Parental depressive and anxiety symptoms during pregnancy and attention problems in children: a cross-cohort consistency study

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Background: Maternal depression and anxiety during pregnancy have been associated with offspring-attention deficit problems. **Aim:** We explored possible intrauterine effects by comparing maternal and paternal symptoms during pregnancy, by investigating cross-cohort consistency, and by investigating whether parental symptoms in early childhood may explain any observed intrauterine effect. **Methods:** This study was conducted in two cohorts (Generation R, $n = 2,280$ and ALSPAC, $n = 3,442$). Pregnant women and their partners completed questionnaires to assess symptoms of depression and anxiety. Child attention problems were measured in Generation R at age 3 with the Child Behavior Checklist, and in ALSPAC at age 4 with the Strengths and Difficulties Questionnaire. **Results:** In both cohorts, antenatal maternal symptoms of depression (Generation R: OR 1.23, 95% CI 1.05–1.43; ALSPAC: OR 1.33, 95% CI 1.19–1.48) and anxiety (Generation R: OR 1.24, 95% CI 1.06–1.46; ALSPAC: OR 1.32, 95% CI 1.19–1.47) were associated with a higher risk of child attention problems. In ALSPAC, paternal depression was also associated with a higher risk of child attention problems (OR 1.11, 95% CI 1.00–1.24). After adjusting for maternal symptoms after giving birth, antenatal maternal depression and anxiety were no longer associated with child attention problems in Generation R. Moreover, there was little statistical evidence that antenatal maternal and paternal depression and anxiety had a substantially different effect on attention problems of the child. **Conclusions:** The apparent intrauterine effect of maternal depression and anxiety on offspring-behavioural problems may be partly explained by residual confounding. There was little evidence of a difference between the strength of associations of maternal and paternal symptoms during pregnancy with offspring-attention problems. That maternal symptoms after childbirth were also associated with offspring-behavioural problems may indicate a contribution of genetic influences to the association. **Keywords:** Parental depression or anxiety, child attention problems, cohort studies, intrauterine effect.

Introduction

Several studies have suggested that an adverse environment in utero has long-term consequences for development, behaviour and physical health in the offspring (Barker, 1995; Susser et al., 1996). A suboptimal foetal environment may be created by undernutrition (Barker, 1995), exposure to teratogens, such as nicotine (Roza et al., 2007) or maternal disease (O'Callaghan, Sham, Takei, Glover, & Murray, 1991). Psychological well-being of the mother during pregnancy has been posited to also play a role in healthy development of the offspring (Talge, Neal,

& Glover, 2007). Most of the evidence for the link between antenatal maternal psychological health and offspring development comes from animal studies. These studies suggest that exposure to antenatal maternal stress can adversely affect somatic health outcome, such as birth weight and brain development (Lesage et al., 2004) and psychological outcomes, such as behavioural functioning (Weinstock, 2001).

Several reviews suggested that exposure to antenatal maternal depression or anxiety increase the offspring's susceptibility to behavioural or emotional problems (Talge et al., 2007; Van den Bergh, Mulder, Mennes, & Glover, 2005). Early human studies investigating the influence of maternal stress on behavioural problems were limited because of their retrospective designs and small sample sizes. In the past decade, however, several prospective studies have shown that antenatal maternal depression or

anxiety were associated with emotional and behavioural problems in the offspring (Talge et al., 2007). In a small study (n = 143) from Belgium, an association between antenatal maternal anxiety and offspring-attention deficit hyperactivity disorder symptoms, externalizing problems, and anxiety at 8- and 9-year-old was found (Van den Bergh & Marcoen, 2004). In previous publications from the Avon Longitudinal Study of Parents and their Children (ALSPAC), one of the cohorts used in the present study, an almost twofold higher risk of behavioural and emotional problems was found in 4 year olds exposed to maternal anxiety during pregnancy (O'Connor, Heron, Golding, Beveridge, & Glover, 2002), and in further follow-up these associations were found to persist to age 7 years (O'Connor, Heron, Golding, & Glover, 2003). Finally, in an Australian birth cohort children of mothers who were anxious during pregnancy were more likely to have persistent attention problems at age 5 and 14 (Clavarino et al., 2010).

Any association of maternal depression or anxiety during pregnancy with later offspring outcomes could be caused by intrauterine mechanisms. For example, maternal depression or anxiety may alter the mother's HPA-axis activity and thereby create an adverse foetal environment. Maternal symptoms may thus impact on foetal development and this may in turn affect offspring behaviour (Talge et al., 2007). In addition, maternal depression or anxiety may be associated with behaviours that have an adverse effect on placenta functioning, blood flow, or nutritional supply to the developing foetus and impact on the risk of offspring-behavioural problems (Brown, van Os, Driessens, Hoek, & Susser, 2000).

However, it is also possible that these associations are due to residual confounding. Unmeasured or inaccurately measured characteristics, such as lifestyle, maternal physical health or socioeconomic factors, that are related to both maternal depression or anxiety and offspring behaviours can generate spurious associations (Rothman, Greenland, & Lash, 2008). Furthermore, mothers who have more depressive and anxiety symptoms during pregnancy are likely to have more of such symptoms after childbirth. Symptoms during their offspring's infancy and childhood can affect parenting skills and mother–child attachment. Such consequences of maternal depression or anxiety could underlie an observed association of antenatal depression or anxiety with offspring behaviours rather than any intrauterine mechanism. Lastly, a genetic predisposition for depression and anxiety that could manifest as behavioural problems in childhood could be inherited by the child from their mother. Distinguishing between these possibilities is important for public health interventions aimed at reducing behavioural problems in children.

One approach that has been suggested to explore whether maternal pregnancy exposures with off-spring outcomes are operating via intrauterine or alternative mechanisms is to include comparisons with paternal exposures in the same prenatal period and child outcomes (Davey Smith, 2008). Where maternal exposures result in direct intrauterine effects, we would expect the maternal associations to be stronger than the paternal associations with child outcomes. Conversely, associations with child outcomes that are similar for maternal and paternal exposures suggest that familial, socioeconomic, environmental or genetic factors, rather than a direct intrauterine mechanism, are likely to be driving the associations (Davey Smith, 2008).

This study investigates whether there is evidence for an intrauterine influence of maternal depression or anxiety on child attention problems. First, this is done by comparing the effects of maternal and paternal symptoms of depression and anxiety on child attention problems. Second, we explore the extent to which parental depression or anxiety when the child is 3 years old might explain any association. Finally, data were used from two different cohorts, which enabled us to study cross-cohort consistency.

Methods

Design and participants

This study is based on the Generation R Study and ALSPAC, two prospective population-based studies.

The Generation R Study is conducted in Rotterdam, the Netherlands and follows children from foetal life onwards (Jaddoe et al., 2010). In short, all pregnant women who were resident in Rotterdam at the time of their delivery and whose delivery data lay between April 2002 and January 2006 were invited to participate. There were 7,893 live-born singletons eligible for follow-up. Information on maternal symptoms of depression and anxiety during pregnancy was available in 5,596 mothers, but only 3,584 partners completed questions on depression and anxiety. In 2,638 children, maternal report about the child's behaviour at age 3 years was available, and in 2,280 children, maternal and paternal reports about their own depressive and anxiety symptoms at 3 years were available. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, and written informed consent was obtained from all adult participants.

ALSPAC is a geographically based prospective cohort study investigating the health and development of children (Fraser et al., 2012). Pregnant women residing in three health districts in the South West of England with an expected date of delivery between 1 April 1991 and 31 December 1992 were eligible to enrol. There were 13,678 live-born singletons. Data on antenatal maternal anxiety and depression were available in 11,812 children and 8,715 children had data on both antenatal maternal and paternal anxiety and depression. Of these, 6,555 children also had data on their own behavioural problems. Maternal and paternal anxiety and depression 3 years after childbirth was available in 4,019 of these children. The final analyses

were conducted in 3,442 singleton children in whom complete confounder data were available. Ethical approval of the study was obtained from the ALSPAC Law and Ethics Committee (IRB00003312) and three Local Research Ethics Committees.

Parental depression and anxiety

Generation R: Symptoms of parental depression and anxiety were assessed with the Brief Symptom Inventory (BSI) at 20 weeks of pregnancy. The BSI is a validated self-report questionnaire with 53 items on a 5-point scale, ranging from 0 = 'not at all' to 4 = 'extremely' (Derogatis & Melisaratos, 1983). The items of the BSI cover nine scales of psychiatric symptoms occurring in the preceding 7 days. For this study, we used the depression and anxiety scale, each containing six questions. The values (0–4) of the items per scale were summed and divided by the number of endorsed items. In this study, the alpha's for internal consistency for maternal and paternal depression and anxiety were between .69 and .79. This assessment was repeated when the child was 3 years old.

ALSPAC: Parental depression and anxiety were measured at 18 weeks of pregnancy. Parental depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS), a widely used 10-item self-report questionnaire that has been shown to be valid in and outside the postnatal period (Cox, Holden, & Sagovsky, 1987). Parental symptoms of anxiety were measured using items from the Crown-Crisp index (CCEI), a validated self-rating inventory (Birtchnell, Evans, & Kennard, 1988). Maternal and paternal postnatal anxiety and depression were assessed again at 33 months using the same instruments.

In both studies, each parent completed the depression and anxiety questionnaires themselves (i.e. these were not administered by interview and one parent did not answer for the other parent).

Outcome: attention problems

Generation R: the Child Behavior Checklist (CBCL/1½–5) was used to obtain standardized maternal reports of children's problem behaviours at 3 years. The CBCL/1½-5 contains 99 problem items, which are scored 0 = 'not true', 1 = 'somewhat true', and 2 = 'very true or often true', based on the preceding two months. The items are scored on seven empirically based syndromes. Good reliability and validity have been reported for the CBCL (Achenbach & Rescorla, 2000). For this study, the Attention Problems syndrome scale was used, which comprised items such as: 'Can't concentrate', 'Can't sit still', and 'Wanders away'. Since our scores were highly skewed and could not be normalized, the Attention Problems syndrome scale was dichotomized. We used the borderline cut-off scores (93rd percentile) of a Dutch norm group (Tick, van der Ende, Koot, & Verhulst, 2007) to classify children as having Attention Problems in the borderline range.

ALSPAC: When children were 4 years old, the primary caregiver (generally the mothers) reported on children's behavioural or emotional problems using the Strengths and Difficulties Questionnaire (SDQ; Goodman & Scott, 1999), an adaptation of a widely used

index of psychiatric symptoms in children (Elander & Rutter, 1996). The SDQ includes three subscales concerning specific kinds of behavioural or emotional disturbances and has established links with clinical levels of disturbance (Goodman, 1999). In this study, we used the SDQ hyperactivity/inattention subscale, which comprised items such as: 'Constantly fidgeting or squirming', 'Easily distracted, concentration wanders', and 'Thinks things out before acting'. Attention problems were categorized as those falling into the 'abnormal' category for this scale (Goodman, 2010, July 10), which is referred to as 'clinical' scores in the remainder of this paper.

Covariables

Generation R: Information on educational level of the mother, maternal smoking and alcohol use during pregnancy, family income and ethnicity of the child were all obtained by postal questionnaires. Educational level was categorized in three levels: low, middle (lower and intermediate vocational training) and high education (higher vocational education, and university) based on Dutch standard classification criteria. Family income, i.e. the net monthly income per month, was reported by the mother and was categorized as '<1,200 euros' (below social security level), '1,200–2,000 euros', and '>2,000 euros' (more than modal income). Child ethnicity was based on the country of birth of the child and its parents. The child's gender and birth weight were obtained from midwife and hospital registries.

ALSPAC: Infant gender and birth weight were obtained from obstetric records or birth notifications. In the 32-week questionnaire, mothers were asked to record their highest educational level, which was collapsed into 'none/Certificate of Secondary Education' (national school exams at 16 years), 'vocational', 'O-level' (national school exams at 16 years, higher than certificate of secondary education), 'A-level' (national school exams at 18 years), or 'university degree'. Family income per week was assessed at 4 years after delivery. Information on ethnicity of mothers and their partners were reported from questionnaires sent to mothers at 32 weeks gestation. Information on maternal smoking and alcohol use was collected from antenatal questionnaires sent to mothers at 18 and 32 weeks gestation.

Statistical analyses

In each cohort, we calculated Spearman's Rho correlation coefficients between depressive and anxiety symptoms, between maternal and paternal symptoms and between antenatal and postnatal symptoms over time.

In the nonresponse analyses, we compared characteristics of mothers and their children with data on attention problems to those with missing data on this outcome with Chi-squared tests, analysis of variance (ANOVA), and Mann–Whitney U-test.

Logistic regression was used to assess the association between parental symptoms of depression or anxiety and child attention problems. Parental depressive and anxiety symptoms during pregnancy were studied as continuous variables. The depression and anxiety scores were divided by their standard deviations to

improve comparability of the odds ratios between parents and across studies, although effect estimates may not be entirely comparable if distributions differ across studies. All analyses were repeated using raw scores (i.e. not SD scores) which gave very consistent results (see Table S1 and S2).

Confounders were selected a priori. The selection was based on earlier research on the association between antenatal maternal anxiety and childhood behavioural problems (O'Connor et al., 2002). All models were adjusted for age, gender and ethnicity of the child, educational level and age of the mother, family income, maternal smoking and alcohol use during pregnancy.

We conducted a series of analyses to test our hypotheses. First, we studied the relation between maternal symptoms of depression and anxiety with child attention problems within Generation R and within the ALSPAC. Second, we compared the associations of antenatal maternal symptoms with child attention problems to those of antenatal paternal symptoms with the same child outcomes. An F-statistic was used to compare the parental associations. In these analyses we also adjusted for all potential confounders and performed mutual adjustments for the other parent's symptoms. The rationale for this adjustment is depicted in Figures S1 and S2. Third, we investigated whether maternal depressive and anxiety symptoms 3 years after childbirth were associated with child behavioural and emotional problems at the same time independently of antenatal symptoms. In addition, in both cohorts we examined whether maternal or paternal symptoms 3 years after the child was born accounted for the association of antenatal depression or anxiety with offspring behaviour. We explored whether adding depression or anxiety when the child was 3 years old to the confounder adjusted antenatal depression or anxiety model resulted in attenuation to the null of the antenatal association. In this final model we examined whether the results may have been biased by collinearity between the maternal antenatal and postnatal depression or anxiety measurements by examining the variance inflation factor.

Finally, we tested consistency of results between the two cohorts. If magnitudes and patterns of association are similar in these two cohorts this provides more robust evidence that they are not a chance finding in one cohort.

We performed several additional analyses. First, although child attention problems were our main outcome, results were contrasted to another outcome, i.e. emotional problems, to examine specificity of association. A specific association with either attention or emotional problems would further support a causal inference. In Generation R, emotional problems were measured by the CBCL broadband scale Internalizing Problems and in ALSPAC the SDQ subscale Emotional Problems were used. Second, we repeated the analyses using dichotomized determinants, because the distributions of parental depression and anxiety scores were skewed and we wanted to examine a possible threshold effect. In both cohorts, we defined 'anxious' or 'depressed' as a score higher than the 85th percentile in the whole cohort in line with previous studies (van Batenburg-Eddes et al., 2009). Third, to assess the representativeness of the final analysis samples in the two cohorts, we calculated the prevalence of attention problems in children of mothers without (participating)

partners, i.e. excluded mothers. Furthermore, we examined the key maternal antenatal symptom-offspring outcome associations in the maximal sample possible (i.e. restricting only to those where there were maternal antenatal exposure data, offspring-outcome data and data on all covariables).

Finally, we tested whether any association between antenatal depression or anxiety of a parent and child attention problems was independent of birth weight and gestational age. In both cohorts, birth weight and gestational age did not change the effect estimates. Results of these analyses are not presented.

Statistical analyses were performed using the Statistical Package of Social Sciences version 15 for Windows and SAS version 9.2 (Generation R) and STATA (ALSPAC).

Nonresponse analyses

Generation R: In comparison with those included in the analyses, mothers of children who were excluded, because of loss to follow-up or missing data had more antenatal depressive symptoms [median (90% range): 0 (0–1.17) vs. 0 (0–0.67), $p < .001$] and anxiety symptoms [median (90% range): 0.17 (0–1.17) vs. 0 (0–0.83), $p < .001$], were more often lower educated [56% vs. 32% low education, $\chi^2(2) = 255.5$, $p < .001$] and on average younger [29.9 vs. 31.7 years, $F(1, 3582) = 154.4$, $p < .001$]; their partners had more depressive symptoms [median (90% range): 0 (0–0.67) vs. 0 (0–0.50), $p < .001$].

ALSPAC: As with the Generation R sample, compared with ALSPAC mothers included in analyses, the excluded mothers had more antenatal depressive symptoms [median (90% range): 7 (0–16) vs. 5 (0–14), $p < .001$] and antenatal anxiety symptoms [median (90% range): 4 (0–12) vs. 4 (0–0.11), $p < .001$], were less educated [24% vs. 11% no higher than CSE; $\chi^2(4) = 422.6$, $p < .001$], and on average younger at childbirth [27.5 vs. 29.2 years $F(1, 13678) = 319.2$, $p < .001$]; their partners also had more depressive symptoms [median (90% range): 4 (0–12) vs. 3 (0–11), $p < .001$] and more anxiety symptoms in the prenatal period [median (90% range): 2 (0–9) vs. 2 (0–8), $p = .01$].

Results

Sample characteristics

In the Generation R Study, participating mothers were mostly high educated (68%) and were on average 32 years old at enrolment. In ALSPAC, 47% of mothers were educated to the level of national school exams at 18 or higher, and were on average 29 years at childbirth. In Generation R, 14% were of non-Dutch ethnic origin, however, in ALSPAC 1% of mothers were not of white European origin. In Generation R and ALSPAC, respectively, 4% and 12% of the children had a score in the borderline or clinical range of attention problems. Detailed participant characteristics are shown in Table S3.

In both cohorts, maternal depressive and anxiety symptoms were correlated with paternal depressive and anxiety symptoms (see Table S4).

Table 1 Associations between parental symptoms of depression and anxiety during pregnancy and child attention problems

| | Odds of attention problems by parental depression or anxiety in Generation R[a] | | | | | | | | |
| | Unadjusted | | | Adjusted for confounders | | | Additionally adjusted for symptoms 3 years after the child was born | | |
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Parental distress, per SD									
Maternal depressive symptoms	1.32	(1.15–1.52)	<.001	1.23	(1.05–1.43)	.009	1.11	(0.92–1.33)	.27
Paternal depressive symptoms	1.13	(0.96–1.33)	.14	1.02	(0.84–1.23)	.85	0.96	(0.78–1.18)	.68
Maternal anxiety symptoms	1.33	(1.15–1.55)	<.001	1.24	(1.06–1.46)	.008	1.12	(0.93–1.35)	.24
Paternal anxiety symptoms	1.16	(0.98–1.39)	.09	1.10	(0.91–1.32)	.35	1.00	(0.81–1.23)	.99
	Odds of attention problems by parental depression or anxiety in ALSPAC[b]								
Parental distress, per SD									
Maternal depressive symptoms	1.41	(1.27–1.56)	<.001	1.33	(1.19–1.48)	<.001	1.17	(1.03–1.33)	.01
Paternal depressive symptoms	1.22	(1.10–1.35)	<.001	1.11	(1.00–1.24)	.05	1.10	(0.97–1.24)	.14
Maternal anxiety symptoms	1.36	(1.23–1.50)	<.001	1.32	(1.19–1.47)	<.001	1.16	(0.98–1.20)	.02
Paternal anxiety symptoms	1.09	(0.98–1.21)	.12	1.05	(0.94–1.17)	.38	0.95	(0.84–1.08)	.43

OR, odds ratio; CI, confidence interval.
In one or more analyses n = 2,280 in the Generation R Study and n = 3,442 in the ALSPAC.
[a]Generation R attention problems (including the borderline range) were defined using a cut-off at the 93rd percentile based on a Dutch norm group.
Models are unadjusted models; adjusted for gender, age and ethnicity of the child, maternal education, age, alcohol use and smoking during pregnancy, family income and adjusted for depression or anxiety of the partner during pregnancy (i.e. mutual adjustment); last models are additionally adjusted for symptoms when the child is 3 years old.
[b]ALSPAC attention problems were based on the SDQ hyperactivity/inattention subscale classification of clinical groups.
Models are unadjusted models; adjusted for gender, and age of the child, ethnicity and age of mother and partner, maternal education, smoking and alcohol use during pregnancy, family income when the child is 4 years old, and adjusted for depression or anxiety of the partner during pregnancy (i.e. mutual adjustment); last models are additionally adjusted for anxiety or depression at 33 months.

Attention problems

Associations between parental depressive and anxiety symptoms during pregnancy and attention problems in their children are presented in Table 1.

Maternal depressive symptoms during pregnancy were associated with child attention problems, adjusted for confounders and paternal symptoms. Associations for paternal depressive symptoms and child attention problems were substantially weaker than those observed for maternal depressive symptoms. In Generation R, there was no strong evidence that the paternal associations differed statistically from the maternal associations with respect to child attention problems, whereas in ALSPAC the paternal associations were statistically weaker than the maternal associations (p for equality between maternal and paternal effect estimates, Generation R: $\chi^2(1) = 2.12$, $p = 0.15$; ALSPAC: $\chi^2(1) = 4.12$, $p = 0.04$).

Antenatal maternal anxiety was associated with an increased risk of child attention problems in both cohorts, after adjusting for confounders and paternal symptoms. As observed for parental depressive symptoms, associations for paternal anxiety and child attention were substantially weaker than those observed for maternal anxiety. There was no strong statistical evidence that the association of paternal anxiety symptoms with child attention problems differed from the same association with maternal anxiety symptoms in Generation R but there was clear evidence that in ALSPAC the two associations did differ

from each other (p for equality between maternal and paternal effect estimates, Generation R: $\chi^2(1) = 0.89$, $p = 0.34$; ALSPAC: $\chi^2(1) = 7.85$, $p = 0.005$).

The associations between maternal and paternal symptoms of depression and anxiety during pregnancy and child attention problems were additionally adjusted for the respective postnatal symptoms of the parents around the time of child behaviour assessment. Maternal symptoms 3 years after childbirth were associated with child attention problems independently of antenatal symptoms. Maternal depressive and anxiety symptoms 3 years after birth were associated with concurrent child attention problems in Generation R ($OR_{depression}$ 1.25, 95% CI 1.10–1.41; $OR_{anxiety}$ 1.24, 95% CI 1.08–1.41) and in ALSPAC ($OR_{depression}$ 1.28, 95% CI 1.14–1.44; $OR_{anxiety}$ 1.26, 95% CI 1.11–1.42), adjusted for confounders and antenatal symptoms. Adjusting for symptoms 3 years after childbirth considerably attenuated all parental associations. In the ALSPAC cohort, some evidence for an association of maternal depression and anxiety with child attention problems remained after this adjustment (see Table 1), although formal statistical testing showed no difference between the maternal and paternal associations ($\chi^2_{depression}(1) = 0.41$, $p = 0.52$; $\chi^2_{anxiety}(1) = 1.59$, $p = 0.21$). The attenuation was not due to collinearity of antenatal symptoms and symptoms when the child was 3 years old as variance inflation factors did not exceed 1.22 in Generation R and 1.40 in ALSPAC in any of the regression models.

Table 2 Associations between parental symptoms of depression and anxiety during pregnancy (continuous) and child emotional problems

| | Odds of emotional problems by parental depression or anxiety in Generation R[a] | | | | | | | | |
| | Unadjusted | | | Adjusted for confounders | | | Additionally adjusted for postnatal symptoms | | |
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Parental distress, per SD									
Maternal depressive symptoms	1.31	(1.16–1.48)	<.001	1.23	(1.07–1.41)	.003	1.07	(0.91–1.26)	.44
Paternal depressive symptoms	1.17	(1.03–1.34)	.02	1.05	(0.90–1.21)	.56	1.00	(0.86–1.17)	.99
Maternal anxiety symptoms	1.41	(1.25–1.60)	<.001	1.32	(1.16–1.51)	<.001	1.17	(1.00–1.37)	.05
Paternal anxiety symptoms	1.20	(1.04–1.38)	.01	1.11	(0.95–1.30)	.18	0.99	(0.84–1.18)	.93
	Odds of emotional problems by parental depression or anxiety in ALSPAC[b]								
Parental distress, per SD									
Maternal depressive symptoms	1.57	(1.33–1.85)	<.001	1.53	(1.28–1.82)	<.001	1.27	(1.03–1.55)	.02
Paternal depressive symptoms	1.18	(0.99–1.39)	.06	1.05	(0.88–1.26)	.59	0.99	(0.81–1.21)	.91
Maternal anxiety symptoms	1.55	(1.32–1.82)	<.001	1.52	(1.28–1.79)	<.001	1.20	(0.99–1.46)	.07
Paternal anxiety symptoms	1.00	(0.84–1.21)	.96	0.94	(0.78–1.14)	.53	0.90	(0.72–1.12)	.34

OR, odds ratio; CI, confidence interval.
In one or more analyses $n = 2,280$ in the Generation R Study and $n = 3,442$ in the ALSPAC.
[a]Generation R emotional problems (including the borderline range) were defined using a cut-off at the 83rd percentile based on a Dutch norm group.
[b]ALSPAC emotional problems were based on the SDQ emotional problems subscale classification of clinical groups.
See Table 1 for explanation of the models (same covariates throughout).

Emotional problems

In Table 2 associations between parental antenatal depressive and anxiety symptoms and child emotional problems are presented. In both cohorts, antenatal maternal depression and antenatal maternal anxiety were associated with increased risk of child emotional problems after adjustment for confounders and symptoms of the partner.

The associations between antenatal maternal depressive and anxiety symptoms and child emotional problems attenuated considerably after additional adjustment for maternal symptoms when the child was 3 years old. In Generation R, antenatal maternal anxiety but not depressive symptoms were still associated with an increased risk of child emotional problems, whereas in ALSPAC, antenatal maternal depressive but not anxiety symptoms remained associated with child emotional problems after adjusting for maternal symptoms 3 years after childbirth (see Table 2).

Additional analyses

Table S5-A (attention problems) and S5-B (emotional problems) show how the magnitude of the associations change after adjustment for measured confounders in Generation R. For both depression and anxiety, adjustment for partner symptoms did not alter the strength of the associations between antenatal maternal depressive or anxiety symptoms and child attention ($OR_{depression}$ 1.31, 95% CI 1.13–1.51; $OR_{anxiety}$ 1.31, 95% CI 1.13–1.53) or emotional problems ($OR_{depression}$ 1.28, 95% CI 1.13–1.45; $OR_{anxiety}$ 1.38, 95% CI 1.22–1.57).

Adding other confounders slightly reduced the magnitude of the associations. Smoking during pregnancy and age of the mother were the strongest confounders. After maternal symptoms at 3 years were also taken into account, antenatal maternal depressive or anxiety symptoms were no longer associated with child attention problems.

Maternal and paternal depression and anxiety symptoms were studied in both cohorts as categorical variables; in these analyses maternal depression and anxiety and paternal depression were associated with increased risk of child attention problems only in ALSPAC.

Again, all associations were markedly attenuated after adjustment for the respective parental symptoms when the child was 3 years old (Table S6).

The study population was limited to mothers with participating partners ($n = 2,280$ in Generation R and $n = 3,442$ in ALSPAC). This may have introduced bias. Therefore, the prevalence of attention problems in offspring and the key maternal antenatal symptom-offspring-outcome associations were also calculated in mothers without (participating) partners (Generation R: $n = 2,012$; ALSPAC $n = 1,392$). The prevalence of attention problems in Generation R was 7% and in ALSPAC it was 16%. In mothers without (participating) partners, antenatal maternal symptoms of depression or anxiety were associated with attention problems (adjusted OR for maternal depression: Generation R 1.24, 95% CI 1.03–1.50 and ALSPAC 1.36, 95% CI 1.18–1.57; adjusted OR for maternal anxiety: Generation R 1.22, 95% CI 1.01–1.48, and ALSPAC 1.35, 95% CI 1.17–1.55). The associations attenuated after correction for maternal symptoms 3 years after

childbirth (adjusted OR for maternal depression: Generation R 1.09, 95% CI 0.87–1.36 and ALSPAC 1.18, 95% CI 0.99–1.42; adjusted OR for maternal anxiety: Generation R 1.08, 95% CI 0.86–1.34, and ALSPAC 1.21, 95% CI 1.02–1.45). These results were very similar to those in mothers with participating partners.

Discussion

The present study showed that, across the cohorts, antenatal maternal depressive and anxiety symptoms were associated with child attention problems. In both cohorts, associations of antenatal paternal symptoms of depression and anxiety were weaker than those observed for maternal symptoms. In ALSPAC but not in Generation R, the paternal associations were different from the associations of maternal symptoms and child attention. Observed associations were largely accounted for by maternal anxiety and depression when the child was 3 years old. In ALSPAC, the maternal associations with child attention problems did not fully attenuate after adjusting for symptoms 3 years after childbirth, but there was no statistical evidence that the maternal associations were different from those observed for the partners anymore.

Taken together these findings give some support for a direct intrauterine mechanism for attention problems. Yet, the findings suggest that the observed associations can also partly be explained by measured confounders (e.g. socioeconomic factors) as well as unmeasured familial or socioeconomic factors (i.e. residual confounders) shared by both parents. In addition, if genetic variants underlie both maternal depression and child attention problems, a similar association pattern should be observable in the fathers that also share 50% of the genetic variants with the child. The persistence of depressive or anxiety symptoms from pregnancy to the postnatal period (and the relationship of these postnatal symptoms to the child's attention behaviours) could further contribute to the observed association of maternal depressive and anxiety symptoms in pregnancy with offspring-attention problems.

Several authors interpreted their findings as indicative of an intrauterine effect of depression during pregnancy on child behaviour. Repeatedly an association between antenatal maternal depression and child behaviour was reported, but most of these studies adjusted only for postnatal psychological state of the mother and not for other important confounders (Davis et al., 2004; Field et al., 2004; Luoma et al., 2001). In Generation R and ALSPAC, we found an association between antenatal maternal depressive symptoms and child attention problems, independent of multiple potential confounders. However, only in ALSPAC and not in Generation R, there was some statistical evidence that the association between antenatal maternal depressive symptoms and child attention problems differed from that of paternal depressive symptoms and child attention problems. These findings suggest that the associations may be partly due to effects of foetal programming caused by antenatal maternal depressive symptoms, but could also well be due to shared familial characteristics (genetic, socioeconomic, lifestyle) that relate depressive symptoms in both parents to offspring behaviours.

Moreover, the association between maternal depressive symptoms during pregnancy and child attention problems markedly attenuated when depressive symptoms round the time child behaviour were assessed and taken into account. This suggests that an important driver of the association is persistence of the symptoms into the postnatal period and the impact of these postnatal symptoms on the child rather than an intrauterine mechanism.

In Generation R and ALSPAC, antenatal maternal anxiety but not paternal anxiety was associated with child attention problems. However, correcting for anxiety symptoms at child age 3 years strongly attenuated all observed associations. The effect estimates for the associations of antenatal maternal and paternal anxiety with child attention problems were not statistically different in both Generation R and ALSPAC. The cross-cohort findings thus provide only some evidence that antenatal maternal anxiety symptoms are related to child attention problems via intrauterine mechanisms, whereas previous studies claimed to have found clear evidence of an association between antenatal maternal anxiety and child behavioural problems (O'Connor et al., 2002; Van den Bergh & Marcoen, 2004). However, none of these studies investigated the effect of exposure to antenatal paternal anxiety symptoms on child behaviour.

Strengths and limitations

This study has several strengths. First, data from two large cohorts made it possible to test consistency of the results in different populations. Second, we were able to compare the effects of maternal and paternal depression and anxiety on child attention problems. Third, in both cohorts we had the opportunity to adjust for a large number of confounders.

Several methodological limitations need to be discussed. First, all analyses focused on the main effects of foetal programming only. We did not address any interaction effects, i.e. whether some children are particularly vulnerable to the effects of maternal depression and anxiety. Second, nonrandom attrition may have influenced our results, for example, if nonparticipating parents with depression or anxiety were more likely than participating parents to have a child with attention problems. Those lost to follow-up were less well-educated, younger and had more depressive and anxiety symptoms than their participating

counterparts. Moreover, mothers without (participating) partners more often had children with behavioural problems than the included mothers. However, the associations in mothers without (participating) partners were of similar magnitude as those in the included sample. Second, child behaviour was assessed by the mother, hence reporter bias may have influenced the results of this study. It is possible that depressed or anxious mothers reported more attention problems in their children than mothers without these symptoms (Najman et al., 2000). Third, different instruments were used in both cohorts to measure parental depression and anxiety and child attention problems. Good validity has been demonstrated for the BSI (Derogatis & Melisaratos, 1983), the CCEI (Birtchnell et al., 1988), and the EPDS (Cox et al., 1987). Using different instruments might have contributed to some inconsistency of findings regarding paternal depression. Overall, the findings largely concur; hence the use of different instruments strengthens conclusions. Furthermore, the CBCL and the SDQ were used to assess child attention problems within Generation R and the ALSPAC respectively. Goodman and Scott (1999) showed that scores from the SDQ and the CBLC were highly correlated and the instruments were equivalent at detecting inattention and hyperactivity. However, the two instruments yielded different rates of attention problems; the CBCL is a more detailed behavioural and emotional assessment instrument that was developed for clinical and nonclinical populations, whereas the SDQ is a brief instrument mainly used to assess nonclinical populations.

Conclusions

Antenatal maternal depression or anxiety regardless of its effect on child attention problems poses a threat to maternal well-being and healthy development in the offspring. In two large population-based cohorts, we found some evidence for a direct intrauterine effect of maternal symptoms of depression and anxiety on child attention problems. Moreover, the patterns of associations between antenatal maternal anxiety and child emotional problems were similar to those observed for child attention problems. Thus, the intrauterine mechanism as a consequence of maternal psychopathology may contribute to several child problems. However, a substantial part of the observed effects could be explained by residual confounding as indexed by the relation observed with paternal symptoms, or by postnatal effects of chronic or recurring parental symptoms. The present study provides little evidence that foetal programming as a consequence of maternal symptoms of depression and anxiety is a very relevant aetiological factor for the development of common problems such as attention or emotional problems in children. Child psychiatric research of intrauterine exposures should perhaps also focus on

alternative mechanisms such as genetic factors, postnatal environment or other risk factors during foetal life such as the susceptibility to antenatal infections.

Supporting information

Additional Supporting Information is provided along with the online version of this article.

Figure S1 The association between antenatal maternal symptoms and child attention problems adjusted for antenatal paternal symptoms.

Figure S2 The association between antenatal maternal symptoms and child attention problems adjusted for antenatal paternal symptoms.

Table S1 Associations between raw scores of parental symptoms of depression and anxiety during pregnancy and child attention problems.

Table S2 Associations between raw scores of parental symptoms of depression and anxiety during pregnancy and child emotional problems.

Table S3 Summary of sample characteristics in the Generation R study and the ALSPAC study population.

Table S4 For each cohort, correlations between antenatal (maternal and paternal) symptoms of depression and anxiety and (maternal and paternal) symptoms of depression and anxiety 3 years after childbirth.

Table S5 (A) Stepwise regression analyses showing the associations between antenatal maternal and paternal symptoms of depression and anxiety with child attention problems. (B) stepwise regression analyses showing the associations between antenatal maternal and paternal symptoms of depression and anxiety with child emotional problems.

Table S6. Associations between high levels of parental symptoms of depression and anxiety during pregnancy (categorical) and child attention problems.

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Key points

- Adverse intrauterine factors may have long-term consequences for the offspring's development.
- Maternal antenatal depression and anxiety are associated with offspring behavioural and emotional problems, but this could represent residual confounding or common genetic effects.
- The intrauterine influence of maternal depression or anxiety on child attention problems was investigated.
  - By comparing the effects of maternal and paternal symptoms of depression and anxiety on child attention problems.
  - By exploring the extent to which parental depression or anxiety in early childhood might explain any association.
  - By studying cross-cohort consistency.
- The associations between antenatal maternal depression and anxiety and child attention problems were mostly accounted for by residual confounding and by parental symptoms after childbirth.

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