Perinatal Maternal Anxiety and Depression and Preschool Children's symptoms of ADHD, Oppositional Defiant Disorder and Conduct Disorder.

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Abstract

Objective: To examine the association between perinatal maternal symptoms of anxiety or depression and preschooler's symptoms of ADHD-IA, ADHD-HI, ODD, and CD, and whether associations varied by time of exposure or gender.

Method: Children, aged 3.5 years (n = 1195), recruited from the Norwegian Mother and Child Cohort Study, were assessed with a semi-structured psychiatric interview. Questionnaires (SCL-5) provided information about perinatal maternal symptoms of anxiety and depression. We used mixed effect Poisson regression.

Results: No significant timing effects were shown for perinatal maternal symptoms of anxiety or depression, which increased the average number of ADHD-IA symptoms by 1.4%, ADHD-HI by 1.1% and ODD by 2.1% and 2.6%. The effects on ADHD symptoms were most marked for boys, whereas girls were more susceptible for ODD symptoms.

Conclusion: Perinatal maternal symptoms of anxiety and depression represented stable, but modest risk factors for developing symptoms of ADHD and ODD in preschool children.

Key words: Perinatal Maternal Anxiety & Depression. Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder, Preschool children.

Introduction

Maternal mood across pregnancy to the postnatal period represent a major public health concern since up to 25% of women show significant symptoms of depression or anxiety during this period (Heron, O'Connor, Evans, Golding, & Glover, 2004). Perinatal maternal mood disturbances may have long term impact on offspring development. Prenatal maternal anxiety, depression or distress have been suggested to affect neurodevelopment of the human offspring through foetal programming mechanisms, but findings compared to

particularly sensitive time points during gestation have shown inconsistent results (Glover, 2011; Sandman, Davis, & Glynn, 2012). Preschool children, whose mothers reported prenatal anxiety (PNA) during early gestation (Loomans et al., 2011), or mid-to-late gestation (O'Connor, Heron, & Glover, 2002; O'Connor, Heron, Golding, & Glover, 2003) have been found to have an increased risk of Attention Deficit Hyperactivity Disorder (ADHD) and Conduct Disorder (CD)/ behaviour problems. However, prenatal maternal depression (PND) (O'Donnell, Glover, Barker, & O'Connor, 2014; Van Batenburg-Eddes et al., 2013) and maternal post-partum depression (PPD) (Carter, Garrity-Rokous, Chazan-Cohen, Little, & Briggs-Gowan, 2001; Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005; Sciberras, Ukoumunne, & Efron, 2011) have also been found related to ADHD and behaviour problems in preschool children. Impaired maternal sensitivity, insecure infant attachment, and less optimal mother-child interactions have been found associated with post-partum depressions (PPD), which may negatively impact on children's further cognitive and behavioural development (Stein et al., 2012a; Carter et al., 2001; Shaw & Vondra, 1995). The increased risk for child symptom development has also been shown equally related to pre- and postnatal exposure to maternal symptoms of anxiety or depression (Giallo, Woolhouse, Gartland, Hiscock, & Brown, 2015; O'Donnell et al., 2014; Carter et al., 2001).

Limitations in previous preschool studies include insufficient assessment of ADHD, CD and Oppositional Defiant Disorder (ODD), where symptom checklists comprise the basis for phenotype definition in most preschool studies, in which symptoms of ODD and CD most often are merged into one behaviour disorder group. Moreover, the ADHD subtypes are found to be associated with different comorbidities and neurocognitive correlates (Willcutt et al., 2012). Perinatal risk relationships may potentially differ for inattentive (ADHD-IA) compared to hyperactive-impulsive (ADHD-HI) symptoms, but preschool studies on this topic have

generally not distinguished between the two symptom dimensions of ADHD for their investigations.

Another issue that warrants attention is the potential moderating role of the child's sex. Some studies have provided support for an overall pattern of greater risk of behaviour problems in boys than girls from both pre- and postnatal maternal depression (Carter et al., 2001; Shaw & Vondra, 1995). Research focusing on antenatal maternal anxiety have found preschool boys to be more susceptible for symptoms of ADHD than girls, while findings of sex-differences linked to other child behaviour problems seem to be inconsistent (O'Connor et al., 2002; Loomans et al., 2011).

In order to address the previously conflicting findings regarding both type of symptoms and timing of exposure (Glover, 2014), this study examined the time variation and the effects of perinatal maternal symptoms of anxiety (PPNA) or depression (PPND) on reports of symptoms of ADHD-HI, ADHD-IA, ODD and CD in preschool children, after haven taken into account potential confounding factors. Further, we examined sex-differences related to the potential impact of PPNA/ PPND.

Methods

Design and participants

"The Preschool ADHD study" is a longitudinal study with participants recruited from the Norwegian Mother and Child Cohort Study (MoBa). MoBa is a prospective birth cohort study run by the Norwegian Institute of Public Health, following about 107000 pregnancies before and after birth (Magnus et al., 2006). The MoBa questionnaires were completed by mothers at week 17 and 30 of gestation, and when children were 6, 18 and 36 months old.

The recruitment of participants to The Preschool ADHD Study has been described in more detail previously (Bendiksen et al., 2014). In brief, this study included 1195 mother and

child pairs. Of these, 1048 were recruited based on scores above the 90th percentile on 11 questions about hyperactivity, impulsivity and inattention, or parental report of hyperactivity as a health problem, in the MoBa questionnaire at 36 months. Six questions were from the Child Behaviour Checklist (CBCL) (Achenbach & Ruffle, 2000) and five from the DSM-IV-TR criteria (American Psychiatric Association, 2000). The comparison group of 147 children was randomly recruited from the MoBa study.

After parental consent, the children, aged 36 to 44 months, participated in a one-day clinical assessment at Oslo University Hospital together with (one of) the parents. One of the parents had to speak Norwegian. The exclusion criteria were severe medical conditions or high scores for autistic symptoms.

Ethics

The study was approved by the Regional Ethics Committee and a license was granted by the Norwegian Data Inspectorate in 2007. Assessments were carried out according to the principles of the Helsinki declaration. Parents returned a written consent prior to the clinical assessment.

The enrollment is shown in Figure 1.

(insert figure one here, please)

Perinatal maternal symptoms of anxiety and depression

A widely used self-administered instrument of psychological distress, the Symptom Check List (SCL-5), derived from the SCL-25 (Hesbacher, Rickels, Morris, Newman, & Rosenfeld, 1980) was included in the MoBa questionnaires at gestational week 17 (T_1) and 30 (T_2), and at 6 months postnatally (T_3). The SCL-5 includes two symptoms of depression ("feeling hopeless about the future", "feeling depressed/sad/blue"), and three questions of anxiety ("constantly frightened/anxious/ fearful", "nervous, inner turmoil", "frequently

worried or uneasy"). Each question is rated on a four-point scale ("not at all", "a little", "quite a bit", "extremely", rated 1-4). We chose to differentiate between anxiety and depression, as preliminary analyses indicated some differences in the effects of the two dimensions on the various outcome measures. The 3-items anxiety scales showed satisfactory internal consistency with Chronbach's α values at .77 (T_1), .76 (T_2) and .80 (T_3), while the respective α values for the depression scales were .72, .62 and .70. The scores on SCL-5 has been shown to correlate strongly with the SCL-25, r = .91 (Strand, Dalgard, Tambs, & Rognerud, 2003). Pearson Product Moment correlation between the 2-items depression scale and the "Edinburgh Postnatal Depression Scale" (EPDS) (Cox, Holden, & Sagovsky, 1987) was .65 at six months postnatally.

Child symptoms of ADHD, ODD and CD

One of the parents, most often the mother, was interviewed with "The Preschool Age Psychiatric Assessment" (PAPA) (Egger & Angold, 2004), a comprehensive psychiatric interview for the assessment of psychiatric symptoms and disorders in preschool children (Egger et al., 2006). The PAPA interviews were performed by trained psychology students and supervised by clinically trained psychologists or child psychiatrists. This semi-structured interview provides information about the scale and frequency of psychiatric symptoms according to DSM-IV (American Psychiatric Association, 2000). In order to be recorded as "present", symptoms had to have lasted for at least three months. Outcome measures were number of symptoms of ADHD-IA (nine symptoms), ADHD-HI (nine symptoms), ODD (eight symptoms) and CD (eight symptoms). Inter rater reliability of the number of DSM-IV symptoms was good with average intraclass correlations (ICC) rangeing from .91 to .99 in this sample.

Covariates

We assessed a range of possible confounders, but we only included covariates that were associated with maternal depression/anxiety at one time point and/or number of ADHD, ODD or CD symptoms in the preliminary analyses. These covariates were: birth weight, child's sex, maternal age, caesarean section (yes/no) from The Norwegian Medical Birth Registry (Magnus et al., 2006) and maternal educational level, civil status, parity, social support, maternal smoking during pregnancy (i.e. assessed at week 17 and week 30 during gestation and postnatal at 6 months), and breastfeeding-duration (yes: 9 months or more/ no: less than 9months) from the MoBa questionnaires. In addition, we chose to include gestational age and APGAR-score from the Medical Birth Registry, in multivariate analyses.

The following potential covariates were not included, as they were not related to either exposure or outcome in our data: Maternal alcohol use during pregnancy, antenatal maternal urogenital and bladder infection, preeclampsia, and neonatal complications. Further, children's intellectual functioning (IQ) at 3.5 years was not included since it was considered to be an outcome and potentially associated with the same risk-, and protective factors as the other outcome-measures.

Data analyses

We conducted mixed effect Poisson regression analyses to examine the relationships, and whether there were variations of these relationships over time, between the number of ADHD-HI, ADHD-IA, ODD and CD symptoms, and maternal symptoms of anxiety and depression measured at week 17 (T_1) and 30 (T_2) of gestation, and at six months post-partum (T_3), with and without adjusting for covariates of interest. Likelihood ratio tests were used to investigate whether the relationship between maternal symptoms of anxiety or depression and the number of symptoms in children differed between the three time points.

Mixed effect Poisson regression models were also fitted separately for boys and girls due to significant interactions between child sex and the covariates of interest (i.e. parity, mother's age and education, caesarean and marital status).

For covariates measured at one time point, Poisson regression models were used to assess the relationships between the four symptom groups and each covariate. Crude and adjusted relative risk (*RR*) with 95% *CI*'s were given using robust sandwich estimator of variance. The two-sided p-values were not corrected for multiple testing.

The analyses were performed with IBM SPSS Statistics for Windows, version 21, and STATA/IC 13 for Windows, version 13.1.

Results

Background and clinical characteristics of 1195 children and mother and child pairs are presented in table 1. As seen from the table, average scores for maternal anxiety and depression were pretty stable over time. The individual SCL-scores were moderately correlated over time. Spearman's correlation coefficient between maternal anxiety score at week 17 of gestation (T_1) and week 30 of gestation (T_2) was .57, between T_1 and postnatal (T_3) .45, and between T_2 and T_3 .49, while the respective figures for maternal depressive scores were .51, .41, and .42.

(insert table 1 here, please)

Timing effects

Table 2 shows that effects of perinatal maternal symptoms of anxiety (PPNA) and depression (PPND) were fairly stable over time for all symptom groups ($P > .9$ for the interactions between PPNA x time and PPND x time). There was a trend towards the

prediction of ADHD-HI symptoms by PPND to be more marked during mid-gestation for boys compared to girls, $P = .05$ vs. $P = .43$, respectively (data not shown).

(insert table 2 here, please)

The effects of perinatal maternal symptoms of anxiety or depression

Crude and adjusted relative risks of PPNA and PPND for the increased mean numbers of ADHD-IA, ADHD-HI, ODD, and CD symptoms are shown in table 3. In the adjusted multivariate model, one additional unit increase in maternal anxiety sum-scores increased the mean number of ADHD-IA symptoms by a cofactor of 1.4%, ADHD-HI by 1.1%, ODD by 2.1% and CD by .2%. Corresponding effects by each unit increase of perinatal maternal depressive symptoms increased the mean number of ADHD-IA symptoms by a cofactor of 1.4%, ADHD-HI by 1.1%, ODD by 2.6%, while the relative risk was .8% and non-significantly associated with CD symptoms. The effect of pre- and postnatal maternal depression scores on CD symptoms decreased by an average cofactor of .8% after the adjustments of maternal anxiety (maternal anxiety model) or depression (maternal depression model) previous to conception, while the effect of PPND on ADHD-IA symptoms decreased approximately by .5% after the adjustments. A positively directed interaction between maternal depression during pregnancy and maternal smoking was shown for the effect on ODD symptoms ($P = .025$), while there were no interactions between PPNA/PPND and other obstetric risks, or breastfeeding-duration. Breastfeeding, maternal age, education, and social support attenuated the effects of PPNA/ PPND on the likelihood of ADHD and CD symptoms.

(insert table 3 here, please)

Sex-differences

We found no interactions between the child's sex and PPNA/ PPND, but stratified analyses were performed because of significant interactions between child sex and a number of covariates. Although the effects generally were small, there was a tendency towards that boys exposed to maternal anxiety, were more likely than girls to display symptoms of ADHD. Crude analyses showed no sex-differences for symptoms of ADHD-IA (table 3), but once PPNA was included in the model, boys were found to have a higher increase in mean number of ADHD-IA symptoms than girls [boys (*RR* = 1.017, 95% *CI* = 1.01, 1.03, *P* = .003) vs. girls (*RR* = 1.005, 95% *CI* = .99, 1.02, *P* = .52)]. Further, the association between PPNA and ADHD-HI symptoms tended to be more marked for boys than girls, (*RR* = 1.012, 95% *CI* = 1.00, 1.02, *P* = .02) vs. (*RR* = 1.008, 95% *CI* = .99, 1.02, *P* = .13). Girls, on the other hand, showed a stronger association between ODD symptoms and PPNA [girls (*RR* = 1.022, 95% *CI* = 1.00, 1.04, *P* = .04) vs. boys (*RR* = 1.001, 95% *CI* = .99, 1.03, P = .22)].

Discussion

In this study, perinatal maternal anxiety and depression were relatively stable during gestational week 17, week 30 and at 6 months postnatally, but modest predictors of the offspring's symptoms of ADHD and ODD. The effects of PPNA/ PPND did not significantly differ during gestation or the post-partum period.

In line with previous research, we found that prenatal maternal symptoms of anxiety as well as depression predicted an increased risk for ADHD (Van Batenburg-Eddes et al., 2013) and behaviour problems (O'Donnell et al., 2014) in preschool children. Even if prenatal maternal symptoms of anxiety on ADHD generally had a more marked effect than depression due to less significant attenuation by covariate adjustments, the magnitude of the effect of PPNA was not substantially different from PPND on most outcomes, which supports a rather broad phenotype.

Developmental or adaptive programming models imply that the in utero exposure instigate an adaptive response, which may be carried forward in development with persisting effects on offspring behaviour. O'Donnell and colleagues (O'Donnell et al., 2014) examined the relationship between prenatal maternal anxiety and child's later emotional and behavioural problems. Total problems assessed at five time points (i.e. at the age of 4, 7, 9 and 13) remained high in the high prenatal maternal anxiety group across development. The effect of the exposure at week 18 did not significantly differ from that at week 32 during gestation (O'Donnell et al., 2014), which is in line with our results. However, both animal and human studies show discrepancies regarding specifically vulnerable periods during gestation (Glover, 2014; Beydoun & Saftlas, 2008), but such findings may be confounded since mothers exposed to stressors early in pregnancy could be affected for a longer period than those exposed at a later time point (O'Connor, Monk, & Fitelson, 2014). The timing of distress could be linked to various defined outcomes, as shown by a large population based study by Class and colleagues (Class et al., 2013), who found that different patterns of psychopathology emerged following prenatal compared to postnatal maternal distress, where the exposure during third-trimester increased the risk of autism spectrum disorders (ASD) and ADHD, whereas an increased risk of suicide was observed in offspring whose mothers were stressed during the first postnatal year.

Results from the ALSPAC study (O'Connor et al., 2002) indicated that mid-gestation was a particularly sensitive period for the prediction of inattentiveness, hyperactive-impulsive symptoms and behaviour problems in preschoolers by maternal anxiety. Further, O'Connor and colleagues (O'Connor et al., 2002) reported that postnatal anxiety also was a significant predictor, but the exposure postnatally did not influence the magnitude of the antenatal prediction. Conversely, other studies have found no effects of prenatal maternal emotional complaints once postnatal effects were taken into account (Bekkhus, Rutter, Barker, & Borge,

2011; Kim-Cohen et al., 2005). Methodological differences may account for some of the discrepancies between studies if postnatal experiences are treated as a possible confounder rather than making direct comparisons with antenatal maternal mood. The case could also be that rather than specific timing-effects, maternal symptoms of anxiety and/or depression over time, even at subclinical levels, may constitute an enduring risk for the development of emotional-and behaviour problems in children (Giallo et al., 2015). Clavarino and colleagues (Clavarino et al., 2010) reported that antenatal maternal anxiety was associated with persistent attention problems in both 5 and 14 year old children, but chronic maternal anxiety during the peripartum period and five years later was the strongest predictor of persistent attention problems in children, which pointed towards an accumulative effect of maternal anxiety. Some studies have found independent effects of antenatal- and postnatal maternal depression on toddler neurodevelopment (Koutra et al., 2013) and preschooler's behavioural problems (Carter et al., 2001). Maternal depression and anxiety post-partum are suggested to interfere with maternal sensitivity and responsiveness to their infants and thereby increase the risk of disturbed mother-child interactions (Stein et al., 2012b). However, a number of studies focusing on postnatal maternal depression did not simultaneously investigate the impact of prenatal maternal mood or postnatal anxiety, which makes comparisons between studies further difficult.

In contrast to previous studies (O'Connor et al., 2002; O'Donnell et al., 2014), PPNA/ PPND did not predict child CD symptoms after the adjustments. On the other hand, preschooler's symptoms of ODD were significantly predicted by both PPNA and PPND. Methodological differences could in part explain some of the observed discrepancies, because of the assessment of CD/ behaviour problems by "The Strength and Difficulties Questionnaire" (SDQ) (Goodman, 1997) used in some of these studies (O'Connor et al., 2002; O'Donnell et al., 2014) includes diagnostic symptoms of both ODD and CD. The inclusion of

covariates may also play a role. In our study, the prediction of ODD was only negligibly attenuated after the adjustments by covariates, whereas the effects of PPNA/ PPND on CD symptoms were strongly attenuated by maternal depression or anxiety previous to conception, which might represent common genetic effects.

Attenuation of risk relationships between PPNA/PPND and outcomes by maternal factors like age, educational level, parity and social support, as well as obstetric factors were minor by each covariate, but totally, the effects of PPNA/PPND on most outcomes were significantly reduced by the covariate adjustments. A number of obstetric factors have been found associated with ADHD (Pettersson et al., 2015), but also related to pre- and postnatal factors (Henderson, Evans, Straton, Priest, & Hagan, 2003; Shamberger, 2012; Seimyr, Edhborg, Lundh, & Sjogren, 2004). The effect of prenatal maternal depressive symptoms on ODD was modified by maternal smoking during pregnancy, but in line with findings by Rodriguez and colleagues (Rodriguez & Bohlin, 2005), the associations between ADHD symptoms and perinatal maternal emotional complaints were independent and not modified by maternal smoking. Likewise, the protective effect of breastfeeding on ADHD symptoms attenuated, but did not modify the effects of PPNA and PPND, which may suggest independent mechanisms. In contrast to previous results (Littleton, Breitkopf, & Berenson, 2007) we found no modifying and minor attenuation of the effects of PPNA or PPND by gestational length or birth weight. A possible explanation could be small variability, as most children in this sample were born at term and had a standard birth weight.

In line with findings by O'Donnell and colleagues (O'Donnell et al., 2014), we found no significant interaction between child sex and PPNA/ PPND. However, separate analyses showed that preschool boys tended to be more susceptible to symptoms of ADHD than girls ensuing PPNA, which is in accordance with previous reports from preschool samples (O'Donnell et al., 2014; Loomans et al., 2011; O'Connor et al., 2002). O'Connor and

colleagues (O'Connor et al., 2002) found no sex-difference related to the prediction of behaviour problems by prenatal maternal anxiety, but findings from preschool samples have been inconsistent, and some studies have found boys being more susceptible than girls (O'Donnell et al., 2014; Loomans et al., 2011). Conversely, we found that girls exposed to both PPNA and PPND tended to be more likely to have symptoms of ODD than boys. These findings are intriguing considering that ODD, in addition to defiance and rule-breaking behaviours, also comprises an irritable dimension that is shown associated with later emotional disturbances that are more common in girls (Stringaris & Goodman, 2009). A greater susceptibility in girls compared to boys could therefore make sense. These findings seem to support the distinction between symptoms of ODD and CD when examining risk factors and correlates, and merging the two groups into one behaviour disorder construct should therefore be avoided. Sandman and colleagues (Sandman, Glynn, & Davis, 2013) have suggested that the adaptive flexibility of the female foetus in gestation might render them susceptible to more subtle, but persisting consequences and to be more vulnerable to emotional or affective problems later in life. Thus, the observed sex-differences may reflect different susceptibility for psychopathology in girls compared to boys.

Regarding timing effects, previous studies have shown inconsistent results even when the same types of exposure and outcome are scrutinized by gender. O'Connor and colleagues (O'Connor et al., 2003) re-examined the children from the ALSPAC-study when aged 7, and found PNA at 18 weeks of gestation to be the strongest predictor of conduct problems in girls, while the prediction at 32 weeks of gestation remained the strongest one for boys. By contrast, a study by De Bruijn and colleagues (de Bruijn, van Bakel, & van Baar, 2009), found early gestational maternal anxiety to predict more externalizing problems among boys than girls, while third trimester maternal anxiety constituted a risk of externalizing problems in girls. Our results pointed towards a more marked prediction of ADHD-HI symptoms by PPND for

boys compared to girls during mid-to-late gestation, but generally, we found no timing effects of PPNA or PPND related to the observed sex-differences in symptoms of ADHD-IA and ODD.

Strengths and Limitations

The strength of this study is the use of a validated, structured diagnostic interview for clinical assessments, which provided detailed information on psychiatric symptoms in 3-year old children. Furthermore, the data were drawn prospectively from a large birth cohort (MoBa), which gave the opportunity to adjust for a large number of possible confounders. A validated instrument was used to assess maternal symptoms of anxiety and depression at two different time points during pregnancy and six months postnatally.

The study also has some methodological limitations. First, the sample selection was a two-step process, first to the MoBa, and then into the Preschool ADHD-study. Although the original MoBa cohort is large and recruited broadly from the general population, the response rate was only 39%, and the cohort has been shown to have an overrepresentation of mothers with high income and high educational level and an under-representation of young mothers, mothers living alone, mothers with more than two children, and mothers smoking during pregnancy (Nilsen et al., 2009). In the Preschool ADHD-study, with participation rates of only 37.5% in the sampled group and 22.5% in the control group, the participating mothers had even higher education compared to the MoBa. However, since the exposure-outcome associations are not greatly affected by selection in the MoBa (Nilsen et al., 2013) , it is uncertain how such selection may affect this study outcome. Because children with severe difficulties may be underrepresented in our sample, the reported risk associations are most likely attenuated.

Secondly, the selection of participants into the preschool ADHD-study was based on high scores on questions about hyperactivity, impulsivity and attention problems implying that findings cannot be generalized to the general population. However, as this study also involves the examination of biological mechanisms, the need for generalizability is questionable (Rothman, Hatch, & Gallacher, 2014). Third, measures were based on maternal reports, raising the possibility of shared method variance and reporter bias. Depressed mothers may tend to report more symptoms in children, however, maternal self-reports of anxiety and depression were three years prior to the assessment of symptoms in children. Moreover, our findings extend to early preschool age and it is not clear that a single assessment is adequate for operationalizing a programming effect or a lasting developmental effect due to postnatal experiences.

A potential bias for our estimation of timing effects is that the assessment of perinatal maternal symptoms of anxiety or depression did not include the last 10 weeks of gestation. Further, in a non-experimental study the observed associations may be due to unmeasured variables. The examination of the relative contribution of genetic versus environmental influence was not possible in this study, neither potential gene-environment interactions, thus, whether genetic vulnerability is greater in those children exposed to PPNA/ PPND is uncertain. However, a variety of covariates were adjusted for, and the associations of still more potential risk factors were explored.

Lastly, we did not correct for multiple testing, which would set the significance level more close to 0.004, thus p-values above this level should be interpreted with caution.

Clinical Implications

Perinatal maternal symptoms of anxiety and depression were found to represent relatively stable, but modest risk factors for symptoms of ADHD and ODD in young

preschoolers, and susceptibility in boys and girls may differ. The effects of perinatal maternal symptoms of anxiety and depression during early gestation or mid-to late gestation did not vary significantly from the effects post-partum, which suggest concomitant and persistent influence on child development. Given that maternal anxiety and depression are quite common mental health problems during the peripartum period, systematic screening and individualized intervention should be implemented for women early on during pregnancy. Improving women's mental health and well-being during childbearing and birth could represent one of the most feasible strategies for modifying the potential risks of developing mental health problems in children.

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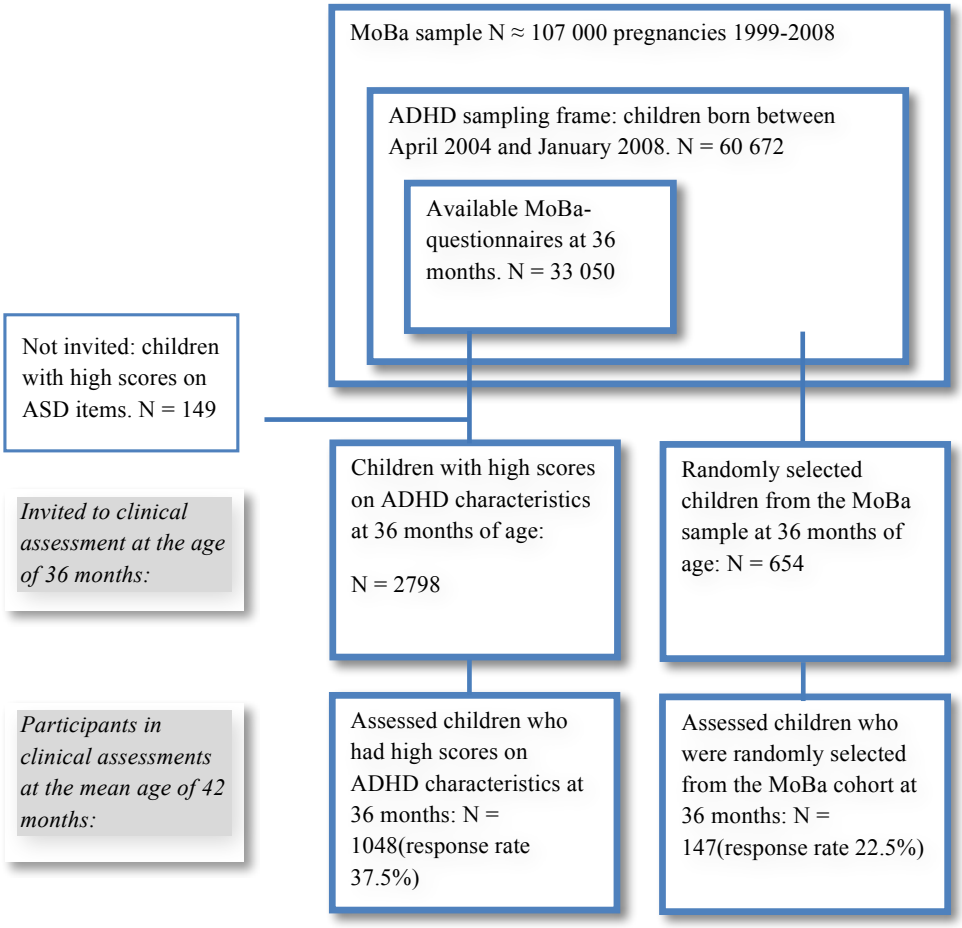
Figure 1. Enrollment into the MoBa and the Preschool ADHD-study.



Note: MoBa: The Norwegian Mother and Child Cohort. ASD = Autism Spectrum Disorder. ADHD = Attention Deficit Hyperactivity Disorder.

Table 1.Sample characteristics and perinatal factors.

	Total N=1195	***M***	***SD***	***Median***	***Interquartile-range***	***Min***	***Max***
Mother's age (years)	1194	30.62	4.29	31	28-34	19.0	43.0
Mother's education (years)	1146	15.24	2.36	15.5	13.6-18.0	9.0	18.0
Maternal smoking status, (T_1), (cigarettes/day)	1147	0.34	1.91	0	0-0	0	20
Maternal smoking status (T_2), (cigarettes/day)	1131	0.31	1.76	0	0-0	0	20
Maternal smoking status (T_3), (cigarettes/day)	1099	0.52	2.33	0	0-0	0	20
Parity	1195	0.46	0.70	0	0-1	0	4
Maternal anxiety (T_1)	1140	4.02	1.44	4	3-5	3	12
Maternal depression (T_1)	1144	2.59	1.02	2	2-3	2	8
Maternal anxiety (T_2)	1134	4.02	1.41	3	3-5	3	12
Maternal depression (T_2)	1134	2.51	0.88	2	2-3	2	7
Maternal anxiety (T_3)	1125	3.94	1.47	3	3-5	3	12
Maternal depression (T_3)	1128	2.69	1.11	2	2-3	2	8
Gestational age (week)	1187	39.29	2.21	40	39-41	24	43
Birth weight (gram)	1192	3499.57	615.34	3630	3181-3896	550.0	5224.0
APGAR-score, 5 min	1191	9.37	0.90	10	9-10	0	10.0
Child's age (months)	1193	41.74	1.34	41.8	40.8-42.6	37.15	46.72
ADHD-IA symptoms	1195	1.33	1.81	1	0-2	0	9.0
ADHD-HI symptoms	1195	2.69	2.49	2	0-4	0	9.0
ODD symptoms	1195	1.68	1.55	1	0-3	0	8.0
CD symptoms	1195	0.66	0.98	0	0-1	0	6.0
					Total N	***N***	***%***
Child's sex (girls)					1195	569	47.3
Preeclampsia					1194	49	4.1
Caesarean					1195	239	20
Breastfeeding >= 9 months					1195	681	57
Marital status (single parent)					1194	38	3.2
Partner satisfaction (good)					1134	1028	86
Social support (good)					1161	1130	94.6
Preconception anxiety					1195	135	11.3
Preconception depression					1195	114	9.5

Note: ADHD-IA symptoms = number of inattentive symptoms. ADHD-HI symptoms = number of hyperactive-impulsive symptoms. ODD symptoms = number of oppositional defiant disorder symptoms. CD symptoms = number of conduct disorder symptoms. T_1 = gestational week 1-17. T_2 = gestational week18-30. T_3 = 0-6 months post-partum. Maternal anxiety = SCL-scores of maternal symptoms of anxiety. Maternal depression = SCL-scores of maternal depressive symptoms. Maternal smoking status = the average number of cigarettes pr. day at each time point. Caesarean = elective or acute operative delivery by caesarean section. APGAR-score: newborns' physical state score 5 minutes after delivery. Breastfeeding >= 9 months = breastfeeding-duration past 9 months.

Table 2. Timing effects for the prediction of child symptoms of ADHD-IA, ADHD-HI, ODD and CD by perinatal maternal symptoms of anxiety and depression.

	Crude estimate				Adjusted estimate			
	RR	95% CI	P-value	Overall p-value	RR	95% CI	P-value	Overall p-value
ADHD-IA								
Prenatal Anxiety, week 1-17	1.020	1.01-1.02	<0.001		1.012	1.00-1.02	0.005	
Prenatal Anxiety, week 18-30	1.023	1.01-1.03	<0.001	0.991	1.015	1.01-1.02	0.001	0.993
Postnatal Anxiety, 0- 6 months	1.023	1.01-1.03	<0.001		1.013	1.00-1.02	0.004	
Prenatal Depression, week 1-17	1.027	1.02-1.04	<0.001		1.014	1.00-1.03	0.019	
Prenatal Depression, week 18-30	1.035	1.02-1.05	<0.001	0.970	1.021	1.01-1.04	0.003	0.977
Postnatal Depression, 0-6 months	1.027	1.02-1.04	<0.001		1.014	1.00-1.03	0.011	
ADHD-HI								
Prenatal Anxiety, week 1-17	1.014	1.01-1.02	<0.001		1.010	1.00-1.02	0.006	
Prenatal Anxiety, week 18-30	1.016	1.01-1.02	<0.001	0.984	1.012	1.01-1.02	<0.001	0.989
Postnatal Anxiety, 0-6 months	1.017	1.01-1.02	<0.001		1.012	1.00-1.02	0.001	
Prenatal Depression, week 1-17	1.019	1.01-1.03	<0.001		1.011	1.00-1.02	0.029	
Prenatal Depression, week 18-30	1.022	1.01-1.03	<0.001	0.993	1.013	1.00-1.02	0.026	0.998
Postnatal Depression, 0-6 months	1.019	1.01-1.03	<0.001		1.011	1.00-1.02	0.005	
ODD symptoms								
Prenatal Anxiety, week 1-17	1.020	1.01-1.03	0.002		1.018	1.00-1.03	0.008	
Prenatal Anxiety, week 18-30	1.025	1.01-1.04	<0.001	0.980	1.024	1.01-1.04	<0.001	0.964
Postnatal Anxiety, 0- 6 months	1.021	1.01-1.03	<0.001		1.019	1.01-1.03	0.001	
Prenatal Depression, week 1-17	1.035	1.02-1.05	<0.001		1.026	1.01-1.04	0.003	
Prenatal Depression, week 18-30	1.039	1.02-1.06	<0.001	0.982	1.033	1.01-1.05	0.001	0.966
Postnatal Depression, 0-6 months	1.032	1.02-1.05	<0.001		1.024	1.01-1.04	0.001	
CD symptoms								
Prenatal Anxiety, week 1-17	1.015	1.00-1.03	0.089		1.002	0.98-1.02	0.874	
Prenatal Anxiety, week 18-30	1.021	1.01-1.04	0.006	0.988	1.011	1.00-1.03	0.136	0.958
Postnatal Anxiety, 0-6 months	1.017	0.99-1.01	0.048		1.004	0.99-1.02	0.647	
Prenatal Depression, week 1-17	1.024	1.01-1.05	0.016		1.008	0.99-1.03	0.479	
Prenatal Depression, week 18-30	1.026	1.00-1.05	0.023	0.999	1.014	0.99-1.04	0.235	0.991
Postnatal Depression, 0-6 months	1.027	1.01-1.04	0.002		1.013	0.99-1.03	0.164	

Note: Mixed effect Poisson regression. RR = relative risk. Overall p-value: the p-value for the interaction term (estimated by a likelihood ratio test). Adjusted estimates: fully adjusted estimates.

Table 3. Crude and adjusted relative risks for the relationship between perinatal maternal symptoms of anxiety and depression and children's symptoms of ADHD-IA, ADHD-HI, ODD and CD.

					Maternal Anxiety Model			Maternal Depression Model		
	scale	Crude RR	95% CI	P-value	Adjusted RR	95% CI	P-value	Adjusted RR	95% CI	P-value
ADHD-IA symptoms	0-9									
SCL sum score anxiety	3-12	1.020	1.01-1.02	<0.001	1.014	1.01-1.02	0.002			
SCL sum score depression	2-8	1.027	1.02-1.04	<0.001				1.015	1.00-1.03	0.007
Preconception anxiety	yes	1.522	1.12-2.07	0.007	1.378	0.86-2.20	0.18			
Preconception depression	yes	1.595	1.27-2.00	<0.001				1.608	1.14-2.27	0.007
Sex	girl	0.884	0.76-1.03	0.119	0.769	0.61-0.96	0.023	0.775	0.62-0.97	0.027
Maternal age (yrs)	19-43	0.960	0.94-0.98	<0.001	0.945	0.92-0.97	<0.001	0.945	0.92-0.97	<0.001
Maternal education (yrs)	9-18	0.932	0.90-0.96	<0.001	0.955	0.91-1.01	0.07	0.955	0.91-1.00	0.07
Breastfeeding >= 9 m	yes	0.729	0.63-0.85	<0.001	0.571	0.45-0.72	<0.001	0.575	0.46-0.72	<0.001
ADHD-HI symptoms	0-9									
SCL sum score anxiety	3-12	1.014	1.01-1.02	<0.001	1.011	1.01-1.02	0.001			
SCL sum score depression	2-8	1.019	1.01-1.03	0.006				1.011	1.00-1.02	0.009
Preconception anxiety	yes	1.259	1.02-1.56	0.033	1.126	0.79-1.62	0.52			
Preconception depression	yes	1.287	1.09-1.61	0.002				1.295	1.01-1.66	0.042
Sex	girl	0.856	0.77-0.95	0.004	0.780	0.66-0.92	0.003	0.783	0.67-0.92	0.003
Maternal age (yrs)	19-43	0.973	0.96-0.99	<0.001	0.967	0.95-0.99	0.002	0.967	0.95-0.99	0.002
Maternal education (yrs)	9-18	0.938	0.92-0.96	<0.001	0.965	0.93-1.00	0.053	0.965	0.93-1.00	0.053
Marital status	single parent	1.367	1.07-1.75	0.014	0.678	0.45-1.03	0.07	0.707	0.46-1.08	0.11
Social support	good	0.887	0.68-1.16	0.38	0.641	0.44-0.94	0.022	0.628	0.43-0.92	0.018
Maternal smoking (cig./day)	0-20	1.009	1.00-1.02	0.014	1.006	1.00-1.01	0.019	1.006	1.00-1.01	0.02
Breastfeeding >= 9 m	yes	0.801	0.72-0.89	<0.001	0.805	0.68-0.95	0.01	0.806	0.68-0.95	0.01
ODD symptoms	0-8									
SCL sum score anxiety	3-12	1.020	1.01-1.03	0.002	1.021	1.01-1.03	<0.001			
SCL sum score depression	2-8	1.035	1.02-1.05	<0.001				1.027	1.01-1.04	<0.001

Sex	girl	1.069	0.96-1.10	0.21	1.029	0.91-1.18	0.67	1.035	0.91-1.18	0.61
Mother's age (yrs)	19-43	0.978	0.97-0.99	<0.001	0.981	0.97-0.99	0.03	0.982	0.97-0.99	0.03
Mother's education (yrs)	9-18	0.968	0.95-0.99	0.004	0.969	0.94-1.00	0.051	0.971	0.94-1.00	0.07
Birth weight	pr.100 grams	0.990	0.982-0.998	0.018	0.987	0.98-0.99	0.027	0.987	0.98-0.99	0.024
CD symptoms	0-6									
SCL sum score anxiety	3-12	1.015	1.00-1.03	0.089	1.007	0.99-1.02	0.42			
SCL sum score depression	2-8	1.024	1.01-1.05	0.016				1.012	0.99-1.03	0.23
Preconception anxiety	yes	1.594	1.21-2.11	0.001	2.001	1.33-3.03	0.001			
Preconception depression	yes	1.543	1.21-1.97	<0.001				1.687	1.18-2.42	0.004
Sex	girl	0.895	0.75-1.06	0.21	0.819	0.64-1.04	0.10	0.814	0.64-1.03	0.09
Parity, total	0-4	1.208	1.09-1.34	<0.001	1.432	1.21-1.70	<0.001	1.449	1.22-1.72	<0.001
Breastfeeding >= 9 m	yes	0.831	0.70-0.99	0.033	0.883	0.69-1.13	0.32	0.897	0.70-1.14	0.38

Note: Mixed effect Poisson model. Only significant associations reported. Crude RR = unadjusted relative risk. Adjusted RR = adjusted relative risk. SCL sum score depression = sum score of maternal depressive symptoms at week 17 and 30 of gestation and at 6 months post-partum. SCL sum score anxiety = sum score of maternal symptoms of anxiety at week 17 and 30 of gestation and at 6 months post-partum. Preconception anxiety = maternal anxiety previous to conception. Preconception depression = maternal depression previous to conception.