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# Prenatal Antidepressant Exposure and Child Behavioural Outcomes at 7-Years of Age: A study within the Danish National Birth Cohort

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**Short Title:** Prenatal Antidepressant Exposure and Child Behaviour

**Abbreviations:** CI- confidence interval; DNBC-Danish national birth cohort; SDQ-strengths and difficulties questionnaire; SSRI- selective serotonin reuptake inhibitor; TCA-tricyclic antidepressant; RR-relative risk

**Abstract**

**Objective**: To investigate the impact of prenatal antidepressant exposure on behavioural problems in children at 7-years of age.

**Design:** Nationwide population-based study

**Setting:** Danish National Birth Cohort

**Population:** A cohort of 49,178 pregnant women recruited between 1996 and 2002.

**Methods:** Data obtained from computer-assisted telephone interviews twice during pregnancy were used to identify children born to 1) depressed women who took antidepressants during pregnancy (N=210), 2) depressed women who did not take any antidepressants during pregnancy (N=231), and 3) nondepressed, healthy women (N=48,737). Childhood behavioural problems at 7-years of age were examined using the validated Danish parent-report version of the Strengths and Difficulties Questionnaire (SDQ).

**Main outcome measures:** SDQ

**Results:** No associations were observed between prenatal antidepressant exposure and abnormal SDQ scores for overall problem behaviour (aRR 1.00; 0.49, 2.05), hyperactivity/inattention (aRR 0.99; 0.56, 1.75), or peer problems (aRR 1.04; 0.57, 1.91). While prenatal antidepressant exposure appeared to be associated with abnormal SDQ scores on the subscales of emotional symptoms (aRR 1.68; 1.18, 2.38) and conduct problems (aRR 1.58; 1.03, 2.42), these associations were significantly attenuated following adjustment for antenatal mood status (aRR 1.20; 0.85, 1.70 and aRR 1.19; 0.77, 1.83 respectively). Untreated prenatal depression was associated with an increased risk of all behavioural outcomes evaluated compared to unexposed children, with significant attenuation following adjustment for antenatal mood status.

**Conclusion**: The results of this study suggest that independent of maternal illness, prenatal antidepressant exposure is not associated with an increased risk of behavioural problems in children at 7-years of age.

**Key Words:** Antidepressive agents; prenatal exposure; pregnancy; child development; selective serotonin reuptake inhibitors

**Manuscript**

**Introduction**:

Over the past 10-15 years there has been a substantial increase in the use of antidepressants during pregnancy worldwide. In Denmark, antidepressant use during pregnancy has increased from 0.2% to 3.2% from 1997 to 2010,[1] a trend mirrored in other countries such as the United States, where use during pregnancy has increased from 2% to 7.6% from 1996 to 2005.[2] Numerous studies have investigated various maternal and neonatal outcomes associated with prenatal antidepressant exposure, but developmental outcomes of the children are less well studied. The potential long-term effects of prenatal antidepressant exposure is of concern given its effect on serotonin (5-HT), which may affect neurogenesis, migration and differentiation of neurons in the fetal brain.[3-5]

Evidence to date is equivocal in relation to the impact of prenatal antidepressant exposure on child neurodevelopment, given major differences in study design, patterns of antidepressant use, outcome measures and adjustment for confounding.[3] In particular, few studies have evaluated developmental outcomes in offspring beyond 5-years of age. Data from the Danish National Birth Cohort (DNBC) has previously been utilised to evaluate developmental outcomes among children aged 6 and 19 months of age following prenatal antidepressant exposure, with developmental outcomes assessed within normal ranges.[6] A further follow-up study of a sub-cohort of these children aged 4- to 5- years of age also identified no differences in behavioural or emotional problems in early childhood.[7] Given these developmental measures in early age (whether normal or abnormal) may not accurately predict later developmental problems, there is a need for continuous long-term assessment of outcomes. In light of this, we expanded the follow-up time to evaluate the association between maternal antidepressant use during pregnancy and behavioural problems in children at 7-years of age.

**Methods**

This study included mother-child dyads participating in the DNBC, an ongoing nationwide, follow-up study of pregnant women and their children.[8] More than 100,000 pregnancies were included from 1996 to 2002, with 60% of invited pregnant women agreeing to participate.

Women reported on medication use during early pregnancy in a self-administered questionnaire (at approx. 6-10 weeks of gestation). Following consent, women were interviewed by telephone twice during pregnancy, at 17 and 32 weeks gestation, and twice after pregnancy, when their children were 6 and 18 months old. The cohort has been described elsewhere.[8] A self-administered questionnaire completed by parents (mainly mothers) was used to follow-up children at age 7. All questionnaires are available from www.dnbc.dk.

Women eligible for this study were those who signed the consent form and participated in both prenatal interviews (N=82 687). We excluded women who did not give birth to live-born singletons (N=1 872) or who were taking psychotropic medications other than antidepressants (N=756), leaving a final study population of 80 107 women. Follow-up data on children at 7-years of age were available for 49 178 (61%) of the eligible cohort.

*Exposure variables*

Use of antidepressants was defined as self-reported use of any drugs in World Health Organization-defined Anatomic Therapeutic Chemical Classification System group N06A during pregnancy.[9] Information on drug use was coded either using predefined names or in a text string recorded by the interviewer and later coded for analysis by the investigators. Women were classified as exposed if they reported taking an antidepressant at any stage

during pregnancy.

Presence of depression during pregnancy was identified based on maternal self-report, according to questions asked at the 2 prenatal interviews. In the first interview women were asked: 1) Have you ever suffered from a mental disorder or neurosis?; 2) Did you see a medical doctor or psychologist for the disorder?; 3) What was the name of the disorder?; and 4) Have you experienced symptoms of the disorder during pregnancy?. In the second interview women were asked whether they had experienced a mental disorder during pregnancy; if they had, they were asked to disclose the diagnosis.

Based on these data, we assigned the offspring to one of three groups: 1) children whose mothers reported antidepressant use during pregnancy ('antidepressant exposure') 2) children whose mothers reported having prenatal depression but no antidepressant use during pregnancy ('untreated depression'), and 3) children whose mothers reported no prenatal depressant and no antidepressant use during pregnancy ('unexposed').

*Outcome variable*

Behavioural problems were estimated using the validated Danish parent-report version of the Strengths and Difficulties Questionnaire (SDQ).[10,11] Compared to diagnostic interviews, the parent-report version of the SDQ has been demonstrated to have excellent discrimination for the identification of emotional (AUC 0.80; 95%CI 0.72-0.89) and behavioural (AUC 0.89; 95%CI 0.81-0.97) disorders.[11] We analysed the SDQ score in the following five subscales ranging from 0 to 10: emotional, conduct, peer relationship and hyperactivity/inattention problems, and pro-social skills. The sum of problem scores corresponding to the first four subscales constituted the total difficulties SDQ score, ranging from 0 to 40. Descriptions of the subgroups can be found at www.sdqinfo.org. The total SDQ score and each subscale score were coded as normal, borderline or abnormal according to cut-offs outlined in the manual for SDQ. We combined normal and borderline scores in the dichotomised measure, considering abnormal score as the diverging score, representing values greater than the 90$^{th}$ percentile. [11]

*Covariates*

Information on maternal age, parity, smoking status and pre-pregnancy weight and height was obtained from the first prenatal interview. Parity was categorised as either nulliparous (0) or multiparous (≥1). Smoking was categorised according to number of cigarettes smoked on average each day (none, 1-10 cigarettes and >10 cigarettes per day). Maternal pre-pregnancy BMI was coded into three categories (<25; 25 to 29, and ≥30). The socioeconomic status score was defined as described by Bech et al [12] by using data from the first prenatal interview. The highest socioeconomic status score of either the woman or her partner was included in the models, coded as high, middle, and low. Antenatal mood was evaluated using a modified version of the short version of the Symptom Checklist (SCL-8d).[13] Mood was assessed by nine questions, each covering the time period since the beginning of pregnancy. Answers (no = 0, a little = 1, a lot = 2) were added up into a score (range: 0 to 18), and have been previously validated.[14]

*Statistical analysis*

We used causal diagrams (directed acyclic graphs) to guide selection of potential covariates for which to control.[15, 16] The first adjusted model included information on the following covariates: child sex, maternal age, parity, smoking status, socioeconomic status, and alcohol consumption during pregnancy. The second adjusted model also included antenatal mood. The sample size did not allow for stratification according to individual antidepressant type.

We compared SDQ estimates of behavioural problems in the three exposure groups using a generalised linear model (Poisson distribution) with robust variance estimates, with resulting relative risks (RR) and 95% confidence intervals (CIs). The sensitivity of the results to patterns of attrition (missing follow-up data) was examined using inverse probability weighting.[17] To assess whether loss to follow-up biased our results, we used logistic regression (complete data vs. lost to follow-up as outcome) to determine weights for each individual using the inverse probability of response.[17] Complete follow-up data was predicted based on exposure to antidepressants or untreated depression during pregnancy, maternal age, parity, smoking status, socioeconomic status, antenatal mood, and child sex. The individual weighting factor for these covariates (their inverse probability) was used as a sample weighting adjustment in later sensitivity analyses. Statistical analyses were performed using Stata 11.1 (Stata, College Station, TX, USA).

**Results:**

Of the 80,107 pregnant women eligible for the study, 395 were exposed to antidepressants, 474 had untreated depression, and 79,238 were unexposed. Rates of loss to follow-up at 7-years of age were greatest among those with antidepressant exposure (47%) and with untreated depression (51%), compared to those who were unexposed (38%) (**Table S1**).

We studied the children of 210 mothers who were exposed to antidepressants and compared these to 231 children of mothers with untreated depression, and 48,737 children of mothers with no prenatal depression and no use of antidepressants during pregnancy (unexposed). Among the 210 women treated with antidepressants, 173 used one type of SSRI only (fluoxetine, n=45; citalopram, n=43; paroxetine, n=43; sertraline, n=42), 12 used only TCAs, and 19 used another type of antidepressant only (e.g. venlafaxine). Six used combinations of SSRIs, TCAs, and other antidepressants.

Women taking antidepressants during pregnancy were more likely to be older and of higher socioeconomic status than women with untreated depression, and were more likely to be smokers, not to drink alcohol, and be of lower socioeconomic status compared to unexposed women (**Table 1**). Importantly, women with untreated depression reported significantly more antenatal mood symptoms during pregnancy than women taking antidepressants, with unexposed women reporting the fewest symptoms (**Table S1 and Table S2**).

The age of children at follow-up (mean ± SD, years) was similar across the antidepressant (7.1 ± 0.1), untreated maternal depression (7.2 ± 0.1) and unexposed (7.2 ± 0.1) groups (P = 0.142). Abnormal SDQ scores for each of the behavioural outcomes assessed were most common among children exposed to untreated antenatal depression (**Figure 1**). When compared to children of unexposed mothers, prenatal antidepressant exposure appeared to be associated with abnormal SDQ scores on the subscales of emotional symptoms (aRR 1.68; 1.18, 2.38) and conduct problems (aRR 1.58; 1.03, 2.42), however, these associations were significantly attenuated following adjustment for antenatal mood status (aRR 1.20; 0.85, 1.70 and aRR 1.19; 0.77, 1.83 respectively) (**Table 2 and 3**). No associations were observed between prenatal antidepressant exposure and abnormal SDQ scores for overall problem behaviour (aRR 1.00; 0.49, 2.05), hyperactivity/inattention (aRR 0.99; 0.56, 1.75), or peer problems (aRR 1.04; 0.57, 1.91), when compared to children of unexposed mothers. Untreated prenatal depression was associated with an increased risk of all behavioural outcomes evaluated compared to unexposed children, with significant attenuation following adjustment for antenatal mood status (**Table 2 and 3**). Sensitivity

analyses undertaken using inverse probability weighting to account for loss to follow-up identified no major differences between the weighted and non-weighted results (**Table S3**). No significant differences in the risk of behavioural problems were evident following stratifying of antidepressant use according to first trimester exposure only or second/third trimester exposure (**Table S4**).

**Discussion:**

*Main findings*

After adjustment for maternal factors, including antenatal mood, prenatal antidepressant exposure was not significantly associated with an increased risk of behavioural difficulties in children at 7-years of age. In light of these findings, our study adds to a growing body of evidence that prenatal antidepressant exposure does not appear to be significantly associated with negative effects on neurodevelopment in children up until 7-years of age.[6, 7, 18-25] Outcomes assessed to date range from developmental milestones, cognitive function, behaviour and psychomotor development. While the evidence is encouraging, it is still only based on a relatively small number of exposed children (<2000) involved in prospective cohort studies. Data pertaining to other neurodevelopmental outcomes are still lacking.

*Strengths and Limitations*

Our study had the strength of prospectively obtained information and that women were unaware of the hypothesis of the study when reporting behaviour when the children were 7-years of age. Furthermore, the inclusion of women with untreated depression enabled the estimation, to some extent, of the effects of prenatal antidepressant exposure independent from underlying maternal illness.

The reliance of parent-reported SDQ as a proxy for emotional or behavioural problems in the offspring represents a study limitation, however, the intention was not to utilise SDQ scores to predict whether the children had an underlying psychiatric disorder, but to identify behavioural problems in groups of children characterised by their prenatal exposure. The main utility of SDQ scores lies in the ability to undertake comparisons between scores in different groups, not in the unique SDQ score for each individual. It is likely that standardised neuropsychological testing may have detected more subtle changes in child behavioural problems than the SDQ score. However, while independent observation could overcome potential bias according to parental self-report, it may lead to the introduction of selection bias as not all parent's may agree to spending the necessary time on testing.

A further limitation of using parental report is that parental state of mind at the time of completing 7- year follow-up questionnaire may have influenced the parent's view of the child and an abnormal SDQ score may reflect perceptions rather than the child's actual problems. It was not possible to investigate this as a potential source of reporting bias as no data were available on parental mood at the time of completing the 7-year follow-up questionnaire. However, in our previous study involving a smaller cohort of children with prenatal antidepressant exposure, we did not observe any differences in maternal reports of child behaviours at 4- to 5-years of age according to whether they were evaluated as having normal or abnormal depressive symptoms at the time of questionnaire completion.[7]

While this study represents the largest cohort of children to be investigated following prenatal antidepressant exposure, a relative limitation of this study remains the inability to generate precise risk estimates and to adjust for a number of potential confounders and/or covariates due to the small number of children in the antidepressant and untreated depression exposed groups. This makes it difficult to demonstrate statistically significant differences

among the two smaller prenatal antidepressant exposure and untreated maternal depression groups, despite clinically significant differences being apparent. The relatively low prevalence of antidepressant use is reflective of the low SSRI use in Denmark during the study period, which has been reported in other studies.[6, 26] Furthermore, it is possible that women with an underlying psychiatric illness, such as depression, were less likely to consent to participate in the study, leading to the observed low prevalence of antidepressant use and untreated depression.

Depression and the use of antidepressants may be associated with a variety of factors that may influence child development. While the inclusion of a control group of women with untreated depression, together with the adjustment for antenatal mood, accounted for confounding by the indication for treatment to some extent, residual confounding may still remain. It is possible that appropriate management of depression during and after pregnancy through the use of either non-pharmacological and/or pharmacological treatments may be associated with differing rates of abnormal behavioural outcomes in the children. As the focus of this study was on determining the relative impact of prenatal antidepressant exposure on child behavioural outcomes, we did not evaluate the impact of maternal postnatal depression. It is also likely that a number of women in the unexposed (control) group developed postnatal depression, which may be associated with child behavioural outcomes. This represents an important area for future research.

A further limitation was that not all women completed the follow-up questionnaire, however, later sensitivity analyses using inverse probability weighting to account for loss to follow-up did little to change the risk estimates. While the potential for residual confounding remains, this suggests that loss to follow-up is unlikely to have substantially biased our findings. This low risk of bias is supported by a previous study estimating bias from loss to follow-up in the DNBC.[27] This study also demonstrated that the presence of childhood developmental disorders at 7-years of age was associated with a non-statistically significant reduced likelihood of children being lost to follow-up (OR 0.87; 95% CI 0.63-1.20), suggesting this is unlikely to be another major source of bias.[27] Additional limitations include relying on maternal self-reported depression and antidepressant use during pregnancy. Finally, the sample size does not permit any strong conclusion concerning specific type of antidepressant use during pregnancy, or in relation to dose and/or duration of antidepressant exposure.

*Interpretation*

Oberlander et al.,[28] showed that infants exposed to SSRIs *in utero* have an attenuated response to acute pain during heel prick compared to infants who were not exposed to SSRIs. Follow-up evaluation of those same infants at 4 years of age (n=22), however, revealed no associations with internalising,[21] externalising, and attentional behaviours[20]. In contrast to these outcomes, a small number of studies have demonstrated an association between prenatal antidepressant exposure and delayed psychomotor development.[6, 22, 24] In the majority of cases, however, observed outcomes have largely remained within previously defined normal ranges of development. Therefore, the clinical relevance of such findings remains unknown. Furthermore, there remains significant potential for residual confounding due to underlying maternal disease, its severity and associated behaviours that contribute towards impaired neurodevelopmental outcomes in childhood. Separating the effects of antidepressant use from underlying maternal illness remains the major challenge, and so far only few studies have utilised stronger sibling designs or designs where both parent's medication use and mental health status are taken into consideration in an attempt to delineate genetic and environmental contributors, in addition to confounding by indication.[29]

While our findings are reassuring, the potential for prenatal antidepressant exposure to be associated with neurodevelopmental abnormalities in later life cannot be ruled out.[30]

Although it was not possible to examine sex-specific differences in this study due to limited statistical power, future studies should consider the potential for such differences. Differences in outcomes according to child sex could relate to underlying differences in human brain development and function,[31, 32] altered susceptibility to maternal depression and/or the use of antidepressants during pregnancy. There is evidence that long-term metabolic outcomes associated with exposure to maternal depression and/or antidepressant use may differ according to fetal sex,[33-35] while potential differences in developmental outcomes are less clear[6, 7]. Additional areas of focus include the potential impact of differing levels of exposure (i.e. illness severity, antidepressant use) and/or timing of exposure to maternal depression and antidepressants during pregnancy. Such effects could be influenced by key genetic factors (e.g. pharmacogenomics). Lastly, future studies should address ways in which to maximise the effectiveness and benefits of antidepressant use during pregnancy. If underlying maternal depression during pregnancy is strongly associated with adverse behavioural outcomes in children at 7-years of age, efforts should focus on improving the management of depression in the antenatal and postnatal period to improve child development and wellbeing in later life. As such, further large population-based studies are required to investigate the potential adverse effects of *in utero* exposure to antidepressants on fetal brain development and child neurodevelopmental outcomes, with longer-term follow-up of children into adulthood required, in addition to consideration for differences in post-natal life of importance for child development.

While the findings from this study support appropriate management of maternal depression during pregnancy with antidepressants, as with any clinical decision, there is a need to consider and balance the benefits and potential risks associated with medication use. This includes the recognition that antidepressant use occurs in the context of maternal psychiatric illness, with increasing evidence to suggest that the combination of both antidepressant use and maternal psychiatric illness is associated with a range of adverse pregnancy outcomes (e.g. preterm delivery).[3]

**Conclusion**

The results of this study suggest that independent of maternal illness, prenatal antidepressant exposure is not associated with an increased risk of behavioural problems in children at 7-years of age. While these findings may provide reassurance regarding the use of antidepressants in pregnancy, the outcomes evaluated in this study represent just one of many outcomes of interest to both clinicians and patients that contribute towards the benefit:risk assessment and should not be used in isolation to guide clinical decision making.

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None

**Conflict of Interest**
All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

**Contributor's Statement Page**

Luke E Grzeskowiak: Dr Grzeskowiak conceptualised and designed the study, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted.

Janna L Morrison, Tine Brink Henriksen, Bodil Hammer Bech, Carsten Obel, Jørn Olsen: Drs. Morrison, Henriksen, Bech, Obel, and Olsen designed the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Lars Henning Pedersen: Dr Pedersen conceptualised and designed the study, carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

**Ethics Approval**
The participants in the DNBC were registered as participants when the study secretary received a signed informed consent form. The Danish Committee on Biomedical Research Ethics has approved the DNBC (ref. no [KF] 01-471/94). The Danish Data Protection Agency has approved the cohort (case no. 2008-54-0431) and the 7-year follow-up (case no. 2004-41-4078). The Danish Data Protection Agency and the Institutional Board Committee of the Danish National Birth Cohort approved the present study (01/10/2010).

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## Table/Figure Caption List

**Table 1. Baseline Antenatal Maternal Characteristics According to Exposure to Antidepressants, Untreated Maternal Depression, or Neither, During Pregnancy**

**Table 1. Baseline Antenatal Maternal Characteristics According to Exposure to Antidepressants, Untreated Maternal Depression, or Neither, During Pregnancy**

| Characteristic | Antidepressants (*N*=210) | | Untreated Depression (*N*=231) | | Unexposed (*N*=48 737) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Age, years | | | | | | |
| <20 | 0 | 0 | 3 | 1.3 | 180 | 0.4 |
| 20-24 | 22 | 10.5 | 27 | 11.7 | 3709 | 7.6 |
| 25-29 | 62 | 29.5 | 82 | 35.5 | 18 815 | 38.6 |
| 30-34 | 87 | 41.4 | 76 | 32.9 | 18 546 | 38.1 |
| >35 | 39 | 18.6 | 43 | 18.6 | 7 487 | 15.4 |
| *Missing* | 0 | | 0 | | 0 | |
| Parity | | | | | | |
| 0 | 107 | 51.9 | 108 | 47.0 | 22 795 | 46.8 |
| >0 | 103 | 49.1 | 122 | 53.0 | 25 914 | 53.2 |
| *Missing* | 0 | | 1 | | 28 | |
| BMI, kg/m$^2$ | | | | | | |
| <18.5 | 9 | 4.3 | 20 | 8.7 | 2 118 | 4.4 |
| 18.6-24.9 | 145 | 69.1 | 147 | 63.6 | 33 225 | 68.2 |
| 25-29.9 | 34 | 16.2 | 43 | 18.6 | 9 155 | 18.8 |
| ≥30 | 22 | 10.5 | 21 | 9.1 | 4 239 | 8.7 |
| *Missing* | 0 | | 0 | | 0 | |
| Smoking | | | | | | |
| No | 114 | 54.3 | 141 | 61.0 | 37 589 | 77.1 |
| Yes | | | | | | |
| 1-10 cigarettes/day | 73 | 34.8 | 65 | 28.1 | 8 681 | 17.8 |
| >10 cigarettes/day | 23 | 10.9 | 25 | 10.8 | 2 467 | 5.1 |
| *Missing* | 0 | | 0 | | 0 | |
| Alcohol | | | | | | |
| No | 133 | 63.3 | 131 | 56.7 | 26 606 | 54.6 |
| Yes | 77 | 36.7 | 100 | 43.3 | 22 085 | 45.4 |
| *Missing* | 0 | | 0 | | 46 | |
| Highest level of education | | | | | | |
| High | 146 | 70.2 | 130 | 56.5 | 33 763 | 69.5 |
| Middle | 47 | 22.6 | 82 | 35.7 | 13 296 | 27.4 |
| Low | 15 | 7.2 | 18 | 7.8 | 1 537 | 3.2 |
| *Missing* | 2 | | 1 | | 141 | |
| Marital status | | | | | | |
| Living with partner | 197 | 93.8 | 217 | 93.9 | 47 907 | 98.3 |
| Living alone | 13 | 6.2 | 14 | 6.1 | 808 | 1.7 |
| *Missing* | 0 | | 0 | | 22 | |
| | Mean | SD | Mean | SD | Mean | SD |
| Antenatal Mood[a] | 5.3 | 3.7 | 8.1 | 4.3 | 2.7 | 2.4 |
| *Missing* | 0 | | 0 | | 0 | |

Abbreviations: BMI, Body Mass Index; SD, Standard Deviation

[a] Evaluated during second prenatal interview at 32 weeks gestation using a modified version of the Symptoms Check List (SCL-8d)[1]

**Table 2. Behavioural Problem Scores in Children at 7-years of Age Following Exposure to Antidepressants, Untreated Maternal Depression, Or Neither, During Pregnancy**

| Question | Antidepressants (*N*=210) | | Untreated Depression (*N*=231) | | *P* for Antidepressants vs Untreated Depression | Unexposed (*N*=48 737) | | *P* for Antidepressants vs Unexposed |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | P-Value[a] | N | % | P-Value[a] |
| **Total Difficulties Score[b]** | | | | | | | | |
| Normal (0-13) | 193 | 91.9 | 201 | 87.0 | 0.191 | 45 679 | 93.8 | 0.358 |
| Borderline (14-16) | 10 | 4.8 | 14 | 6.1 | | 1 573 | 3.2 | |
| Abnormal (17-40) | 7 | 3.3 | 16 | 3.9 | | 1 457 | 3.0 | |
| *Missing* | 0 | | 0 | | | 28 | | |
| **Internalising Problems** | | | | | | | | |
| **Emotional Symptoms Score** | | | | | | | | |
| Normal (0-3) | 164 | 78.1 | 171 | 74.0 | 0.373 | 42 003 | 86.2 | 0.003 |
| Borderline (4) | 19 | 9.1 | 19 | 8.2 | | 3 167 | 6.5 | |
| Abnormal (5-10) | 27 | 12.9 | 41 | 17.8 | | 3 547 | 7.3 | |
| *Missing* | 0 | | 0 | | | 21 | | |
| **Peer Problems Score** | | | | | | | | |
| Normal (0-2) | 169 | 88.6 | 196 | 84.9 | 0.468 | 44 581 | 91.5 | 0.167 |
| Borderline (3) | 14 | 6.7 | 18 | 7.8 | | 2 036 | 4.2 | |
| Abnormal (4-10) | 10 | 4.8 | 17 | 7.4 | | 2 101 | 4.3 | |
| *Missing* | 0 | | 0 | | | 19 | | |
| **Externalising Problems** | | | | | | | | |
| **Conduct Problems Score** | | | | | | | | |
| Normal (0-2) | 165 | 78.6 | 175 | 75.8 | 0.730 | 41 918 | 86.0 | 0.008 |
| Borderline (3) | 26 | 12.4 | 30 | 13.0 | | 4 202 | 8.6 | |
| Abnormal (4-10) | 19 | 9.1 | 26 | 11.3 | | 2 600 | 5.3 | |
| *Missing* | 0 | | 0 | | | 17 | | |
| **Hyperactivity-Inattention Score** | | | | | | | | |
| Normal (0-5) | 190 | 90.5 | 198 | 85.7 | 0.212 | 44 525 | 91.4 | 0.754 |
| Borderline (6) | 9 | 4.3 | 11 | 4.8 | | 1 716 | 3.5 | |
| Abnormal (7-10) | 11 | 5.2 | 22 | 9.5 | | 2 473 | 5.1 | |
| *Missing* | 0 | | 0 | | | 23 | | |
| **Other Measures** | | | | | | | | |
| **Pro-Social Score** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Normal (6-10) | 202 | 96.2 | 209 | 90.5 | 0.045 | 45 953 | 94.3 | 0.528 |
| Borderline (5) | 6 | 2.9 | 13 | 5.6 | | 1 759 | 3.6 | |
| Abnormal (0-4) | 2 | 1.0 | 9 | 3.9 | | 1 018 | 2.1 | |
| *Missing* | 0 | | 0 | | | 7 | | |
| **Impact Score** | | | | | | | | |
| Normal (0) | 176 | 83.8 | 185 | 81.9 | 0.321 | 44 400 | 91.6 | <0.001 |
| Borderline (1) | 18 | 8.6 | 15 | 6.6 | | 1 846 | 3.8 | |
| Abnormal (2) | 16 | 7.6 | 26 | 11.5 | | 2 242 | 4.6 | |
| *Missing* | 0 | | 5 | | | 249 | | |

[a] Fisher's Exact Test

[b] Total difficulties score calculated from emotional symptoms, peer problems, conduct problems and hyperactivity-inattention scores.

**Table 3. RRs for Behavioural Problems in Children at 7-years of Age Following Exposure to Antidepressants, Untreated Maternal Depression, or Neither, During Pregnancy**

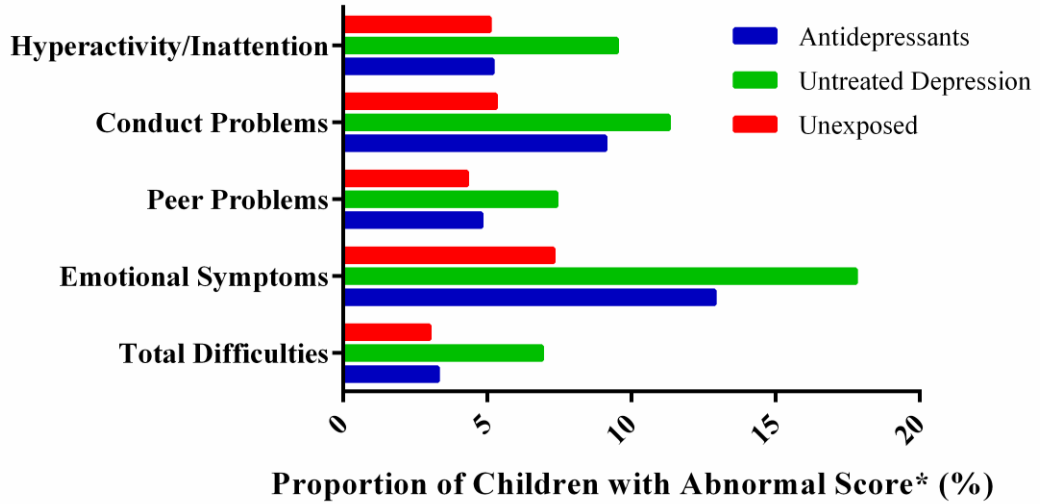
| | Antidepressants vs Unexposed | | | | Antidepressants vs Untreated Depression | | | | Untreated Depression vs Unexposed | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Adjusted[a] | | Adjusted[a] + Antenatal Mood | | Adjusted[a] | | Adjusted[a] + Antenatal Mood | | Adjusted[a] | | Adjusted[a] + Antenatal Mood | |
| | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** |
| **Total Difficulties Score[b]** | | | | | | | | | | | | |
| Abnormal | 1.00 | 0.49, 2.05 | 0.68 | 0.34, 1.36 | 0.54 | 0.23, 1.30 | 0.84 | 0.31, 2.31 | **1.91** | **1.20, 3.04** | 0.89 | 0.55, 1.46 |
| **Internalising Problems** | | | | | | | | | | | | |
| **Emotional Symptoms Score** | | | | | | | | | | | | |
| Abnormal | **1.68** | **1.18, 2.38** | 1.20 | 0.85, 1.70 | 0.74 | 0.47, 1.14 | 0.80 | 0.50, 1.28 | **2.24** | **1.69, 2.97** | 1.23 | 0.91, 1.66 |
| **Peer Problems Score** | | | | | | | | | | | | |
| Abnormal | 1.04 | 0.57, 1.91 | 0.82 | 0.45, 1.51 | 0.65 | 0.30, 1.42 | 0.76 | 0.32, 1.85 | 1.53 | 0.97, 2.43 | 0.96 | 0.59, 1.54 |
| **Externalising Problems** | | | | | | | | | | | | |
| **Conduct Problems Score** | | | | | | | | | | | | |
| Abnormal | **1.58** | **1.03, 2.42** | 1.19 | 0.77, 1.83 | 0.82 | 0.47, 1.43 | 0.90 | 0.49, 1.67 | **1.83** | **1.27, 2.62** | 1.00 | 0.69, 1.46 |
| **Hyperactivity-Inattention Score** | | | | | | | | | | | | |
| Abnormal | 0.99 | 0.56, 1.75 | 0.78 | 0.44, 1.37 | 0.57 | 0.28, 1.19 | 0.75 | 0.34, 1.64 | **1.66** | **1.12, 2.46** | 1.02 | 0.68, 1.53 |
| **Other Measures** | | | | | | | | | | | | |
| **Pro-Social Score** | | | | | | | | | | | | |
| Abnormal | 0.46 | 0.12, 1.82 | 0.40 | 0.10, 1.60 | 0.23 | 0.05, 1.18 | **0.19** | **0.05, 0.77** | **1.90** | **1.01, 3.62** | 1.39 | 0.71, 2.70 |
| **Impact Score** | | | | | | | | | | | | |
| Abnormal | 1.56 | 0.97, 2.52 | 1.15 | 0.71, 1.85 | 0.66 | 0.36, 1.20 | 0.76 | 0.40, 1.46 | **2.28** | **1.60, 3.25** | 1.22 | 0.84, 1.79 |

Abbreviations: RR, Relative Risk; CI, Confidence Interval

[a] Adjusted for child sex, maternal age, parity, smoking status, alcohol use, and socioeconomic status

[b] Total difficulties score calculated from emotional symptoms, peer problems, conduct problems and hyperactivity-inattention scores

**Figure 1. Child Behavioural Problems at 7-years of Age Following Exposure to Antidepressants, Untreated Maternal Depression, or Neither, During Pregnancy**




*Behavioural problems defined as scores above the 90th percentile on the parent-report version of the Strengths and Difficulties Questionnaire (SDQ)

**Table S1. Characteristics of Eligible Women Lost and Not Lost to Follow-Up**

| Characteristic | Not Lost (*N*= 49 178) | | Lost (*N*= 30 929) | |
|---|---|---|---|---|
| | N | % | N | % |
| Age, years | | | | |
| <20 | 183 | 0.4 | 258 | 0.8 |
| 20-24 | 3 758 | 7.6 | 3 236 | 10.5 |
| 25-29 | 18 959 | 38.6 | 12 054 | 39.0 |
| 30-34 | 18 709 | 38.0 | 11 152 | 36.1 |
| >35 | 7 569 | 15.4 | 4 229 | 13.7 |
| *Missing* | 0 | | 0 | |
| Parity | | | | |
| 0 | 23 010 | 46.8 | 14 299 | 46.3 |
| >0 | 26 139 | 53.2 | 16 610 | 53.7 |
| *Missing* | 29 | | 20 | |
| BMI, mean, kg/m$^2$ | | | | |
| <18.5 | 2 147 | 4.4 | 1 491 | 4.8 |
| 18.6-24.9 | 33 517 | 68.2 | 19 557 | 63.2 |
| 25-29.9 | 9 232 | 18.8 | 6 369 | 20.6 |
| ≥30 | 4 282 | 8.7 | 3 512 | 11.4 |
| *Missing* | 0 | | 0 | |
| Smoking | | | | |
| No | 37 844 | 76.9 | 21 955 | 71.0 |
| Yes | | | | |
| 1-10 cigarettes per d | 8 819 | 17.9 | 6 645 | 21.5 |
| >10 cigarettes per d | 2 515 | 5.1 | 2 329 | 7.5 |
| *Missing* | 0 | | 0 | |
| Alcohol | | | | |
| No | 26 870 | 54.7 | 17 389 | 56.3 |
| Yes | 22 262 | 45.3 | 13 504 | 43.7 |
| *Missing* | 46 | | 36 | |
| Highest level of education | | | | |
| High | 34 039 | 69.4 | 19 495 | 63.3 |
| Middle | 13 425 | 27.4 | 9 791 | 31.8 |
| Low | 1 570 | 3.2 | 1 498 | 4.9 |
| *Missing* | 144 | | 145 | |
| Marital status | | | | |
| Living with partner | 48 321 | 98.3 | 30 246 | 97.8 |
| Living alone | 835 | 1.7 | 676 | 2.2 |
| *Missing* | 22 | | 7 | |
| Exposure group | | | | |
| Unexposed | 48 737 | 99.1 | 30 501 | 98.6 |
| Untreated depression | 231 | 0.5 | 243 | 0.8 |
| Antidepressant Use | 210 | 0.4 | 185 | 0.6 |
| *Missing* | 0 | | 0 | |

[a] percentage calculated from non-missing values

**Table S2. Maternal Self-reported Antenatal Mood Symptoms According to Exposure to Antidepressants, Untreated Maternal Depression, or Neither, During Pregnancy**

| Question[a] | Antidepressants | Untreated | Unexposed |
|---|---|---|---|

| Second prenatal interview (32 wk gestation), n (%) | (*N*=210) | | Depression (*N*=231) | | (*N*=48 737) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Overall mood** | | | | | | |
| How have you felt on average during pregnancy? | | | | | | |
| Very good | 62 | 29.5 | 40 | 17.3 | 21 993 | 45.1 |
| Good | 72 | 34.3 | 69 | 29.9 | 19 005 | 39.0 |
| Average | 60 | 28.6 | 84 | 36.4 | 6 610 | 13.6 |
| Bad | 12 | 5.7 | 25 | 10.8 | 958 | 2.0 |
| Very bad | 4 | 1.9 | 13 | 5.6 | 153 | 0.3 |
| *Missing* | 0 | | 0 | | 18 | |
| **Depression** | | | | | | |
| Have you felt that the future looked hopeless? | | | | | | |
| No | 135 | 64.3 | 106 | 45.9 | 43 881 | 90.1 |
| A little | 53 | 25.2 | 66 | 28.6 | 4 316 | 8.9 |
| A lot | 22 | 10.5 | 59 | 25.5 | 534 | 1.1 |
| *Missing* | 0 | | 0 | | 6 | |
| Have you felt sad or blue? | | | | | | |
| No | 77 | 36.7 | 20 | 8.7 | 30 717 | 63.0 |
| A little | 91 | 43.3 | 108 | 46.8 | 16 597 | 34.1 |
| A lot | 42 | 20.0 | 103 | 44.6 | 1 413 | 2.9 |
| *Missing* | 0 | | 0 | | 10 | |
| Have you felt that everything was a big effort? | | | | | | |
| No | 126 | 60.0 | 109 | 47.2 | 39 114 | 80.3 |
| A little | 70 | 33.3 | 75 | 32.5 | 8 658 | 17.8 |
| A lot | 14 | 6.7 | 47 | 20.4 | 955 | 2.0 |
| *Missing* | 0 | | 0 | | 10 | |
| **Anxiety** | | | | | | |
| Have you felt scared or anxious without reason? | | | | | | |
| No | 103 | 49.3 | 88 | 38.1 | 35 445 | 72.8 |
| A little | 84 | 40.2 | 85 | 36.8 | 11 699 | 24.0 |
| A lot | 22 | 10.5 | 58 | 25.1 | 1 536 | 3.2 |
| *Missing* | 1 | | 0 | | 57 | |
| Have you felt nervous or at unease? | | | | | | |
| No | 78 | 37.1 | 46 | 20.0 | 32 953 | 67.6 |
| A little | 104 | 49.5 | 120 | 52.2 | 14 647 | 30.1 |
| A lot | 28 | 13.3 | 64 | 27.8 | 1 125 | 2.3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Missing* | 0 | | 1 | | 12 | |
| Have you felt tense and exhausted? | | | | | | |
| No | 102 | 48.6 | 68 | 29.4 | 33 579 | 69.8 |
| A little | 93 | 44.3 | 123 | 53.3 | 14 249 | 29.3 |
| A lot | 15 | 7.1 | 40 | 17.3 | 890 | 1.8 |
| *Missing* | 0 | | 0 | | 19 | |
| **Stress** | | | | | | |
| Have you felt under constant pressure? | | | | | | |
| No | 149 | 70.9 | 120 | 51.9 | 43 885 | 90.1 |
| A little | 51 | 24.3 | 70 | 30.3 | 4 220 | 8.7 |
| A lot | 10 | 4.8 | 41 | 17.8 | 625 | 1.3 |
| *Missing* | 0 | | 0 | | 7 | |
| Have you been more touchy and quick-tempered than usual? | | | | | | |
| No | 69 | 32.9 | 55 | 23.9 | 20 265 | 41.6 |
| A little | 100 | 47.6 | 93 | 40.4 | 24 700 | 50.7 |
| A lot | 41 | 19.5 | 82 | 35.6 | 3 735 | 7.7 |
| *Missing* | 0 | | 1 | | 61 | |
| Have you felt that demands on you were too big? | | | | | | |
| No | 145 | 69.1 | 123 | 53.5 | 41 084 | 84.3 |
| A little | 52 | 24.8 | 72 | 31.3 | 6 913 | 14.2 |
| A lot | 13 | 6.2 | 35 | 15.2 | 727 | 1.5 |
| *Missing* | 0 | | 1 | | 13 | |

[a] Questions taken from a modified version of the Symptoms Check List (SCL-8d)[1]

**Table S3. RRs for Behavioural Outcomes in Children at 7-years of Age According to Exposure During Pregnancy Using Inverse Probability Weighting to Adjust for Loss to Follow-Up**

| | Antidepressants vs Unexposed | | | | Antidepressants vs Untreated Depression | | | | Untreated Depression vs. Unexposed | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Adjusted[a] | | Adjusted[a] + IPW | | Adjusted[a] | | Adjusted[a] + IPW | | Adjusted[a] | | Adjusted[a] + IPW | |
| | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** |
| **Total Difficulties Score[b]** | | | | | | | | | | | | |
| Abnormal | 0.68 | 0.34, 1.36 | 0.74 | 0.37, 1.49 | 0.84 | 0.31, 2.31 | 0.93 | 0.34, 2.54 | 0.89 | 0.55, 1.46 | 0.88 | 0.54, 1.45 |
| **Internalising Problems** | | | | | | | | | | | | |
| **Emotional Symptoms Score** | | | | | | | | | | | | |
| Abnormal | 1.20 | 0.85, 1.70 | 1.20 | 0.85, 1.69 | 0.80 | 0.50, 1.28 | 0.86 | 0.54, 1.37 | 1.23 | 0.91, 1.66 | 1.17 | 0.86, 1.59 |
| **Peer Problems Score** | | | | | | | | | | | | |
| Abnormal | 0.82 | 0.45, 1.51 | 0.81 | 0.44, 1.49 | 0.76 | 0.32, 1.85 | 0.81 | 0.33, 2.00 | 0.96 | 0.59, 1.54 | 0.89 | 0.54, 1.45 |
| **Externalising Problems** | | | | | | | | | | | | |
| **Conduct Problems Score** | | | | | | | | | | | | |
| Abnormal | 1.19 | 0.77, 1.83 | 1.18 | 0.77, 1.82 | 0.90 | 0.49, 1.67 | 0.94 | 0.51, 1.74 | 1.00 | 0.69, 1.46 | 0.96 | 0.66, 1.40 |
| **Hyperactivity-Inattention Score** | | | | | | | | | | | | |
| Abnormal | 0.78 | 0.44, 1.37 | 0.84 | 0.48, 1.47 | 0.75 | 0.34, 1.64 | 0.79 | 0.36, 1.74 | 1.02 | 0.68, 1.53 | 1.05 | 0.70, 1.57 |
| **Other Measures** | | | | | | | | | | | | |
| **Pro-Social Score** | | | | | | | | | | | | |
| Abnormal | 0.40 | 0.10, 1.60 | 0.36 | 0.09, 1.43 | 0.19 | 0.05, 0.77 | 0.17 | 0.04, 0.70 | 1.39 | 0.71, 2.70 | 1.30 | 0.66, 2.57 |
| **Impact Score** | | | | | | | | | | | | |
| Abnormal | 1.15 | 0.71, 1.85 | 1.10 | 0.68, 1.78 | 0.76 | 0.40, 1.46 | 0.72 | 0.38, 1.38 | 1.22 | 0.84, 1.79 | 1.22 | 0.83, 1.79 |

Abbreviations: RR, Relative Risk; CI, Confidence Interval; IPW, Inverse Probability Weighting

[a] Adjusted for child sex, maternal age, parity, smoking status, alcohol use, socioeconomic status, and antenatal mood

[b] Total difficulties score calculated from emotional symptoms, peer problems, conduct problems and hyperactivity-inattention scores.

**Table S4. RRs for Behavioural Problems in Children at 7-years of Age According to Timing of Antidepressant Exposure During Pregnancy**

| | Adjusted[a] | | Adjusted[a] + Antenatal Mood | |
|---|---|---|---|---|
| | **RR** | **95% CI** | **RR** | **95% CI** |
| **Total Difficulties Score[b]** | | | | |
| Untreated depression (n=231) | Ref | | Ref | |
| Exposure at any point during pregnancy (n=210) | 0.54 | 0.23, 1.30 | 0.84 | 0.31, 2.31 |
| First-trimester exposure only (n=49) | 0.88 | 0.28-2.74 | 1.11 | 0.33-3.73 |
| Second/third-trimester exposure (n=161) | 0.41 | 0.14-1.19 | 0.60 | 0.20-1.88 |
| **Internalising Problems** | | | | |
| **Emotional Symptoms Score** | | | | |
| Untreated depression (n=231) | Ref | | Ref | |
| Exposure at any point during pregnancy (n=210) | 0.74 | 0.47, 1.14 | 0.80 | 0.50, 1.28 |
| First-trimester exposure only (n=49) | 0.96 | 0.50-1.86 | 1.03 | 0.52-2.03 |
| Second/third-trimester exposure (n=161) | 0.66 | 0.40-1.08 | 0.69 | 0.41-1.15 |
| **Peer Problems Score** | | | | |
| Untreated depression (n=231) | Ref | | Ref | |
| Exposure at any point during pregnancy (n=210) | 0.65 | 0.30, 1.42 | 0.76 | 0.32, 1.85 |
| First-trimester exposure only (n=49) | 0.73 | 0.20-2.65 | 0.80 | 0.20-3.29 |
| Second/third-trimester exposure (n=161) | 0.58 | 0.24-1.36 | 0.64 | 0.25-1.61 |
| **Externalising Problems** | | | | |
| **Conduct Problems Score** | | | | |
| Untreated depression (n=231) | Ref | | Ref | |
| Exposure at any point during pregnancy (n=210) | 0.82 | 0.47, 1.43 | 0.90 | 0.49, 1.67 |
| First-trimester exposure only (n=49) | 1.44 | 0.68-3.08 | 1.52 | 0.67-3.41 |
| Second/third-trimester exposure (n=161) | 0.63 | 0.32-1.22 | 0.71 | 0.34-1.48 |
| **Hyperactivity-Inattention Score** | | | | |
| Untreated depression (n=231) | Ref | | Ref | |
| Exposure at any point during pregnancy (n=210) | 0.57 | 0.28, 1.19 | 0.75 | 0.34, 1.64 |
| First-trimester exposure only (n=49) | 0.35 | 0.09-1.42 | 0.42 | 0.10-1.69 |
| Second/third-trimester exposure (n=161) | 0.64 | 0.30-1.40 | 0.82 | 0.37-1.82 |

Abbreviations: RR, Relative Risk; CI, Confidence Interval

[a] Adjusted for child sex, maternal age, parity, smoking status, alcohol use, and socioeconomic status

[b] Total difficulties score calculated from emotional symptoms, peer problems, conduct problems and hyperactivity-inattention scores