Towards a Comprehensive Prediction Model of Perinatal Mental Health

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Abstract

Perinatal mental illnesses affect approximately 1 out of 5 women in Canada, with postpartum depression (PPD) the most common complication of pregnancy, affecting 1 out of 10 women in Canada. Women who experience PPD often show symptoms during pregnancy, and best practice clinical guidelines increasingly call for screening of maternal mental health symptoms in the antenatal period. To do so effectively we must first identify relevant risk factors that associate with, and predict, risk of perinatal mental illness. Epidemiological and genomic studies carried out to date suggest contributions of a number of environmental and genetic risk factors to perinatal mental illness. Prediction models that consider both environmental and biological risk factors may be able to better identify women at risk of perinatal mental illness. In this thesis, I examined the relationship between environmental risk factors for perinatal mental illness in a large prospective cohort from the United Kingdom: the Avon Longitudinal Study of Parents and Children (ALSPAC, N=15242). Women provided detailed assessments of maternal anxiety and depression twice during pregnancy (at 18 and 32 weeks of gestation) and at multiple timepoints in the postpartum where I focus on the 8 week and 8 months postpartum assessments. Paired genetic data and epigenetic data (DNA methylation), were available on 9299 and 924 women, respectively. Linear regression models identified an 'environmental' risk model for maternal depressive/anxiety symptoms in the ALSPAC cohort including prenatal social support that cumulatively explained 17.4-32.5% of the variance in maternal symptoms in perinatal period. Next, leveraging recent advances in population genetics and large genome-wide association studies of psychiatric disorders, I integrated polygenic risk scores (PRS: a summary measure of genetic risk for a given phenotype) within the 'environmental' risk model. The PRS for depressive symptoms explained approximately 1% of the variance in perinatal depressive and anxiety symptoms. Lastly, I explored known epigenetic biomarkers of PPD to predict PPD in the ALSPAC mothers, and found evidence of an association between epigenetic variation and PPD. Based on the findings of the current study, perinatal mental health can be influenced by various environmental and biological factors, however environmental factors including history of sexual abuse and prenatal social support account for the largest proportion of variance in maternal mood. Together these findings highlight the importance of social support in pregnancy as well as the necessity to prevent sexual abuse in order to promote maternal perinatal mental health.

Abstract

La santé mentale périnatale touche 1 femme sur 5 au Canada, et la dépression post-partum est la complication la plus courante de la grossesse qui touche 1 femme sur 10 au Canada. Les femmes qui vivent la dépression de post-partum démontrent souvent les symptômes pendant la grossesse, et la meilleure pratique de guide clinique demande de plus en plus le dépistage des symptômes de santé mentale de la mère pendant la période prénatale. Afin de le faire efficacement, nous devons d'abord identifier les facteurs de risque pertinents qui prédisent et qui sont associés au risque de santé mentale périnatale. Les études génétiques et épidémiologiques réalisées suggèrent la contribution d'un certain nombre de facteurs de risque environnementaux et génétiques à la maladie mentale périnatale. Les modèles de prédiction qui tiennent compte des deux facteurs de risque environnementaux et biologiques peuvent mieux identifier les femmes à risque de maladie mentale périnatale. Dans cette thèse, j'ai examiné la relation entre les facteurs de risque environnementaux de la maladie mentale périnatale dans une grande cohorte prospective du Royaume-Uni: l'étude longitudinale Avon sur les parents et les enfants [Avon Longitudinal Study of Parents and Children (ALSPAC, N=15242)]. Les femmes ont fourni des évaluations détaillées de l'anxiété et de la dépression à deux reprises pendant la grossesse (à 18 et 32 semaines de la gestation) et à plusieurs moments dans le post-partum où je me concentre sur les évaluations à 8 semaines et à 8 mois post-partum. Les données génétiques appariées (methylation de l'ADN) étaient disponibles pour 9299 et pour 924 des femmes, respectivement. Les modèles de régression linéaire ont identifié un modèle de risque « environnemental » pour les symptômes de la dépression/anxiété dans la cohorte ALSPAC, y compris le soutien social prénatal, qui expliquait cumulativement 17.4-32.5% de la variance des symptômes maternels pendant la période périnatale. Ensuite, en utilisant les progrès récents de la génétique des populations et des grandes études d'association pangénomique des maladies psychiatriques, j'ai intégré des scores de risque polygénique (Le score de risque polygénique: une mesure synthétique du risque génétique pour un phénotype donné) dans le modèle de risque « environnemental ». Le score de risque polygénique pour les symptômes dépressifs expliquait environ 1% de la variance des symptômes dépressifs et anxieux périnataux. En dernier lieu, j'ai exploré les biomarqueurs épigénétiques connus de la dépression post-partum pour prédire la dépression post-partum chez les mères ALSPAC, et j'ai trouvé des preuves d'une association entre la variation épigénétique et la dépression post-partum. Selon les résultats d'étude actuelle, la santé mentale périnatale peut être influencé par plusieurs facteurs environnementaux et biologique. Cependant, les facteurs environnementaux, y compris les antécédents d'abus sexuels et le soutien social prénatal, expliquent la plus grande proportion de variance de l'humeur maternelle. Ensemble, ces résultats soulignent l'importance du soutien social pendant la grossesse ainsi que la nécessité de prévenir les abus sexuels pour promouvoir la santé mentale périnatale maternelle.

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GLOSSARY OF ABBREVIATIONS

1. AD: Anxiety Disorder
    a. Mental health condition characterized by anxiety symptoms leading to internalizing or externalizing behaviors at a level that disrupts the ability to carry out daily activities, diagnosed based on the Diagnostic and Statistical Manual of mental disorders
2. AIC: Akaike Information Criterion
    a. Criterion that is used to compare model fit of an equation to explain the data, lower AIC indicates better fit of a model than a model that has a higher AIC
3. ALSPAC: Avon Longitudinal Studies of Parents and Children
    a. Cohort of pregnant mothers and children from the United Kingdom
4. ANOVA: Analysis of Variance
    a. Statistical tool that can be used to compare differences between groups such as variation and mean
5. AUC: Area under the receiver operating characteristic (ROC) curve
    a. The ROC curve is a probability curve of a model detecting the class of the data and the AUC of an ROC curve is the measure of the accuracy of the model to detect the class correctly
6. BD: Bipolar Disorder
    a. Mental health condition characterized by alternating manic and depressive states at a level that leads to dysfunction in daily activity, diagnosed based on the Diagnostic and Statistical Manual of mental disorders
7. CCEI: Crown-Crisp Experiential Index
    a. Questionnaire that measures anxiety symptoms from scale of 0 to 16, particularly free-floating anxiety subscale of CCEI that measures the level of anxiety based on 8 questions was used in this study
8. DOHaD: Developmental Origin of Health and Disease
    a. Framework of health and disease that focuses on how the prenatal period of the mother affects the development of the fetus and has long-term effects after birth on the child into adolescence and adulthood
9. DSM: Diagnostic and Statistical Manual of Mental Disorders
    a. Set of criteria for mental disorders that are used to guide diagnosis and treatment by healthcare professionals, published by the American Psychiatric Association
10. EPDS: Edinburgh Postpartum Depression Score
    a. Questionnaire that measures depressive symptoms during the postpartum period from a scale of 0 to 30 based on 10-questions
11. *ESR1*: Estrogen Receptor 1
    a. This gene encodes an estrogen receptor and a transcription factor that regulates the transcription of genes that play a role in growth, metabolism, sexual

development, gestation, and other reproductive functions and is expressed in many non-reproductive tissues. [RefSeq, Jul 2020]

12. GEE: Generalized Estimating Equation
    a. Equation that is used to estimate the average response over the population with possible unknown correlation between outcomes
13. GWAS: Genome-Wide Association Studies
    a. Large scale population studies of associations between single nucleotide polymorphisms and traits or diseases in humans or any other organisms based on the whole-genome
14. IPSM: Interpersonal Sensitivity Measure
    a. Questionnaire to measure negative emotion in social interactions based on 36 questions that are scored from 1 to 4
15. MDD: Major Depressive Disorder
    a. Continuous low mood for at least 2 weeks, characterized by low energy, self-esteem and loss of interest in activities in addition to other symptoms such as pain without clear cause, hallucinations or delusions to a level that disrupts daily activities, diagnosed based on DSM
16. PGC: Psychiatric Genomics Consortium
    a. Internationally collaborative initiative to identify genetic basis of psychiatric disorders
17. PMD: Perinatal Mood Disorders
    a. Maternal mental health disorders during pregnancy or after childbirth including anxiety, depression, bipolar disorder and postpartum psychosis
18. PPD: Postpartum Depression
    a. Depression of the mother during the period after pregnancy, definitions of the postpartum ranging from 4 weeks to 12 months after giving birth
19. PRS: Polygenic Risk Scores
    a. Sum of genetic risk for an outcome that has been calculated from known associations of single nucleotide polymorphisms and outcome based on GWAS
20. SD: Standard Deviation
    a. Measure of variation in dataset
21. SNP: Single Nucleotide Polymorphism
    a. Common genetic variation arising from differences at a single point/position within the human genome

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INTRODUCTION

Epidemiology of Perinatal Mental Health

The prevalence of perinatal depression prevalence has been found to be 11.9% globally with greater burden in low- and middle-income countries and lower number of studies based in low- and middle-income countries[1]. Previously, the prevalence of antenatal depression and postpartum depression (PPD) had been reported as 25.3% and 19.7% in women in low-income countries respectively, with the prevalence of perinatal depression estimated between 6.5% to 12.9% in women in high income countries[2,3]. Such estimates can vary and likely depend on the definition of 'postpartum' which ranges across studies from 4 weeks to 12 months after giving birth[4]. Perinatal depression is not only a difficult experience for the mother but is also associated with postpartum mortality[5]. Women with bipolar disorder or previous history of psychiatric disorders such as major depressive disorder (MDD) or anxiety disorder are at a greater risk for PPD. Existing research on PPD have identified history of psychiatric disorder, adverse early life events or trauma, antenatal depression or anxiety, stressful life events, poverty and social support as the environmental and psychosocial risk factors of PPD[4]. Approximately 50% of women reporting elevated depressive symptoms in the postpartum report high depressive symptoms during pregnancy, while women reporting high levels of prenatal anxiety are 3 times more likely to develop PPD[6]. There is considerable heterogeneity in trajectories of perinatal depressive symptoms, and the environmental or biological factors that contribute to such individual differences are poorly understood[7-9]. Recent studies of perinatal mental health have used the term perinatal maternal anxiety and depression (PMAD) to consider anxiety and depression together, although the use of this acronym has recently been called into question[10]. Therefore we will instead

use the term perinatal mental disorders (PMD) in this study to refer to perinatal anxiety and depression, the two perinatal mental illnesses that we have focused on in this study.

Among the known environmental factors identified to play a role in PMD, interpersonal adversity is one potential risk factor for PMD. A study that has focused on intimate partner violence prior to or during pregnancy has shown evidence of decreased relational resilience in women who have experienced intimate partner violence that indirectly affects perinatal mental health[11]. This study suggested that screening for intimate partner violence and targeting relational resilience may improve women's mental health and physical well-being. On the other hand, sensitivity to negative social interaction measured by Interpersonal Sensitivity Measure (IPSM) has been found to be a mediator of the effects of early life adversity on depressive symptoms in adulthood[12]. In a study conducted in a Japanese cohort, IPSM was found to be higher in individuals who had lower parental bonding and higher lifetime depression[13]. It is possible that greater IPSM which indicates greater negative sensitivity in relationships is related to lower relational resilience and adverse mental health, but the contribution of IPSM to PMDs has not been studied. In contrast, social support, a modifiable factor, has been found to be a strong buffering factor for PMD and PPD in diverse cohorts, and a moderator of the effect of intimate partner violence[14-16]. Therefore, lack of social support is a strong risk factor for PMD, and possibly an even greater risk factor than early life adversity[17,18]. Finally, despite an extensive literature on the psychological and social determinants of perinatal mental health, less is known about clinically-relevant biological factors that contribute to maternal mental health. Recent advances in population genetics and epigenetic biomarker discovery, provide unprecedented opportunities to now integrate biological risk factors in prediction models of PMDs.

Genome-Wide Association Studies (GWAS) and Genetic Contribution to Psychiatric Disorders

GWAS of psychiatric disorders have begun to identify genetic risk factors for psychiatric disorders. The Psychiatric Genomics Consortium (PGC) was founded to conduct large-scale genome-wide association studies (GWASes) of attention-deficit/hyperactivity disorder, autism, bipolar disorder (BD), major depressive disorder (MDD) and schizophrenia, and includes >800 scientists from >40 countries to conduct GWASes of psychiatric disorders[19,20]. The PGC seeks to describe the fundamental biology of psychiatric disorders to inform new therapeutic targets and clinical management[21]. GWASes are an improvement from the previous candidate gene studies of genetic risk of psychiatric disorders which typically focused on single nucleotide polymorphisms (SNP) within specific genes and their association with psychiatric traits. However, a lack of reproducibility across candidate gene studies have called such targeted approaches into question[22]. Rather than focusing on single genes or single SNPs, GWASes identify associations between SNPs across the whole genome and a given trait or disease phenotype, often in very large cohorts. Large-scale GWASes, such as those performed by the PGC, have revealed the polygenic nature of psychiatric disorders[23]. In turn, the availability of such GWASes has informed a new approach to quantify the polygenic risk for psychiatric disorders. Polygenic risk scores (PRS) are simply summary scores of an individual's genetic risk for a given disorder or phenotype. PRS are calculated by using a count function, adding together the number of 'risk' alleles at a given SNP weighted by the effect size between a given risk allele at that SNP and a disorder of interest. Weights are provided by large-scale GWASes such as the PGC. Thus, PRS can be calculated in any sample that provides genetic data and benefits from the accurate effect size estimates of 'genetic risk' identified from a much larger cohort.

Biological risk factors for Perinatal Mental Illness

The genetic architecture of PMD has not yet been studied in a large-scale GWAS. One study, making use of PRS for MDD and BD (N=1420 cases of PPD and 9473 controls), reported a stronger association between a PRS for BD and PPD than between a PRS for MDD and PPD[24]. This is noteworthy as women who are hospitalized during the postpartum period for perinatal mental illnesses other than BD can be at four times the risk of developing BD compared to women admitted outside of the postpartum period[25], which provides indirect evidence of an association between PPD and BD. However, a study in a larger Danish cohort has found that PRS for MDD was associated with postpartum psychiatric disorders but genetic risk for BP was not[26]. Rantalainen et al., (2020) in a cohort of 742 pregnant women reported that PRS calculated from recent GWASes of MDD, schizophrenia disorder and cross-disorder, but not BD, predicted PPD accounting for ~1% variance in PPD[27]. Further, Rantalainen et al., (2020) demonstrated that the associations between PPD and PRS for MDD, schizophrenia and cross-disorder were fully mediated by the effects of the PRS on prenatal symptoms. These findings highlight the importance of longitudinal data in quantifying the relative contribution of the genome to PMDs.

Hormonal sensitivity and PPD

The estrogen sensitivity hypothesis of PPD suggests that subgroups of women may be especially sensitive to the dynamic fluctuation of estrogens and progesterone that occurs across the peripartum[28-30]. Estrogens (e.g., estradiol and estriol), progesterone, and cortisol increase during pregnancy, and drop precipitously after giving birth. This 'reproductive subtype' of PPD finds support from elegant functional studies, which manipulate circulating estrogen levels and produce differences in mood symptoms, in some but not all, women[28,29]. Similarly, women who experience

depression around the premenstrual, postpartum, and perimenopausal phases may represent a reproductive subtype of MDD, and benefit from treatment with selective serotonin reuptake inhibitors[30]. One small case-control study reported an association between PPD and genetic variation in *ESR1*, which encodes the estrogen receptor, which mediates genomic and non-genomic actions of estrogens. Pinsonneault et al., (2013) identified a microsatellite marker, a TA repeat, which associated with PPD up to 12 weeks after delivery[31]. Costas et al., (2010) also identified 4 SNPs in the *ESR1* gene that were significantly associated with PPD defined as depression within 2 days to 8 months after giving birth, but these associations did not survive adjustment for multiple testing[32].

In addition to preliminary associations between genetic variation in estrogen sensitive genes, a growing number of studies report an association between the epigenetic regulation of estrogen sensitive genes and PPD. Epigenetics is the study of changes in heritability of traits that does not result from changes in the DNA but changes related to the DNA, including DNA methylation, and histone modification from binding of chemical compounds to histone proteins, and regulation of activity of genes by small RNAs. Meaney and colleagues provided one of the first examples of how epigenetics affect behavior in a rodent model of maternal care, with greater physiological stress reactivity associated with lower levels of maternal care and altered DNA methylation of the glucocorticoid receptor gene (*Nr3c1*)[33]. Studies that have focused on perinatal mood have also identified differential methylation of estrogen-sensitive genes in women who were at risk for PPD[29,34]. These studies have been replicated to suggest that differential methylation of estrogen-sensitive genes may be a marker of risk for MDD in women and men[35,36]. Collectively, these

existing studies highlight the need for additional, large-scale analyses of epigenomic biomarkers in the prediction of PMDs.

Towards a Biopsychosocial Prediction Model of Perinatal Mental Health

The biopsychosocial model of health emphasizes the importance of integrating biological, psychological and socio-environmental factors to build a comprehensive understanding of health and disease[37]. In the context of PMD, genetic and hormonal factors have been shown to indirectly influence women's mood by influencing women's responses to psychosocial stressors[38]. In this study, we applied the biopsychosocial model to study factors that influence PMD and also assessed whether there is an interaction of environmental and biological factors. To begin to build a biopsychosocial model for perinatal mental health we made use of the ALSPAC cohort, which provides detailed measures of psychosocial risk factors, individual-level psychological factors and paired genetic/epigenetic data. We do so by integrating relevant measures of psychological and social risk factors in a single 'environmental' model of perinatal mental health. Next, we incorporated individual-level measures of biological risk, specifically PRS for major psychiatric disorders, to build a more comprehensive biopsychosocial model of perinatal mental health. These analyses allow us to test the hypothesis that prediction models that consider both environmental *and* biological factors will provide a better understanding of individual's differences in perinatal mental health across pregnancy and into the postpartum.

THESIS AIMS and HYPOTHESES

Aim 1: Evaluate the contribution of established 'environmental' factors to risk for adverse perinatal mental health outcomes in a large prospective longitudinal cohort: (ALSPAC mothers)

Hypothesis 1: Maternal demographic and psychosocial risk factors (e.g., Age, Stressful life events, Socioeconomic status, High IPSM, Low social support) will partially predict increased perinatal depressive and anxiety symptoms

Aim 2: Examine whether history of sexual abuse can identify women who are more at risk of perinatal mental illness in ALSPAC mothers

Hypothesis 2: Women with history of sexual abuse will have greater perinatal depressive and anxiety symptoms than women without history of sexual abuse

Aim 3: Test if PRS for depressive symptoms can predict perinatal depression in addition to the environmental factors in ALSPAC mothers

Hypothesis 3: PRS for depressive symptoms will partially predict increased perinatal depressive and anxiety symptoms

Aim 4: Examine whether a previously identified epigenetic biomarker of PPD can predict perinatal depression in ALSPAC mothers

Hypothesis 4: Epigenetic biomarkers will identify women with clinical levels of depressive symptoms in the postpartum period

CHAPTER 1: ENVIRONMENTAL AND GENETIC PREDICTION OF PERINATAL MENTAL HEALTH

Environmental factors that have been identified as risk factors for perinatal mental health and child outcome are maternal age at delivery, stressful life events, history of sexual abuse, maternal education, and social support[14,39-42]. To build a biopsychosocial model of maternal perinatal mental health, first, we specified an 'environmental' risk model. The environmental model incorporates both socioeconomic, demographic and psychosocial risk factors for maternal perinatal mental health. Next, we capitalized on advances in population genetics, specifically polygenic risk score methodology, to integrate a measure of biological factor in our 'environmental' (E) risk model: this integrated model was termed the 'Genetic + Environment' (G+E) model. In doing so, we test if a G+E model outperforms a conventional E model in the prediction of maternal perinatal mental health.

Sample

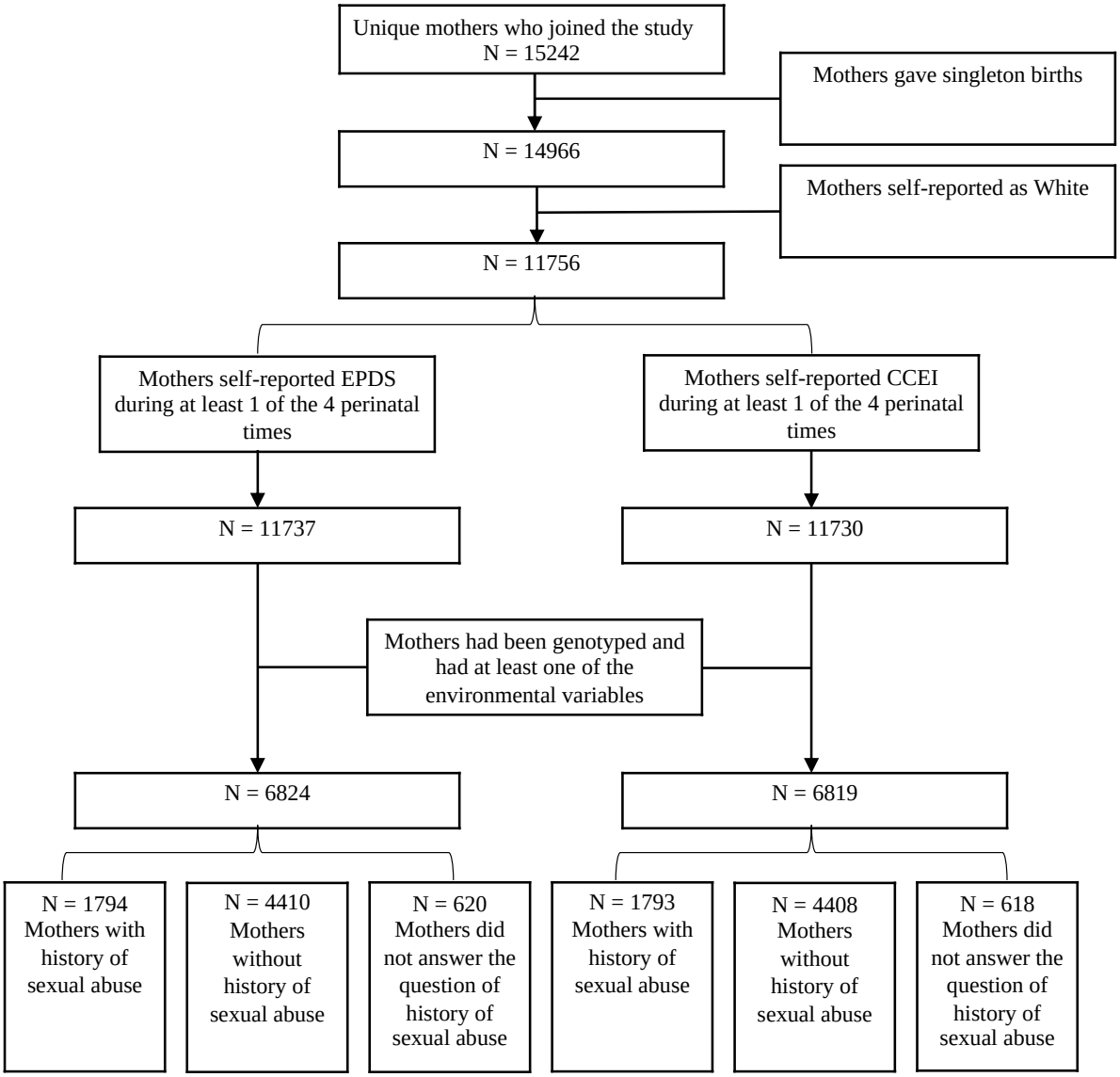
Cohort Description

The data used in this study comes from an existing cohort of the Avon Longitudinal Study of Parents and Children (ALSPAC) which began in 1991 in Southwest England[43]. Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. More information on the cohort profile of ALSPAC mothers can be found elsewhere[44].

Current study sample selection: We included women who gave singleton births, and had self-reported Edinburgh Postpartum Depression Score (EPDS) or Crown-Crisp Experiential Index (CCEI) in at least one of the 4 perinatal times at 18 weeks prenatal, 32 weeks prenatal, 8 weeks postnatal, and 8 months postnatal time (Figure 1). We selected for women who self-reported as

White because the GWASes that informed the PRS used in this study were derived from GWASes in European-ancestry cohorts. We selected again to those who have been genotyped and have at least one of the environmental variables. Table 1 describes the cohort considered for this study. We also compared the environmental factors and mood symptoms of women with and without history of sexual abuse in Table 2. Ethnicity of all ALSPAC mothers are available in Table 3.

Figure 1 ALSPAC Mothers Considered for the Study of Environmental and Genetic Models of Perinatal Mental Health. Mothers from the complete ALSPAC cohort were selected for the current study based on availability of information on their perinatal mood symptoms, environmental variables and genetic variable.



Measures of perinatal mental health: We assessed *maternal symptoms of depression* using the EPDS, which is validated for use in the pre- and postnatal periods[45]. The EPDS is a self-report 10-questionnaire and is one of the most commonly used screening tools for perinatal depression with a score of 13 or above indicating an evidence of clinically relevant symptoms of depression. *Maternal anxiety* was assessed using the free-floating anxiety subscale of the CCEI that includes 8 questions related to anxiety and measures the anxiety from scale of 0 to 16. We examined depression and anxiety symptoms reported at 18 weeks prenatal, 32 weeks prenatal, 8 weeks postnatal and 8 months postnatal period. Primary analysis was carried out on depressive symptoms. Our primary analyses focused on maternal symptoms of depression with secondary analyses of maternal anxiety.

Proxy measures of socioeconomic status: *Household crowding* was defined as the ratio of people per number of rooms. Women reported this information between 0 to 14 weeks in pregnancy if women enrolled before 14 weeks gestation, and between 24 to 41 if they enrolled after 14 weeks gestation. *Maternal education* was self-reported at 32 weeks in pregnancy and scaled from 1 to 5 where 1 indicated certificate of secondary education, 2 indicated vocational education, 3 indicated O-level, 4 indicated A-level, and 5 indicated university degree.

Childhood sexual abuse: History of sexual abuse before the age of 16 was assessed at 32 weeks in pregnancy through self-report of questions regarding non-contact sexual abuse (e.g., flashing) and 4 questions on contact sexual abuse (e.g., unwanted touching or penetration).

Psychosocial risk factors: *Maternal age at delivery* was self-reported in pregnancy. *Stressful life events* within 12 months before pregnancy were asked at 18 to 20 weeks in pregnancy using 41 questions related to loss or illness of partner or family, conflict with partner or family, illness or hospitalizations of the woman, possible harm to baby or child, bleeding and possibility of miscarriage, marriage, starting a new job or problem at work, relocation, financial problem, homelessness, accident, trouble with the law, and attempted suicide. Higher score indicated greater perception that the event affected the person. *IPSM* questions were asked and self-reported at 18 week prenatal period. The questionnaire included 36 questions and higher score indicated greater negative interpersonal sensitivity. The median of the score was used as the threshold for high and low IPSM.

Social 'protective' factors: *Social support* questions were asked between 14 to 37 weeks in pregnancy for 90% of the mothers and 4 months after delivery for 10% of the mothers who enrolled after 30 weeks in pregnancy. For the purpose of this study, we focused on the prenatal social support scores to examine the role of prenatal environment on perinatal mental health. Social support was measured with 10 questions related to sharing feelings and support from partner, other pregnant women, neighbors, family, friends and the state. Higher score indicated feeling highly supported and summated to a weighted perceived social support score. The median of the score was used as the threshold for high and low social support.

Genotyping and Quality Control

Genetic data were generated using the Illumina human660W-quad array at Centre National de Génotypage based on blood samples taken during the pregnancy or during follow up clinics.

Genotypes were called with Illumina GenomeStudio followed by extensive quality control. First, duplicate SNPs (i.e., markers assessing genetic variation at the same site) were removed, SNPs with call rate <95% were removed, and the sex assignments were checked based. Then identity by descent was calculated using Plink v2.0 on chromosome 22 of ALSPAC mothers. Identity-by-descent is a measure of relatedness where individuals are defined as relatives based on the ratio of identical SNPs which provides a kinship coefficient. Kinship coefficient >0.9 is defined as identical individuals or monozygous twins, kinship coefficient equal to 0.5 is defined as first-degree relatives, and kinship coefficient equal to 0.25 is defined as second-degree relatives[46]. We did not identify any women who were identical, monozygous twins, or first-degree relatives, therefore no mothers were removed in this process. Lastly, we used a measure of imputation accuracy (INFO score) to remove any imputed SNPs with a low probability of accurate imputation (INFO score < 0.3). INFO score reflects the imputation accuracy of each genetic variant from 0 to 1, where higher score suggests greater accuracy.

Polygenic Risk Score (PRS) Calculation

We used summary statistics from 9 datasets representing 7 GWASes to derive multiple PRS for depressive symptoms, BD and anxiety disorder[47-53]. For two of the GWASes that included a specific cohort (from the commercial genotyping service 23andme) summary statistics from only the top 10,000 SNPs were provided to protect participant privacy, therefore, we calculated the PRS with and without the 23andme cohort. PRS was calculated using PRSoS including high quality imputed SNPs with p-value less than 0.05 or 0.01 based on which threshold selected SNPs with the highest Pearson correlation with depressive and anxiety symptoms[54]. We examined the bivariate association PRS calculated at different p-value thresholds and maternal mental health

symptoms and selected the PRS that was the most highly correlated with depressive symptoms over time.

Population stratification

We described population structure using a Principal Components Analysis of non-imputed (directly called) genotypes[55]. Only SNPs in approximate linkage disequilibrium (r^2 <0.2 within a window of 50 SNPs) with minor allele frequency >5% were used. The first 10 principal components were regressed out of the PRS to reduce dimensionality and maximize the variance of the data.

Data Analysis

Linear Regression Models and Model Fit based on R^2 values

Known environmental risk factors for perinatal mental health were used to build models of perinatal mental health in ALSPAC mothers or the Environmental Model (E). We created a model with known environmental risk factors (E Eq1), and subsequently added Prenatal Social Support, a known environmental protective factor (E Eq2). Then we added IPSM, a strong environmental risk factor that may mediate between other environmental factors (E Eq3). We built the Genetic + Environmental Model (G+E) by adding the PRS score for depressive symptoms that had the highest correlation with perinatal depressive symptoms to Eq2 of the E model (G+E Eq4). We also tested the G+E model of Eq3 (G+E Eq5). Linear regression was carried out in SPSS.

Environmental Model Equation 1 (E Eq1)

Maternal Mood ~ Maternal Age at Delivery + Crowding + Stressful Life Events + Level of Education + History of Sexual Abuse

Environmental Model Equation 2 (E Eq2)

Maternal Mood ~ Maternal Age at Delivery + Crowding + Stressful Life Events + Level of Education + History of Sexual Abuse + Prenatal Social Support

Environmental Model Equation 3 (E Eq3)

Maternal Mood ~ Maternal Age at Delivery + Crowding + Stressful Life Events + Level of Education + History of Sexual Abuse + Prenatal Social Support + Prenatal IPSM

Genetic + Environmental Model Equation 4 (G+E Eq4)

Maternal Mood ~ Eq2 + PRS for Depressive Symptoms

Genetic + Environmental Model Equation 5 (G+E Eq5)

Maternal Mood ~ Eq3 + PRS for Depressive Symptoms

Statistical Comparison of Models based on R^2 or adjusted R^2 of linear regression models and significant difference between models based on ModelCompare, Akaike Information Criteria (AIC) and Confidence Interval (CI)

In order to compare the E model and the G+E model, we examined the R^2 values of linear regression models. The R^2 values that indicate the percent variance of maternal mood symptoms

explained by the models were examined at the 4 perinatal times separately. The E models and G+E models were compared using the adjusted R^2 values. In additional analysis, women were stratified to those with history of sexual abuse and without history of sexual abuse in order to examine the difference in prediction of perinatal mood by the models across the two groups. The significance of change in R^2 from E model to G+E model was calculated using ModelCompare function in RStudio. We indicated with asterisks the significant changes in R^2 ($p < 0.05$). We also compared the AIC of the E model and the G+E Model to identify which model had a better fit. Models that have lower AIC values are considered as better fit for the cohort. If AIC of G+E model minus AIC of E model is <2, the probability that the G+E model is better than E model is high, if >2 but <4, the probability is strongly supported, and if >10, the G+E model is not a better model than the E model. We calculated the probability that the i^{th} model is a better model than an original model (pi), defined as $e^{-(\text{AIC of G+E} - \text{AIC of E})/2}$. Lastly, we calculated the Confidence Interval (CI) after bootstrapping for 1000 times. We calculated the CI using the function Boot.regression and Boot.CI from the package Boot in RStudio.

Generalized Estimating Equation (GEE) for Longitudinal Symptom Analyses

GEE is a form of a generalized linear model that can accommodate repeated and inter-correlated dependent variables that assessed over time. Estimates from GEE models provide a population averaged effect of an exposure/predictor variable on the dependent variable i.e., a regression of population means of outcome estimated by changes in the mean of covariates[56]. In this study, GEE was calculated in RStudio using the function Geeglm from the package Geepack. We used the structure autoregressive order 1 based on the assumption that maternal mood at two consecutive timepoints are likely to be more highly correlated than non-consecutive timepoints. GEE allows

us to examine the prediction of longitudinal symptoms by relevant environmental or genetic risk factors. The analysis was repeated after the variables in the model were scaled by *(x-mean of x)/SD of x* in order to report the standardized beta estimates in addition to non-standardized beta estimates. When examining interaction of terms, we ensured to include the interaction of the variables of interest with other variables in the model in addition to the interaction between the variables of interest to account for ther effects on the interaction between the variables of interest[57].

Mediation Analysis

We sought to independently replicate the findings of Rantalainen et al., (2020) who showed that the association between maternal PRS for psychiatric disorders and depressive symptoms in the postpartum were fully mediated by the association between PRS and maternal symptoms of depression in pregnancy. Mediation analyses were carried out using SPSS v24 and PROCESS macro v3.5. Model 4 with bootstrapping (N=10000). The environmental variables from Eq2 were used as the covariates. The variables in the model were scaled by *(x-mean of x)/SD of x* in order to report the standardized beta estimates in addition to non-standardized beta estimates.

Results

Demographics and Selective Attrition

The current study had total of 11756 participants, out of whom 6832 had been genotyped and 4924 who had not been genotyped (Figure 1). It has been shown previously that women with greater depressive or anxiety symptoms were less likely to return the questionnaires[6]. Based on student's t-tests, women who were genotyped had on average higher age at delivery, lower household crowding, lower stressful life events, higher prenatal social support, and lower depressive and

anxiety symptoms (Table 1). Based on chi-squared test, the level of maternal education higher in women who have been genotyped while history of sexual abuse status were not significantly different (Table 1).

Correlation analyses

To identify the genetic contribution to perinatal depression, we calculated PRS from 9 recent GWASes on MDD, anxiety disorder, and BD, and examined their correlation with perinatal depressive symptoms in ALSPAC mothers (Figure 2). The different GWASes came from multiple cohorts including PGC, UK Biobank, 23andMe, GERA, SSGAC, and GPC, and different GWASes had different numbers of SNPs. PRS 1 and 2 provided genetic risk for MDD based on the most recent GWAS of MDD[47], PRS 3 was the genetic risk for depressive symptoms based on multi-trait analysis of subjective well-being and neuroticism[52], and PRS 4[53], 5[53], 6[48], and 7[49] were also genetic risk for MDD calculated from earlier GWASes. Then we examined PRS of anxiety disorder (PRS 8)[50], and PRS of BD (PRS 9)[51], due to the known association of these psychiatric disorders with perinatal depressive symptoms. Out of the 9 PRS correlated with perinatal depressive symptoms in ALSPAC mothers, PRS 1-4 were similarly correlated at r = 0.063 to R = 0.13. Among PRS 1-4, PRS that had the highest correlation at all perinatal periods came from PRS of depressive symptoms, or PRS 3. It was correlated to perinatal depressive symptoms in the ALSPAC mothers at r = 0.096 to 0.13 (Figure 2). Therefore, PRS 3 was used as the genetic risk for perinatal mood in all subsequent analyses.

All of the variables in the E model (E Eq1, E Eq2) were significantly correlated with perinatal mood (Figure 3). Household crowding, stressful life events, and history of sexual abuse were

positively correlated with mood at all perinatal periods, and stressful life events were correlated at the highest level ranging from r = 0.26 to 0.41. Maternal age at delivery and level of education were negatively correlated with mood (Figure 3). Prenatal social support was correlated at the highest level among the negatively correlated variables, ranging from r = –0.26 to –0.33. Prenatal social support was considered as a protective factor against perinatal depressive and anxiety symptoms and it was included in the second version of the E model (E Eq2). Stressful life events were positively correlated with crowding and history of sexual abuse while prenatal social support was negatively correlated with the given values. Prenatal social support was positively correlated with age at delivery and level of education. Stressful life events and prenatal social support were negatively correlated with each other at r = –0.23. In summary, stressful life events during pregnancy and interpersonal sensitivity had the highest positive correlation with perinatal depressive and anxiety symptoms. Social support had the highest negative correlation with the mood symptoms. History of sexual abuse and interpersonal sensitivity were highly positively correlated with stressful life events while social support was highly negatively correlated with stressful life events.

We examined correlations between PRS and measures considered in our environmental model to examine potential gene-environment correlations. Correlations between PRS and environmental variables were generally modest but significant. The PRS was positively correlated with maternal history of sexual abuse, stressful life events, crowding and interpersonal sensitivity, and PRS was negatively correlated with maternal age at delivery, level of education and social support in pregnancy. However, the correlation r values were less than 0.5 therefore the PRS was not considered to be colinear with the environmental variables.

Linear regression analyses

Figure 4 compares the R^2 values of E model without social support (E Eq1) and with social support (E Eq2) and the adjusted R^2 values of E model with social support (E Eq2) and G+E model with social support (G+E Eq4). When the environmental risk factors without social support (E Eq1) were used to predict perinatal depressive symptoms in the ALSPAC mothers, they could predict 19.5% of the variance at 18 weeks prenatal, 13.8% at 32 weeks prenatal, 7.64% at 8 weeks postnatal, and 7.87% at 8 months postnatal. When the protective factor of prenatal social support was added to the E model (E Eq1), the percentage variance explained increased to 23.7% at 18 weeks prenatal, 19.9% at 32 weeks prenatal, 13.5% at 8 weeks postnatal and 12.7% at 8 months postnatal. The E model with social support (E Eq2) was also able to explain anxiety symptoms more than the E model without social support (E Eq1). The E model explained depressive symptoms more in the prenatal period compared to the postnatal period. The PRS score was added to the E model to make the G+E model (G+E Eq4), and adjusted R^2 were compared between E and G+E model. The G+E model had higher adjusted R^2 than E model at 18 weeks prenatal and 8 months postnatal for depressive symptoms but had lower adjusted R^2 at 32 weeks prenatal and 8 weeks postnatal. The G+E model had higher adjusted R^2 than E model at all perinatal period for anxiety symptoms. The change in R^2 between the G+E and E models were all statistically significant. G+E model was a better fit compared to the E model at all timepoints for both depressive and anxiety symptoms based on lower Akaike Criterion (AIC) in G+E model. The probability that the E model is a better model than the G+E model was 0. The 95% confidence interval of the coefficient of PRS predicting perinatal depression were significant (Table 4 and 5).

Considering that the PRS for depressive symptoms was predicting perinatal depressive symptoms in ALSPAC mothers, although with small contribution, we also examined whether the PRS for depressive symptoms alone could identify women with higher or lower perinatal depressive symptoms (Figure 5). We found that women who had PRS that was 1 standard deviation (SD) or higher above the mean had on average greater depressive symptoms throughout the perinatal period than women who had PRS that was 1 SD or higher below the mean. This further supported the potential for PRS of depressive symptoms to identify women at greater risk for higher perinatal depressive symptoms, although the accuracy for predicting depressive symptoms will vary by person.

Longitudinal Analyses: GEE Models

GEE models of maternal symptoms over time showed that the PRS of depressive symptoms is significant during the perinatal period (Table 6, 7). The environmental variables also predicted depressive symptoms throughout the perinatal period. We analyzed the interaction of PRS with time. We considered interaction of all of the G+E variables with time and PRS to account for potential confounding of interaction of PRS with time by the interaction of the other variables with PRS and time[57]. In contrast to previous findings, we did not find any interaction between PRS and time (Table 6, 7). We also did not find any interaction between PRS and history of sexual abuse (Table 8, 9).

Mediation analyses

In a previous study, the association between a PRS for MDD and PPD was fully mediated by maternal prenatal symptoms of depression[27]. To replicate these findings, we tested if the

association between maternal PRS and maternal postnatal symptoms of depression was mediated by increased symptoms of depression in the prenatal period (Figure 6). We analyzed PRS of depressive symptoms (PRS 3) and PRS of MDD from the most recent GWAS of MDD (PRS 1). We found that the prediction of postpartum mood by PRS was partially mediated by prenatal mood symptoms for both PRSes.

Stratification by abuse and social support

We identified that history of sexual abuse was strongly positively correlated with depressive and anxiety symptoms (Figure 3). On the other hand, prenatal social support had high negative correlation with perinatal depression and anxiety, low negative correlations with history of childhood sexual abuse, and moderate negative correlations with stressful life events around pregnancy (Figure 3). In order to examine the buffering effect of social support for history of sexual abuse, we stratified the women to those with and without history of sexual abuse and stratified those women subsequently to those with high or low prenatal social support (Figure 7). We found that women who had history of sexual abuse and low social support had the highest perinatal depressive and anxiety symptoms, and women without history of sexual abuse and high social support had the lowest perinatal mood symptoms. However, women who had history of sexual abuse and had high social support had on average lower mood symptoms than women who did not have history of sexual abuse but low social support. Prenatal social support was a better predictor of perinatal mood than history of sexual abuse alone. We replicated this analysis for more severe history of sexual abuse involving contact abuse and found that women without contact sexual abuse and low social support had higher depressive symptoms than women with abuse and

high social support (Figure 8). Therefore, the finding that social support has a strong protective effect was relevant for women with contact and non-contact history of sexual abuse.

Exploratory analyses: the impact of abuse on the genetic prediction of maternal depression

Previous findings in large studies of depression provide conflicting evidence that a history of abuse influence the genetic prediction of depression. Peterson et al., (2018) first reported that a history of adversity associated with a weaker genetic signal in a GWAS of depression in a large group of Chinese women. In contrast Coleman et al., (2019) showed the genetic prediction of depression was strengthened in UK Biobank participants reporting a history of adversity. We sought to examine these associations in the ASLAPC cohort by comparing the strength of association between maternal PRS and maternal symptoms of depression in women with and without history of sexual abuse. We found that women with history of sexual abuse had on average higher depressive and anxiety symptoms and that the E model explained depressive and anxiety symptoms better in women with history of sexual abuse (Figure 9a,9b,10a,10b). In the ALSPAC mothers, PRS alone predicted depressive symptoms at 18 weeks prenatal better in women without history of sexual abuse. In contrast, in the later perinatal periods, the PRS performed better in the prediction of depression in women with history of sexual abuse (Figure 9c). The association between the PRS and depression in early pregnancy is in line with the findings from Peterson et al., (2018) while the prediction of depression in the later perinatal period followed the findings from Coleman et al., (2019). When we predicted anxiety symptoms with PRS alone, the PRS predicted better in women with history of sexual abuse at all perinatal times (Figure 10c). Regardless of abuse status, the G+E model (G+E Eq3) was a better predictor of depressive and

anxiety symptoms than E model alone (E Eq2) at all perinatal periods based on greater adjusted R^2 values of the G+E model and AIC of the models (Figure 9d,9e,10d,10e).

We explored the relationship between the environmental and genetic variables by building a dendrogram of the variables (Figure 11). The dendrogram identified that the PRS of depressive symptoms was most closely related to household crowding and next closely related to history of sexual abuse and stressful life events. Maternal age at delivery, level of education and prenatal social support were most closely related to each other, and negatively correlated with the PRS. Then it was possible that the PRS was contributing to the prediction of perinatal mood by association with crowding, history of sexual abuse and stressful life events which were all associated with greater perinatal mood. Therefore, we carried out an additional analysis where the three environmental variables were regressed out of the PRS of depressive symptoms (PRS 3) and the residual of the linear regression was correlated with the environmental variables and perinatal mood (Table 10). When the three environmental variables were regressed out of the PRS, we found that the correlation of the PRS with perinatal mood decreased, but remained significant, and concluded that the PRS was contributing independently to the prediction of perinatal mood.

Environmental and Genetic model of perinatal mental health with prenatal IPSM

Lastly, we explored the role of prenatal interpersonal sensitivity measured by IPSM in perinatal mood in the ALSPAC mothers. We had stratified women to those with or without history of sexual abuse and with high or low prenatal IPSM (Figure 7). Group of women with history of sexual abuse and high prenatal IPSM had on average the highest depressive and anxiety symptoms while group of women without history of sexual abuse and low prenatal IPSM had on average the lowest depressive and anxiety symptoms. We also found that women with history of sexual abuse with

low prenatal IPSM had on average lower depressive and anxiety symptoms than women without history of sexual abuse with high prenatal IPSM. We interpreted that prenatal IPSM may be a reflection of the long-term effect of history of sexual abuse in addition to the proximal effect of stressful life events around pregnancy, based on the significant correlation between IPSM and the given environmental factors (Figure 3). Therefore, we compared the prediction of perinatal depressive symptoms using environmental variables that included prenatal IPSM (E Eq3) as well as PRS of depressive symptoms (G+E Eq5). We found that when the prenatal IPSM was added as an environmental risk factor, the percent variance of depressive symptoms explained by the E model increased (Figure 12). The environmental model for maternal depression/anxiety in the ALSPAC cohort including prenatal social support and prenatal IPSM cumulatively explained 17.4%-32.5% of the variance in maternal symptoms from early pregnancy to the postpartum. When the PRS of depressive symptoms was added to the model, it remained significant, however the percent variance of depressive symptoms explained increased less than 1%.

CHAPTER 2: ESTROGEN-SENSITIVITY HYPOTHESIS AND EPIGENETIC BIOMARKERS OF POSTPARTUM DEPRESSION

Epigenetic mechanisms, such as DNA methylation, are chemical modifications to the genome that can alter genomic function without changing the underlying genomic sequence and have been proposed as one mechanism for how environment can influence genomic function. Further, biomarkers based on DNA methylation are beginning to be explored as clinically relevant predictors of health and disease. In the context of perinatal mental health, Guintivano et al., (2014) described an estrogen-sensitive epigenetic biomarker of PPD based on DNA methylation of estrogen sensitive genes, building on a number of studies linking estrogen sensitivity to increased risk for PPD.

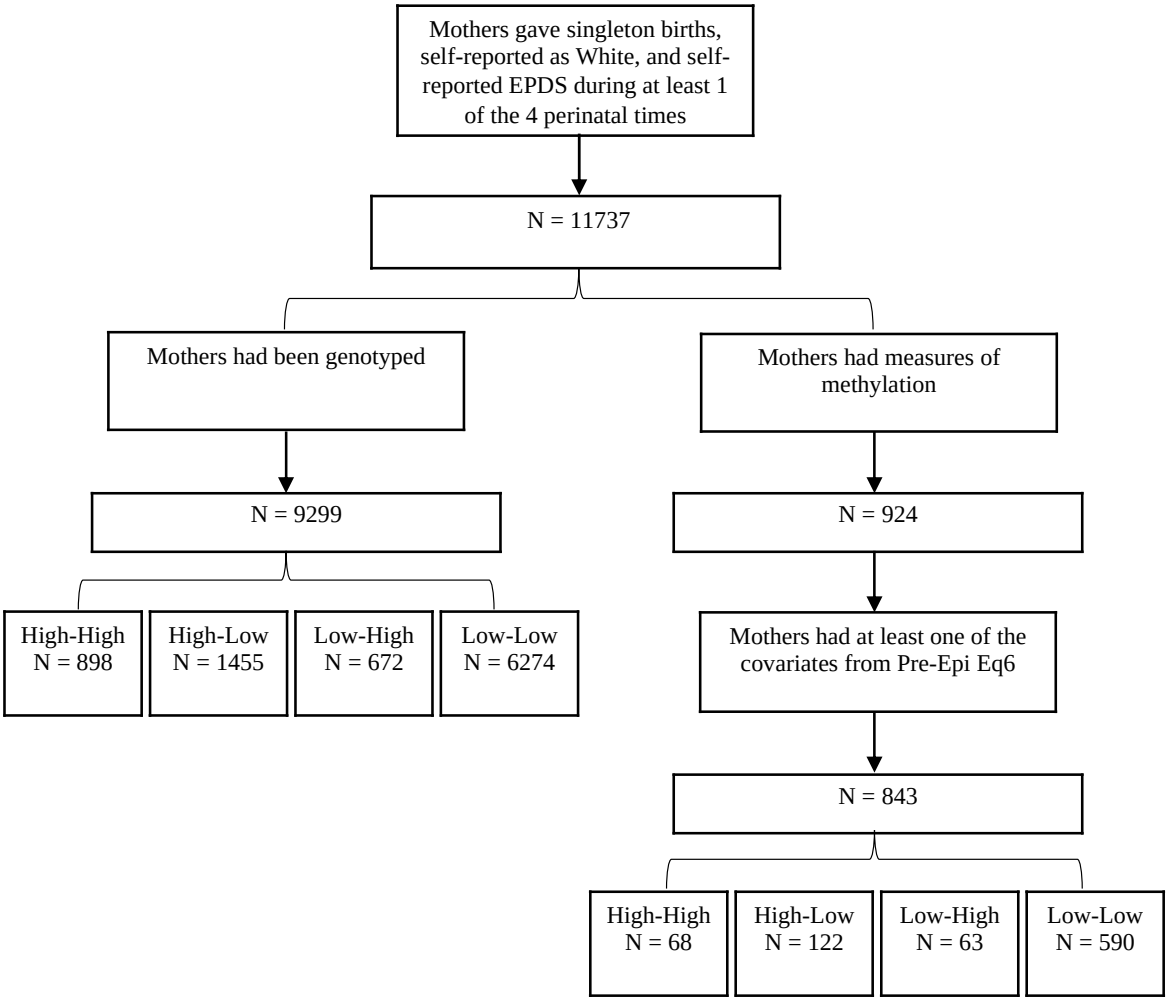
The estrogen-sensitivity hypothesis of PPD posits that depression during the perinatal period may be a distinct reproductive subtype of MDD that occurs as a result of the sensitivity towards the drop in pregnancy-related hormones after giving birth[30]. The estrogen sensitivity hypothesis of PPD has been studied through genetic and epigenetic biomarker studies. Guintivano et al., (2014) identified two biomarker loci at *HP1BP3* and *TTC9B,* estrogen-sensitive genes, that were differentially methylated in women who developed PPD compared to women who did not. Methylation levels were measured from blood collected during pregnancy, and the methylation levels at the two biomarkers alone predicted PPD in pregnant women with history of BD or MDD with a high degree of accuracy (Model area under the curve [AUC]= 0.87) for women who had not been depressed antenatally, and with AUC of 0.12 for women who had been depressed antenatally. The difference in prediction of PPD in women with and without prenatal depression was attributed in part to the contribution of the effects of differences in the proportions of specific

blood cells (monocytes) across groups. When a measure of cell type proportions was considered together with DNA methylation of *HP1BP3* and *TTC9B* the prediction accuracy of the model improved (AUC of 0.96 for both antenatally depressed and euthymic women). Osborne et al., (2016) replicated the association between this epigenetic biomarker and PPD in women with (N=51) and without (N=240) previous history of psychiatric disorder. In both women with and without history of psychiatric disorder, the model could predict PPD in pregnancy with AUC of 0.81, and the PPD status could be predicted similarly in antenatally depressed or euthymic women. In this study, *HP1BP3* contributed significantly to the prediction of PPD in antenatally depressed women but not in women who had not been depressed in pregnancy.

Women with previous histories of MDD may be more affected by changes in estrogen-signaling and therefore are more vulnerable in the postpartum period when pregnancy-related hormones drop drastically. Collectively, the two replication studies have demonstrated that the epigenetic biomarker of DNA methylation within HP1BP3 and TTC9B and measure of cell-type heterogeneity is a potential predictor for MDD or PPD. We replicated this study in the ALSPAC cohort, a larger study than the previous replication studies, to test if a biomarker of estrogen sensitivity predicts PPD in women with and without antenatal depressive symptoms. Prior to replicating the previous studies, we first stratified the ALSPAC mothers with different trajectories of perinatal depressive symptoms. It is plausible that the estrogen-sensitive biomarker predicts PPD in some but not all women. Given the neuroprotective effects of circulating estrogens on risk of depression, but the increased risk of PPD associated with dramatic declines in estrogens, we hypothesized that the estrogen-sensitive biomarker would most closely associate with the 'low-high' trajectory of symptoms of depression.

Sample

Figure 13 ALSPAC Mothers Considered for the Study of Estrogen-Sensitive Epigenetic Models of Perinatal Mental Health. Mothers from the complete ALSPAC cohort were selected for the current study based on availability of information on their perinatal mood symptoms, genetic or epigenetic variables, cell ratio and covariates. The number of women included in the four trajectories of depressive symptoms (high-high, high-low, low-high, low-low) are based on clinical threshold of EPDS >=10).



Cohort Description

ALSPAC mothers with genetic and DNA methylation data were stratified by trajectories of perinatal depressive symptoms based on clinical or subclinical thresholds. Subclinical threshold of high depressive symptoms was EPDS >=10 and low was EPDS <10 while clinical threshold of high depressive symptoms was EPDS >=13 and low was EPDS <13. Women were stratified to 4

groups of low-low, low-high, high-low and high-high depressive symptoms trajectories based on the mean prenatal depressive symptoms and mean postnatal depressive symptoms, and if there were missing values in one of the two time points in the prenatal or postnatal period, the existing value was used as the overall depressive symptoms during that period.

Epigenetic Data

The methylation levels were measured during the pregnancy from peripheral blood provided by total of 1018 mothers who participated in the ALSPAC cohort[58]. For the analysis in the current study, we selected 924 mothers who had available information on the methylation level based on the selection criteria of self-reporting as White, giving singleton birth, and self-reporting EPDS in at least 1 of the perinatal periods (Figure 13). Cell count in peripheral blood estimated by Houseman algorithm was provided for ALSPAC mothers, and cell ratio was calculated as the ratio of monocytes to the sum of CD8 T cells, CD4 T cells, B cells and granulocytes.

Data Analysis

Linear Regression Models

We built a model of perinatal depression with known risk factors and added epigenetic biomarkers of PPD[34-36]. In addition to the environmental risk factors of perinatal mental health, our 'base model' also included additional risk factors for PPD (Pre-Epi Eq6). Women with previous pregnancies have already experienced the drop in pregnancy related hormones. Therefore, number of previous pregnancies was added as a covariate as previous pregnancies might have affected DNA methylation in the epigenetic biomarkers of interest in the ALSPAC mothers[59]. History of hospitalization for psychiatric disorder or family history of psychiatric disorder were added

because the epigenetic biomarkers have predicted PPD better in women with history of psychiatric disorders. Next, we examined whether the epigenetic biomarkers predicted PPD independent of these relevant covariates in an 'epigenetic biomarker model' (Epi Eq7). Lastly, we combined the covariates and epigenetic biomarkers to build the 'combined epigenetic biomarker model' (Epi Eq8). We carried out additional analysis after stratifying the women to those with and without history of sexual abuse and compared the AIC of the models and calculated the AUC to evaluate the models.

Base Model Equation 6 (Pre-Epi Eq6):

Maternal Mood ~ Maternal Age at Delivery + Crowding + Stressful Life Events + Level of Education + Number of Previous Pregnancies + History of Hospitalization for Psychiatric Disorder + Family History of Psychiatric Disorder

Epigenetic Biomarker Model Equation 7 (Epi Eq7):

Maternal Mood ~ Methylation at Cpg21326881 + Methylation at Cpg00058938 + Cell Ratio + Cell Ratio x Methylation at Cpg21326881

Combined Epigenetic Biomarker Model Equation 8 (Epi Eq8):

Maternal Mood ~ Pre-Epi Eq6 + Epi Eq7

Results

When we stratified the ALSPAC mothers based on trajectories of perinatal depressive symptoms, women in the low-high group was the smallest in number, followed by the high-high group, high-low group and low-low group (Figure 14a). Unlike the findings of Guintivano et al., (2014), the difference in blood cell-ratio in the 4 groups of women were not significant (Table 11). However, the difference in the methylation level at cpg00058938 was significant (Table 11). Moreover, this difference was significant only between low-high group of women and the other three groups, suggesting differential methylation at cpg00058938 for women who were euthymic in pregnancy and developed PPD (Table 12). To compare the epigenetic predictors with genetic predictors, we also examined whether the difference of PRS for depressive symptoms was significant between women in the low-high group and the other three groups. We found that the PRS was significantly different between groups, but this was not limited to women from the low-high group (Table 15, 16). Then we compared the R^2 values of the Epi Eq7 including only the epigenetic biomarkers in the four groups of women (Table 13, 14). The epigenetic biomarkers could explain 8% of the variance in depressive symptoms at 8 months postnatal in the low-high group with statistical significance when the subclinical threshold was used (Table 13). However, the epigenetic biomarkers could also explain prenatal depressive symptoms in the low-low and high-high group or postpartum depressive symptoms in the low-low group as well (Table 13, 14). The epigenetic biomarkers could not explain prenatal depressive symptoms in high-low group (Table 13, 14). These results suggest that the epigenetic biomarkers alone could predict depressive symptoms in the perinatal period, and could predict PPD in women who were antenatally euthymic when subclinical threshold of depression is used.

As we had identified that women with history of sexual abuse had greater mean perinatal depressive symptoms in Chapter 1, we examined the prediction of depressive symptoms using epigenetic biomarkers stratified by history of sexual abuse again. We carried out a stratified analysis of perinatal depressive symptoms in women with and without history of sexual abuse with Pre-Epi Eq6 and with Epi Eq8 and measured the change in AIC (Figure 14b). The change of AIC of the Pre-Epi Eq6 to Epi Eq8 was positive in women without history of sexual abuse while it was negative in women without history of sexual abuse (Figure 14b). A negative change in AIC indicates that AIC of Epi Eq8 was smaller than AIC of Pre-Epi Eq6 and that Epi Eq8 is a model with a better fit. This finding suggested that adding the epigenetic biomarkers to the covariates improved prediction of perinatal depressive symptoms only in women with history of sexual abuse.

Taken together, These analyses support the findings of Guintivano et al., (2014) that estrogen-sensitive epigenetic biomarker predicts perinatal depressive symptoms in a large low risk community sample of ALSPAC mothers. We extend the findings of Guintivano et al., (2014) to show that this biomarker may be of especial relevance for identifying a sub-group of women who experience low symptoms in pregnancy followed by high symptoms postpartum. However, we note that the predictive value of this biomarker was generally small and was contingent upon other psychosocial risk factors (e.g., history of sexual abuse). The epigenetic biomarkers predicted perinatal depressive symptoms better in women with history of sexual abuse.

DISCUSSION

Findings from the Current Study in Context

In this study, we sought to develop a comprehensive model of perinatal depression integrating biological, psychological, and social risk factors in a large pregnancy cohort that provided repeated measures of maternal mental health across pregnancy and into the postpartum. We add to the literature in several important ways 1) we identified a genetic risk factor that accounted for a small but significant proportion of the variance in maternal perinatal symptoms of depression, 2) we provide evidence against previous findings[27] that the prediction of postpartum depressive symptoms by maternal PRS for depression is fully mediated by prenatal symptoms of depression, as we found only partial mediation, 3) we highlighted the critical importance of prenatal social support, which had a larger influence on maternal symptoms of depression than other prominent risk factors e.g., childhood sexual abuse, 4) we found that including the prenatal IPSM into the known environmental and genetic model provided the most predictive model of perinatal mood symptoms, and 5) we showed that an estrogen-sensitive epigenetic biomarker predicts prenatal and postnatal depressive symptoms, and predicts postpartum depressive symptoms best in women who were antenatally euthymic and in women with history of sexual abuse. These findings advance our understanding of the genetic and epigenetic contribution to perinatal mental health and identify key targets for interventions designed to improve maternal perinatal mental health.

Our findings highlight the profound importance of social support as a protective factor for perinatal mental health that have been previously identified in diverse cohorts[14,16,18]. Specifically, in our study social support appeared to be of greater relative importance than childhood sexual abuse on perinatal depression and anxiety. Women with history of sexual abuse and low prenatal social

support were at the greatest risk for high depressive and anxiety symptoms, while women without history of sexual abuse and high prenatal social support were most protected from depressive and anxiety symptoms. Furthermore, women who had history of sexual abuse and high prenatal social support had lower depressive symptoms than women without history of sexual abuse and low prenatal social support, and the level of anxiety symptoms were also higher for women without history of sexual abuse and low prenatal social support. Based on these findings, social support during pregnancy may have a stronger effect on predicting perinatal mental health due to the proximity of its effect, while the long-term effects of history of sexual abuse should not be discounted. Clinically, these findings suggest that women with and without history of sexual abuse may both benefit from social support during pregnancy and that social support may offset the effects of sexual abuse on perinatal depression. These findings highlight the importance of preventing early life sexual abuse to promote women's mental health during the perinatal period and contribute to the existing studies that social support has a buffering effect on the adverse effects of interpersonal adversities that occurred before the perinatal period[15,17].

We examined multiple known environmental predictors of perinatal mental health and added to these predictors PRS for depressive symptoms, a potential biological predictor of perinatal mental health. Our PRS of depressive symptoms was selected from multiple PRSes calculated from GWASes of MDD, anxiety disorder, BD and the depressive symptoms. The PRS that most closely associated with maternal perinatal depression was a PRS derived from the findings of Turley et al., (2018) who used a multi-trait analysis of genome-wide association studies to identify the genetic contributions to depressive symptoms, considering the joint associations of the genetic contributions to subjective well-being and neuroticism[52]. We found that the PRS of depressive

symptoms had the highest correlation with perinatal depressive and anxiety symptoms, followed by PRS of MDD from the most recent GWAS of MDD with the largest sample size. Perinatal depression and anxiety were correlated in the given cohort, and the PRSes of depressive symptom or MDD were correlated with depressive and anxiety symptoms, suggesting that depression and anxiety may have a shared etiology. PRS for depressive symptoms was also correlated with a history of sexual abuse and a proxy measure of SES (household crowding), although further analysis showed that the PRS was contributing to the prediction of perinatal mood independently of these environmental factors.

Our GEE analysis showed that the environmental and genetic variables predicted perinatal depression longitudinally and that there was no interaction between PRS and time. Thus, the specific genetic predictors used in this study did not discriminate pre from postnatal symptoms. We also tested for interaction between PRS and history of sexual abuse as we had found that PRS predicted depressive symptoms better in women without history of sexual abuse at 18 weeks prenatal but not at later perinatal periods (Figure 9c). We did not find any significant interaction between history of sexual abuse and PRS through the GEE analysis. We interpreted this finding that the effect of the PRS predicting depressive symptoms at 18 week prenatal is marginal, and overall there is no interaction between PRS and history of sexual abuse when the entire perinatal period is considered.

We sought to compare the findings from the ALSPAC cohort with existing genetic studies of perinatal depression. Rantalainen et al., (2020) reported that PRS of MDD of multiple publicly available GWASes were predicting PPD fully mediated by prenatal depression[27]. We found only

a partial mediation of prediction of postnatal mood by PRS through prenatal mood, in contrast to the previous study. We tested for both anxiety and depressive symptoms and found the same result. Compared to the study by Rantalainen et al., (2020) which considered the covariates of age at delivery, family structure, BMI in early pregnancy, cigarette smoking, education and alcohol use in early pregnancy and had 742 participants, we have different covariates and a larger population size. We did not include family structure, BMI in early pregnancy, cigarette smoking and alcohol use in early pregnancy as covariates. However, we considered crowding, stressful life events around pregnancy, history of sexual abuse, and prenatal social support that had not been considered in the previous study. Therefore the current study additionally contributes to the knowledge of genetic predictors of perinatal depression by identifying that PRS of depressive symptoms or MDD can predict postnatal mood independently from prenatal mood even when important covariates were considered.

Adverse childhood experiences have emerged as clinically relevant risk factors for perinatal mental illness[39]. However few studies have examined how childhood sexual abuse may influence the genetic prediction of depression, with contrasting evidence that early life adversity weakens[60] or strengthens[61] the genetic prediction of MDD. In a study of Han Chinese women with recurrent depression, a new genetic locus associated with MDD was identified only in women who did not experience any major life adversity or childhood sexual abuse[60]. In contrast, Coleman et al., (2020) had found that heritability of depression is greater in women with trauma, suggesting a stronger genetic contribution to MDD in this group. In the current study, we found that the PRS of depressive symptoms predicted depressive symptoms at 18 weeks prenatal more in the non-abused group of women than in the abused group of women. In light of the findings from this previous

study, the finding from the current study could support that the experience of childhood maltreatment including sexual abuse can mask the effect of genetic predisposition for depression[60]. Women with history of childhood sexual abuse have previously found to be at a greater risk for depression or anxiety in antenatal or later postpartum period[39,62]. The stronger effect of history of sexual abuse in early pregnancy may explain why the history of sexual abuse status masked the effect of PRS of depressive symptoms at 18 weeks prenatal only and not at later prenatal or postpartum periods in the ASLPAC mothers.

Interpersonal sensitivity as a potential proximal marker of effect of environment

In light of the relatively stronger influence of social support, rather than childhood sexual abuse, on PPD we also examined if more proximal psychological risk factors would more strongly associate with PPD than more distal risk factors e.g., childhood sexual abuse. IPSM has been found to be a mediator of the effects of early life adversity on depressive symptoms in adulthood and may explain how early adversity influences depression in adulthood[12]. In the current study, we stratified the cohort to women with or without history of sexual abuse and then stratified those groups to women with high or low IPSM score. We found that women who had history of sexual abuse and high IPSM score had the highest perinatal mood symptoms, and women without history of sexual abuse and low IPSM score had the lowest perinatal mood symptoms. However, many women who had history of sexual abuse did not have high IPSM score and many women who did not have history of sexual abuse had high IPSM score, and the IPSM score was a better predictor of postpartum mood than history of sexual abuse alone. It could be a proxy for existing long-term effect of early life adversity as well as other environmental stressors on prenatal mood. These findings are of relevance in light of current screening practices for perinatal depression. In

Australia, screening tools such as the Antenatal Risk Questionnaire (ANRQ) have been widely adopted to screen for PMDs[63,64]. The debate around using screening tools for perinatal depression is that they can overidentify at-risk women and are not cost effective, and that for lower-middle income countries they can have the potential for increasing the stigmatization or that they will not be accurate if they are not made acceptable to the specific culture[64]. In addition to these limitations, self-report of early life adversity in perinatal screening also has the potential for recall bias or limited disclosure by the participants while women who do report early life adversity can also not have long-term effects as adults but be identified as at-risk. Thus, measures such as IPSM used as a measure of long-term effect of early life adversity could overcome the limitations of recall bias or fear of stigmatization associated with disclosure of traumatic experiences. Future work is required to determine if IPSM would improve existing screening tools.

Epigenetic Biomarkers of PPD

In this study, we found that estrogen-sensitive epigenetic biomarkers identified by Guintivano et al., (2014) predicted prenatal and postpartum depressive symptoms in ALSPAC mothers, but more so the postpartum depressive symptoms of mothers who were not depressed antenatally and in mothers who had history of sexual abuse. Guintivano et al., (2014) had identified epigenetic biomarkers and blood cell-ratio that can predict PPD in women with history of BD or MDD, and Osborne et al., (2016) had replicated the finding in women without history of psychiatric disorder and found that the biomarkers could predict with an AUC of 0.81. In contrast, Lapato et al., (2020) recently reported findings from a multi-racial cohort of women that the estrogen-sensitive biomarker could predict PPD better in women with previous histories of MDD with AUC of 0.94 and that they could also predict MDD in male and female adolescents. Therefore, they

hypothesized that the epigenetic biomarkers were of relevance for MDD rather than specifically PPD. Evidence from mice studies have demonstrated that estrogen receptor α is an important regulator of transcriptional changes in the nucleus accumbens that promote resilience to chronic stress[65]. This could explain how the estrogen-sensitive epigenetic biomarkers predict MDD in both males and females because estradiol is produced in both sexes. With respect to the previous findings, our results support the hypothesis that estrogen sensitive epigenetic biomarkers predict perinatal depressive symptoms, with effects that are stronger for predicting postpartum depressive symptoms in women who are not depressed during the antenatal period and in women with history of sexual abuse.

LIMITATIONS

Limitations of GWAS of Psychiatric Disorders

There are a number of limitations of the polygenic predictors used in the current study. First, we used GWASes of MDD, symptoms of depression, BD and anxiety, however none of these GWASes were focused on perinatal samples or PMDs. Thus we cannot exclude the possibility that genetic predictors built on GWASes that are PMDs specific may reveal a larger genetic contribution to PMDs. Second, the GWASes that informed the PRS used in this study were derived from GWASes in European-ancestry cohorts only and may be of limited value for predicting perinatal mental health phenotypes in more diverse samples. For example, the effect sizes (or 'weights') of specific SNPs on a phenotype may depend on the ethnicity of the population that the GWASes were carried out in, and PRSes built on European ancestry cohorts but implemented in more diverse samples can lead to an inflation of risk that is confounded by simple population differences in allele frequency of specific SNPs[66]. Third, a major limitation of conventional GWASes, and PRSes derived from such GWASes, is that the 'weights' applied to each SNP simply reflect the degree of association between a given SNP and phenotype of interest but is not informed by the biological function of each SNP. Innovative new approaches to creating biologically informed PRS are promising in this regard and should be considered in future analyses of maternal perinatal mental health[67]. Similarly, recent multi-trait GWASes may provide genetic predictors that are of greater predictive value for understanding complex phenotypes. For example, an integrative analysis of multiple GWASes have also been carried out for summary statistics of 36 phenotypes related to immunity, anthropometry, metabolism, cardiovascular and brain to identify clusters of SNPs that were associated with the given traits[68]. In order to improve the current understanding of the genetic contribution for psychiatric conditions, we could benefit from

GWASes that consider multiple traits and that consider how the traits are related to the environment to build models of psychiatric conditions that are informed by shared environmental and biological factors between the conditions.

Heritability of social support

We carried out the current study under the assumption that environmental variables e.g., social support are purely environmental (non-genetic) in nature. We only considered genetic risk for depressive symptoms or MDD, and therefore have identified only small correlations between environmental factors and genetic risk. Even so, we identified small but significant correlations between the environmental factors and genetic risk, including a significant negative correlation between social support quality in pregnancy and PRS of depressive symptoms (r=0.1) and a significant positive correlation between stressful life events and PRS of depressive symptoms (r=0.08). Likewise, Wang et al., (2017) that has examined the influence of genetics in social support and mental health in 1,215 18 year old mixed gender twin pairs identified a negative genetic correlation between depression and social support quality of r = -0.60[69]. This finding suggests that common genetic influences contributed to both mental health and social support phenotypes than environmental factors alone. They also found a moderate positive genetic correlations between perceived wellbeing and social support, and that the genetic correlations between social support quality and mental health was higher than social support quantity and mental health. This finding emphasized the importance of social support quality for better wellbeing and possible shared genetic contribution that play a role in the two phenotypes. Thus, we cannot exclude the possibility that a proportion of the variance in maternal perinatal depression, which we attribute to environmental factors, may be partly explained by underlying genetic

variation. Large-scale GWASes of social and other 'environmental' phenotypes will be informative for understanding genetic and environmental contributions to mental health phenotypes, and the work of the Social Science Genetic Consortium is interesting in this regard[70]. Similarly, alternative research designs such as twin studies in perinatal women could better identify environmental effects from genetic effects on perinatal depression. Finally, novel analytical approaches could shed light on the genetic contribution to social/environmental phenotypes. For example, Greml, identifies the heritability of phenotypes in unrelated individuals based on genetic similarity. Such approaches could also identify the contribution of genetics to environmental factors.

Limitations of Theoretical Models of Mental Health

In this study, we have applied the biopsychosocial theoretical model of mental health to study perinatal mental health in order to take into account both environmental and biological factors that are relevant for perinatal mental health. However, the limitation of the biopsychosocial model is that the social, psychological and biological influences are considered as separate systems. In reality, the multiple influences are integrated, and members of social groups also have capacity to influence the society they are part of and affect the psychology and biology and mental health as a result[71]. Similarly, theoretical model of the Developmental Origins of Health and Disease that is applied to studying mental health and development is beneficial to consider the long-term effect of the developmental periods. However, the DOHaD approaches to maternal mental health which focuses on the individual behaviors of mothers on child outcome has potential to inadvertently place the blame for the perinatal illness or outcome in children on the mother[72]. This could be

relevant for black women in the US who have the highest rates of preterm births, and in women marginalized on basis of ethnicity, sexuality, or religion living in high income countries.

Cultural considerations in assessments of Perinatal Mental Health

Lastly, this study did not take into consideration the role of culture in the experience of perinatal depression. Our analyses were restricted to a predominately Caucasian sample from a low-risk community based in the United Kingdom. However, cultural factors must be considered when seeking to improve screening approaches for perinatal mental health. Such factors may influence physician-patient interactions for Indigenous women coming to non-Indigenous health care systems for perinatal care that leads to distress from language barrier, stigmatization from healthcare providers, and leaving behind children or family members to come to southern healthcare facilities[73]. Cultural expressions of mental health are also important to study to better communicate with women during the perinatal period and identify barriers that are different for different cultures. One study of South Asian women living in Toronto, Canada has found that women explained their depression as a result of their social environment and migration rather than using a biomedical framework[74]. Similarly, South Asian women in the U.S. were found to underutilize mental health services due to cost and due to culturally-linked stigma of psychiatric disorders[75]. One example of how culturally appropriate care can become possible is through community-based participatory research that involved Bangladeshi women living in the U.S. to identify idiom of distress of "tension" that place the distress in context of culture[76]. At the same time, lack of social support has been found to have a negative impact on mental health of women in context of perinatal mental health based on meta-analysis of multiple studies conducted across Africa[18]. Therefore, considering the effect of culture on people from diverse backgrounds are

critical for identifying factors of resilience that are transcultural. In this context, research in the biological and environmental factors of perinatal mental health should aim to understand how the social environment and biology contribute together to well-being of mother and the child[77,78].

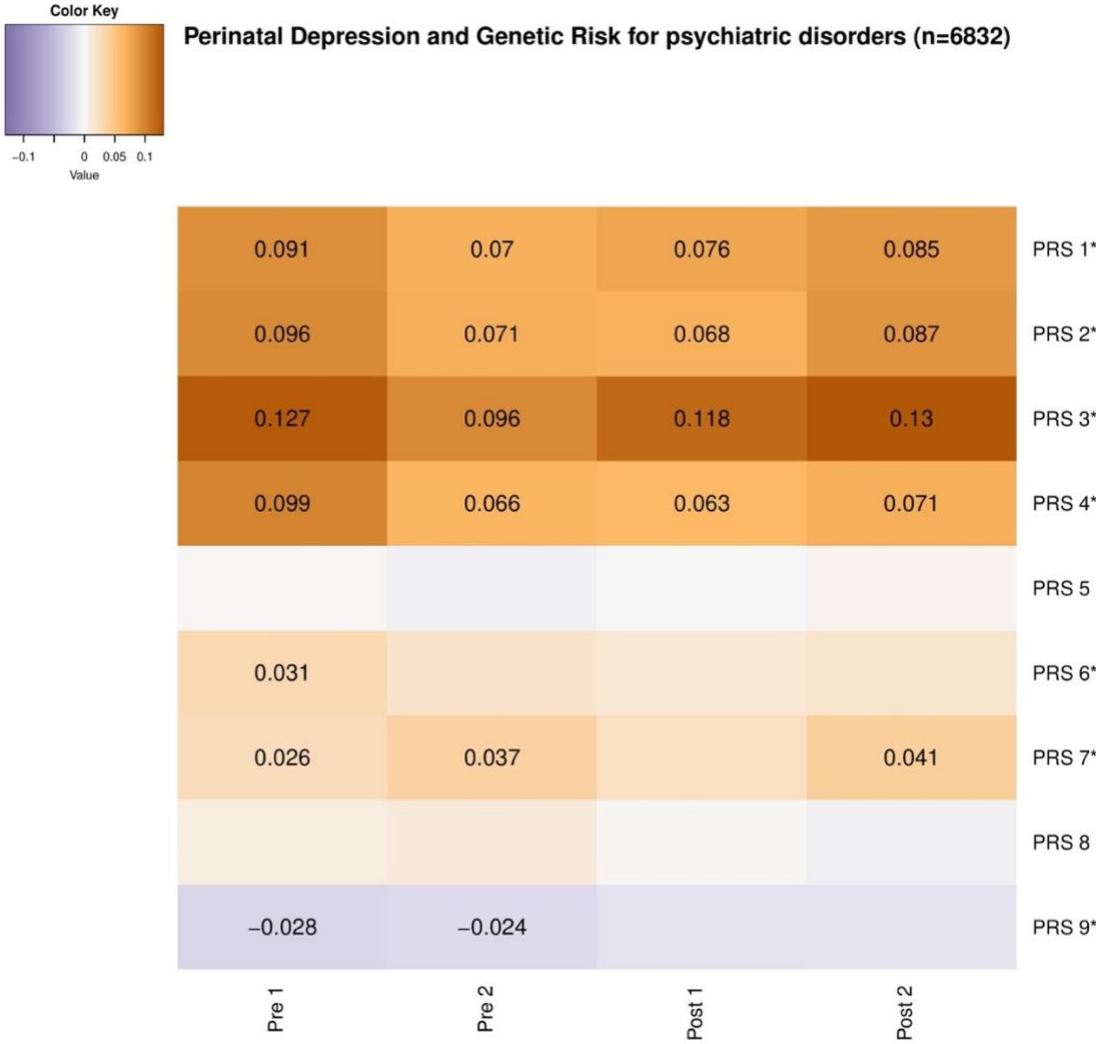
CONCLUSIONS

The findings from this program of research provide the most comprehensive, integrated analysis of biological, psychological and social factors that associate with perinatal mental health. While a number of biological factors associated with perinatal depression, social support emerged as the factor with the largest effect on perinatal mental health. This is of interest in light of the on-going global pandemic, and associated public health measures, which may decrease social support. A recent study in Ireland, Norway, Switzerland, the Netherlands, and the UK showed that up to 15% of pregnant women experienced perinatal depression and 11% of pregnant women experienced perinatal anxiety in 2019 during the pandemic, similar to previously reported rates of PMD in high income countries[79]. However, this rate increased in the UK to 43% of pregnant women experiencing perinatal depression and 61% of pregnant women experiencing perinatal anxiety when social distancing and lockdown measures were implemented[80]. Studies on PMD of mothers in low- and middle-income countries during the pandemic are currently unavailable. Taken together with our findings, providing pregnant people with social support is an important and urgent intervention target, which may buffer the effects of other adversities and improve maternal perinatal mental health.

FIGURES AND TABLES

Figure 1 ALSPAC Mothers Considered for the Study of Environmental and Genetic Models of Perinatal Mental Health. This figure is in-text.

Figure 2 Perinatal Depression and Genetic Risk for Psychiatric disorders. The PRSes calculated from 9 recent GWASes were correlated with perinatal depressive and anxiety symptoms in ALSPAC mothers. The SNP statistics for all of these GWAS were publicly available, however if the GWAS included the cohort 23andMe, summary statistics for only the top 10,000 SNPs were available. PRS used in this correlation came from only statistically significant SNPs, and the first 10 PCs were regressed out of the PRS before correlating with EPDS. The P-value threshold for SNP inclusion was <0.05 or <0.01 based on which threshold would select SNPs with the highest Pearson correlation with depressive and anxiety symptoms. For PRS 8, there is 17,310 Case-Control version, but the Factor Score GWAS was used for PRS. Most significant SNPs, top 1000 in Case-Control and top 1500 in Factor Score had the same direction of effect, but more SNPs were significant for Factor Score phenotype than for Case-Control phenotype, therefore Factor Score was used.



*Correlation coefficient that is statistically significant ($p < 0.05$) is annotated in black

PRS #	**Year**	**Cohorts**	**Phenotype**	**N of SNPs in GWAS**	**N of participants**
1	2019	PGC 2018 + UK Biobank + 23andMe	MDD	Top 10,000 reported of 8,098,588 SNPs (N of SNPs < P-value 0.01: 9,223)	807,533

2	2019	PGC 2018 + UK Biobank	MDD	8,098,588 SNPs (N of SNPs < P-value 0.05: 81,301)	500,199
3	2018	UK Biobank + 23andMe + Genetic Epidemiology Research on Aging + Social Science Genetic Association Consortium + Genetics of Personality Consortium	Multi-trait Analysis of GWAS (MTAG) of Depressive symptoms	Top 10,000 reported of 6,100,000 SNPs (N of SNPs < P-value 0.01: 7,117)	Effect N= 449,649
4	2018	PGC 2018 + 23andMe	MDD	Top 10,000 reported of ~9,600,000 SNPs (N of SNPs < P-value 0.05: 7,558)	480,359
5	2018	PGC 2018	MDD	~9,600,000 SNPs (N of SNPs < P-value 0.05: 129,840)	404,752
6	2016	23andMe	MDD	13,519,496 SNPs (N of SNPs < P-value 0.05: 133,487)	307,354
7	2013	PGC	MDD	~6,500,000 SNPs (N of SNPs < P-value 0.05: 11,178)	18,759
8	2016	PGC	Anxiety Disorder	~6,500,000 SNPs (N of SNPs < P-value 0.05: 32,800)	18,186 Factor Score
9	2019	PGC	Bipolar Disorder	9,372,253 SNPs (N of SNPs < P-value 0.05: 127,393)	Effect N = 46,582

Figure 3 Perinatal Mood and G+E variables are Significantly Correlated. Dep: Depression; Anx: Anxiety; 1: At 18 Weeks Gestational Age; 2: At 32 Weeks Gestational Age; 3: At 8 Weeks Postnatal Period; 4: At 8 Months Postnatal Period; ***Environmental variables*** Age: Maternal Age at Delivery; Crowd: Number of people per room as proxy for Socioeconomic Status; Life: Cumulative stressful life events during pregnancy; Educ: Maternal education; Abus: History of sexual abuse before 16 years of age; IPSM: Interpersonal sensitivity measure; Supp: Social support; ***Genetic variables*** PRS1: Polygenic Risk Score for depressive symptoms; PRS2: Polygenic Risk Score for depression possibly related to pregnancy. Only the significant correlations ($p < 0.05$) have been annotated. (N = 11756)

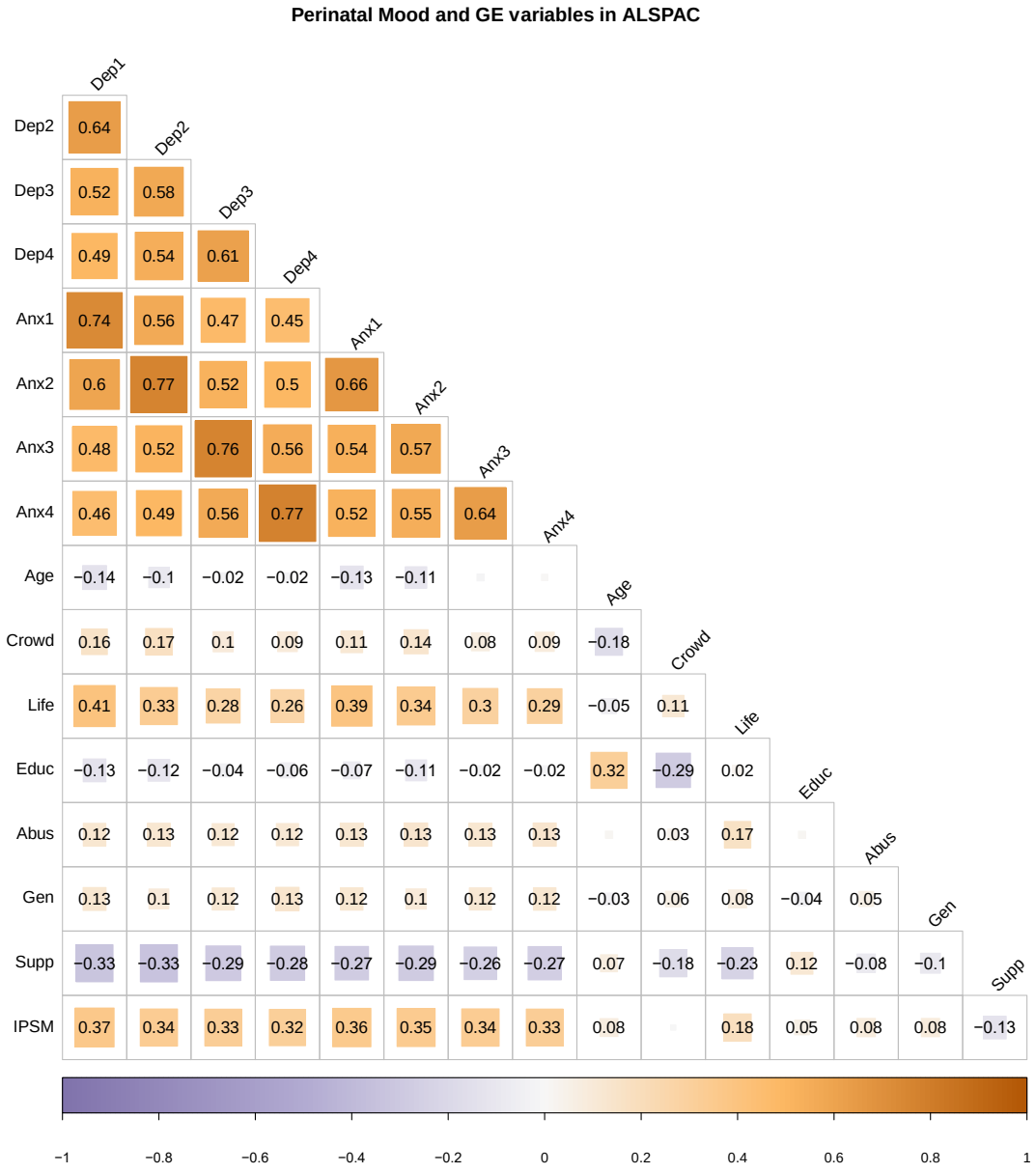


Figure 4 E and G+E variables explain 13.4 to 23.7% of the Variance in Perinatal Mood. Before adding social support, E model explains 19.5, 13.8, 7.64 and 7.87% of EPDS and E model explains 17.1, 14.5, 9.53 and 8.91% of CCEI. After adding social support, the E model explains 23.7, 19.9, 13.5 and 12.7% of EPDS and 20.5, 18.4, 13.4 and 13.8% of CCEI. The change in adjusted R^2 value of the E model to G+E model is significant based on Pi of 0. This means that the probability that E model is a better model than G+E model is 0. Even if the R^2 value is larger for E model at some time points, G+E is still a better model based on the Pi.

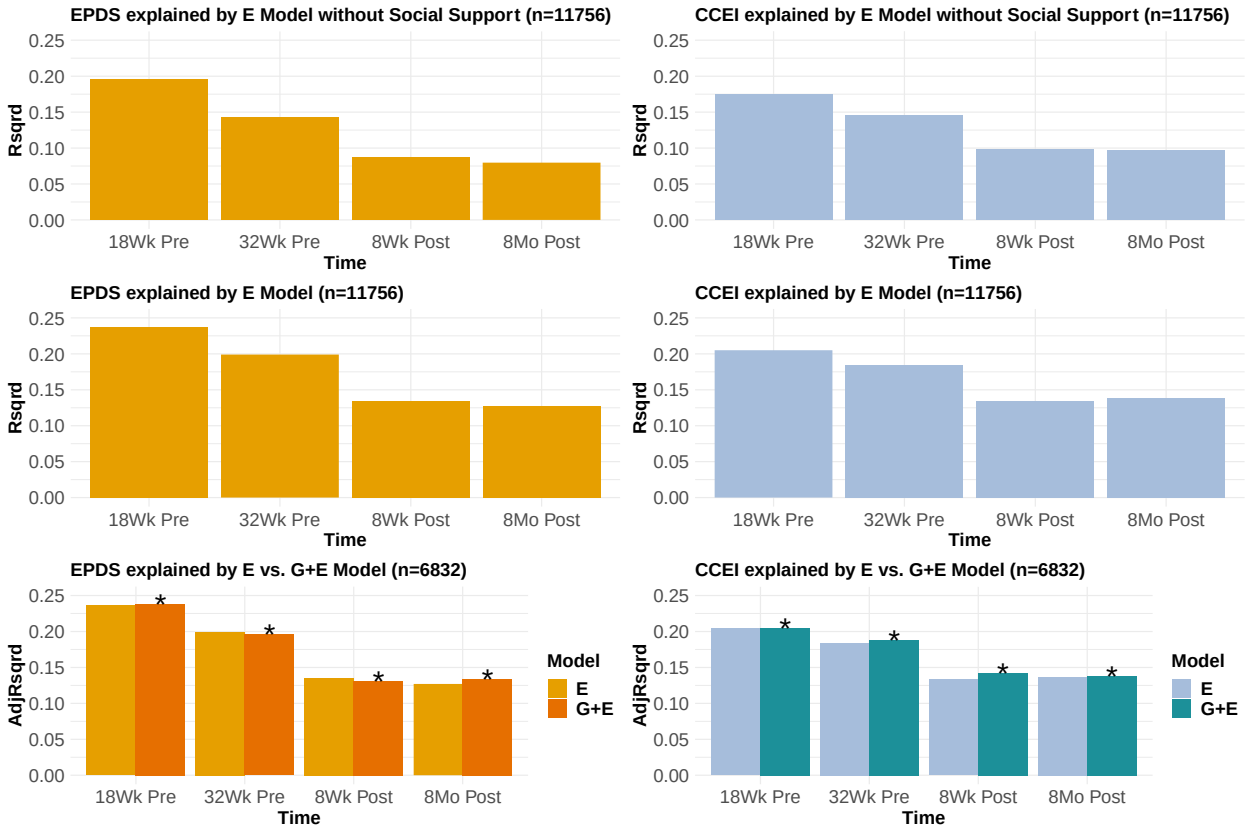


Figure 5 PRS of Depressive Symptoms Stratify Populations of Women with High or Low Perinatal Depressive Symptoms. The PRS for depressive symptoms was able to identify women with greater perinatal depressive symptoms. This figure shows the mean depressive symptoms of women when women were stratified to those who had PRS scores that were 1 Standard Deviation (SD) above the mean or greater and those who had 1 SD below the mean or lower. Women who had higher PRS scores have greater depressive symptoms throughout the perinatal period compared to women with lower PRS scores.

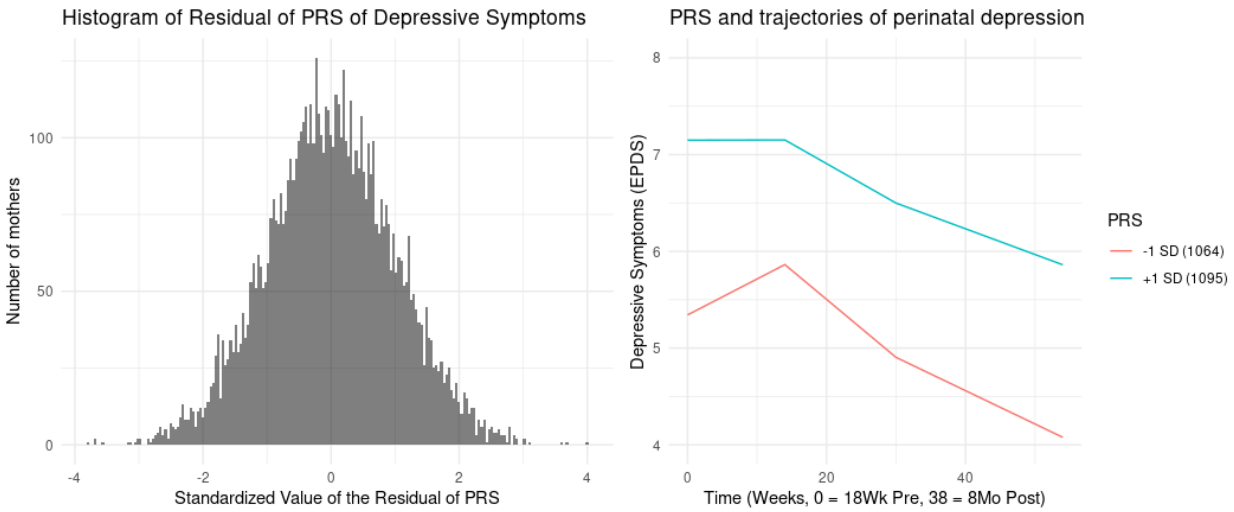
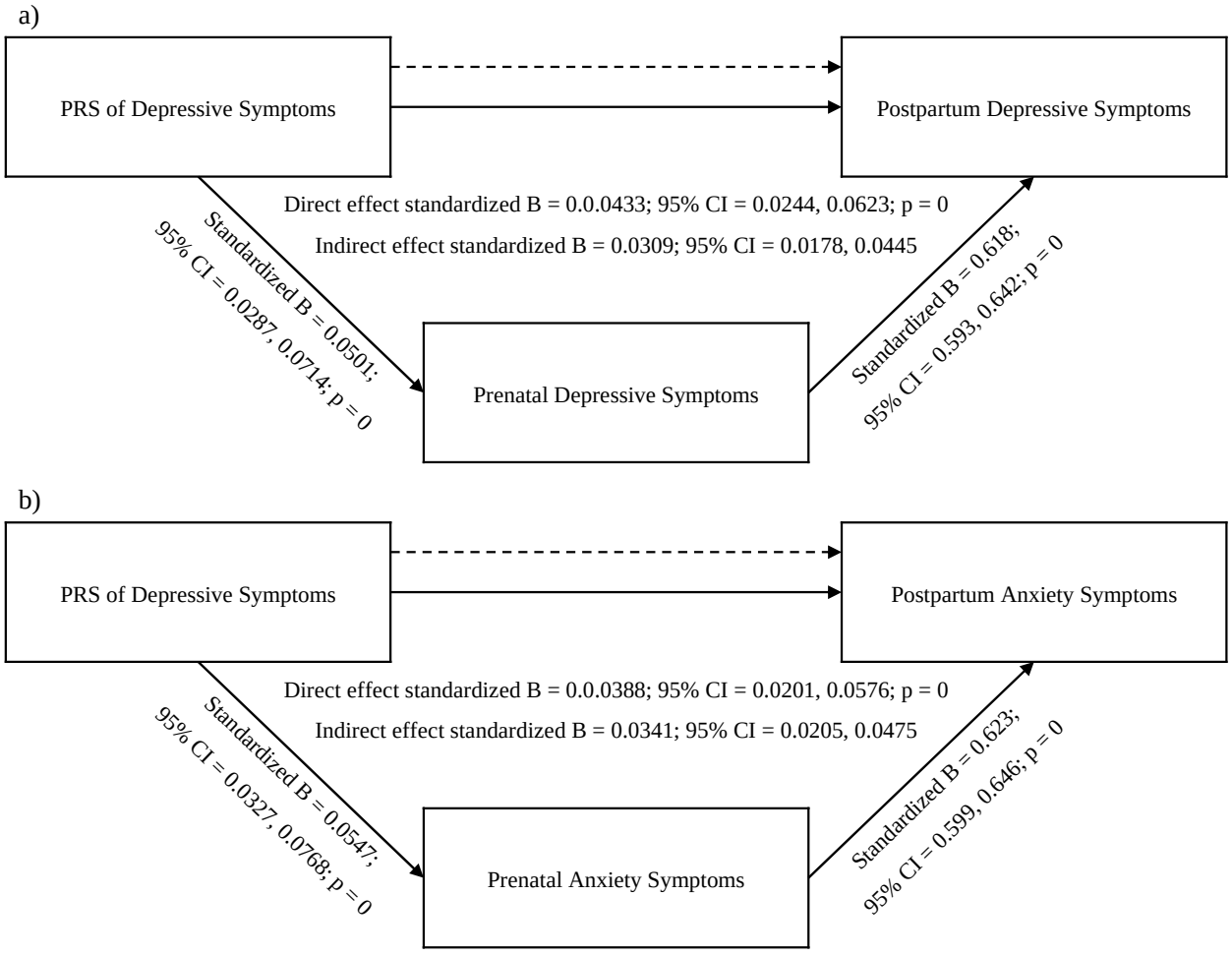


Figure 6 Predicting Postpartum Mood by PRS for Depressive Symptoms and PRS for MDD is Partially Mediated by Prenatal Mood. Prediction of postnatal mood with PRS 1 and 3 were partially mediated by prenatal mood, meaning that PRS 1 and 3 could predict postnatal mood independently of the prenatal mood or indirectly through predicting prenatal mood. This finding stands in contrast to the findings of Rantalainen et al., (2020) that PRS for MDD can predict postpartum mood only through full mediation by prenatal mood. The beta coefficients are non-standardized values. The significance of the association can be determined based on whether the 95% CI crosses zero and P-value that is less than 0.05. In the given analysis, the direct and indirect prediction of postpartum mood by PRS are significant and the prediction of prenatal mood by PRS as well as prediction of postpartum mood by prenatal mood are significant.



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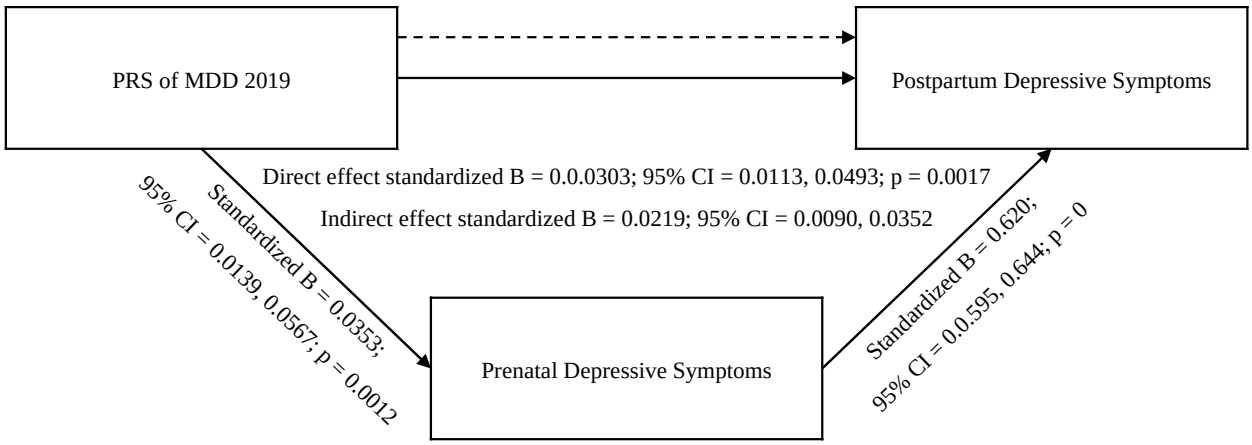
PRS of MDD 2019
Postpartum Depressive Symptoms
Direct effect standardized B = 0.0.0303; 95% CI = 0.0113, 0.0493; p = 0.0017
Indirect effect standardized B = 0.0219; 95% CI = 0.0090, 0.0352
Standardized B = 0.0353;
95% CI = 0.0139, 0.0567; p = 0.0012
Prenatal Depressive Symptoms
Standardized B = 0.620;
95% CI = 0.0.595, 0.644; p = 0

d)

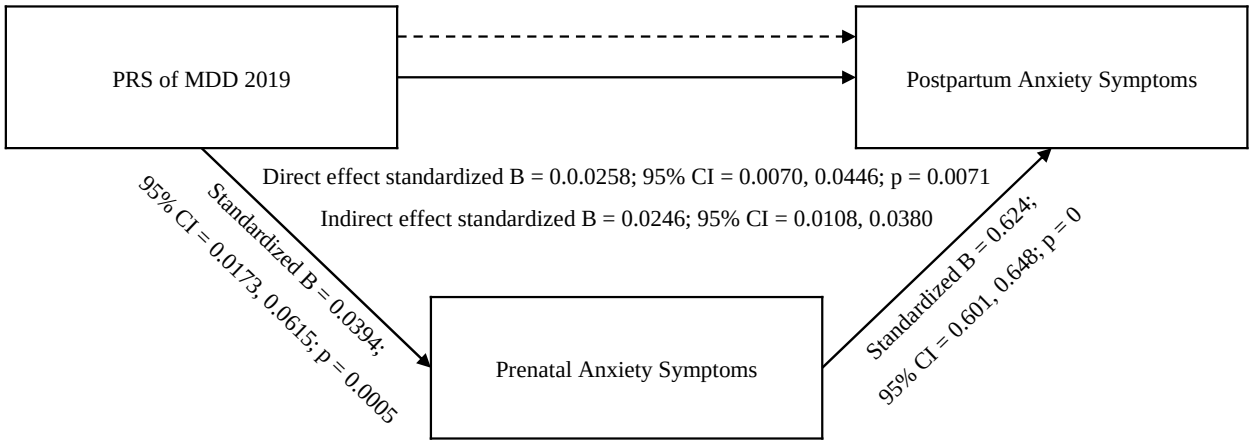
PRS of MDD 2019
Postpartum Anxiety Symptoms
Direct effect standardized B = 0.0.0258; 95% CI = 0.0070, 0.0446; p = 0.0071
Indirect effect standardized B = 0.0246; 95% CI = 0.0108, 0.0380
Standardized B = 0.0394;
95% CI = 0.0173, 0.0615; p = 0.0005
Prenatal Anxiety Symptoms
Standardized B = 0.624;
95% CI = 0.601, 0.648; p = 0

Figure 7 Average Perinatal Mood of Women Stratified by History of Sexual Abuse and Prenatal Social Support or IPSM. The mean depressive and anxiety symptoms of women who have been stratified by their history of sexual abuse status and high or low prenatal social support or IPSM levels are plotted as boxplots. High social support or interpersonal sensitivity measured by IPSM is defined as prenatal social support or IPSM higher than the median, and low social support or IPSM is defined as lower than or equal to the median. The outliers are shown as dots. Average perinatal depressive and anxiety symptoms of women with history of sexual abuse and high social support are lower than average mood symptoms of women without history of sexual abuse and low social support. Average perinatal depressive and anxiety symptoms of women with history of sexual abuse and low IPSM are lower than average mood symptoms of women without history of sexual abuse and high IPSM. EPDS: Edinburgh Postnatal Depression Scale; CCEI: Crown Crisp Experiential Index.

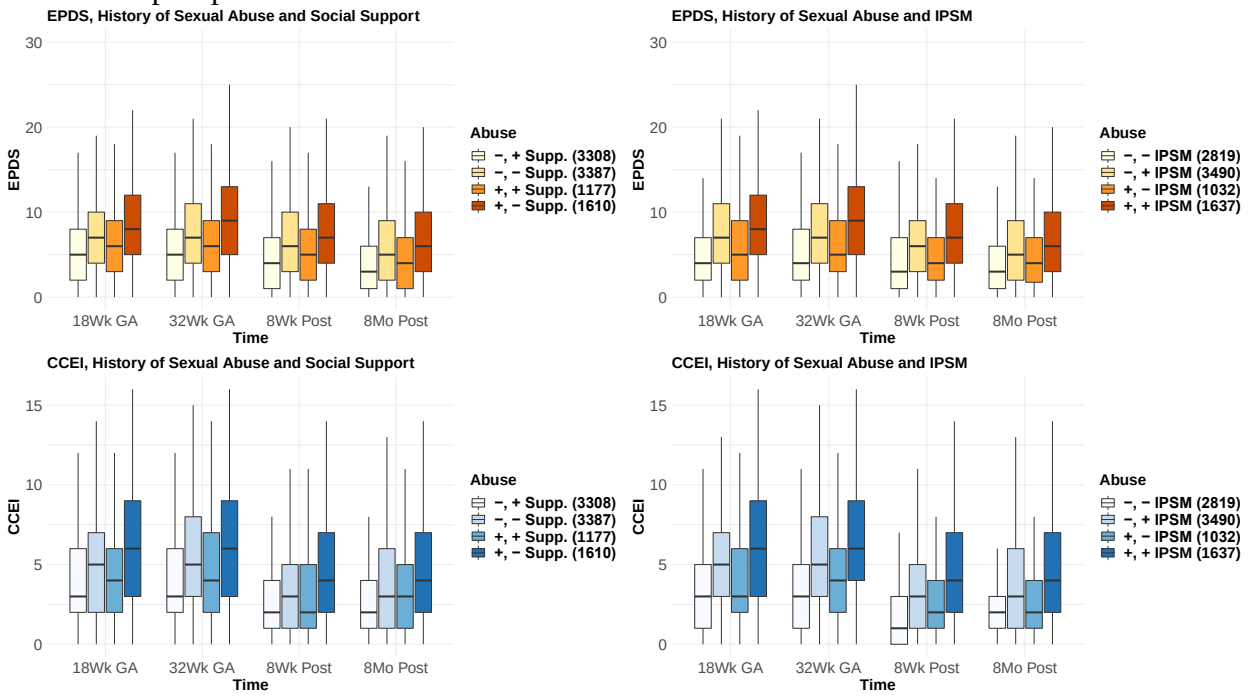

Figure 8 Average Perinatal Mood of Women Stratified by History of Contact Sexual Abuse and Prenatal Social Support. The mean depressive and anxiety symptoms of women who have been stratified by their history of sexual abuse status and high or low prenatal social support levels are plotted as boxplots. The outliers are shown as dots. In this replication of Figure 7, only contact form of sexual abuse was considered as history of sexual abuse. Contact abuse included unwanted fondling, arousal, genital rubbing, sexual intercourse, and oral sex while noncontact abuse included flashing or forced to observe masturbation. Average perinatal depressive and anxiety symptoms of women with history of sexual abuse and high social support are lower than average mood symptoms of women without history of sexual abuse and low social support. EPDS: Edinburgh Postnatal Depression Scale; CCEI: Crown Crisp Experiential Index.

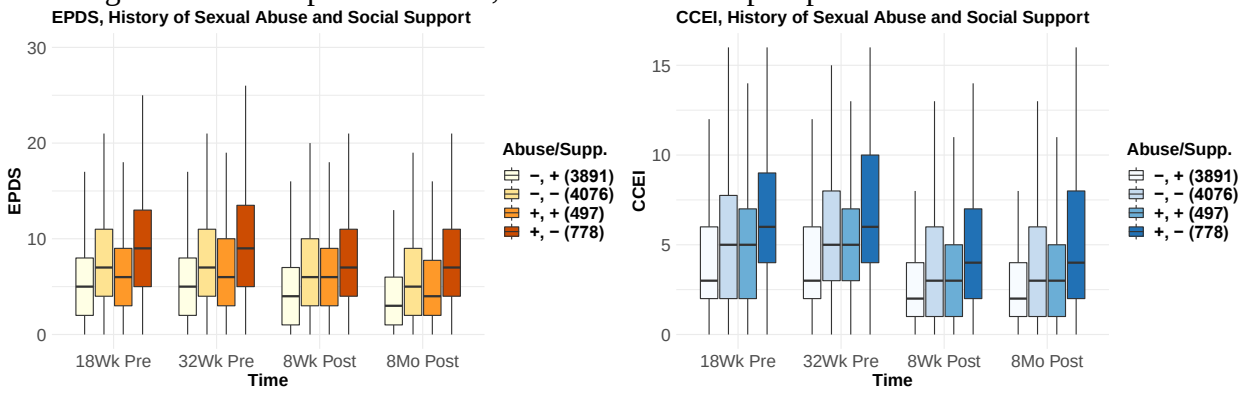

Figure 9 E and G+E Models Explain Higher % of the Variance in Perinatal Depressive Symptoms of Women with History of Sexual Abuse. In this figure, we divided the cohort of women to those with and without history of sexual abuse under 16 years of age. Those with history of sexual abuse had greater average depressive symptoms than those without history of sexual abuse, and the E model explained mood better in women with history of sexual abuse than without history of sexual abuse. When the G+E model (G+E Eq4) was applied to the two cohorts, the G+E model explained mood better than the E model for both cohorts. In figure 5, only the PRS from MTAG was used to predict mood in the cohorts with and without history of sexual abuse. The result replicated the findings from Peterson et al., 2018 at 18 weeks gestational age where the G model (PRS of depressive symptoms only) explained depressive symptoms more in women without history of sexual abuse compared to women with history of sexual abuse. At the other perinatal time points of 32 weeks gestational age, 8 weeks postnatal, and 8 months postnatal, this was the opposite and the G model explained depressive symptoms more in women with history of sexual abuse.

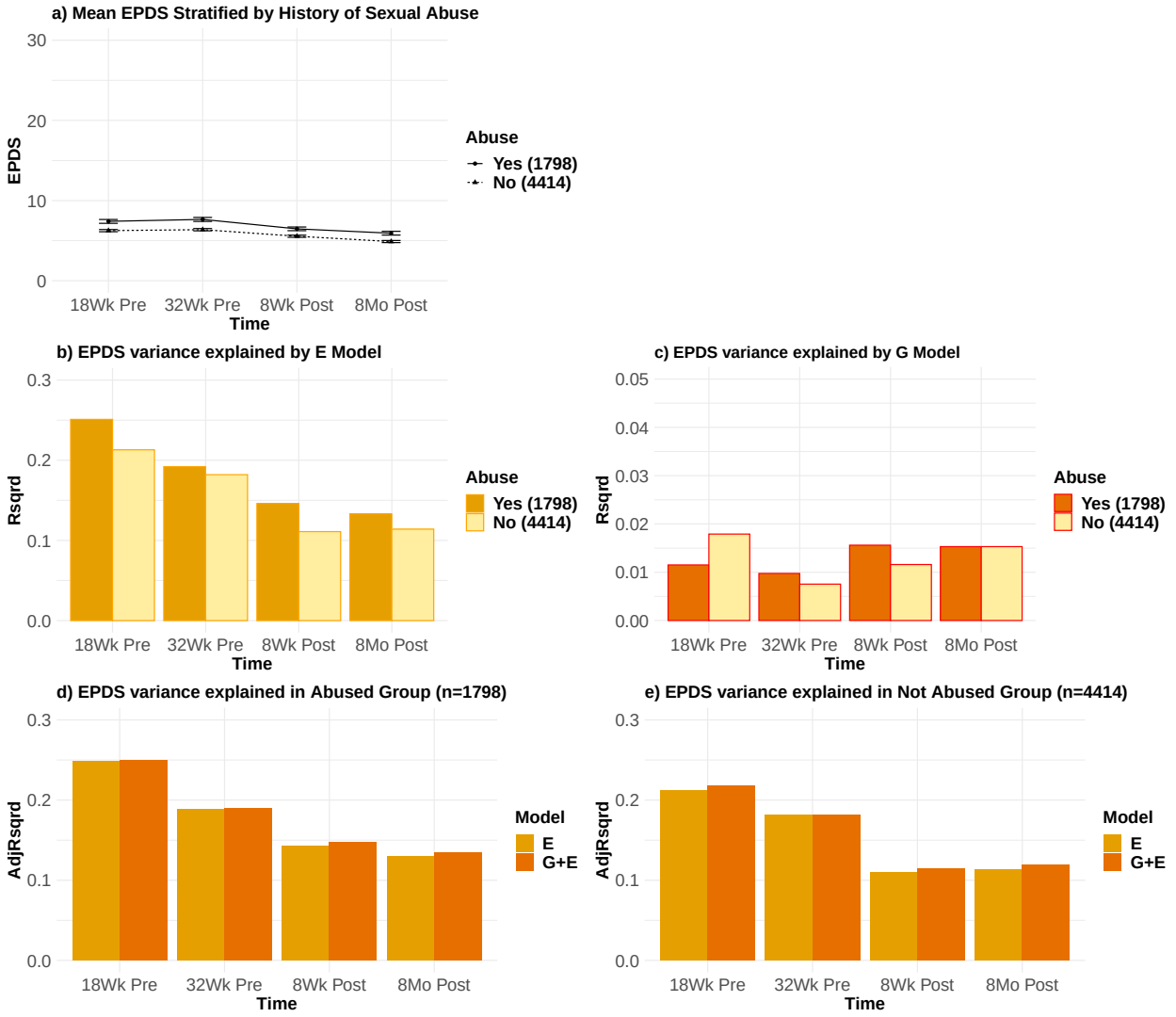

Figure 10 E and G+E Models Explain Higher % of the Variance in Perinatal Anxiety Symptoms of Women with History of Sexual Abuse. We repeated the same analysis as in Figure 9 of using G+E model (G+E Eq4) to explain anxiety symptoms during perinatal period in women stratified by history of sexual abuse. We found that the average anxiety symptoms were higher women with history of sexual abuse, and the environmental explained the anxiety symptoms more in women with history of sexual abuse. When we used only the PRS to predict anxiety symptoms, the PRS predicted anxiety more in women with history of sexual abuse at all perinatal time. The PRS was able to contribute to the prediction of perinatal anxiety in addition to the environmental model.

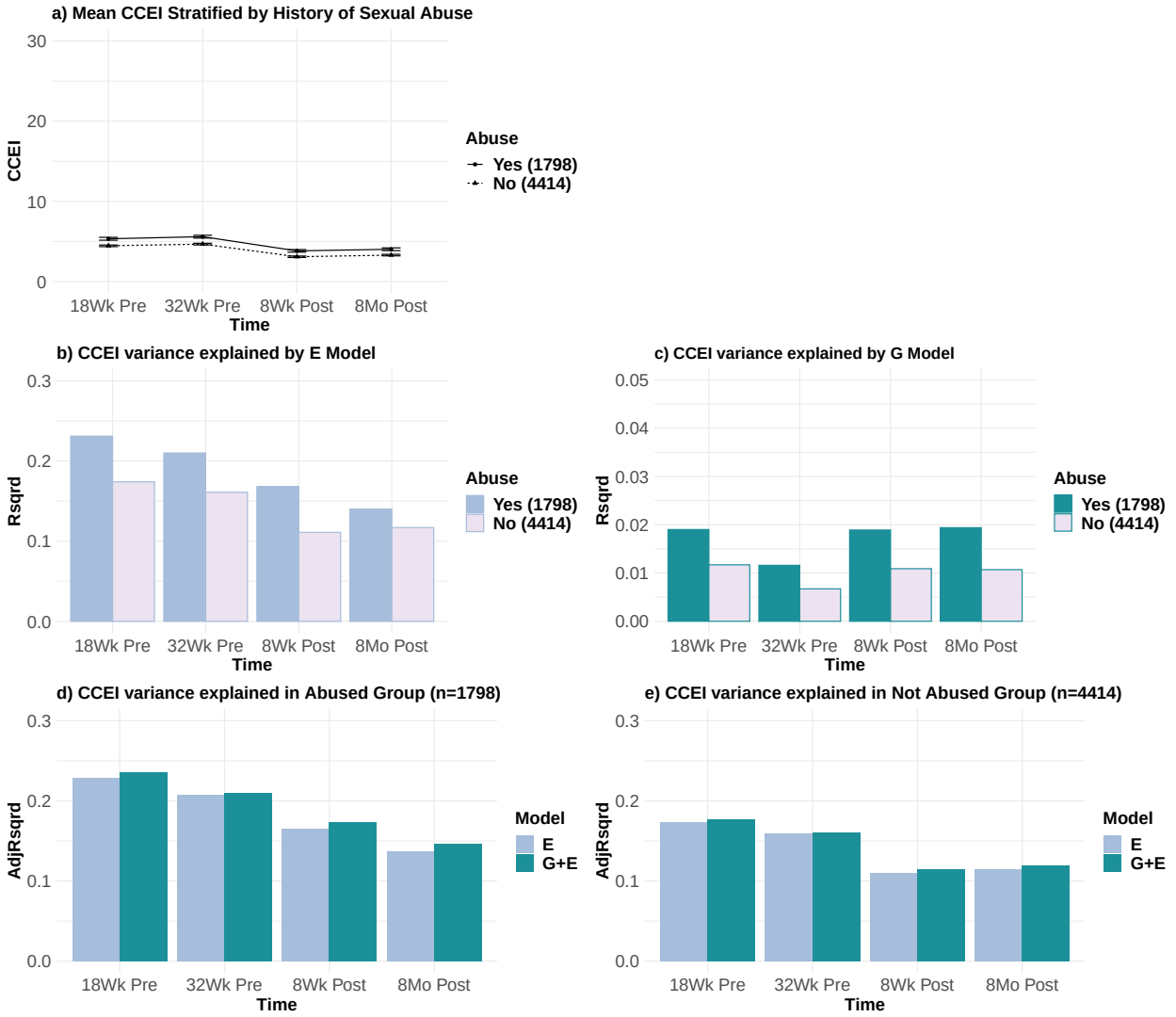

Figure 11 Dendrogram of Perinatal Mood and G+E Variables Show that PRS of Depressive Symptoms is Closely Related to History of Sexual Abuse and Crowding. This heatmap shows the Pearson correlations of perinatal mood with environmental and genetic factors from the G+E model (G+E Eq5) and the dendrogram of the variables that has been calculated based on Euclidean distance and clustered using Ward.D method. The correlation coefficients of the significant correlations are annotated in black. Based on the dendrograms, anxiety and depressive symptoms are most closely related to the other from the same time point. For the G+E variables, PRS and crowding were most closely related. Stressful life events and history of sexual abuse were most closely related to each other. Maternal education, age and prenatal social support were all negatively correlated with perinatal mood and were most closely related to each other.

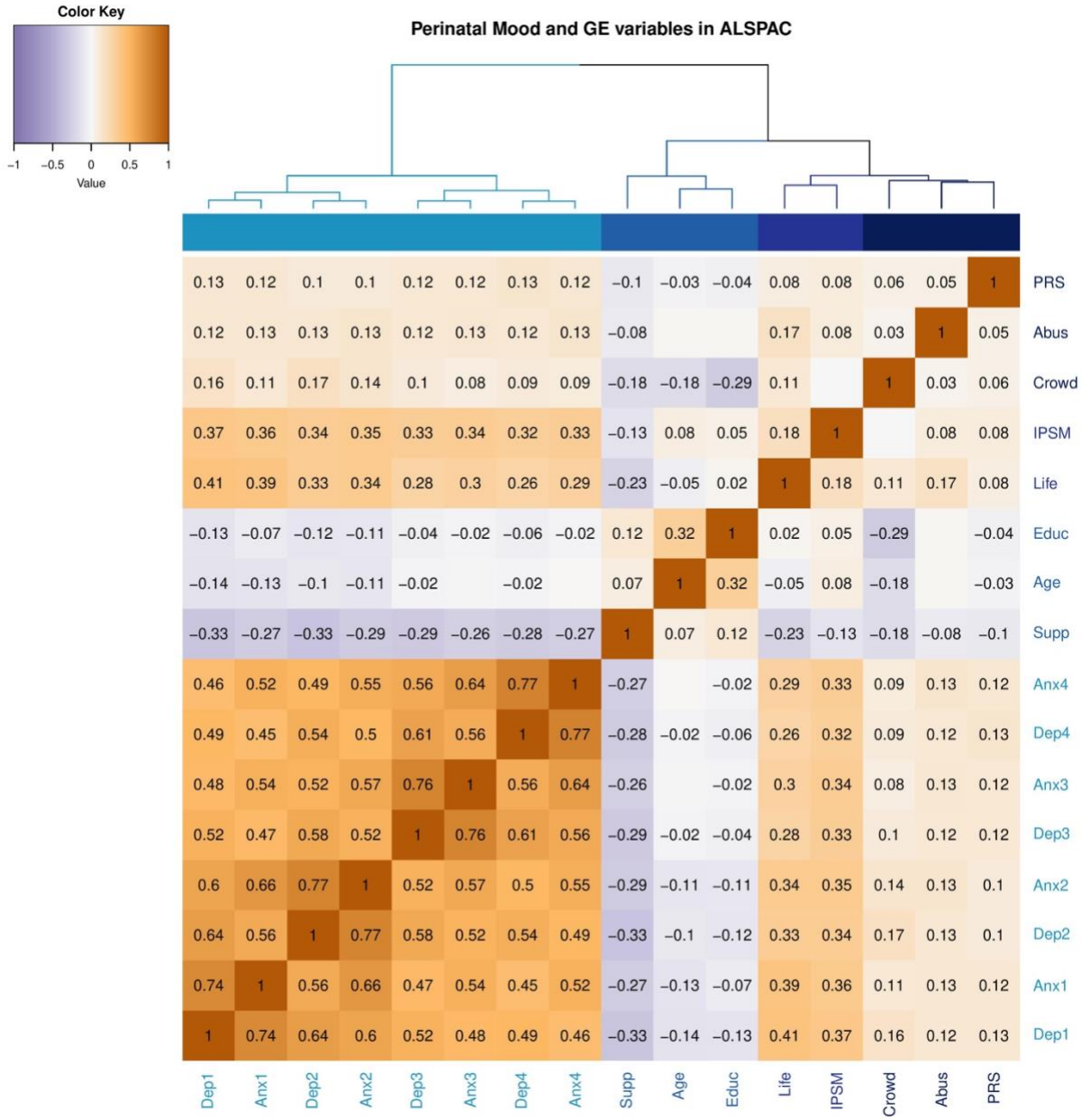

Figure 12 E and G+E Models with Prenatal Social Support and Prenatal IPSM Explain 17.4 to 32.5% of the Variance in Perinatal Depressive Symptoms in Women Stratified by History of Sexual Abuse. When IPSM scores from pregnancy were added to the G+E model (G+E Eq5), the model is able to explain depressive symptoms in women with and without history of sexual abuse more equally. As well, the model is able to account for larger percent variation in the depressive symptoms. This supports the finding that not all women are affected by environmental and genetic risks equally in their mood, and measures such as social support and IPSM can provide more accurate predictions of the perinatal mood of the mothers in addition the other environmental and genetic risk factors.

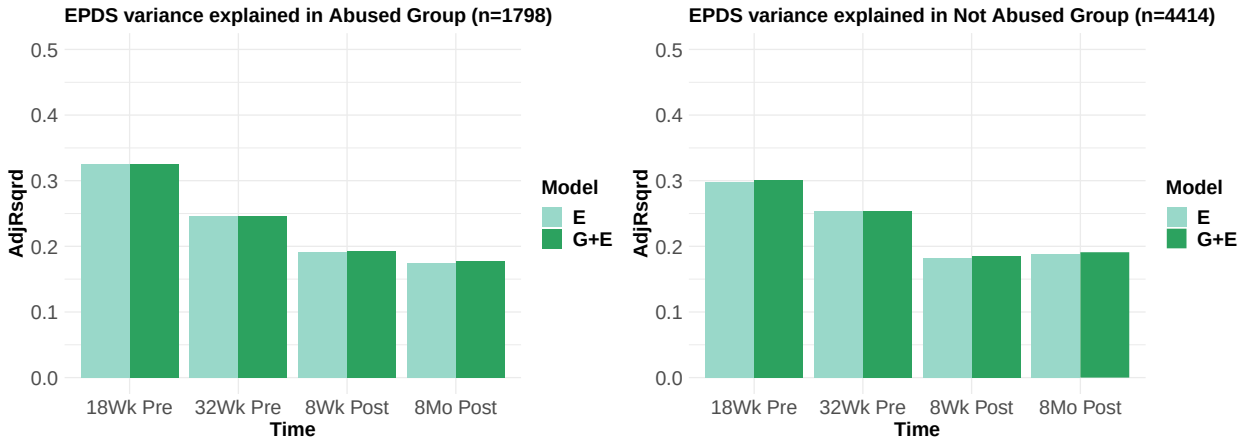

Figure 13 ALSPAC Mothers Considered for the Study of Estrogen-Sensitive Epigenetic Models of Perinatal Mental Health. This figure is in-text.

Figure 14 Estrogen-Sensitive Epigenetic Model is a Better Model of Perinatal Depressive Symptoms in Women with History of Sexual Abuse. Panel a) is a figure of the trajectory of four groups of perinatal depressive symptoms identified in ALSPAC mothers who self-reported as White, gave singleton births, had reported EPDS symptoms on at least 1 perinatal period and had covariates from Pre-Epi Eq6. The threshold used in this analysis is clinical. Panel b) demonstrates the change in AIC when epigenetic biomarkers in Epi Eq7 are added to the covariates in Pre-Epi Eq6 to build Epi Eq8 in women with and without history of sexual abuse. The change in AIC is negative in women with history of sexual abuse and positive in women without history of sexual abuse, indicating that the epigenetic biomarkers improved prediction of perinatal depressive symptoms only in women with history of sexual abuse.

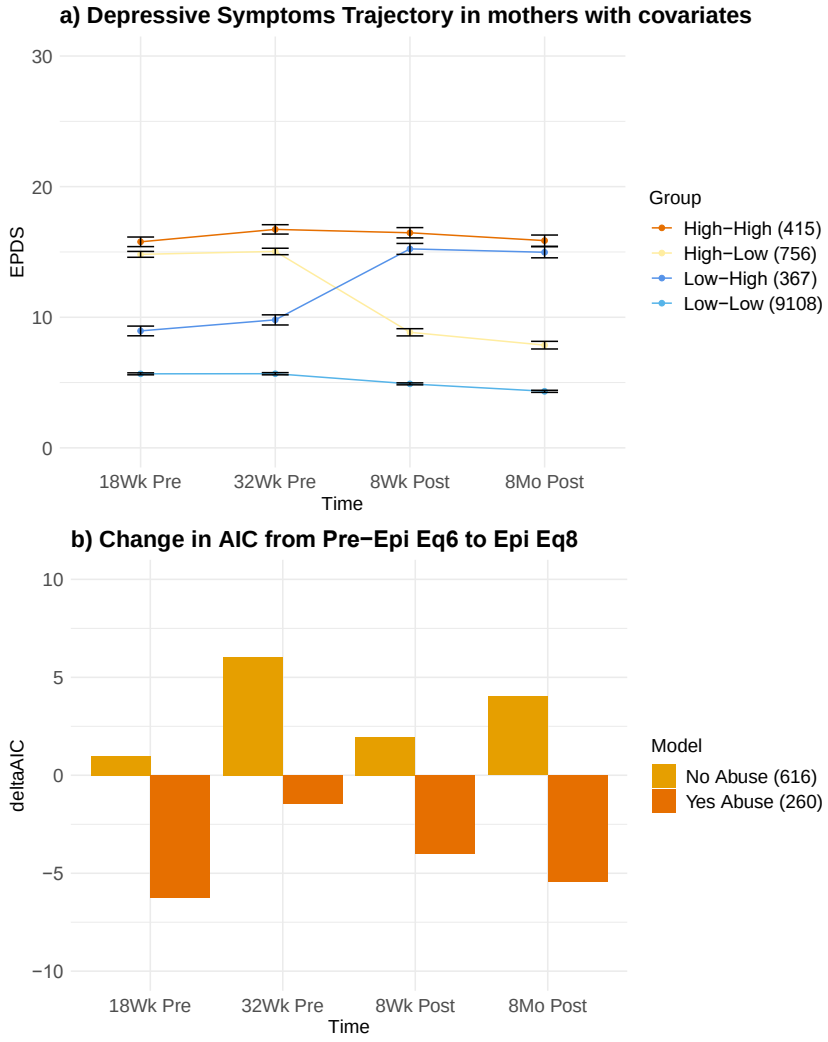

Table 1 Cohort Demographics Demonstrate the Effect of Selective Attrition in Genotyped Women

	White, Singleton birth mothers (11756)	Genotyped (6832)	Not Genotyped (4924)
Average maternal age in years (SD)	28.24 (4.87)	28.68 (4.68)	27.64 (5.05)***
(% missing)	(0.01%)	(0%)	(0.02%)
Average crowding index (SD)	1.88 (0.92)	1.80 (0.89)	1.99 (0.95)***
(% missing)	(4.46%)	(3.34%)	(6.01%)
>= 0.5	41.32%	45.18%	35.95%
> 0.5-0.75	30.04%	30.08%	29.98%
> 0.75-1.0	18.55%	16.76%	21.04%
> 1	5.64%	4.64%	7.03%
Average stressful life events (SD)	8.32 (7.49)	8.20 (7.38)	8.51 (7.63)*
(% missing)	(10.10%)	(8.02%)	(12.98%)
Average maternal education (SD)	2.19 (1.00)	2.31 (1.01)	2.02 (0.96)
(% missing)	(0.58%)	(0.42%)	(0.79%)
CSE/vocational (1)	29.13%	24.62%	35.38%
O-Level (2)	35.01%	34.59%	35.60%
A-Level (3)	22.57%	25.22%	18.89%
Higher degree (4)	12.72%	15.15%	9.34%
Average history of sexual abuse (SD)	0.29 (0.45)	0.29 (0.45)	0.29 (0.46)
(% missing)	(9.74%)	(9.07%)	(10.66%)
Yes (1)	26.27%	26.32%	26.20%
No (0)	63.99%	64.61%	63.14%
Prenatal Social Support (SD)	19.67 (5.02)	19.9 (4.95)	19.32 (5.10)***
(% missing)	(11.48)	(9.34%)	(14.46%)
Interpersonal Sensitivity (SD)	2.57 (0.46)	2.57 (0.45)	2.57 (0.48)
(% missing)	(16.00%)	(14.12%)	(18.6%)
Average EPDS (SD)			
(% missing)			
18 Week Prenatal	6.82 (4.76)	6.60 (4.68)	7.15 (4.87)***
	(10.23%)	(8.18%)	(13.08%)
32 Week Prenatal	7.00 (5.03)	6.75 (4.96)	7.36 (5.12)***
	(3.42%)	(3.22%)	(3.70%)
8 Week Postnatal	5.97 (4.73)	5.81 (4.57)	6.20 (4.94)***
	(9.77%)	(7.35%)	(13.12%)
8 Month Postnatal	5.33 (4.63)	5.18 (4.55)	5.56 (4.75)***
	(13.10%)	(10.04%)	(17.34%)
Average CCEI (SD)			
(% missing)			
18 Week Prenatal	4.86 (3.51)	4.72 (3.45)	5.06 (3.58)***
	(9.88%)	(7.82%)	(12.75%)
32 Week Prenatal	5.10 (3.59)	4.95 (3.52)	5.32 (3.66)***
	(5.77%)	(5.11%)	(6.68%)
8 Week Postnatal	3.37 (3.28)	3.30 (3.19)	3.48 (3.42)**
	(10.80%)	(8.40%)	(14.13%)
8 Month Postnatal	3.57 (3.32)	3.50 (3.25)	3.66 (3.41)*
	(13.15%)	(10.08%)	(17.40%)

*p < 0.05, **p < 0.01, ***p < 0.001

Table 2 Cohort Demographics Demonstrate the Effect of Selective Attrition in Women with History of Sexual Abuse Before 16 Years of Age

	Genotyped mothers with Answers to History of Sexual Abuse (6212)	Yes Abuse History (1798)	No Abuse History (4414)
Average maternal age in years (SD)	28.8 (4.66)	28.8 (4.85)	28.72 (4.59)
(% missing)	(0%)	(0%)	(0%)
Average crowding index (SD)	1.79 (0.89)	1.83 (0.90)	1.78 (0.88)
(% missing)	(3.27%)	(3.34%)	(3.24%)
>= 0.5	64.09%	43.88%	46.22%
> 0.5-0.75	42.34%	30.70%	29.84%
> 0.75-1.0	23.33%	16.80%	16.49%
> 1	6.37%	5.28%	4.21%
Average stressful life events (SD)	8.25 (7.33)	10.09 (8.30)	7.50 (6.77)***
(% missing)	(7.94%)	(8.40%)	(7.75%)
Average maternal education (SD)	2.34 (1.01)	2.35 (1.02)	2.34 (1)
(% missing)	(0.39%)	(0.28%)	(0.43%)
CSE/vocational	32.99%	23.86%	23.27%
O-Level	48.50%	34.20%	34.57%
A-Level	36.43%	24.69%	26.37%
Higher degree	22.27%	16.96%	15.36%
Prenatal Social Support (SD)	19.92 (4.94)	19.42 (4.98)	20.13 (4.91)***
(% missing)	(8.66%)	(7.95%)	(8.95%)
Interpersonal Sensitivity (SD)	2.58 (0.44)	2.64 (0.45)	2.55 (0.44)***
(% missing)	(13.73%)	(12.35%)	(14.30%)
Average EPDS (SD)			
(% missing)			
18 Week Prenatal	6.58 (4.69)	7.40 (5.01)	6.25 (4.51)***
	(8.1%)	(8.18%)	(8.04%)
32 Week Prenatal	6.74 (4.94)	7.65 (5.24)	6.37 (4.77)***
	(3.04%)	(3.28%)	(2.95%)
8 Week Postnatal	5.82 (4.57)	6.47 (4.76)	5.55 (4.46)***
	(6.99%)	(7.29%)	(6.86%)
8 Month Postnatal	5.19 (4.54)	5.93 (4.90)	4.89 (4.35)***
	(9.45%)	(9.90%)	(9.31%)
Average CCEI (SD)			
(% missing)			
18 Week Prenatal	4.71 (3.45)	5.33 (3.65)	4.46 (3.33)***
	(7.73%)	(8.12%)	(7.57%)
32 Week Prenatal	4.93 (3.52)	5.59 (3.71)	4.66 (3.40)***
	(4.99%)	(4.67%)	(5.12%)
8 Week Postnatal	3.30 (3.18)	3.82 (3.35)	3.09 (3.09)***
	(7.87%)	(8.06%)	(7.79%)
8 Month Postnatal	3.50 (3.26)	4.02 (3.50)	3.29 (3.13)***
	(9.55%)	(10.30%)	(9.24%)

*p < 0.05, **p < 0.01, ***p < 0.001

Table 3 Ethnicity of the ALSPAC Mothers Demonstrate Under-representation of Non-Caucasian Women. This table demonstrates the number of women of different ethnicities in the ALSPAC cohort. In the current study, we focused on women who self-reported as White to account for possible variation in genetics. However, information about women who are not white are under-represented in population studies including the ALSPAC cohort, and is a limitation of the current study.

	White	Black Caribbean	Black African	Other black	Indian	Pakistani	Bangla deshi	Chinese	Other	NA
N	11756	72	11	44	53	22	7	30	75	2896

Table 4 PRS of Depressive Symptoms Alone Significantly Predict Perinatal Mood Based on 95% Confidence Interval. This table shows the 95% CI for the standardized Beta and R^2 values of linear regression of predicting perinatal depression with PRS alone. The 95% CI have been calculated by bootstrapping resampling method with 1000 iterations. The 95% CI of the standardized Beta and R^2 values do not cross zero and indicate that PRS alone can significantly predict perinatal depression.

Mood	Measures	18 Week Prenatal	32 Week Prenatal	8 Week Postpartum	8 Month Postpartum
EPDS N=6824	PRS Beta (95% CI)	0.127 (0.102, 0.151)	0.0964 (0.072, 0.12)	0.117 (0.0932, 0.143)	0.130 (0.104, 0.154)
	PRS R^2 (95% CI)	0.0162 (0.0100, 0.0224)	0.00926 (0.0041, 0.0137)	0.0139 (0.0079, 0.0196)	0.017 (0.0102, 0.0233)
CCEI N=6819	PRS Beta (95% CI)	0.121 (0.0966, 0.144)	0.0989 (0.0744, 0.125)	0.118 (0.0949, 0.144)	0.122 (0.0978, 0.148)
	PRS R^2 (95% CI)	0.0145 (0.0087, 0.0201)	0.00975 (0.0049, 0.0144)	0.0141 (0.008, 0.0195)	0.015 (0.0088, 0.0209)

Table 5 PRS of Depressive Symptoms Combined with Environmental Factors Significantly Predict Perinatal Mood Based on 95% Confidence Interval. This table shows the 95% CI for the standardized Beta and R^2 values of linear regression of predicting perinatal depression with the G+E model (G+E Eq4). The 95% CI have been calculated by bootstrapping with 1000 iterations. The 95% CI of the standardized Beta value of PRS in the G+E model do not cross zero and indicate that the PRS is significantly predicting perinatal depression in addition to the environmental variables in the G+E model.

Mood	Measures	18 Week Prenatal	32 Week Prenatal	8 Week Postpartum	8 Month Postpartum
EPDS N=6824	PRS Beta (95% CI)	0.0675 (0.0430, 0.0907)	00296 (0.0051, 0.0553)	0.0696 (0.0433, 0.0962)	0.0772 (0.0508, 0.103)
	GE Model R^2 (95% CI)	0.239 (0.216, 0.261)	0.197 (0.174, 0.216)	0.133 (0.111, 0.150)	0.135 (0.113, 0.156)
CCEI N=6819	PRS Beta (95% CI)	0.0699 (0.0459, 0.0938)	0.0379 (0.0141, 0.0627)	00762 (0.050, 0.102)	0.0713 (0.0462, 0.0949)
	GE Model R^2 (95% CI)	0.206 (0.184, 0.228)	0.144 (0.121, 0.164)	0.144 (0.121, 0.164)	0.139 (0.117, 0.159)

Table 6 Generalized Estimating Equation (GEE) of G+E Model Demonstrates that Genetic and Environmental Factors Predict Perinatal Depressive Symptoms Longitudinally. This table shows the non-standardized beta coefficients and the significance of the GEE of predicting perinatal depression with the variables in the G+E model calculated by RStudio. The complete cases of women who have self-reported depressive symptoms at all 4 perinatal period, and have available the environmental and genetic variables have been considered. We found the environmental and genetic variables predicted depressive symptoms longitudinally. We did not find an interaction of time and PRS for predicting depressive symptoms.

Outcome: Perinatal EPDS (4599)	**Non-standardized Beta Estimate**	**Standardized Beta Estimate**	**Standard Error**	**P value**
(Intercept)	11.507	-0.0197	0.478	<2e-16***
Time	-0.0627	0.000149	0.0107	5.4e-9***
PRS	0.211	0.0614	0.101	0.0362*
Age	-0.0738	-0.0749	0.0124	2.5e-09***
Crowding	0.253	0.0478	0.0667	0.00014***
Life Events	0.198	0.308	0.00849	<2e-16***
Education	-0.283	-0.0585	0.0578	1e-6***
History of Sexual Abuse	0.417	0.0391	0.122	0.00065***
Prenatal Social Support	-0.214	-0.222	0.0120	<2e-16***
Time x PRS	0.000230	0.00237	0.000306	0.453
Time x Age	0.00148	0.00151	0.000284	2.1e-7***
Time x Crowding	-0.00339	-0.000637	0.00151	0.0248*
Time x Life Events	-0.00135	-0.00196	0.000202	2.4e-11***
Time x Education	0.00269	0.000542	0.00129	0.0372*
Time x History of Sexual Abuse	0.00140	0.000167	0.00277	0.613
Time x Prenatal Social Support	0.000209	0.000071	0.000268	0.435
PRS x Age	0.00106	-0.00417	0.00263	0.687
PRS x Crowding	-0.0265	-0.0205	0.0147	0.0727
PRS x Life Events	0.00182	0.0117	0.00196	0.353
PRS x Education	-0.0219	-0.0182	0.0122	0.074
PRS x History of Sexual Abuse	-0.00697	-0.00268	0.0262	0.790
PRS x Prenatal Social Support	-0.00111	-0.00462	0.00262	0.672

*p < 0.05, **p < 0.01, ***p < 0.001

Table 7 Generalized Estimating Equation (GEE) of G+E Model Demonstrates that Genetic and Environmental Factors Predict Perinatal Anxiety Symptoms Longitudinally. This table is a replication of the GEE analysis in Supplementary Table 6 for perinatal anxiety symptoms. We found the environmental and genetic variables predicted anxiety symptoms longitudinally. We did not find an interaction of time and PRS for predicting anxiety symptoms.

Outcome: Perinatal CCEI (4520)	**Non-standardized Beta Estimate**	**Standardized Beta Estimate**	**Standard Error**	**P value**
(Intercept)	8.30	-0.0178	0.361	<2e-16***
Time	-0.0681	0.000273	0.00774	<2e-16***
PRS	0.0789	0.0626	0.0767	0.304
Age	-0.0791	-0.109	0.00928	<2e-16***
Crowding	0.0471	0.0116	0.0494	0.340
Life Events	0.149	0.317	0.00627	<2e-16***
Education	-0.0702	-0.0193	0.0429	0.101
History of Sexual Abuse	0.323	0.0412	0.0897	0.00032***
Prenatal Social Support	-0.132	-0.187	0.00892	<2e-16***
Time x PRS	-0.0000436	0.0000308	2.08e-4	0.834
Time x Age	0.00181	0.0025	2.05e-4	<2e-16***
Time x Crowding	0.000498	0.000173	0.00196	0.637
Time x Life Events	-0.000796	-0.00144	1.43e-4	2.9e-8***
Time x Education	0.000221	0.0000197	8.91e-4	0.804
Time x History of Sexual Abuse	0.000653	0.000159	0.00193	0.734
Time x Prenatal Social Support	0.00000795	-0.000188	1.89e-4	0.966
PRS x Age	0.00323	0.0182	0.002	0.106
PRS x Crowding	-0.026	-0.0281	0.0105	0.0133*
PRS x Life Events	0.00101	0.00939	0.00141	0.475
PRS x Education	-0.017	-0.0199	0.00897	0.0573
PRS x History of Sexual Abuse	0.0292	0.0157	0.0188	0.115
PRS x Prenatal Social Support	-0.00232	-0.0135	0.00194	0.231

*p < 0.05, **p < 0.01, ***p < 0.001

Table 8 Generalized Estimating Equation (GEE) of G+E Model Demonstrates that PRS and History of Sexual Abuse Do Not Interact to Predict Depressive Symptoms. In order to investigate whether the history of sexual abuse interact with PRS, we carried out a GEE analysis with environmental and genetic variables and included an interaction term of history of sexual abuse and PRS. We also included the interaction terms of history of sexual abuse with all of the environmental factors and the interaction terms of PRS with all of the environmental factors to identify the effect of interaction between history of sexual abuse and PRS that is independent from the interaction of the given variables with other environmental factors. We did not find an interaction of PRS and history of sexual abuse when predicting depressive symptoms.

Outcome: Perinatal EPDS (4599)	**Non-standardized Beta Estimate**	**Standardized Beta Estimate**	**Standard Error**	**P value**
(Intercept)	10.691	-0.0323	0.475	<2e-16***
Time	-0.0256	0.000665	0.00121	<2e-16***
PRS	0.223	0.0671	0.101	0.0271*
Age	-0.0401	-0.0377	0.0127	0.0016**
Crowding	0.143	0.0323	0.0673	0.034*
Life Events	0.163	0.258	0.00932	<2e-16***
Education	-0.174	-0.0448	0.0588	0.0031**
History of Sexual Abuse	0.132	0.0461	0.906	0.884
Prenatal Social Support	-0.212	-0.220	0.0123	<2e-16***
History of Sexual Abuse x PRS	-0.009	-0.00348	0.0263	0.732
History of Sexual Abuse x Age	0.00887	0.00417	0.0241	0.713
History of Sexual Abuse x Crowding	0.0976	0.00837	0.131	0.458
History of Sexual Abuse x Life Events	0.00496	0.00375	0.0158	0.753
History of Sexual Abuse x Education	-0.141	-0.0135	0.112	0.211
History of Sexual Abuse x Prenatal Social Support	0.00931	0.00429	0.0228	0.683
PRS x Age	-0.00126	-0.00496	0.00265	0.633
PRS x Crowding	-0.0275	-0.0212	0.0148	0.0632
PRS x Life Events	0.00179	0.0116	0.00198	0.367
PRS x Education	-0.0207	-0.0172	0.0123	0.0914
PRS x Prenatal Social Support	-0.00116	-0.00483	0.00264	0.659

*p < 0.05, **p < 0.01, ***p < 0.001

Table 9 Generalized Estimating Equation (GEE) of G+E Model Demonstrates that PRS and History of Sexual Abuse Do Not Interact to Predict Anxiety Symptoms. This table is a replication of the GEE analysis in Supplementary Table 8 for perinatal anxiety symptoms. We did not find an interaction of PRS and history of sexual abuse when predicting anxiety symptoms.

Outcome: Perinatal CCEI (4520)	**Non-standardized Beta Estimate**	**Standardized Beta Estimate**	**Standard Error**	**P value**
(Intercept)	6.932	-0.0280	0.365	<2e-16***
Time	-0.0204	0.000684	0.000843	<2e-16***
PRS	0.0766	0.0631	0.0767	0.318
Age	-0.0280	-0.0465	0.00951	0.0033**
Crowding	0.0490	0.0157	0.0498	0.325
Life Events	0.127	0.280	0.00702	<2e-16***
Education	-0.0512	-0.0188	0.0439	0.243
History of Sexual Abuse	1.0171	0.0489	0.68	0.135
Prenatal Social Support	-0.131	-0.192	0.00934	<2e-16***
History of Sexual Abuse x PRS	0.0265	0.0140	0.0188	0.159
History of Sexual Abuse x Age	-0.0216	-0.0139	0.0178	0.224
History of Sexual Abuse x Crowding	0.0332	0.00336	0.101	0.741
History of Sexual Abuse x Life Events	0.00467	0.00492	0.0116	0.687
History of Sexual Abuse x Education	-0.0465	-0.00680	0.0839	0.579
History of Sexual Abuse x Prenatal Social Support	-0.002	-0.000903	0.0171	0.907
PRS x Age	0.00328	0.0185	0.002	0.101
PRS x Crowding	-0.0261	-0.0281	0.0105	0.0131*
PRS x Life Events	0.00095	0.00890	0.00143	0.507
PRS x Education	-0.0166	-0.0193	0.009	0.0653
PRS x Prenatal Social Support	-0.00231	-0.0134	0.00195	0.236

*p < 0.05, **p < 0.01, ***p < 0.001

Table 10 Correlation of PRS and Perinatal Mood Remain Significant when History of Sexual Abuse, Crowding and Stressful Life Events were Regressed Out. History of sexual abuse, crowding and stressful life events were found to be positively correlated to PRS. This table compares the correlation of PRS 3 with perinatal mood when history of sexual abuse, crowding and stressful life events are regressed out. This is to see whether the PRS 3 is correlated with perinatal mood due to the correlation of PRS 3 with the environmental variables or if PRS 3 is independently correlated to perinatal mood. In the PRS 3 version 2, the positively correlated environmental variables have been regressed out in addition to PC1-10. Based on this table, the correlation of PRS 3 version 2 is correlated with perinatal mood less. However, the correlation still remains significant and therefore PRS 3 is correlated to perinatal mood independently from the contribution of the given environmental variables. (N=5577)

Variables	**Pearson Correlation with PRS 3**		**Pearson Correlation with PRS 3 version 2**	
	Coefficient	**P-value**	**Coefficient**	**P-value**
EPDS Pre 1	0.131	<2e-16	0.894	<3e-11
EPDS Pre 2	0.0938	3e-12	0.0564	3e-5
EPDS Post 1	0.122	<2e-16	0.0954	5e-12
EPDS Post 2	0.131	<2e-16	0.103	1e-13
CCEI Pre 1	0.123	<2e-16	0.0853	2e-10
CCEI Pre 2	0.0981	4e-13	0.0616	5e-6
CCEI Post 1	0.126	<2e-16	0.0978	2e-12
CCEI Post 2	0.119	<2e-16	0.0898	1e-10
Age	-0.0430	0.001	-0.0332	0.01
Education	-0.0428	0.001	-0.0297	0.03
Prenatal Social Support	-0.0950	7e-12	-0.0649	3e-6
PRS 3	1	0	0.994	<2e-16
PRS 3 version 2	0.994	<2e-16	1	0

Table 11 Methylation Level at Estrogen-Sensitive Epigenetic Biomarker is Significantly Different between Women in Four Trajectories of Depressive Symptoms. Descriptive statistics of the epigenetic biomarkers in ALSPAC mothers stratified to those with 4 different trajectories of perinatal depressive symptoms show that level of methylation at Cpg00058938 was significantly different in the 4 groups. (Subclinical threshold used for stratifying the trajectory groups)

	High-High (68)	**High-Low (122)**	**Low-High (63)**	**Low-Low (590)**	**ANOVA Pr(>F)**
Cpg21326881	Mean: 0.0391 Sd: 0.00718	Mean: 0.0419 Sd: 0.0182	Mean: 0.0378 Sd: 0.00706	Mean: 0.0404 Sd: 0.00993	0.0861
Cpg00058938	Mean: 0.312 Sd: 0.00718	Mean: 0.313 Sd: 0.0182	Mean: 0.282 Sd: 0.00706	Mean: 0.315 Sd: 0.00993	0.00291**
CellRatio	Mean: 0.0864 Sd: 0.00718	Mean: 0.0882 Sd: 0.0182	Mean: 0.0894 Sd: 0.00706	Mean: 0.0843 Sd: 0.00993	0.505
CellRatiox cpg21326881	Mean: 0.00334 Sd: 0.00718	Mean: 0.00349 Sd: 0.0182	Mean: 0.00337 Sd: 0.00706	Mean: 0.00336 Sd: 0.00993	0.85

Table 12 Methylation Level at Estrogen-Sensitive Epigenetic Biomarker is Significantly Different between Women with Low-High Trajectory and Women with Three Other Trajectories of Depressive Symptoms When the methylation level and cell ratios in women with the 4 different depressive symptoms trajectories were compared, those in women with low-high trajectory was significantly different with those in women from the 3 other trajectory groups. (Subclinical threshold used for stratifying the trajectory groups)

	High-High vs. High-Low	**High-High vs. Low-High**	**High-High vs. Low-Low**	**High-Low vs. Low-High**	**High-Low vs. Low-Low**	**Low-High vs. Low-Low**
Cpg21326881	0.223	0.287	0.295	0.0832	0.196	0.041*
Cpg00058938	0.907	0.0127*	0.671	0.00396**	0.713	0.000194***
CellRatio	0.72	0.601	0.645	0.819	0.252	0.263
CellRatiox cpg21326881	0.457	0.876	0.899	0.583	0.397	0.949

Table 13 Estrogen-Sensitive Epigenetic Model Explains Perinatal Depressive Symptoms in Women with Low-Low, Low-High and High-High Trajectories Based on Subclinical Threshold The R^2 values of the epigenetic model demonstrate that the biomarkers explain different level of the % variance of the mood symptoms depending on the trajectory groups (Epi Eq 7). When the significance of the epigenetic biomarkers were examined, they were significant at different timpoints in the different trajectory groups. They were not significant at any time points in the group of women with high-low depressive symptoms trajectory.

	18 Wk Prenatal	**32 Wk Prenatal**	**8 Wk Postnatal**	**8 Mo Postnatal**	**Significant P values?**
High-High (n=68)	0.0519	0.168	0.0607	0.0784	At 32 weeks prenatal
High-Low (n=122)	0.00773	0.0535	0.0268	0.0157	None
Low-High (n=63)	0.0198	0.0790	0.0896	0.0833	At 8 month postnatal
Low-Low (n=590)	0.00207	0.00434	0.0207	0.00642	At 8 week postnatal

Table 14 Estrogen-Sensitive Epigenetic Model Explains Perinatal Depressive Symptoms in Women with Low-Low and High-High Trajectories Based on Clinical Threshold The analysis with Epi Eq7 as Table 13 is repeated in this table after stratifying women to different trajectory groups based on clinical thresholds. The R^2 values demonstrate that the biomarkers explain different level of the % variance of the mood symptoms depending on the trajectory groups. When the significance of the epigenetic biomarkers were examined, they were significant at different timpoints in the different trajectory groups. They were not significant at any time points in the group of women with high-low or low-high depressive symptoms trajectory.

	18 Wk Prenatal	**32 Wk Prenatal**	**8 Wk Postnatal**	**8 Mo Postnatal**	**Significant P values?**
High-High (n=24)	0.0932	0.121	0.141	0.140	At 32 weeks prenatal
High-Low (n=57)	0.0620	0.124	0.0492	0.0572	None
Low-High (n=43)	0.117	0.233	0.0325	0.0930	None
Low-Low (n=719)	0.00459	0.00762	0.0232	0.0102	At 8 weeks and 8 months postnatal

Table 15 PRS of Depressive Symptoms is Significantly Different Between Women with Four Trajectories of Depressive Symptoms Descriptive statistics of the PRS in ALSPAC mothers stratified to those with 4 different trajectories of perinatal depressive symptoms show that PRS was significantly different in the 4 groups. (Subclinical threshold used for stratifying the trajectory groups)

	High-High (898)	**High-Low (1455)**	**Low-High (672)**	**Low-Low (6274)**	**ANOVA Pr(>F)**
PRS 3	Mean: 1.14 Sd: 3.77	Mean: 0.358 Sd: 3.80	Mean: 0.614 Sd: 3.90	Mean: -0.341 Sd: 3.99	<2e-16***

Table 16 The Difference in PRS of Depressive Symptoms Between Women with Four Trajectories of Depressive Symptoms is Not Specific to Women with Low-High Trajectory PRS of depressive symptoms in women with the 4 different depressive symptoms trajectories were different between all groups except in high-low and low-high groups. (Subclinical threshold used for stratifying the trajectory groups)

	High-High vs. High-Low	**High-High vs. Low-High**	**High-High vs. Low-Low**	**High-Low vs. Low-High**	**High-Low vs. Low-Low**	**Low-High vs. Low-Low**
PRS 3	0.000205***	0.0393*	8.19e-16***	0.276	3.41e-06***	6.36e-06***

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