NEW RESEARCH

Independent Prediction of Child Psychiatric Symptoms by Maternal Mental Health and Child Polygenic Risk Scores

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Objective: Prenatal maternal symptoms of depression and anxiety are associated with an increased risk for child socioemotional and behavioral difficulties, supporting the fetal origins of mental health hypothesis. However, to date, studies have not considered specific genomic risk as a possible confound.

Method: The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (n = 5,546) was used to test if child polygenic risk score for attention-deficit/hyperactivity disorder (ADHD), schizophrenia, or depression confounds or modifies the impact of prenatal maternal depression and anxiety on child internalizing, externalizing, and total emotional/behavioral symptoms from age 4 to 16 years. Longitudinal child and adolescent symptom data were analyzed in the ALSPAC cohort using generalized estimating equations. Replication analyses were done in an independent cohort (Prevention of Preeclampsia and Intrauterine Growth Restriction [PREDO] cohort; n = 514) from Finland, which provided complementary measures of maternal mental health and child psychiatric symptoms.

Results: Maternal depression and anxiety and child polygenic risk scores independently and additively predicted behavioral and emotional symptoms from childhood through mid-adolescence. There was a robust prediction of child and adolescent symptoms from both prenatal maternal depression (generalized estimating equation estimate = 0.093, 95% CI 0.065-0.121, $p = 2.66 \times 10^{-10}$) and anxiety (generalized estimating equation estimate = 0.065, 95% CI 0.037-0.093, $p = 1.62 \times 10^{-5}$) after adjusting for child genomic risk for mental disorders. There was a similar independent effect of maternal depression ($B = 0.156$, 95% CI 0.066-0.246, $p = .001$) on child symptoms in the PREDO cohort. Genetically informed sensitivity analyses suggest that shared genetic risk only partially explains the reported association between prenatal maternal depression and offspring mental health.

Conclusion: These findings highlight the genomic contribution to the fetal origins of mental health hypothesis and further evidence that prenatal maternal depression and anxiety are robust in utero risks for child and adolescent psychiatric symptoms.

Key words: ALSPAC; child development; fetal origins of mental health; maternal depression; polygenic risk score

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Prenatal maternal depression and anxiety affect approximately 15% of pregnant women worldwide.[1] Children exposed to prenatal maternal depression or anxiety have a significantly increased risk of developing clinically significant mental health problems across childhood into adolescence[2] and early adulthood.[3,4] In addition to these human costs is the economic impact of untreated perinatal mental illness, estimated at $18 billion a year in the United States alone,[5] which is largely derived from the adverse effects of untreated maternal perinatal mental illness on child mental health outcomes.[6] These findings extend the fetal origins hypothesis, proposed by Barker *et al.*[7-9] and initially applied to coronary heart disease, to highlight the persisting influence of the prenatal period on offspring mental health.[10]

Notwithstanding the number of studies linking prenatal maternal affective symptoms with child behavioral and emotional symptoms, questions have been raised about a causal connection because of the reliance on observational study designs.[11] A limited number of studies have sought to assess genetic confounding using assisted reproduction or sibling/twin designs, with mixed findings.[12,13] The very sizable literature on prenatal depression and anxiety and child mental health has largely ignored genomic risk

(although see references[14-16]), leaving untested an important alternative hypothesis for the presumed effect of in utero exposure to maternal affective symptoms.

Polygenic risk scores (PRSs) provide a single measure of genomic risk for complex phenotypes, eg, attention-deficit/hyperactivity disorder (ADHD), and are derived from the summation of multiple single nucleotide polymorphisms (SNPs) weighted by the degree of their association with a disorder of interest.[17] Such scores show improved predictive value for a range of mental health disorders, including ADHD and externalizing symptoms,[18,19] schizophrenia, and depression,[20] than any one genetic variant alone, emphasizing the polygenic basis of these conditions.

In this study, we capitalized on more than a decade of longitudinal data, spanning distinct developmental stages, with direct assessments of genomic variation in more than 5,000 children across 2 cohorts.[21-23] We used established PRSs and a novel statistical approach (genetic sensitivity analysis[24]) to determine if genetic confounding underlies the association between prenatal maternal affective symptoms and offspring mental health.

METHOD

Participants

Data for this study are part of the Avon Longitudinal Study of Parents and Children (ALSPAC)[21,22]; details of the ALSPAC are available at https://www.bristol.ac.uk/alspac/. Pregnant women from the Avon region around Bristol, United Kingdom, between April 1, 1991, and December 31, 1992, were invited to participate in the study. The study cohort consisted of 15,454 pregnancies and 14,901 children who were still alive at 1 year of age. The current analyses focus on mothers and their children who provided measures of maternal mood, child genetic variation, and maternal ratings of their child's socioemotional and behavioral difficulties. Written informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Consent for biological samples was collected in accordance with the Human Tissue Act (2004). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. A fully searchable data dictionary and variable search tool are provided through the ALSPAC study website (https://www.bristol.ac.uk/alspac/researchers/our-data/).

Exclusion criteria for the current study included nonsingleton births (ie, twins; n = 87), very preterm births (<32 weeks' gestational age; n = 42), low birth weight (<1500 g; n=35), and parent-reported child ethnicity other than White (n = 18). A total of 7,975 children of European ancestry were genotyped in the ALSPAC cohort. We focused our analyses on children for whom symptom data on socioemotional and behavioral problems were available for at least one time point. After further excluding participants with missing data for maternal or child mental health phenotypes, missing genetic data, and relevant covariates (eg, household crowding, prenatal smoking or alcohol consumption), 4,980 participants were available for our primary analyses (see Figure S1, available online).

Child Mental Health

Maternal reports of child mental health symptoms were obtained using the Strengths and Difficulties Questionnaire (SDQ),[25] measured at 4, 7, 8, 9, 11, 13, and 16 years of age. Total emotional/behavioral problems were assessed using the total SDQ score, where higher values indicate greater problems. Externalizing problems were assessed by combining the inattention/hyperactivity subscale and the conduct problems subscale scores.[26] Internalizing problems were assessed by combining the emotional symptoms subscale and the peer problems subscale scores.[26] A nationally representative survey in the United Kingdom indicated that a total SDQ score $\geq$14 indicates elevated symptom levels, while a total SDQ score $\geq$17 is consistent with high/very high clinical risk.[25]

Maternal Symptoms of Depression and Anxiety

Maternal depressive symptoms at 32 weeks of gestation were assessed using the Edinburgh Postnatal Depression Scale (EPDS).[27] The EPDS is a 10-item questionnaire that provides a total score ranging from 0 to 30. Secondary analyses focused on maternal symptoms of anxiety, which were assessed using the Crown Crisp Experiential Index (CCEI) also at 32 weeks of gestation. The CCEI is a well-validated self-rating inventory with a total score ranging from 0 to 16.[28]

Polygenic Risk Scores

We focused our PRSs on publicly available summary statistics from large-scale genome-wide association studies (GWASs) of depression,[29] ADHD,[17] and schizophrenia,[30] disorders that have previously been associated with exposure to prenatal adversity.[31] In the present study, we used the PRSs for depression and ADHD as indicators of individual-level genetic risk for internalizing and externalizing symptoms, respectively; the schizophrenia PRS provides a measure of genetic risk for a severe neurodevelopmental disorder.

Following extensive genotype quality control and imputation of missing genotypes, genetic data from 8,530,392 autosomal SNPs in the ALSPAC cohort were available for the PRS computation (see Supplement 1, available online, for further details). PRSs were calculated using a conventional

weighted sum approach. Risk alleles and their respective weights (ie, the effect size for the association between a risk allele and a disorder of interest) were identified using summary statistics from recent large-scale GWASs of ADHD,[17] schizophrenia,[30] and depression.[29] PRSs for ADHD and schizophrenia focused on the top 10,000 SNPs identified from the GWASs of ADHD and schizophrenia. The PRS for depression contained 6,159 SNPs, which represented all depression-associated SNPs made publicly available by Turley *et al.*[29] (see Supplement 1, available online).

Covariates

We prioritized covariates to ensure our genetically informed analyses were comparable to earlier studies, which reported associations between prenatal maternal mental health and child SDQ scores in the ALSPAC cohort.[2,16] All models included child biological sex recorded from birth records, gestational age at birth in weeks, birth weight in grams, maternal age at delivery, a 4-level household crowding index (derived from the number of household members per room), a 4-level measure of maternal educational attainment at the time of pregnancy (based on the United Kingdom education system, ie, certificate of secondary education/vocational, O level, A level, or a higher degree), prenatal maternal smoking (yes/no) and alcohol use, and maternal symptoms of depression (EPDS) or anxiety (CCEI) at 8 months postnatally and at approximately 3 years after delivery; the last-mentioned measures at 3 years postpartum were included to adjust for maternal mental health symptoms proximal to the first assessment of child mental health at 4 years of age. We used principal component analysis of genetic data to describe genetic ancestry in the ALSPAC cohort[32,33] and included the top 10 principal components in our analyses.

Statistical Analyses

To capitalize on the rich longitudinal data within the ALSPAC cohort, we used the geepack R package[34] to build longitudinal models with generalized estimating equations (GEEs), which provide the population-averaged effect of an exposure on an outcome. GEE is particularly suited to repeated measures where the correlation structure violates assumptions required for parametric models. Children were included if measures of maternal mood, child genotype, and at least one SDQ time point were available for analysis. Child age at the time of the SDQ assessment (time) was considered in each model to examine developmental changes in child mental health symptoms. We also explored potential interactions between time and child PRS or prenatal maternal depression to test if the prediction of child outcome by prenatal maternal depression or child genomic risk varied across development. We report standardized GEE estimates (Est.), 95% CIs, and adjusted p values using Bonferroni correction adjusting for 3 tests (which corresponds to the number of different PRSs tested).

Missing Data Strategy. Primary analyses considered all participants who provided data on at least one SDQ time point (n = 4,980). For comparison, we also performed an analysis on a subset of complete cases (n range from 2,443 to 2,472). Finally, we performed multivariate imputations by chained equations with 20 imputed dataset iterations using the mice R package.[35] We used all available SDQ data to inform the imputation of missing values. GEE analyses were repeated across each of the 20 imputed datasets with pooled effect sizes and CIs reported.

Genetic Sensitivity Analysis. PRSs represent individual-level measures of genomic risk for complex phenotypes. However, PRSs rarely account for the proportion of variance in any outcome as might be expected based on measures of heritability, eg, calculated from large-scale GWASs. Thus, PRSs may bias analyses of genetic confounding by underestimating the contribution of shared genetic risk to child mental health. To address this issue, we performed genetic sensitivity analyses using the Gsens R package.[24] Gsens uses structural equation modeling to create a latent genetic factor that accounts for the expected proportion of variance in an outcome of interest (eg, ADHD) based on an established heritability estimate for that phenotype (eg, from a preexisting GWAS). Gsens provides an adjusted effect size estimate for the association between an exposure and the dependent variable after accounting for potential genetic confounding. We focused our Gsens analyses on child internalizing symptoms (as a proxy for depression), externalizing symptoms (as a proxy for ADHD), and total SDQ scores as an index of the burden of mental health symptoms. We used the corresponding SNP-based heritability estimates for depression ($h^2 = 0.089$)[36] and ADHD ($h^2 = 0.216$)[17] in Gsens models of child internalizing and externalizing symptoms, respectively. For Gsens analyses of total SDQ scores, we used an average heritability estimate ($h^2 = 0.178$) combining across heritability estimates for depression,[36] ADHD,[17] and schizophrenia ($h^2 = 0.23$).[37] Finally, we also considered a Gsens model of total SDQ scores using a measure of SNP-based heritability from a recently published GWAS of total child psychiatric symptoms ($h^2 = 0.054$).[38]

Additional Sensitivity Analyses. Our study relies on maternal report of both the exposure (prenatal depression)

and the outcome (child SDQ scores). We sought to determine if reporter bias influenced our findings using 2 approaches. First, we repeated our primary analyses replacing maternal depression in early childhood (proximal to the first SDQ time point) with a measure of maternal depression in mid-childhood (at 8 years; n = 4,351). Second, we excluded any mother who reported clinical symptoms of depression (EPDS ≥13) at any point in the postpartum period (8 months), early childhood (3, 5, or 6 years), or mid-childhood (8 or 11 years) to avoid a potential confound between severe maternal depression and maternal ratings of child symptoms (1,227 mothers excluded).

Replication Analyses

We computed PRSs for ADHD, schizophrenia, and depression using genetic data from the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) cohort (n = 514) (see Supplement 1, available online), a prospective Finnish pregnancy cohort with detailed phenotyping of maternal mental health and child development.[23] Prenatal maternal depression was measured biweekly during the third trimester of pregnancy between 28 and 39 weeks of gestation using the Center for Epidemiologic Studies Depression Scale (CES-D).[39] Maternal reports of child mental health symptoms were provided using the Preschool and School-Age versions of the Child Behavior Checklist[40,41] total problems t scores in early childhood and later in early school age, respectively (median ages at the 2 follow-ups = 3.4 and 8.7 years). We used linear regression models to test if prenatal maternal depression during the third trimester predicted child total psychiatric symptom scores across early and later childhood, independent of child PRSs for ADHD, schizophrenia, and/or depression and covariates (maternal education, maternal age at delivery, substance use during early pregnancy, birth weight and gestational age, child age at follow-up, child sex, and maternal symptoms of depression at the time of child assessment). Prediction models also included the top 10 principal component scores to adjust for genetic ancestry. Independent and dependent variables were expressed in standard deviation units to facilitate the comparison of effect sizes. The PREDO study protocol was approved by the Ethics Committee of Obstetrics and Gynaecology and Women, Children and Psychiatry of the Helsinki and Uusimaa Hospital District and by the participating hospitals. All participants provided written informed consent. Consent of participating children was provided by the parent/guardian. The authors assert that all procedures contributing to this work (across both cohorts) comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

Demographics

Table 1 shows the demographic information of the children considered in our analyses contrasted with the remainder of the ALSPAC cohort. The children in the subsample available for our analyses were born to older mothers with lower household crowding and higher birth weight and who reported lower levels of prenatal depression and anxiety both in pregnancy and in the postpartum assessments. Differences, although statistically reliable, were generally modest. Among the study participants from ALSPAC, 10% to 12% of the mothers had prenatal depressive symptoms of clinical concern, and 4% to 6% of the children had high or very high total SDQ scores between ages 4 and 16 (Table 2). See Table S1, available online, for the prevalence of clinical severity in the PREDO cohort.

Table S2, available online, describes the bivariate associations between our predictors and outcomes of interest. Prenatal maternal affective symptoms were only weakly correlated with child PRSs (all $r \leq 0.069$), providing little evidence of gene–environment correlation (see Supplement 1, available online).

Longitudinal Analysis of Child Mental Health

We tested if prenatal maternal depression symptoms predicted symptoms from early childhood through mid-adolescence in GEE models that did not consider child PRSs. These analyses revealed a consistent, positive association between prenatal maternal depression and increased symptom scores with the strongest effect size observed for child total symptoms (Est. = 0.090, 95% CI 0.066-0.114, adjusted $p = 2.66 \times 10^{-10}$) (see Table S3, available online). Next, we asked if such effects were confounded by child PRSs for psychiatric disorders. Prenatal maternal depression predicted child total, externalizing, and internalizing symptoms independent of covariates and child PRSs for depression, ADHD, or schizophrenia (Table 3 and Figure 1; see Figure S2, available online). Our findings did not depend on the number of SNPs included in our PRSs (see Supplement 1, available online).

We also explored child PRSs as potential effect modifiers by testing the interaction between child PRSs and prenatal maternal depression in the prediction of child symptoms. Child PRSs for ADHD, schizophrenia, or depression did not moderate the association between prenatal maternal depression and child symptoms (all interaction terms $p > .10$) (Table 4). Next, we tested if child

TABLE 1 Study Cohort Characteristics

	ALSPAC PRS cohort		ALSPAC cohort (incomplete data)	
	n	(%)	n	(%)
Participants (% female)	4,980	(49.1)	6,030	(48.2)
	Mean	(SD)	Mean	(SD)
Gestational weeks	39.6	(1.6)	39.6	(1.6)
Birth weight, g[a]	3,474	(491)	3,438	(509)
Maternal age at birth, y[a]	29.4	(4.4)	27.5	(5.0)
	%		%	
Crowding index[a,b]				
(0, 0.5]	50.3		35.0	
(0.5, 0.75]	31.3		29.5	
(0.75, 1]	15.0		21.0	
	3.4		7.0	
Maternal highest education qualification[a,b]				
CSE/vocational	19.7		35.7	
O-level	35.1		35.5	
A-level	27.1		19.2	
University degree	18.1		8.7	
Maternal alcohol consumption during pregnancy[a,b]				
Never	43.3		43.5	
	41.3		36.4	
≥1 drinks per week	15.4		15.1	
Mothers who smoked cigarettes during pregnancy[a]	17.3		26.4	
	Mean	(SD)	Mean	(SD)
Maternal mood during pregnancy				
EPDS depression score[a]	6.4	(4.8)	7.3	(5.2)
CCEI anxiety score[a]	4.7	(3.4)	5.3	(3.7)
Maternal mood postnatally at 8 months				
EPDS depression score[a]	5.0	(4.5)	5.6	(4.8)
CCEI anxiety score[a]	3.4	(3.2)	3.7	(3.4)

Note: Descriptive statistics for participants included in the current analysis (ALSPAC PRS cohort) vs the rest of the ALSPAC cohort that met the selection criteria but had missing data for any predictors or covariates. See Figure S1 for further details. ALSPAC = Avon Longitudinal Study of Parents and Children; CCEI = Crown Crisp Experiential Index; CSE = Certificate of Secondary Education; EPDS = Edinburgh Postnatal Depression Scale; PRS = polygenic risk score.

[a]*$p < .001$ between sample groups using χ^2 or t tests.*

[b]*Total percentage is <100% due to missing data in the excluded samples.*

TABLE 2 Maternal and Child and Adolescent Mental Health Symptoms in the Avon Longitudinal Study of Parents and Children (ALSPAC)

	Age 4 years (n = 4,714)		Age 16 years (n = 3,180)	
	Mean	(SD)	Mean	(SD)
Prenatal maternal depression				
EPDS score	6.40	(4.8)	6.18	(4.6)
	n	(%)	n	(%)
Normal	4,160	(88.2)	2,860	(89.9)
Of clinical concern	554	(11.8)	320	(10.1)
	Mean	(SD)	Mean	(SD)
Child mental health symptoms				
Total SDQ score	8.59	(4.5)	5.95	(4.6)
	n	(%)	n	(%)
Normal	4,059	(86.1)	2,943	(92.5)
Raised	376	(8.0)	121	(3.8)
High/very high	279	(5.9)	116	(3.7)

Note: Symptoms of depression of clinical concern are defined as EPDS score ≥13. Child and adolescent mental health symptom severity is defined by the total SDQ score ranging from low/normal (0–13), raised (14–16), to high/very high (17–40). EPDS = Edinburgh Postnatal Depression Scale; SDQ = Strengths and Difficulties Questionnaire.

biological sex moderated the association between prenatal maternal depression or child PRS and child symptoms: it did not (see Table S4, available online).

Time-Varying Effects of Child PRSs and Prenatal Depression on Child Mental Health

We asked if the prediction of child outcomes by prenatal maternal symptoms of depression or child PRSs changed across development. The association between prenatal maternal depression and child symptoms did not change significantly over time (all prenatal depression × time interaction terms $p > .10$). In contrast, GEE models revealed a significant interaction between time and specific child PRSs in the prediction of child symptoms (Table 3). Namely, the association between child depression PRS and total SDQ score (Est. = 0.052, 95% CI 0.020-0.083, adjusted $p = 3.93 \times 10^{-3}$) and externalizing symptoms (Est. = 0.044, 95% CI 0.013-0.074, adjusted $p = .015$) strengthened over time. Similarly, the association between child schizophrenia PRS and externalizing symptoms (Est. = 0.053, 95% CI 0.023-0.082, adjusted $p = 1.40 \times 10^{-3}$) strengthened over time (Table 3), with a similar trend observed in the prediction of total symptoms (Est. = 0.036, 95% CI 0.006-0.066, adjusted $p = .060$).

Finally, we sought to determine if our primary findings extended to an independent cohort. In line with our findings from the ALSPAC cohort, the positive association between prenatal maternal depression and child average total psychiatric symptoms across early and later childhood

observed in the PREDO cohort was independent of child PRSs for ADHD, schizophrenia, or depression (see Table S5, available online).

Prenatal Maternal Anxiety

Prenatal maternal depression and anxiety were highly intercorrelated ($r = 0.754$, $p < 2.0 \times 10^{-10}$). Replacing prenatal maternal depression with prenatal maternal anxiety in our GEE models yielded very similar results (see Table S6 and Figure S3, available online).

Clinically Significant Child Symptoms

We used logistic regression models to predict elevated child and adolescent mental health symptoms (SDQ total score $\geq$14). Elevated prenatal maternal depression (EPDS $\geq$13; 12% of mothers) or anxiety (CCEI $\geq$9; 14% of mothers) was associated with a significantly increased risk of elevated mental health symptoms in children at 4 years of age (adjusted odds ratio for prenatal depression = 1.51 and prenatal anxiety = 1.62) and 16 years of age (adjusted odds ratio for prenatal depression =1.78 and prenatal anxiety = 1.70), after adjustment for covariates and the 3 child PRSs (see Supplement 1, available online).

Sensitivity Analyses

Genetic Sensitivity Analyses. We used genetic sensitivity analysis to probe further potential genetic confounding of the association between prenatal maternal mental health and child SDQ scores at 4 or 16 years of age (see Table S7, available online). We observed a significant main effect of prenatal maternal depression on child and adolescent symptoms at the majority of time points after accounting for genetic confounding (using a latent genetic factor based on SNP-based heritability estimates for depression, ADHD, and schizophrenia). These analyses also suggest a significant contribution of shared genetic risk factors to child symptoms. Shared genetic risk factors accounted for 43% and 46% of the association between prenatal maternal depression and externalizing symptoms at 4 and 16 years of age, respectively. Similarly shared genetic risk factors may account for 42% of the association between prenatal maternal depression and internalizing symptoms at age 16 years. Likewise, genetic confounding explained 45% and 48% of the association between prenatal maternal depression and total SDQ score at 4 and 16 years of age, respectively. Using a recent and alternative heritability estimate for child total psychiatric symptoms[38] suggested that genetic confounding explained approximately 15% of the variance in the association between prenatal maternal depression and child total SDQ score at 4 and 16 years of age. Adjusting Gsens models for sex and genetic principal components or when using PRSs with a greater number of SNPs (ie, a higher p value threshold) gave similar results (see Table S7, available online).

Impact of Maternal Mental Health on Ratings of Child Symptoms. To examine potential rater bias, we excluded all mothers who reported clinically significant symptoms of depression at any postpartum time point (from 8 weeks postpartum to child age 16 years; n = 2,467). The exclusion of these cases did not alter our main findings (see Table S8, available online).

Missing Data. The proportion of missing outcome data (SDQ scores) varied from 9% (at 4 years) to 38% (at 16 years). SDQ data were not missing completely at random (Little's missing completely at random [MCAR] test[42]: $\chi^2 = 1{,}892$, $p < 2.0 \times 10^{-10}$). We tested if this selective attrition influenced our main findings and found largely consistent findings using a complete case analysis and a series of datasets with imputation of missing SDQ data (see Supplement 1 and Table S9, available online).

DISCUSSION

We found that prenatal maternal affective symptoms were persistently associated with child and adolescent mental health independent of child PRSs for psychiatric disorders. Prenatal maternal affective symptoms and genetic risk were independently and additively (and not multiplicatively) associated with symptoms of common psychiatric disorders in children. The results provide a novel test of a genetic confound for the putative causal association between prenatal maternal mental health and child mental health and extend previous research by demonstrating a distinct risk of in utero exposure—a key component of the fetal origins of mental health hypothesis.

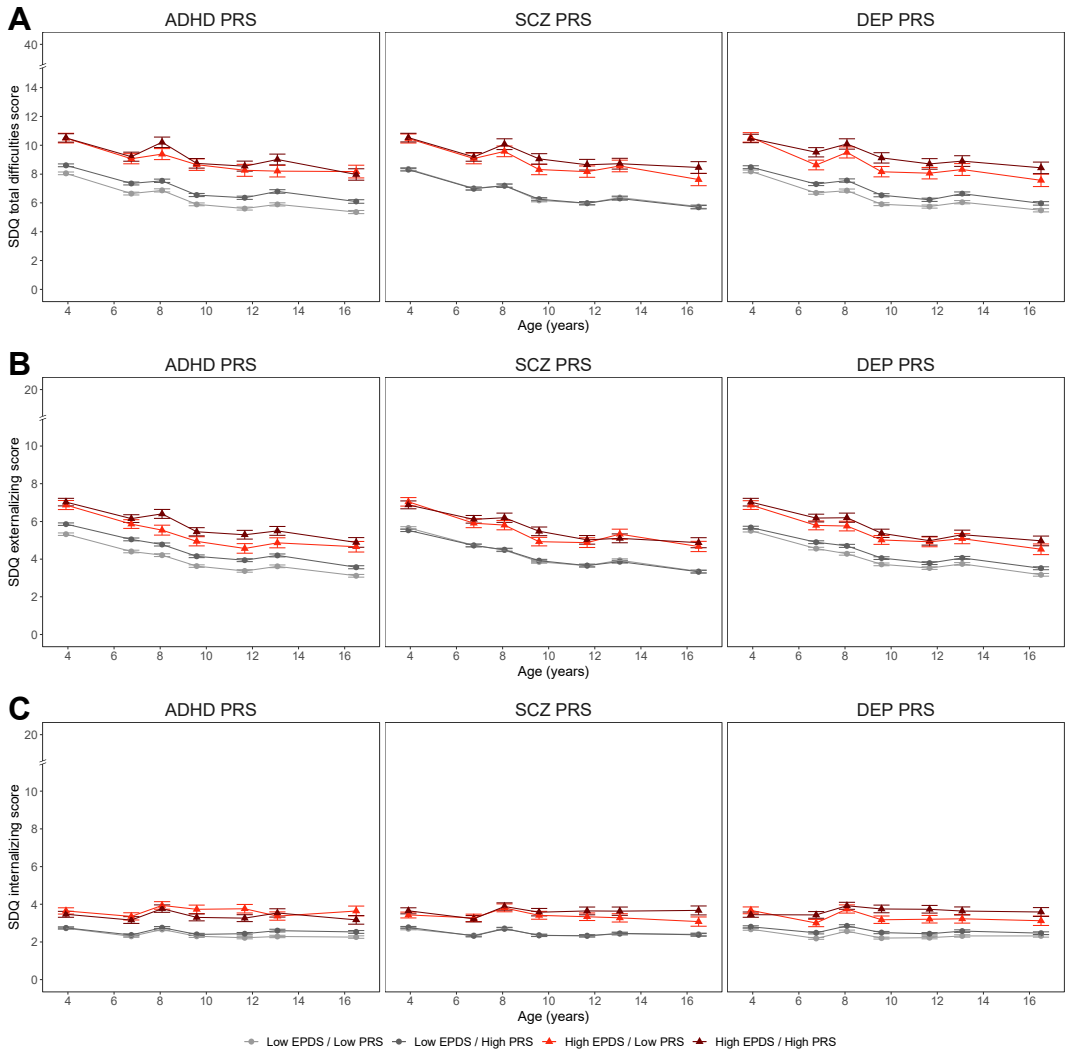
Our findings document prenatal maternal mood as a robust risk factor for child and adolescent psychiatric symptoms in 2 independent cohorts and provide some of the strongest evidence to date for supporting mental health during pregnancy for maternal and child health outcomes. In the ALSPAC cohort, child and adolescent total SDQ scores increased by approximately 0.1 point per 1-point increase in prenatal maternal EPDS score. Thus, after accounting for obstetric, socioeconomic, polygenic, and postnatal risk factors, including postpartum maternal depression, variation in prenatal maternal depression from low to very high exposure could account for a 3-point difference in child and adolescent total SDQ score. A nationally representative study in the United Kingdom found that every 1-point increase in total SDQ score was associated with a 1.28 increased odds of a childhood mental disorder,[25] which emphasizes the clinical significance of our findings.

TABLE 3 Integrated Longitudinal Models of Child Mental Health Symptoms

	Total problems			Externalizing problems			Internalizing problems		
	Est.	**(95% CI)**	**Adj. *p***	**Est.**	**(95% CI)**	**Adj. *p***	**Est.**	**(95% CI)**	**Adj. *p***
Additive models									
ADHD PRS model: SDQ ~ ADHD PRS + prenatal EPDS + time + covariates									
PRS	**0.055**	(0.034 to 0.075)	5.30×10^{-7}	**0.074**	(0.053 to 0.095)	$< 2.0 \times 10^{-10}$	0.010	(−0.010 to 0.030)	1.00
Prenatal EPDS	**0.093**	(0.065 to 0.121)	2.66×10^{-10}	**0.077**	(0.049 to 0.104)	1.69×10^{-7}	**0.079**	(0.052 to 0.107)	3.50×10^{-8}
Time	**−0.169**	(−0.180 to −0.158)	$< 2.0 \times 10^{-10}$	**−0.209**	(−0.220 to −0.198)	$< 2.0 \times 10^{-10}$	**−0.046**	(−0.058 to −0.034)	$< 2.0 \times 10^{-10}$
SCZ PRS model: SDQ ~ SCZ PRS + prenatal EPDS + time + covariates									
PRS	0.014	(−0.006 to 0.034)	.526	0.007	(−0.014 to 0.027)	1.00	0.017	(−0.003 to 0.037)	.305
Prenatal EPDS	**0.094**	(0.065 to 0.122)	2.19×10^{-10}	**0.077**	(0.050 to 0.105)	1.43×10^{-7}	**0.079**	(0.052 to 0.107)	3.32×10^{-8}
Time	**−0.169**	(−0.180 to −0.158)	$< 2.0 \times 10^{-10}$	**−0.209**	(−0.221 to −0.198)	$< 2.0 \times 10^{-10}$	**−0.046**	(−0.058 to −0.034)	$< 2.0 \times 10^{-10}$
DEP PRS model: SDQ ~ DEP PRS + prenatal EPDS + time + covariates									
PRS	**0.037**	(0.016 to 0.057)	1.27×10^{-3}	**0.028**	(0.007 to 0.048)	.026	**0.035**	(0.015 to 0.055)	1.80×10^{-3}
Prenatal EPDS	**0.093**	(0.065 to 0.121)	2.59×10^{-10}	**0.077**	(0.049 to 0.105)	1.66×10^{-7}	**0.079**	(0.052 to 0.106)	3.76×10^{-8}
Time	**−0.169**	(−0.180 to −0.158)	$< 2.0 \times 10^{-10}$	**−0.209**	(−0.221 to −0.198)	$< 2.0 \times 10^{-10}$	**−0.046**	(−0.058 to −0.034)	$< 2.0 \times 10^{-10}$
Interaction (PRS × time) models									
ADHD PRS model: SDQ ~ ADHD PRS + prenatal EPDS + time + ADHD PRS × time + covariates									
PRS	**0.056**	(0.024 to 0.089)	2.17×10^{-3}	**0.067**	(0.033 to 0.101)	3.14×10^{-4}	0.017	(−0.016 to 0.050)	.954
Prenatal EPDS	**0.093**	(0.065 to 0.121)	2.66×10^{-10}	**0.077**	(0.049 to 0.104)	1.69×10^{-7}	**0.079**	(0.052 to 0.107)	3.48×10^{-8}
Time	**−0.169**	(−0.180 to −0.158)	$< 2.0 \times 10^{-10}$	**−0.209**	(−0.220 to −0.198)	$< 2.0 \times 10^{-10}$	**−0.046**	(−0.058 to −0.034)	$< 2.0 \times 10^{-10}$
PRS × time	−0.002	(−0.031 to 0.028)	1.00	0.008	(−0.021 to 0.037)	1.00	−0.008	(−0.040 to 0.024)	1.00
SCZ PRS model: SDQ ~ SCZ PRS + prenatal EPDS + time + SCZ PRS × time + covariates									
PRS	−0.019	(−0.051 to 0.014)	.802	−0.042	(−0.076 to −0.007)	.052	0.015	(−0.018 to 0.048)	1.00
Prenatal EPDS	**0.094**	(0.065 to 0.122)	2.18×10^{-10}	**0.077**	(0.050 to 0.105)	1.44×10^{-7}	**0.079**	(0.052 to 0.107)	3.32×10^{-8}
Time	**−0.169**	(−0.180 to −0.157)	$< 2.0 \times 10^{-10}$	**−0.209**	(−0.220 to −0.198)	$< 2.0 \times 10^{-10}$	**−0.046**	(−0.058 to −0.034)	$< 2.0 \times 10^{-10}$
PRS × time	0.036	(0.006 to 0.066)	.060	**0.053**	(0.023 to 0.082)	1.40×10^{-3}	0.002	(−0.030 to 0.034)	1.00
DEP PRS model: SDQ ~ DEP PRS + prenatal EPDS + time + DEP PRS × time + covariates									
PRS	−0.010	(−0.044 to 0.024)	1.00	−0.012	(−0.048 to 0.023)	1.00	−0.001	(−0.035 to 0.033)	1.00
Prenatal EPDS	**0.093**	(0.065 to 0.121)	2.39×10^{-10}	**0.077**	(0.049 to 0.105)	1.58×10^{-7}	**0.079**	(0.052 to 0.106)	3.59×10^{-8}
Time	**−0.169**	(−0.180 to −0.158)	$< 2.0 \times 10^{-10}$	**−0.209**	(−0.220 to −0.198)	$< 2.0 \times 10^{-10}$	**−0.046**	(−0.058 to −0.034)	$< 2.0 \times 10^{-10}$
PRS × time	**0.052**	(0.020 to 0.083)	3.93×10^{-3}	**0.044**	(0.013 to 0.074)	.015	0.039	(0.005 to 0.074)	.077

Note: Additive models are generalized estimating equation models that include the main effects of prenatal maternal depression (EPDS), child polygenic risk score (PRS), and child age (time) together with covariates. Interaction (PRS × time) models are generalized estimating equation models that include the main effects of prenatal EPDS, PRS, and time together with covariates and the interaction term (PRS × time). Covariates in the models include child sex, gestational weeks, birth weight, maternal age at delivery, crowding index, maternal highest education qualification, prenatal smoking, prenatal alcohol consumption, postnatal maternal depression at 8 and 33 months, and the top ten genetic principal components. Standardized estimates and 95% CIs are reported; p values are after adjustment for multiple testing (Bonferroni). Boldface indicates significant independent effects. ADHD = attention-deficit/hyperactivity disorder; Adj. = adjusted; DEP = depression; EPDS = Edinburgh Postnatal Depression Scale; Est. = generalized estimating equation estimate; PRS = polygenic risk score; SCZ = schizophrenia; SDQ = Strengths and Difficulties Questionnaire.

FIGURE 1 Associations Between Prenatal Maternal Depression, Child Genetic Risk for Psychiatric Disorders, and Trajectories of Child Mental Health



Note: *Mean child total emotional/behavioral difficulties scores (A), externalizing scores (B), and internalizing scores (C) from the Strengths and Difficulties Questionnaire (SDQ) are plotted from early childhood to mid-adolescence. For illustrative purposes, child polygenic risk score (PRS) is displayed as high vs low (median split), with prenatal maternal symptoms of depression dichotomized (high/low) using established clinical cutoff (Edinburgh Postnatal Depression Scale [EPDS] score ≥13). Error bars depict standard errors. ADHD = attention-deficit/hyperactivity disorder; DEP = depressive symptoms; SCZ = schizophrenia.*

Notably, despite changes in symptom expression from early childhood through mid-adolescence, the prediction of child and adolescent outcomes by prenatal maternal depression was consistent and congruent with the developmental programming hypothesis.[8,9] We also found little evidence of domain-specific effects of prenatal maternal depression on child and adolescent symptoms. These findings are consistent with a previous study suggesting that maternal depression may contribute to a general child psychopathology factor rather than specific dimensions of child psychopathology.[43]

The consistent prediction of child and adolescent symptoms by maternal depression contrasted with the pattern observed for genetic risk: the strength of prediction of child total and externalizing symptoms by child PRSs for depression and schizophrenia increased significantly over time. These results are somewhat consistent with those reported by Riglin *et al.*,[44] who found that the association between a PRS for depression and child and adolescent psychopathology factor scores was observed only in adolescence and not earlier in childhood. Although not an initial target of the study, the developmental moderation of PRS prediction of child and adolescent psychiatric symptoms we report emphasizes the importance of considering trajectories of mental health symptoms as well as associated change in symptom expression

TABLE 4 Longitudinal Models of Child Emotional/Behavioral Problems and Maternal Symptoms of Depression Over Time

	Total problems			Externalizing problems			Internalizing problems		
	Est.	**(95% CI)**	**Adj. *p***	**Est.**	**(95% CI)**	**Adj. *p***	**Est.**	**(95% CI)**	**Adj. *p***
ADHD PRS model: SDQ ~ ADHD PRS + prenatal EPDS + ADHD PRS × prenatal EPDS + time + covariates									
PRS	0.027	(−0.007 to 0.062)	.366	**0.046**	(0.011 to 0.082)	.032	−0.005	(−0.037 to 0.027)	1.00
Prenatal EPDS	**0.093**	(0.065 to 0.121)	3.02×10^{-10}	**0.076**	(0.049 to 0.104)	1.85×10^{-7}	**0.079**	(0.052 to 0.106)	3.86×10^{-8}
Time	**−0.169**	(−0.180 to −0.157)	$< 2.0 \times 10^{-10}$	**−0.209**	(−0.220 to −0.198)	$< 2.0 \times 10^{-10}$	**−0.046**	(−0.058 to −0.034)	$< 2.0 \times 10^{-10}$
PRS × EPDS	0.034	(−0.004 to 0.072)	.241	0.035	(−0.004 to 0.073)	.230	0.019	(−0.017 to 0.054)	.925
SCZ PRS model: SDQ ~ SCZ PRS + prenatal EPDS + SCZ PRS × prenatal EPDS + time + covariates									
PRS	0.018	(−0.016 to 0.052)	.899	0.021	(−0.014 to 0.055)	.711	0.007	(−0.026 to 0.040)	1.00
Prenatal EPDS	**0.094**	(0.065 to 0.122)	2.09×10^{-10}	**0.077**	(0.049 to 0.105)	1.51×10^{-7}	**0.080**	(0.052 to 0.107)	2.99×10^{-8}
Time	**−0.169**	(−0.180 to −0.158)	$< 2.0 \times 10^{-10}$	**−0.209**	(−0.221 to −0.198)	$< 2.0 \times 10^{-10}$	**−0.046**	(−0.058 to −0.034)	$< 2.0 \times 10^{-10}$
PRS × EPDS	−0.005	(−0.045 to 0.035)	1.00	−0.017	(−0.057 to 0.022)	1.00	0.012	(−0.025 to 0.050)	1.00
DEP PRS model: SDQ ~ DEP PRS + prenatal EPDS + DEP PRS × prenatal EPDS + time + covariates									
PRS	0.025	(−0.009 to 0.059)	.448	0.013	(−0.021 to 0.048)	1.00	0.032	(0.000 to 0.064)	.160
Prenatal EPDS	**0.093**	(0.065 to 0.121)	2.89×10^{-10}	**0.077**	(0.049 to 0.104)	1.97×10^{-7}	**0.079**	(0.052 to 0.106)	3.66×10^{-8}
Time	**−0.169**	(−0.180 to −0.158)	$< 2.0 \times 10^{-10}$	**−0.209**	(−0.221 to −0.198)	$< 2.0 \times 10^{-10}$	**−0.046**	(−0.058 to −0.034)	$< 2.0 \times 10^{-10}$
PRS × EPDS	0.015	(−0.022 to 0.052)	1.00	0.018	(−0.020 to 0.056)	1.00	0.004	(−0.031 to 0.039)	1.00

Note: The models are generalized estimating equation models that include the main effects of prenatal maternal depression (EPDS), child polygenic risk score (PRS), and child age (time) with covariates and the interaction term (PRS × EPDS). Covariates in the models include child sex, gestational weeks, birth weight, maternal age at delivery, crowding index, maternal highest education qualification, prenatal smoking, prenatal alcohol consumption, postnatal maternal depression at 8 and 33 months, and the top ten genetic principal components. Standardized estimates and 95% CIs are reported; p values are after adjustment for multiple testing (Bonferroni). Boldface indicates significant independent effects. ADHD = attention-deficit/hyperactivity disorder; Adj. = adjusted; DEP = depression; EPDS = Edinburgh Postnatal Depression Scale; Est. = generalized estimating equation estimate; PRS = polygenic risk score; SCZ = schizophrenia; SDQ = Strengths and Difficulties Questionnaire.

(eg, heterotypic continuity)[45] to improve the performance of polygenic predictors in child and adolescent cohorts.

We observed no sex difference in the association between prenatal depression and child symptoms, which is consistent with our earlier report, and sex did not moderate the association between child PRSs and mental health symptoms.[2] We note previous reports of prenatal maternal stress predicting sex-specific child outcomes, effects that may depend on the specific aspect of development under study.[46]

We found no evidence to suggest that child PRSs for ADHD, schizophrenia, or depression moderate the association between prenatal maternal depression or anxiety and child and adolescent mental health symptoms. The absence of an interaction between prenatal maternal mood and child genotype contrasts with previous single SNP analyses in this cohort.[15,16] The contrasting findings may be explained by the difference in how genetic risk—and gene × environment interaction—was operationalized. In contrast to targeting a specific SNP, an approach that dominates gene × environment examples, PRSs capture variation across thousands of SNPs, optimized for identifying main effects on a particular phenotype and not for gene × environment interactions. Furthermore, PRSs within a gene × environment framework have shown inconsistent interaction effects.[47,48] Second-generation PRSs prioritizing SNPs that alter genomic function may be better suited to detect the moderating influence of child genomic variation.[49-51]

Our genetic sensitivity analyses revealed a robust association between prenatal maternal depression and child and adolescent mental health, but we did find evidence of genetic confounding across almost all models, suggesting that the magnitude of the association between prenatal maternal depression and child and adolescent outcomes is partly explained by shared genetic risk. Our findings contrast somewhat with those of Hannigan *et al.*[12] Their family-based design (multiple children of twins and siblings) suggested that passive genetic transmission accounts for most (86%) of the association between prenatal maternal depression and child psychopathology vs approximately 45% in our study. The multiple children of twins and siblings design relies on between-pregnancy and within-sibling variability in prenatal mood, which, if limited relative to the sample or population, would likely attenuate associations. In contrast, we used observed genotypes to quantify child genomic risk for common mental health disorders in a large sample of children and did not rely on within-pregnancy differences in maternal affective symptoms. Our findings suggest that genetics alone do not fully account for the association between prenatal depression and child mental health. Nonetheless, future studies moving beyond observational cohorts (eg, randomized controlled trials) are required to strengthen causal inference in this field.[11]

Our study is not without limitations. First, we observed selective attrition; specifically, children from the ALSPAC cohort who provided genetic data were born to women who reported less prenatal depression or anxiety (and less variation in mood symptoms) than the remainder of the cohort. Similarly, as previously reported, children with higher PRSs for risk phenotypes are less likely to participate in long-term follow-up within the ALSPAC cohort,[52] which may have limited our power to detect PRSs by maternal distress interactions.[49,52] Second, our analyses focused on PRSs that consider only measures of common genetic variation (eg, SNPs) and not other genomic risks, such as copy number variants, rare variants, or mitochondrial DNA. Third, our results are based on cohorts of European ancestry; both the ALSPAC and the PREDO cohorts have a limited number of individuals from other ancestral groups. Large-scale GWASs in more diverse populations are needed. Fourth, we relied on maternal reports of child mental health, which may have led to reporter bias; however, our sensitivity analyses and empirical analyses suggest that reporter bias is unlikely to be a major confound.[53] These limitations are offset by many important strengths of this study, including a well-characterized large sample with direct measures of genetic risk and repeated assessments of child outcomes across different developmental stages, and the use of a second independent cohort of children.

Prenatal mental health is one of the more robust predictors of child mental health, and it is among the more modifiable risk factors given that there are interventions that can improve or prevent perinatal mood or affective disorders.[54] Yet current screening guidelines in the United States[55] place a greater relative emphasis on postpartum assessments of maternal mental health, which may delay the identification and treatment of women at-risk of adverse mental health outcomes. Regardless of the potential impact on child development, supporting the mental health of pregnant women should be a public health priority. Furthermore, the study results emphasize the need for large-scale interventions to examine the clinical benefits of prenatal interventions on both maternal and child mental health; studies of this nature may also benefit from using a genetically informed design.

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The data that support the findings of this study are available upon request from the ALSPAC executive committee (see http://www.bristol.ac.uk/alspac) and the PREDO Study Board (e-mail: predo.study@helsinki.fi).

The research was performed with permission from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees (for ALSPAC) and the Ethics Committee of Obstetrics and Gynaecology and Women, Helsinki and Uusimaa Hospital District (for PREDO).

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Author Contributions
LMC, TGO, VG, KR, MJM, and KJO contributed to the conception and design of the study. LMC analyzed the ALSPAC data. MLP, TK, JL and KR contributed to the acquisition and analysis of the PREDO data. All authors contributed to the interpretation of data. LMC and KJO drafted the initial manuscript, and all authors have read and approved the final version of the manuscript. LMC and KJO will serve as guarantors for the contents of this paper.

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REFERENCES

1. Dadi AF, Miller ER, Bisetegn TA, Mwanri L. Global burden of antenatal depression and its association with adverse birth outcomes: an umbrella review. BMC Public Health. 2020;20(1):173. https://doi.org/10.1186/s12889-020-8293-9
2. O'Donnell KJ, Glover V, Barker ED, O'Connor TG. The persisting effect of maternal mood in pregnancy on childhood psychopathology. Dev Psychopathol. 2014;26(2):393-403. https://doi.org/10.1017/S0954579414000029
3. Capron LE, Glover V, Pearson RM, *et al*. Associations of maternal and paternal antenatal mood with offspring anxiety disorder at age 18 years. J Affect Disord. 2015;187:20-26. https://doi.org/10.1016/j.jad.2015.08.012
4. Betts KS, Williams GM, Najman JM, Alati R. The relationship between maternal depressive, anxious, and stress symptoms during pregnancy and adult offspring behavioral and emotional problems. Depress Anxiety. 2015;32(2):82-90. https://doi.org/10.1002/da.22272
5. O'Neil S, Platt I, Vohra D, *et al*. The high costs of maternal morbidity show why we need greater investment in maternal health. The Commonwealth Fund; 2021. Accessed June 21, 2023. https://www.commonwealthfund.org/publications/issue-briefs/2021/nov/high-costs-maternal-morbidity-need-investment-maternal-health
6. Luca DL, Garlow N, Staatz C, Margiotta C, Zivin K. Societal costs of untreated perinatal mood and anxiety disorders in the United States. Mathematica Policy Research. 2019. Accessed February 22, 2023. https://www.mathematica.org/publications/societal-costs-of-untreated-perinatal-mood-and-anxiety-disorders-in-the-united-states
7. Barker DJP. The fetal and infant origins of adult disease. BMJ. 1990;301(6761):1111. https://doi.org/10.1136/bmj.301.6761.1111
8. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet. 1993;341(8850):938-941. https://doi.org/10.1016/0140-6736(93)91224-a
9. Barker DJP. The origins of the developmental origins theory. J Intern Med. 2007;261(5):412-417. https://doi.org/10.1111/j.1365-2796.2007.01809.x
10. O'Donnell KJ, Meaney MJ. Fetal origins of mental health: the Developmental Origins of Health and Disease hypothesis. Am J Psychiatry. 2017;174(4):319-328. https://doi.org/10.1176/appi.ajp.2016.16020138
11. Glover V, O'Connor TG, O'Donnell KJ. Fetal programming and public policy. J Am Acad Child Adolesc Psychiatry. 2023;62(6):618-620. https://doi.org/10.1016/j.jaac.2022.11.010
12. Hannigan LJ, Eilertsen EM, Gjerde LC, *et al*. Maternal prenatal depressive symptoms and risk for early-life psychopathology in offspring: genetic analyses in the Norwegian Mother and Child Birth Cohort Study. Lancet Psychiatry. 2018;5(10):808-815. https://doi.org/10.1016/S2215-0366(18)30225-6
13. Rice F, Harold GT, Boivin J, van den Bree M, Hay DF, Thapar A. The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. Psychol Med. 2010;40(2):335-345. https://doi.org/10.1017/S0033291709005911
14. Ahmadzadeh YI, Schoeler T, Han M, Pingault JB, Creswell C, McAdams TA. Systematic review and meta-analysis of genetically informed research: associations between parent anxiety and offspring internalizing problems. J Am Acad Child Adolesc Psychiatry. 2021;60(7):823-840. https://doi.org/10.1016/j.jaac.2020.12.037
15. Babineau V, Green CG, Jolicoeur-Martineau A, *et al*. Prenatal depression and 5-HTTLPR interact to predict dysregulation from 3 to 36 months—a differential susceptibility model. J Child Psychol Psychiatry. 2015;56(1):21-29. https://doi.org/10.1111/jcpp.12246
16. O'Donnell KJ, Glover V, Lahti J, *et al*. Maternal prenatal anxiety and child COMT genotype predict working memory and symptoms of ADHD. PLoS One. 2017;12(6):1-16. https://doi.org/10.1371/journal.pone.0177506
17. Demontis D, Walters RK, Martin J, *et al*. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019;51(1):63-75. https://doi.org/10.1038/s41588-018-0269-7

18. Brikell I, Larsson H, Lu Y, *et al*. The contribution of common genetic risk variants for ADHD to a general factor of childhood psychopathology. Mol Psychiatry. 2020;25:1809-1821. https://doi.org/10.1038/s41380-018-0109-2
19. Ronald A, de Bode N, Polderman TJC. Systematic review: how the attention-deficit/hyperactivity disorder polygenic risk score adds to our understanding of ADHD and associated traits. J Am Acad Child Adolesc Psychiatry. 2021;60(10):1234-1277. https://doi.org/10.1016/j.jaac.2021.01.019
20. Martin AR, Daly MJ, Robinson EB, Hyman SE, Neale BM. Predicting polygenic risk of psychiatric disorders. Biol Psychiatry. 2019;86(2):97-109. https://doi.org/10.1016/j.biopsych.2018.12.015
21. Boyd A, Golding J, Macleod J, *et al*. Cohort profile: the 'Children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. Int J Epidemiol. 2013;42(1):111-127. https://doi.org/10.1093/ije/dys064
22. Fraser A, Macdonald-Wallis C, Tilling K, *et al*. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. Int J Epidemiol. 2013;42(1):97-110. https://doi.org/10.1093/ije/dys066
23. Girchenko P, Lahti M, Tuovinen S, *et al*. Cohort profile: prediction and prevention of preeclampsia and intrauterine growth restriction (PREDO) study. Int J Epidemiol. 2017;46(5):1380-1381g. https://doi.org/10.1093/ije/dyw154
24. Pingault JB, Rijsdijk F, Schoeler T, *et al*. Genetic sensitivity analysis: adjusting for genetic confounding in epidemiological associations. PLoS Genet. 2021;17(6):e1009590. https://doi.org/10.1371/journal.pgen.1009590
25. Goodman A, Goodman R. Strengths and difficulties questionnaire as a dimensional measure of child mental health. J Am Acad Child Adolesc Psychiatry. 2009;48(4):400-403. https://doi.org/10.1097/CHI.0b013e3181985068
26. Goodman A, Lamping DL, Ploubidis GB. When to use broader internalising and externalising subscales instead of the hypothesised five subscales on the Strengths and Difficulties Questionnaire (SDQ): data from British parents, teachers and children. J Abnorm Child Psychol. 2010;38(8):1179-1191. https://doi.org/10.1007/s10802-010-9434-x
27. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782-786.
28. Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. Br J Med Psychol. 1988;61(3):255-266. https://doi.org/10.1111/j.2044-8341.1988.tb02787.x
29. Turley P, Walters RK, Maghzian O, *et al*. Multi-trait analysis of genome-wide association summary statistics using MTAG. Nat Genet. 2018;50(2):229-237. https://doi.org/10.1038/s41588-017-0009-4
30. Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. Cell. 2018;173(7):1705-1715.e1716. https://doi.org/10.1016/j.cell.2018.05.046
31. Khashan AS, Abel KM, McNamee R, *et al*. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. Arch Gen Psychiatry. 2008;65(2):146-152. https://doi.org/10.1001/archgenpsychiatry.2007.20
32. Patterson N, Price AL, Reich D. Population structure and eigenanalysis. PLoS Genet. 2006;2(12):2074-2093. https://doi.org/10.1371/journal.pgen.0020190
33. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 2006;38(8):904-909. https://doi.org/10.1038/ng1847
34. Højsgaard S, Yan J, Halekoh U. The R package geepack for generalized estimating equations. J Stat Softw. 2006;15(2):1-11. https://doi.org/10.18637/jss.v015.i02
35. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1-67. https://doi.org/10.18637/jss.v045.i03
36. Howard DM, Adams MJ, Clarke TK, *et al*. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci. 2019;22(3):343-352. https://doi.org/10.1038/s41593-018-0326-7
37. Lee SH, DeCandia TR, Ripke S, *et al*. Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. Nat Genet. 2012;44(3):247-250. https://doi.org/10.1038/ng.1108
38. Neumann A, Nolte IM, Pappa I, *et al*. A genome-wide association study of total child psychiatric problems scores. PLoS One. 2022;17(8):e0273116. https://doi.org/10.1371/journal.pone.0273116
39. Radloff LS. The CES-D scale: a self-reported depression scale for research in the general population. Appl Psychol Meas. 1977;1(3):385-401. https://doi.org/10.1177/014662167700100306
40. Achenbach TM, Rescorla L. Manual for the ASEBA Preschool Forms & Profiles. Burlington, VT: University of Vermont; 2000.
41. Achenbach TM, Rescorla L. Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont; 2001.
42. Little RJA. A test of missing completely at random for multivariate data with missing values. J Am Stat Assoc. 1988;83(404):1198-1202. https://doi.org/10.1080/01621459.1988.10478722
43. Swales DA, Snyder HR, Hankin BL, Sandman CA, Glynn LM, Davis EP. Maternal depressive symptoms predict general liability in child psychopathology. J Clin Child Adolesc Psychol. 2022;51(1):85-96. https://doi.org/10.1080/15374416.2020.1723598
44. Riglin L, Thapar AK, Leppert B, *et al*. Using genetics to examine a general liability to childhood psychopathology. Behav Genet. 2020;50(4):213-220. https://doi.org/10.1007/s10519-019-09985-4
45. Shevlin M, McElroy E, Murphy J. Homotypic and heterotypic psychopathological continuity: a child cohort study. Soc Psychiatry Psychiatr Epidemiol. 2017;52(9):1135-1145.
46. Sutherland S, Brunwasser SM. Sex differences in vulnerability to prenatal stress: a review of the recent literature. Curr Psychiatry Rep. 2018;20(11):102. https://doi.org/10.1007/s11920-018-0961-4
47. Peyrot WJ, Van der Auwera S, Milaneschi Y, *et al*. Does childhood trauma moderate polygenic risk for depression? A meta-analysis of 5765 subjects from the Psychiatric Genomics Consortium. Biol Psychiatry. 2018;84(2):138-147. https://doi.org/10.1016/j.biopsych.2017.09.009
48. Qiu A, Shen M, Buss C, *et al*. Effects of antenatal maternal depressive symptoms and socio-economic status on neonatal brain development are modulated by genetic risk. Cereb Cortex. 2017;27(5):3080-3092. https://doi.org/10.1093/cercor/bhx065
49. Arnau-Soler A, Macdonald-Dunlop E, Adams MJ, *et al*. Genome-wide by environment interaction studies of depressive symptoms and psychosocial stress in UK Biobank and Generation Scotland. Transl Psychiatry. 2019;9(1):14. https://doi.org/10.1038/s41398-018-0360-y
50. Chen LM, Tollenaar MS, Hari Dass SA, *et al*. Maternal antenatal depression and child mental health: moderation by genomic risk for attention-deficit/hyperactivity disorder. Dev Psychopathol. 2020;32(5):1810-1821. https://doi.org/10.1017/S0954579420001418
51. Silveira PP, Pokhvisneva I, Parent C, *et al*. Cumulative prenatal exposure to adversity reveals associations with a broad range of neurodevelopmental outcomes that are moderated by a novel, biologically informed polygenetic score based on the serotonin transporter solute carrier family C6, member 4 (SLC6A4) gene expression. Dev Psychopathol. 2017;29(5):1601-1617. https://doi.org/10.1017/S0954579417001262
52. Taylor AE, Jones HJ, Sallis H, *et al*. Exploring the association of genetic factors with participation in the Avon Longitudinal Study of Parents and Children. Int J Epidemiol. 2018;47(4):1207-1216. https://doi.org/10.1093/ije/dyy060
53. Olino TM, Michelini G, Mennies RJ, Kotov R, Klein DN. Does maternal psychopathology bias reports of offspring symptoms? A study using moderated non-linear factor analysis. J Child Psychol Psychiatry. 2021;62(10):1195-1201. https://doi.org/10.1111/jcpp.13394
54. Goodman SH, Cullum KA, Dimidjian S, River LM, Kim CY. Opening windows of opportunities: evidence for interventions to prevent or treat depression in pregnant women being associated with changes in offspring's developmental trajectories of psychopathology risk. Dev Psychopathol. 2018;30(3):1179-1196. https://doi.org/10.1017/S0954579418000536
55. ACOG committee opinion No. 757: screening for perinatal depression. Obstet Gynecol. 2018;132(5):e208-e212. https://doi.org/10.1097/AOG.0000000000002927