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 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 (n = 514).

**Results:** Maternal depression and anxiety and child genomic 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 = 0.096, 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 in the United States, estimated at $18 billion a year,[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



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(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 made 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 $\geq$ 2,471). Finally, we performed multivariate imputations by chained equations with 20 imputed dataset iterations using the mice 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 $p = 2.660 \times 10^{-10}$) (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 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 $\chi^2$ or t tests.

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

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

**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.*

### 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 PRS in the prediction of child symptoms (Table 3). For example, 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 ≥14). Elevated prenatal maternal depression (EPDS ≥13; 12% of mothers) or anxiety (CCEI ≥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 cases 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) | $5.30 \times 10^{-7}$ | **0.074** | (0.053 to 0.095) | $< 2. \times 10^{-10}$ | 0.010 | (−0.010 to 0.030) | 1.00 |
| Prenatal EPDS | **0.093** | (0.065 to 0.121) | $2.66 \times 10^{-10}$ | **0.077** | (0.049 to 0.104) | $1.69 \times 10^{-7}$ | **0.079** | (0.052 to 0.107) | $3.50 \times 10^{-8}$ |
| 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) | $2.19 \times 10^{-10}$ | **0.077** | (0.050 to 0.105) | $1.43 \times 10^{-7}$ | **0.079** | (0.052 to 0.107) | $3.30 \times 10^{-8}$ |
| 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) | $1.27 \times 10^{-3}$ | **0.028** | (0.007 to 0.048) | .026 | **0.035** | (0.015 to 0.055) | $1.80 \times 10^{-3}$ |
| Prenatal EPDS | **0.093** | (0.065 to 0.121) | $2.59 \times 10^{-10}$ | **0.077** | (0.049 to 0.105) | $1.66 \times 10^{-7}$ | **0.079** | (0.052 to 0.106) | $3.76 \times 10^{-8}$ |
| 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) | $2.17 \times 10^{-3}$ | **0.067** | (0.033 to 0.101) | $3.14 \times 10^{-4}$ | 0.017 | (−0.016 to 0.050) | .954 |
| Prenatal EPDS | **0.093** | (0.065 to 0.121) | $2.66 \times 10^{-10}$ | **0.077** | (0.049 to 0.104) | $1.69 \times 10^{-7}$ | **0.079** | (0.052 to 0.107) | $3.48 \times 10^{-8}$ |
| 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) | $2.18 \times 10^{-10}$ | **0.077** | (0.050 to 0.105) | $1.44 \times 10^{-7}$ | **0.079** | (0.052 to 0.107) | $3.32 \times 10^{-8}$ |
| 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) | $1. \times 10^{-3}$ | 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) | $2.39 \times 10^{-10}$ | **0.077** | (0.049 to 0.105) | $1.58 \times 10^{-7}$ | **0.079** | (0.052 to 0.106) | $3.59 \times 10^{-8}$ |
| 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) | $3.93 \times 10^{-3}$ | **0.044** | (0.013 to 0.074) | .015 | 0.039 | (0.005 to 0.074) | .077 |

*Note*: *Covariates in the models include sex, gestational weeks, birth weight, maternal age, crowding index, maternal highest education qualification, prenatal smoking, prenatal alcohol consumption, and postnatal maternal depression at 8 and 33 months. Standardized estimates and 95% CIs are reported; p values are after adjustment for multiple testing (Bonferroni). Boldface indicates significant independent effects. PRS + EPDS = main effects of prenatal maternal EPDS, child PRS, and child age (time) together with covariates. PRS × Time + EPDS = main effects of prenatal maternal EPDS, child PRS, and time together with covariates and the interaction term (PRS × Time). 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.*





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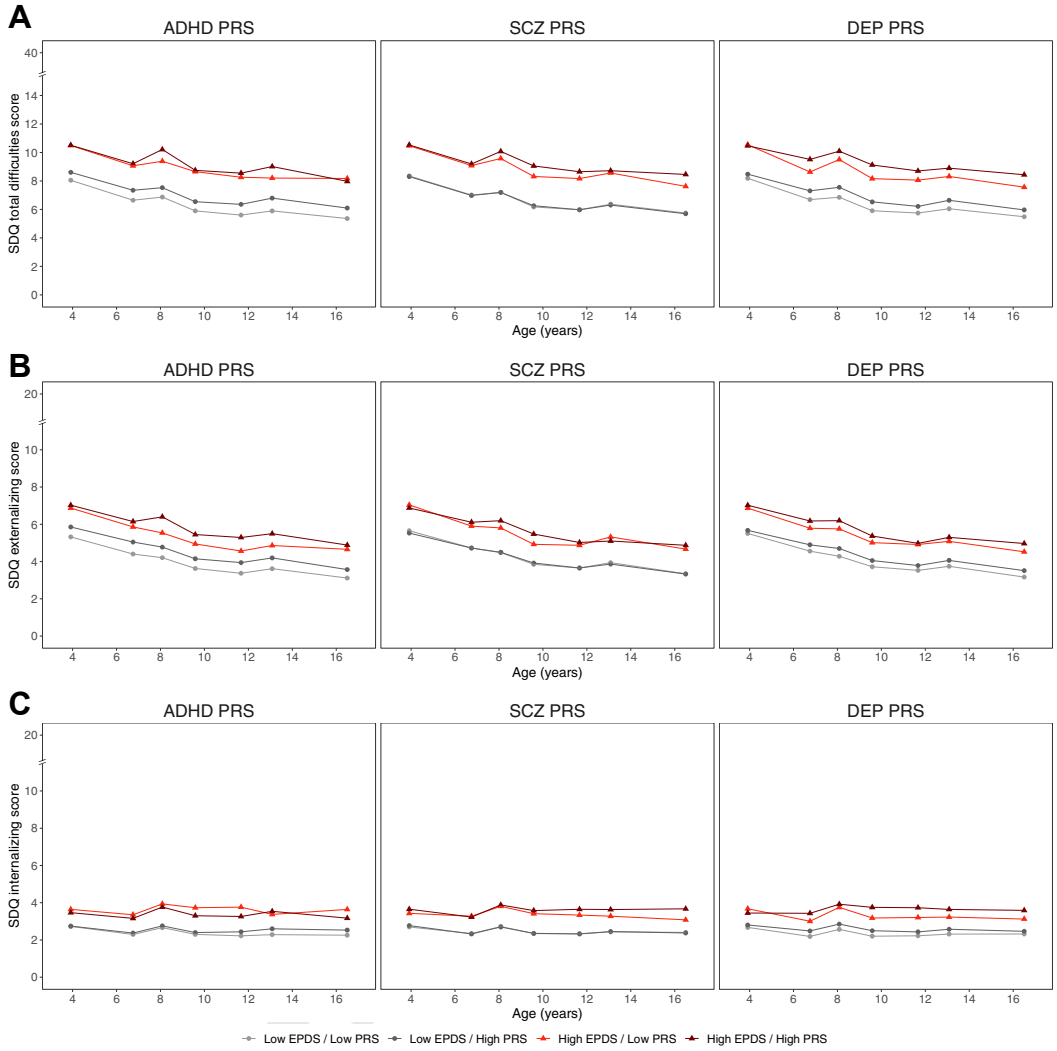
**FIGURE 1** Associations Between Prenatal Maternal Depression, Child Genetic Risk for Psychiatric Disorders, and Trajectories of Child Mental Health




*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) | $3.02 \times 10^{-10}$ | **0.076** | (0.049 to 0.104) | $1.85 \times 10^{-7}$ | **0.079** | (0.052 to 0.106) | $3.86 \times 10^{-8}$ |
| 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) | $2.09 \times 10^{-10}$ | **0.077** | (0.049 to 0.105) | $1.51 \times 10^{-7}$ | **0.080** | (0.052 to 0.107) | $2.99 \times 10^{-8}$ |
| 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) | $2.89 \times 10^{-10}$ | **0.077** | (0.049 to 0.104) | $1.97 \times 10^{-7}$ | **0.079** | (0.052 to 0.106) | $3.66 \times 10^{-8}$ |
| 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*: *Covariates in the models include sex, gestational weeks, birth weight, maternal age, crowding index, maternal highest education qualification, prenatal smoking, prenatal alcohol consumption, and postnatal maternal depression at 8 and 33 months. Standardized estimates and 95% CIs are reported; p values are after adjustment for multiple testing (Bonferroni). Boldface indicates significant independent effects. PRS × EPDS + time = main effects of prenatal maternal EPDS, child PRS, and child age (time) together with covariates and the interaction term (PRS × EPDS). 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.*





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(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, PRS capture variation across thousands of SNPs, optimized for main effect for a particular phenotype and not for gene × environment interactions. Furthermore, PRSs within a gene × environment framework have shown inconsistent interaction effects.[49,50] Second-generation PRSs prioritizing SNPs that alter genomic function may be better suited to detect moderating influence of child genomic variation.[51]

Our genetic sensitivity analyses revealed a robust association between maternal prenatal 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 disturbance.[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 at-risk children. 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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