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Original article

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Behavioural effects of fetal antidepressant exposure in a Norwegian cohort of discordant siblings

Ragnhild Eek Brandlistuen,[1,2]* Eivind Ystrom,[2,3] Malin Eberhard-Gran,[2] Irena Nulman,[4] Gideon Koren[4] and Hedvig Nordeng[1,2]

[1]Pharmacoepidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway, [2]Division of Mental Health, Norwegian Institute of Public Health, Oslo, Norway, [3]Department of Psychology, Faculty of Social Sciences, University of Oslo, Oslo, Norway and [4]Motherisk Program, Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada

*Corresponding author. Department of Pharmacy, School of Pharmacy, University of Oslo, PO Box 1068 Blindern, 0316 Oslo, Norway. E-mail: r.e.brandlistuen@farmasi.uio.no

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Abstract

Objective: Potential adverse effects of prenatal antidepressant exposure on child development are still debated. The possibility that associations are due to genetic or familial environmental risk factors rather than antidepressant use per se cannot easily be ruled out in conventional studies. Our objective was therefore to evaluate the association between prenatal antidepressant exposure and behavioural problems in a sibling controlled study.

Method: This study used data on 20 180 siblings identified from the population-based Norwegian Mother and Child Cohort Study recruited between 1999 and 2008. The mothers were asked to report antidepressant use at gestational weeks 17 and 30 and 6 months post-partum. Child Behavioral Checklist syndrome scales were used to assess externalizing and internalizing behavioural problems by questionnaires sent to mothers at 18 and 36 months postpartum. We performed unmatched and matched sibling analyses using both random- and fixed-effects linear models, respectively, to determine potential behavioural effects of antidepressant exposure.

Results: Prenatal exposure to antidepressants was associated with increased levels of anxiety symptoms in 3 year old children after adjusting for maternal familial effects and confounding by indication (i.e. maternal depression). Effect of prenatal exposure to antidepressants was specific to anxiety, and not associated with emotional reactivity, somatic complaints, sleep problems, attention problems or aggression.

Conclusion: Using a sibling design, we showed that prenatal antidepressant use was specifically associated with increased anxiety symptoms after adjusting for maternal familial factors and confounding by indication.

Key words: Antidepressants, child behaviour, depression, sibling design, Norwegian Mother and Child Cohort Study (MoBa), pregnancy

Key Messages

- Prenatal antidepressant use was associated with increased anxiety symptoms in the child at 3 years.
- Prenatal antidepressant use was not associated with emotional reactivity, somatic complaints, sleep problems, attention problems or aggression in the child at 3 years.
- Maternal depression was independently associated with child behaviour problems.

Introduction

During their childbearing years up to 20% of women experience depression or other mood disorders.[1–4] An increasing number of pregnant women are prescribed antidepressants[2] which cross the human placenta and the blood–brain barrier.[5,6] These medications primarily work by inhibiting reuptake of serotonin (5-HT) and thereby increasing extracellular serotonin levels. When used in pregnancy, antidepressants alter the central serotonin signalling of the fetus during early brain growth and may contribute to developmental risk.[7] However, untreated maternal depression also alters neonatal serotonin levels,[8] leaving important questions unanswered about how the effects of prenatal antidepressant exposure differ from the impact of the underlying maternal disorder.

The effects of antidepressant exposure during pregnancy on child behaviour have been examined in some previous studies, but the results have been conflicting. Several previous studies have shown no adverse consequences following *in utero* antidepressant exposure on behavioural development in preschool and early school-age children.[9–11] However, other findings suggested adverse behaviour outcomes. Toddlers and preschoolers exposed to selective serotonin receptor inhibitors (SSRIs) *in utero* were reported to exhibit reduced adaptive behavior[12] and increased internalizing behaviours.[13] In addition, two recent studies showed increased risk of autism spectrum disorders (ASD) after prenatal exposure to antidepressants.[14,15] On the other hand, other studies did not find any association with ASD but did with attention deficit/hyperactivity disorder (ADHD).[16] Accordingly, the long-term neurodevelopmental safety of antidepressant exposure during pregnancy remains uncertain.

A key challenge to understanding the developmental consequences of antidepressant exposure is distinguishing between the effects of the exposure and the effects of the underlying indication for the drug treatment, i.e. the maternal depression. Several previous studies have shown that untreated maternal depression during pregnancy was associated with child behaviour problems.[13,17,18] In addition, a major confounding issue is that antidepressant use during pregnancy could be associated with genetic and family environmental risks for behavioural problems. A family history of mental illness is a significant risk factor for subsequent affective disorder[19,20] and externalizing behaviours in children.[21,22] Similarly, internalizing psychopathology has a substantial genetic component,[23] and women with high levels of negative emotionality exhibit a 6-fold risk for taking antidepressants during pregnancy.[24]. The possibility that associations between antidepressant exposure during pregnancy and behavioural problems in the child are due to genetic or family environmental risks rather than antidepressant use per se cannot easily be ruled out in conventional studies where unrelated individuals are compared. The sibling design may provide one of the most effective approaches to control for family factors when large epidemiological cohorts and sufficient discordant siblings are available.[25] This sibling-control design is suitable because siblings share familial environment and 50% of their genetic predisposition, but may differ on medication exposure during pregnancy. In this study we identified sibling clusters within a large cohort of children prospectively followed from pregnancy up to 3 years of age. The main aim was to estimate the association between prenatal antidepressant exposure and internalizing and externalizing behavioural problems using a sibling-relationship comparison, and thereby adjusting for shared genetic and familial confounding. Furthermore, to meet this aim we also assessed the effects of maternal depression on child internalizing and externalizing behaviour problems.

Methods

Participants

This study used data on sibling pairs identified from the population-based Norwegian Mother and Child Cohort

Study (MoBa; for a complete description, please see reference 26 and http://www.fhi.no/moba-en). All women in Norway giving birth between late 1999 and 2010 at hospitals and maternity units with more than 100 births annually were eligible for the study. Women were invited to participate when they attended routine ultrasound examinations on the 17th week of gestation. During the period of recruitment, 108 841 pregnant women enrolled in the study, a participation rate of 40.6%. Information on medication use, sociodemographic characteristics, maternal health and lifestyle was collected by questionnaires at the 17th and 30th weeks of gestation. In addition, the women completed a questionnaire 6 months after the birth, reporting on the remaining weeks of pregnancy after week 30. Until the children reached 3 years of age, the follow-up included questionnaires assessing child development, periodically sent to mothers at 18 and 36 months. The maternal questionnaire response rates at 18 and 36 months were 77% and 62%, respectively.[26] The cohort was linked to the Medical Birth Registry of Norway (MBRN)[27] by using the woman's personal identification number. The MBRN contains detailed medical information regarding the infant, including birthweight, gestational age, malformations etc., originating from mandatory notification forms completed by midwives, obstetricians and paediatricians during pregnancy, at delivery and during the hospital stay.[27]

A total of 29 762 siblings participated during pregnancy (gestation week 17) (Figure 1). Siblings were assessed at the same ages, each child being assessed at 18 and 36 months. At 18 months 20 180 siblings were participating and at 36 months 14 435 siblings were eligible for analyses.

We used MoBa data version 7 for this study. All questionnaires used in MoBa can be found online at [http://www.fhi.no/moba-en]. Written informed consent was obtained from all participating women. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Externalizing and internalizing problems

Externalizing and internalizing problems were measured at 18 and 36 months by using selected items from the mother-reported Child Behavior Checklist for Ages 2–3 (CBCL/2–3) (8 items at 18 months and 12 items at 36 months were included in the MoBa on externalizing problems; 7 items at 18 months and 11 items at 36 months were included on internalizing problems).[28] Items were selected by a team of clinical and developmental psychologists, based on clinical and theoretical standards as well as empirical representativeness (high factor loadings) for externalizing and internalizing behaviour. Mothers rated whether each item statement reflected their child's behaviour during the past 2 months, from 1 = not true to 3 = very true or often true. Scale reliability was adequate at both time points (Cronbach's $\alpha = 0.62$ at 18 months and 0.74 at 36 months). The subset of items used in the MoBa study was found to be representative, with a correlation of 0.92 with the full scale.[29] The following subscales of externalizing behaviour were assessed: Attention Problem scale (at 18 months, 3 items were used) and Aggressive Behavior scale (at 18 months, 5 items were used). At 36 months, 1 item was added to the Attention Problem scale and 2 items were added to the Aggressive Behavior scale.

Internalizing problems were assessed by the following subscales: 'Anxious' (3 items at 18 months repeated at 36 months); 'Emotionally reactive' (1 item at 18 months, 1 item was added at 36 months); 'Somatic complaints' (1 item at 18 months, 3 items added at 36 months); and 'Sleep problems' (2 items at 18 months repeated at 36 months). Means scores were calculated and standardized (z-scores).

Antidepressant use

Information on antidepressant use was available from two prenatal and one postnatal questionnaires. The woman reported on her health problems and whether she had taken medication. She was specifically asked about the following mental health disorders to enhance medication reporting: depression, anxiety, other mental disorders. For each indication, the woman could specify the following exposure windows: gestational weeks 0 to 4, 5 to 8, 9 to 12, and 13+ (until completion of the first questionnaire), 13 to 16, 17 to 20, 21 to 24, 25 to 28, and 29+ (until completion of the second questionnaire) and 30+ (until birth), and could name the medication taken in an open textbox. If multiple medication use was reported and multiple time periods indicated, we assumed all drugs had been used in all time periods. We classified and grouped drug exposure according to the Anatomical Therapeutic Chemical (ATC) Classification System developed by the World Health Organization.[30] Antidepressant use was defined as reported use of a drug belonging to ATC code: N06A.

Maternal mental health

Mothers reported on symptoms of depression and anxiety using a validated short version of the Hopkins Symptom Checklist, the SCL-5[31] at the 17th and 30th weeks of gestation and then again when their child was 6 months old (post-partum symptoms of anxiety and depression). Items in the SCL are scored on a Likert scale ranging from 1 (not at all bothered) to 4 (very much bothered). The

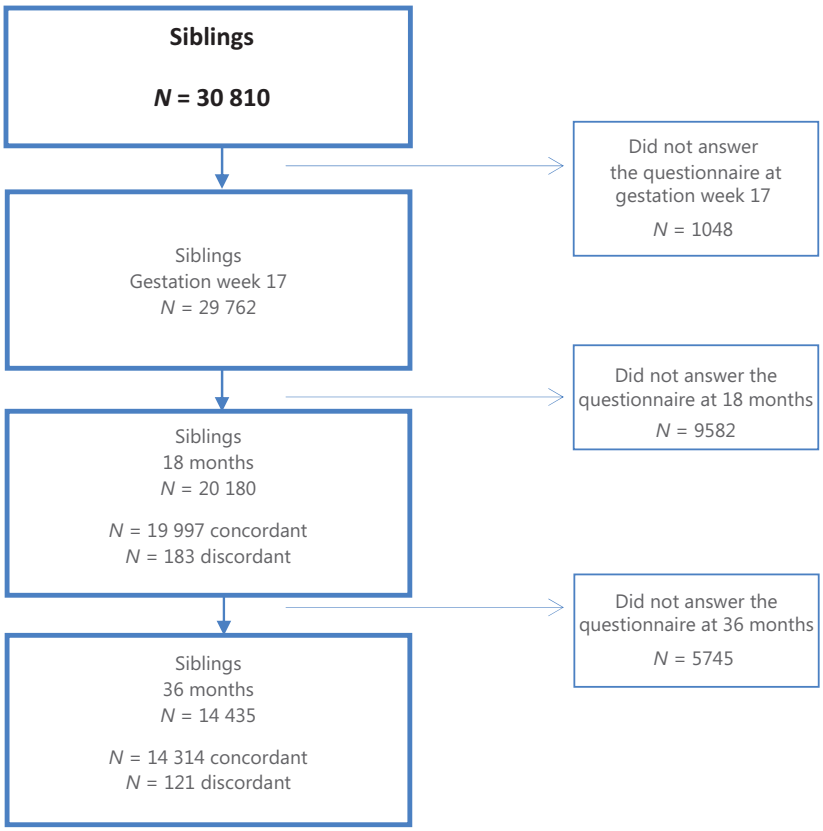

Figure 1. Flow chart of siblings in the Norwegian Mother and Child Cohort study from pregnancy to 36 months post-partum.

SCL-5 scores were calculated as the mean value of the five items. Presence of symptoms of anxiety and depression during pregnancy was defined by the 85th percentile and divided into short-term: only present at 17 th or 30th week of gestation and long-term: present at both 17th and 30th week of gestation. Mothers also reported their lifetime history (LTH) of major depression (MD) by answering the lifetime occurrence of five key depressive symptoms chosen from the nine symptomatic criteria for Major Depression in the Diagnostic and Statistical Manual of Mental Disorders (DSM-lll-R): (1) sad mood, (2) change in appetite, (3) loss of energy, (4) feelings of guilt or worthlessness and (5) problems in concentration.[32] They were then asked whether any three of these symptoms co-occurred in their life for at least 2 weeks. In this study, individuals who responded positively to this item and admitted to sad mood were considered to have reported an LTH of MD.

Other potential risk factors for externalizing and internalizing problems

Differences across siblings in maternal and child risk factors were evaluated as covariates for relations between antidepressants use and behaviour problems. Maternal concomitant use of other drugs: nonsteroidal anti-inflammatory drugs (NSAIDs) (M01A and N02BA), paracetamol (N02BE01), triptans (N02CC), opioids (N02A), other analgesics (N02CA and N02CX), benzodiazepines (N05CD, N05BA), antipsychotics (N05A), and anti-epileptic drugs (N03A) was reported at gestation weeks 17 and 30, and 6 months after birth.

In addition, smoking and alcohol use during pregnancy was measured at week 17 and week 30. Information on maternal age at delivery and parity, and child gender, birthweight and gestational age was retrieved from the Medical Birth Registry of Norway.

Statistical analysis

Using maximum likelihood, we estimated unmatched and sibling-matched associations using the xtreg function in STATA 13 for random- and fixed-effects linear models. As default in STATA, we used the observed information matrix to calculate 95% confidence intervals. The sibling fixed-effect models controlled for potential bias by unobserved variables that were fixed within families (i.e. constant across siblings), such as shared family environments or genetic transmission of risk (e.g. factors for maternal

chronic disease, personality and intellectual ability). In addition, variables were included as confounders if they were associated with discordance in antidepressant use and the outcome variable, or if the effect of antidepressants changed by >1% when the variable was included in the model. The beta coefficient represented the standardized mean difference in the developmental outcomes after familial factors and observed confounders are adjusted for, and can be interpreted as the effect sizes of Cohen's d.

The study was adequately powered to detect even fairly small differences in behavioural outcomes. With power analysis for paired samples of the difference between two dependent means (matched pairs, αerr prob = 0.05) we observed 80% power to detect effect sizes of 0.3 and 95% power in detecting effects of 0.4. At 36 months we had 65% power to detect effect sizes of 0.3 and 90% power to detect moderate effect sizes of 0.4.

Results

Among the 20 180 siblings with complete data on antidepressant exposure at 18 months, 183 (0.8%) were discordant for antidepressant exposure. At 36 months, the number of discordant siblings was 121. Figure 1 shows a flow chart of the participants in the study. Descriptive characteristics according to use of antidepressants are presented in Table 1. The sibling sample showed comparable numbers on measures such as maternal depression during pregnancy and maternal use of antidepressants in the total MoBa cohort sample[33] (the numbers on antidepressant use were 1% of the total MoBa sample, 0.8% at 18 months and 0.9% at 36 months in the current sibling sample), as well as on pregnancy outcomes such as major birth defects (the numbers were 2.9% of the MoBa participants, 2.8% in the total Norwegian population, 2.7% in the 18 months sibling participants and 2.8% in the 36 months sibling participants).[34] The intraclass correlations (i.e. the similarity between the siblings) for the outcomes were 0.35 (internalizing) and 0.41, (externalizing) (both $P < 0.001$).

The effects of prenatal antidepressant exposure on child internalizing and externalizing behaviour outcomes at ages 18 and 36 months are presented in Table 2. For each outcome, results from three models are presented: (i) crude regression analyses in the full unmatched sibling sample; (ii) crude regression analyses fixed among siblings; and (iii) adjusted regression analyses fixed among siblings. In the crude unmatched sibling analyses for children age 18 months, prenatal antidepressant exposure was associated with internalizing behaviour problems [standardized values (Table 2)]. The analyses of the subscales showed an association with anxiety but not with emotional reactivity, somatic complaints or sleep problems. In the crude sibling-matched analysis for children aged 18 months, prenatal antidepressant exposure was still associated with internalizing behaviour problems (Table 2). The analyses of the subscales showed no significant association with anxiety, emotional reactivity, somatic complaints or sleep problems. After adjusting for the difference in symptoms of maternal depression or anxiety during pregnancy and lifetime depression, as well as the difference in symptoms of postpartum depression, discordance in smoking during pregnancy, alcohol use during pregnancy and co-medication, there was no effect of antidepressant use on child internalizing behaviour problems. Externalizing behaviour problems were not associated with antidepressant use during pregnancy, either by crude or adjusted measures.

At 36 months of age, the crude unmatched regression analyses showed significant associations between prenatal antidepressant exposure and internalizing behaviour. The crude unmatched analyses of the subscales showed that the only subscale significantly associated with exposure was anxiety. In the sibling-matched models, the effects on internalizing behaviour and anxiety remained significant and did not decrease by the adjustment of shared familial factors. The estimate increased even further and remained significant after adjusting for symptoms of maternal depression or anxiety during pregnancy and lifetime depression, as well as symptoms of postpartum depression, discordance in smoking during pregnancy, alcohol use during pregnancy and co-medication.

Table 3 shows the multiple generalized regression sibling models of internalizing and externalizing behaviour problems following prenatal antidepressant exposure, maternal history of lifetime depression or maternal symptoms of depression at child age 3, according to the same three groups of analyses as described for Table 2. The unmatched analyses show that lifetime history of major depression, short-term symptoms of anxiety/depression during pregnancy and long-term symptoms of anxiety/depression in pregnancy were significantly associated with internalizing and externalizing behaviour in the child. Adjusting for shared familial factors in the crude sibling-matched model, lifetime history of major depression was still significantly associated with internalizing behaviour. This effect remained significant after adjusting for parity, use of antidepressants, maternal symptoms of depression short-term or long-term (SCL-5), smoking during pregnancy, alcohol use during pregnancy and co-medication.

Discussion

The potential adverse effects of antidepressant exposure during pregnancy on child development are still under

Table 1. Descriptive characteristics by antidepressant (AD) exposure in the total sibling sample at 18 and 36 months

Characteristics	18 months sample		36 months sample	
	No use of AD *N* = 20 039 *N* (%)	Use of AD *N* = 141 *N* (%)	No use of AD *N* = 14 323 *N* (%)	Use of AD *N* = 112 *N* (%)
Maternal characteristics				
Age at delivery in years				
<25	1 640 (8.2)	14 (9.9)	1 079 (7.5)	13 (11.6)
25–29	7 056 (35.2)	49 (34.8)	5 052 (35.3)	36 (32.1)
30–34	8 440 (42.1)	57 (40.4)	6 124 (42.8)	38 (33.9)
≥35	2 903 (14.5)	21 (14.9)	2 068 (14.5)	25 (22.3)
Parity				
0	7 482 (37.3)	63 (44.7)	5 382 (37.6)	54 (48.2)
1	9 037 (45.1)	57 (40.4)	6 548 (45.7)	41 (36.6)
≥2	3 520 (17.6)	21 (14.9)	2 393 (16.7)	17 (15.2)
Higher education[a]				
Yes	14 254 (71.1)	83 (58.9)	10442 (72.9)	68 (66.7)
No	4 852 (24.2)	48 (34.0)	3 243 (22.6)	35 (31.3)
Missing	933 (4.7)	10 (7.1)	638 (4.4)	9 (8.0)
Type of AD use during pregnancy				
SSRI	–	113 (80.1)	–	92 (82.1)
TCA	–	11 (7.8)	–	8 (7.1)
Other AD	–	17 (12.1)	–	12 (10.7)
Lifetime history of major depression				
No	15 868 (79.2)	22 (15.7)	11 344 (79.3)	16 (14.3)
Yes	3 701 (18.5)	115 (82.1)	2 664 (18.6)	91 (81.3)
Missing	470 (2.3)	4 (2.7)	315 (2.2)	5 (4.5)
Maternal symptoms of anxiety/depression during pregnancy[b]				
No	16 208 (80.9)	51 (36.2)	11 724 (81.9)	39 (34.8)
Yes, short term	2 673 (13.3)	40 (28.4)	1 838 (12.8)	31 (27.7)
Yes, long term	1 158 (5.8)	50 (35.5)	761 (5.3)	42 (37.5)
Smoking during pregnancy				
Yes	895 (4.5)	16 (11.3)	598 (4.3)	12 (10.7)
No	17 990 (89.8)	118 (83.7)	13 202 (92.2)	93 (83.0)
Missing	1 154 (5.7)	7 (5.0)	523 (3.7)	7 (6.3)
Alcohol use during pregnancy				
Yes	2 092 (10.4)	22 (15.6)	1 522 (10.6)	16 (14.3)
No	15 117 (75.4)	97 (68.8)	11 146 (77.8)	81 (72.3)
Missing	2 830 (14.1)	22 (15.6)	1 655 (11.6)	15 (13.4)
Other medication during pregnancy[c]	7 953 (39.7)	81 (57.4)	5 800 (40.5)	62 (55.4)
Child characteristics				
Child sex (male)	10 293 (51.4)	59 (41.8)	7 433 (51.9)	52 (46.4)
Malformations	465 (2.3)	1 (0.7)	347 (2.4)	2 (1.8)
Premature birth	780 (3.9)	6 (4.3)	561 (3.9)	4 (3.6)

SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant.

[a]College or university degree.

[b]Maternal symptoms of anxiety and depression during pregnancy measured by 85th percentile on SCL-5 gestation week 17 and/or 30. (Short term is either week 17 or week 30; long term is both week 17 and week 30.)

[c]Nonsteroidal anti-inflammatory drugs (NSAIDs) (M01A and N02BA), paracetamol (N02BE01) more than 28 days, triptans (N02CC), opioids (N02A), other analgesics (N02CA and N02CX), benzodiazepines (N05CD, N05BA), antipsychotics (N05A) and anti-epileptic drugs (N03A).

debate. To the best of our knowledge, this is the first study investigating the associations between prenatal antidepressant exposure and child behavioural development using a sibling-relationship comparison, and thereby adjusting for shared genetic and familial confounding. Prenatal exposure to antidepressants was associated with increased levels of internalizing behaviour problems in the adjusted analyses at 36 months for the subdomain of anxiety. This finding is in line with previous studies showing the same association of increased internalizing behaviours.[13] Our study suggests

Table 2. Behavioural effects of prenatal exposure to antidepressants. Sibling random- and fixed-effect models

Behaviour problems	18 months			36 months		
	Unmatched $N = 20\,180$	Sibling matched $N = 20\,180$		Unmatched $N = 14\,352$	Sibling matched $N = 14\,352$	
	Crude β (95% CI)	Crude β (95% CI)	Adjusted[a] β (95% CI)	Crude β (95% CI)	Crude β (95% CI)	Adjusted[a] β (95% CI)
Internalizing	0.21 (0.05, 0.37)*	0.23 (0.01, 0.46)*	0.16 (−0.14, 0.46)	0.28 (0.10, 0.45)*	0.34 (0.06, 0.61)*	0.34 (−0.01, 0.68)
Anxiety	0.20 (0.04, 0.36)*	0.21 (−0.03, 0.46)	0.14 (−0.19, 0.47)	0.23 (0.05, 0.41)*	0.44 (0.14, 0.74)*	0.64 (0.26, 1.02)*
Emotional reactivity	−0.02 (−0.18, 0.14)	0.03 (−0.22, 0.29)	0.05 (−0.28, 0.38)	0.16 (−0.03, 0.33)	0.20 (−0.09, 0.49)	−0.06 (−0.42, 0.30)
Somatic	0.07 (−0.09, 0.24)	−0.07 (−0.35, 0.20)	−0.05 (−0.41, 0.30)	0.17 (−0.01, 0.35)	0.15 (−0.17, 0.46)	0.04 (−0.36, 0.43)
Sleep	0.16 (−0.001, 0.32)	0.23 (−0.01, 0.46)	0.20 (−0.11, 0.51)	0.14 (−0.04, 0.32)	0.09 (−0.20, 0.37)	0.25 (−0.11, 0.60)
Externalizing	0.08 (−0.08, 0.24)	0.21 (−0.03, 0.44)	0.26 (−0.05, 0.56)	0.06 (−0.13, 0.24)	−0.02 (−0.30, 0.26)	−0.08 (−0.44, 0.27)
Attention	0.12 (−0.05, 0.28)	0.20 (−0.05, 0.44)	0.15 (−0.16, 0.47)	0.14 (−0.05, 0.32)	0.13 (−0.17, 0.41)	−0.01 (−0.38, 0.36)
Aggression	0.02 (−0.14, 0.19)	0.17 (−0.09, 0.42)	0.30 (−0.03, 0.64)	−0.002 (−0.19, 0.19)	−0.11 (−0.40, 0.18)	−0.11 (−0.49, 0.27)

[a]Adjusted for: parity, maternal symptoms of depression during pregnancy (SCL-5 at week 17), lifetime depression, symptoms of post-partum depression, smoking during pregnancy, alcohol use during pregnancy and co-medication.

*$P = <0.05$.

Table 3. Multiple generalized regression sibling models of internalizing and externalizing behaviour problems following prenatal antidepressant exposure or maternal symptoms of depression at child age 3 years

Behaviour problems	Unmatched $N = 14\,352$	Sibling-matched $N = 14\,352$	
	Crude β (95% CI)	Crude β (95% CI)	Adjusted[a] β (95% CI)
Internalizing			
Use of antidepressants			
No (reference)			
Yes	0.28 (0.10, 0.45)*	0.34 (0.06, 0.61)*	0.34 (−0.01, 0.68)
Lifetime depression[b]			
No (reference)			
Yes	0.27 (0.22, 0.31)*	0.12 (0.05, 0.19)*	0.19 (0.02, 0.38)*
Symptoms of anxiety/depression in pregnancy[c]			
No (reference)			
Short term	0.31 (0.28, 0.35)**	0.03 (−0.03, 0.09)	0.05 (−0.02, 0.11)
Long term	0.36 (0.30, 0.43)**	−0.05 (−0.15, 0.04)	−0.09 (−0.20, 0.02)
Externalizing			
Use of antidepressants			
No (reference)			
Yes	0.06 (−0.13, 0.24)	−0.02 (−0.30, 0.26)	−0.08 (−0.44, 0.27)
Lifetime depression[b]			
No (reference)			
Yes	0.18 (0.14, 0.22)*	0.05 (−0.02, 0.12)	0.02 (−0.05, 0.10)
Symptoms of anxiety/depression in pregnancy[c]			
No (reference)			
Short term	0.29 (0.25, 0.33)**	0.06 (0.002, 0.12)*	0.05 (−0.02, 0.12)
Long term	0.27 (0.21, 0.34)*	−0.05 (−0.15, 0.04)	−0.13 (−0.25, 0.02)

*P = <0.05, **P = <0.01

[a]Adjusted for: parity, use of antidepressants, maternal symptoms of depression during pregnancy (SCL-5 at week 17), lifetime history of major depression, smoking during pregnancy, alcohol use during pregnancy and co-medication.

[b]Lifetime depression was measured by symptoms of lifetime history of major depression.

[c]Symptoms of anxiety and maternal depression were measured in pregnancy either at week 17 or 30 (short term) or in both weeks 17 and 30 (long term) (SCL-5).

that this association is not confounded by shared familial factors. Importantly, the increased internalizing problems seen in crude sibling comparisons were not attenuated when we took into account the difference in symptoms of maternal depression during, before and after pregnancy. However, we found evidence that prenatal maternal depression is also associated with child behaviour problems, but the effects observed in the unmatched sibling analyses were attenuated when we performed a sibling-matched control. This could suggest that the effect of prenatal depression on child behaviour is confounded by genetic or familial factors. However, a measure of lifetime history of major depression did remain significant in the sibling-matched adjusted analyses, suggesting that there is a remaining effect of maternal depression on child behaviour outcomes. The measure of lifetime history of major depression was reported at week 17 during pregnancy. Because it resembles the diagnostic criteria of DSM-5 of Major Depression, it might have served as a more valid measure of severe depression compared with the milder symptoms of anxiety and depression measured by the SCL-5. Taken together, these findings form a strong basis for identifying and implementing interventions to reduce antenatal depression if possible with effective non-medical treatment such as cognitive behavioural therapy (CBT).

A few previous studies have been designed to separate the effect of depression from the effects of its pharmacological treatment. A recent study by Nulman and colleagues based on thorough standardized psychological assessment of children aged 3 to 6 years exposed to venlafaxine, SSRIs or untreated maternal depression found no effect of the pharmacological treatment.[17] Instead, they reported that untreated maternal depression was associated with child behaviour problems. In line with these findings, we found no association between antidepressant exposure during pregnancy and child externalizing behaviour development at 18 or 36 months after adjusting for the differences in the levels of depression between pregnancies. In contrast we did find an association with internalizing behaviour problems that were not attenuated when adjusting for maternal depression. Moreover, we found that both short-term and long-term symptoms of depression in pregnancy were significantly associated with both internalizing and externalizing behaviour problems in the unmatched sibling analyses. This is in line with the results from the previous findings of Nulman *et al.*[11] However, in the sibling-matched analyses the effects of both short- and long-term depression during pregnancy attenuated, suggesting a confounding effect of unmeasured shared familial factors.

As seen in the significant sibling intraclass correlations, there was strong evidence for familial confounding for both externalizing and internalizing behaviours. We effectively adjusted for 35% (internalizing) and 41% (externalizing) of the variance in the outcomes by using sibling control.

The hypothalamic-pituitary-adrenal (HPA) axis has been implicated as a causal mechanism underlying the prenatal stress/anxiety effect on child behaviour. This leading biological model suggests that elevated levels of cortisol from the (anxious or depressed) mother may cross the placenta, by altering the barrier enzyme 11b-HSD2,[35] to affect obstetric outcomes as well as fetal and child development via the influence on the developing HPA axis.[36] Direct evidence for this model has been reported in animal studies.[37] The role of the maternal emotional state in pregnancy on fetal and child neurodevelopment in humans is also beginning to be explored. In a study based on the Avon Longitudinal Study of Parents and Children (ALSPAC), mothers who reported high levels of anxiety in late pregnancy had approximately a 2-fold increased risk of children with significantly elevated behavioural/emotional problems, after controlling for the effects of antenatal, obstetric, psychosocial risk and postnatal anxiety and depression.[18] The effect was still present in children at age 81 months.[38] In line with this hypothesis, small but persisting associations between maternal prenatal mood and diurnal cortisol in the child were reported to persist into adolescence.[39] A recent study showed a significant association between antenatal maternal depression and the neonatal microstructure of the right amygdala, a brain region closely associated with stress reactivity.[40] Thus, it is biologically plausible that increased levels of maternal distress during pregnancy influence the fetus and lead to permanent effects on long-term child outcomes, independent of maternal post-partum status and genetic predisposition. However, because none of the studies on humans could rule out genetic confounding, it is also plausible that the effects are reflecting a vulnerability for anxiety in the child inherited from the mother. A family history of mental illness is a significant risk factor for subsequent affective disorder [19,20] and externalizing behaviours in children.[21,22] Similarly, internalizing psychopathology has a substantial genetic component.[23] Our findings, that maternal short- and long-term symptoms of depression were attenuated when taking into account shared genetic and familial factors, are in line with these findings. On the other hand, our finding that LTH of MD was still associated with child behaviour outcomes after adjusting for shared familial confounding suggests that there is a remaining negative effect of maternal depression on child behaviour. It remains unclear from our findings whether this effect is specific to the pregnancy or reflects an incidence happening between pregnancies resulting in the difference in LTH of MD between siblings.

Some potential limitations should be addressed, including self-reporting of the use of antidepressants and symptoms of depression in pregnancy. This might introduce reporting bias. The validity of self-reported SSRI use in MoBa has been studied by comparing reports of use in MoBa with redeemed SSRI prescription registered in the Norwegian Prescription Database (NorPD). The percentages of total agreement were reported to be substantial (99.5%; kappa 0.69),[41] supporting the validity of self-reported antidepressant use. The sibling design of this study was enabled by a large prospective cohort study, which at the same time limited the opportunity for clinically assessing the mothers for depression. Even though SCL-5 and LTH of MD are both validated measures of depression, a score above cutoff on any of the instruments does not necessarily reflect diagnoses of depression. The finding that LTH of MD was significantly associated with behaviour outcomes in the child whereas SCL-5 was not, could be due to the fact that LTH of MD is based on the diagnostic criteria of major depression.

Second, the relatively low participation rate in MoBa could potentially cause a selection bias. However, stable selection factors (e.g. socioeconomic status) are completely adjusted for in the sibling-control design, creating a robust approach to selection bias. Moreover, the sibling sample was comparable to the total MoBa sample on important measures such as maternal depression and use of antidepressants during pregnancy as well as on pregnancy outcomes such as severe malformations in the child, confirming a representative sample selection.

Third, we could not take the dose of antidepressants into consideration because it was not reported. Therefore we cannot rule out that particularly high doses of antidepressants could have an effect on the other child behaviour subdomains that we did not detect.

Finally, the relatively small number of siblings prevented stratified analyses or interaction analyses of sex differences. However, the ALSPAC study found that the strength of the association between antenatal anxiety and behavioural/emotional problems at both 47 and 81 months of age was similar for boys and girls.

Clinically, the finding that maternal history of lifetime depression predicted a long-term disturbance in offspring behaviour would encourage a greater use of assessments emphasizing maternal mood and mental health—not only for predicting maternal postnatal adjustment (e.g. postnatal depression), but also to ensure a positive adjustment of the child. These findings form a strong basis for considering preventive interventions to reduce antenatal depression and anxiety. The application of the many existing programmes for treating depression and anxiety may not only benefit mothers but also the child, and has been suggested for mild and moderate depression to be a better alternative than medical treatment. However, in the case of severe depression, medical treatment could be necessary and the potential risks observed in the child have to be balanced against the gain for both the mother and the baby from the mother remaining stable in her condition.

Overall, in this sibling-controlled study we found that antidepressant medication had a significant effect on children's internalizing behavioural outcome, and specifically on anxiety at 36 months of age. We also found evidence that maternal depression is independently associated with child behaviour problems.

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