above mean in the PRS) and those with lower risk (1 SD below mean in the PRS) demonstrated strong evidence that depressive symptoms were higher for those with greater PRS risk at all ages of adolescence and young adulthood from age 12 onwards (P_{FDR} ≤ 0.037), and weaker evidence at age 10 (P_{FDR} = 0.063) (Table 3). The largest difference between these two trajectories was observed at age 24 with roughly a one-point difference of the SMFQ (β_{diff} = 0.980, 95 CIs = 0.580, 1.380, P = 1.24x10^{-06}).
Discussion

In this longitudinal cohort study, we focused on a cross-sectional analysis and a growth curve modelling approach that utilised a repeated measures framework to explore the association between genetic risk (as measured by a polygenic risk score for depressive symptoms) and depressive symptoms across adolescence. In the cross-sectional analysis, we found that a PRS developed around adult common genotypic contributions to depression was associated with higher levels of depressive symptoms throughout adolescence and early adulthood. There were stronger associations between the PRS and depressive symptoms at older ages. In the growth curve analysis, we found that a higher PRS for depressive symptoms was associated with steeper trajectories of depressive symptoms, that were characterised by greater overall depressive symptoms across adolescence, as well as a greater increase in the rate of change of depressive symptoms.

Our results suggest that a higher PRS is associated with greater depressive symptoms in adolescence and early adulthood and may influence how depressive symptoms change across adolescence and adulthood. Importantly, we see that those with a higher PRS for depressive symptoms begin to have higher symptoms scores between the ages of 12 and 14, suggesting that genetic liability may play a role in the onset of adolescent depression. Such results are consistent with research in high risk family studies (Weissman et al., 2006), and place further emphasis on the idea that depression is not only heritable, but genetic liability may also influence the rate of phenotypic change that is expressed (in this case depressive symptoms across adolescence and young adulthood).

Our repeated measures analysis suggested that the PRS had stronger associations as age increased and that differences in trajectories could be the result of varying genetic liability across development. This is consistent with longitudinal twin research showing the genetic contribution to depression increases throughout adolescent development (Bergen et al., 2007; Rice et al., 2002). There are several possible explanations as to why genetic liability may influence change over time. First, genetic liability to depression may act upon biological and hormonal pathways, especially during adolescence (Paus, Keshavan, & Giedd, 2008). This may result in changes to brain development and hormonal responses that put an individual at greater risk of depression (Blakemore, 2008). Second, gene environment correlation with key environmental risk exposures such as stressful life events may increase with age (Jaffee & Price, 2012; Rice, Harold, & Thapar, 2003; Thapar et al., 2012). This in turn may produce indirect pathways to depression that are a
result of increased environmental exposures that occur in later development. Third, differences in genetic liability could be the result of measurement error and noise at the varying occasions, but this may be reduced in repeated measures designs (Lubke et al., 2016).

Previous research has shown that PRS can be included into longitudinal models that examine change in a trait over time (Khera et al., 2019; Paternoster et al., 2011; Warrington, Howe, et al., 2013). Research has suggested that it is also possible to examine genetic influences on age related changes in depression (Lubke et al., 2016). We were able to expand upon this previous work to examine genetic contributions to varying trajectories of depressive symptoms. We demonstrated that genetic influences may be age specific (i.e., may begin to onset at different times) and our results highlight a useful approach for a repeat measures framework (such as a growth curve model) to quantify the extent to which genetics may influence traits over time (by examining rate of change).

This study had several strengths. First, we were able to use a large longitudinal population cohort with repeated assessments of depressive symptoms using the same measure and informant across adolescence to adulthood – a key transition period of heightened vulnerability to depression. We were able to utilise these assessments to characterise trajectories of depressive symptoms across this developmental period. Second, we were then able to expand upon previous research by using a repeat measures model that is a powerful alternative to cross-sectional analysis. By using the correlation between the repeated measurements, it may be possible to reduce measurement error and boost statistical power. Our negative control analysis examining the association between a PRS for height and trajectories of depressive symptoms, and then a depressive symptoms PRS for trajectories of height support this claim and did not show any evidence for non-specific genomic predictors influencing unrelated trajectories (see Supplementary Tables S16-S17 and Figures S2-S3). Third, we were also able to use the same sample across our analysis as the repeated measures model used full information maximum likelihood (FIML) to account for missing data, which is an advantage of this method compared to the cross-sectional analysis.

This study had several limitations. First, this study did suffer from attrition as sample sizes varied across ages in the cross-sectional analysis, which may bias the results if missingness is not random. One of the advantages of using the repeat measures model is that we can instead use FIML to account for missing data. This approach also minimises the bias that may be present if each occasion (age wave) represents a different sample. However, even this approach may be biased if
the data are missing not at random. For example, genetic risk for depression may predict missing assessments in ALPSAC (Rice et al., 2018; A. E. Taylor et al., 2018). This could lead to bias in this study and an underestimation of the true estimate for the trajectories of depressive symptoms and a further underestimation of the genetic contributions to depressive symptoms. Second, depression is a heterogeneous condition and there may be a genetic difference between sum scores, and specific symptoms of depression (Nagel, Watanabe, Stringer, Posthuma, & van der Sluis, 2018). Depression symptoms may also differ at different ages (Rice et al., 2019). We used the same summary score of depressive symptoms throughout our study, which therefore only captures the sum of depressive symptoms and does not highlight if certain symptoms of depression (i.e., anhedonia, lack of appetite or depressive thoughts) are more related to genetic liability for depressive symptoms. Future research should look to examine if different profiles of depression change across time and if these profiles are more related to genetic or environmental factors. Thirdly, our results lack generalisability to all populations as the original GWAS was conducted on individuals of European ancestry, and this may have consequences on further clinical applications (Mostafavi, Harpak, Conley, Pritchard, & Przeworski, 2019). However, research is beginning to capture GWAS of non-European populations (Bigdeli et al., 2017), and future studies will be able to examine the impact of genetic liability on adolescent depression in other populations. Finally, whilst our results highlight a potential role for PRS in understanding and examining pathways to depression, the amount of variance in depressive symptoms explained by the PRS was relatively low (never more than 1.07%). As such the clinical implications of these results are not clear and PRS should continue to be used for making group-level, rather than individual-level predictions (Morris, Davies, & Davey Smith, 2019).

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

Angold, A., Costello, E. J., Messer, S. C., & Pickles, A. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research, 5*(4), 237-249.

Balazs, J., Miklosi, M., Kereszteny, A., Hoven, C. W., Carli, V., Wasserman, C., . . . Wasserman, D. (2013). Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. *J Child Psychol Psychiatry, 54*(6), 670-677. doi:10.1111/jcpp.12016

Bergen, S. E., Gardner, C. O., & Kendler, K. S. (2007). Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. *Twin Res Hum Genet, 10*(3), 423-433. doi:10.1375/twin.10.3.423

Bigdeli, T. B., Ripke, S., Peterson, R. E., Trzaskowski, M., Bacanu, S. A., Abdellaoui, A., . . . Kendler, K. S. (2017). Genetic effects influencing risk for major depressive disorder in China and Europe. *Transl Psychiatry, 7*(3), e1074. doi:10.1038/tjtp.2016.292

Blakemore, S. J. (2008). The social brain in adolescence. *Nat Rev Neurosci, 9*(4), 267-277. doi:10.1038/nrn2353

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., . . . Davey Smith, G. (2013). Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol, 42*(1), 111-127. doi:10.1093/ije/dys064

Copeland, W. E., Shanahan, L., Costello, J., & Angold, A. (2009). Childhood and Adolescent Psychiatric Disorders as Predictors of Young Adult Disorders. *Arch Gen Psychiatry, 66*(7), 746-772.

Copeland, W. E., Wolke, D., Shanahan, L., & Costello, E. J. (2015). Adult Functional Outcomes of Common Childhood Psychiatric Problems: A Prospective, Longitudinal Study. *JAMA Psychiatry, 72*(9), 892-899. doi:10.1001/jamapsychiatry.2015.0730

Curran, P. J., & Hussong, A. M. (2003). The use of latent trajectory models in psychopathology research. *J Abnorm Psychol, 112*(4), 526-544. doi:10.1037/0021-843X.112.4.526

Edwards, A. C., Joinson, C., Dick, D. M., Kendler, K. S., Macleod, J., Munafò, M., . . . J., H. (2014). The Association Between Depressive Symptoms from Early to Late Adolescence and Later Use and Harmful Use of Alcohol. *Eur Child Adolesc Psychiatry, 23*, 1219-1230. doi:10.1007/s00787-014-0600-5

Euesden, J., Lewis, C. M., & O’Reilly, P. F. (2015). PRSice: Polygenic Risk Score software. *Bioinformatics, 31*(9), 1466-1468. doi:10.1093/bioinformatics/btu848

Fergusson, D. M., Boden, J. M., & Horwood, J. (2007). Recurrence of major depression in adolescence and early adulthood, and later mental health, educational and economic outcomes. *Br J Psychiatry, 191*, 335-342. doi:10.1192/bjp.bp.107.036079

Fergusson, D. M., Horwood, L. J., Ridder, E. M., & Beautrais, A. L. (2005). Subthreshold Depression in Adolescence and Mental Health Outcomes in Adulthood. *Arch Gen Psychiatry, 62*(1), 66-72.

Flint, J., & Kendler, K. S. (2014). The genetics of major depression. *Neuron, 81*(3), 484-503. doi:10.1016/j.neuron.2014.01.027

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., . . . Lawlor, D. A. (2013). Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol, 42*(1), 97-110. doi:10.1093/ije/dys066

Halldorsdotir, T., Piechaczek, C., Soares de Matos, A. P., Czamara, D., Pehl, V., Wagenbuechler, P., . . . Binder, E. B. (2019). Polygenic Risk: Predicting Depression Outcomes in Clinical and Epidemiological Cohorts of Youths. *Am J Psychiatry, appiajp201918091014*. doi:10.1176/appi.ajp.2019.18091014
Hankin, B. L., Fraley, R. C., Lahey, B. B., & Waldman, I. D. (2005). Is depression best viewed as a continuum or discrete category? A taxometric analysis of childhood and adolescent depression in a population-based sample. *J Abnorm Psychol, 114*(1), 96-110. doi:10.1037/0021-843X.114.1.96

Hannigan, L. J., Walaker, N., Waszczuk, M. A., McAdams, T. A., & Eley, T. C. (2017). Aetiological influences on stability and change in emotional and behavioural problems across development: a systematic review. *Psychopathol Rev, 4*(1), 52-108. doi:10.5127/pr.038315

Hatoun, A. S., Rhee, S. H., Corley, R. P., Hewitt, J. K., & Friedman, N. P. (2018). Etiology of Stability and Growth of Internalizing and Externalizing Behavior Problems Across Childhood and Adolescence. *Behav Genet, 48*(4), 298-314. doi:10.1007/s10519-018-9900-8

Hedeker, D., & Gibbons, R. D. (2006). *Longitudinal Data Analysis*. Hoboken, New Jersey: John Wiley & Sons, Inc.

Hill, R. M., Pettit, J. W., Lewinsohn, P. M., Seeley, J. R., & Klein, D. N. (2014). Escalation to Major Depressive Disorder among adolescents with subthreshold depressive symptoms: evidence of distinct subgroups at risk. *J Affect Disord, 158*, 133-138. doi:10.1016/j.jad.2014.02.011

Howard, D. M., Adams, M. J., Clarke, T. K., Hafferty, J. D., Gibson, J., Shirali, M., . . . McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci, 22*(3), 343-352. doi:10.1038/s41593-018-0326-7

Howard, D. M., Adams, M. J., Shirali, M., Clarke, T. K., Marioni, R. E., Davies, G., . . . McIntosh, A. M. (2018). Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. *Nat Commun, 9*(1), 1470. doi:10.1038/s41467-018-0319-3

Jaffee, S. R., & Price, T. S. (2012). The implications of genotype-environment correlation for establishing causal processes in psychopathology. *Dev Psychopathol, 24*(4), 1253-1264. doi:10.1017/S0954579412000685

Kessler, R. C., Avenevoli, S., & Merikangas, K. R. (2001). Mood disorders in children and adolescents: an epidemiologic perspective. *Biological Psychiatry, 49*(12), 1002-1014.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry, 62*.

Khera, A. V., Chaffin, M., Wade, K. H., Zahid, S., Brancale, J., Xia, R., . . . Kathiresan, S. (2019). Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood. *Cell, 177*(3), 587-596 e589. doi:10.1016/j.cell.2019.03.028

Kwong, A. S. F., López-López, J. A., Hammerton, G., Manley, D., Timpson, N. J., Leckie, G., & Pearson, R. M. (2019). Genetic and Environmental Risk Factors Associated with Trajectories of Depressive Symptoms from Adolescence to Young Adulthood. *JAMA Netw Open, 2*(6). doi:10.1001/jamanetworkopen.2019.6587

Kwong, A. S. F., Maddalena, J. M., Croft, J., Heron, J., & Leckie, G. (2019). Childhood Trauma and Trajectories of Depressive Symptoms Across Adolescence *medRxiv*, 19002519. doi:https://doi.org/10.1101/19002519

Kwong, A. S. F., Manley, D., Timpson, N. J., Pearson, R. M., Heron, J., Sallis, H., . . . Leckie, G. (2019). Identifying Critical Points of Trajectories of Depressive Symptoms from Childhood to Young Adulthood. *J Youth Adolesc, 48*, 815-827. doi:10.1007/s10964-018-0976-5

Leckie, G., & Charlton, C. (2013). runmlwin: A Program to Run the MLwiN Multilevel Modeling Software from within Stata. *Journal of Statistical Software, 52*(11).

López-Lopez, J. A., Kwong, A. S. F., Pearson, R. M., Tilling, K. M., Fazel, M. S., Washbrook, L., . . . Hammerton, G. (In press). Trajectories of depressive symptoms through adolescence and
associations with education and employment: a growth mixture modelling approach. *British Journal of Psychiatry Open.*

Lubke, G. H., Miller, P. J., Verhulst, B., Bartels, M., van Beijsterveldt, T., Willemsen, G., ... Middeldorp, C. M. (2016). A powerful phenotype for gene-finding studies derived from trajectory analyses of symptoms of anxiety and depression between age seven and 18. *Am J Med Genet B Neuropsychiatr Genet, 171*(7), 948-957. doi:10.1002/ajmg.b.32375

Malhi, G. S., & Mann, J. J. (2018). Depression. *Lancet, 392,* 2299-2312. doi:10.1016/S0140-6736(18)31948-2

Martin, A. R., Daly, M. J., Robinson, E. B., Hyman, S. E., & Neale, B. M. (2018). Predicting Polygenic Risk of Psychiatric Disorders. *Biol Psychiatry.* doi:10.1016/j.biopsych.2018.12.015

Morris, T. T., Davies, N. M., & Davey Smith, G. (2019). Can education be personalised using pupils’ genetic data? *bioRxiv.* doi:https://www.biorxiv.org/content/10.1101/645218v1

Mostafavi, H., Harpak, A., Conley, D. C., Pritchard, J. K., & Przeworski, M. (2019). Variable prediction accuracy of polygenic scores within an ancestry group. *bioRxiv.* doi:https://www.biorxiv.org/content/10.1101/629949v1

Mullins, N., & Lewis, C. M. (2017). Genetics of Depression: Progress at Last. *Curr Psychiatry Rep, 19*(4), 43. doi:10.1007/s11920-017-0803-9

Nagel, M., Watanabe, K., Stringer, S., Posthuma, D., & van der Sluis, S. (2018). Item-level analyses reveal genetic heterogeneity in neuroticism. *Nat Commun, 9*(1), 905. doi:10.1038/s41467-018-03242-8

Nivard, M. G., Dolan, C. V., Kendler, K. S., Kan, K. J., Willemsen, G., van Beijsterveldt, C. E., ... Boomsma, D. I. (2015). Stability in symptoms of anxiety and depression as a function of genotype and environment: a longitudinal twin study from ages 3 to 63 years. *Psychol Med, 45*(5), 1039-1049. doi:10.1017/S003329171400213X

Northstone, K., Lewcock, M., Groom, A., Boyd, A., Macleod, J., Timpson, N., & Wells, N. (2019). The Avon Longitudinal Study of Parents and Children (ALSPAC): an update on the enrolled sample of index children in 2019. *Wellcome Open Res, 4,* 51. doi:10.12688/wellcomeopenres.15132.1

Okbay, A., Baselmans, B. M., De Neve, J. E., Turley, P., Nivard, M. G., Fontana, M. A., ... Cesarini, D. (2016). Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat Genet, 48*(6), 624-633. doi:10.1038/ng.3552

Paternoster, L., Howe, L. D., Tilling, K., Weedon, M. N., Freathy, R. M., Frayling, T. M., ... Lawlor, D. A. (2011). Adult height variants affect birth length and growth rate in children. *Hum Mol Genet, 20*(20), 4069-4075. doi:10.1093/hmg/ddr309

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience, 9*(12). doi:http://dx.doi.org/10.1038/nrn2513

Pine, D. S., Cohen, E., Cohen, P., & Brook, J. (1999). Adolescent depressive symptoms as predictors of adult depression moodiness or mood disorder? *Am J Psychiatry, 156,* 133-135.

Raudenbush, S. W., & Bryk, A. S. (2002). *Hierarchical Linear Models: Applications and Data Analysis Methods* (Second Edition ed.). Thousand Oaks, California: Sage Publications, Inc.

Rawana, J. S., & Morgan, A. S. (2014). Trajectories of depressive symptoms from adolescence to young adulthood: the role of self-esteem and body-related predictors. *J Youth Adolesc, 43*(4), 597-611. doi:10.1007/s10964-013-9995-4

Rice, F. (2009). The genetics of depression in childhood and adolescence. *Curr Psychiatry Rep, 11*(2), 167-173. doi:https://doi.org/10.1007/s11920-009-0026-9

Rice, F. (2014). *Genetic Influences on Depression and Anxiety in Childhood and Adolescence* (Vol. 2). New York, NY: Springer.
Rice, F., Harold, G., & Thapar, A. (2003). Negative life events as an account of age-related differences in the genetic aetiology of depression in childhood and adolescence. *J Child Psychol Psychiatry, 44*(7), 977-987.

Rice, F., Harold, G. T., & Thapar, A. (2002). Assessing the effects of age, sex and shared environment on the genetic aetiology of depression in childhood and adolescence. *J Child Psychol Psychiatry, 43*(8), 1039-1051. doi:10.1111/1469-7610.00231

Rice, F., Riglin, L., Lomax, T., Souter, E., Potter, R., Smith, D. J., . . . Thapar, A. (2019). Adolescent and adult differences in major depression symptom profiles. *J Affect Disord, 243*, 175-181. doi:10.1016/j.jad.2018.09.015

Rice, F., Riglin, L., Thapar, A. K., Heron, J., Anney, R., O’Donovan, M. C., & Thapar, A. (2018). Characterizing Developmental Trajectories and the Role of Neuropsychiatric Genetic Risk Variants in Early-Onset Depression. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2018.3338

Riglin, L., Collishaw, S., Richards, A., Thapar, A. K., Rice, F., Maughan, B., . . . Thapar, A. (2018). The impact of schizophrenia and mood disorder risk alleles on emotional problems: investigating change from childhood to middle age. *Psychol Med, 48*(13), 2153-2158. doi:10.1017/S0033291717003634

Rohde, P., Lewinsohn, P. M., Klein, D. N., Seeley, J. R., & Gau, J. M. (2013). Key Characteristics of Major Depressive Disorder Occurring in Childhood, Adolescence, Emerging Adulthood, Adulthood. *Clin Psychol Sci, 1*(1). doi:10.1177/2167702612457599

Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry, 47*(3-4), 276-295. doi:10.1111/j.1469-7610.2006.01614.x

Singer, J. D., & Willett, J. B. (2003). *Applied Longitudinal Data Analysis: Modelling Change and Event Occurrence*. New York: Oxford University Press.

Sullivan, P. F., Neale, M., & Kendler, K. S. (2000). Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry, 157*(10), 1552-1562.

Taylor, A. E., Jones, H. J., Sallis, H., Euesden, J., Stergiakouli, E., Davies, N. M., . . . Tilling, K. (2018). Exploring the association of genetic factors with participation in the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol*. doi:10.1093/ije/dyy060

Taylor, M., Simpkin, A. J., Haycock, P. C., Dudbridge, F., & Zuccolo, L. (2016). Exploration of a Polygenic Risk Score for Alcohol Consumption: A Longitudinal Analysis from the ALSPAC Cohort. *PLoS One, 11*(11), e0167360. doi:10.1371/journal.pone.0167360

Thapar, A., Collinshaw, S., Pine, D. S., & Thapar, A. J. (2012). Depression in adolescence. *Lancet, 379*, 1056-1067.

Thapar, A., & McGuffin, P. (1998). Validity of the shortened Mood and Feelings Questionnaire in a community sample of children and adolescents: a preliminary research note. *Psychiatry Research, 81*, 259-268.

Turner, N., Joinson, C., Peters, T., J., Wiles, N., & Lewis, G. (2014). Validity of the Short Mood and Feelings Questionnaire in Late Adolescence. *Psychological Assessment*. doi:10.1037/a0036572.supp

Warrington, N. M., Howe, L. D., Wu, Y. Y., Timpson, N. J., Tilling, K., Pennell, C. E., . . . Briollais, L. (2013). Association of a body mass index genetic risk score with growth throughout childhood and adolescence. *PLoS One, 8*(11), e79547. doi:10.1371/journal.pone.0079547

Warrington, N. M., Wu, Y. Y., Pennell, C. E., Marsh, J. A., Beilin, L. J., Palmer, L. J., . . . Briollais, L. (2013). Modelling BMI trajectories in children for genetic association studies. *PLoS One, 8*(1), e53897. doi:10.1371/journal.pone.0053897

Weissman, M. M., Wickramaratne, P., Nomura, Y., Warner, V., Pilowsky, D., & Verdeli, H. (2006). Offspring of Depressed Parents 20 Years Later. *Am J Psychiatry, 163*(6), 1001-1008.
WHO. (2012). Depression: A Global Crisis.

Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., . . . Major Depressive Disorder Working Group of the Psychiatric Genomics, C. (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet, 50*(5), 668-681. doi:10.1038/s41588-018-0090-3
### Tables and Figures

**Table 1.** Descriptive statistics of the Short Mood and Feelings Questionnaire (SMFQ) between those with and without genetic data (PRS)

| Occasion (Total N) | N Without PRS | N With PRS | Mean Age Without PRS | Mean Age With PRS | Mean SMFQ Without PRS | Mean SMFQ With PRS | Source of SMFQ |
|--------------------|---------------|------------|----------------------|-------------------|-----------------------|-------------------|----------------|
| 1 (N = 7,364)      | 2,040         | 5,324      | 10.67 (0.29)         | 10.64 (0.25)      | 4.15 (3.55)           | 4.00 (3.49)       | Clinic         |
| 2 (N = 6,716)      | 1,785         | 4,931      | 12.83 (0.24)         | 12.81 (0.23)      | 4.05 (3.90)           | 3.94 (3.84)       | Clinic         |
| 3 (N = 6,019)      | 1,521         | 4,498      | 13.85 (0.22)         | 13.83 (0.21)      | 4.91 (4.49)           | 4.92 (4.49)       | Clinic         |
| 4 (N = 4,997)      | 1,470         | 3,527      | 16.68 (0.24)         | 16.68 (0.24)      | 6.04 (5.66)           | 5.85 (5.63)       | Questionnaire  |
| 5 (N = 4,497)      | 1,284         | 3,213      | 17.89 (0.45)         | 17.82 (0.37)      | 6.79 (5.33)           | 6.50 (5.21)       | Clinic         |
| 6 (N = 3,335)      | 946           | 2,389      | 18.67 (0.49)         | 18.64 (0.49)      | 7.05 (6.12)           | 6.73 (5.85)       | Questionnaire  |
| 7 (N = 3,305)      | 925           | 2,380      | 21.97 (0.53)         | 21.95 (0.52)      | 6.05 (5.84)           | 5.56 (5.46)       | Questionnaire  |
| 8 (N = 3,856)      | 1,149         | 2,707      | 22.92 (0.53)         | 22.88 (0.51)      | 6.54 (5.87)           | 6.07 (5.40)       | Questionnaire  |
| 9 (N = 3,915)      | 1,178         | 2,737      | 23.89 (0.52)         | 23.86 (0.51)      | 7.48 (6.38)           | 6.84 (5.91)       | Questionnaire  |

PRS: Polygenic Risk Score. Standard deviations are given in (parenthesis).
Table 2. Association between the depressive symptoms PRS and depressive symptoms at various across adolescence

| Age  | PRS Beta (95% CIs) | FDR p Value | ΔR² (95% CIs) | Predicted SMFQ Score (95% CIs) | Predicted SMFQ Score with PRS (95% CIs) |
|------|-------------------|-------------|---------------|-----------------------------|-----------------------------------------|
| 10.67 | 0.091 (-0.003, 0.185) | 0.121 | 0.07% (0.05%, 0.09%) | 4.19 (4.02, 4.37) | 4.29 (4.09, 4.48) |
| 12.81 | 0.145 (0.038, 0.252) | 0.024 | 0.14% (0.11%, 0.17%) | 3.47 (3.27, 3.68) | 3.62 (3.39, 3.85) |
| 13.83 | 0.163 (0.034, 0.292) | 0.035 | 0.13% (0.08%, 0.18%) | 3.94 (3.69, 4.19) | 4.11 (3.83, 4.39) |
| 16.68 | 0.349 (0.170, 0.528) | 0.0009 | 0.39% (0.35%, 0.43%) | 4.19 (3.84, 4.55) | 4.54 (4.14, 4.94) |
| 17.82 | 0.364 (0.186, 0.543) | 0.0008 | 0.48% (0.44%, 0.52%) | 5.72 (5.36, 6.07) | 6.08 (5.68, 6.48) |
| 18.64 | 0.453 (0.225, 0.681) | 0.0007 | 0.61% (0.47%, 0.76%) | 5.43 (4.96, 5.91) | 5.89 (5.36, 6.41) |
| 21.95 | 0.371 (0.153, 0.590) | 0.005 | 0.47% (0.35%, 0.58%) | 4.86 (4.41, 5.31) | 5.23 (4.73, 5.73) |
| 22.88 | 0.427 (0.224, 0.630) | 0.002 | 0.61% (0.47%, 0.77%) | 5.2 (4.78, 5.62) | 5.63 (5.16, 6.10) |
| 23.86 | 0.608 (0.389, 0.828) | 2.12x10^{-6} | 1.07% (0.76%, 1.37%) | 5.91 (5.45, 6.36) | 6.51 (6.00, 7.02) |

PRS: Polygenic Risk Score; FDR: False Discovery Rate. Upper and lower 95% confidence intervals for the beta are given in (parenthesis). Incremental $R^2$ ($\Delta R^2$) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models. The confidence intervals for $\Delta R^2$ were derived using bootstrapping with 1000 repetitions. The average beta and $\Delta R^2$ were calculated by taking the average across all occasions.
Table 3. Comparisons across multiple ages between trajectories that were +/- 1 SD Above for the PRS (N=6,305)

| Age  | Low DS PRS Estimate (95% CIs) | High DS PRS Estimate (95% CIs) | Difference Estimate (95% CIs) | p Value  | FDR p Value |
|------|-------------------------------|-------------------------------|-------------------------------|----------|-------------|
| 10.67| 3.54 (3.36, 3.71)             | 3.73 (3.56, 3.91)             | 0.2 (0.01, 0.38)              | 0.036    | 0.036       |
| 12.81| 3.71 (3.53, 3.89)             | 3.98 (3.80, 4.16)             | 0.27 (0.07, 0.46)             | 0.007    | 0.008       |
| 13.83| 4.23 (4.04, 4.41)             | 4.62 (4.43, 4.80)             | 0.39 (0.19, 0.59)             | 0.0001   | 0.0001      |
| 16.68| 5.54 (5.32, 5.77)             | 6.28 (6.06, 6.51)             | 0.74 (0.47, 1.01)             | 6.67x10^{-08} | 2.0x10^{-07} |
| 17.82| 5.73 (5.50, 5.96)             | 6.55 (6.32, 6.79)             | 0.82 (0.54, 1.11)             | 1.10x10^{-08} | 4.95x10^{-08} |
| 18.64| 5.72 (5.48, 5.95)             | 6.58 (6.34, 6.81)             | 0.86 (0.57, 1.15)             | 5.67x10^{-09} | 5.10x10^{-08} |
| 21.95| 5.15 (4.89, 5.42)             | 6.01 (5.74, 6.28)             | 0.86 (0.52, 1.19)             | 4.96x10^{-07} | 7.44x10^{-07} |
| 22.88| 5.24 (4.99, 5.50)             | 6.12 (5.86, 6.39)             | 0.88 (0.56, 1.21)             | 9.35x10^{-08} | 2.10x10^{-07} |
| 23.86| 5.75 (5.46, 6.03)             | 6.71 (6.42, 7.0)              | 0.96 (0.59, 1.33)             | 4.13x10^{-07} | 7.43x10^{-07} |

PRS: Polygenic Risk Score. DS: Depressive Symptoms. FDR: False Discovery Rate. Upper and lower 95% confidence intervals for the estimates are given in (parenthesis). The low PRS was for trajectories which were 1 SD below. The high PRS was for trajectories which were 1 SD above. Differences were calculated using the delta method. Analysis were adjusted for sex and the first ten principal components of ancestry.
**Figure 1.** Cross-sectional analysis between the depressive symptoms PRS and depressive symptoms across adolescence with predicted SMFQ scores

PRS: Polygenic Risk Score (with a threshold of 0.005). SMFQ: Short Mood and Feelings Questionnaire (depressive symptoms). Analysis were adjusted for sex, age and the first ten principal components of ancestry.
**Figure 2.** Association between depressive symptoms PRS and trajectories of depressive symptoms

PRS: Polygenic Risk Score (with a threshold of 0.005). SMFQ: Short Mood and Feelings Questionnaire (depressive symptoms). Averaged population trajectories of depressive symptoms for greater and less genetic liability (+/- 1 SD PRS [PT = 0.005]). Analysis were adjusted for sex and the first ten principal components of ancestry.
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