

# Antidepressant Use During Pregnancy and Asthma in the Offspring

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abstract

**BACKGROUND AND OBJECTIVES:** It has been suggested that maternal depression during pregnancy is associated with asthma in the offspring, but the role of medical treatment of depression is not known. Our goal was to examine whether prenatal antidepressant use increases the risk of asthma in the offspring.

**METHODS:** A cohort study was performed among all live singletons born in Denmark between 1996 and 2007. Mothers who had a diagnosis of depressive disorder and/or who used antidepressants 1 year before or during the index pregnancy were identified. Using a Cox proportional hazards regression model, we estimated the hazard ratio (HR) for asthma in the offspring after antidepressant use during pregnancy.

**RESULTS:** Of the 733 685 children identified, 84 683 had a diagnosis of asthma. A total of 21 371 children were exposed to prenatal maternal depression (ie, a diagnosis of depressive disorder or use of antidepressants 1 year before or during pregnancy). Prenatal maternal depression was associated with childhood asthma (HR: 1.25 [95% confidence interval (CI): 1.20–1.30]). Overall, 8895 children were exposed to antidepressants in utero. Compared with children born to mothers with prenatal depression and no antidepressant use during pregnancy, the HR for asthma after any antidepressant use during pregnancy was 1.00 (95% CI: 0.93–1.08). HRs after use of selective serotonin reuptake inhibitors only, newer antidepressants only, and older antidepressants only were 0.95 (95% CI: 0.88–1.03), 1.11 (95% CI: 0.89–1.39), and 1.26 (95% CI: 1.02–1.55), respectively.

**CONCLUSIONS:** Antidepressant use during pregnancy generally did not increase the risk of asthma. Only use of older antidepressants was associated with an increased risk of asthma.

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**WHAT'S KNOWN ON THIS SUBJECT:** Asthma is one of the most common chronic diseases in children. It has been suggested that maternal depression during pregnancy is associated with asthma in the offspring, but the role of antidepressant use during pregnancy is not known.

**WHAT THIS STUDY ADDS:** In our prospective cohort study, we found that maternal antidepressant use during pregnancy generally did not increase the risk of asthma except for use of older antidepressants, which could reflect confounding by the severity of maternal depression.

Depression affects up to 7% to 13% of pregnant women.<sup>1,2</sup> The use of antidepressants during pregnancy has increased, from 0.2% of pregnancies in 1997 to 3.2% in 2010 in Denmark,<sup>3</sup> and from 2.0% in 1996 to 7.6% in 2005 in the United States.<sup>4</sup> Antidepressants may cross the placenta and enter the fetal circulation,<sup>5</sup> thus making use of antidepressants during pregnancy a public health and a clinical concern.

Antidepressants may impact the fetal development of the respiratory system.<sup>6,7</sup> Studies have linked exposure to antidepressants in utero to persistent pulmonary hypertension of the newborn and pulmonary diseases.<sup>8,9</sup> Exposure to antidepressants in utero may also increase the possibility of fetal growth restriction,<sup>10</sup> a risk factor for the development of asthma.<sup>11,12</sup> Little is known, however, about the effects of exposure to antidepressants in utero on the development of asthma. To our knowledge, only 1 study has been published on this topic, which suggested an association between antidepressant use during pregnancy and asthma in the offspring.<sup>13</sup> However, the underlying maternal depression was not taken into consideration in this study. Furthermore, the effects associated with subtypes of antidepressant use or the timing of medication were not investigated.

The goal of the present population-based study was to explore whether maternal antidepressant use during pregnancy is associated with asthma in children. We postulated that maternal depression would play a role, and we expected the associations to be varied according to subtypes of antidepressant used and the timing of medication.

## METHODS

### Study Population

The study was based on linkage of several national registers in Denmark.

All citizens in Denmark are assigned a unique personal identification number, which permits accurate linkage of data at the individual level between all national registers. The Danish Medical Birth Registry (DMBR) contains data on all live births since 1973 and includes data on gestational age at birth from 1978.<sup>14</sup> We identified all live singletons born between January 1, 1996, and December 31, 2007, recorded in the DMBR ( $N = 755\,358$ ). We excluded 85 infants due to inability to link them to their mothers, 5215 infants who had missing gestational age at birth or gestational age at birth  $<154$  or  $>315$  days, and 16 373 infants who emigrated or died before 3 years of age. A total of 733 685 singletons were thus included in the analysis.

### Data on Depressive Disorder and Antidepressant Use

Data on maternal or paternal diagnosis of depressive disorder 1 year before or during pregnancy were obtained from the Danish Psychiatric Central Register and the Danish National Patient Register.<sup>15,16</sup> The Danish Psychiatric Central Register includes all admissions to psychiatric hospitals and psychiatric wards in general hospitals in Denmark since 1969, as well as all psychiatric outpatient contacts since 1995. The Danish National Patient Register has collected data on all inpatient contacts since 1977 and from 1995 for all emergency department and outpatient contacts.<sup>16</sup> During the study period, the *International Classification of Diseases, 10th Revision* (ICD-10), was used in Denmark. The diagnostic information on depressive disorder was identified based on ICD-10 codes F32.00 through F33.99.

Data on maternal or paternal antidepressants dispensed 1 year before or during the index pregnancy and dispensing date were extracted from the Danish National Prescription Registry.<sup>17</sup> This registry covers all

redeemed prescriptions in Denmark since 1995. Since 1996, drugs prescribed for children have been registered under their own identification number. Antidepressant use was identified based on the Anatomical Therapeutic Chemical codes<sup>18</sup>: selective serotonin reuptake inhibitors (SSRIs, fluoxetine, citalopram, escitalopram, paroxetine, sertraline, and fluvoxamine [N06AB03-10]), newer antidepressants (nefazodone, mirtazapine, venlafaxine, reboxetine [N06AX06, -11, -16, -18, and -21]), or older antidepressants consisting mainly of tricyclic antidepressants (TCAs) (imipramine, clomipramine, trimipramine, lofepramine, amitriptyline, nortriptyline, doxepin, dosulepin, amoxapine, maprotiline; mianserin, isocarboxazid, and moclobemide [N06AA02-7, N06AA09-12, N06AA16-17, N06AA21, N06AX03, N06AF01, and N06AG02]). We allowed for exposure to multiple antidepressants.

### Asthma

Asthma in children was identified by using the Danish National Patient Register and the Danish National Prescription Registry. Because a definitive diagnosis of asthma cannot be made before the age of 3 years,<sup>19</sup> asthma was defined as at least 2 prescriptions for antiasthmatic medications or 1 asthma hospital contact after 3 years of age from 1999 through 2010. Asthma hospital contact was identified based on ICD-10 codes J45 and J46. The Anatomical Therapeutic Chemical codes for inhaled asthma drugs were as follows: inhaled  $\beta_2$ -agonists, R03AC02, R03AC03, R03AC04, R03AC12, and R03AC13; inhaled glucocorticoids, R03BA01, R03BA02, and R03BA05; fixed-dose combinations of inhaled  $\beta_2$ -agonists and glucocorticoids, R03AK06 and R03AK07; and leukotriene receptor antagonists, R03DC03. Two or more medications prescribed on the same day were considered to represent 1

prescription. The first diagnosis of asthma was defined as the date of first admission, emergency department or outpatient contact for asthma, or first antiasthmatic drugs redeemed in the registers, whichever came first after 3 years of age.

### Covariates

The following potential factors were adjusted for in the models: maternal country of origin (Nordic countries, non-Nordic countries), maternal parity (first, second, and third and higher), maternal age at delivery (<25, 25–29, 30–34, and ≥35 years), maternal social status at birth (not in labor market, unskilled workers, skilled workers and white collar workers, and top level status), maternal smoking during pregnancy (yes, no), maternal history of asthma, gender of the child, and calendar year of birth (each year as a category). Information on gender of the child, calendar year of birth, maternal parity, maternal age at delivery, and paternal age at delivery were obtained from the DMBR. Information on maternal social status and maternal country of origin were obtained from the Danish Integrated Database for Longitudinal Labor Market Research.<sup>20</sup> Information on maternal history of asthma was obtained from the Danish National Patient Register and the Danish National Prescription Registry.

### Statistical Analysis

A Cox proportional hazards regression model was used to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) for maternal pregnancy antidepressant use and asthma in children. Robust SEs were used to account for the fact that some mothers contributed data for >1 live singleton. A diagnosis of maternal depressive disorder or use of antidepressants 1 year before or during pregnancy was used as an indicator of prenatal maternal depression. The HRs were calculated for asthma in children born to

mothers who had prenatal depression and children born to mothers who used antidepressants during pregnancy. The reference group comprised children born to mothers without a diagnosis of depressive disorder and no antidepressant use 1 year before or during pregnancy.

To explore whether the association between maternal antidepressant use during pregnancy and asthma in children accounted for the underlying maternal depression, we restricted our analyses to children born to mothers with prenatal depression. The reference group consisted of children born to mothers with depression and not taking any antidepressant during the index pregnancy. To examine whether the association between antidepressant use during pregnancy and asthma depended on the subtypes of exposure to antidepressants, we categorized the subtypes of exposure to antidepressants into 4 groups: SSRIs only, newer antidepressants only, older antidepressants only, and >1 subtype of antidepressants. Exposure to >1 subtype of antidepressants was further categorized into 4 groups: SSRIs and newer antidepressants, SSRIs and older antidepressants, newer antidepressants and older antidepressants, and all 3 subtypes of antidepressants. To examine whether the association between antidepressant use during pregnancy and asthma modifiable by the timing of exposure to antidepressants, the timing was divided into 3 groups: the first trimester (first 90 days after the last menstrual period [LMP] only, the second trimester (91–180 days after the LMP) or the third trimester (181 days after the LMP to date of delivery) only, and >1 trimester.

To examine whether the associations between prenatal maternal depression, antidepressant use during pregnancy, and asthma in the offspring was confounded by shared environmental or genetic variables,<sup>21</sup>

comparisons with associations between prenatal paternal depression, paternal antidepressant use during the index pregnancy, and asthma were included; we also adjusted for maternal depressive disorder and maternal antidepressant use 1 year before or during pregnancy, as well as paternal age at delivery. If the potential effects are due to an intrauterine exposure, maternal depression and antidepressant use during pregnancy should have a greater influence than paternal depression or antidepressant use during the index pregnancy.

All analyses were performed by using Stata version 11.2 (Stata Corp, College Station, TX).

### Ethics

The study was approved by the Danish Data Protection Agency and the Science Ethics Committee of Central Region Jutland in Denmark. According to the legislation in Denmark, no informed consent is needed for a register-based study with public health interest based on encrypted data.

### RESULTS

Of the 733 685 children in the cohort, 21 371 were born to mothers with prenatal depression. Among these, 8895 children were born to mothers who had redeemed prescriptions for antidepressants during the index pregnancy, and the remaining 12 476 children were born to mothers not using any antidepressant during pregnancy. Compared with mothers with no record of prenatal depression, mothers with prenatal depression were characterized as having more previous pregnancies, having lower income, being smokers, having a higher proportion of asthma history, and giving birth in later calendar years. In contrast, mothers with prenatal depression and no antidepressant use during pregnancy and mothers with antidepressant use

during pregnancy were comparable, except for maternal age at delivery and their children's calendar year of birth (Table 1).

Asthma was diagnosed in 84 683 children during follow-up in the entire cohort. Prenatal maternal depression was associated with a 25% increased risk of asthma in the offspring (95% CI: 1.20–1.30), and use of antidepressants during pregnancy corresponded to a 25% increased risk of asthma (95% CI: 1.18–1.33) compared with children born to mothers without depression.

When restricting analyses to children born to mothers with depression, the

overall HR for asthma after any antidepressant use during pregnancy was 1.00 (95% CI: 0.93–1.08). Among mothers who used antidepressants during pregnancy, 80.8% of mothers were prescribed SSRIs only, 6.8% were prescribed newer antidepressants only, 5.7% were prescribed older antidepressants only, and 6.7% were prescribed >1 subtype of antidepressants. The HRs for asthma after use of SSRIs only, newer antidepressants only, and older antidepressants only were 0.95 (95% CI: 0.88–1.03), 1.11 (95% CI: 0.89–1.39), and 1.26 (95% CI: 1.02–1.55), respectively (Table 2).

Of mothers who were prescribed older antidepressants only during pregnancy, 81% of them were prescribed TCAs. The HR for asthma after use of TCAs only was 1.28 (95% CI: 1.06–1.56).

There was little evidence of any association modifiable by the timing of exposure to antidepressants (Table 3).

Compared with children born to fathers with no prenatal depression, children born of fathers who had prenatal depression was associated with an increased risk of asthma in the offspring (HR: 1.11 [95% CI: 1.06–1.16]), and paternal use of antidepressants during the index pregnancy corresponded to an HR of 1.12 (95% CI: 1.06–1.18). When restricting analyses to children born to fathers with prenatal depression, the HRs for asthma in children exposed to paternal use of SSRIs only, newer antidepressants only, and older antidepressants only during pregnancy were 1.01 (95% CI: 0.91–1.12), 0.98 (95% CI: 0.83–1.16), and 1.09 (95% CI: 0.93–1.29), respectively.

## DISCUSSION

In this cohort study based on prospective data, both prenatal maternal depression and paternal depression were associated with a moderately increased risk of asthma in children. Antidepressant use during pregnancy in general did not increase the risk of asthma in the offspring among women with depression, with the exception of use of older antidepressants. The negative control, paternal use of antidepressants during the index pregnancy, was not associated with asthma in the offspring regardless of subtypes of antidepressants.

We found that maternal depression during pregnancy was associated with an increased risk of asthma in the offspring, which was consistent with results from a previous study.<sup>22</sup> Interestingly, paternal depression per

**TABLE 1** Characteristics (%) of the Cohort According to Prenatal Depression and Antidepressant Use During Pregnancy of Mother

Characteristic	Use of Antidepressants During Pregnancy (N = 8895)	Prenatal Depression and Not Taking Antidepressants During Pregnancy (N = 12 476)	No Prenatal Depression (N = 712 314)
Maternal country of origin			
Nordic countries	99.3	99.0	99.0
Other countries	0.7	1.0	1.0
Maternal age at delivery, y			
<25	13.5	16.6	14.1
25–29	30.4	32.0	35.5
30–34	33.8	32.7	34.9
≥35	22.3	18.7	15.5
Maternal parity			
1	42.8	42.6	43.0
2	32.7	32.6	37.7
≥3	24.5	24.8	19.3
Maternal social status			
Not in labor market	0.7	0.5	1.2
Unskilled workers	57.1	54.7	34.9
Skilled workers and white collar workers	28.8	31.0	38.8
Top level status	13.3	13.8	25.0
Unknown	0.1	0	0.1
Maternal smoking during pregnancy			
Yes	35.4	32.9	19.6
No	61.1	64.0	77.0
Unknown	3.5	3.1	3.4
Maternal history of asthma			
Yes	24.2	23.9	15.1
No	75.8	76.1	84.9
Gender of the child			
Boy	51.9	51.3	51.3
Girl	48.1	48.7	48.7
Calendar year of birth			
1996–1998	8.2	13.3	26.0
1999–2001	14.6	19.7	25.5
2002–2004	30.6	29.5	24.3
2005–2007	46.6	37.5	24.2

**TABLE 2** HRs for Asthma According to Subtypes of Maternal Antidepressant Use During Pregnancy Among Children Born to Mothers With Prenatal Depression

Maternal Antidepressant Use During Pregnancy	N	Asthma Cases in the Offspring	Crude HR	Adjusted HR <sup>a</sup>
Not taking antidepressants during pregnancy	12 476	1727	1	1 (Ref)
Any antidepressant during pregnancy	8895	1148	1.00	1.00 (0.93–1.08)
SSRIs only	7186	882	0.95	0.95 (0.88–1.03)
Newer antidepressants only	606	85	1.12	1.11 (0.89–1.39)
Older antidepressants only	505	91	1.25	1.26 (1.02–1.55)
More than 1 subtype of antidepressants	598	90	1.30	1.29 (1.04–1.60)
SSRIs + newer antidepressants	348	42	1.07	1.07 (0.78–1.47)
SSRIs + older antidepressants	200	40	1.66	1.64 (1.20–2.24)
Newer + older antidepressants	23	4	1.58	1.49 (0.54–4.16)
All 3 subtypes of antidepressants	27	4	1.16	1.18 (0.48–2.90)

<sup>a</sup> Adjusted for maternal country of origin, maternal age at delivery, maternal parity, maternal social status, maternal smoking during pregnancy, maternal history of asthma, gender of the child, and calendar year of birth.

se was associated with childhood asthma, suggesting that either genetic or environmental effects outside the intrauterine environment may at least partly explain the association found between maternal depression and asthma.

SSRIs and TCAs are believed to cross the placenta and enter the fetal circulation,<sup>5,23</sup> and many antidepressants influence the serotonin homeostasis. Because serotonin modulates the activity of the respiratory rhythm generator and regulates cell proliferation and maturation of the lung,<sup>6,24</sup> antidepressants may, thereby, influence the development of the lung. As a consequence, exposure to antidepressants in utero may be associated with asthma later in life. Evidence for this finding, however, is

sparse. A previous study found that antidepressant use during the second and third trimesters increased the risk of asthma by 30%.<sup>13</sup> However, if maternal depression increases the risk of asthma in children,<sup>22</sup> the association between antidepressant use and asthma may be confounded by indication (as shown in the present study).

The potential association between antidepressant use and health outcomes in children might depend on the subtypes of antidepressants used.<sup>8,10,18,25</sup> We observed only an increased risk for asthma after maternal use of older antidepressants during pregnancy (mainly TCAs). The risk of congenital malformations, large for gestational age, and respiratory problems was higher after exposure to TCAs than after exposure

to SSRIs or other antidepressants.<sup>8,25,26</sup> It is possible that TCAs may have different pharmacokinetic properties than SSRIs and thereby have an effect on asthma. Uncontrolled confounding is another possible explanation. The underlying severity of depression may vary substantially between women treated with different subtypes of antidepressants. TCAs are widely used to treat severe endogenous depression,<sup>27</sup> and women treated with older antidepressants may therefore suffer from a more severe or treatment-resistant disorder. The association we found between older antidepressants and asthma in children could reflect confounding by indicators.

The linkage of several population-based registers in Denmark enabled us

**TABLE 3** HRs for Asthma According to Subtypes of Maternal Antidepressant Use and the Timing of Medication Among Children Born to Mothers With Prenatal Depression

Maternal Antidepressant Use During Pregnancy	N	Asthma Cases in the Offspring	Crude HR	Adjusted HR <sup>a</sup>
Not taking antidepressants during pregnancy	12 476	1727	1	1 (Ref)
SSRIs				
First trimester only	2748	384	1.01	0.98 (0.87–1.09)
Second or third trimester only	760	90	0.93	0.97 (0.79–1.20)
More than 1 trimester	4253	494	0.95	0.93 (0.84–1.04)
Newer antidepressants				
First trimester only	462	69	1.22	1.22 (0.94–1.57)
Second or third trimester only	34	4	0.85	0.90 (0.34–2.35)
More than 1 trimester	508	62	1.03	0.99 (0.68–1.42)
Older antidepressants				
First trimester only	283	54	1.35	1.31 (1.00–1.71)
Second or third trimester only	78	14	1.23	1.20 (0.67–2.13)
More than 1 trimester	394	71	1.38	1.25 (0.90–1.74)

<sup>a</sup> Adjusted for maternal country of origin, maternal age at delivery, maternal parity, maternal social status, maternal smoking during pregnancy, maternal history of asthma, gender of the child, calendar year of birth, and use of other subtypes antidepressants.

to use a large study population to estimate the effect of antidepressant use during pregnancy on asthma with almost complete follow-up. Prescription data were used as proxy measures for exposure to eliminate recall bias and to increase the precision of the information on subtypes of antidepressants. We defined our outcome (ie, asthma) based on objective medical records. The sensitivity of asthma diagnosis in the Danish National Patient Register was 0.44, and in the Danish National Prescription Registry, it was 0.63.<sup>28,29</sup> There is a substantial nonoverlap between the asthma cases ascertained by the 2 registers ( $\kappa = 0.21$ ). The hospitalization registry may capture more severe asthma cases, whereas the prescription registry identifies a heterogeneous mix of asthma cases (ranging from suspected cases to more severe cases).<sup>30</sup> The use of prescription and hospitalization registers probably enabled us to identify ~85% of asthma cases, estimated by the capture-recapture method.<sup>31</sup> The

availability of population-based data on potential confounding variables provides some options for confounder control when studying the relationship between prenatal maternal depression, antidepressant use during pregnancy, and asthma.

Our findings should be interpreted in the light of limitations. First, misclassification of the exposure is a potential problem, because nondifferential misclassification will tend to bias the results toward the null.<sup>32</sup> It is unknown whether the prescribed drugs were actually taken. Furthermore, it is possible that some women may actually receive antidepressant treatment during inpatient admissions that is not recorded in the prescription registry, although we expect this problem to be minor. Second, asthma is a difficult clinical diagnosis that is not easily captured in population-based studies. We used first hospitalization or first prescription for asthma as the outcome and thus did not include mild asthma cases not seeking

medical contacts. Our findings may therefore not necessarily be generalizable to mild cases of asthma. Third, maternal depression is related to the occurrence of asthma.<sup>22</sup> Although we accounted for confounding by maternal depression, confounding by the severity of depression may still prevail. If women with untreated depression during pregnancy have more pregnancy and postpartum depression symptoms than women treated with antidepressants during pregnancy, we may have underestimated the risk of antidepressant use during pregnancy. Conversely, if women treated with antidepressants during pregnancy experience more severe depression, we may have overestimated the risk.

## CONCLUSIONS

Maternal antidepressant use during pregnancy did not increase the risk of asthma except for use of older antidepressants. This finding could reflect confounding by the severity of maternal depression.

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