**Re-examining the Link between Prenatal Maternal Anxiety and Child Emotional Difficulties using a Sibling Design.**

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**Abstract**

**Background:** Prenatal exposure to maternal anxiety has been associated with child emotional difficulties in a number of epidemiological studies. One key concern, however, is that this link is vulnerable to confounding by pleiotropic genes or environmental family factors.

**Method**: Data on 82,383 mothers and children from the population-based Mother and Child Cohort study and data on 21,980 siblings were used in this study. Mothers filled out questionnaires for each unique pregnancy, for infant difficulties at 6 months and emotional difficulties at 36 months. The link between prenatal maternal anxiety and child difficulties were examined using logistic regression analyses and multiple linear regression analyses for the full study sample and the sibling sample.

**Results**: In the conventional full-cohort analyses prenatal exposure to maternal anxiety was associated with child difficulties at both 6 months [OR= 2.1 (1.94-2.27)] and 36 months [OR= 2.72(2.47-2.99)]. The findings were essentially the same whether we examined difficulties at 6 months or at 36 months. However these associations were no longer present once we controlled for potential social and genetic confounders in the sibling comparison analyses, either at 6 months [OR= 1.32(0.91-1.90)] or at 36 months [OR= 1.28(0.63-2.60)]. Findings from multiple regression analyses with continuous measures were essentially the same.

**Conclusions**: Our finding lends little support for there being an independent prenatal effect on child emotional difficulties, rather our findings suggest that the link between prenatal maternal anxiety and child difficulties could be confounded by pleiotropic genes or environmental family factors.

**Key Messages**

* In the full cohort (n=82,383) we found that children exposed to maternal anxiety in pregnancy had about twice the risk for short and long-term difficulties in the child.
* When the same association was examined within a sibling design (n=21,980) of this cohort, this association disappeared.
* The findings from our sibling analyses, suggests that the association between prenatal maternal anxiety and emotional difficulties is confounded by genetic or other familial factors.

During the past half-century, animal research and parallel human findings suggest that prenatal exposure to maternal stress and anxiety influence offspring psychopathology (1). Prenatal maternal anxiety has been associated with both short and long-term mental health problems in the child (i.e. difficulties such as emotional reactivity, symptoms of anxiety, somatic complaints and sleep problems) (1-7). This link may be mediated through a programming effect, perhaps through increased production of cortisol, which can influence foetal brain development (8-10).

Although findings in animal models have been robust in showing the link between elevated glucocorticoid levels following stress and adverse outcome in the offspring (1,10,11), scepticism has been raised to the validity of the concepts and methods of several of the findings in human studies. Some interpretations are based on inconsistent results, low sample sizes and poor research designs and lack of appropriate genetic and postnatal controls (12, 13). One key concern is that observational studies are vulnerable to confounding by pleiotropic genes (14, 15). Rice and colleges (16) used a ‘prenatal cross-fostering’ design to examine the intra-uterine environment where pregnant mothers were either related or unrelated to their child, as a result of *in vitro fertilization* (IVF). The results suggest that the associations with prenatal stress were caused by either postnatal risks or common genes. However, this finding was limited by the use of retrospective recall of prenatal stress, and small sample size.

Another powerful way of examining prenatal risk effects within epidemiological studies is through the use of sibling designs. For example, D’Onofrio and colleagues (17) examined the well-established link between smoking during pregnancy and antisocial behaviour in a sibling design where they compared siblings that differed in their exposure to maternal smoking during pregnancy. Findings showed that siblings discordant in exposure to prenatal smoking did not differ in their risk for antisocial behaviour. This finding has been confirmed by other quasi-experimental studies (18, 19, 20). The implication from these studies is that relying on measured covariates to account for confounding could result in false positive conclusions, because of insufficient control for postnatal exposure or pleiotropic genes.

 A sibling comparison design, where one sibling has been exposed to prenatal maternal anxiety and the other has not, would control for both genetic and environmental factors that are shared by the siblings. Because each child receives a random set of its mother´s genes through the process of meiosis (21), the sibling design provides a good control for pleiotropic genes that influence maternal anxiety and behaviour as well as emotional difficulties in the child (15). Using data from pregnancy questionnaires as well as responses to questions on child behaviour at 6 and 36 months, we aim to examine the risk associated with maternal anxiety in pregnancy on short (6 months) and long-term (36 months) outcomes in the child, and to control potential social and genetic confounding using a sibling comparison design.

**Methods**

**Study population and data collection**

This study is a subproject of the Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health (22). MoBa is a cohort comprising 113 000 pregnancies recruited from 1999 to 2008 with a participation rate of 40.6% (22). All but two of a total of 52 hospitals around Norway agreed to participate in the recruitment to the study. Women were invited to participate when they attended routine ultrasound examination offered to all pregnant women at 17-18 weeks of gestation (www.fhi.no/moba-en). The mothers filled out questionnaires about characteristics including their age, education, smoking and drinking habits, partner harmony and anxiety at 17th and 30th gestational week. In addition, the current study used data from the questionnaires about child somatic health, infant difficulties and emotional difficulties at 6 months and 36 months after birth. The cohort was also linked to the Medical Birth Registry of Norway (MBRN) (23). The MBRN contains detailed medical information about the infant, including birth weight and birth complications.

The maternal questionnaire response rates at 17th and 30th week of gestation, and at 6 and 36 months after birth were approximately 95.1%, 91.4%, 87.0% and 61.4%, respectively (24). Written informed consent was obtained from all participating women. The Regional Committees for Medical and Health Research Ethics (REK) and the Norwegian Data Inspectorate have approved the study.

 Within MoBa, a total of 15 256 mothers participated with more than one pregnancy. Mothers filled out questionnaires for each unique pregnancy and for infant difficulties at 6 months, as well as for emotional difficulties at 36 months. For women participating with three or more pregnancies, two siblings were randomly selected. We used version 7 of the quality-assured data files for participants recruited in the period 1999 to 2009, see flow-chart (Figure 1).

**Measure of maternal general anxiety**

Mothers reported on symptoms of anxiety using a validated short version of the Hopkins Symptom Checklist, the SCL-5 (25) and SCL-8 (26). The Symptom Checklist scale (SCL) is scored on a Likert scale ranging from 1-4. The short scale has been found to be valid with a correlation of 0.92 with the SCL-25 (26). Assessments of anxiety were made twice during pregnancy (17th and 30th gestational week), and again when the child was 6 months. Two out of five questions from the SCL-5 and four out of eight questions from the SCL-8 measured anxiety at 17th and 30th gestational week and at 6months, respectively. The mean score for the 17th and 30th gestational week and 6months measure ranged from 1-2 and 1-4. Both continuous scores and a quasi-clinical cut-off (in the absence of an established cut-off, the top 15% of the sample was identified, which is equivalent to other studies, e.g. O’Donnell and colleagues (3), and Brandlistuen and colleagues (27)), are used in the analyses. Exploring alternative cut-points suggested essentially the same results. Based on these dichotomized variables a four level factor variable was constructed to represent “no exposure to maternal anxiety”, “high anxiety in week 17 only”, “high anxiety in week 30 only” or “both”.

**Main outcome variables:**

*Infant difficulties at 6 months****:*** Infant difficulties were measured at 6 months postpartum by 9 items from the Infant Characteristic Questionnaire (ICQ) (28). Mothers responded to seven ordered response categories. The responses were scored 1-7, and the mean score calculated (range 1-7). The categorical variable was based on 1SD above mean, and coded as low infant difficulties (’0’), and high infant difficulties (’1’). That is, the top 15%, which is equivalent to one standard deviation away from the centre, is regarded as high infant difficulties.

*Emotional difficulties* were measured by ten items from the Child Behaviour Checklist (CBCL/TRF), (29), which represented four subscales: emotionally reactive, anxious/depressed, somatic complaints and sleep problems. Mothers reported the extent to which they agreed with the difficulties statements on a three-point Likert scale, from not true (’0’), sometimes true (’1’) and often true (’2’). Mean scores were calculated and ranged from 0-2, and the Cronbach`s alpha was 0.56. The categorical variable was based on 1SD above mean, and coded as low emotional difficulties (’0’), and high emotional difficulties (’1’). That is, approximately the top 15 % is regarded as high in emotional difficulties.

A team of clinical and developmental psychologists selected the items from the CBCL used in MoBa. The selected items were based on theoretical and empirical representativeness and have been found to be representative with a correlation of 0.92 to the full scale (30).

**Assessment of potential confounders**

Potential confounding factors were considered based on discussions of whether it could be influencing the path from prenatal maternal anxiety to child outcomes, and were included in the adjusted model if associated with the exposure (prenatal maternal anxiety) or one of the two outcome measures. The following variables as potential controls: Alcohol consumption during pregnancy (coded as never “0” and more than once a month “1”); Smoking in pregnancy, (coded as never “0”, sometimes “1” or daily “2”). In addition we controlled for maternal anxiety reported at 6 months low=”0” and high =”1”; Partner (dis) harmony (good partner relation=0, and poor partner relation=1); Somatic disease (not present at 6 months “0” and present “1”); Marital status (married/living together “0” and single “1”); Maternal education (coded as higher university degree +4years “0”, College/university of 3 years “1”, college 1-2 years “2”, secondary school “3”); and Maternal age (coded as <25 “0”, 25-29 “1”, 30-34 “2” and >=35 “3”). We also controlled for the following variables extracted from the MBRN: Parity was coded 0 “0”, and >=1 “1”; Gestational age (coded as <37 “0”, and >= 37 “1”; Birth complications, coded as yes “1” or no “0”; Child sex (girl “0”, boy “1”); and Birth weight (coded as >= 2500g = “0”, <2500g = “1”).

**Statistical analyses**

We present descriptive data on the full sample and the sibling sample including the distribution on confounders and covariates for infant difficulties at 6 months, and emotional difficulties at 36 months. After reporting descriptive data we present the analyses for the full sample (n=82,383) and the sibling sample (n=21,980). We present the results from the logistic regression analyses and multiple linear regression analyses for the full study sample and the sibling sample. We also adjusted for the following control variables: maternal age, educational level, marital status, parity, partner relation, prenatal alcohol consumption, prenatal smoking, birth complications, child’s gender, birth weight, child’s somatic diseases and child’s gestational age. We also examined the potential mediating effect of the control variables birth complication, birth weight, gestational age and child somatic disease in a proportion, however the mediation effect, was not clearly present. The mediating effect of the four variables was 0.11%, 0.09%, 6.27% and 1.42% respectively.

For the sibling data with the binary outcomes, we used a conditional logistic regression model containing a family specific term in the linear predictor that captures environmental and genetic factors common to the family. When conditioning on the number of siblings in each family with the reported outcome these nuisance terms vanish, but the remaining terms are unchanged. This gives a conditional logistic regression model and we used the “clogit” function in R to fit the model.

Also for the continuous scores, we can include family specific terms in the linear predictors that will cancel out when conditioning on the total reported scores in each family. Equivalently, as we considered only two siblings in each family, we analysed the differences in the siblings’ scores using differences in sibling covariates as explanatory variables.

To handle missing values we used pairwise deletion of missing. For the full cohort (n=82,383), the crude model deleted 2,145 observations due to missing. In the sibling design (n=21,980), only 413 were taken out when we have the crude model fitted. The total number of discordant siblings was 1476 at 6 months and 786 at 36 months.

**Results**

The characteristics of the full cohort sample are shown in Table 1 and the sibling sub-sample in Table 2. In the sibling sub-sample the proportion of children with difficulties at 6 months after birth was 20.4% among mothers reporting anxiety at week 17 and 20 % among mothers with anxiety at week 30. This is comparable to 22%, which was found in the full cohort. In the sibling sub-sample approximately 26% of the children exposed to high prenatal maternal anxiety at both 17th and 30th week of gestation had emotional difficulties at 36 months. This is somewhat lower than for the full cohort, which was approximately 30% at both 17th and 30th week of gestation. Of 10,990 pairs of siblings (n= 21,980), 86.3% and 86.9% turned out to be concordant for not being exposed to maternal anxiety at 17th and 30th week of gestation. Also, 1.8% (17th) and 2.5% (30th) of the sibling pairs were both exposed to anxiety at these two points in time. However, 9.9% and 9.7% differed in exposure for maternal anxiety at 17th and 30th week respectively. The proportion of children with high score on child difficulties at both 6 and 36 months were 3.4%.

---Insert Table 1 and 2 -----

*Full cohort analyses*

In the logistic regression analyses on the full cohort we found that children exposed to maternal anxiety at both 17th and 30th week of gestation had a higher risk of infant difficulties at 6 months and emotional difficulties at 36 months, as compared to those who had not been exposed to maternal anxiety (Table 3). These associations remained, but were somewhat reduced in size after controlling for a number of potential confounders, including maternal anxiety measured at 6 months. Examination of different cut-points did not indicate fundamentally different findings, e.g. 90th percentile suggested a positive change in OR of 0.32 at 6 months and OR.0.58 at 36 months.

We also examined these associations using multiple regression analyses with continuous measures for the full sample. The results showed moderate associations with infant difficulties at 6 months, as well as emotional difficulties at 36 months. The follow-up analyses at 36 months showed that there was no difference in effects when we examined the associations between prenatal maternal anxiety on infant difficulties at 6 months and emotional difficulties at 36 months, suggesting that some overall liability is involved.

*Sibling- comparison analyses*

We examined the same associations in a sibling comparison design, to control for potential social and genetic confounders. In the crude and adjusted sibling analyses for the conditional logistic regression, no associations were found between prenatal maternal anxieties, measured either at 17th or 30th week of gestation - or both, on infant difficulties at 6 months or emotional difficulties at 36 months of age (Table 4).

We also examined these associations using multiple regression analyses (Table 4). In contrast to what was found in the full cohort, there were no associations between prenatal maternal anxiety and infant difficulties either at 6 months, or emotional difficulties at 36 months. However, a moderate association with maternal anxiety reported at 6 months postnatal remained.

---Insert Table 3 and Table 4 -----

**Discussion**

Using a large population based longitudinal cohort-study we assessed the link between prenatal maternal anxiety and child emotional difficulties using a sibling design. There are two key findings that stand out. First, the conventional full-cohort analyses replicated common findings (e.g. 9) but the same analyses, controlled for pleiotropic genes or environmental family factors , did not. Second, the findings were essentially the same whether we examined infant difficulties at 6 months or emotional difficulties at 36 months.

In the first analyses using the full-cohort, children prenatally exposed to maternal anxiety had twice the risk of infant difficulties at 6 months, and almost three times the risk of emotional difficulties at 36 months. This association did not change substantially after controlling for multiple covariates. This is consistent with a number of other studies (e.g. 3, 6, 9), and almost an exact replicate of the recent findings by O’Donnell et al (3). They found that a twofold increase in risk of a probable child mental disorder was associated with exposure to prenatal maternal anxiety (3). This is equivalent to our findings from the full-cohort analyses (both logistic and multiple regression). However, once the same analyses were conducted using a sibling design, these associations were no longer found either for infant difficulties at 6 months or emotional difficulties measured at 36 months. This suggests that the substantial findings on the full cohort are likely to be confounded by pleiotropic genetic or constant environmental family factors. Although, the use of sibling-design of discordant siblings reflects a reduction in sample size, a major strength of our study is the consistency in the findings across 6 and 36 months outcomes, as well as across both logistic regression and multiple regression analyses.

Our finding further suggests little support for there being an independent prenatal effect on child difficulties and suggest that statistical control for confounders does not deal adequately with the issues, but that the sibling design comparing exposed and non-exposed siblings does. However, although the within-pair estimates will not be confounded by factors that are shared by the siblings, bias could still occur due to non-shared factors (31). Therefore, several covariates (i.e. birth order, maternal age etc.) were adjusted for, without significant changes to the results. However, although our finding lends little support for there being an independent prenatal effect on child emotional difficulties, there is still the possibility that there may be a prenatal effect on other child outcomes.

To our knowledge this is the first study to examine the link between prenatal maternal anxiety and child difficulties at both 6 months and 36 months of age in siblings that differed in exposure to prenatal maternal anxiety. Because we cannot randomize pregnant mothers to anxiety exposure and because twins will always be concordant in prenatal risk exposure, the sibling-comparison design is optimal when examining prenatal risk effects and offers a powerful quasi-experimental approach to study prenatal risks.

There are, however, limitations that need to be mentioned. The sample size in MoBa limits the possibility of providing clinical interviews in assessing anxiety in the mothers, or clinical diagnosis of difficulties, such as anxiety, in children. However, this study used validated questionnaires, that although short-scales, have been found to correlate highly with the original large-scale questionnaires (25, 26, 30). Bias could still occur due to attrition or because of halo effects. Maternal reports of infant difficulties and emotional difficulties are subjective and therefore their levels of stress during the pre- and postnatal period could affect their perceptions of child difficulties. That is, anxious mothers may report their child´s difficulties as more negative than non-anxious mothers. However, using the same informant- the mother, is unavoidable when investigating behavior in very young children within large-scale population cohort studies, and is a common feature for similar studies (see e.g. The Avon Longitudinal Study of Parents and Children; Quebec Longitudinal Study of Child Development). Bias due to selective recruitment is another possible limitation regarding prevalence, but has minimal influence on associations (22, 32, 33), which was the focus in this study.

In sum our finding suggests that statistical control for confounders does not deal adequately with issues of confounding, but that a sibling design comparing exposed and non-exposed siblings does (15).

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