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ORIGINAL ARTICLE

Prenatal maternal depressive symptoms and infant DNA methylation: a longitudinal epigenome-wide study

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ABSTRACT

Background: Prenatal maternal stress increases the risk of offspring developmental and psychological difficulties. The biological mechanisms behind these associations are mostly unknown. One explanation suggests that exposure of the fetus to maternal stress may influence DNA methylation. However, this hypothesis is largely based on animal studies, and human studies of candidate genes from single timepoints.

Aim: The aim of this study was to investigate if prenatal maternal stress, in the form of maternal depressive symptoms, was associated with variation in genome-wide DNA methylation at two timepoints.

Methods: One-hundred and eighty-four mother-child dyads were selected from a population of pregnant women in the Little-in-Norway study. The Edinburgh Postnatal Depression Scale (EPDS) measured maternal depressive symptoms. It was completed by the pregnant mothers between weeks 17 and 32 of gestation. DNA was obtained from infant saliva cells at two timepoints (age 6 weeks and 12 months). DNA methylation was measured in 274 samples from 6 weeks ($n = 146$) and 12 months ($n = 128$) using the Illumina Infinium HumanMethylation 450 BeadChip. Linear regression analyses of prenatal maternal depressive symptoms and infant methylation were performed at 6 weeks and 12 months separately, and for both timepoints together using a mixed model.

Results: The analyses revealed no significant genome-wide association between maternal depressive symptoms and infant DNA methylation in the separate analyses and for both timepoints together.

Conclusions: This sample of pregnant women and their infants living in Norway did not reveal associations between maternal depressive symptoms and infant DNA methylation.

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Prenatal maternal depression; maternal depressive symptoms; early life stress; infant outcome; DNA methylation

Background

It is estimated that 10–15% of women suffer from symptoms of depression during pregnancy [1]. Prenatal maternal stress increases the risk of developmental and psychological difficulties in children [2–4], and is recognized as a risk factor for neurological and cognitive disturbances and brain functioning in offspring [5]. Stress in the form of prenatal maternal depression is associated with an increased risk of adolescent depression [6,7], independent of postnatal maternal depression [8]. The biological mechanisms behind these interactions are not well understood. The fetal programing hypothesis suggests that maternal hormones pass through the placenta to program the offspring tissue during fetal development having life-long impact on health [9,10]. Current theories, largely based on animal studies, suggest that epigenetic modifications function as a biological mechanism regulating the effects of stress on offspring [11–13]. Epigenetics refers to both mitotically heritable changes in gene activity and expression, as well as stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable [14]. Epigenetic modifications include DNA methylation and histone modifications and are important in regulating cell differentiation [15].

Epigenetic studies of the effects of prenatal maternal depression have mostly been limited to DNA methylation studies in candidate genes, but one recent study of pregnant mothers found that prenatal depression was associated 39 differentially methylated regions (DMRs) in cord blood [16]. Other epigenome-wide studies of DNA methylation from cord blood analyzed ~27,000 CpG sites and found no significant associations with depressive symptoms in pregnancy [17]. Two other epigenome-wide association studies (EWAS) analyzing ~450,000 CpG sites from cord blood have reported significant associations between infant methylation and prenatal maternal depression or anxiety [18,19]. Other types of maternal stress have also been studied epigenome-wide. Project Ice Storm found differences in DNA methylation

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between blood samples from children of women exposed to a natural disaster during pregnancy, depending on mothers' cognitive appraisal of the storm [20–22]. A study of prenatal war stress from Congo found no epigenome-wide associations in 25 cord blood samples [23], nor did a large epigenome-wide study of prenatal maternal everyday life-distress in 1740 cord blood samples [24].

The most studied single gene is the glucocorticoid receptor (*NR3C1*). The first study reported associations between maternal depression and *NR3C1* DNA methylation in cord blood [25]. This finding was replicated by other studies of prenatal stress and *NR3C1* in cord blood [26], placental tissue [27] and buccal epithelial cells [28]. A meta-analysis study in 2015 supported an association between prenatal stress and *NR3C1* methylation [29], but was followed in 2016 by two new studies of 68 and 481 participants, from buccal epithelial cells and cord blood respectively, that could not replicate these findings [30,31]. Candidate-gene studies have also found an association between prenatal maternal depression and DNA methylation of the oxytocin receptor gene (*OXTR*) in cord blood [32], and of placental FKB506 binding protein 5 (*FKBP5*) [33]. An association was also shown with the serotonin transporter (*SCL6A4*) promoter region in cord blood [34], but this was not replicated in a later study of cord blood from 90 participants [35].

The evidence for an association between prenatal maternal depression and DNA methylation in the offspring is inconclusive. Many of the previous studies have been limited by small sample sizes, a focus on single genes, and differ in how stress was measured. The epigenome is highly variable between cell types. This makes a comparison of different studies analyzing different cell types challenging. In addition, the variety of methods used to measure DNA methylation, and the different CpG sites studied, makes comparing studies difficult. More EWAS are therefore needed for progression in this field [24]. In this EWAS study, DNA methylation from saliva was measured at two timepoints postnatally. The aim of the study was to test if prenatal maternal depressive symptoms were associated with changes in infant DNA methylation.

Methods

Study population

For this study, a total of 184 mother-child dyads were drawn from a population of pregnant women in the Little-in-Norway (LiN) study [36,37]. The LiN study is a community-based population study with a prospective cohort design, investigating factors important for child development. Nine Norwegian well-baby clinics invited all pregnant women having their first visit from September 2011 to October 2012 to participate. All women consenting to take part in the study were contacted by a nurse for inclusion. Most mothers were of Norwegian heritage, only three were from different minority groups; Filipino, Slovakian and American. Maternal depressive symptoms were rated by the Norwegian version of the Edinburgh Postnatal Depression Scale (EPDS), completed by the women at inclusion. The time of inclusion varied from gestational week 17–week 32 for this sample. Major depressive symptoms most often last for more than 7 days [38] and we could therefore assume that the mothers' reports were representative for the same time period.

Information about age, education level, marital status and parity was obtained from the women, and the information about fetal sex and gestational age at birth was collected from birth records. Infant saliva samples were collected by specially trained nurses in the well-baby clinics at 6 weeks and 12 months, but for some infant's saliva samples were obtained only at one of the time points. Some infants had their 6-week assessment before the saliva collection was started, others were prevented from attending the specific assessment when the saliva was to be collected. For an overview of infant saliva samples, see Table 1.

Table 1. Infant saliva sample collection.

Time of collection	Mother-child dyads	Infant saliva samples
6 Weeks only	47	47
12 Months only	29	29
Both timepoints	99	198
Total	184	274

The Norwegian Regional Ethics Board for South-East Norway approved the study. All mothers gave written informed consent for participation and for the collection of infant saliva samples. Reference no: 2011/560/REK.

Rating of depressive symptoms

The Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-report measure of maternal depressive symptoms, was completed at the time of inclusion. The EPDS is a common screening tool for postpartum depressive symptoms [39]. It has also been validated for use during pregnancy [1,40]. Symptoms of depression during the previous week were registered. A total score of maternal depressive symptoms (EPDS sum) was calculated, with a possible range from 0–30 [39]. A cutoff of 12 was recommended for patients with major depression when validating the Norwegian version of the EPDS [41], and is therefore used as the cutoff for symptoms of major depression in this study. For statistical analysis, EPDS was modeled as continuous.

Saliva sample collection and DNA isolation

Infant saliva samples were collected at 6 weeks and 12 months using the Oragene DNA Assisted collection kit (OG-575). Parental DNA was not collected for comparison. DNA was extracted from the samples using the Oragene prep-IT L2P kit (DNA Genotek, Ottawa, ON, Canada). DNA quantity was assessed using PicoGreen (ThermoFisher, Waltham, MA, USA). A total of 274 samples met our minimum requirement of 320 ng of DNA for DNA methylation analysis.

Microarray pre-processing and quality control

Bisulfite conversion of 320–500 ng of saliva sample DNA was carried out using EZ-96 DNA Methylation-Gold Kit (Zymo Research) according to the manufacturer's instructions. To minimize potential batch effects, the samples were randomly located on 96 well plates and bisulfite conversion was run on a Beckman Biomek FX workstation. DNA methylation was measured using the Infinium HumanMethylation 450 BeadChip (Illumina). All statistical analyses were carried out using the R programing language (http://www.r-project.org/) and the raw data were preprocessed with RnBeads v.1.2.1 [42] (http://rnbeads.mpi-inf.mpg.de).

Cross-reactive probes (29,233) [43], probes with SNPs at the CpG site (4232), and probes and samples with unreliable measurements (detection p values $>$.01) (16,819 probes and 18 samples) were removed. Background subtraction was performed using *noob.methylumi* [44] and β-values were normalized using BMIQ [45]. Finally, probes located on the sex chromosomes (9675) and non-CpG probes (2303) were removed, resulting in a final data set consisting of 423,315 probes. After quality control, 18 samples were removed, leaving 256 infant DNA samples for analyses.

Cell type composition

The epigenome is highly variable between cell types. The body consists of over 250 different cell types that are originally derived from one single stem cell. In the oral cavity, both leucocytes and epithelial cells are found [46]. To estimate the amount of leucocytes in the saliva samples, LUMP (leukocytes unmethylation for purity) scores were calculated and the LUMP score was used as a covariate in the analyses to adjust for this [47].

Statistical analyses

We used the following linear regression model to look for associations between methylation and prenatal maternal depressive symptoms: $CpG_{ijk} = \beta_{0ik} + \beta_{1ik}\ dep_j + \beta_{2ik}\ age_j + \beta_{3ik}\ smoke_j + \beta_{4ik}\ sex_j + \beta_{4ik}\ LUMP_j + \varepsilon_{ijk}$, where CpG_{ij} is methylation (M-value) for CpG i ($i = 1, \ldots,$ 423,315) in infant j ($j = 1, \ldots, n\_t$) at timepoint k ($k = 6$ *week, 12 months*); where dep_j, age_j, $smoke_j$, sex_j *and* $lump_j$ represent maternal prenatal depressive symptoms, maternal age, maternal smoking status, sex and LUMP score for infant j. For CpG i at timepoint k, β_{0ik} is the intercept, (β_{1ik}, β_{2ik}, β_{3ik}, β_{4ik}, β_{4ik}) are the regression coefficients and ε_{ijk} is a normally distributed error term with mean 0.

For each CpG i at timepoint k the null hypothesis is that the coefficient of the maternal depressive symptoms term, β_{1i}, is equal to zero and the test statistic is a Wald test,

$$\hat{\beta}_{1ik} / se(\beta_{1ik})$$

where *se* is the standard error.

We also considered a linear mixed model with a random intercept (b_{0ik}) for individual. Maternal depressive symptoms, maternal age, maternal smoking status, infant sex, timepoint and lump score are here modeled as fixed effects, and individual is modeled as a random effect.

$$CpG_{ij} = \beta_{0i} + b_{0ik} + \beta_{1i} dep_j + \beta_{2i} age_j + \beta_{3i} smoke_j + \beta_{4i} sex_j + \beta_{4i} time_j + \beta_{4i} LUMP_j + \varepsilon_{ij}$$

Differentially methylated regions (DMR) analysis was performed with the DMR Scan R package [48].

Multiple testing

We visualized the epigenome-wide association study results using quantile-quantile plots (Q-Q plots) to compare the observed distribution of p values for the Wald test for the maternal depressive symptoms term to what would be expected under the global null hypothesis of no association. To control for the family-wise error rate, we applied a Bonferroni correction for 423,315 tests. The Bonferroni threshold was 0.05/423315 = 1.18e-07.

Power

We calculated power for the first time point ($n = 146$), assuming a per test alpha of 1.18e–07 and no covariates. Based on the parameters in this study ($n = 146$ at the first time point, alpha = 1.18e-07) and no covariates, we have 65% power to detect an association between methylation and EPDS, assuming an R^2 of 0.2. For lower values of R^2, this study is further underpowered.

Results

Descriptive analyses

The descriptive socio-demographic characteristics of the mother-child dyads from the LiN study are shown in Table 2. Attrition analyses have been done by Fredriksen et al. [49] and showed that high levels of depressive symptoms during pregnancy significantly predicted dropout (ORs: 1.06–1.10, $p = .05$). Further, lower education (OR: 0.93, 95% CI [0.87, 0.99], $p = .02$); parity (OR: 0.75, 95% CI [0.57, 0.99], $p = .04$); and childhood trauma (OR: 1.20, 95% CI [1.06, 1.37], $p = .01$) predicted dropout at 12 months.

Epigenome-wide association analysis

When analyzed separately, there were no epigenome-wide significant associations between prenatal maternal depressive symptoms and CpG methylation at 6 weeks or 12 months (see EWAS Q-Q plots in Figure 1, plots A and B). Although there is greater power when both methylation timepoints were analyzed together in a mixed model with a random intercept for individual, there were still no epigenome-wide significant associations between prenatal maternal depressive symptoms. The results for the three CpGs with p value $<$10e–6 are given in Table 3. The results are stable to the inclusion or exclusion of smoking as a covariate. No significant DNRs were found.

Table 2. Socio-demographic data.

	Mean	SD (range)
Mean maternal age	30 years	5 years (20–43 years)
Infant birth weight	3624 g	471 g (1860–4825 g)
Gestational age at inclusion	25 weeks	4 weeks (17–32 weeks)
Gestational age at birth	40 weeks	1 week (33–43 weeks)
EPDS	4.4 total score	3.6 (0–22)
	Total (%) $N = 166$	
Maternal marital status		
Living with partner	104 (63%)	
Married	55 (33%)	
Single	5 (3%)	
Other	2 (1%)	
Completed education		
Primary education	2 (1%)	
Secondary education	34 (20%)	
College	59 (36%)	
University	71 (43%)	
Smoking in pregnancy	13 (8 %)	
Infant sex		
Girls	76 (46%)	
Boys	90 (54%)	

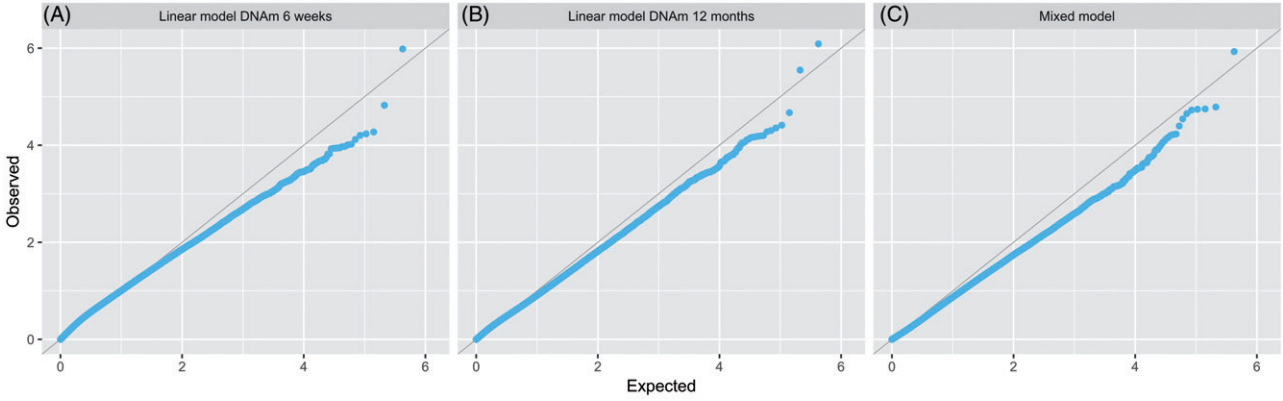

Figure 1. Q-Q plots for the association between DNA methylation and maternal depression. (A) Linear regression model for methylation at 6 weeks, (B) Linear regression model for methylation at 12 months and (C) Linear mixed model with random intercept for individual.

Table 3. Association of CpG sites with maternal depressive symptoms with p value <10e-6.

Gene symbol	Chr	Position	CpG	Linear model 6 week methylation	Linear model 12 month methylation	Mixed model both timepoints
TBR1	2	162271859	cg06747888	−0.049(0.010) $p = 1.0e{-}06$	−0.017(0.014) $p = 0.23$	−0.034(0.009) $p = 8.1e{-}05$
KLF6	10	3823758	cg13454226	−0.035(0.011) $p = 0.0019$	−0.047(0.009) $p = 8.1e{-}07$	−0.0391(0.008) $p = 1.2e{-}06$
CCDC114 (Closest gene)	19	48825620	cg04655299	0.01(0.009) $p = 0.28$	0.045(0.009) $p = 2.8e{-}06$	0.026(0.006) $p = 6.0e{-}05$

Estimated regression coefficient for maternal depressive symptoms (standard error) and p value. $p < 1.181154e{-}07$ is the Bonferroni threshold for global alpha = 0.05 so none of this CpGs reach genome-wide significance.

Discussion

In this study, we hypothesized that prenatal maternal depressive symptoms would be associated with infant DNA methylation. This sample of mother-child dyads did not show significant epigenome-wide associations between prenatal maternal depressive symptoms and DNA methylation at 6 weeks or 12 months alone, nor did it show associations when both timepoints were analyzed together in a mixed model. When interpreting these results, one should take into consideration that the mothers scored low on depressive symptoms and that high maternal education status was overrepresented in this population [50], possibly affecting the results. The highest associations were found in the T-box, brain 1 (*TBR1*) gene, the Krüppel-like factor 6 (*KLF6*) gene and at the un-annotated CpG position; cg04655299. None of these CpG positions reached genome-wide significance following the Bonferroni threshold for global alpha = 0.05. As the study was found to be underpowered, it is possible that the results would have been different if we had studied a larger group of pregnant mothers.

T-box, brain 1 is a member of a family of genes that share the T-box as their common DNA-binding domain and is

mainly expressed in brain tissue. *TBR1* variants have been identified in sporadic autism, and in interaction with *FOXP2* have been found to be involved in speech and language disorders [51]. Single nucleotide polymorphism (SNP) array analysis showed that de novo deletions in *TBR1* were associated with intellectual disability and growth retardation [52]. In mice, prenatal maternal obesity has been associated with an increased number of *Tbr1* in neurons in offspring that showed anxiety-like behavior as adults [53]

The Krüppel-like family of transcription factors are a set of zinc finger DNA-binding proteins (*KLF*) that regulate gene expression. They are relevant to human cancers due to their involvement in the control of cell proliferation, apoptosis, migration, and differentiation [54]. To our knowledge *KLF6* infant epigenetic variation has not previously been found to be associated with prenatal maternal depression, though several studies have found associations between early life stress and increased cancer risk [55–62]. Further research is needed to understand the mechanisms driving the effects of prenatal maternal depression on long-term health.

In the first study to examine epigenome-wide effects of maternal psychiatric illness, using the 27K Illumina platform, assessing only 27,000 methylation sites, the study identified no CpG sites associated with maternal depression [17]. The study by Viuff et al. [16] reported 39 DMRs in neonates exposed to maternal depression and Non et al. [18], reported 10 CpG sites that differed significantly between neonates exposed to maternal depression/anxiety and controls, using a similar method of analysis to ours, We collected DNA from saliva samples, the two other studies used cord blood. As epigenetic marks differ between different tissues makes the comparison of the results challenging.

Our study has several limitations and strengths that need to be considered when interpreting the results. This study is limited by the accessibility of cells of interest. The cells studied are epithelial saliva cells, and the preferred cells of interest are neurons and as epigenetics is cell specific, one must interpret the results with caution. In addition, our study only included maternal depressive symptoms as maternal stress measurements and very few pregnant women in our population reported high levels of depressive symptoms. While it is estimated that 10–15% of women suffer from depression during pregnancy [1], in our population only 4% scored above cutoff for major depression. It is possible that women with higher scores on maternal depressive symptoms declined the invitation to participate in the study, possibly influencing the results. Another limitation was that the time of registration of maternal depressive symptoms varied in our study. A single low score does not preclude that a woman may show depressive symptoms at other time points during pregnancy. Also, the study did not assess the extent of other maternal stress variables. A large part of the women in the current sample had completed higher education (79%), compared to 33% in the general Norwegian female adult population [50].

A major strength of the study was the possibility to analyze infant DNA methylation genome-wide at two timepoints. With a longitudinal study design, mother-child dyads were studied from pregnancy till the infant was one year old. The sample size was relatively large compared to samples in studies in this field using epigenome-wide approaches [17,18,63], but small compared to the study by Viuff et al. [16]

Conclusions

In conclusion, prenatal maternal depressive symptoms were not associated with infant DNA methylation when analyzed separately at 6 weeks or 12 months, nor were they significantly associated when both timepoints were analyzed together. The findings do not support the hypothesis that prenatal maternal stress influences offspring epigenetic variation, but our study was limited by being underpowered and the lack of clinically depressed women. These findings illustrate the difficulties of studying possible associations between prenatal maternal emotions and infant DNA methylation.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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